2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

Supplementary data

Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC)

Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC)

Authors/Task Force Members: Katja Zeppenfeld*† (Chairperson) (Netherlands), Jacob Tfelt-Hansen*† (Chairperson) (Denmark), Marta de Riva** (Task Force Coordinator) (Netherlands), Bo Gregers Winkel** (Task Force Coordinator) (Denmark), Elijah R. Behr (United Kingdom), Nico A. Blom1 (Netherlands), Philippe Charron (France), Domenico Corrado (Italy), Nikolaos Dagres (Germany), Christian de Chillou (France), Lars Eckardt (Germany), Tim Friede (Germany), Kristina H. Haugaa (Norway), Mélèze Hocini (France), Pier D. Lambiase (United Kingdom), Eloi Marijon (France), Jose L. Merino (Spain), Petr Peichl (Czech Republic), Silvia G. Priori (Italy), Tobias Reichlin (Switzerland), Jeanette Schulz-Menger (Germany), Christian Sticherling (Switzerland), Stylianos Tzeis (Greece), Axel Verstrael (Belgium), Maurizio Volterrani (Italy), and ESC Scientific Document Group

*Corresponding authors: Katja Zeppenfeld, Department of Cardiology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, Netherlands. Tel +31 715262020, E-mail: K.Zeppenfeld@LUMC.nl
Jacob Tfelt-Hansen, The Department of Cardiology, The Heart Centre, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100, Copenhagen, Denmark. Tel +45 61360399, E-mail: jacob.tfelt@regionh.dk
†The two Chairpersons contributed equally to the document and are joint corresponding authors.
**The two Task Force Coordinators contributed equally to the document.

Author/Task Force Member affiliations are listed in Author information in the full text.

1Representing the Association for European Paediatric and Congenital Cardiology (AEPC).

ESC Clinical Practice Guidelines (CPG) Committee: listed in the Appendix in the full text.

ESC subspecialty communities having participated in the development of this document:

Associations: Association for Acute CardioVascular Care (ACVC), Association of Cardiovascular Nursing & Allied Professions (ACNAP), European Association of Cardiovascular Imaging (EACVI), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Working Groups: Cardiac Cellular Electrophysiology, Myocardial and Pericardial Diseases.

Patient Forum

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Document-Reviewers: Maja Cikes (CPG Review Coordinator) (Croatia), Paulus Kirchhof (CPG Review Coordinator) (Germany), Magdy Abdelhamid (Egypt), Victor Aboyans (France), Elena Arbelo (Spain), Fernando Arribas (Spain), Riccardo Asteggiano (Italy), Cristina Basso (Italy), Axel Bauer (Austria), Emanuele Bertaglia (Italy), Tor Biering-Sørensen (Denmark), Carina Blomström-Lundqvist (Sweden), Michael A. Borger (Germany), Jelena Čelutkiénė (Lithuania), Bernard Cosyns (Belgium), Volkmar Falk (Germany), Laurent Fauchier (France), Bulent Gorenek (Turkey), Sigrun Halvorsen (Norway), Robert Hatala (Slovakia), Hein Heidbuchel (Belgium), Stefan Kaab (Germany), Aleksandra Konradi (Russian Federation), Konstantinos C. Koskinas (Switzerland), Dipak Kotecha (United Kingdom), Ulf Landmesser (Germany), Basil S. Lewis (Israel), Ales Linhart (Czech Republic), Maja-Lisa Lochen (Norway), Lars H. Lund (Sweden), Andreas Metzner (Germany), Richard Mindham (United Kingdom), Jens Cosedis Nielsen (Denmark), Tone M. Norekvål (Norway), Monica Patten (Germany), Eva Prescott (Denmark), Amina Rakisheva (Kazakhstan), Carol Ann Remme (Netherlands), Ivo Roca-Luque (Spain), Andrea Sarkozy (Belgium), Daniel Scherr (Austria), Marta Sitges (Spain), Rhian M. Touyz (Canada/United Kingdom), Nicolas Van Mieghem (Netherlands), Vedran Velagic (Croatia), Sami Viskin (Israel), and Paul G. A. Volders (Netherlands)

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Abbreviations and acronyms

AED Automated external defibrillator
ARVC Arrhythmogenic right ventricular cardiomyopathy
ATP Anti-tachycardia pacing
AV Atrio-ventricular
BBR-VT Bundle branch re-entrant ventricular tachycardia
BLS Basic life support
b.p.m. Beats per minute
CA Cardiac arrest
CAD Coronary artery disease
CIED Cardiac implantable electronic devices
CMR Cardiac magnetic resonance
CPR Cardiopulmonary resuscitation
CPVT Catecholaminergic polymorphic ventricular tachycardia
CRT Cardiac resynchronization therapy
CRT-D Cardiac resynchronization therapy defibrillator
CT/CTA Computed tomography/computed tomography angiography
DCM Dilated cardiomyopathy
DNA Deoxynucleic acid
EAM Electroanatomic mapping
ECG Electrocardiogram
EF Ejection fraction
EPS Electrophysiological study
ERP Early repolarization pattern
ERS Early repolarization syndrome
HCM Hypertrophic cardiomyopathy
HNDCM Hypokinetic non-dilated cardiomyopathy
HR Hazard ratio
ICD Implantable cardioverter defibrillator
ILR Implantable loop recorder
IRR Incident rate ratio
IVF Idiopathic ventricular fibrillation
LBBB Left bundle branch block
LCSD Left cardiac sympathetic denervation
LGE Late gadolinium enhancement
LQTS Long QT syndrome
LV Left ventricular
LVEF Left ventricular ejection fraction
MI Myocardial infarction
NICM Non-ischaemic cardiomyopathy
NSVT Non-sustained ventricular tachycardia
NYHA New York Heart Association
OHCA Out-of-hospital cardiac arrest
OR Odds ratio
PCI Percutaneous coronary intervention
PES Programmed electrical stimulation
PLN Phospholamban
PVC Premature ventricular complex
RBBB Right bundle branch block
RCT Randomized control trial
RFCA Radiofrequency catheter ablation
RV Right ventricular
RVOT Right ventricle outflow tract
SADS Sudden arrhythmic death syndrome
SCA Sudden cardiac arrest
SCD Sudden cardiac death
SD Sudden death
SHD Structural heart disease
S-ICD Subcutaneous implantable cardioverter defibrillator
<table>
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<th>Abbreviation</th>
<th>Description</th>
<th>Abbreviation</th>
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<tr>
<td>SMVT</td>
<td>Sustained monomorphic ventricular tachycardia</td>
<td>VA</td>
<td>Ventricular arrhythmia</td>
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<td>STEMI</td>
<td>ST elevation myocardial infarction</td>
<td>VF</td>
<td>Ventricular fibrillation</td>
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<td>SUDY</td>
<td>Sudden unexpected death in the young</td>
<td>VT</td>
<td>Ventricular tachycardia</td>
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<td>SVT</td>
<td>Supraventricular tachycardia</td>
<td>WCD</td>
<td>Wearable cardioverter defibrillator</td>
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<td>TOF</td>
<td>Tetralogy of Fallot</td>
<td>WES</td>
<td>Whole-exome sequencing</td>
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ESC Guidelines
1. Epidemiology of sudden cardiac death, public awareness, and risk stratification

1.1. Awareness and intervention: public basic life support and access to automated external defibrillators

Table of Evidence 1 for Table of Recommendations for public basic life support and access to automated external defibrillators

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
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<tr>
<td>Hallstrom, A., et al.1</td>
<td>Public-access defibrillation and survival after out-of-hospital cardiac arrest. PMID: 15306665 Year of publication: 2004</td>
<td>Aim: The rate of survival after OHCA is low. It is not known whether this rate will increase if laypersons are trained to attempt defibrillation with the use of AEDs. Study type: Prospective, community-based study. Number of patients: &gt;19,000 Enrolment period: 2000–2003 Study endpoints: Survival to hospital discharge.</td>
<td>Inclusion: Community units with a pool of potential volunteer responders and the ability to deliver an AED within 3 min to a person having a cardiac arrest. Exclusion: Facilities having on-site personnel with a duty to respond to medical emergencies. Facilities with existing AED programmes.</td>
<td>Results: Survival to hospital discharge was significantly higher among patients in the group of CPR-plus-AED units than in the CPR-only group (24.5% vs. 14.0%; P = 0.03; relative risk, 2.0; 95% CI 1.07–3.77).</td>
<td>Other findings: Functional status at hospital discharge did not differ between the two groups.</td>
<td>Conclusions: Enhancing a well-developed, monitored, layperson-enacted CPR-response plan by adding AEDs and AED training can increase the number of survivors of OHCA in public locations.</td>
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<td>Nakashima, T., et al.2</td>
<td>Public-access defibrillation and neurological outcomes in patients with out-of-hospital cardiac arrest in Japan: a population-based cohort study. PMID: 23862250 Year of publication: 2014</td>
<td>Aim: To assess whether public-access defibrillation affected the neurological outcome of patients with OHCA arrest who did not achieve return of spontaneous circulation before arrival of emergency medical service personnel. Study type: Retrospective analysis of a cohort study. Number of patients: 28,019 Enrolment period: 2005–2015 Study endpoint: Favourable neurological outcome in patients at 30 days after the OHCA.</td>
<td>Inclusion: Patients with OHCA of cardiac origin and a shockable heart rhythm witnessed by a bystander, resuscitated by a bystander, admitted alive at hospital.</td>
<td>Results: Significantly higher proportion of patients with a favourable neurological outcome in those who received public-access defibrillation than those who did not (37.2 vs. 22.6; P &lt; 0.001; adjusted OR 1.45; 95% CI 1.24–1.69; P &lt; 0.0001).</td>
<td>Other findings: Significantly higher proportion of patients who survived at 30 days after the OHCA in those who received public-access defibrillation than those who did not (33.0% vs. 11.4%; P &lt; 0.001; adjusted OR 1.31; 95% CI 1.13–1.52; P &lt; 0.0001).</td>
<td>Conclusions: A significantly higher proportion of patients with OHCA achieved a favourable neurological outcome if they received public-access defibrillation before initiation of an emergency medical service response than those who did not. Limitations: Inherent weaknesses of epidemiological study.</td>
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<td>Pollock, R., et al.3</td>
<td>Impact of bystander automated external defibrillator use on survival and functional outcomes in shockable observed public cardiac arrests. PMID: 29493086 Year of publication: 2018</td>
<td>Aim: to determine the association of bystander AED use with survival and functional outcomes in shockable observed public OHCA. Study type: Prospective registry. Number of patients: 4115 Enrolment period: 2011–2015 Study endpoints: Discharge with normal or near-normal (favourable) functional status. Survival to hospital discharge.</td>
<td>Inclusion: All adult patients with non-traumatic shockable observed public OHCA on whom defibrillation was attempted by emergency medical service or a bystander. Exclusion: Patients on whom CPR was not attempted. Emergency medical service-observed cardiac arrest.</td>
<td>Results: Patients shocked by a bystander were significantly more likely to survive to discharge (66.5% vs. 43.0%) and be discharged with favourable functional outcome (57.1% vs. 32.2%) than patients initially shocked by emergency medical service.</td>
<td>Other findings: The OR associated with a bystander shock was 2.62 (95% CI 2.07–3.31) for survival to hospital discharge and 2.73 (95% CI 2.17–3.44) for discharge with favourable functional outcome.</td>
<td>Conclusions: Bystander AED use prior to emergency medical service arrival in shockable observed public OHCA was associated with better survival and functional outcomes.</td>
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Kitaoka T, et al.  
Public-access de
fibrillation and out-of-hospital cardiac arrest in Japan.  
PMD: 27783922  
Year of publication: 2016  
Aim:  
To assess whether nationwide dissemination of public-access defibrillators has been associated with an increase in the rate of survival with a favourable neurological outcome after ventricular-fibrillation arrest.  
Study type:  
Registry.  
Number of patients: 43,762  
Enrolment period: 2005–2013  
Study endpoints:  
Survival with a favourable neurological outcome at one month after OHCA.  
Inclusion:  
Patients with bystander-witnessed VF arrests of cardiac origin.  
Results:  
The rate of one month survival with a favourable neurological outcome was significantly higher in recipients of public-access defibrillation than in the group that did not receive public-access defibrillation (38.5% vs. 18.2%; adjusted OR 2.03; 95% CI 1.87–2.20).  
Other findings:  
The percentage of patients receiving shocks from public-access AEDs for bystander-witnessed VF arrest of cardiac origin increased significantly during the study period (1.1% in 2005 to 16.5% in 2013; P < 0.001).  
Conclusions:  
Increased use of public-access defibrillation by bystanders was associated with an increase in the number of survivors with a favourable neurological outcome after out-of-hospital VF cardiac arrest.

95  
Hasselqvist-Ax I, et al.  
Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest.  
PMD: 26061835  
Year of publication: 2015  
Aim:  
To assess whether CPR initiated before the arrival of emergency medical services was associated with an increase in the 30-day survival rate among persons who collapsed due to an OHCA.  
Study type:  
Registry.  
Number of patients: 30,381  
Enrolment period: 1990–2011  
Study endpoints:  
30-day survival.  
Inclusion:  
Patients who had a bystander-witnessed OHCA and recorded data on both the start of CPR and survival.  
Results:  
The 30-day survival rate was 10.5% among patients who underwent CPR before emergency medical service arrival, as compared with 4% among those who did not (P < 0.001).  
CPR before the arrival of emergency medical service was associated with an increased 30-day survival rate (OR 2.15; 95% CI 1.88–2.45).  
Other findings:  
Significant association was observed between the time from collapse to the start of CPR and the 30-day survival rate.  
Conclusions:  
CPR performed before emergency medical service arrival was associated with a 30-day survival rate after an OHCA that was more than twice as high as that associated with no CPR before emergency medical service arrival.

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Krågholm K, et al.  
Bystander efforts and 1-year outcomes in out-of-hospital cardiac arrest.  
PMD: 28467879  
Year of publication: 2017  
Aim:  
To assess the 1-year risk of anoxic brain damage or nursing home admission and of death from any cause among 30-day survivors of an OHCA according to whether bystander CPR or defibrillation was performed.  
Study type:  
Registry.  
Number of patients: 2855  
Enrolment period: 2001–2012  
Study endpoints:  
Anoxic brain damage, Nursing home admission.  
Death from any cause.  
Composite endpoint of anoxic brain damage, nursing home admission, or death.  
Inclusion:  
30-day adult survivors of an OHCA.  
Exclusion:  
Patients in nursing homes.  
Anoxic brain damage before the OHCA.  
Results:  
Bystander CPR was associated with a significantly lower risk of brain damage or nursing home admission (HR 0.62; 95% CI 0.47–0.82), as well as a lower risk of death from any cause (HR 0.70; 95% CI 0.50–0.99) and a lower risk of the composite endpoint of brain damage, nursing home admission, or death (HR 0.67; 95% CI 0.53–0.84) than that associated with no bystander resuscitation.  
Other findings:  
During the study period, the rates of bystander CPR and defibrillation among the 30-day survivors increased significantly, while the risk of anoxic brain damage or nursing home admission and the risk of death from any cause at one year decreased markedly.  
Conclusions:  
The risk of anoxic brain damage or nursing home admission at one year and the risk of death from any cause at one year were substantially lower among OHCA survivors who received bystander CPR or bystander defibrillation than among those who received no bystander resuscitation.

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Fordyce C, et al.  
Association of public health initiatives with outcomes for out-of-hospital cardiac arrest at home and in public locations.  
PMD: 28979980  
Year of publication: 2017  
Aim:  
To describe temporal trends in bystander CPR and first-responder defibrillation for OHCA stratified by home vs. public location and their association with survival and neurological outcomes  
Inclusion:  
Patients with OHCA.  
Exclusion:  
Cases witnessed by emergency medical service.  
Do-not-resuscitate orders.  
Results:  
Compared with emergency medical services-initiated CPR and resuscitation, patients with home OHCA were significantly more likely to survive to hospital discharge if they received  
Other findings:  
Patients with arrests in public were most likely to survive if they received both bystander-initiated CPR and defibrillation (OR 4.3; 95% CI 2.11–8.87).  
Conclusions:  
Bystander CPR and first-responder defibrillation at home and in public was associated with improved survival.

Continued
| 97 | Karam N, et al. | Major regional differences in automated external defibrillator placement and basic life support training in France: further needs for coordinated implementation. | Observational study. | Number of patients: 8269. | Year of publication: 2017 | Inclusion: 51 French districts. | Results: Only the rate of population BLS education remained independently associated with survival (OR 1.64; 95% CI 1.17–2.31; \( P = 0.0045 \)). | Conclusions: Population education in CPR is important. |
| 101 | Ringuet M, et al. | Mobile-phone dispatch of laypersons for CPR in out-of-hospital cardiac arrest. | RCT. | Number of patients: 667. | Year of publication: 2015 | Inclusion: Suspected OHCA. | Results: The rate of bystander-initiated CPR was 62% in the intervention group and 48% in the control group (absolute difference for intervention vs. control, 14 percentage points; 95% CI 6–21; \( P < 0.001 \)). | Conclusions: A mobile-phone positioning system to dispatch by volunteers who were trained in CPR was associated with significantly increased rates of bystander-initiated CPR among persons with OHCA. |
| 102 | Stroop R, et al. | Mobile phone-based alerting of CPR-trained volunteers simultaneously with the ambulance can reduce the resuscitation-free interval and improve outcome after out-of-hospital cardiac arrest: a German, population-based cohort study. | Population-based cohort study. | Number of patients: 730. | Year of publication: 2020 | Inclusion: All OHCA cases in which the CPR was started by laypersons that were at the scene but were not part of the organized emergency response system. | Results: There was a significant difference in response time between mobile rescuers (4 min) and emergency medical service teams (7 min) (\( P < 0.001 \)). | Conclusions: Simultaneous alerting of nearby CPR-trained volunteers complementary to professional emergency medical service teams can reduce both the response time and resuscitation-free interval and might improve hospital discharge rate and neurological outcomes after OHCA. |
| 103 | Lee S, et al. | Text message alert system and bystander CPR. | Observational study. | Number of patients: 869. | Year of publication: 2017 | Inclusion: OHCA patients with a presumed cardiac arrest. | Results: The bystander CPR rate increased during the study period. | Conclusions: OHCA patients treated in the period after... |
2. Evaluation and treatment. General aspects

2.1. Genetic testing

**Table of Evidence 2 for Table of Recommendations for genetic testing**

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Study type</th>
<th>Inclusion criteria (patients)</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>59</td>
<td>Aim: To define aetiology of SCD in Australia and New Zealand 2010–2012. Endpoints: Clinical/genetic diagnosis in proband and family. Study type: Prospective population study. Number of patients: 490.</td>
<td>All SCD cases aged 1–35 years. Exclusion: NA.</td>
<td>Results: The annual incidence of SCD in Australia and New Zealand was 1.3 cases per 100,000 persons (95% CI 1.2–1.4). The most common causes of SCD were coronary artery disease (CAD; 24% of cases) and inherited cardiomyopathies (16% of cases). Unexplained SCD (40% of cases) was the predominant finding among persons in all age groups, except for those 31–35 years of age, for whom CAD was the most common finding. A clinically relevant cardiac gene mutation was identified in 31 of 113 cases (27%) of unexplained SCD in which genetic testing was performed.</td>
<td>Other findings: Unexplained death was the most common aetiology statistically associated with women sex and nocturnal SCD.</td>
<td>Conclusions: Not enough evidence to include all cases. The study did not include resuscitated cardiac arrest cases.</td>
</tr>
</tbody>
</table>

| 186 | Aim: To define the utility of post-mortem genetic testing following a SADS death. Study type: Retrospective multicentre case series and case–control study. Number of patients: 302 SCD cases. (270 case vs. 30 healthy controls of European descent). | SCD cases with available DNA and negative autopsy and available families who underwent evaluation. Exclusion: SHD or non-specific pathological features at autopsy. | Results: Death with exercise (10%) or extreme emotion (1.5%). Family history in 7.1%. 18% personal history of syncpe or seizures. 21% (7%) diagnosed with epilepsy or prior history of epilepsy. 24 had consulted healthcare provider. Next-generation sequencing using a panel of 77 primary electrical disorder and cardiomyopathy genes was performed. | Other findings: Only excess burden of rare variants seen in KIR2 gene. Combining molecular autopsy with clinical evaluation in 82 surviving families increased diagnostic yield from 26% to 39%. | Conclusions: Molecular autopsy for electrical and cardiomyopathy genes, using ACMG guidelines for variant classification identified a modest but realistic yield in SADS. Stringent variant calling is vital. The study showed the enhanced utility of combined clinical and genetic evaluation. Limitations: 88% European heritage; limited family evaluation; referral bias. |
| Study endpoints: Genetic and clinical diagnosis in the decedent and family. | performed. ACMG criteria were used for variant adjudication. Overall yield in 40/302 cases (13%) of pathogenic and likely pathogenic variants: 19 pathogenic and 15 likely pathogenic variants in RYR2, KCNH2, KCNQ1, SCN5A, one pathogenic variant in PLN, likely pathogenic variants in TTN (2), PKP2 (1), MYH7 (1). |

| 182 Conte G, et al. Importance of dedicated units for the management of patients with inherited arrhythmia syndromes. PMID: 33797288 Year of publication: 2021 | Aim: To evaluate the relationship between the presence of dedicated IAS units, centre volume, and management of patients with IAS. Study type: Survey. Number of centres: 44 | Inclusion: EHRA Research Network Centres and ECGen members. Exclusion: NA. | Results: Of 27 centres with dedicated units, 10 (37%) managed >100 patients in the previous 12 months, whereas all centres without a dedicated unit had lower volumes. Moreover, centres without a dedicated unit were more likely to have very low volumes (<20 patients/year) of adults (47% vs. 7%; P < 0.01) and paediatric patients (87% vs. 41%; P = 0.03). There were no significant differences between centres on the use of pharmacological challenges in the diagnostic assessment of IAS. However, centres without a dedicated unit performed less genetic testing for all the different types of IAS, including those where a genetic diagnosis can influence therapeutic choices. Specifically, genetic testing for LQTS was performed in 92% and 59% of centres with and without dedicated units, respectively (P = 0.01). Centres with a dedicated unit were more likely to perform an electrophysiology study with programmed ventricular stimulation for risk stratification (71% vs. 41%) and substrate ablation procedures (82% vs. 53%) for patients with Brugada syndrome. |

| Conclusions: In conclusion, dedicated IAS units frequently combine specialized care for adult and paediatric patients, genetic testing, and specific diagnostic and therapeutic procedures more frequently compared to centres with a low volume. However, treatment/outcome superiority of IAS units was not examined in this survey. | ACMG, American College of Medical Genetics and Genomics; CAD, coronary artery disease; DNA, deoxyribonucleic acid; EHRA, European Heart Rhythm Association; IAS, inherited arrhythmia syndrome; LQTS, long QT syndrome; NA, not applicable; SADS, sudden arrhythmic death syndrome; SCD, sudden cardiac death; SHD, structural heart disease. |
2.2. Diagnostic evaluation at first presentation with ventricular arrhythmias in patients without known cardiac disease

2.2.1. Scenario 1: Incidental finding of a non-sustained ventricular tachycardia

Table of Evidence 3 for Table of Recommendations for evaluation of patients presenting with newly documented ventricular arrhythmias

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>197</td>
<td>Nicofara G, et al. 15</td>
<td>Aim: To investigate the prognostic value of LGE-CMR in patients with VAs of LV origin. Study type: Retrospective observational. Number of patients: 46 patients and 74 controls. Enrolment period: Not reported. Study endpoints: Composite outcome: SCD, VF, SMVT requiring cardioversion or appropriate ICD therapy.</td>
<td>Inclusion: Patients with monomorphic VA of LV origin and normal ECG, echocardiogram, and negative non-invasive or invasive ischaemia evaluation who underwent LGE-CMR. Exclusion: NA.</td>
<td>Results: 46 consecutive patients (65% men, 44 ± 15 years) were included. 74 consecutive patients (60% men, 40 ± 17 years) with apparently idiopathic VAs from RV served as control group. CMR demonstrated myocardial structural abnormalities (intramyocardial fat and/or LGE) in 19 (41%) patients with LV origin vs. four (5%) patients with VAs of RV origin (P &lt; 0.001). Median follow-up was 14 (IQR 7–37) months. Composite endpoint occurred in nine patients, all with VAs of LV origin. Family history of SCD/ cardiomyopathy (HR 6.3), SMVT (HR 19.8) and LGE/fat on CMR (HR 41.6) were associated with the outcome event.</td>
<td>Conclusions: Myocardial structural abnormalities (mainly LGE) were found in 41% of patients with LV VA of apparent idiopathic origin. Presence of myocardial structural abnormalities was associated with the occurrence of malignant VA.</td>
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<td>198</td>
<td>Musar D, et al. 16</td>
<td>Aim: To assess the prognostic significance of a specific LV-LGE phenotype (ring-like pattern) in patients with apparent VA. Study type: Retrospective observational multicentre study. Number of patients: 486. Enrolment period: 2002–2018. Study endpoints: Composite outcome: death from any cause, resuscitated cardiac arrest (VF non-tolerated VT), appropriate ICD therapy.</td>
<td>Inclusion: Patients with apparent idiopathic non-sustained VA according to ECG, echo, and non-invasive or invasive ischaemia evaluation who underwent LGE-CMR. Exclusion: Patients with any abnormality on ECG, echocardiogram or ischaemia detection.</td>
<td>Results: 28 (4%) patients (group A) had a ring-like pattern of scar (defined as LV subepicardial/midmyocardial LGE involving at least three contiguous segments in the same short-axis slice), 78 (11%, group B) had a non-ringlike scar pattern and 580 (85%, group C) had no LGE. After a median of 61 (34–84) months, the composite outcome occurred in 14 (50%) patients in group A vs. 15 (19%) in group B and two (0.3%) in group C (P &lt; 0.01). After multivariate analysis, presence of LGE with ring-like pattern was independently associated with increased risk of the composite endpoint (HR 6.88 [95% CI 14.67–324.39], P &lt; 0.01).</td>
<td>Other findings: Patients in group A were younger (median age 40 vs. 52 vs. 45 years; P &lt; 0.01), more frequently men (96% vs. 82% vs. 55%; P &lt; 0.01), had more frequent family history of SCD/cardiomyopathy (39% vs. 14% vs. 6%; P &lt; 0.01). All patients in group A showed VA with RBBB morphology vs. 69% in group B and 21% in group C (P &lt; 0.01). Multifocal VAs were present in 46% of patients in group A, 26% of group B and 4% of group C (P &lt; 0.01).</td>
<td>Conclusions: In patients with apparently idiopathic non-sustained VA, nonischaemic LV scar with a ring-like pattern is associated with malignant arrhythmic events.</td>
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CMR, cardiac magnetic resonance; ECG, electrocardiogram; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LGE, late gadolinium enhancement; LV, left ventricular; NA, not applicable; RBBB, right bundle branch block; RV, right ventricular; SCD, sudden cardiac death; SMVT, sustained monomorphic ventricular arrhythmia; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
### 2.2.2. Scenario 2: First presentation of sustained monomorphic ventricular tachycardia

**Table of Evidence 4** for Table of Recommendations for evaluation of patients presenting with a first episode of sustained monomorphic ventricular tachycardia

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
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<tbody>
<tr>
<td>200</td>
<td>Corrado D, et al. 17</td>
<td>To assess whether RV electroanatomic voltage mapping increases the accuracy for diagnosing ARVC patients fulfilling non-invasive Task Force criteria.</td>
<td>Consecutive ARVC patients fulfilling non-invasive Task Force criteria.</td>
<td>31 consecutive patients (22 men, 31 ± 7 years) were included. 20 (65%) had abnormal RV electroanatomical map showing ≥1 area of bipolar voltage &lt;0.5 mV surrounded by an area &lt;1.5 mV with fractionated/delayed electrograms. Low-voltage areas corresponded to echocardiographic RV wall motion abnormalities and were associated with myocyte loss and fibrofatty replacement on endomyocardial biopsy and familial ARVC. 11 patients with low-voltage areas had haemodynamically non-tolerated VA or unexplained syncope vs. only one patient without low-voltage areas in RV map (P = 0.02).</td>
<td>-</td>
<td>Abnormal voltage with delayed/fractionated electrograms were found in more than half of patients fulfilling non-invasive criteria for ARVC. Patients with abnormal RV maps had more frequently malignant VA. Areas of low voltage were correlated with myocyte loss and fibrofatty replacement in endomyocardial biopsy.</td>
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</tbody>
</table>

| 201                            | Casella M, et al. 18                     | To evaluate the feasibility, safety, and diagnostic value of endocardial voltage mapping-guided endomyocardial biopsy. | Consecutive patients undergoing endomyocardial biopsy in one institution. | 162 patients (73% men, 41 ± 15 years) were included. In the majority the suspected clinical diagnosis was ARVC (n = 67) and myocarditis (n = 49). CMR was performed in 143/162 patients and showed LGE in 70% of them. RV and LV voltage mapping was performed in 123 (77%) and 59 (37%) patients, respectively. Low-voltage areas (bipolar and/or unipolar) were identified in 61%. Endomyocardial biopsy was taken from RV in 116 (72%) patients, from LV in 31 (19%), and both RV/LV in 13 (8%). Biopsy confirmed the clinical diagnosis in 72 (60%) patients and a different diagnosis was reached in 48 (40%). | - | Electroanatomical voltage mapping had a similar accuracy to CMR to detect myocardial pathological substrates. The combination of endocardial voltage mapping and CMR for guiding endomyocardial biopsy increased the positive predictive value of endomyocardial biopsy to 89%. |

**Continued**
were concordant for identifying pathological areas, the diagnostic yield of endomyocardial biopsy was 89%.

**Aim:**
To describe our experience with electroanatomic mapping (EAM)-guided endomyocardial biopsy and provide a comprehensive review of the literature.

**Study type:**
Case series and review.

**Inclusion:**
Five patients (age 49.4 ± 11.4 years) with suspected cardiac sarcoidosis.

**Results:**
EAM-guided endomyocardial biopsy. Biopsy samples (2–9 samples) were taken from both LV and RV sites, guided by EAM and areas with abnormal electrograms. Cardiac sarcoidosis diagnosis was based on endomyocardial biopsy in 2/5 patients. A granuloma was captured in one patient at the LV basal septum with normal bipolar and abnormal unipolar voltage. All patients with delayed enhancement on CMR revealed fibrosis in the biopsy sample. In one patient with suspected isolated cardiac sarcoidosis, diagnosis could not be confirmed by histopathology analysis, while unipolar voltage mapping was abnormal and diastolic potentials were present. Literature search revealed seven reports (18 patients) describing EAM-guided endomyocardial biopsy in cardiac sarcoidosis patients, with 100% of the endomyocardial biopsy taken from the RV.

**Conclusion:**
Unipolar voltage mapping may be superior to target active inflamed tissue and should be evaluated in future research regarding EAM-guided endomyocardial biopsy in cardiac sarcoidosis.

**Aim:**
To evaluate whether RV electroanatomic scar patterns related to SMVT can distinguish exercise-induced arrhythmogenic remodelling from ARVC and post-inflammatory cardiomyopathy.

**Study type:**
Retrospective, single-centre observational.

**Number of patients:**
57

**Enrollment period:**
2010–2019

**Study endpoints:**
NA.

**Inclusion:**
Consecutive patients undergoing mapping and ablation for scar-related RV VT.

**Exclusion:**
Idiopathic VA, CAD, congenital heart disease, dominant LV cardiomypathy.

**Results:**
57 patients (83% men, 48 ± 16 years) were included. Two scar patterns were identified: (1) scars involving the subtricuspid RV in 46 patients (group A), and (2) scars restricted to the subepicardial anterior RVOT in 11 (group B). Definite ARVC or post-inflammatory cardiomyopathy was diagnosed in 40 (87%) patients of group A but in no patient of group B. All patients from group B had a history of intensive endurance training (median 15 h/week for a median of 13 years). During a median follow-up of 27 (IQR 6–62) months, 30% of patients in group A but none in group B had VT recurrence. Other findings: 38 (83%) of patients in group A had >1 VT with superior axis, whereas all VTs in group B patients had inferior axis. 10/11 group B patients had two different VT morphologies with either a dominant negative or isoelectric/positive deflection in lead I. In group A, 14 (30%) of patients had family history of ARVC and 29 (64%) had a (likely) pathogenic mutation. In group B, no patient had family history of ARVC and none had mutations.

**Conclusions:**
This study describes a particular clinical entity of exercise-induced arrhythmogenic remodelling that can be distinguished by a particular scar pattern from ARVC and post-inflammatory cardiomyopathy.
### 2.2.3. Scenario 3: Aborted sudden cardiac death

#### Table of Evidence 5

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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</thead>
<tbody>
<tr>
<td>65</td>
<td>Waldmann V, et al. 21</td>
<td>Burden of coronary artery disease as a cause of sudden cardiac arrest in the young. PMID: 31023437 Year of publication: 2019</td>
<td>Inclusion: Every case of out-of-hospital SCA in those &gt;18 years of age. Exclusion: NA.</td>
<td>Among young SCA patients, 146 (41.4%) had no definite aetiology identifiable due to early death and/or negative/incomplete initial work-up. A cardiac cause was identified in 142 (40.2%) patients, with CAD being the most frequent, seen in 58 (40.8%) subjects. Of these, 50 (86.2%) had acute coronary syndrome with culprit lesion. CAD represented 53.7% of cardiac aetiologies identified in the 30- to 40-year age group.</td>
<td>-</td>
<td>Conclusions: CAD is the main cause of SCA in young adults, representing &gt;50% of cardiac causes identified between 30 and 40 years of age. A high index of suspicion to ensure timely intervention and a greater focus on cardiovascular preventive measures among the young is urgently needed.</td>
</tr>
<tr>
<td>120</td>
<td>Giudicessi JR, et al. 22</td>
<td>Exercise testing oversights underlie missed and delayed diagnosis of catecholaminergic polymorphic ventricular tachycardia in young sudden cardiac arrest survivors. PMID: 30763784 Year of publication: 2019</td>
<td>Inclusion: SCA survivors (younger than 35 years at the time of SCA) with otherwise structurally normal hearts was used to identify those with a missed or delayed CPVT diagnosis because of overlooked evidence or lack of an exercise stress test or catecholamine provocation test post-SCA. Exclusion: Patients who (1) suffered non-cardiac arrests, (2) were 35 years or older at the time of SCA, and/or (3) had a pre- or post-SCA diagnosis of complex congenital heart disease, CAD, suspected myocarditis, NICM, or valvular heart disease.</td>
<td>Results: Of the 101 young SCA survivors, 41 (41%) had exertion-motion-associated SCA. After primary post-SCA investigations, a probable root cause was established in 20 of 41 exertion-motion-associated SCA survivors (49%; CPVT in 8) and in 30 of 60 non-exertion-motion-associated SCA survivors (50%; CPVT in 2) (P = 1). Only 14 of 21 unexplained exertion-motion-associated SCA survivors (67%) had an exercise stress test/catecholamine provocation test performed before their referral evaluation. Secondary review of these prior exercise stress test/catecholamine provocation test provided evidence of CPVT in 3 of 14 (21%). Of the seven remaining unexplained cases of EAA-SCA who had never undergone an exercise stress test/catecholamine provocation test, two (29%) underwent their first exercise stress test at our institution that led to CPVT diagnosis.</td>
<td>Other findings: Exercise stress test/catecholamine provocation test must become the standard of care after SCA in the young, especially if the SCA occurred during either exertion or emotion.</td>
<td>Conclusions: Exercise stress test/catecholamine provocation test must become the standard of care after SCA in the young, especially if the SCA occurred during either exertion or emotion.</td>
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Continued
Conclusions:
Specialized cardiac genetic clinics are better adjusted and worry less than those who do not attend. An integrated approach, including a genetic counsellor, is important in the management of HCM families.

Other findings:
Within the disease group, logistic regression analysis adjusting for age, gender, and education revealed adjustment to HCM and worry about HCM scores to be significantly associated with anxiety, while adjustment scores and location of patient follow-up (i.e. HCM clinic or another cardiologist) to be significantly associated with depression scores.

Results:
Completed questionnaires were returned by 109 participants (59.2%). Logistic regression analysis adjusting for age, gender, and education revealed adjustment to HCM and worry about HCM scores to be significantly associated with anxiety, while adjustment scores and location of patient follow-up (i.e. HCM clinic or another cardiologist) to be significantly associated with depression scores.

Study endpoints:
Intensive care unit survival was significantly higher for patients with a diagnosis identified by coronary angiography as compared with CT scan (43% vs. 10%; P < 0.001).

Other findings:
The use of an early diagnosis protocol with immediate coronary angiography and/or CT scan provided the aetiology of nearly two-thirds of OHCA cases. In this large retrospective database, coronary angiography yielded a better diagnostic value than brain and/or chest CT scan.
Bradycaardia pacing-induced short-long-short sequences at the onset of ventricular tachyaryrhythmias: a possible mechanism of proarrhythmia?

**PMID:** 17692746
**Year of publication:** 2007

**Aim:** To characterize interactions between normal pacing system operation and the initiating sequence of VT/VF.

**Study type:** Subanalysis of RCT.

**Number of patients:** 1055

**Enrolment period:** 2001–2002

**Study endpoints:** NA.

**Inclusion:** Patients with >1 spontaneous ventricular episode that satisfied VT/VF detection criteria and with corresponding electrograms and sufficient beats (generally >5) with cycle length < detection interval before VT/VF onset.

**Exclusion:** Electrogram pre-storage revealed VT with cycle length < detection interval (i.e. below detection rate cut-off), insufficient beats before onset with cycle length < detection interval or therapy (indicating an ongoing episode).

**Results:** Initiating sequences of 1356 VT/VF episodes in the PainFree Rx II (n = 634) and EnTrust Trial (n = 421) were analysed with stored electrograms and by pacing mode (DDD/R, VVI/R, and managed ventricular pacing [MVP]). Interactions between pacing and VT/VF initiation were classified as: non-pacing-associated, pacing-associated, pacing-permitted, and pacing-facilitated. Non-pacing-associated (no pacing, no S-L-S) and pacing-associated (ventricular pacing without S-L-S) onset accounted for 44.0% and 29.8% of all VT/VF, respectively. Pacing-permitted (S-L-S sequences without ventricular pacing) episodes accounted for 6.4% (DDD/R), 20.0% (MVP), and 25.6% (VVI/R) of 1356 VT/VF episodes. Pacing-facilitated onset (S-L-S sequences actively facilitated by ventricular pacing including the terminal beat after a pause) accounted for 8.2% (MVP), 9.4% (VVI/R), and 14.8% (DDDR/R) of 1356 VT/VF episodes. Pacing-facilitated onset (S-L-S sequences actively facilitated by ventricular pacing including the terminal beat after a pause) accounted for 40.4% and 29.8% of all VT/VF, respectively. Pacemaker-S-L-S sequences without ventricular pacing episodes accounted for 64% (DDD/R), 20.0% (MVP), and 25.6% (VVI/R) of 1356 VT/VF episodes. Pacing-facilitated onset (S-L-S sequences actively facilitated by ventricular pacing including the terminal beat after a pause) accounted for 40.4% and 29.8% of all VT/VF, respectively. Pausedurations during pacing-facilitated S-L-S differed between modes (DDDR/R 793 ± 172 ms vs. MVP 865 ± 278 ms vs. VVI/R 1180 ± 414 ms; P = 0.002). The majority of these episodes were monomorphic VT.

**Conclusions:** VT/VF in some ICD patients might be initiated by S-L-S sequences that are actively facilitated by bradycardia pacing operation and might constitute an important mechanism of ventricular proarrhythmia.

Sudden death in patients with cardiac implantable electronic devices.

**PMID:** 26098676
**Year of publication:** 2015

**Aim:** To determine causes of death in individuals with CIEDs.

**Study type:** Prospective autopsy study.

**Number of patients:** 517

**Enrolment period:** 2011–2013

**Study endpoints:** To determine causes of death in individuals with CIEDs. Cumulative incidence of death and SCD and the proportion of deaths with an ICD concern.

**Inclusion:** All cases of SCD according to definition.

**Exclusion:** Other clear non-cardiac cause.

**Results:** Of 712 San Francisco residents with an ICD during the study period, 109 died (15.3% cumulative 35-month incidence of death), and the 7 ICD concerns represent 6.4% of all ICD deaths.

**Conclusions:** Systematic interrogation and autopsy of SDS in one city identified concerns about CIED function that might otherwise not have been observed. Current passive surveillance efforts may underestimate device malfunction. These methods can provide unbiased data regarding causes of SD in individuals with CIEDs and improve surveillance for CIED problems.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Title</th>
<th>Am:</th>
<th>Inclusion:</th>
<th>Results:</th>
<th>Other findings:</th>
<th>Conclusions:</th>
</tr>
</thead>
<tbody>
<tr>
<td>223</td>
<td>Curdio A, et al.(^2) Clinical presentation and outcome of Brugada syndrome diagnosed with the new 2013 criteria. PMID: 27098113 Year of publication: 2016</td>
<td>To assess the role of high-ICS in the analysis of Brugada syndrome and the clinical profile of the patients diagnosed only when ECG leads are moved to upper ICS. Study type: Retrospective observational study. Number of patients: 300 Enrolment period: 2014 Study endpoints: NA.</td>
<td>Subjects without a diagnostic covered ST-segment elevation in conventional V1–V3 leads, both at baseline and after provocative drug challenge. Exclusion: NA.</td>
<td>64 subjects (21.3%, mean age at last follow-up 42 ± 11 years) were diagnosed with high-ICS. Diagnosis was possible at baseline only in four subjects, while in 60 it was made after drug challenge with sodium channel blockers. Three subjects (4.7%) with spontaneous abnormal ECG experienced cardiac events with an annual event rate (0.11%) superimposable to that of the low-risk category of Brugada syndrome diagnosed in standard leads.</td>
<td>Use of new diagnostic criteria for Brugada syndrome allows increasing the diagnostic yield by 20% and that the arrhythmic risk is low when Brugada syndrome can be established only in high-ICS.</td>
<td>The prognostic value of spontaneous ECG pattern is confirmed in this subgroup.</td>
</tr>
<tr>
<td>225</td>
<td>Krahn AD, et al.(^3) Systematic assessment of patients with unexplained cardiac arrest: Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPER). PMID: 19597050 Year of publication: 2009</td>
<td>To evaluate the extent to which systematic clinical testing, including drug provocation and advanced imaging, results in unmasking the cause of apparently unexplained cardiac arrest. Study type: Prospective observational. Number of patients: 63 Enrolment period: 2004–2008 Study endpoints: Proportion of patients with apparently unexplained CA with clear aetiology after systematic additional investigations, including drug provocation and advanced imaging.</td>
<td>Patients with apparently unexplained cardiac arrest and no evident cardiac disease (normal cardiac function on echocardiogram, no evidence of CAD, and a normal ECG). Exclusion: NA.</td>
<td>63 patients in nine centres were enrolled (age 43.0 ± 13.4 years, 29 women). A diagnosis was obtained in 35 patients (56%): LQT5 in 8, CPVT in 8, ARVC in 6, early repolarization in 5, coronary spasm in 4, Brugada syndrome in 3, and myocarditis in 1. Targeted genetic testing demonstrated evidence of causative mutations in nine (47%) of 19 patients. Screening of 64 family members of these patients identified 15 affected individuals who were treated (24%). The remaining 28 patients (44%) were considered to have IVF.</td>
<td>This approach assists in determining SCA pathogenesis for Brugada syndrome and prognosis in survivors.</td>
<td>Systematic clinical testing, including drug provocation and advanced imaging, results in unmasking of the cause of apparently unexplained cardiac arrest in &gt;50% of patients.</td>
</tr>
<tr>
<td>229</td>
<td>Rodrigues P, et al.(^4) Diagnosis and prognosis in sudden cardiac arrest survivors without coronary artery disease: utility of a clinical approach using cardiac magnetic resonance imaging. PMID: 29237609 Year of publication: 2017</td>
<td>To evaluate the role of CMR in determining SCA pathogenesis and prognosis in survivors. Study type: Retrospective observational. Number of patients: 164 Enrolment period: 2008–2014 Study endpoints: Major adverse cardiac events, comprising significant non-fatal VA or death, was the primary outcome.</td>
<td>All consecutive survivors of potentially fatal arrhythmias without CAD admitted to our institutions with cardiac investigations and clinical outcomes. After coronary angiography and echocardiography, all underwent CMR and, when indicated, electrophysiology studies. Exclusion: NA.</td>
<td>Of 164 included subjects (65% men; mean age 48 [18–80] years), CMR contributed to the diagnosis in 80 (49%) and was decisive in 50 cases (30%). DCM (n = 27), myocarditis or sarcoidosis (n = 22), occult MI (n = 13), and HCM (n = 9) were most frequent. Arrhythmic causes were found in 4% while no cause was identified in 36%. Major adverse cardiac events occurred in 31% of subjects during a median follow-up of 32 months. Major adverse cardiac events associated with presence of a CMR diagnosis, extent of LGE, and LV and RV ejection fractions. RV ejection fraction—associated with prognosis.</td>
<td>CMR identified a likely pathogenesis for SCA in nearly half of survivors in whom CAD had been excluded. One in three subjects had major adverse cardiac events; risk doubled in those with a CMR diagnosis and some CMR parameters—LGE, LV EF, and especially RV ejection fraction—associated with prognosis.</td>
<td>Continued</td>
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<tr>
<td>243</td>
<td>Waldmann V, et al.21</td>
<td>Coronary vasospasm-related sudden cardiac arrest in the community. PMID: 30092958 Year of publication: 2018</td>
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<tr>
<td>Am:</td>
<td>To assess the extent to which coronary vasospasm-related SCA is investigated and managed in the real-world setting. Study type: Population-based prospective study.</td>
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<td>Inclusion:</td>
<td>1557 patients with a definite cardiac aetiology, 31 SCA were diagnosed as related coronary vasospasm.</td>
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<td>Exclusion:</td>
<td>NA.</td>
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<tr>
<td>Results:</td>
<td>Among the 1557 patients with a definite cardiac aetiology, 31 SCA were diagnosed as related to coronary vasospasm, representing 2.0% of cardiac causes. The diagnosis of coronary vasospasm was made by typical major spontaneous spasm during initial coronary angiography in 16 (51.6%) cases, by provocative test with ergonovine in 12 (38.7%), and ST segment elevation accompanied by chest pain during ECG monitoring with initial normal angiography in three (9.7%) patients.</td>
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<td>Other findings:</td>
<td>Coronary vasospasm provocative test was performed in only 63.9% of apparently unexplained SCA patients, with a diagnostic yield of 30.8%.</td>
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<tr>
<td>Conclusions:</td>
<td>Coronary vasospasm as a cause of SCA is under-investigated in the general population and ICD therapy remains poorly utilized.</td>
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<thead>
<tr>
<th>254</th>
<th>Karam N, et al.22</th>
<th>Psychological support and medical screening of first-degree relatives of sudden cardiac arrest victims. PMID: 32439046 Year of publication: 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Am:</td>
<td>The extent to which psychological support and cascade screening are offered to first-degree relatives of sports-related SCD cases. Study type: Observational retrospective community-based.</td>
<td></td>
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<tr>
<td>Inclusion:</td>
<td>First-degree relatives of sports-related SCD cases (dead or survivor).</td>
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<tr>
<td>Exclusion:</td>
<td>NA.</td>
<td></td>
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<tr>
<td>Results:</td>
<td>Overall, 30 (12.0%) families were given psychological support/referral. Regarding medical screening, 149 (59.4%) families were aware of its necessity, and it was performed in 72 families (28.7%). Screening was self-initiated after personal active Internet search in 51 cases (70.8%), following emergency or hospital physician advice in 10 cases (13.9%), and following general practitioners’ advice in 11 cases (15.2%).</td>
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<tr>
<td>Other findings:</td>
<td>Coronary vasospasm as a cause of SCA is under-investigated in the general population and ICD therapy remains poorly utilized.</td>
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<tr>
<td>Conclusions:</td>
<td>This community-based study demonstrates that there is a major felt need for both psychological support and medical screening among families of SCD victims, which is insufficiently offered. Concerted efforts are needed to educate treating physicians and teams towards this relatively neglected aspect.</td>
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<tr>
<td>Am:</td>
<td>To establish the diagnostic yield of cardiological and genetic assessment of surviving relatives of SUD victims. Study type: Observational, prospective. Number of patients: 43 families.</td>
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<tr>
<td>Inclusion:</td>
<td>Consecutive families with &gt; or = 1 SUD victim who died at ≤ 40 years of age.</td>
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<tr>
<td>Exclusion:</td>
<td>NA.</td>
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<tr>
<td>Results:</td>
<td>The authors identified an inherited disease and likely cause of death in 17 of 43 families (40%). 12 families had primary electrical disease: CPVT (five families), LQTS (four families), Brugada syndrome (two families), and long QT/Brugada syndrome (one family). Furthermore, we found ARVC (three families), HCM (one family), and familial hypercholesterolaemia (one family). Molecular genetic analysis provided confirmation in 10 families. Finding the diagnosis was more likely when more relatives were examined and in families with &gt;2 SUD victims ≤40 years of age. The resting/exercise ECG had a high diagnostic yield. These efforts unmasked 151 pre-symptomatic disease carriers (8.9 per family).</td>
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<tr>
<td>Other findings:</td>
<td>Finding the diagnosis was more likely when more relatives were examined and in families with &gt;2 SUD victims ≤40 years of age. The resting/exercise ECG had a high diagnostic yield. These efforts unmasked 151 pre-symptomatic disease carriers (8.9 per family).</td>
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<tr>
<td>Conclusions:</td>
<td>Examination of relatives of young SUD victims has a high diagnostic yield, with identification of the disease in 40% of families and 8.9 pre-symptomatic carriers per family. Simple procedures (examining many relatives) and routine tests (resting/exercise ECG) constitute excellent diagnostic strategies. Molecular genetics provide strong supportive information.</td>
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</tbody>
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Continued
| 257 | Lemkes JS, et al.  
Coronary angiography after cardiac arrest without ST-segment elevation.  
PMID: 30883057  
Year of publication: 2019 | **Aim:** To evaluate the benefit of immediate coronary angiography and PCI in the treatment of patients who have been successfully resuscitated after cardiac arrest in the absence of STEMI.  
**Study type:** Multicentric RCT.  
**Number of patients:** 552  
**Enrolment period:** 2015–2018  
**Study endpoints:** The primary endpoint was survival at 90 days. Secondary endpoints included survival at 90 days with good cerebral performance or mild or moderate disability, myocardial injury, duration of catecholamine support, markers of shock, recurrence of VT, duration of mechanical ventilation, major bleeding, occurrence of acute kidney injury, need for renal-replacement therapy, time to target temperature, and neurological status at discharge from the intensive care unit. | **Inclusion:** OHCA with an initial shockable rhythm and were unconscious after the return of spontaneous circulation.  
**Exclusion:** Patients were excluded if they had signs of STEMI on ECG in the emergency department, shock, or an obvious non-coronary cause of the arrest. | **Results:**  
At 90 days, 176 of 273 patients (64.5%) in the immediate angiography group and 178 of 265 patients (67.2%) in the delayed angiography group were alive (OR 0.89; 95% CI 0.62–1.27; *P* = 0.51). The median time to target temperature was 5.4 h in the immediate angiography group and 4.7 h in the delayed angiography group (ratio of geometric means 1.19; 95% CI 1.04–1.36). No significant differences between the groups were found in the remaining secondary endpoints. | **Conclusions:** Among patients who had been successfully resuscitated after OHCA and had no signs of STEMI, a strategy of immediate angiography was not found to be better than a strategy of delayed angiography with respect to overall survival at 90 days, and one year. |
| 258 | Kern KB, et al.  
Randomized pilot clinical trial of early coronary angiography versus no early coronary angiography after cardiac arrest without ST-segment elevation: the PEARL study.  
PMID: 32985249  
Year of publication: 2020 | **Aim:** To evaluate the efficacy and safety of early coronary angiography and to determine the prevalence of acute coronary occlusion in resuscitated OHCA patients without ST elevation.  
**Study type:** Multicentric RCT.  
**Number of patients:** 99  
**Enrolment period:** 2016–2018  
**Study endpoints:** The primary endpoint was cognitive status at discharge, including efficacy parameters of survival to discharge, favourable neurological status at discharge (Cerebral Performance Category ≤2), echocardiographic measures of LVEF ≥50%, and a normal | **Inclusion:** Adult (≥18 years) comatose survivors without ST elevation after resuscitation from OHCA, with a suspected cardiac aetiology for their SCA.  
**Exclusion:** STE or new left bundle branch block on ECG.  
Ongoing chest compressions, pregnancy, a known do-not-resuscitate order, or an opt out bracelet for the PEARL trial. | **Results:** The study was prematurely terminated before enrolling the target number of patients. A total of 99 patients were enrolled from 2015 to 2018, including 75 with initially shockable rhythms. 49 patients were randomized to early coronary angiography. The primary endpoint of efficacy and safety was not different between the two groups (55.1% vs. 46.0%; *P* = 0.64). Early coronary angiography was not associated with any significant increase in survival (51.1% vs. 48.0%; *P* = 0.35 or adverse events (28.5% vs. 26.0%; *P* = 1.00). | **Conclusions:** This underpowered study, when considered together with previous clinical trials, does not support early coronary angiography for comatose survivors of cardiac arrest without ST elevation. Whether early detection of occluded potential culprit arteries leads to interventions that improve outcomes requires additional study. |
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<th>Page</th>
<th>Reference</th>
<th>Title</th>
<th>Details</th>
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<tbody>
<tr>
<td>259</td>
<td>Desch S, et al.</td>
<td>Angiography after out-of-hospital cardiac arrest without ST-segment elevation.</td>
<td>Aim: Benefits of early coronary angiography and revascularization in resuscitated patients without ECG evidence of ST-segment elevation are unclear. Study type: Multicentre RCT. Number of patients: A total of 530 patients. Inclusion: OHCA without STEMI. Exclusion: NA. Results: At 30 days, 143 of 265 patients (54.0%) in the immediate-angiography group and 122 of 265 patients (46.0%) in the delayed-angiography group had died (HR 1.28; 95% CI 1.00–1.63; P = 0.06). The composite of death or severe neurological deficit occurred more frequently in the immediate-angiography group (in 164 of 255 patients [64.3%]) than in the delayed-angiography group (in 138 of 248 patients [55.6%]), for a relative risk of 1.16 (95% CI 1.00–1.34). Values for peak troponin release and for the incidence of moderate or severe bleeding, stroke and renal-replacement therapy were similar in the two groups. Conclusions: Among patients with resuscitated OHCA without ST-segment elevation, a strategy of performing immediate angiography provided no benefit over a delayed or selective strategy with respect to the 30-day risk of death from any cause.</td>
</tr>
<tr>
<td>260</td>
<td>Arnaout M, et al.</td>
<td>Out-of-hospital cardiac arrest from brain cause: epidemiology, clinical features, and outcome in a multicenter cohort.</td>
<td>Aim: To describe clinical features and prognosis of these patients and identify characteristics that could suggest a cerebrovascular etiology of the OHCA. Study type: Retrospective review of databases of three regional referral intensive care unit centres for OHCA. Number of patients: 86. Inclusion: Patients were included when subarachnoid haemorrhage, intracranial haemorrhage, ischaemic stroke, sub/epidural haematoma, or cerebral thrombophlebitis was identified as the primary cause of OHCA. Exclusion: Traumatic or infectious causes were excluded. Results: Among 3710 patients admitted for OHCA, 86 were included (mainly subarachnoid haemorrhage, n = 73). Prodromes were mostly neurological but falsely evoked a cardiac origin in six patients. ECG displayed abnormalities in 64% of patients, with 23% of pseudoischaemic pattern (ST-segment elevation or LBBB). Mortality rate was 100%, with brain death as the leading cause. Other findings: In comparison with the non-neurological OHCA group, women gender, onset of neurological prodromes, lack of other prodromes, initial non-shockable rhythm, and unspecified ECG repolarization abnormalities were independent predictive factors of a primary cerebrovascular etiology. When present, the combination of these elements displayed an area under the receiver operating characteristic curve of 0.86 (95% CI 0.81–0.91). Conclusions: Presentation of cerebrovascular event complicated with OHCA may mimic coronary etiology, but several clinical elements may help to identify brain causes.</td>
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<tr>
<td>261</td>
<td>Homer JM, et al.</td>
<td>The diagnostic utility of recovery phase QTc during treadmill exercise stress testing in the evaluation of long QT syndrome.</td>
<td>Aim: To determine the diagnostic significance of peak exercise and recovery phase QTc values during treadmill stress testing in LQTS. Study type: Retrospective observational. Number of patients: 243. Inclusion: 243 patients including 82 LQT1, 55 LQT2, 18 LQT3, and 88 genotype-negative patients dismissed as normal. Exclusion: NA. Results: Compared with those dismissed as normal, the average QTc was greater at all scored stages in LQT1 and LQT3 patients and at all stages in LQT2 patients except peak exercise and 1 min of recovery (P &lt; 0.01). Either an absolute QTc &gt; 460 ms during the recovery phase or a maladaptive, paradoxical increase in QTc, defined as QTc recovery – QTc baseline &gt; 30 ms (DeltaQTc) distinguished patients with either manifest or concealed LQT1 from all other subsets (P &lt; 0.0001). Other findings: The presence of beta-blockers did not blunt these abnormal repolarization profiles. Conclusions: Treadmill stress testing can unmask patients with concealed LQTS, particularly LQT1, with good diagnostic accuracy.</td>
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<td><strong>Aim:</strong></td>
<td>To determine if exercise treadmill testing could expose a latent electrical substrate of ARVC in asymptomatic gene carriers.</td>
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<tr>
<td><strong>Study type:</strong></td>
<td>Comparative study.</td>
<td></td>
<td></td>
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<tr>
<td><strong>Number of patients:</strong></td>
<td>85</td>
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<tr>
<td><strong>Enrolment period:</strong></td>
<td>Not reported.</td>
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<td><strong>Study endpoints:</strong></td>
<td>NA.</td>
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<tr>
<td><strong>Inclusion:</strong></td>
<td>30 asymptomatic ARVC gene carriers and 30 healthy controls. 25 patients with ARVC with histories of sustained VA or cardiac arrest.</td>
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<tr>
<td><strong>Exclusion:</strong></td>
<td>NA.</td>
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<tr>
<td><strong>Results:</strong></td>
<td>Depolarization abnormalities during ETT were found to develop more frequently in asymptomatic gene carriers compared with healthy controls: epsilon waves appeared in 4 of 28 (14%) compared with 0 of 30 (0%) ($P = 0.048$), PVCs in 17 of 30 (57%) compared with 3 of 30 (10%) ($P = 0.0003$), and new QRS terminal activation duration $&gt; 55$ ms in 7 of 22 (32%) compared with 2 of 29 (7%) ($P = 0.03$). Superior axis PVCs occurred only in gene carriers.</td>
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<td><strong>Other findings:</strong></td>
<td>In the second phase of the study, the frequency of these abnormalities was found to be high in patients with symptomatic ARVC: new epsilon waves appeared in 3 of 18 (17%), superior axis PVCs in 21 of 25 (84%), and new terminal activation duration $&gt; 55$ ms in 8 of 12 (67%).</td>
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<td><strong>Conclusions:</strong></td>
<td>Exercise testing exposes a latent electrical substrate in asymptomatic ARVC gene carriers that is shared by patients with ARVC with histories of VA. ETT may be useful in guiding treatment decisions, exercise prescription, and prioritizing medical surveillance in asymptomatic ARVC gene carriers.</td>
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<thead>
<tr>
<th>263</th>
<th>Waldmann V, et al. Characteristics and clinical assessment of unexplained sudden cardiac arrest in the real-world setting: focus on idiopathic ventricular fibrillation. PMID: 29566157 Year of publication: 2018</th>
</tr>
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<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>Recent studies have shown that in more than half of apparently unexplained SCA, a specific aetiology can be unmasked by a careful evaluation. The characteristics and the extent to which such cases undergo a systematic thorough investigation in real-life practice are unknown. Study type: ongoing study, collecting all cases of OHCA in Paris area.</td>
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<tr>
<td><strong>Number of patients:</strong></td>
<td>18,622 OHCA, 717 survivors.</td>
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<tr>
<td><strong>Enrolment period:</strong></td>
<td>2011–2016</td>
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<td><strong>Study endpoints:</strong></td>
<td>NA.</td>
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<tr>
<td><strong>Inclusion:</strong></td>
<td>Survival to discharge.</td>
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<tr>
<td><strong>Exclusion:</strong></td>
<td>NA.</td>
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<tr>
<td><strong>Results:</strong></td>
<td>88 (12.3%) remained unexplained after ECG, echocardiography, and coronary angiography. CMR yielded the diagnosis in 25 (3.5%) cases, other investigations accounted for 14 (2.4%) additional diagnoses, and 49 (6.8%) patients were labelled as IVF (48.7 ± 15 years, 69.4% men). Among these labelled IVF, only eight (16.3%) cases benefited from a complete work-up (including pharmacological testing). Younger patients (OR 6.00; 95% CI 1.80–22.26) and those admitted to university centres (OR 3.60; 95% CI 1.12–12.45) were more thoroughly investigated. Genetic testing and family screening were initiated in only nine (18.4%) and 12 (24.5%) cases, respectively.</td>
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<td><strong>Conclusions:</strong></td>
<td>Complete investigations are carried out in a very low proportion of unexplained SCA. Standardized, systematic approaches need to be implemented to ensure that opportunities for specific therapies and preventive strategies (including relatives) are not missed.</td>
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<tr>
<td><strong>Aim:</strong></td>
<td>To establish the sensitivity and specificity of the hyperventilation test and to clarify the characteristics of hyperventilation test-positive patients. Study type: observational prospective.</td>
</tr>
<tr>
<td><strong>Number of patients:</strong></td>
<td>206</td>
</tr>
<tr>
<td><strong>Enrolment period:</strong></td>
<td>Not reported.</td>
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<td><strong>Study endpoints:</strong></td>
<td>NA.</td>
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<tr>
<td><strong>Inclusion:</strong></td>
<td>206 patients in whom coronary spasm was documented by angiography (spasm group), and 183 patients without angina at rest in whom acetylcholine failed to induce spasm (non-spasm group).</td>
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<td><strong>Results:</strong></td>
<td>Of the spasm group patients, 127 showed positive responses to the test, including ST elevation (n = 111), ST depression (n = 15), and negative U wave (n = 1). None in the non-spasm group showed any ischaemic ECG change. Thus, the sensitivity and specificity of this test for diagnosis of coronary spasm were 62% and 100%, respectively.</td>
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<td><strong>Conclusions:</strong></td>
<td>The findings imply that hyper-ventilation is a highly specific test for the diagnosis of coronary artery spasm, and that hyper-ventilation test-positive patients are likely to have life-threatening arrhythmias during attacks and multivessel spasm.</td>
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</table>
### 2.2.4. Scenario 4: Sudden death victim

#### Table of Evidence 6 for Table of Recommendations for evaluation of sudden death victims

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study Study type Number of patients Enrolment period Study endpoints</th>
<th>Inclusion criteria (patients) Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Stecker EC, et al. (2014) Public health burden of sudden cardiac death in the United States. PMID: 24610738 Year of publication: 2014</td>
<td>Aim: To estimate the burden of premature death from SCD and compared it with other diseases. Study type: Registry. Number of patients: NA. Enrolment period: 2002-2004 (Oregon-SUDS). 2008–2009 (US death certificate reporting, Centers for Disease Control and Prevention’s National Program of Cancer Registries, US Census Bureau). Study endpoints: Years of Potential Life Lost according to specific mortalities.</td>
<td>Inclusion: Analyses were based on the following data sources: (1) leading causes of death among men and women from 2009 US death certificate reporting; (2) individual cancer mortality rates from 2008 death certificate reporting from the Centers for Disease Control and Prevention’s National Program of Cancer Registries; (3) county, state, and national population data for 2009 from the US Census Bureau; and (4) SCD rates from the Oregon Sudden Unexpected Death Study (SUDS) population-based surveillance study of SC. Exclusion: NA.</td>
<td>Results: The age-adjusted national incidence of SCD was 60 per 100,000 population (95% CI 54–66 per 100,000). The burden of premature death for men (2.04 million years of potential life lost; 95% uncertainty interval, 1.86–2.23 million) and women (1.29 million years of potential life lost; 95% uncertainty interval, 1.13–1.45 million) was greater for SCD than for all individual cancers and most other leading causes of death.</td>
<td>Other findings:</td>
<td>Conclusions: The societal burden of SCD is high relative to other major causes of death.</td>
</tr>
<tr>
<td>28</td>
<td>Winkel BG, et al. (2011) Nationwide study of sudden cardiac death in persons aged 1–35 years. PMID: 21131293 Year of publication: 2011</td>
<td>Aim: To study the incidence of SCD in persons aged 1–35 years in a nationwide setting (5.38 million people) by systematic evaluation of all deaths. Study type: Retrospective, nationwide. Death certificate and autopsy review. Number of patients: 625. Enrolment period: 2000–2006 Study endpoints: NA.</td>
<td>Inclusion: All deaths in persons aged 1–35 years in Denmark in 2000–2006 were included. 625 cases of SUD were identified (10% of all deaths), of which 156 (25%) were not autopsied. Of the 469 autopsied cases, 314 (67%) were SCD. Exclusion: NA.</td>
<td>Results: The most common cardiac cause of death was CAD (13%); 29% of autopsied SUD cases were unexplained. In 45% of SCD cases, the death was witnessed; 34% died during sleep; 89% were out-of-hospital deaths.</td>
<td>Other findings: Highest possible incidence rate of SCD in the young was 2.8 per 100,000 person-years including non-autopsied cases of SUD. Excluding those, the incidence rate declined to 1.9 per 100,000 person-years.</td>
<td>Conclusions: A total of 7% of all deaths in the young can be attributed to SCD, when including non-autopsied cases (autopsy ratio 75%). The incidence rate of SCD in the young of 2.8 per 100,000 person-years is higher than previously reported.</td>
</tr>
<tr>
<td>226</td>
<td>van der Werf C, et al. (2011) Diagnostic yield in sudden unexplained death and aborted cardiac arrest in the young: the experience of a tertiary referral center</td>
<td>Aim: To establish the diagnostic yield in families with SUD victim and in SCA survivors. Study type: Retrospective single-centre case series.</td>
<td>Inclusion: (1) All consecutive families who presented to the cardiology department for examination because of ≥1 first-degree related SUD victim aged 1–50 years, and (2) all</td>
<td>Results: A certain or probable diagnosis was made in 47 (33%) of 140 SUD families, including 45 (96%) cases of inherited cardiac diseases. LQTS (19%) was the most prevalent diagnosis. In 42 (61%) of 69 SCA victims, the cause of the event was other. Conclusions: The yield of the current diagnostic work-up in relatives of young SUD victims is 33% and is almost twice as high in young SCA victims. Inherited cardiac diseases are predominantly causative in both groups.</td>
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### Conclusions:

Expert cardiac pathology improves the accuracy of coronial post-mortem diagnoses in young SCD. This is important as the majority of cases may be due to inherited cardiac diseases and the autopsy guides the appropriate Other findings:

- Cardiological evaluation of blood Referring pathologists were more inclined to diagnose cardiomyopathy than relatives for their risk of SD. (63%) normal hearts being described correctly.

### Results:

- Most SCDs occurred in men (66%), with the median age being 32 years. The majority (57%) of deaths occurred at home. The main diagnoses were a morphologically normal heart (n = 321; 45%), cardiomyopathy (n = 207, 29%), and coronary artery pathology (n = 71; 10%). In 158 out of a sample of 200 consecutive cases, a cardiac examination was also performed by the referring pathologist with a disparity in diagnosis in 41% of the cases (κ = 0.48).

### Limitations:

- Retrospective and single centre; not all cases autopsied.

### 267

**de Noronha SV, et al.**

The importance of specialist cardiac histopathological examination in the investigation of young sudden cardiac deaths. PMID: 24148315

**Year of publication:** 2014

**Am:** To demonstrate the improvement in diagnostic quality offered by a specialist cardiac pathology service established to investigate SCD with fast-track reporting on hearts sent by pathologists in cases of SCD.

**Study type:** Prospective observational study.

**Number of patients:** 720

**Enrolment period:** 2007–2009

**Inclusion:** Cases of SCD referred by coroners and pathologists from 2007 to 2009

**Exclusion:** NA.

**Results:** Most SCDs occurred in men (66%), with the median age being 32 years. The majority (57%) of deaths occurred at home. The main diagnoses were a morphologically normal heart (n = 321; 45%), cardiomyopathy (n = 207, 29%), and coronary artery pathology (n = 71; 10%). In 158 out of a sample of 200 consecutive cases, a cardiac examination was also performed by the referring pathologist with a disparity in diagnosis in 41% of the cases (κ = 0.48).

**Other findings:** Referring pathologists were more inclined to diagnose cardiomyopathy than normal hearts being described correctly.

**Conclusions:** Expert cardiac pathology improves the accuracy of coronial post-mortem diagnoses in young SCD. This is important as the majority of cases may be due to inherited cardiac diseases and the autopsy guides the appropriate cardiological evaluation of blood relatives for their risk of SD.

### 269

**Hansen BL, et al.**

Diagnostic yield in victims of sudden cardiac death and their relatives. PMID: 32307520

**Year of publication:** 2020

**Am:** To assess the diagnostic yield of inherited cardiac diseases in consecutively referred SCD families.

**Study type:** Retrospective, single centre.

**Number of patients:** 304 families/685 relatives.

**Enrolment period:** 2005–2018

**Inclusion:** Consecutively included families referred to a tertiary unit due to SCD on suspicion of inherited cardiac disease.

**Exclusion:** NA.

**Results:** In probands, mean age at death was 39 years (75% men) and in relatives mean age at screening was 35 years (47% men). The proband diagnosis was established through autopsy findings (n = 89), genetic analyses (n = 7), or based on pre-mortem findings (n = 21). In the remaining 187 families with borderline/no diagnosis in the proband, screening of relatives yielded a diagnosis in 26 additional families. In total, an inherited cardiac disease was identified in 143 out of 304 families (47%). In relatives, 73 (11%) were diagnosed.

**Conclusions:** 47% of SCD families were diagnosed. 11% of the screened relatives received a definite diagnosis and were offered treatment according to guidelines. A low rate of serious cardiovascular events was observed among SCD relatives.

### 270

**Bjune T, et al.**

Post-mortem toxicology in young sudden cardiac death victims: a nationwide cohort study. PMID: 28339816

**Year of publication:** 2018

**Am:** To investigate in detail the toxicological findings of all young SCD throughout Denmark.

**Study type:** Retrospective.

**Number of patients:** 620 medico-legal autopsied cases of SCD of which 477 with tox profile.

**Enrolment period:** 2000–2009

**Inclusion:** Deaths in persons aged 1–49 years were included over a 10-year period. Death certificates and autopsy reports were retrieved and read to identify cases of SCD and establish cause of death.

**Exclusion:** Deaths due to overdose excluded beforehand.

**Results:** Identified 620 medico-legal autopsied cases of SCD, of which 77% (n = 477) were toxicologically investigated post-mortem, and 57% (n = 270) had a positive toxicology profile. SCD with positive toxicology had higher rates of SADS, compared with SCD with negative toxicology (56% vs. 42%; P < 0.001). In total, 752 agents were detected, and polypharmacy (defined as the presence of more than one drug) was present in 61% (n = 164), all substances combined.

**Other findings:** Psychotropic drugs were the most frequent (62%, n = 467), and 82% (n = 385) were in pharmacological or subpharmacological levels.

**Conclusions:** More than half of all toxicologically investigated SCD victims had positive post-mortem toxicological findings. SCD with positive toxicology had higher rate of SADS, suggesting that the compounds may play a proarrhythmic role in these cases.
### Table 271

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<th>Author</th>
<th>Title</th>
<th>Year of Publication</th>
<th>Enrolment Period</th>
<th>Study Type</th>
<th>Aim</th>
<th>Inclusion</th>
<th>Results</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Allan KS, et al.</td>
<td>Presumed cardiac arrest in children and young adults: a misnomer?</td>
<td>2017</td>
<td>2009–2012</td>
<td>Retrospective, Case control</td>
<td>All emergency medical service attended OHCA patients in a large urban area, between 2009 and 2012, aged 2–45 years, treated or untreated, who died or survived, and that were designated as ‘no obvious cause’.</td>
<td>Only 29.9% (595/1993) were due to confirmed cardiac causes; the rest were due to other causes (non-cardiac aetiologies: confirmed drug overdose (n=62), trauma (n=108), cancer (n=69), complex chronic care (n=65), and non-cardiac acute illness—mostly vascular, infectious, and metabolic (n=376). The annual incidence rate of ‘no obvious cause’ OHCAs after initial field classification was 12.97/100 000 patient-years (95% CI 12.40; 13.50), compared to 3.87/100 000 patient-years (95% CI 3.56; 4.18) for the confirmed cardiac OHCAs after adjudication. The predominant underlying aetiologies of confirmed cardiac OHCAs were coronary heart disease and SHD.</td>
<td>In young adults with OHCA, confirmed cardiac causes were responsible in a minority of cases, and they differed in presentation from those with confirmed non-cardiac causes. Establishing rigorous case ascertainment strategies with linkage to multiple data sources will facilitate a more reliable evaluation of the causes of these events.</td>
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### Table 272

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</thead>
<tbody>
<tr>
<td>Lahrouchi N, et al.</td>
<td>The yield of postmortem genetic testing in sudden death cases with structural findings at autopsy</td>
<td>2020</td>
<td>1995–2015</td>
<td>Retrospective</td>
<td>57 SCD cases with structural findings at cardiac autopsy</td>
<td>In 29 cases (51%) autopsy findings of uncertain significance were identified. In contrast, for cardiac channel molecular autopsy, the yield trended higher among the 1–10-year-olds (4/27 [14.8%]; P = 0.01). In contrast, for those who died during a period of sleep, the 11–20-year-olds had a higher yield (2/25 [8.0%]) than the 1–10-year-olds (1/24 [4.2%]; P = 0.01).</td>
<td>Genetic testing in cases with findings of uncertain significance offers lower clinical utility than in cardiomyopathy, with lower yields than detected previously. This highlights the need for stringent evaluation of variant pathogenicity.</td>
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### Table 273

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<th>Author</th>
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<tr>
<td>Tester DJ, et al.</td>
<td>Cardiac channel molecular autopsy: insights from 173 consecutive cases of autopsy-negative sudden unexplained death referred for postmortem genetic testing</td>
<td>2012</td>
<td>1998–2010</td>
<td>Retrospective</td>
<td>173 cases of SUD</td>
<td>Overall, 45 putative pathogenic mutations absent in 400–700 controls were identified in 45 autopsy-negative SUD cases (26.0%). Femens had a higher yield (26.67 [38.8%]) than males (19/106 [17.9%]; P &lt; 0.005). Among SUD cases with exercise-induced death, the yield trended higher among the 1–10-year-olds (8/12 [66.7%]) compared with the 11–20-year-olds (4/27 [14.8%]; P = 0.02). In contrast, for those who died during a period of sleep, the 11–20-year-olds had a higher yield (9/25 [36.0%]) than the 1–10-year-olds (1/24 [4.2%]; P = 0.01).</td>
<td>Several interesting genotype-phenotype observations may provide insight into the expected yields of post-mortem genetic testing for SUD and assist in selecting cases with the greatest potential for mutation discovery and directing genetic testing efforts.</td>
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*NOTE:* The tables continue on the next page.
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<tbody>
<tr>
<td>274</td>
<td>Papadakis M, et al.</td>
<td>2013</td>
<td>To explore to what extent autopsies with structural abnormalities of uncertain significance represent/simic SADS cases. Study type: Retrospective, single centre. Number of patients: 41 families of SCD cases with structural abnormalities of uncertain significance at autopsy. Enrolment period: 2003–2009</td>
<td>Families of SCD cases with structural abnormalities of uncertain significance at autopsy referred for cardiac evaluation. Exclusion: NA.</td>
<td>Results: 21 families (51%) with autopsy findings of uncertain significance received a diagnosis based on the identification of an inherited cardiac condition in ≥1 relatives: 14 Brugada syndrome; four long QT syndrome; one CPVT; and two cardiomyopathy. A similar proportion of families (47.2%) received a diagnosis in the SADS cohort (P = 0.727). An arrhythmogenic syndrome was the predominant diagnosis in both cohorts (46% vs. 45%; P = 0.863).</td>
<td>Conclusions: Familial evaluation after SCD with autopsy findings of uncertain significance identified a similar proportion of primary arrhythmogenic syndromes to a contemporary series of SADS. Limitations: Retrospective, single centre, referral bias.</td>
</tr>
<tr>
<td>275</td>
<td>Jacobsen EM, et al.</td>
<td>2020</td>
<td>The purpose was to assess the prevalence and spectrum of inherited cardiac diseases and the long-term outcome in a consecutive cohort of non-ischaemic SCA survivors (probands) and their relatives. Study type: Retrospective, single centre. Number of patients: 155 probands/282 relatives. Enrolment period: 2005–2018</td>
<td>Non-ischaemic SCA survivors referred for evaluation and family screening</td>
<td>Results: 153 probands (age 41.2 ± 15.5 years; 61% men) and 282 relatives (age 35.7 ± 18.8 years; 51% men). Mean follow-up was 7.1 years for probands and 4.4 years for relatives. Identified an inherited cardiac disease in 76 (49%) probands and 42 (15%) relatives. An implantable cardioverter-defibrillator was inserted in 147 (95%) probands and nine (3%) relatives. During follow-up, four (3%) probands and three (1%) relatives died, and 37 probands and two relatives received appropriate shock therapy. All relatives received genetic counselling, and 18 (6%) relatives started pharmacological treatment during follow-up.</td>
<td>Systematic work-up of non-ischaemic SCA survivors and their relatives identified an inherited cardiac disease in 49% of referred probands and 15% of their relatives. The favourable long-term prognosis of diagnosed relatives probably not only reflects lower age but also the effects of early diagnosis, treatment, and follow-up. These findings support systematic work-up of SCA survivors and their relatives.</td>
</tr>
<tr>
<td>276</td>
<td>Kjerrumgaard A, et al.</td>
<td>2020</td>
<td>Describe diagnostic findings and follow-up outcomes in relatives to young non-autopsied sudden death victims. Study type: Retrospective, single centre. Number of patients: 149 relatives from 84 families. Enrolment period: 2005–2018</td>
<td>Families referred to a tertiary referral centre due to a non-autopsied possible SCD (pSCD) in the family. Exclusion: NA.</td>
<td>Results: 149 relatives (43 ± 16 years, 48% men) from 84 pSCD non-autopsied cases (44 ± 11 years, 79% men). In 11 (13%) families a definite inherited cardiac diagnosis was established, a borderline diagnosis in eight (10%) families, and 65 (77%) families remained undiagnosed. One-third of the diagnosed relatives were offered pharmaco- or device-based therapy. During follow-up for 4.7 ± 3.6 years no relatives from the families with definite diagnoses died. No events were seen in the groups with borderline or no diagnoses.</td>
<td>The diagnostic yield and need for treatment in diagnosed relatives warrant work-up, also of families with non-autopsied pSCD victims. No or reduced follow-up of relatives without signs or symptoms of heart diseases may be safe.</td>
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<tr>
<td>277</td>
<td>Shank’s GW, et al.</td>
<td>Importance of variant interpretation in whole-exome molecular autopsy: population-based case series.</td>
<td>2018</td>
<td>Investigate the yield of whole-exome molecular autopsy (99 genes) in the setting of sudden unexpected death in the young (SUDY).</td>
<td>SUDDY from 1 to 40 years of age.</td>
<td>NA</td>
<td>A whole-exome molecular autopsy with analysis of 99 SD-susceptibility genes was performed. Average age at death 27 ± 5.7 years; 13 White, 12 Black. Overall, 27 ultra-rare non-synonymous variants were seen in 16/25 (64%) victims of SUDDY. Among Black individuals, 9/12 (75%) had an ultra-rare non-synonymous variant compared with 7/13 (54%) White individuals. Of the 27 variants, 10 were considered pathogenic or likely pathogenic in 7/25 (28%) individuals in accordance with the American College of Medical Genetics guidelines. Pathogenic/likely pathogenic variants were identified in 5/16 (31%) of autopsy-negative cases and in 2/6 (33%) victims of SUDDY with equivocal findings of cardiomyopathy. Overall, six pathogenic/likely pathogenic variants in 4/25 (16%) cases were congruent with the phenotypic findings at autopsy and therefore considered clinically actionable.</td>
<td>Whole-exome molecular autopsy with gene-specific surveillance is an effective approach for the detection of potential pathogenic variants in SUDDY cases. However, systematic variant adjudication is crucial to ensure accurate and proper care for surviving family members.</td>
</tr>
<tr>
<td>278</td>
<td>Narula N, et al.</td>
<td>Post-mortem whole exome sequencing with gene-specific analysis for autopsy-negative sudden unexplained death in the young: a case series.</td>
<td>2015</td>
<td>Determine whether post-mortem whole exome sequencing (WES) is an efficient strategy to detect ultra-rare, potentially pathogenic variants in the young (SUDY) cases (117 gene panel).</td>
<td>SUDDY case referred for research based genetic testing.</td>
<td>NA</td>
<td>Average age at death 17.4 ± 8.6 years. On average, each SUDDY case had 12,758 ± 2,016 non-synonymous variants, of which 79 ± 15 localized to these 117 genes. Overall, eight ultra-rare variants (7 missense, one in-frame insertion) absent in three publically available exome databases were identified in six genes (3 in TTN and one each in CACNA1C, JPH2, MYH7, VCL, RYR2) in 7 of 14 cases (50%). Of the seven missense alterations, two (T171M-CACNA1C, D1216T-TTN) were predicted damaging by three independent in silico tools.</td>
<td>Although WES and gene-specific surveillance is an efficient means to detect rare genetic variants that might underlie the pathogenic cause of death, accurate interpretation of each variant is challenging. Great restraint and caution must be exercised otherwise families may be informed prematurely and incorrectly that the root cause has been found.</td>
</tr>
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</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; NA, not applicable; OHCA, out of hospital cardiac arrest; SADS, sudden arrhythmic death syndrome; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SD, sudden death; SUDDY, sudden unexpected death; WES, whole exome sequencing.
### Table of Evidence 7 for Table of Recommendations for evaluation of relatives of sudden arrhythmic death syndrome decedents

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study Study type</th>
<th>Inclusion criteria (patients) Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tbody>
<tr>
<td>184</td>
<td>Wong L, et al.56</td>
<td>Cardiac evaluation of pediatric relatives in sudden arrhythmic death syndrome: a 2-center experience. PMID: 25194972</td>
<td>Inclusion: Paediatric patients with a family history of SADS assessed from 2010 to 2013 in two centres. Exclusion: NA.</td>
<td>Results: A probable diagnosis was made in 18 (29.5%) families: Brugada syndrome, 13/18 (72%); LQTS, 3/18 (17%); and CPVT 2/18 (11%). Genetic testing identified mutations in 20% of Brugada syndrome (2/10) and 50% of LQTS (1/2) and CPVT families (1/2) who were tested. Paediatric evaluation diagnosed 6/112 relatives (5.4%), increasing to 7% (6/85) if only first-degree relatives were assessed. The only useful diagnostic tests were the 12-lead and exercise ECG and ajmaline provocation test. The median duration of follow-up was 2.1 years (range, 0.2–8.2 years) with no cardiac events.</td>
<td></td>
<td>Conclusions: The yield of evaluating paediatric relatives is significant and higher when focused on first-degree relatives and on conditions usually expressed in childhood. We propose a management pathway for these children.</td>
</tr>
<tr>
<td>255</td>
<td>Behr E, et al.57</td>
<td>Cardiological assessment of first-degree relatives in sudden arrhythmic death syndrome. PMID: 14602442</td>
<td>Inclusion: First-degree relatives of consecutive SADS decedents recruited to national study. Exclusion: NA.</td>
<td>Results: 109/147 first-degree relatives of 32 SADS cases underwent cardiological assessment. 7/32 (22%) families were diagnosed with inherited cardiac disease.</td>
<td>Other findings: Diagnoses were: Four LQTS; one with non-structural cardiac electrophysiological disease; one with myotonic dystrophy; and one with HCM.</td>
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<tr>
<td>280</td>
<td>Behr ER, et al.58</td>
<td>Sudden arrhythmic death syndrome: familial evaluation identifies inheritable heart disease in the majority of families. PMID: 18508782</td>
<td>Inclusion: Consecutively referred families with SADS death. Exclusion: NA.</td>
<td>Results: First-degree relatives (18/4262 [70%]) underwent evaluation. 30 families (53%) were diagnosed with inheritable heart disease: 16 LQTS, five Brugada syndrome, five ARVC, and four other cardiomyopathies.</td>
<td>Other findings: Mutations were identified in 5/13 (38%) definite LQTS families, 1/5 (20%) Brugada syndrome families, and 1/4 (25%) ARVC families.</td>
<td></td>
</tr>
</tbody>
</table>
Study endpoints:
Genetic and/or clinical diagnosis in the family and/or decedent.

Inclusion:
Consecutive SADS family referrals.

Exclusion:
NA.

Results:
Evaluation included resting ECG with conventional and high ECG leads, echocardiography, exercise, and 24-h ECG monitor. Then systematic ajmaline testing. An inherited cardiac disease was diagnosed in 128 (42%) families and 201 (22%) relatives. Brugada syndrome was the most prevalent diagnosis ($n=85$, 28% of families; $n=140$, 15% of relatives). Ajmaline testing was required to unmask the Brugada syndrome in 97% of diagnosed individuals.

Other findings:
At initial evaluation, four (0.4%) individuals showed a spontaneous type 1 Brugada pattern on the resting ECG, of which two were seen only on the high leads.

Conclusions:
Systematic use of ajmaline testing with high ECG leads increases substantially the yield of Brugada syndrome in SADS families.

Limitations:
Retrospective and single centre.

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van der Werf C, et al.

Low rate of cardiac events in first-degree relatives of diagnosis-negative young sudden unexplained death syndrome victims during follow-up.

PMID: 24882506
Year of publication: 2014

Aim:
Study the prognosis of first-degree relatives of young SUDS victims, in whom the initial cardiological and genetic examination did not lead to a diagnosis.

Study type:
Retrospective single-centre case series.

Enrolment period:
1996–2009

Number of patients:
340 first-degree relatives from 77 families.

Inclusion:
Diagnosis-negative families who presented to our cardigenetics department between 1996% and 2009 because of SUDS in ≥1 relatives aged 1–50 years.

Exclusion:
NA.

Results:
Median follow-up 6.6 years; IQR 4.7–9.6 years. 20 relatives (4.9%) died during follow-up, including one natural death before the age of 50. 234 of 340 first-degree relatives (68.8%) underwent cardiological examination. Of these, 76 (32.5%) were re-evaluated. Inherited cardiac disease was diagnosed in three families (3.6%).

Conclusions:
In first-degree relatives of young SUDS victims with no manifest abnormalities during the initial examination, the risk of developing manifest inherited cardiac disease or cardiac events during follow-up is low. This does not apply to families with obvious familial SUDS.
3. Therapies for ventricular arrhythmias. General aspects

3.1. Acute management
3.1.1. Treatment of reversible causes

Table of Evidence 8 for Table of Recommendations for treatment of reversible conditions

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
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</thead>
<tbody>
<tr>
<td>296</td>
<td>Gibbs C, et al. (2018)</td>
<td>To determine predictors of mortality in patients with corrected QT interval (QTc) ≥ 500 ms in a community hospital. Study type: Retrospective study. Number of patients: 1531 Enrolment period: 2004–2014 Study endpoints: All-cause mortality.</td>
<td>Inclusion: QTc &gt; 500 ms, QRS &lt; 120 ms, HR 30–100 b.p.m. Exclusion: NA.</td>
<td>Results: All-cause mortality during 952 (range 0–4161) days of follow-up was 50% (n = 765/1531). Main predictors of mortality were aborted cardiac arrest (HR 2.40; 95% CI 1.44–4.01; P = 0.001), cerebral stroke/head trauma (HR 2.28; 95% CI 1.70–3.05; P &lt; 0.001), and heart failure (HR 1.74; 95% CI 1.43–2.12; P &lt; 0.001).</td>
<td>Other findings: A total of 433 (28%) patients received at least one drug from the group ‘known risk for torsades de pointes’ and 166 (11%) patients received at least one drug from the group ‘possible risk for torsades de pointes’. Furthermore, 663 (43%) patients received at least one drug from the group ‘conditional risk for torsades de pointes’ and 189 (12%) patients received at least one drug from the group ‘drugs to be avoided by congenital long QT’.</td>
<td>Conclusions: QTc ≥ 500 ms was associated with high all-cause mortality with increased mortality in men compared with women. Drugs were one of the main contributors of QT prolongation.</td>
</tr>
<tr>
<td>297</td>
<td>Simpson TF, et al. (2020)</td>
<td>To evaluate the association between QT-prolonging medication and autopsy-defined sudden arrhythmic death vs. non-arrhythmic cause of SD. Study type: Subanalysis of prospective POST SCD study. Number of patients: 535 Enrolment period: 2011–2014 Study endpoints: Death due to trauma, presumed SCD, and autopsy-defined non-sudden arrhythmic death and sudden arrhythmic death with no post-mortem findings of extracardiac cause.</td>
<td>Inclusion: SCD and autopsy. Exclusion: NA.</td>
<td>Results: Individuals with presumed SCDs had higher exposure and were more likely to be taking any QT-prolonging medication (29.1 [55.4%] vs. 2.8 [26.9%] P &lt; 0.001) than trauma controls. Use of QT-prolonging medication was associated with increased risk of presumed SCD in low (OR 2.25 [95% CI 1.03–4.96]; P = 0.04) and high (OR 6.70 [95% CI 1.47–30.67]; P = 0.01) exposure groups.</td>
<td>Other findings: After autopsy adjudication, use of QT-prolonging medication was associated with increased risk of non-sudden arrhythmic death (low-risk OR 2.88 [95% CI 1.18–6.99]; P = 0.02; moderate-risk OR 2.62 [95% CI 1.20–5.73]; P = 0.02; and high-risk OR 14.22 [95% CI 2.91–69.30]; P = 0.001) but not sudden arrhythmic death in all exposure groups.</td>
<td>Conclusions: These findings confirm the association between QT-prolonging medication and presumed SCD, however, after autopsy, this risk was specific for non-arrhythmic causes of SD.</td>
</tr>
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Continued
**Aim:** To assess the effect of an invasive strategy on hospital survival.

**Study type:** Observational.

**Number of patients:** 714 (435 with obvious extracardiac cause of arrest).

**Enrolment period:** 2003–2008

**Study endpoint:** Hospital survival.

**Inclusion:** Patients with OHCA referred to one tertiary centre; if no obvious extracardiac cause of arrest, an immediate coronary angiogram was performed at admission followed, if indicated, by coronary angioplasty.

**Exclusion:** NA.

**Results:** At least one significant coronary artery lesion was found in 304 (70%) patients, in 128 (96%) of 134 patients with ST-segment elevation on the ECG performed after the return of spontaneous circulation, and in 176 (58%) of 301 patients without ST-segment elevation.

**Other findings:** Multivariable analysis showed successful coronary angioplasty to be an independent predictive factor of survival, regardless of the post-resuscitation ECG pattern (OR 2.06; 95% CI 1.16–3.66).

**Conclusions:** Successful immediate coronary angioplasty is associated with improved hospital survival in patients with or without ST-segment elevation. Therefore, our findings support the use of immediate coronary angiography in patients with OHCA with no obvious non-cardiac cause of arrest regardless of the ECG pattern.

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**Aim:** To evaluate the prognostic impact of potassium levels on recurrences of VTs in consecutive ICD recipients.

**Study type:** Retrospective registry.

**Number of patients:** 530

**Enrolment period:** 2002–2016

**Study endpoint:** VT recurrence at 1-year follow-up.

**Inclusion:** ICD carriers presenting with VA.

**Exclusion:** NA.

**Results:** Whereas hyperkalaemia was not associated with increasing risk of recurrent VA, hypokalaemia was associated with decreasing freedom from recurrent VA (HR 2.135; 95% CI 1.158–3.937; P = 0.015), even after multivariable adjustment (HR 2.577; 95% CI 1.236–5.372; P = 0.012).

**Other findings:** Higher risk of recurrences was especially attributed to higher rates of electrical storm in the presence of hypokalaemia (15% vs. 3–4%). Negative impact of hypokalaemia was mainly attributed to secondary preventive ICD (HR 2.637; 95% CI 1.325–5.248; P = 0.006). Moreover, hypokalaemia was associated with increasing risk of appropriate ICD therapies (HR 1.920; 95% CI 0.912–4.042; statistical trend: P = 0.086).

**Conclusions:** In consecutive ICD recipients with VA, hypokalaemia—but not hyperkalaemia—was associated with increasing risk of recurrent VA and appropriate ICD therapies.

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**Exclusion:** NA.

**Results:** Whereas hyperkalaemia was not associated with increasing risk of recurrent VA, hypokalaemia was associated with decreasing freedom from recurrent VA (HR 2.135; 95% CI 1.158–3.937; P = 0.015), even after multivariable adjustment (HR 2.577; 95% CI 1.236–5.372; P = 0.012).

**Other findings:** Higher risk of recurrences was especially attributed to higher rates of electrical storm in the presence of hypokalaemia (15% vs. 3–4%). Negative impact of hypokalaemia was mainly attributed to secondary preventive ICD (HR 2.637; 95% CI 1.325–5.248; P = 0.006). Moreover, hypokalaemia was associated with increasing risk of appropriate ICD therapies (HR 1.920; 95% CI 0.912–4.042; statistical trend: P = 0.086).

**Conclusions:** In consecutive ICD recipients with VA, hypokalaemia—but not hyperkalaemia—was associated with increasing risk of recurrent VA and appropriate ICD therapies.
<table>
<thead>
<tr>
<th>Page</th>
<th>Authors</th>
<th>Title</th>
<th>PMID</th>
<th>Year of publication</th>
<th>Aim</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
<th>Other findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>299</td>
<td>Ladejobi A, et al.</td>
<td>Implantable defibrillator therapy in cardiac arrest survivors with a reversible cause.</td>
<td>29545361</td>
<td>2018</td>
<td>To examine the impact of ICD therapy on mortality in survivors of SCA associated with reversible causes. Study type: Retrospective observational study.</td>
<td>1433</td>
<td>2000–2012</td>
<td>All-cause mortality.</td>
<td>SCA due to VA, discharged alive from hospital.</td>
<td>Presence of ICD, &lt;18 years.</td>
<td>In patients with reversible cause of SCA, ICD therapy is delivered to 26% of patients and is associated with a lower all-cause mortality (HR 0.10; 95% CI 0.03–0.33). In subgroup analysis, ICD therapy was associated with lower mortality in all survivors of SCA because of a reversible cause, except in those who presented with acute MI and underwent complete revascularization.</td>
<td>More than half of the patients who survive an SCA in the context of a reversible and correctable cause have an acute MI or myocardial ischaemia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>302</td>
<td>Gupta A, et al.</td>
<td>Implantable cardioverter-defibrillator therapy in device recipients who survived a cardiac arrest associated with a reversible cause.</td>
<td>30015993</td>
<td>2018</td>
<td>To examine the impact of ICD therapy on mortality in survivors of SCA associated with reversible causes. Study type: Retrospective observational study.</td>
<td>207</td>
<td>2002–2012</td>
<td>All-cause mortality.</td>
<td>Cardiac arrest due to VA, discharged alive from hospital with ICD.</td>
<td>Presence of ICD, &lt;18 years.</td>
<td>Over a follow-up period of 3.8 ± 3.1 years, more patients without MI/ischaemia who received an ICD experienced appropriate (adjusted HR 3.96; 95% CI 1.32–11.84) but not inappropriate (adjusted HR 0.65; 95% CI 0.14–2.97) ICD therapy.</td>
<td>The proportion of patients receiving appropriate (P = 0.012) but not inappropriate (P = 0.80) ICD therapy was also higher in the non-MI + ICD group compared with the MI + ICD group.</td>
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</tbody>
</table>

CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; SCA, sudden cardiac arrest; SD, sudden death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
**3.1.2. Acute management of sustained monomorphic ventricular tachycardia**

**Table of Evidence 9** for Table of Recommendations for the acute management of sustained ventricular tachycardia and electrical storm

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>306</td>
<td>Ortiz M, et al. (2017)</td>
<td>Randomized comparison of intravenous procainamide vs. intravenous amiodarone for the acute treatment of tolerated wide QRS tachycardia: the PROCAMIO study. PMID: 27354046 Year of publication: 2017</td>
<td>To assess the safety and efficacy of intravenous procainamide and amiodarone for the acute treatment of tolerated wide QRS complex (probably VT). Study type: RCT. Number of patients: 74 included, 62 analysed. Enrolment period: 2006–2016. Study endpoints: Incidence of major predefined cardiac adverse events within 40 min after infusion initiation.</td>
<td>Efficacy: Tolerated wide QRS tachycardia. Exclusion: Previous recent treatment with amiodarone/procainamide, presumed VT.</td>
<td>Results: The primary endpoint occurred in 3 of 33 (9%) procainamide and 12 of 29 (41%) amiodarone patients (OR 0.1; 95% CI 0.03–0.6; P = 0.02), but this survival advantage persisted at 3 years (19.1% vs. 11.0%; adjusted RR of 1.45; 95% CI 1.23; 1.69; P &lt; 0.0001).</td>
<td>Propranolol was associated with fewer major cardiac adverse events and a higher proportion of tachycardia termination within 40 min.</td>
</tr>
<tr>
<td>342</td>
<td>Patel KK, et al. (2018)</td>
<td>Association between prompt defibrillation and epinephrine treatment with long-term survival after in-hospital cardiac arrest. PMID: 29279412 Year of publication: 2018</td>
<td>To assess the survival with prompt defibrillation and epinephrine treatment in patients suffering in-hospital cardiac arrest. Study type: Retrospective registry. Number of patients: 8119. Enrolment period: 2000–2011. Study endpoints: Incidence of major predefined cardiac adverse events within 40 min after infusion initiation.</td>
<td>Inclusion: In-hospital cardiac arrest due to pulseless VT or VF or pulseless electrical activity were stratified by prompt (&lt;5 min) vs. delayed (&gt;5 min) epinephrine treatment. Exclusion: Age &lt;65 years.</td>
<td>Results: Median follow-up of at least one year. The rate of 1-year survival was higher in those treated with prompt defibrillation than with delayed defibrillation (25.7% [1466/5714] vs. 15.5% [373/2405]; adjusted RR 1.49 [1.32, 1.69]; P &lt; 0.0001). This survival advantage persisted at 3 years (19.1% vs. 11.0%; adjusted RR of 1.45; 95% CI 1.23; 1.69; P &lt; 0.0001).</td>
<td>Prompt defibrillation for in-hospital cardiac arrest due to VT/VF was associated with higher rates of long-term survival throughout 5 years of follow-up, whereas prompt epinephrine treatment for asystole/ pulseless electrical activity was associated with greater survival at 1 year, but not at three or five years.</td>
</tr>
<tr>
<td>309</td>
<td>Buxton AE, et al. (1984)</td>
<td>Repetitive, monomorphic ventricular tachycardia: clinical and electrophysiologic characteristics in patients with and without organic heart disease. PMID: 6496364 Year of publication: 1984</td>
<td>To compare repetitive, monomorphic VT post-MI (group A) and without SHD (group B). Study type: Retrospective, single centre. Number of patients: 22 idiopathic RVOT VT patients. Enrolment period: Not reported. Study endpoints: Incidence of VT by anti-arrhythmic drugs.</td>
<td>Inclusion: Patients with repetitive VT and without SHD. Exclusion: NA.</td>
<td>Results: Type I anti-arrhythmic agents suppressed in 14 group B patients, whereas propranolol suppressed VT in 12 of 20 group B patients. Verapamil suppressed spontaneous VT in four group B patients.</td>
<td>During a mean follow-up of 40 months for group B, no patient had died suddenly or had a cardiac arrest.</td>
</tr>
</tbody>
</table>
### 3.10

**Efficacy of intravenous adenosine on verapamil-sensitive 'idiopathic' ventricular tachycardia.**

**PMID:** 9160612  
**Year of publication:** 1994  
**Aim:** To study the effects of vagotonic manoeuvres, and intravenous adenosine (up to 0.25 mg/kg in incremental doses) and verapamil (0.145 mg/kg) in patients with 'idiopathic' VT.  
**Study type:** Prospective, single centre.  
**Number of patients:** Nine (seven left fascicular and two idiopathic RVOT VT).  
**Enrolment period:** Not reported.  
**Study endpoints:** Tachycardia termination.

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine may terminate RVOT VT but not fascicular left VT. Verapamil terminates both forms.</td>
<td>Verapamil produced stuttering termination of RVOT tachycardia with no preceding change in RR interval in patients with this arrhythmia and in patients with fascicular VT was followed by gradual slowing of the arrhythmia (cycle length increased from 397 ± 45 to 506 ± 86 ms; P &lt; 0.01) in all seven patients and by termination of VT in six.</td>
</tr>
</tbody>
</table>

#### Results

- **15 s** that was dependent on Vagal manoeuvres did not have any effect on any VT.
- Adenosine interrupted both RVOT tachycardias for a period (2 min) that was dependent on the dose of adenosine, but had no effect on VT in any patient with fascicular VT.

#### Other findings

- **Verapamil produced stuttering termination of RVOT tachycardia with no preceding change in RR interval in patients with this arrhythmia and in patients with fascicular VT was followed by gradual slowing of the arrhythmia (cycle length increased from 397 ± 45 to 506 ± 86 ms; P < 0.01) in all seven patients and by termination of VT in six.**
- **Mean LVEF 38%.** Lidocaine terminated VT in 4 of 31 patients, ajmaline in 19 of 30 patients. **Lidocaine had no effect on VT in any patient with fascicular VT.**

### 3.03

**Adenosine for wide-complex tachycardia: efficacy and safety.**

**PMID:** 9620309  
**Year of publication:** 2009  
**Aim:** To determine whether adenosine is useful and safe for patients with uniferentiated wide QRS complex tachycardia.  
**Study type:** Retrospective study.  
**Number of patients:** 197  
**Enrolment period:** 1991–2006  
**Study endpoints:** Response to adenosine.

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenosine is useful and safe for patients with undifferentiated wide QRS complex tachycardia.</td>
<td>The rate of primary adverse events for patients with SVT and VT was zero (0%) of 116 and zero (0%) of 81, respectively.</td>
</tr>
</tbody>
</table>

#### Results

- Regular wide complex tachycardia for 2 min >120 b.p.m.

### 3.07

**Efficacy of flecaïnine, sotalol, and verapamil treatment of right ventricular tachycardia in patients without overt cardiac abnormality.**

**PMID:** 1499922  
**Year of publication:** 1992  
**Aim:** To assess the efficacy of verapamil, sotalol, and flecaïnine to suppress right VT in patients with a clinically normal heart.  
**Study type:** Prospective, single centre.  
**Number of patients:** 23  
**Enrolment period:** 1990–1992  
**Study endpoints:** Number of ventricular events on 24 h Holter monitoring, and the ability of VT to be induced by treadmill exercise testing and programmed ventricular stimulation compared with drug-free baseline tests.  
**Study endpoints:** VT suppression.

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Other findings</th>
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<tbody>
<tr>
<td>Efficacy of flecaïnine, sotalol, and verapamil.</td>
<td>VT associated with a clinically normal heart can be suppressed by flecaïnine, sotalol, or verapamil.</td>
</tr>
</tbody>
</table>

#### Results

- **All three drugs suppressed ventricular salvos (>3, <5 consecutive PVCs) (P < 0.01) and VT (P < 0.05) on Holter monitoring and did not differ statistically in effect.**
- Exercise-induced VT was also suppressed by all three drugs (P < 0.01), and of these sotalol was the most effective, although this was not statistically significant (14/23 inducible when drug-free, 4/23 on flecaïnine, 2/23 on sotalol, 5/23 on verapamil).

#### Other findings

- Sustained and NSVT induced by programmed stimulation was also suppressed by the three drugs (P < 0.01) and again sotalol was the best of these, although the differences did not achieve statistical significance (17/23 inducible when drug-free, 4/17 on flecaïnine, 2/17 on sotalol, and 6/17 on verapamil).  
- Pro-arrhythmic effects of drugs were found in a few patients.

### 3.08

**Electrophysiological and haemodynamic effects of lidocaine and ajmaline in the management of sustained ventricular tachycardia.**

**PMID:** 1505562  
**Year of publication:** 1992  
**Aim:** To analyse electrophysiological and haemodynamic effects of lidocaine (100 mg) and ajmaline (50 mg).

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>Other findings</th>
</tr>
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<tbody>
<tr>
<td>Electrophysiological and haemodynamic effects of lidocaine and ajmaline in the management of sustained ventricular tachycardia.</td>
<td>Anti-arrhythmic agents such as ajmaline, which slow conduction velocity and prolong refractoriness, are more effective than lidocaine in the medical treatment of</td>
</tr>
</tbody>
</table>

#### Results

- **Mean LVEF 38%.** Lidocaine terminated VT in 4 of 31 patients, ajmaline in 19 of 30 patients (P < 0.001).

#### Other findings

- **QRS and RR intervals during VT were prolonged by ajmaline from 164 ± 28 ms to 214 ± 49 ms and from 371 ± 86 ms to 479 ± 137 ms (P < 0.001), respectively; lidocaine did not influence these parameters.**
<table>
<thead>
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<th>Page</th>
<th>Description</th>
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</table>
Aim: To analyse outcome of patients in whom verapamil was given for tolerated VT.  
Study type: Retrospective case study.  
Number of patients: 25  
Enrolment period: 1983–1986  
Study endpoints: VT termination, side effects.  
Inclusion: Emergency room visits for stable monomorphic VT.  
Exclusion: NA.  
Results: In 11 of 25 patients (44%) with VT who received intravenous verapamil (5–10 mg), acute severe hypotension or loss of consciousness developed, necessitating immediate cardioversion. Other findings: Although most patients with severe adverse effects after verapamil had prior MI, deterioration also occurred in patients without coronary disease and in patients with a normal LVEF.  
Conclusions: Although verapamil may terminate VT, severe adverse effects occur much more often. Use of verapamil to differentiate SVT with aberrant conduction from VT is hazardous. |
Aim: To analyse the response to verapamil in VT.  
Study type: Retrospective case review.  
Number of patients: 32 patients, 57 episodes.  
Enrolment period: Not reported.  
Study endpoints: VT termination, side effects.  
Inclusion: Patients with VT episodes.  
Exclusion: NA.  
Results: Intravenous verapamil (mean dose 9.8 mg) failed to terminate the tachycardia in 45 episodes (79%). Two patients sustained cardiac arrest after verapamil (one VF, one asystole), and in 22 episodes severe hypotension occurred. At least one serious adverse effect occurred in 19 patients (59%).  
Conclusions: Verapamil is ineffective and potentially hazardous in most patients with VT. It should not be used to treat broad-complex tachycardia unless a supraventricular origin has been established. |
Aim: To compare the efficacy of a non-selective (propranolol) vs. a β1-selective blocker (metoprolol) in the management of electrical storms.  
Study type: Monocentric RCT.  
Number of patients: 60  
Enrolment period: 2011–2016  
Study endpoints: Primary endpoint: Time-to-last occurrence of VT/VF requiring ICD intervention. Secondary endpoints: Event rate, proportion of patients who remained free of VT/VF at pre-specified time points, total number of ICD discharges, length of hospital stay.  
Inclusion: Patients with electrical storm (≥ 3 VA episodes separated by >5 min in 24 h requiring ICD intervention). Randomization 1:1 to oral short-acting propranolol or metoprolol. All patients received amiodarone iv.  
Exclusion: Drug-induced arrhythmias. QT >500 ms. Hypokalemia, impaired hepatic or renal function, systolic blood pressure <90 mmHg.  
Results: 60 patients (mean age 65 ± 8.5 years, 45 men). Patients under propranolol presented a 2.67 (IRR 0.375; 95% CI 0.207–0.678; P = 0.001) decrease in incidence of VA requiring therapy and a 2.34 (IRR 0.428; 95% CI 0.227–0.892; P = 0.009) decrease in ICD shocks. Other findings: Median time from initiation of therapy to VT or VF termination was three (CI 95% 1–8) vs. 18 (95% CI 8–37) h in propranolol vs. metoprolol groups (P = 0.001).  
24h after treatment 90% in propranolol vs. 53.3% of patients in metoprolol groups were free of VA.  
Conclusions: The combination of iv amiodarone and oral propranolol is safe, effective, and superior to the combination of amiodarone and oral metoprolol in the management of electrical storm in ICD recipients. |
<table>
<thead>
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<th>Page</th>
<th>Study Details</th>
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<tr>
<td></td>
<td><strong>Aim:</strong> To determine whether amiodarone plus beta-blocker or sotalol are better than beta-blocker alone for prevention of ICD shocks. <strong>Study type:</strong> RCT. <strong>Inclusion:</strong> Randomized to beta-blocker (recommended metoprolol 100 mg/day, carvedilol 50 mg/day, bisoprolol 10 mg/day), beta-blocker and amiodarone or sotalol (recommended 240 mg/day). <strong>Number of patients:</strong> 412 <strong>Enrolment period:</strong> 2001–2004 <strong>Study endpoints:</strong> ICD shock for any reason. <strong>Results:</strong> Median follow-up: 359 days. Mean LVEF: 34 ± 12%. NYHA II or III: 65%. ICD shocks occurred in: beta-blocker 38.5%, sotalol 24.3%, and amiodarone + beta-blocker 0.3%. Amiodarone + beta-blocker vs. beta-blocker (HR 0.27; 95% CI 0.14–0.52; P = 0.001). Amiodarone + beta-blocker vs. sotalol (HR 0.43; 95% CI 0.22–0.85; P = 0.02). Sotalol vs. beta-blocker (HR 0.61; 95% CI 0.37–1.01; P = 0.055). <strong>Other findings:</strong> All patients received dual chamber ICD. The rates of study drug discontinuation at one year were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for beta-blocker alone. Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone. <strong>Conclusions:</strong> High-risk population, does not re...</td>
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<td></td>
<td><strong>Aim:</strong> To assess the effect of intravenous magnesium sulfate in patients with torsade de pointes. <strong>Study type:</strong> Retrospective observational. <strong>Inclusion:</strong> Consecutive patients that developed torsade de pointes with QT prolongation. <strong>Exclusion:</strong> NA. <strong>Results:</strong> In nine of the patients a single bolus of 2 g completely abolished the torsade de pointes within 1–5 min, and in three others complete abolition of the torsade de pointes was achieved after a second bolus was given 5–15 min later. <strong>Other findings:</strong> Magnesium sulfate is a very effective and safe treatment for torsade de pointes, and its application is rapid and simple. Its use is therefore recommended as the first line of therapy for torsade de pointes. <strong>Conclusions:</strong> Amiodarone plus beta-blocker is effective for preventing these shocks and is more effective than sotalol, but has an increased risk of drug-related adverse effects. Limitations: High-risk population, does not reflect today's primary preventive ICD recipients. Very high event rate probably due to old-fashioned ICD programming.</td>
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<td></td>
<td><strong>Aim:</strong> To assess short- and long-term outcomes of cardiac arrest for the treatment of electrical storm in patients with ICD. <strong>Study type:</strong> Prospective registry, single centre. <strong>Inclusion:</strong> Consecutive patients (CAD [72 patients], idiopathic DCM [10 patients], and ARVC [13 patients]) undergoing catheter ablation for drug-refractory electrical storm. <strong>Exclusion:</strong> NA. <strong>Results:</strong> After 1–3 procedures, induction of any clinical VT(s) by PES was prevented in 85 patients (89%). Electrical storm was acutely (&gt;7 days) suppressed in all patients. At a median follow-up of 22 months (range, 1–43 months), 87 patients (90%) were free of electrical storm and 63 patients (66%) were free of VT recurrence. <strong>Other findings:</strong> 8 of 10 patients with persistent inducibility of clinical VT(s) had electrical storm recurrence; four of them died suddenly despite appropriate ICD intervention. Altogether, 11 of 95 patients (12%) died of cardiac-related reasons. <strong>Conclusions:</strong> Advanced strategies of catheter ablation applied to a large population of patients are effective in the short-term treatment of electrical storm. By preventing electrical storm recurrence, catheter ablation may play a protective role over the long term and, together with long-term pharmacological therapy, may favourably affect cardiac mortality.</td>
</tr>
</tbody>
</table>
### Conclusion:
Patients with electrical storm have a high risk of VT recurrence and mortality. Patient and procedure characteristics are consistent with and more complex procedures. In patients with electrical storm, acute procedural success is associated with improved 1-year survival.

#### 328 Martins R, et al.

**Aim:**
To determine the effectiveness of deep sedation in patients presenting with intractable electrical storm refractory to antiarrhythmic drugs.

**Inclusion:**

**Results:**
55 (47.4%) patients had electrical storm termination within 15 min and were considered acute responders to deep sedation. Pulmonary oedema before deep sedation (OR 3.31 [95% CI 1.001–10.97], P = 0.049) was the only independent predictor of non-response.

**Other findings:**
13 (23.6%) responders died, and 42 were discharged after 20.5 (IQR 13.0–32.0) days. 19 (34.5%) had a non-clinical VT only (P < 0.001 for all).

**Conclusion:**
Acute response to deep sedation, within 15 min, occurred in almost half of the cases and is an independent predictor of in-hospital mortality, VT recurrence, and 1-year mortality (P = 0.001).

#### 328 Haïssaguerre M, et al.

**Aim:**
To analyse impact of catheter ablation on patient survival.

**Inclusion:**

**Results:**
For patients with electrical storm, those without any inducible VT after ablation had a higher survival rate (86.3%) than did those with non-clinical VTs only (72.9%), those with VTs inducible at PES (51.2%), and not-tested patients (65.0%) (log-rank; P < 0.001 for all).

**Conclusion:**
Successful ventricular tachycardia ablation in patients with electrical storm reduces recurrences and improves survival.

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**334**

Vergara P, et al.

Success of ventricular tachycardia ablation in patients with electrical storm reduces recurrences and improves survival.

**Aim:**

**Inclusion:**
ShM with myocardial scar on mapping, catheter ablation of electrical storm. Exclusion: NA.

**Results:**
Other findings: 13 (23.6%) responders died, and 42 were discharged after 20.5 (IQR 13.0–32.0) days. 19 (34.5%) had a non-clinical VT only (P < 0.001 for all).

**Conclusion:**
In multivariate analysis, electrical storm remained an independent predictor of in-hospital mortality, VT recurrence, and 1-year mortality (P < 0.001).

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**335**

Komatsu Y, et al.

Catheter ablation of refractory ventricular fibrillation storm after myocardial infarction: a multicenter study.

**Aim:**

**Inclusion:**
VF storm (>3 episodes/24 h) after MI, who underwent RFCA. Exclusion: Patients with monomorphic VTs.

**Results:**
The focal triggers were found to originate from the scar border zone in 88 patients (80%). During in-hospital stay after ablation, VF storm subsided in 92 patients (84%). Overall, 30 (27%) in-hospital deaths occurred. The duration from the VF occurrence to the ablation procedure was associated with in-hospital mortality (OR for each 1-day increase, 1.11 [95% CI 1.03–1.20]; P = 0.008).

**Conclusion:**
In patients with MI presenting with focally triggered VF storm, RFCA of culprit triggers is life-saving and appears to be associated with short- and long-term freedom from recurrent VF storm. Mortality over the long-term follow-up is associated with the severity of underlying cardiovascular disease and comorbidities in this specific patient population.

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**334**

Vergara P, et al.

Success of ventricular tachycardia ablation in patients with electrical storm reduces recurrences and improves survival.

**Aim:**

**Inclusion:**
ShM with myocardial scar on mapping, catheter ablation of electrical storm. Exclusion: NA.

**Results:**
Other findings: 13 (23.6%) responders died, and 42 were discharged after 20.5 (IQR 13.0–32.0) days. 19 (34.5%) had a non-clinical VT only (P < 0.001 for all).

**Conclusion:**
In multivariate analysis, electrical storm remained an independent predictor of in-hospital mortality, VT recurrence, and 1-year mortality (P < 0.001).

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In patients with MI presenting with focally triggered VF storm, RFCA of culprit triggers is life-saving and appears to be associated with short- and long-term freedom from recurrent VF storm. Mortality over the long-term follow-up is associated with the severity of underlying cardiovascular disease and comorbidities in this specific patient population.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Authors</th>
<th>Title</th>
<th>Year of publication</th>
<th>Study type</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Aim</th>
<th>Results</th>
<th>Other findings</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>336</td>
<td>Knecht S, et al.</td>
<td>Long-term follow-up of idiopathic ventricular fibrillation ablation. A multicenter study. PMID: 19643313</td>
<td>2009</td>
<td>Prospective cohort multicentric</td>
<td>Patients with at least one documented VF, ablation of primary IVF initiated by short coupled PVC. Catheter ablation was guided by activation mapping of PVC or pace mapping during sinus rhythm.</td>
<td>NA</td>
<td>To evaluate the long-term follow-up of patients ablated for IVF.</td>
<td>38 patients (21 men) age 42 ± 13 years, refractory to a median of two anti-arrhythmic drugs. Triggering PVC originated from the right (n = 16), the left (n = 14), or both (n = 3) Purkinje systems and from the myocardium (n = 5).</td>
<td>During a median post-procedural follow-up of 63 months, seven (18%) of 38 patients experienced VF recurrence at a median of 4 months. Five of these seven patients underwent repeat ablation without VF recurrence. Survival free of VF was predicted only by transient bundle branch block in the originating ventricle during the electrophysiological study (P = 0.0001).</td>
<td>Ablation of IVF, targeted to its PVC triggers, is feasible and results in correct long-term outcomes. Short coupled PVC triggering VF originates predominantly from the Purkinje system and the RVOT.</td>
</tr>
<tr>
<td>326</td>
<td>Viskin S, et al.</td>
<td>Quinidine-responsive polymorphic ventricular tachycardia in patients with coronary heart disease. PMID: 30496367</td>
<td>2019</td>
<td>Retrospective observational study</td>
<td>Patients with at least one documented VF, ablation of primary IVF initiated by short coupled PVC. Catheter ablation was guided by activation mapping of PVC or pace mapping during sinus rhythm.</td>
<td>NA</td>
<td>To assess the effect of quinidine in patients with polymorphic VT in subacute phase of MI or after revascularization.</td>
<td>These arrhythmic storms were always refractory to conventional anti-arrhythmic therapy, including intravenous amiodarone, but invariably responded to quinidine therapy. In-hospital mortality was 17% for patients with arrhythmic storm. Patients treated with quinidine invariably survived to hospital discharge.</td>
<td>During-long term follow-up (of 5.6 ± 6 years, range 1 month to 18 years), three (16%) patients discharged without quinidine developed recurrent polymorphic VT. There were no recurrent arrhythmias during quinidine therapy.</td>
<td>Atrial fibrillation ablation. A multicenter study.</td>
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<tr>
<td>327</td>
<td>Viskin S, et al.</td>
<td>Quinidine-responsive out-of-hospital polymorphic ventricular tachycardia in patients with coronary heart disease. PMID: 31713589</td>
<td>2020</td>
<td>Observational retrospective analysis</td>
<td>Patients with at least one documented VF, ablation of primary IVF initiated by short coupled PVC. Catheter ablation was guided by activation mapping of PVC or pace mapping during sinus rhythm.</td>
<td>NA</td>
<td>To assess effect of quinidine in CAD patients presenting with out-of-hospital polymorphic VT without a recent coronary event or an obvious precipitating factor.</td>
<td>(1) Presence of CAD, and. (2) Unheralded spontaneous polymorphic VT (VT with changing QRS morphology and rates faster than 200 beats/min). (3) Patients 3–8 days after a MI or coronary revascularization intervention.</td>
<td>The polymorphic VT events were triggered by extrasystoles with short (376 ± 49 ms) coupling interval. Arrhythmic storms occurred in 72% of patients. These arrhythmic storms were generally refractory to conventional anti-arrhythmic therapy but invariably responded to quinidine therapy.</td>
<td>Quinidine-responsive polymorphic VT in patients with coronary heart disease.</td>
</tr>
<tr>
<td>329</td>
<td>Fudim M, et al.</td>
<td>Stellate ganglion blockade for the treatment of refractory ventricular arrhythmias. A systematic review and meta-analysis of published studies of a temporary</td>
<td>2019</td>
<td>Systematic review and meta-analysis</td>
<td>Patients with stellate ganglion blockade for the treatment of refractory ventricular arrhythmias.</td>
<td>NA</td>
<td>To conduct a systematic review and meta-analysis of published studies of a temporary Stellate ganglion blockade.</td>
<td>Unilateral (left)-sided stellate ganglion blockade in 85.7% (30 of 35); the remaining were bilateral.</td>
<td>Patients were 57 ± 17 years old and 69% were men with a high burden of VA.</td>
<td>Stellate ganglion block is associated with an acute reduction in the VA burden.</td>
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</table>
### Conclusions:

In patients with VT storm, bilateral cardiac sympathetic denervation is more beneficial than ICD. The symptomatic effect of cardiac sympathetic denervation extended beyond the acute post-sympathectomy period, with continued freedom from CD shocks in patients with bilateral sympathetic denervation in 48% of patients.

### Exclusion:

Refractory VT or VT storm.

### Other findings:

- Of the 120 patients taking anti-arrhythmic medications before cardiac sympathetic denervation, 39 (32%) no longer required them at follow-up.

### Results:

- One-year freedom from sustained VT/ICD shock and ICD shock, heart transplantation, and death were 58% and 50%, respectively. Cardiac sympathetic denervation reduced the burden of ICD shocks from a mean of 18.251 days pre-procedure to 0.6 post-procedure (P = 0.0026).
- The number of ICD shocks was reduced from a mean of 19.6 ± 2.9 post-procedure, survival free of ICD shock was 30% in the left cardiac sympathetic denervation group and 48% in the bilateral cardiac sympathetic denervation group. Shock-free survival was greater in the bilateral group than in the left cardiac sympathetic denervation group (P = 0.017).

### Meta-analysis:

- 1960 Enrolment period: 2009–2017 Number of patients: 26 Study type: Retrospective registry
- 384 Other findings: At mean follow-up of 307 ± 253 days post-procedure, survival free of ICD shock was 20% in the left cardiac sympathetic denervation group and 23% in the bilateral cardiac sympathetic denervation group. Shock-free survival was greater in the bilateral group than in the left cardiac sympathetic denervation group (P = 0.04).

### References:

- Vaseghi M, et al. 2017
- Le Pennec-Prigent S, et al. 2017
- Prigent S, Le Pennec. 2017

### Abbreviations:

ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CI, confidence interval; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IVF, idiopathic ventricular fibrillation; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; PES, percutaneous electrical stimulation; PFT, percutaneous left ventricular tachycardia; PCI, percutaneous coronary intervention; PMR, percutaneous mitral ring; PVC, premature ventricular contraction; RFA, radiofrequency catheter ablation; RV, right ventricle; VT, ventricular tachycardia; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT storm, ventricular tachycardia storm; VT/VF, ventricular tachycardia/ventricular fibrillation; VAD, ventricular assist device; VAB, ventricular assist device; VAD, ventricular assist device; VAD, ventricular assist device; VAD, ventricular assist device.
### 3.2. Long-term management

#### 3.2.1. Device therapy

#### 3.2.1.1. Implantable cardioverter defibrillator

**Table of Evidence 10** for Table of Recommendations for secondary prevention of sudden cardiac death

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>352</td>
<td>Connolly S, et al. [92] Canadian implantable defibrillator study (CIDS). A randomized trial of the implantable cardioverter defibrillator against amiodarone. PMID: 10725290 Year of publication: 2000</td>
<td>To study whether the implantation of an ICD as compared to amiodarone reduces mortality in survivors of CA secondary to VA or unmonitored syncope. Study type: RCT. Number of patients: 659 (VF 48). Enrolment period: 1990–1997 Study endpoints: Primary: all-cause mortality. Secondary: arrhythmic death. Inclusion: Documented VF; OHCA requiring defibrillation or cardioversion; documented sustained VT causing syncope; other documented sustained VT &gt; 150 b.p.m. causing pre-syncope in patients with LVEF &lt; 35%; all in the absence of recent acute MI (&lt; 72 h). Exclusion: ICD or amiodarone considered; high risk for ICD implantation, amiodarone for longer than six weeks, life expectancy &lt; 1 year, LQTS.</td>
<td>Results: Mean follow-up: 2.9 years (ICD) and 3 years (amiodarone). Mean LVEF: 34 ± 14%. NYHA I or II 39%. Non-significant reduction in the risk of death (ICD 8.3%/year vs. amiodarone 10.2%/year; relative RR 19.7%; 95% CI 7.7%; 57.8%; P = 0.094).</td>
<td>Conclusions: A 20% relative risk reduction occurred in all-cause mortality and a 33% reduction occurred in arrhythmic mortality with ICD therapy compared with amiodarone; this reduction did not reach statistical significance. Limitations: Thoracotomy for ICD implantation in 33, no ICD implanted in 18 patients.</td>
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<td>353</td>
<td>McAnulty J, et al. [93] (AVID investigators). Comparison of antiarrhythmic-drug therapy with ICDs in patients resuscitated from near-fatal ventricular arrhythmias — AVID trial. PMID: 9411221 Year of publication: 1997</td>
<td>To test whether the implantation of an ICD as compared to anti-arrhythmic drugs reduces mortality in survivors of life-threatening VA. Study type: RCT. Number of patients: 1016 (45% VF, 55% VT). Enrolment period: 1993–1997 Study endpoints: Overall mortality. Inclusion: Resuscitated from VF; sustained VT with syncope; or sustained VT with EF &lt; 40% and haemodynamic compromise. Exclusion: NA.</td>
<td>Results: Mean follow-up: 18 ± 12 months. Mean EF: 31%. NYHA III 9%. Overall survival greater in the ICD group (1-year 89% vs. 82%; 2-years 82% vs. 75%; 3-years 75% vs. 64%; P &lt; 0.02). Mortality reduction (95% CI): 39 ± 20%; 27 ± 21% 31 ± 21%.</td>
<td>Conclusions: Among survivors of VF or sustained VT causing severe symptoms, the ICD is superior to anti-arrhythmic drugs for increasing overall survival.</td>
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<tr>
<td>354</td>
<td>Kuck KH, et al. [94] Comparison of antiarrhythmic drug therapy with ICD in patients resuscitated from cardiac arrest—CASH trial. PMID: 10942742 Year of publication: 2000</td>
<td>To study whether the implantation of an ICD as compared to anti-arrhythmic drugs reduces mortality in survivors of cardiac arrest secondary to VA. Inclusion: Patients resuscitated from cardiac arrest secondary to documented VA. Exclusion: Cardiac arrest within 72 h of an</td>
<td>Results: Mean follow-up: 57 ± 34 months. Mean LVEF: 46 ± 19%. NYHA III 57%. Overall survival did not differ between ICD and</td>
<td>Conclusions: During long-term follow-up of cardiac arrest survivors, therapy with an ICD is associated with a 23% (non-significant) reduction of all-cause mortality rates when</td>
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</table>
Study type: RCT (ICD vs. amiodarone, propafenone or metoprolol 1:3).
Number of patients: 288 (VF 84%, VT 16%).
Enrolment period: 1987–1996

amiodarone/metoprolol group (HR 0.76; 97.5% CI upper bound 1.112; P = 0.081).
Crude death rate ICD 36.4% (95% CI 26.9%; 47.6%) vs. amiodarone/metoprolol 44.4% (95% CI 37.2%; 51.8%).

compared with treatment with amiodarone/metoprolol. The benefit of ICD therapy is more evident during the first 5 years after the index event.
Limitations: Propafenone assignment discontinued in 1992 because of 61% increased mortality.

355 Connolly SJ, et al. 
Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. PMID: 11102258
Year of publication: 2000

Aim: To assess the degree of consistency of benefit of the ICD vs. amiodarone among the three secondary preventive ICD trials, to provide the most precise estimate of the efficacy of the ICD, and to identify subgroups with different benefit from ICD therapy.
Study type: Meta-analysis.
Number of patients: 1866
Enrolment period: 1986–1997
Primary endpoint: All-cause mortality.

Inclusion: Criteria of the AVID, CASH and CIDS trials (see above).
Exclusion: NA.

Results: Significant reduction in death from any cause with the ICD; with a summary HR (ICD: amiodarone) of 0·72 (95% CI 0·60; 0·87; P = 0·0006). For the outcome of arrhythmic death, the HR was 0.50 (95% CI 0.37; 0.67; P < 0·0001). Survival was extended by a mean of 4.4 months by the ICD over a follow-up period of 6 years. Patients with LVEF <35% derived significantly more benefit from ICD therapy than those with better preserved left ventricular function.

Conclusions: Results from the three trials of the ICD vs. amiodarone are consistent with each other. There is a 28% reduction in the relative risk of death with the ICD that is due almost entirely to a 50% reduction in arrhythmic death.
3.2.1.2. Adding cardiac resynchronization therapy

**Table of Evidence 12** for Table of Recommendations for cardiac resynchronization therapy to implantable cardioverter defibrillator

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tbody>
<tr>
<td>370</td>
<td>Cleland JGF, et al.97</td>
<td>Aim:</td>
<td>RCT</td>
<td>813</td>
<td>2001–2003</td>
<td>Primary:</td>
<td>Heart failure symptoms</td>
<td>NYHA Class III and IV</td>
<td>Mean follow-up: 29.4 months.</td>
<td></td>
<td>Conclusions: In patients with heart failure and cardiac dyssynchrony, CRT improves symptoms and the quality of life and reduces complications and the risk of death. These benefits are in addition to those afforded by standard pharmacological therapy.</td>
</tr>
<tr>
<td></td>
<td>The effect of cardiac resynchronization on morbidity and mortality in heart failure. (CARE-HF). PMID: 15753115</td>
<td>To study the impact of CRT on top of optimal medical therapy as compared to optimal medical treatment alone on mortality and morbidity in heart failure patients. Study type: RCT. Number of patients: 813. Enrolment period: 2001–2003 Study endpoints: Primary: all-cause mortality or hospitalization for MACE. Secondary: death from any cause.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heart failure symptoms</td>
<td>NYHA Class III and IV</td>
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</table>

CI, confidence interval; CRT, cardiac resynchronization therapy; EF, ejection fraction; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LV, left ventricle; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; S-ICD, subcutaneous ICD.
### Table of Evidence 13 for Table of Recommendations for wearable cardioverter defibrillator

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tbody>
<tr>
<td>374</td>
<td>Garcia R, et al. 33257972</td>
<td>Aim: To provide contemporary real-world data on effectiveness, safety, compliance and acceptability of WCD. Study type: Multicentre observational retrospective and prospective study. Number of patients: 1157 (529 prospective). Enrolment period: May 2014–December 2016 (retrospective cohort). January 2017–March 2018 (prospective cohort). Study endpoints: Appropriate shock for VT/VF.</td>
<td>Inclusion: WCD indication due to: ICD removal due to device infection, bridge to heart transplantation, and CAD with LVEF &lt;30% early post-MI or after recent coronary revascularization. Exclusion: NA.</td>
<td>Results: Mean age 60 ± 11.5 years, 84.2% men, mean LVEF 27.3 ± 8.9%; CAD with LVEF &lt;30%; NYHA III–IV 42%. Median WCD use was 62 (37–97) days, 23.4 (22.2–23.8) h per day. 42 sustained VA occurred in 36 patients (3.1%) and only 18 (1.6%) received an appropriate shock (10 VT/8 VF).</td>
<td>Other findings: VAs occurred mainly in the first month of use. Eight inappropriate shocks occurred in eight patients (0.7%). 24 patients died during the WCD use (2.1%), nine while using the WCD: seven non-arrhythmic death, two electrical storm.</td>
<td>Conclusions: The WCD was effective for terminating VA, safe, and the compliance and tolerance of the patient to the device was high. Limitations: Observational study, low incidence of VA does not allow for identifying subgroups with higher risk.</td>
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<tr>
<td>375</td>
<td>Olgin JE, et al. 30280654</td>
<td>Aim: To determine the efficacy of the WCD in the early phase after MI in patients with reduced LVEF. Study type: Multicentre RCT (2:1 ratio). Number of patients: 2302 Enrolment period: 2008–2017. Study endpoints: Primary composite of SCD or death from VA at 90 days (arrhythmic death). Secondary: death from any cause; non-arrhythmic death.</td>
<td>Inclusion: Acute MI and LVEF ≤35% (measured ≥8 h after MI or PCI and &gt;48 h after CABG). Exclusion: Implanted ICD or unipolar pacemaker, clinically significant valvular disease, on haemodialysis, chest circumference too small or too large for WCD.</td>
<td>Results: Median follow-up: 90 days. Median wear time: 18 h/day (IQR 38–227). Mean LVEF: 28 ± 6%. NYHA II: 33%. Primary endpoint: No difference in arrhythmic death between WCD and control (1.6% vs. 2.4%; RR 0.67, 95% CI 0.37, 1.21; P = 0.18). Secondary endpoint: Reduction of death from any cause (3.1% vs. 4.9%; RR 0.64, 95% CI 0.43, 0.98, uncorrected P = 0.04). No difference in non-arrhythmic death (1.4% vs. 2.2%; RR 0.63, 95% CI 0.33, 1.19, uncorrected P = 0.15).</td>
<td>Other findings: Only 12 of 48 patients who died in the WCD wore the WCD at the time of death. 1.3% received an appropriate and 0.6% an inappropriate shock. Median WCD wear time 18 h.</td>
<td>Conclusions: In patients with recent MI and LVEF ≤35%, the WCD did not lead to a lower rate of arrhythmic death.</td>
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</table>

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; ICD, implantable cardioverter defibrillator; IQR, interquartile range; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; RR, relative risk; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia; WCD, wearable cardioverter defibrillator.
3.2.2. Special aspects of device therapy

3.2.2.1. Optimization of device programming

Table of Evidence 14 for Table of Recommendations for optimization of device programming

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>376</td>
<td>Scott PA, et al.100 Impact of prolonged implantable cardioverter-defibrillator arrhythmia detection times on outcomes: A meta-analysis. PMID: 24530622 Year of publication: 2014</td>
<td>Aim: To assess the impact of prolonged arrhythmia detection times on the rates of ICD shock therapy and other adverse outcomes. Study type: Meta-analysis. Number of patients: 488. Enrolment period: Literature search up to 2013. Study endpoints: Relative risk of death, syncope, and appropriate and inappropriate shocks.</td>
<td>Inclusion: Prospective studies that examined the impact of programming longer vs. shorter ICD arrhythmia detection times on clinical outcomes. Exclusion: Retrospective studies, lack of control group, use of historical controls, no specific statement on the programmed detection times.</td>
<td>Results: In the long detection group, there were significant reductions in mortality (RR 0.77; 95% CI 0.62–0.96), and inappropriate shocks (RR 0.50; 95% CI 0.39–0.65), without significant increase in syncope. (RR 1.23; 95% CI 0.84–1.79).</td>
<td>Other findings: No significant difference in the risk of syncope was observed with conventional vs. therapy reduction programming (P = 0.036) in the experimental group compared to the control group.</td>
<td>Conclusions: Higher detection rates, longer detection intervals, optimized SVT discriminators, and empiric ATP therapy compared to conventional parameters will prolong time to first shock without increasing incidence of arrhythmic syncope in primary prevention ICD recipients.</td>
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<td>377</td>
<td>Tan VH, et al.101 Impact of programming strategies aimed at reducing nonessential implantable cardioverter-defibrillator therapies on mortality: a systematic review and meta-analysis. PMID: 24446023 Year of publication: 2014</td>
<td>Aim: To assess the relationship between therapy reduction programming with the risks of death from any cause, ICD shocks, and syncope. Study type: Meta-analysis. Number of patients: 7687. Enrolment period: Literature search up to 2013. Study endpoints: Primary endpoints: all-cause mortality. Secondary endpoints: rates of syncope, appropriate shocks, and inappropriate shocks.</td>
<td>Inclusion: Therapy reduction programming studies with patient follow-up ≥6 months and data on patient mortality.</td>
<td>Results: Therapy reduction programming was associated with a 30% relative reduction in mortality (95% CI 16–41%; P &lt; 0.001).</td>
<td>Other findings: No significant difference in the risk of syncope was observed with conventional vs. therapy reduction programming (P = 0.5).</td>
<td>Conclusions: Therapy reduction programming results in a large significant, and consistent reduction in mortality, with no apparent increase in the risk of syncope.</td>
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<tr>
<td>378</td>
<td>Saeed M, et al.102 Programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock: results from the PROVIDE study. PMID: 24112717 Year of publication: 2014</td>
<td>Aim: To assess whether a combination of higher detection rates, prolonged detection intervals, optimized SVT discriminators, and empiric ATP therapy compared to conventional parameters will prolong time to first shock without increasing incidence of arrhythmia-related syncope in primary prevention ICD recipients. Study type: Multicentre randomized trial. Number of patients: 1670.</td>
<td>Inclusion: Patients who met primary prevention criteria for ICD or CRT-D implantation and were implanted with a St. Jude Medical ICD/CRT-D. Exclusion: History of spontaneous sustained VT or VF prior to the implant, inducible sustained VT at a rate below 180 bpm, presence of ICD or CRT-D device prior to the currently implanted device.</td>
<td>Results: The median time to first shock was significantly longer in the experimental group (13.1 months) than it was in the control group (7.8 months; HR 0.62; 95% CI 0.47–0.82; P = 0.0005).</td>
<td>Other findings: There was no increase in arrhythmic syncope (HR 1.64; 95% CI 0.69–3.90; P = 0.26), while the overall mortality was reduced (HR 0.7; 95% CI 0.50–0.98; P = 0.036) in the experimental group compared to the control group.</td>
<td>Conclusions: A combination of programmed parameters utilizing higher detection rate, longer detection intervals, empiric ATP, and optimized SVT discriminators reduced ICD therapies without increasing arrhythmic syncope and was associated with reduction in all-cause mortality among ICD patients.</td>
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<td>381</td>
<td>Barsheshet A, et al. 203</td>
<td>Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator.</td>
<td>Aim: To evaluate the effect of RV pacing on the long-term survival benefit of primary ICD therapy. Study type: Retrospective analysis. Number of patients: 1037 patients. Enrolment period: 1997–2001 Study endpoints: Mortality. Inclusion: All patients enrolled in the MADIT-II trial during an extended follow-up period of 8 years with available information on the cumulative rate of RV pacing. Exclusion: NA. Results: During the late follow-up phase (4–8 years), the long-term survival benefit of the ICD was maintained among patients with low RV pacing (HR 0.60; ( P &lt; 0.001 )) and attenuated among those with the high RV pacing (HR 0.89; ( P = 0.45 )). Other findings: An increased risk for late mortality associated with high vs. low RV pacing was evident only among patients without LBBB at enrolment (HR 1.63; ( P = 0.002 )). Conclusions: Among ICD recipients, high RV pacing is associated with a significant increase in the risk of long-term mortality and with attenuated device efficacy.</td>
<td>381</td>
<td>Barsheshet A, et al. 203</td>
<td>Long-term implications of cumulative right ventricular pacing among patients with an implantable cardioverter-defibrillator.</td>
<td>Aim: To evaluate the effect of RV pacing on the long-term survival benefit of primary ICD therapy. Study type: Retrospective analysis. Number of patients: 1037 patients. Enrolment period: 1997–2001 Study endpoints: Mortality. Inclusion: All patients enrolled in the MADIT-II trial during an extended follow-up period of 8 years with available information on the cumulative rate of RV pacing. Exclusion: NA. Results: During the late follow-up phase (4–8 years), the long-term survival benefit of the ICD was maintained among patients with low RV pacing (HR 0.60; ( P &lt; 0.001 )) and attenuated among those with the high RV pacing (HR 0.89; ( P = 0.45 )). Other findings: An increased risk for late mortality associated with high vs. low RV pacing was evident only among patients without LBBB at enrolment (HR 1.63; ( P = 0.002 )). Conclusions: Among ICD recipients, high RV pacing is associated with a significant increase in the risk of long-term mortality and with attenuated device efficacy.</td>
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<td>382</td>
<td>Wilkoff BL, et al. 204</td>
<td>Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial.</td>
<td>Aim: To determine the efficacy of dual-chamber pacing compared with back-up ventricular pacing in patients with standard indications for ICD implantation but without indications for anti-bradycardia pacing. Study type: Prospective multicentre, randomized trial. Number of patients: 506 Enrolment period: 2000–2002 Study endpoints: Freedom from death and absence of hospitalization for heart failure. Inclusion: ICD patients with LVEF ≤ 40%, no indication for anti-bradycardia pacemaker therapy, and no persistent atrial arrhythmias. Exclusion: NA. Results: One-year survival free of the composite endpoint was 83.9% for patients treated with VVI-40 compared with 73.3% for patients treated with DDDR-70 (relative hazard, 1.61; 95% CI 1.06–2.44). Conclusions: For ICD patients without indication for cardiac pacing and an LVEF ≤ 40%, dual-chamber pacing offers no clinical advantage over ventricular back-up pacing and may be detrimental by increasing the combined endpoint of death or hospitalization for heart failure.</td>
<td>382</td>
<td>Wilkoff BL, et al. 204</td>
<td>Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial.</td>
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<tr>
<td>383</td>
<td>Olshansky B, et al. 205</td>
<td>Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV study.</td>
<td>Aim: To compare the outcomes (all-cause mortality or heart failure hospitalization) of ICD patients randomized to either DDDR with the activated AV Search Hysteresis algorithm or VVI programming. Study type: Prospective multicentre, randomized trial. Number of patients: 988 Enrolment period: 2003–2004 Primary endpoints: All-cause mortality or heart failure hospitalization. Inclusion: Patients implanted with a VITALITY AVT ICD with &lt;20% RV pacing when programmed consistently to DDDR AVSH 60–130 for the first week. Exclusion: NA. Results: A total of 32 patients (6.4%) in the DDDR AVSH arm and 46 patients (9.5%) in the VVI arm died or were hospitalized for heart failure during a mean follow-up of 10.4 months (relative risk = 0.67; ( P = 0.072 )) in favour of DDDR AVSH. Conclusions: For ICD patients without indication for cardiac pacing, and an LVEF ≤ 40%, dual-chamber pacing offers no clinical advantage over ventricular back-up pacing and may be detrimental by increasing the combined endpoint of death or hospitalization for heart failure.</td>
<td>383</td>
<td>Olshansky B, et al. 205</td>
<td>Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV study.</td>
<td>Aim: To compare the outcomes (all-cause mortality or heart failure hospitalization) of ICD patients randomized to either DDDR with the activated AV Search Hysteresis algorithm or VVI programming. Study type: Prospective multicentre, randomized trial. Number of patients: 988 Enrolment period: 2003–2004 Primary endpoints: All-cause mortality or heart failure hospitalization. Inclusion: Patients implanted with a VITALITY AVT ICD with &lt;20% RV pacing when programmed consistently to DDDR AVSH 60–130 for the first week. Exclusion: NA. Results: A total of 32 patients (6.4%) in the DDDR AVSH arm and 46 patients (9.5%) in the VVI arm died or were hospitalized for heart failure during a mean follow-up of 10.4 months (relative risk = 0.67; ( P = 0.072 )) in favour of DDDR AVSH. Conclusions: For ICD patients without indication for cardiac pacing, and an LVEF ≤ 40%, dual-chamber pacing offers no clinical advantage over ventricular back-up pacing and may be detrimental by increasing the combined endpoint of death or hospitalization for heart failure.</td>
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<td>385</td>
<td>Gasparini M, et al.** Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: The ADVANCE III randomized clinical trial.</td>
<td>Aim: To determine whether using 30 of 40 intervals to detect VT (long detection) during spontaneous fast VT episodes reduces ATP and shock delivery more than 18 of 24 intervals (standard detection). Study type: Multicentre, randomized trial. Number of patients: 1902. Enrolment period: 2008–2010. Study endpoints: Primary endpoints: total number of ATPs and shocks delivered for all episodes. Secondary endpoints: inappropriate shocks, mortality, and syncopal rate. Inclusion: Patients at least 18 years old who underwent their first ICD or CRT-D implantation. Exclusion: Patients with prior ICD, patients with Brugada syndrome, LQTS, HCM, VA associated with reversible cause. Results: Long-detection group had 42 therapies per 100 person-years (95% CI 38–47) vs. 557 in the standard-detection group: 67 therapies per 100 person-years (95% CI 62–71); IR 0.63 (95% CI 0.51–0.78); P = 0.001. Other findings: Significant reduction in first occurrence of inappropriate shock in the long- vs. the standard-detection group (5.1 per 100 patient-years [95% CI 3.7–6.9] vs. 11.6 [95% CI 9.4–14.1]; IR 0.55 [95% CI 0.36–0.85]; P = 0.008). Conclusions: Among patients receiving an ICD, the use of a long- vs. standard-detection interval resulted in a lower rate of ATP and shocks, and inappropriate shocks. Limitations: Small number of deaths.</td>
<td></td>
<td>386</td>
<td>Moss AJ, et al.** Reduction in inappropriate therapy and mortality through ICD programming—MADIT RIT trial.</td>
<td>Aim: To determine whether programmed high-rate therapy or delayed therapy was associated with a decrease in the number of patients with a first occurrence of inappropriate ATP or shocks, as compared with conventional programming. Study type: Multicentre, randomized trial. Number of patients: 1500. Enrolment period: 2009–2011. Study endpoints: First occurrence of inappropriate therapy either ATP or shock. Inclusion: Patients older than 20 years with CAD or NICM, in sinus rhythm, who met approved guidelines for primary prevention with an ICD or CRT-D. Exclusion: permanent atrial fibrillation; CABG or PCI or had an enzyme-positive MI within 3 months before enrolment. Results: High-rate therapy and delayed ICD therapy, as compared with conventional device programming, were associated with reductions in a first occurrence of inappropriate therapy and reductions in all-cause mortality. Other findings: No significant differences in procedure-related adverse events among the three treatment groups. Conclusions: Programming of ICD therapies for tachyarrhythmias of 200 b.p.m. or higher or with a prolonged delay in therapy at 170 b.p.m. or higher, as compared with conventional programming, was associated with reductions on inappropriate therapy and all-cause mortality during long-term follow-up. Limitations: Small number of deaths.</td>
<td></td>
<td>387</td>
<td>Wilkoff BL, et al.** A comparison of empiric to physician-tailored programming of implantable cardioverter-defibrillators results from the prospective randomized multicenter EMPIRIC trial.</td>
<td>Aim: To determine whether a strategically chosen standardized set of programmable settings is at least as effective as physician-tailored choices, as measured by the shock-related morbidity of ICD therapy. Study type: Multicentre RCT. Number of patients: 900. Enrolment period: 2002–2003. Study endpoints: Shock-related morbidity. Inclusion: First placement of an ICD. Exclusion: Patients with permanent atrial fibrillation. Results: The adjusted percentages of both VT/VF (22.3% vs. 28.7%) and SVT episodes (11.9% vs. 26.1%) that resulted in a shock were non-inferior and lower in the EMPIRIC arm compared to the TAILORED arm. Other findings: The EMPIRIC trial had a significant reduction of patients with five or more shocks for all-cause (0.9% vs. 2.0%; P = 0.039) and true VT/VF (0.9% vs. 3.3%; P = 0.018). Conclusions: Standardized empiric ICD programming for VT/VF settings is at least as effective as patient-specific, physician-tailored programming, as measured by many clinical outcomes.</td>
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<td>Page</td>
<td>Reference</td>
<td>Aim</td>
<td>Study Type</td>
<td>Number of Patients</td>
<td>Study Duration</td>
<td>Study Endpoints</td>
<td>Inclusion/Exclusion</td>
<td>Results</td>
<td>Other Findings</td>
<td>Conclusions</td>
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<td>394</td>
<td>Wathen MS, et al. 109 Prospective randomized multicenter trial of empirical antitachycardia pacing versus shocks for spontaneous rapid ventricular tachycardia in patients with implantable cardioverter-defibrillators: PainFREE Rx II trial results. PMID: 15492306 Year of publication: 2004</td>
<td>To examine the efficacy, safety, and quality of life associated with treatment of fast VT with ATP compared with shocks in a broad ICD population.</td>
<td>Multicentre RCT.</td>
<td>634</td>
<td>2001–2002</td>
<td>Shock-related morbidity, Acceleration, episode duration, syncope, and SD were similar between arms.</td>
<td>ATP was effective in 229 of 284 episodes in the ATP arm (81%, 72% adjusted).</td>
<td>Compared with shocks, empirical ATP for fast VT is highly effective, is equally safe, and improves quality of life. ATP may be the preferred fast VT therapy in most ICD patients.</td>
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<td>388</td>
<td>Wilkoff BL, et al. 110 Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE (Primary Prevention Parameters Evaluation) study. PMID: 18687248 Year of publication: 2008</td>
<td>To demonstrate that strategically chosen ICD VT or VF detection and therapy parameters can reduce the combined incidence of device-delivered shocks, arrhythmic syncope, and untreated sustained symptomatic VT/VF (morbidity index).</td>
<td>Prospective, controlled, parallel, multicentre, non-randomized study.</td>
<td>700</td>
<td>2003–2005</td>
<td>Morbidity index, morbidity synchycardia index.</td>
<td>The PREPARE programming significantly reduced the morbidity index incidence density (0.26 events/patient-year for PREPARE study patients vs. 0.69 control cohort; P = 0.003). The PREPARE study patients were less likely to receive a shock in the first year compared with control patients (9% vs. 17%; P &lt; 0.01).</td>
<td>Strategically chosen VT/VF detection and therapy parameters can safely reduce shocks and other morbidities associated with ICD therapy in patients receiving an ICD for primary prevention indications. Limitations: Use of a historical control cohort instead of a randomized control design.</td>
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<td>400</td>
<td>Ploux S, et al. 111 Towards eradication of inappropriate therapies for ICD lead failure by combining comprehensive remote monitoring and lead noise alerts. PMID: 29858871 Year of publication: 2018</td>
<td>To assess the effectiveness of remote monitoring associated or not with a lead noise alert for early detection of ICD lead failure.</td>
<td>Prospective single-centre registry.</td>
<td>1958</td>
<td>2013–2017</td>
<td>ICD lead failure diagnosis.</td>
<td>95% lead failure diagnoses were made before any clinical complication occurred. Annual rate of inappropriate shock delivery of 0.04%.</td>
<td>The absence of a lead noise alert was associated with a 16-fold increase in the likelihood of initiating either a shock or ATP (OR 16.0; 95% CI 1.8–143.3; P = 0.01).</td>
<td>ICD remote monitoring with systematic review of all transmitted data is associated with a very low rate of inappropriate shocks related to lead failure.</td>
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<td>Study ID</td>
<td>Title and Authors</td>
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<td>Results</td>
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<td>401</td>
<td>Ellenbogen KA et al.</td>
<td>To compare the performance of lead integrity alert with conventional impedance monitoring for identifying lead system events and lead failures in lead families that differ from Fidelis.</td>
<td>Patients with lead integrity alert-enabled ICD and lead combinations followed in the CareLink remote monitoring network for lead system events and lead failures.</td>
<td>Results: Lead integrity alert identified &gt;66% more lead system events and &gt;67% more lead failures compared with conventional impedance monitoring and did not differ by lead family for lead system events (P = 0.573) or lead failure (P = 0.332).</td>
<td>Conclusions: Lead integrity alert markedly increased the detection rate of lead system events compared with conventional impedance monitoring.</td>
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<td>402</td>
<td>Swordlow CD et al.</td>
<td>To determine whether the lead integrity alert reduces inappropriate shocks in patients with Fidelis lead fractures.</td>
<td>Patients with Fidelis lead fractures confirmed by analysis of explanted leads who had the lead integrity alert downloaded.</td>
<td>Results: The lead integrity alert group had a 46% relative reduction in the percentage of patients with ≥1 inappropriate shock (lead integrity alert 38% vs. control 70%; P &lt; 0.001) and a 50% relative reduction in the percentage with ≥5 shocks (25% vs. 50%; P &lt; 0.001).</td>
<td>Conclusions: Lead integrity alert software download that upgrades previously implanted ICDs without surgical revision reduces inappropriate shocks caused by lead fractures.</td>
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<td>398</td>
<td>Guédon-Moreau L et al.</td>
<td>To examine prospectively the long-term safety and effectiveness of home monitoring of ICDs.</td>
<td>Patients in NYHA Class IV at the time of ICD implantation.</td>
<td>Results: The overall number of shocks delivered was significantly lower in the active (n = 193) than in the control (n = 11) groups (P &lt; 0.05). The proportion of patients who received inappropriate shocks was 52% lower in the active (n = 11) than in the control (n = 22) group (P &lt; 0.05).</td>
<td>Conclusions: Lang-term home monitoring of ICD is at least as safe as standard ambulatory follow-up with respect to a broad spectrum of major adverse events. It also lowered significantly the number of appropriate and inappropriate shocks delivered. Limitations: The investigators who made decisions regarding hospitalizations, which was a criterion to classify major adverse events, were aware of the assignments. No inclusion of CRT-D recipients.</td>
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<tr>
<th>ID</th>
<th>Authors</th>
<th>Title</th>
<th>Year of publication</th>
<th>Study Type</th>
<th>Number of Patients</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Results</th>
<th>Other Findings</th>
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<tr>
<td>395</td>
<td>Gulizia MM, et al.</td>
<td>A randomized study to compare Ramp versus Burst antitachycardia pacing therapies to treat fast ventricular tachyarrhythmias in patients with implantable cardioverter defibrillators: The PITAGORA ICD trial.</td>
<td>2009</td>
<td>Prospective, single-blind, parallel, randomized study.</td>
<td>206</td>
<td>Adults with ICD capable of detecting fast VT episodes via VF and of ATP treatment.</td>
<td>VA due to a reversible cause, Brugada syndrome, LQTS, HCM.</td>
<td>Burst terminated 75.2% of fast VT episodes, whereas ramp terminated 54.3%; ( P = 0.015 ).</td>
<td>Burst is significantly more efficacious than ramp in terminating fast VT episodes. ATP carries a low risk of acceleration or syncopal events.</td>
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<td>391</td>
<td>Gold MR, et al.</td>
<td>Primary results from the Understanding Outcomes with the S-ICD in Primary Prevention Patients with Low Ejection Fraction (UNTOUCHED) Trial.</td>
<td>2021</td>
<td>Prospective multinational study.</td>
<td>1111</td>
<td>Eighteen-month freedom from inappropriate shock was 95.9%. Inappropriate shock rate 3.1% at one year.</td>
<td>Pacing indication for bradycardia or CRT, history of sustained VT/VF, NYHA Class IV, life expectancy &lt;18 months.</td>
<td>This study demonstrates high efficacy and safety with contemporary S-ICD devices and programming despite the relatively high incidence of comorbidities in comparison to earlier S-ICD trials.</td>
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<td>392</td>
<td>Mesquita J, et al.</td>
<td>Effectiveness of subcutaneous implantable cardioverter-defibrillators and determinants of inappropriate shock delivery.</td>
<td>2017</td>
<td>Prospective registry.</td>
<td>54</td>
<td>The yearly rate of inappropriate shocks was 17.7%/year with single-zone detection vs. 4.8%/year with tiered-therapy programming (( P = 0.007 )).</td>
<td>Life expectancy &lt;1 year, acute MI on the previous 30 days, active infection, need for antichycardia and/or anti-bradycardia pacing, failing the initial screening test.</td>
<td>S-ICDs proved effective in preventing SCD. Tiered-therapy was independently associated with a lower rate of inappropriate shock delivery.</td>
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### Use of a discrimination algorithm to reduce inappropriate shocks with a subcutaneous implantable cardioverter-defibrillator.

**Aim:**
To evaluate the role of the S-ICD discrimination algorithm in reducing the incidence of spontaneous inappropriate shocks.

**Study type:**
Prospective non-randomized multicentre.

**Number of patients:**
314

**Enrolment period:**
Not reported.

**Study endpoints:**
Incidence of inappropriate shocks.

**Inclusion:**
Adult patients with subcutaneous ICD system.

**Exclusion:**
NA.

**Results:**
Inappropriate shocks occurred in 10.2% of patients with dual-zone programming as compared to 26.1% with single-zone programming ($P < 0.001$).

**Other findings:**
Mean time to appropriate therapy did not differ between compared groups, and there was only one episode of arrhythmic syncope in the cohort (single-zone group).

**Conclusions:**
The addition of a second shock zone with an active discrimination algorithm was strongly associated with a reduction in inappropriate shocks with the S-ICD system.

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### Real world evaluation of dual-zone ICD and CRT-D programming compared to single-zone programming: the ALTITUDE REDUCES study.

**Aim:**
To evaluate the frequency of appropriate and inappropriate shocks in an unselected patient population and to compare outcomes according to detection rate and to single- vs. dual-zone therapy programming with ATP and detection enhancements active.

**Study type:**
Retrospective analysis.

**Number of patients:**
15,991

**Enrolment period:**
2008–2010

**Study endpoints:**
First occurrence of inappropriate therapy, either antitachycardia pacing or shock.

**Inclusion:**
ICD or CRT-D patients enrolled in the LATITUDE remote monitoring system, programming data available from 30 days of implant, consistent programming from implant to first shock, minimum of six months follow-up if no shock episodes.

**Exclusion:**
NA.

**Results:**
The 12-month incidence of any shock was lower for dual- vs. single-zone programmed detection at rates $\leq 170$ b.p.m. and between 170 and 200 b.p.m. ($P < 0.001$). No detectable differences between single- and dual-zone shock incidence at detection rates $\geq 200$ b.p.m. ($P = 0.14$).

**Other findings:**
The lowest risk of appropriate and inappropriate shock was associated with dual-zone programming and detection rates $\geq 200$ b.p.m. (2.1%).

**Conclusions:**
Shock incidence is lowest with either single- or dual-zone detection $\geq 200$ b.p.m. For detection rates $<200$ b.p.m., dual-zone programming is associated with a reduction in the incidence of total shocks, appropriate shocks, and inappropriate shocks.

**Limitations:**
Retrospective analysis containing only Boston Scientific devices.

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**ATP**, anti-tachycardia pacing b.p.m., beats per minute; **CABG**, coronary artery bypass grafting; **CAD**, coronary artery disease; **CI**, confidence interval; **CRT**, cardiac resynchronization therapy; **CRT-D**, cardiac resynchronization therapy defibrillator; **HCM**, hypertrophic cardiomyopathy; **HR**, hazard ratio; **ICD**, implantable cardioverter defibrillator; **LBBB**, left bundle branch block; **LQTS**, long QT syndrome; **LVEF**, left ventricular ejection fraction; **MI**, myocardial infarction; **NA**, not applicable; **NICM**, non-ischemic cardiomyopathy; **NYHA**, New York Heart Association; **OR**, odds ratio; **PCI**, percutaneous coronary intervention; **PES**, programmed electrical stimulation; **RCT**, randomized controlled trial; **RR**, relative risk; **RV**, right ventricle; **SD**, sudden death; **S-ICD**, subcutaneous implantable cardioverter defibrillator; **SVT**, supraventricular tachycardia; **VA**, ventricular arrhythmia; **VT**, ventricular fibrillation; **VF**, ventricular fibrillation.
### Concomitant treatment to avoid inappropriate implantable cardioverter defibrillator therapy

#### Table of Evidence 15 for Table of Recommendations for concomitant treatment to avoid inappropriate implantable cardioverter defibrillator therapy

<table>
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<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tr>
<td>404</td>
<td>Miyazaki S, et al. 130 Catheter ablation of atrial tachyarrhythmias causing inappropriate implantable cardioverter-defibrillator shocks. PMID: 25061229 Year of publication: 2015</td>
<td>Aim: To evaluate the feasibility of RFCA therapy for atrial tachyarrhythmias causing inappropriate ICD shocks. Study type: Retrospective single-centre study. Number of patients: 108 Enrolment period: 2002–2011 Study endpoints: Inappropriate ICD shock.</td>
<td>Inclusion: ICD patients with inappropriate shock due to atrial tachyarrhythmias. Exclusion: NA.</td>
<td>Results: Among the 22 patients with atrial arrhythmias, 18 patients underwent RFCA because of arrhythmias causing inappropriate shocks (AF: 14, atrial flutter:2, AVNRT:2). During the median follow-up of 19.0 (9.5–37.3) months after the last procedure, no patients experienced any inappropriate shocks.</td>
<td>Other findings: No procedural complication.</td>
<td>Conclusions: RFCA is a feasible therapeutic option for treating atrial arrhythmias responsible for inappropriate shock(s) in patients with ICD. Limitations: Retrospective, analysis of single centre experience.</td>
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<tr>
<td>405</td>
<td>Mainigi SK, et al. 121 Usefulness of radiofrequency ablation of supraventricular tachycardia to decrease inappropriate shocks from implantable cardioverter-defibrillators. PMID: 22000775 Year of publication: 2012</td>
<td>Aim: To analyse the incidence of SVT leading to inappropriate ICD shocks and assess the efficacy of RFCA in decreasing these therapies. Study type: Retrospective analysis. Number of patients: 84 Enrolment period: 2005–2009 Study endpoints: Inappropriate ICD shock.</td>
<td>Inclusion: Patients with ICDs and non-AF SVT. Exclusion: Patients with documented preimplantation SVT.</td>
<td>Results: 95% of patients who underwent successful SVT ablation had no further inappropriate ICD therapies compared to 63% of patients in whom ablation was not performed during a mean follow-up of 20.7 ± 11.9 months.</td>
<td>Other findings: SVT is responsible for a significant number of inappropriate ICD therapies. RFCA is an effective strategy to substantially decrease subsequent inappropriate ICD therapies. Limitations: Retrospective analysis of a single-centre registry.</td>
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| 408                           | Gasparini M, et al. 122 Atrioventricular junction ablation in patients with atrial fibrillation treated with cardiac resynchronization therapy: positive impact on ventricular arrhythmias, implantable | Aim: To determine whether atrioventricular junction ablation in patients with CRT-D and with permanent AF has a positive impact on | Inclusion: CRT-D recipients with at least 3-month follow-up and device diagnostic data available. | Results: Mean (95% CI) annual rate of all-cause ICD shocks per 100 patient years was 8.0 (5.3–11.9) in AF+AV junction ablation, 43.6 (37.7–50.4) in AF+Drugs, 34.4 (Continued)
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<th>Cardiac Resynchronization Therapy (CRT-D) and ICD Shock Reduction</th>
<th>Year of publication: 2018</th>
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<tr>
<td>Study type:</td>
<td>Pooled analysis (2 RCTs and one prospective observational study)</td>
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<tr>
<td>Number of patients:</td>
<td>3358</td>
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<tr>
<td>Enrollment period:</td>
<td>Not reported</td>
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<td>Study endpoints:</td>
<td>All-cause ICD shocks, all-cause hospitalizations</td>
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**Exclusion:** NA

**Inclusion:** (32.5–36.5) in sinus rhythm patients resulting in IRR reductions of 0.18 (0.10–0.32) for AF + AV junction ablation vs. AF + Drugs ($P < 0.001$) and 0.48 (0.35–0.66) for AF + AV junction ablation vs. sinus rhythm ($P < 0.001$).

**Results:** P $<$ 0.001, vs. AF + Drugs and inappropriate ICD shocks (IRR 0.09 [0.04–0.21]; $P < 0.001$; vs. AF + Drugs).

**Conclusions:** Inappropriate ICD shocks, as well as fewer all-cause and heart failure hospitalizations.

**Limitations:** No randomized allocation of AV junction ablation or rate-control drugs.

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**410**


**Aim:** To evaluate the efficacy of AF ablation for paroxysmal AF for prevention of inappropriate ICD therapy.

**Study type:** Retrospective analysis.

**Number of patients:** 76

**Enrollment period:** 2006–2014

**Study endpoints:** Rate of inappropriate ICD therapy.

**Inclusion:** Patients with Brugada syndrome and ICD. Exclusion: NA.

**Results:** 14 Brugada syndrome patients with paroxysmal AF underwent pulmonary vein isolation. All eight patients with inappropriate therapy because of paroxysmal AF before pulmonary vein isolation had no recurrences of AF and no inappropriate therapy after ablation (mean follow-up period 3.1 ± 1.2 years).

**Conclusions:** RFCA is effective in patients with Brugada syndrome and an ICD, and prevents inappropriate ICD therapy owing to paroxysmal AF. Limitations: Retrospective, analysis of single-centre experience.

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AF, atrial fibrillation; AV, atrioventricular; AVNRT, atrioventricular nodal reentry tachycardia; CI, confidence interval; CRT-D, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IRR, incidence rate ratio; NA, not applicable; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; SVT, supraventricular tachycardia.
### Table of Evidence 16

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<thead>
<tr>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tr>
<td>Berg SK et al. (2020) 424</td>
<td>Cognitive behavioral therapy significantly reduces anxiety in patients with an ICD compared with usual care.</td>
<td>Randomized clinical trial.</td>
<td>88</td>
<td>2016–2018</td>
<td>Hospital Anxiety and Depression Scale-Anxiety mean score at 16 weeks.</td>
<td>ICD patients with a positive screening for anxiety.</td>
<td>NA.</td>
<td>The association between receipt of shocks and psychological distress was mediated by high ICD-related concerns.</td>
<td>Cognitive behavioral therapy provided by trained cardiac nurses plus usual care compared with usual care alone in patients with an ICD. Cognitive behavioral therapy provided by cardiac nurses compared with usual care.</td>
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<tr>
<td>Schulz SM et al. (2020) 425</td>
<td>To evaluate the efficacy of a web-based intervention vs. usual care for improving psychosocial well-being in ICD patients with elevated psychosocial distress.</td>
<td>Multicentre RCT.</td>
<td>118</td>
<td>2012–2015</td>
<td>A composite assessing change in heart-focused fear, depression, and mental quality of life six weeks after randomization.</td>
<td>ICD patients 18–75 years, at least mildly increased psychosocial distress.</td>
<td>Medical or technical reasons preventing participation in the web-based intervention, current suicidal ideation, severe cognitive deficit, inadequate command of German language, current psychiatric disorder.</td>
<td>Web-based intervention was superior to usual care in change from pre-intervention to six weeks (overprotective support; P = 0.004), pre-intervention to one year (depression; P = 0.004; self-management; P = 0.03; mobilization of social support; P = 0.047).</td>
<td>Although the primary outcome was neutral, this is the first RCT showing that web-based intervention can improve psychosocial well-being in ICD patients.</td>
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<td>van den Broek KC et al. (2020) 426</td>
<td>To examine the predictive value of general negative and positive affect, and depressive symptoms for mortality.</td>
<td>A prospective cohort study.</td>
<td>497</td>
<td>2018–2020</td>
<td>All-cause mortality.</td>
<td>ICD implantation, age between 18 and 80 years.</td>
<td>NA.</td>
<td>Negative affect was significantly related to all-cause mortality (HR 1.034; P = 0.002).</td>
<td>Epidemiological data on the predictive value of general negative and positive affect, and depressive symptoms for mortality.</td>
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<td>PMID: 21963213</td>
<td>Study type:</td>
<td>Depressive symptoms were also independently associated with an increased mortality risk (HR 1.031; P = 0.03).</td>
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<td>Year of publication: 2013</td>
<td>Number of patients: 591</td>
<td>Enrolment period: 2003–2009</td>
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<td>Study endpoints:</td>
<td>Association of covariates with mortality.</td>
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<td>Limitations:</td>
<td>Depression was assessed with a self-report questionnaire.</td>
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</table>

**Thylén I, et al.**

Concerns about implantable cardioverter-defibrillator shocks mediate the relationship between actual shocks and psychological distress.  

PMID: 26324839  
Year of publication: 2015

**Aim:** To examine whether the relationship between receipt of defibrillating shocks and psychological distress was mediated by patients’ concerns related to their ICD.  

**Study type:** Cross-sectional correlational design.  
**Number of patients:** 3067  
**Enrolment period:** Not reported.  
**Study endpoints:** Level of anxiety and depression (HADS score).

**Inclusion:** ICD patients from the Swedish ICD and Pacemaker Registry who agreed to participate in the study.  
**Exclusion:** NA.

**Results:** The association between receipt of shocks and psychologically distress was mediated by high ICD-related concerns.

**Other findings:** 26% of patients had high ICD-related concerns.

**Conclusions:** ICD-related concerns have a bigger impact on psychological distress than receipt of an actual shock. Assessing ICD-related concerns in clinical practice can identify patients at risk for psychological distress.  
**Limitations:** Cross-sectional design.

**Hauptman PJ, et al.**

Patient perceptions, physician communication, and the implantable cardioverter-defibrillator.  

PMID: 23420455  
Year of publication: 2013

**Aim:** To examine patient-physician communication at the time the decision is made to implant an ICD.  

**Study type:** Survey study.  
**Number of patients:** 41  
**Enrolment period:** Not reported.  
**Study endpoints:** Patient focus group findings and the results of standardized patient interviews.

**Inclusion:** ICD patients who had not experienced a SD event before ICD placement.  
**Exclusion:** NA.

**Results:** On a scale of 1 to 10, the mean (standard deviation) rating of the degree to which patients felt informed before the implant procedure was 5.7 (3.2).

**Other findings:** Cardiologists frequently did not address, minimized, or denied quality of life issues and long-term consequences of ICD placement.

**Conclusions:** Patient-physician communication about ICDs is characterized by unclear representation and omission of information to patients, with notable lack of attention to psychological and long-term risks.  
**Limitations:** Small sample size.

HR, hazard ratio; ICD, implantable cardioverter-defibrillator; NA, not applicable; RCT, randomized controlled trial; SD, sudden death.
### Table of Evidence 17 for Table of Recommendations for after implantable cardioverter defibrillator implantation in left ventricular assist device recipients

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Type of study</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>428</td>
<td>Cikes M, et al. [129] Cardiac implantable electronic devices with a defibrillator component and all-cause mortality in left ventricular assist device carriers: results from the PCHF-VAD registry. PMID: 31410955</td>
<td>Aim: To evaluate the incidence, clinical impact, and predictors of late VA in LVAD recipients. Study type: Observational study (PCHF-VAD registry). Number of patients: 448</td>
<td>Number of patients</td>
<td>Enrolment period: 2006–2018</td>
<td>Study endpoints: Primary endpoints: all-cause mortality. Secondary endpoints: cardiovascular mortality, hospitalization for heart failure, clinically significant VAs after LVAD implantation, device-related infections requiring antibiotic treatment, intracranial bleeding and non-cerebral bleeding events.</td>
<td>Inclusion: Patients implanted with a continuous-flow LVAD. Exclusion: Patients with pulsatile LVADs, patients with RV and biventricular assist devices, patients with missing ICD/CRT carrier status.</td>
<td>Results: Prevalence of either ICD or CRT-D carriers prior to LVAD implantation of 54%. A reduction of 36% in the risk of all-cause mortality in patients with an active defibrillator (HR 0.64; 95% CI 0.46–0.91; ( P = 0.012 )).</td>
<td>Other findings: Incident VA post-LVAD portended a 2.4- and 2.6-fold increased risk of all-cause and cardiovascular death, respectively.</td>
<td>Conclusions: In this LVAD cohort from a multicentre European registry, a significant reduction in the crude and adjusted risk of all-cause death was shown in patients carrying a CIED with an active defibrillator component during LVAD support. Limitations: The analysis was limited by typical features of retrospective registry studies.</td>
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<tr>
<td>434</td>
<td>Makki N, et al. [130] Meta-analysis of the relation of ventricular arrhythmias to all-cause mortality after implantation of a left ventricular assist device. PMID: 26361826</td>
<td>Aim: To evaluate the impact of ICD presence on mortality in continuous LVAD recipients. Study type: Meta-analysis. Number of patients: 1179</td>
<td>Enrolment period: Database search from 2001 to 2015</td>
<td>Study endpoints: Primary endpoints: association of VAs post LVAD implantation and all-cause mortality. Secondary endpoints: potential risk factors for all-cause mortality in patients with post LVAD-VAs.</td>
<td>Incidence: Observational studies exploring association of VAs post LVAD implantation with all-cause mortality, patients age &gt;18 years, studies of LVADs and no other types of ventricular assist devices. Exclusion: NA.</td>
<td>Results: Post-LVAD VAs were associated with increased risk of all-cause mortality after adjusting for competing risk factors at 60 days (adjusted OR 1.91, 95% CI 1.18–3.11; ( P = 0.001 )), 120 days (adjusted OR 1.97; 95% CI 1.81–3.85; ( P = 0.05 )) and 180 days (adjusted OR 2.04; 95% CI 1.81–4.15; ( P = 0.05 )).</td>
<td>Other findings: Using meta-regression analysis, only history of VA was a risk factor for mortality after LVAD implantation.</td>
<td>Conclusions: Post-LVAD VA was associated with increased risk of all-cause mortality.</td>
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</table>

CI, confidence interval; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy defibrillator; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; NA, not applicable; RV, right ventricle; VA, ventricular arrhythmia.
### 3.2.2.5. Complications of devices

#### Table of Evidence 18 for Table of Recommendations for prevention of after-implantable cardioverter-defibrillator complications

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study Type of study</th>
<th>Inclusion criteria (patients)</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>450</td>
<td>Defaye P, et al.131 Dual- vs. single-chamber defibrillators for primary prevention of sudden cardiac death; long-term follow-up of the Défibrillateur Automatique Implantable-Prévention Primaire registry. PMID: 28340096 Year of publication: 2017</td>
<td>Aim: To compare the short- and long-term safety and efficacy of single-chamber vs. dual-chamber ICD implanted for primary prevention indications. Study type: Retrospective analysis of registry. Number of patients: 2538 Enrolment period: 2002–2012 Study endpoints: Appropriate therapies, ICD-related morbidity, deaths from all and from specific causes. Inclusion: Consecutive patients with CAD or NICM referred to 12 high-volume French medical centres for primary prevention ICD implantation. Exclusion: NA.</td>
<td>Results: The rates of peri-procedural complications were 12.1% in the dual-chamber vs. 8.8% in the single-chamber ICD groups ($P = 0.008$). Other findings: The proportions of patients treated with $\geq 1$ appropriate therapies (24.7 vs. 23.8%) and $\geq 1$ inappropriate shocks (8.4 vs. 7.8%), and all-cause mortality (12.4 vs. 13.2%) were similar in both groups.</td>
<td>Other findings: The proportions of patients treated with $\geq 1$ appropriate therapies (24.7 vs. 23.8%) and $\geq 1$ inappropriate shocks (8.4 vs. 7.8%), and all-cause mortality (12.4 vs. 13.2%) were similar in both groups.</td>
<td>Conclusions: Dual-chamber ICDs were associated with higher rates of peri-implant complications and generator replacements, whereas the survival and rates of inappropriate shocks were similar in both groups. Limitations: Retrospective data collection from a registry.</td>
<td></td>
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<tr>
<td>451</td>
<td>Dewland RA, et al.132 Dual-chamber implantable cardioverter-defibrillator selection is associated with increased complication rates and mortality among patients enrolled in the NCDR implantable cardioverter-defibrillator registry. PMID: 21867834 Year of publication: 2011</td>
<td>Aim: To examine the prevalence and procedural complication rates of single- vs. dual-chamber ICD implantation in primary prevention patients. Study type: Meta-analysis. Number of patients: 104 049 Enrolment period: 2006–2007 Study endpoints: procedural complication defined as any adverse event occurring between the time of ICD implantation and hospital discharge. Inclusion: All patients undergoing first ICD implantation who were enrolled in the National Cardiovascular Data Registry (NCDR) ICD Registry. Exclusion: NA.</td>
<td>Results: Adverse events were more frequent with dual-chamber than with single-chamber device implantation (3.17% vs. 2.11%; $P &lt; 0.001$). Other findings: After adjusting for demographics, comorbidities, diagnostic test data, and ICD indication, the odds of any complication (OR 1.40; 95% CI 1.28–1.52; $P &lt; 0.001$) and in-hospital mortality (OR 1.45; 95% CI 1.20–1.74; $P &lt; 0.001$) were increased with dual-chamber vs. single-chamber ICD implantation.</td>
<td>Other findings: No difference in the rate of inappropriate therapy between the dual-chamber and single-chamber groups.</td>
<td>Conclusions: Dual-chamber device implantation was associated with increases in peri-procedural complications and in-hospital mortality compared with single-chamber defibrillator selection.</td>
<td></td>
</tr>
<tr>
<td>453</td>
<td>Chen B-W, et al.133 Are dual-chamber implantable cardioverter-defibrillators really better than single-chamber ones? A systematic review and meta-analysis.</td>
<td>Aim: To compare the clinical efficacy and complications of dual- and single-chamber ICDs. Study type: Meta-analysis. Inclusion: Studies with controlled design comparing dual- and single-chamber ICDs providing data on mortality, rate of patients with</td>
<td>Results: Pooled results from four non-randomized studies showed more complications in dual-chamber group. Other findings: No difference in the rate of inappropriate therapy between the dual-chamber and single-chamber groups.</td>
<td>Other findings: No conclusive superiority in terms of differentiating SVT from VT as well as all-cause mortality over S-ICDs, but were associated with</td>
<td>Conclusions: Dual-chamber ICDs showed no conclusive superiority in terms of differentiating SVT from VT as well as all-cause mortality over S-ICDs, but were associated with</td>
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<tr>
<td>PMID: 24532113</td>
<td>Number of patients: Six randomized studies including 2388 patients and 14 non-randomized studies including 113 931 patients.</td>
<td>inappropriate therapy, and ICD-related complications. Exclusion: NA.</td>
<td>(RR 1.83; 95% CI 1.32–2.54; <em>P</em> &lt; 0.001).</td>
<td>more complications. Limitations: Meta-analyses were conducted separately for randomized and non-randomized studies.</td>
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</table>

| 454 | Epstein LM, et al. Superion vena cava defibrillator coils make transvenous lead extraction more challenging and riskier. PMID: 23449433 | Aim: To determine the relationship between the presence of a superior vena cava coil and the risk of major complications and the difficulty of transvenous lead extraction. | Inclusion: Consecutive patients undergoing ICD lead extraction at nine high-volume centres. Exclusion: NA. | Results: 18 major complications were observed, all in cases involving dual-coil ICD leads (*P* = 0.031). No single-lead model predominated in the cases with complications. Other findings: After multivariate adjustment, dual-coil ICD leads were 2.6 times more difficult to remove (*P* < 0.0001). Conclusions: The presence of a superior vena cava coil is associated with significantly higher complication rates and transvenous lead extraction of dual-coil ICD leads is 2.6 times more difficult as compared with single-coil ICD. Limitations: Retrospective analysis. |

CAD, coronary artery disease; CI, confidence interval; ICD, implantable cardioverter defibrillator; NA, not applicable; NICM, non-ischemic cardiomyopathy; OR, odds ratio; RR, relative risk; S-ICD, subcutaneous implantable cardioverter defibrillator; SVT, supraventricular tachycardia; VT, ventricular tachycardia.
### 3.2.2.6. End-of-life issues

**Table of Evidence 19** for Table of Recommendations for end-of-life issues in after implantable cardioverter defibrillator carriers

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study Type of study Number of patients Enrolment period Study endpoints</th>
<th>Inclusion criteria (patients) Exclusion criteria</th>
<th>Main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>461</td>
<td>Stoelvael R, et al.¹³⁵</td>
<td>Aim: To examine trends in time (2007–2016) in how and when decisions are made about ICD deactivation, and to examine patient- and disease-related factors that may have influenced these decisions. <strong>Study type:</strong> Retrospective study. <strong>Number of patients:</strong> 380 <strong>Enrolment period:</strong> 2007–2016 <strong>Study endpoints:</strong> ICD deactivation discussions and ICD deactivation rates.</td>
<td><strong>Inclusion:</strong> Patients older than 18 years of age who had an ICD implanted and who died between 2007 and 2016. <strong>Exclusion:</strong> NA.</td>
<td>Results: ICD deactivation discussions increased from 6% for patients who had died between 2007 and 2009 to 35% for patients who had died between 2013 and 2016. ICD deactivation rates increased in these periods from 16% to 42%.</td>
<td>Other findings: Predictors of ICD deactivation were the occurrence of ICD deactivation discussions after implantation (OR 69.30, 95% CI 26.45–181.59), do not reanimate order (OR 6.83; 95% CI 4.19–11.12), do-not-intubate order (OR 6.41; 95% CI 3.75–10.96), and palliative care consultations (OR 8.67; 95% CI 2.76–27.21).</td>
<td>Conclusions: ICD deactivation discussions and deactivation rates have increased since 2007. ICDs remain active in the majority of patients at the end of life, some of whom experience shocks. <strong>Limitations:</strong> Retrospective study that relied on the medical records of patients.</td>
</tr>
</tbody>
</table>

Cl, confidence interval; ICD, implantable cardioverter defibrillator; NA, not applicable; OR, odds ratio.
4. Diagnostic evaluation, management, and risk stratification according to clinical presentation and known (likely) disease

4.1. Specific structural heart diseases

4.1.1. Coronary artery disease

4.1.1.1. Acute coronary syndromes and vasospasm

Table of Evidence 20 for Table of Recommendations for treatment of ventricular arrhythmias in acute coronary syndrome and vasospasm

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>554</td>
<td>Piccini JP, et al. (2008)</td>
<td>To investigate use of and outcomes associated with acute beta-blocker therapy in patients with acute MI complicated by sustained VT/VF and heart failure.</td>
<td>All consecutive patients with acute MI. Exclusion: Incomplete data.</td>
<td>Results: Of 5391 patients in the VAJANT Registry, sustained VT/VF occurred in 306 (5.7%), with an in-hospital mortality rate of 20.3%. Of those with sustained VT/VF, 55.2% were treated with intravenous or oral beta blockade in the first 24 h. After adjusting, beta-blocker therapy within 24 h was associated with decreased in-hospital mortality in patients with sustained VT/VF (RR 0.28; 95% CI 0.10–0.75; P = 0.013) without evidence of worsening heart failure. Patients with sustained VT/VF were less likely to receive beta-blockers within 24 h (P = 0.001).</td>
<td>Other findings: Multivariable logistic regression identified sustained VT/VF as a major predictor of in-hospital death (RR 4.18).</td>
<td>Conclusions: Sustained VT/VF was common after acute MI. In patients with sustained VT/VF, beta-blocker therapy in the first 24 h after acute MI was associated with decreased in-hospital mortality without worsening heart failure. Unfortunately, beta-blockers were underused acutely in patients with sustained VT/VF.</td>
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</table>

555 Nadaramee K, et al. (2007) Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. PMID: 10412741 Year of publication: 2000 Aim: To evaluate the efficacy of sympathetic blockade in treating electrical storm patients and compared with that of patients treated according to the ACS guidelines. Study type: Observational. Number of patients: 16. Inclusion: Patients with electrical storm associated with recent MI. Exclusion: Patients in group 1 (n = 27) received sympathetic blockade treatment: six left stellate ganglionic blockade, seven esmolol, and 14 propranolol. Results: The 1-week mortality rate was higher in group 2, 18 (82%) of the 22 patients died, all of refractory VF; six (22%) of the 27 group 1 patients died three of refractory VF (P < 0.0001). Other findings: Patients who survived the initial electrical storm event did well over the 1-year follow-up period: overall survival in group 1 was 67%, compared with 53% in group 2 (P < 0.0001). Conclusions: Sym pathetic blockade is superior to the anti-arrhythmic therapy recommended by the ACS guidelines in treating electrical storm patients. Our study emphasizes the role of increased sympathetic activity in the genesis of electrical storm. Sympathetic blockade—not class 1 anti-arrhythmic drugs—should be the treatment of choice for electrical storm.

557 Piccini JP, et al. (2011) Antiarrhythmic drug therapy for sustained ventricular arrhythmias complicating acute myocardial infarction. PMID: 20957985 Year of publication: 2011 Aim: To describe survival of patients with sustained VT/VF post-MI. Study type: Retrospective analysis. Number of patients: 3664. Inclusion: Sustained VT/VF post-MI. Patients received lidocaine (n = 664, 59.0%), amiodarone (n = 50, 4.4%), both (n = 110, 9.8%), or no anti-arrhythmic (n = 302, 26.8%). Exclusion: NA. Results: Among patients who survived 3 h, amiodarone was associated with increased mortality at 30 days (adjusted HR 1.71; 95% CI 1.02–2.86) and 6 months (adjusted HR 1.56; 95% CI 1.21–1.96), but lidocaine was not at 30 days (adjusted HR 1.19; 95% CI 1.04–1.36). Other findings: Among patients with acute MI complicated by sustained VT/VF who survived 3 h, amiodarone, but not lidocaine, is associated with an increased risk of death. Conclusions: Among patients with acute MI complicated by sustained VT/VF who survived 3 h, amiodarone, but not lidocaine, is associated with an increased risk of death.
<table>
<thead>
<tr>
<th>Page No.</th>
<th>Title</th>
<th>Authors</th>
<th>Year of publication</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Aim</th>
<th>Study type</th>
<th>Study endpoints</th>
<th>Results</th>
<th>Other findings</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>358</td>
<td>Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation.</td>
<td>Dorian P, et al.</td>
<td>2002</td>
<td>Out-of-hospital VF resistant to three shocks, iv epinephrine, and a further shock; recurrent VF after initially successful defibrillation.</td>
<td>NA</td>
<td>To compare iv lidocaine with iv amiodarone as an adjunct to defibrillation in victims of OHCA.</td>
<td>Randomized trial.</td>
<td>Number of patients: 347</td>
<td>Study endpoints: Mortality.</td>
<td>Indications: Out-of-hospital VF resistant to three shocks, iv epinephrine, and a further shock; recurrent VF after initially successful defibrillation.</td>
<td>Results: After treatment with amiodarone, 22.8% of 180 patients survived to hospital admission, as compared with 12.0% of 167 patients treated with lidocaine (OR 2.17; 95% CI 1.21–3.83).</td>
</tr>
<tr>
<td>325</td>
<td>Prophylactic lidocaine for myocardial infarction.</td>
<td>Marti-Camaj R, et al.</td>
<td>2015</td>
<td>acute MI patients.</td>
<td>–</td>
<td>To determine the clinical effectiveness and safety of prophylactic lidocaine in preventing death among people with MI.</td>
<td>Meta-analysis.</td>
<td>Number of patients: 37 RCTs involving 11948 participants.</td>
<td>Study endpoints: Mortality.</td>
<td>Results: Indications: Prophylactic lidocaine showed no significant differences regarding all-cause mortality (213/5879 (3.62%) vs. 199/5848 (3.40%); RR 1.02; 95% CI 0.83–1.22). Other findings: Cardiac mortality and prevention of VF was not observed for lidocaine.</td>
<td>Other findings: Cardiac mortality and prevention of VF was not observed for lidocaine.</td>
</tr>
<tr>
<td>365</td>
<td>Prognosis of variant angina manifesting as aborted sudden cardiac death.</td>
<td>Akar A-M, et al.</td>
<td>2016</td>
<td>patients with variant angina and aborted SCD.</td>
<td>–</td>
<td>To evaluate the long-term mortality and ventricular tardy arrhythmic events of variant angina with and without aborted SCD.</td>
<td>Retrospective observational cohort study.</td>
<td>Number of patients: 188 patients with variant angina and aborted SCD. Enrolment period: 1996–2014 Study endpoints: Mortality.</td>
<td>Indications: Aborted SCD due to VA, pulseless electrical activity-variant angina defined as spontaneous vasospasm or after ergonovine provocation. Exclusion: Poor neurological outcome of SCD; significant coronary stenosis; known heart disease.</td>
<td>Results: Indications: Predictors of aborted SCD manifestation included age (OR 0.980 by one year increase; 95% CI 0.96–1.00; P = 0.013), hypertension (OR 3.51; 95% CI 1.37–0.70; P &lt; 0.001), hyperlipidaemia (OR 0.38; 95% CI 0.25–0.58; P &lt; 0.001), family history of SCD (OR 3.27; 95% CI 1.37–0.7; P = 0.016), multivessel spasm (OR 2.06; 95% CI 1.33–3.19; P &lt; 0.001), and LAD spasm (OR 1.40; 95% CI 1.02–1.92; P = 0.04). Other findings: Over a median follow-up of 7.5 years, the incidence of cardiac death was significantly higher in patients with aborted SCD (24.1 per 1000 patient-years vs. 2.7 per 1000 patient-years; adjusted HR 7.26; 95% CI 4.21–12.3; P &lt; 0.001). A total of 24 patients with aborted SCD received ICDs. There was a non-significant trend of a lower rate of cardiac death in patients with ICDs than those without ICDs (P = 0.15).</td>
<td>Other findings: Over a median follow-up of 7.5 years, the incidence of cardiac death was significantly higher in patients with aborted SCD (24.1 per 1000 patient-years vs. 2.7 per 1000 patient-years; adjusted HR 7.26; 95% CI 4.21–12.3; P &lt; 0.001). A total of 24 patients with aborted SCD received ICDs. There was a non-significant trend of a lower rate of cardiac death in patients with ICDs than those without ICDs (P = 0.15).</td>
</tr>
<tr>
<td>566</td>
<td>Optimal medications and appropriate implantable cardioverter-defibrillator shocks in aborted sudden cardiac death due to coronary spasm.</td>
<td>Suski S, Kohno H</td>
<td>2018</td>
<td>patients who survived to be admitted to the hospital.</td>
<td>–</td>
<td>To analyze the incidence of ICD therapies in patients that received ICD after aborted SCD for coronary vasospasm.</td>
<td>Analysis of PubMed published cases of patients with vasospastic angina pectoris and ICD. Number of patients: 137</td>
<td>Study endpoints: Mortality.</td>
<td>Indications: Studies published in PubMed including cardiac arrest due to coronary vasospasm.</td>
<td>Results: Appropriate ICD shocks were observed in 24/163 (33.1%) of patients with aborted SCD due to coronary spasm during 41 months of follow-up. Only 15 (15.6%) of the 96 patients with ICDs received aggressive medical therapy, including two or three calcium-channel antagonists. Other findings: The rate of appropriate ICD shocks was significantly higher in Western countries than in Asian countries (42.9% vs. 19.3%; P &lt; 0.01), whereas the medications did not differ between the two regions. Appropriate ICD shocks successfully resuscitated 33 patients. Three patients died due to second serious fatal arrhythmias.</td>
<td>Other findings: The rate of appropriate ICD shocks was significantly higher in Western countries than in Asian countries (42.9% vs. 19.3%; P &lt; 0.01), whereas the medications did not differ between the two regions. Appropriate ICD shocks successfully resuscitated 33 patients. Three patients died due to second serious fatal arrhythmias.</td>
</tr>
</tbody>
</table>
Enrolment period: 1994–2016

Study endpoints: Appropriate ICD shocks.

**Aim:**
To evaluate the clinical outcomes of patients with a history of life-threatening VA due to coronary vasospasm with various medical interventions, as well as the need for ICD placement in the setting of optimal medical therapy.

**Study type:**
A multicentre EU retrospective survey.

**Number of patients:**
49

**Study endpoints:**
Appropriate ICD therapies, SCD.

**Inclusion:**
Patients with cardiac arrest due to VF in the setting of coronary vasospasm.

**Exclusion:**
NA.

**Results:**
ICD implantation was performed in 44 (89.8%). During follow-up (59 [17–117] months), appropriate ICD shocks were documented in 12. In 8/12 (66.6%) no more ICD therapies were recorded after optimizing calcium-channel blocker therapy.

**Other findings:**
SCD occurred in one patient without ICD. Treatment with beta-blockers was predictive of appropriate device discharge. Conversely, non-dihydropyridine calcium-channel blocker therapy was significantly protective against VAs.

**Conclusions:**
Patients with life-threatening VA secondary to coronary spasm are at particularly high risk for recurrence, especially when insufficient medical therapy is administered. Non-dihydropyridine calcium-channel blockers are capable of suppressing episodes whereas beta-blocker treatment is predictive of VAs. Ultimately, in spite of medical intervention, some patients exhibited arrhythmogenic events in the long term, suggesting that ICD implantation may still be indicated for all.

ACS, acute coronary syndrome; CI, coefficient interval; HR, hazard ratio; LAD, left anterior descendant; MI, myocardial infarction; NA, not applicable; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
Conclusions:
This study demonstrates the linkage between attenuation of LV enlargement by captopril after MI and improved clinical outcome. Irrespective of treatment assignment, baseline LV systolic area and percent change in area were strong predictors of cardiovascular mortality and adverse cardiovascular events.

571 Søholm H, et al.

Improvement in systolic function group was seen in 58 patients (64%), and 11 patients (79%) with severe systolic dysfunction at baseline were reclassified as having preserved or mild/moderate systolic dysfunction at follow-up. Other findings: Irrespective of baseline LVEF, deterioration in systolic function group was noted in 14 patients (11%), but no patients declined from preserved to severe systolic dysfunction.

Conclusions: The majority of patients with severely depressed LVEF immediately after STEMI significantly improved systolic function after 3 months. This study emphasizes the importance of a repeated LV function assessment at follow-up in patients with mild/moderate or severe systolic dysfunction after STEMI, but reassessment may not be needed in patients with preserved LVEF at baseline.

572 St John Sutton M, et al.

At 1 year, LV end-diastolic and LV end-systolic areas were larger in the placebo than in the captopril group (P = 0.038; P = 0.015, respectively), and percent change in cavity area was greater in the captopril group (P = 0.005). 69 patients with adverse cardiovascular events were in the placebo group compared with 42 patients in the captopril-treated group (a RR of 35%; P = 0.010).

Conclusions: Irrespective of treatment assignment, baseline LV systolic area and percent change in area were strong predictors of cardiovascular mortality and adverse cardiovascular events.

573

Table of Evidence 21 for Table of Recommendations for risk stratification and treatment of ventricular arrhythmia early after myocardial infarction

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>570</td>
<td>St John Sutton M, et al.194</td>
<td>Arm: To assess whether captopril would attenuate progressive LV enlargement in patients with LV dysfunction after acute MI and, if so, whether this would be associated with improved clinical outcome. Study type: Substudy of the SAVE RCT. Number of patients: 512</td>
<td>Inclusion: Patients (between 21 and 80 years) with LVEF ≤40% but without overt heart failure or symptoms of myocardial ischemia. Patients were randomly assigned to placebo (n = 259) or captopril (n = 253). Exclusion: Failure to undergo randomization within 16 days after the MI; relative contraindication to the use of an ACE inhibitor or the need for such an agent to treat symptomatic congestive heart failure or systemic hypertension; a serum creatinine ≥2.5 mg/dL, limited survival.</td>
<td>Results: At one year, LV end-diastolic and LV end-systolic areas were larger in the placebo than in the captopril group (P = 0.038; P = 0.015, respectively), and percent change in cavity area was greater in the captopril group (P = 0.005). 69 patients with adverse cardiovascular events were in the placebo group compared with 42 patients in the captopril-treated group (a RR of 35%; P = 0.010).</td>
<td>Other findings: Irrespective of treatment assignment, baseline LV systolic area and percent change in area were strong predictors of cardiovascular mortality and adverse cardiovascular events.</td>
<td>Conclusions: This study demonstrates the linkage between attenuation of LV enlargement by captopril after MI and improved clinical outcome.</td>
</tr>
<tr>
<td>571</td>
<td>Sahalin M, et al.195</td>
<td>Arm: To assess changes in LV function from baseline to follow-up after 3 months to identify predictors of change in LV function and evaluate whether repeated imaging is necessary. Study type: Substudy of the POSTCON-II RCT. Number of patients: 138</td>
<td>Inclusion: Patients with first STEMI were treated with primary PCI and examined with 2D-echocardiography and CMR at baseline (&lt;72 h) and at a 3-month follow-up. Exclusion: Unconsciousness, cardiogenic shock, atrial fibrillation, stent thrombosis, renal insufficiency, or previous coronary artery bypass graft surgery.</td>
<td>Results: Improvement in systolic function group was seen in 58 patients (64%), and 11 patients (79%) with severe systolic dysfunction at baseline were reclassified as having preserved or mild/moderate systolic dysfunction at follow-up.</td>
<td>Other findings: Irrespective of baseline LVEF, deterioration in systolic function group was noted in 14 patients (11%), but no patients declined from preserved to severe systolic dysfunction.</td>
<td>Conclusions: The majority of patients with severely depressed LVEF immediately after STEMI significantly improved systolic function after 3 months. This study emphasizes the importance of a repeated LV function assessment at follow-up in patients with mild/moderate or severe systolic dysfunction after STEMI, but reassessment may not be needed in patients with preserved LVEF at baseline.</td>
</tr>
<tr>
<td>576</td>
<td>Daubert MA, et al.196</td>
<td>Arm: To evaluate the extent and time course of cardiac remodelling among patients with a reduced LVEF after STEMI in the current therapeutic era. Study type: Secondary analysis of the PRESERVATION I trial (RCT). Number of patients: 145</td>
<td>Inclusion: Patients who had a post-PCI echocardiogram with at least moderately reduced LV systolic function (LVEF ≤ 40%). Exclusion: EF &gt; 40%.</td>
<td>Results: transthoracic echocardiograms were performed immediately post-PCI and at 1, 3, 6, and 12 months following STEMI. 74% had at least moderately reduced systolic function (mean LVEF 32 ± 5%) immediately after primary PCI. Mean EF.</td>
<td>Other findings: At 1 month, 46% demonstrated reverse remodelling, which was associated with a significantly lower rate of death, recurrent MI, and repeat cardiovascular hospitalization at one year (HR 0.64; 95% CI 0.19–0.99).</td>
<td>Conclusions: The first month following primary reperfusion is a critical period during which the greatest degree of cardiac remodelling occurs. Limitations: The reduction in LV function was presumed to be acute due to the index infarct; however, EF was not evaluated until after primary PCI.</td>
</tr>
</tbody>
</table>
Enrolment period: 2012–2015

Study endpoints:
A reduction in LV end-diastolic volume index at 6 months.

Post-PCI: $32.4 \pm 4.6$.
1 month: $36.4 \pm 6.9$.
3 months: $37.7 \pm 7.2$.
6 months: $37.9 \pm 7.8$.
12 months: $37.5 \pm 7.9$.

and no historical information on prior EF was available. Medication doses and dose titrations were not evaluated. Procedures such as implantable defibrillators and CRT were not individually captured.

577 Chew DS, et al. 147
Change in left ventricular ejection fraction following first myocardial infarction and outcome. PMID 22979879
Year of publication: 2018

Aim:
To assess the prognostic value in LVEF change post-MI.

Study type:
Post-hoc analysis of three independent MI cohorts (REFINE, CARISMA, ISAR).

Number of patients:
REFINE: 322
CARISMA: 312
ISAR: 2343

Study endpoints:
Primary endpoints: REFINE = a cardiac death or resuscitated SCA. CARISMA = electrocardiography-documented SCA. ISAR = all-cause mortality.
Secondary endpoints: REFINE = all-cause and cause-specific mortality. CARISMA = all-cause mortality and cardiac death. ISAR = cardiac and fatal SCA.

Inclusion:
Patients with first presentation MI.

Note: There is heterogeneity of patient inclusion criteria and among the three independent MI cohorts. Exclusion: NA.

Results:
In REFINE, patients with no LVEF recovery had a higher risk of SCA (HR 5.8; 95% CI 2.1–16.6; $P = 0.001$) and death (HR 3.9; 95% CI 1.5–10.1; $P < 0.001$), independent of revascularization, baseline LVEF, and medical therapy compared with patients with recovery. Similar findings were observed in the other cohorts.

Other findings:
The absence of LVEF recovery is independently associated with increased risk of serious events in follow-up, including a nearly six-fold risk of non-fatal and fatal cardiac arrest, or over a four-fold risk of all-cause mortality.

Conclusions:
The degree of improvement in LVEF over the initial 3 months after a first MI is a consistent predictor of cardiac mortality across three patient cohorts. Reassessment of LVEF too early following MI (i.e. <6 weeks following index MI) may not adequately discriminate between myocardial stunning and adverse LV remodelling; whereas, LVEF reassessment beyond six weeks more likely reflects presence or absence of adverse remodelling.

Limitations:
LVEF recovery was treated categorically instead of as a continuum. The time to LVEF reassessment post-MI varied across the three MI cohorts (from 2 to 8 weeks).

ACE, Angiotensine converting enzyme; CI, confidence interval; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; EF, ejection fraction; HR, hazard ratio; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCA, sudden cardiac arrest; STEMI, ST elevation myocardial infarction.
4.1.1.3. Chronic coronary artery disease

**Table of Evidence 22** for Table of Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in chronic coronary artery disease

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>149</td>
<td>Gatzoulis KA, et al. [149] Prognostic value of programmed ventricular stimulation for sudden death in selected high risk patients with structural heart disease and preserved systolic function. PMID: 25150471 Year of publication: 2014</td>
<td>Aim: To evaluate the prognostic value of PES in high-risk patients with SHD and preserved LV function. Study type: Retrospective, observational study. Number of patients: 111 Enrolment period: 2004–2011 Study endpoints: Appropriate ICD therapies, SCD, recurrent (pre-)syncope.</td>
<td>Inclusion: CAD and DCM patients with preserved LVEF and unexplained syncope (n=26), NSVT (≥3 beats, ≥120 b.p.m) or ≥3 PVCs/24 h. Exclusion: NA.</td>
<td>Results: PES was performed with up to three extras, three basic drive cycle length from RV apex and RVOT. SMVT was induced in 23 (33%) CAD patients and 8 DCM patients. VF was induced in 5 DCM patients. All but three inducible DCM patients received an ICD. Mean follow-up was 55 months. ICD appropriate therapies occurred in 12/23 (52%) CAD patients and 8/10 (80%) DCM patients. No SCD or recurrent syncope/pre-syncope in non-inducible patients.</td>
<td>Other findings: One inducible DCM patient who refused ICD implantation, experienced SCD.</td>
<td>Conclusions: High-risk patients with DCM or CAD and preserved LVEF who were inducible for VT/VF by PES had high rate of appropriate ICD therapies on follow-up. Non-inducible patients did not experience recurrence of syncope or SCD. Limitations: Non-randomized, retrospective study. Relatively short ICD detection programmed.</td>
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<tr>
<td>587</td>
<td>Olshansky B, et al. [587] Clinical significance of syncope in the electrophysiologic study versus electocardiographologic monitoring (ESVEM) trial. PMID: 10220637 Year of publication: 1999</td>
<td>Aim: To test the hypothesis that VT induced at EPS in patients with syncope has the same prognosis as those with spontaneous sustained VT or VF. Study type: Subgroup analysis of a randomized prospective trial. Number of patients: 486 Study endpoints: Total mortality.</td>
<td>Inclusion: (1) documented VT of at least 15 s in duration or VF (or resuscitation from cardiac arrest), or (2) syncope of unclear cause and inducible VT. Exclusion: NA.</td>
<td>Results: Of all patients randomly assigned, arrhythmic death and total mortality rates were the same for those with syncope alone, with VT and syncope, with VT alone, or with VF. At one year, arrhythmic and total mortality rate for all patients was 21% and 24%, respectively; for patients with syncope alone, 30% and 29%, respectively (P=NS). At four years, arrhythmic death and total mortality rate for all patients was 33% and 42%, respectively; for patients with syncope alone, 37% and 42%, respectively (P=NS).</td>
<td>Conclusions: Syncope, associated with induced ventricular tachyarrhythmias at electrophysiologic testing, indicates high risk for death, similar to that of patients with documented spontaneous ventricular tachyarrhythmias.</td>
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<td>357</td>
<td>Moss AJ, et al. [357] Prophylactic ICD in patients with myocardial infarction and reduced ejection fraction. PMID: 11907286 Year of publication: 2002</td>
<td>Aim: To evaluate the effect of an ICD on survival in patients with reduced LVEF after MI. Study type: RCT ICD vs. control (3:2 ratio). Number of patients: 1322 Enrolment period: 1997–2001</td>
<td>Inclusion: MI &gt;1 month before entry, LVEF &lt;30%. Exclusion: NYHA Class IV, MI within the past month, coronary revascularization within the preceding 3 months, advanced cerebrovascular disease.</td>
<td>Results: Mean follow-up: 20 months. Mean EF: 24% NYHA II 35%. Mortality reduction by ICD: 14% vs. control. 95% CI 0.51; 0.93. P=0.0016.</td>
<td>Conclusions: In patients with prior MI and LVEF &lt;30%, prophylactic ICD implantation improves survival.</td>
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<tr>
<th>359</th>
<th>Bardy GH, et al.</th>
<th>Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. PMID: 15659722 Year of publication: 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aim:</strong> To compare the efficacy of amiodarone vs. shock-only single-lead ICD in mortality reduction in patient with mild to moderate heart failure. Study type: RCT, three arms: ICD, amiodarone, or placebo. Number of patients: 2521 Enrolment period: 1997–2001 Study endpoints: Primary: death from any cause.</td>
<td><strong>Inclusion:</strong> CAD or NCM, LVEF &lt;35%; NYHA II or III. Exclusion: NA.</td>
<td><strong>Results:</strong> Median follow-up: 45.5 months. Median LVEF 25%. NYHA II 70%. Compared to placebo, ICD decreased mortality by 23% (placebo 244 deaths, 29%; ICD 182; HR 0.77; 97.5% CI 0.62–0.96; P = 0.007). No difference between placebo and amiodarone (amiodarone 240 deaths; 28%; HR 0.86–1.30; P = 0.53).</td>
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<td><strong>Aim:</strong> To test whether anti-arrhythmic therapy guided by EPS can reduce SD in patients with CAD, LV dysfunction, and spontaneous unsustained VT. Study type: RCT. Number of patients: 2022/704 randomized after inducible VT. Enrolment period: 1990–1996 Study endpoints: Primary: cardiac arrest or death from arrhythmia. Secondary: death from all causes, death from cardiac causes, and spontaneous, sustained VT.</td>
<td><strong>Inclusion:</strong> CAD, LVEF &lt;40% asymptomatic NSVT (≥3 beats). (a) patients inducible at EPS were randomized to either anti-arrhythmic drugs or no medication (followed in a registry). (b) patients with anti-arrhythmic drugs inducible at EPS; if still inducible patients could be recommended ICD implantation. Exclusion: History of syncope, sustained VT or VF &gt;48 h after MI.</td>
<td><strong>Results:</strong> Mean follow-up: 39 months. Mean LVEF: 30%. Reduction of primary endpoint in the EP-guided anti-arrhythmic drug group as compared to no anti-arrhythmic drugs (RR 0.73; 95% CI 0.53; 0.99). No difference in overall mortality EP-guided anti-arrhythmic drug 42%, no anti-arrhythmic drug 48% (RR 0.8; 95% CI 0.64; 1.01). Reduction of primary endpoint in the ICD recipients (RR 0.24; 95% CI 0.13; 0.45; P &lt; 0.001).</td>
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<td><strong>Aim:</strong> To determine whether the suppression of ventricular ectopy by flecainide or encainide in post-infarct patients reduces the incidence of SD. Study type: Randomized double-blind placebo-controlled. Number of patients: 1498 Enrolment period: 1987–1989 Study endpoints: Primary: death or cardiac arrest with resuscitation.</td>
<td><strong>Inclusion:</strong> Post-MI patients (6 days to 2 years post-MI) with ≥6 PVCs per hour on Holter ECG, LVEF &lt;55% if &lt;90 days post-MI and LVEF &lt;40 if &gt;90 days post-MI. Exclusion: VT &gt;14 beats and &gt;120 b.p.m.</td>
<td><strong>Results:</strong> Mean follow-up 10 months. Study terminated by DSMB because of excess mortality on encainide and flecainide. 59 patients died of arrhythmia (43 on drug vs. 16 placebo; P = 0.0004), 22 of non-arrhythmic cardiac cause (17 vs. 5; P = 0.01), and eight of non-cardiac cause (3 vs. 8).</td>
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<td><strong>Aim</strong></td>
<td>To assess the effect of amiodarone on the risk of incessant VF or arrhythmic death among survivors of MI with frequent or repetitive PVCs (&gt;10 PVCs per hour; &gt;1 run of VT).</td>
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<tr>
<td><strong>Study type</strong></td>
<td>Randomized double-blind placebo-controlled trial.</td>
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<tr>
<td><strong>Number of patients</strong></td>
<td>1202</td>
<td></td>
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<tr>
<td><strong>Enrollment period</strong></td>
<td>1990–1995</td>
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<tr>
<td><strong>Primary endpoints</strong></td>
<td>Primary: resuscitated VF or arrhythmic death.</td>
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<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Secondary: cardiac mortality, all-cause mortality, ventricular arrhythmias, sedation, bradycardia, sinus pauses ≥3 s, second- or third-degree AV-blocking QT, thyrotoxicosis.</td>
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<tr>
<td><strong>Exclusion</strong></td>
<td>Past or ongoing amiodarone treatment, bradycardia &lt;50 b.p.m., sinus pauses &gt;2.5 s, second- or third-degree AV-block, QT, thyrotoxicosis.</td>
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<tr>
<td><strong>Inclusion</strong></td>
<td>6–45 days post-MI and a mean of 10 or more PVCs or one run of VT &gt;120 b.p.m. for 3–10 beats in &gt;18 h Holter recording.</td>
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<tr>
<td><strong>Results</strong></td>
<td>Mean follow-up: 1.79 years.</td>
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<tr>
<td><strong>Other findings</strong></td>
<td>In the intention-to-treat analysis, primary outcome events occurred in 24 (6.9%) patients in the placebo group and in 15 (4.5%) in the amiodarone group (38.2% [95% CI 2.1–62.6]; P = 0.029).</td>
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<tr>
<td><strong>Conclusions</strong></td>
<td>Amiodarone reduces the incidence of VF or arrhythmic death among survivors of acute MI with frequent or repetitive PVCs.</td>
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<tr>
<td><strong>Aim</strong></td>
<td>To assess the effect of amiodarone on all-cause mortality, cardiac mortality, and anti-arrhythmic death in post-MI patients with depressed LVEF.</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td>Randomized double-blind placebo-controlled.</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>1483</td>
</tr>
<tr>
<td><strong>Enrollment period</strong></td>
<td>1990–1995</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td>Primary: all-cause mortality.</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td>Secondary: cardiac mortality, all-cause mortality, ventricular arrhythmias, sedation, bradycardia, sinus pauses ≥3 s, second- or third-degree AV-blocking QT, thyrotoxicosis.</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td>Post-MI patients with LVEF ≤40% 5–21 days after admission to coronary care unit.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Median follow-up: 21 months.</td>
</tr>
<tr>
<td><strong>Other findings</strong></td>
<td>No difference in all-cause mortality (RR 0.99; P = 0.96) or cardiac mortality (RR 0.94; P = 0.67).</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>The systematic prophylactic use of amiodarone in all patients with depressed LV function after MI is not indicated. However, the lack of pro-arrhythmias and the reduction in arrhythmic death support the use of amiodarone in patients for whom anti-arrhythmic therapy is indicated.</td>
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<tbody>
<tr>
<td><strong>Aim</strong></td>
<td>To compare ablation of VT with escalation of anti-arrhythmic drugs in ICD patients with VT.</td>
</tr>
<tr>
<td><strong>Study type</strong></td>
<td>Multicentre, RCT.</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>259</td>
</tr>
<tr>
<td><strong>Enrollment period</strong></td>
<td>2009–2014</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td>Composite of death occurring at any time after randomization or VT storm (3 or more documented episodes of VT within 24 h), or appropriate ICD shock after a 30-day treatment period.</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td>Each of the components of primary outcome and adverse events.</td>
</tr>
<tr>
<td><strong>Inclusion</strong></td>
<td>Prior MI, ICD carrier, VT during treatment with amiodarone or another Class I or Class III anti-arrhythmic drug within the previous 6 months. Episodes of VT were defined as any one of the following ≥3 episodes of VT treated with ATP, ≥1 appropriate ICD shock; ≥3 episodes of VT within 24 h; or sustained VT below detection cut-off of the ICD. VTs had to be monomorphic and slower than 250 b.p.m.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td>Mean follow-up: 27.9 ± 17.1 months. Primary outcome occurred in 59.1% of patients in the ablation group and 68.8% of those in the escalated-therapy group (HR in the ablation group 0.72; 95% CI 0.53–0.98; P = 0.04).</td>
</tr>
<tr>
<td><strong>Conclusions</strong></td>
<td>ventricular tachycardia ablation versus escalation of anti-arrhythmic drugs.</td>
</tr>
</tbody>
</table>

**Extended Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Type</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Aim</th>
<th>Results</th>
<th>Other findings</th>
<th>Conclusions</th>
</tr>
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<tr>
<td>EMIAT</td>
<td>1990–1995</td>
<td>Randomized double-blind placebo-controlled</td>
<td>Prior MI, ICD carrier, VT during treatment with amiodarone or another Class I or Class III anti-arrhythmic drug within the previous 6 months.</td>
<td>Episodes of VT were defined as any one of the following ≥3 episodes of VT treated with ATP, ≥1 appropriate ICD shock; ≥3 episodes of VT within 24 h; or sustained VT below detection cut-off of the ICD. VTs had to be monomorphic and slower than 250 b.p.m.</td>
<td>Prior MI, ICD carrier, VT during treatment with amiodarone or another Class I or Class III anti-arrhythmic drug within the previous 6 months.</td>
<td>Mean follow-up: 27.9 ± 17.1 months. Primary outcome occurred in 59.1% of patients in the ablation group and 68.8% of those in the escalated-therapy group (HR in the ablation group 0.72; 95% CI 0.53–0.98; P = 0.04).</td>
<td>In patients with CAD and an ICD who had VT despite anti-arrhythmic drug therapy, there was a significantly lower rate of the composite primary outcome of death, VT storm, or appropriate ICD shock among patients undergoing RFCA than among those receiving an escalation in anti-arrhythmic drug therapy.</td>
<td>Amiodarone reduces the incidence of VF or arrhythmic death among survivors of acute MI with frequent or repetitive PVCs.</td>
</tr>
</tbody>
</table>
### 584

**Pacifico A. et al.**

**Prevention of implantable-defibrillator shocks treatment by treatment with sotalol.**  
PMID: 10369848  
**Year of publication:** 1999

**Aim:** Efficacy of sotalol for the prevention of ICD shocks.  
**Study type:** RCT. Randomized to sotalol 160–320 mg/day vs. placebo.  
**Number of patients:** 302  
**Study endpoints:** First shock for any reason or death of any cause; first appropriate shock for VT or death of any cause; first inappropriate shock for SVT or death from any cause.

**Inclusion:** Only secondary preventive ICD recipients.  
**Exclusion:** Incipient VT, QT interval > 450 ms, LQTS, unstable CAD; NYHA IV.

**Results:** As compared with placebo, treatment with sotalol was associated with a lower risk of death from any cause or the delivery of a first shock for any reason (reduction in risk, 48%; P < 0.001 by the log-rank test), death from any cause or the delivery of a first appropriate shock (reduction in risk, 44%; P = 0.007), or death from any cause or the delivery of a first inappropriate shock (reduction in risk, 64%; P = 0.004). Sotalol also reduced the mean (+ standard deviation) frequency of shocks due to any cause (1.43 ± 3.53 shocks per year, as compared with 3.89 ± 10.65 in the placebo group; P = 0.008).

**Conclusions:** Oral sotalol was safe and effective in reducing the risk of death or the delivery of a first defibrillator shock whether or not ventricular function was depressed.

### 483

**Maury P. et al.**

**Radio-frequency ablation as primary management of well-tolerated sustained monomorphic ventricular tachycardia in patients with structural heart disease and left ventricular ejection fraction over 30%.**  
PMID: 24536081  
**Year of publication:** 2014

**Aim:** To study patients with SHD with LVEF over 30% presenting with a well-tolerated first episode of SMVT who were discharged after RF ablation as a primary strategy without a concomitant ICD.  
**Study type:** Multicentric, retrospective.  
**Number of patients:** 166  
**Enrollment period:** 2005–2010  
**Study endpoints:** VT recurrence rates in non-implanted patients.

**Inclusion:** SHD patients with LVEF >30% admitted for the occurrence of one or several well-tolerated first episode(s) of SMVT and who were treated by RF ablation as a first-choice therapy.  
**Control group:** Patients with SHD with LVEF >30% and similar SMVT (no syncope) implanted with an ICD.  
**Exclusion:** NA.

**Results:** 166 patients (84% men), mean age 62 ± 15 years and mean LVEF of 50 ± 10%. 55% CAD, 19% NICM and 12% ARVC. All-cause mortality was 12% (20 patients) over a mean follow-up of 32 ± 27 months. Eight patients (40%) died from non-cardiovascular causes, eight (40%) died from non-arrhythmic cardiovascular causes, and four (20%) died suddenly (2.4% of the population). All-cause mortality in the control group was 12%. 27 patients (16%) had a non-fatal recurrence at a median time of 5 months, while 20 patients (12%) required an ICD, of whom four died (20%).

**Other findings:** None of the 27 patients with documented recurring SMVT suffered a cardiac arrest at the time of relapse and none of the four patients with SD presented with recurring SMVT before.

**Conclusions:** Patients with well-tolerated SMVT, SHD, and LVEF >30% undergoing primary VT ablation without a back-up ICD had a very low rate of arrhythmic death and recurrences were generally non-fatal.  
**Limitations:** Non-randomized retrospective observational study, need for RCT.

### 583

**Clemens M. et al.**

**Catheter ablation of ventricular tachycardia as the first-line therapy in patients with coronary artery disease and preserved left ventricular systolic function: long-term results: VT ablation in patients with preserved LV function.**  
PMID: 26179108  
**Year of publication:** 2015

**Aim:** Outcome in patients with CAD, LVEF >40% and haemodynamically stable VT who received RFCA as first-line therapy.  
**Study type:** Retrospective monocentric.  
**Number of patients:** 31  
**Enrollment period:** 2001–2013  
**Study endpoints:** Procedural outcomes (inducibility) and long-term outcomes (plaque and ICD implantation).

**Inclusion:** History of CAD and haemodynamically tolerated monomorphic VT and relatively preserved (≥40%) LVEF.  
**Exclusion:** Survivors of cardiac arrest or subjects with a history of haemodynamically unstable VT.

**Results:** Clinical and all inducible VTs were abolished in 90% (28/31) and 58% (18/31) of the patients, respectively. An ICD was subsequently implanted in 42% of cases. Over a mean follow-up of 38 ± 2.9 years, 42% (13/31) patients died. Survival of the patients with or without the ICD was not significantly different (P = 0.47). VT recurrence was observed in 11%.

**Conclusions:** RFCA of VT as first-line treatment in patients with CAD and relatively preserved LVEF is a viable strategy. It may prevent implantation of an ICD in a considerable proportion of patients. Ablation of all inducible VTs confers low VT recurrence rate over a long-term follow-up.  
**Validity yes, external.**  
**Limitations:** Monocentric, retrospective, few patients.
Other findings: Mortality was not increased in the group assigned to ablation as compared with the control group (9% vs. 17%; P = 0.29).

Conclusions: Preventive VT ablation reduced the incidence of ICD therapy in post-MI patients receiving the ICD for secondary prevention of SCD.

---


Aim: To assess if prophylactic VT ablation followed by implantation of an ICD in patients with previous MI first episode of stable VT, and reduced left-ventricular function. Study endpoints: Primary endpoint: the time from defibrillator implantation to recurrence of any sustained VT or VF. Secondary endpoints were survival free from severe clinical events (death, syncope, hospital admission for a cardiac reason, and VT storm, defined as more than 3 VT episodes in 24 h), number of appropriate ICD interventions (ATP or shock), and quality of life. Study type: Prospective Randomized multicentre clinical trial. Number of patients: 110. Enrolment period: Enrolment began in August 2002, lasting 42 months, and follow-up was completed in January 2006.

Inclusion: Patients aged 18–80 years were eligible for enrolment if they had an indication for an ICD as secondary prevention after documented stable clinical VT without any reversible cause, CAD, previous MI, and reduced LVEF (<50%) measured by echocardiography or contrast ventriculography. Stable clinical VT was defined as a VT not leading to CA or syncope and during which the systolic blood pressure was higher than 90 mmHg. Exclusion: an acute MI within the preceding month, cardiac surgery within the preceding 2 months, a protruding left-ventricular thrombus on echocardiogram before ablation, valvular heart disease, or a mechanical heart valve that precluded left-ventricular access, unstable angina, incessant VT, or syncope and during which the systolic blood pressure was higher than 90 mmHg.

Results: Mean follow-up of 22.5 ± 5.5 months. 21 patients assigned to ICD implantation alone (33%) and eight patients assigned to ICD plus ablation (12%) received appropriate ICD therapy (antitachycardia pacing or shocks) (HR in the ablation group 0.35; 95% CI 0.15–0.78; P = 0.007). Among these patients, 20 in the control group (31%) and six in the ablation group (9%) received shocks (P = 0.003).

Other findings: The secondary endpoints of VT storm, syncope, or death did not differ between the groups. Estimates for survival free from hospital admission for cardiac reasons were 75% in the ablation group and 63% in the control group after 12 months, and 67% and 45% after 24 months, respectively (HR in ablation group 0.546; 95% CI 0.30–0.99; P = 0.044, log-rank test).

In patients with an LVEF > 30%, the estimate for survival free from any VT or VF episode after 12 months. After 24 months, 47% of patients in the ablation group and 29% of controls were free from any VT or VF episode (HR in ablation group 0.61; 95% CI 0.37–0.99).

Conclusions: In post-MI patients with reduced EF and stable VT, prophylactic VT ablation before ICD implantation prolonged time to VT recurrence.
<table>
<thead>
<tr>
<th>Page</th>
<th>Secondary: include sustained VA and appropriate ICD therapy.</th>
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<tbody>
<tr>
<td>586</td>
<td>Kuck KH et al.163 Impact of substrate modification by catheter ablation on implantable cardioverter-defibrillator interventions in patients with unstable ventricular arrhythmia and coronary artery disease results from the multicenter randomized controlled SMS (Substrate Modification Study). PMID: 28292751 Year of publication: 2017</td>
</tr>
</tbody>
</table>

**Aim:** To assess whether prophylactic ablation of the arrhythmogenic substrate reduces or prevents the recurrence of VT/VF in patients with CAD, unstable VA, and ICDs.

**Study type:** Randomized multicentre controlled trial

**Number of patients:** 111

**Enrolment period:** 2002–2010

**Study endpoint:**
1. Time to first recurrence of VT/VF.
2. Appropriate ICD therapies, quality of life according to the Medical Outcome Study Short Form-36 score, number of hospital readmissions because of a cardiac indication, cardiac surgery within the past 2 months, serum creatinine >220 mg/dL (>2.5 mg/dL), thrombocytopenia or coagulopathy, a contraindication to heparin, pregnancy, or participation in another investigational study.

**Inclusion:** Patients between 18 and 80 years of age with CAD, LVEF ≤ 40%, and clinically unstable spontaneous VT, or cardiac arrest or syncope with unstable VT inducible at the baseline electrophysiological study.

**Exclusion:** LV thrombus, NYHA functional Class IV, an acute MI within the preceding 2 months, valvular heart disease or a mechanical heart valve, unstable angina, cardiac surgery within the past 2 months, serum creatinine >220 mg/dL (>2.5 mg/dL), thrombocytopenia or coagulopathy, a contraindication to heparin, pregnancy, or participation in another investigational study.

**Results:** Patients were followed up for 2.3 ± 1.1 years. The primary endpoint was reached by 25 ablation patients and 26 ICD-only patients. Two-year event-free survival was estimated at 49.0% (95% CI 33.3%–62.9%) in the former and 52.4% (36.7%–65.9%) in the latter groups. Comparison of episode incidence revealed no significant difference in the primary endpoint (P = 0.84).

**Conclusions:** SMS failed to meet the primary endpoint of time to first VT/VF recurrence. However, RFCA did reduce the total number of ICD interventions during the duration of follow-up.

**Limitations:** Small number of patients, multiple types of VA (with the common denominator of haemodynamic instability), possible heterogeneous ablative approach among individual investigators and participating centres, proper randomization was affected by six patients (10%) from the ablation arm excluded from the analysis because of missing data.

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ARVC, arrhythmogenic right ventricular cardiomyopathy; ATP, anti-tachycardia pacing; CA, cardiac arrest; CAD, coronary artery disease; CI, confidence interval; DCM, dilated cardiomyopathy; EF, ejection fraction; EPS, electrophysiological study; HR, hazard ratio; ICD, implantable cardioverter defibrillator; LQTS, long QT syndrome; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NICM, non-ischemic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PES, programmed electrical stimulation; PVC, premature ventricular contraction; PVS, programmed ventricular stimulation; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; RR, relative risk; RV, right ventricle; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; SD, sudden death; SHD, structural heart disease; SMVT, sustained monomorphic ventricular tachycardia; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
### Table of Evidence 23 for Table of Recommendations for sudden cardiac death prevention in patients with coronary anomalies

<table>
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<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
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<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
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<th>Conclusions and limitations</th>
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<tr>
<td>590</td>
<td>Jegatheeswaran A, et al. [164] Features associated with myocardial ischemia in anomalous aortic origin of a coronary artery. Congenital Heart Surgeons Society study. PMID: 31235351 Year of publication: 2019</td>
<td>Aim: To determine anatomic features associated with ischemia and SCD in anomalous aortic origin of a coronary artery patients ≤30 years. Study type: Multicentre study (Congenital Heart Surgery Database US). Retrospective 1998-2009, prospective registry 2009-2016. Number of patients: 560 (131 retrospective, 429 prospective).</td>
<td>Inclusion: Subjects ≤30 with an anomalous aortic origin of a coronary artery. Exclusion: NA.</td>
<td>Results: Median age was 11.6 years, 66% men. Of 560 patients, 275 underwent ischemia testing: of those, 49 (9%) had ischemia (including 18 presenting with aborted SCD) and 236 (42%) did not. Patients with ischemia were more likely to have anomalous origin of the left coronary artery (28/49 vs. 46/236; P &lt; 0.0001), intramural course or high or slit-like ostium (anomalous left coronary artery), or longer intramural course (anomalous right coronary artery). Among patients with ischemia, the occurrence of SCA was not shown to have any associated anatomic features.</td>
<td>Other findings: ICD was implanted in three post-operative patients. No pre-operative ICD was implanted.</td>
<td>Conclusions: In this large and partially prospective registry of paediatric and young adults with anomalous aortic origin of a coronary artery, presence of ischemia was related to anomalous left coronary artery and intramural course or high or slit-like ostium.</td>
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<tr>
<td>588</td>
<td>Molossi S, et al. [165] Outcomes in anomalous aortic origin of a coronary artery following a prospective standardized approach. PMID: 32069111 Year of publication: 2020</td>
<td>Aim: To evaluate the outcomes of a standardized approach following diagnosis of anomalous aortic origin of a coronary artery in a paediatric population. Study type: Observational, prospective. Number of patients: 163.</td>
<td>Inclusion: Paediatric anomalous aortic origin of a coronary artery patients. Exclusion: NA.</td>
<td>Results: 163 patients (116 anomalous right coronary artery, 25 anomalous left coronary artery, 17 single coronary artery, five anomalous circumflex [3%]). Median age at diagnosis was 11.6 (6.8-15.1) years. Anomalous aortic origin of a coronary artery was an incidental finding in 80 patients, 31 patients had exertional and 32 non-exertional symptoms and only five had SCA (3%). 82 patients (50.3%) were considered high risk (ischemia testing, acute angle/slit-like ostium). At a median follow-up of 1.6 (IQR 0.7-2.8) years, all patients were alive. 57% of the high-risk group (anomalous right coronary artery/anomalous left coronary artery 36/11) had surgical intervention. Predictors of high risk were older age at diagnosis, black race, intramural course, and exertional syncope.</td>
<td>Other findings: 82% of the surgical/non-surgical group had no sports limitation.</td>
<td>Conclusions: Half of the high-risk paediatric cohort underwent surgery. Only 3% presented with SCA; 50% was completely asymptomatic.</td>
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<td>Reference</td>
<td>Title</td>
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<td>Enrolment period</td>
<td>Study endpoints</td>
<td>Results</td>
<td>Conclusions</td>
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<tr>
<td>589</td>
<td>Krasuski RA, et al. [1]</td>
<td>Long-term outcome and impact of surgery on adults with coronary arteries originating from the opposite coronary cusp. PMID: 21200009</td>
<td>2011</td>
<td>Cardiovascular symptoms, exertional chest pain, shortness of breath, syncope, MI or SCA.</td>
<td>Observational retrospective study</td>
<td>210 700</td>
<td>1966–2007</td>
<td>Inclusion: Adults with anomalous aortic origin of a coronary artery with interarterial course detected by coronary angiogram. Exclusion: NA.</td>
<td>54 patients had anomalous aortic origin of a coronary artery with interarterial course. Mean age at diagnosis was 58 ± 14 years. 36 patients had an anomalous right coronary artery and 18 had an anomalous left coronary artery. Follow-up was 9.2 (4.5–16.1) years. Surgery was performed in 28 (50%), 20/36 with anomalous right coronary artery and 8/18 with anomalous left coronary artery. In patients with interarterial course, lower all-cause mortality was observed if surgery was performed (18% vs. 47%).</td>
<td>Conclusions: In patients with anomalous aortic origin of a coronary artery with interarterial course, surgery possibly reduces all-cause mortality. Limitations: Study was underpowered for comparison.</td>
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<tr>
<td>591</td>
<td>Jegatheeswaran A, et al. [2]</td>
<td>Outcomes after anomalous aortic origin of a coronary artery repair: a Congenital Heart Surgeons’ Society Study. PMID: 32800265</td>
<td>2020</td>
<td>Ischaemia after surgery, death, reoperation.</td>
<td>Multicentre study (Congenital Heart Surgery Database US). Retrospective 2000–2009. Prospective registry 2009–2018.</td>
<td>682 anomalous aortic origin of a coronary artery patients, 395 after surgery.</td>
<td>2000–2018</td>
<td>Inclusion: Subjects ≤ 30 years undergoing surgery for anomalous aortic origin of a coronary artery. Exclusion: NA.</td>
<td>Median age at surgery was 13.3 years (range 0.9–30.7), 66% men. Of 395 patients undergoing surgery, 108 had anomalous left coronary artery, 282 had anomalous right coronary artery, and four single coronary artery. Pre-operative ischaemia testing was done in 163/395 (ischaemia in 39% of tested cases). Median follow-up was 2.8 years (range 0.0–16.2). There were four post-operative deaths (1%), 13 reoperations (3%), neo-aortic regurgitation in 10%, reduced LVEF (2%). New or persistent ischaemia in 15% of tested cases.</td>
<td>Conclusions: In this large mainly paediatric cohort of anomalous aortic origin of a coronary artery surgery, a high complication rate was observed, including mortality (1%), neo-aortic regurgitation, reoperation, and persistent or new ischaemia. Other findings: Among non-surgical patients (287), anomalous right coronary artery/anomalous left coronary artery 224/57, there were three deaths (1%) during exercise. Different surgical techniques were used (unroofing, etc.). ICD was implanted after surgery in three patients. Limitations: In patients with interarterial course, lower all-cause mortality was observed if surgery was performed (18% vs. 47%).</td>
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</table>

ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NA, not applicable; SCA, sudden cardiac arrest; SCD, sudden cardiac death.
### 4.1.2. Idiopathic premature ventricular complex PVC/ventricular tachycardia and premature ventricular complex-induced cardiomyopathy

#### 4.1.2.1. Idiopathic premature ventricular complex/ventricular tachycardia

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, year of publication, PMID, Year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
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<th>Inclusion criteria (patients)</th>
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<tr>
<td>605</td>
<td>Sharma N, et al. 168</td>
<td>Aim: To assess the prevalence of LV systolic dysfunction in children with frequent PVCs and determine whether PVC characteristics were predictive of LV dysfunction. Study type: Retrospective, single-centre. Number of patients: 134 Enrolment period: 2 years enrolment, 2.8 years follow-up. Study endpoints: LVEF and PVC burden at follow-up.</td>
<td>Inclusion: Age 6 months–21 years, structurally normal hearts (except tachycardiomyopathy) and PVCs on Holter monitoring. Exclusion: Chemotherapy, inflammatory disease, or family history of cardiomyopathy or channelopathy.</td>
<td>Results: The PVC burden decreased by 67% of baseline PVC burden in those who did not undergo any intervention.</td>
<td>Other findings: There were no deaths.</td>
<td>Conclusions: PVCs in children with structurally normal hearts are associated with a relatively benign course, with trend toward spontaneous resolution.</td>
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<tr>
<td>606</td>
<td>Niwano S, et al. 189</td>
<td>Aim: To determine the prognostic significance of frequent PVCs originating from the ventricular outflow tract in patients with normal left ventricular function. Study type: Prospective, observational, single-centre. Number of patients: 239 Enrolment period: 5.6 ± 1.7 years. Study endpoints: LVEF and PVC burden at follow-up.</td>
<td>Inclusion: Frequent PVCs (&gt;1000 beats/day) originating from the right or LV outflow tract without any detectable heart disease. Exclusion: 42/281 patients who exhibited syncope due to NSVT or &lt;55% LVEF</td>
<td>Results: No significant change in the mean LVEF and mean LV diastolic dimension. However, there was a significant negative correlation between the PVC burden and Delta LVEF (P &lt; 0.001) and positive correlation between the PVC prevalence and Delta LV diastolic diameter (P &lt; 0.001).</td>
<td>Other findings: For the prediction of the development of LV dysfunction (13 patients), PVC prevalence and LVEF at the initial evaluation were independent predicting factors (P &lt; 0.01).</td>
<td>Conclusions: The prognosis in patients with frequent PVCs is relatively benign. However, attention should be paid to the progression of the LV dysfunction during a long-term observation, especially in those with a high PVC burden.</td>
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<tr>
<td>538</td>
<td>Latchamsetty R, et al. 170</td>
<td>Aim: To assess outcomes and complications of RFCA of idiopathic PVCs and to determine the predictors of acute and long-term efficacy. Study type:</td>
<td>Inclusion: Patients who underwent ablation for frequent idiopathic PVCs. Exclusion: History of prior MI or delayed enhancement identified by CMR.</td>
<td>Results: Acute procedural success was achieved in 84% of patients. Continued success at clinical follow-up without use of anti-arrhythmic drugs was 71%. The only significant predictor of continued</td>
<td>Other findings: In 245 patients (21%) with PVC-induced cardiomyopathy, the mean LVEF improved from 38% to 50% (P &lt; 0.01) after ablation. Independent predictors for</td>
<td>Conclusions: RFCA of frequent PVCs is a low-risk and often effective treatment strategy to eliminate PVCs and associated symptoms. In patients with PVC-induced cardiomyopathy, cardiac function is</td>
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*ESC Guidelines*
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<th>Study (ID)</th>
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<tr>
<td>596</td>
<td>Hanson D, et al.174 Premature ventricular contraction diurnal profiles predict distinct clinical characteristics and beta-blocker responses. PMID: 3064570 Year of publication: 2019</td>
</tr>
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</table>

### Conclusions:

Conclusions: RFCA is more effective than antiarrhythmic drugs for the treatment of patients with frequent PVCs originating from the RVOT. Ablation was associated with a greater decrease in the burden of PVCs compared with antiarrhythmic drugs.

### Other findings:

- PVC recurrence was significantly lower in patients randomized to ablation group (32 patients, 19.4%) vs. anti-arrhythmic drug group (146 patients, 88.6%; P < 0.001).
- Ablation was associated with a greater decrease in the burden of PVCs (IRR 0.105; 95% CI [0.104-0.001) compared with anti-arrhythmic drugs.

### Study endpoints:

- PVC ablation outcomes at follow-up.
- Procedural complications.

### Inclusion:

- Consecutive patients with predominant PVCs originating from the RVOT by RFCA.
- Children with idiopathic VT.
- Premature ventricular contraction (PVC) diurnal variability patterns are associated with different clinical profiles and predict drug response.

### Exclusion:

- RVOT origin appearance on ECG.
- Right ventricular outflow tract tachycardia.
- Consecutive patients with >1% PVCs per day.
- No procedure-related mortality.
- Study endpoints: Absolute number and burden of PVCs at follow-up.
- One year.
- SHD.
- Previous anti-arrhythmic drug therapy.
- QT interval ≥ 450 ms.
- AV conduction disease or RBBB/LBBB.
- Sodium channel blockers.
- Other (hyperthyroidism, electrolyte disturbance, drug toxicity, diabetes mellitus, renal insufficiency, blood pressure 165/100).

### Study type:

- Retrospective, single centre.
- Retrospective, single centre.
- Retrospective, single centre.

### Enrolment period:

- 3.8 years.
- 16
- 144
- 330

### Number of patients:

- 135 (92.4%)
- 128 (88%)
- 135 (92.4%)
- 1185

### Results:

- Ablation was successful in 135 (92.4%) patients and 128 (88%) patients had no arrhythmia recurrence requiring repeated ablation.
- Success at last follow-up: Five children with left and six with right idiopathic VT.
- The correlation coefficient was the only predictor of beta-blocker success (area under the curve = 0.84; sensitivity = 100%, specificity = 67.7%; P ≥ 0.4).
- Development of PVC-induced cardiomyopathy were more frequent, PVC burden, lack of symptoms, and epicardial PVC origin (P < 0.05).

### Other findings:

- PVC recurrence was significantly lower in patients randomized to ablation group (32 patients, 19.4%) vs. anti-arrhythmic drug group (146 patients, 88.6%; P < 0.001).
- Ablation was associated with a greater decrease in the burden of PVCs (IRR 0.105; 95% CI [0.104-0.001) compared with anti-arrhythmic drugs.

### Conclusions:

Conclusions: RFCA is a safe and effective therapeutic option of idiopathic VT in children.
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<th>Study Title</th>
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<tr>
<td>595</td>
<td>Kjeldhus J. et al.</td>
<td>Retrospective, single centre. Number of patients: 416 Enrolment period: 2014-2016 Study endpoints: PVC burden.</td>
<td>Rate-PVC (IHR-PVC) when no correlation was found (14.2%). Beta-blocker therapy was successful in 34.0% of patients; patients with fast-heart rate-PVCs had a decrease in PVC burden (18.8 ± 10.4% to 9.3 ± 6.6%, P &lt; 0.0001; 62% success), independent heart rate-PVCs had no change (18.4 ± 17.9% to 20.6 ± 17.9%, P = 0.175; 0% success), whereas slow-heart rate-dependent-PVCs had an increase in burden (14.6 ± 15.3% to 20.8 ± 13.8%, P = 0.016; 0% success).</td>
<td>May have no effect or can even be harmful.</td>
<td>ESC Guidelines 73</td>
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<tr>
<td>608</td>
<td>Komatsu Y. et al.</td>
<td>Aim: To characterize re-entrant fascicular VT originating from papillary muscles: Purkinje network involvement in the reentrant circuit. PMID: 28292752 Year of publication: 2017</td>
<td>Inclusion: Patients in whom fascicular VT was successfully eliminated by ablation at the posterior papillary muscles (n = 8; posterior papillary muscle fascicular VT) and anterior papillary muscles (n = 5; anterior papillary muscle fascicular VT). Exclusion: (1) Repetitive PVCs or NSVT without sustained VT. (2) SHD.</td>
<td>Results: PVCs were significantly less during fascainide than during disopyramide treatment, 92 and 39%, respectively (P &lt; 0.01). No difference was observed between the two drugs in the incidence or severity of reported side effects.</td>
<td>Conclusions: Papillary muscle fascicular VT is a distinct entity with less sensitivity to verapamil administration compared with common fascicular VT. Ablation targeting the mid-diastolic Purkinje potentials around the papillary muscles can be effective in suppressing this arrhythmia.</td>
</tr>
<tr>
<td>603</td>
<td>Baman TS. et al.</td>
<td>Aim: To determine a cut-off PVC burden that can result in PVC-induced cardiomyopathy. Study type: Retrospective, single centre. Number of patients: 174 Enrolment period: Not reported Study endpoints: LVEF.</td>
<td>Inclusion: Patients referred for ablation of frequent idiopathic PVCs. Exclusion: NA.</td>
<td>Results: A reduced LVEF (mean 0.37 ± 0.10) was present in 57/174 patients (33%). Patients with a decreased LVEF had a mean PVC burden of 33 ± 13% as compared with those with normal LVEF 13 ± 12% (P &lt; 0.0001). A PVC burden of &gt;24% best separated the patients with impaired as compared with preserved LVEF (sensitivity 79%, specificity 78%, area under the curve 0.89). The lowest PVC burden resulting in a reversible cardiomyopathy was 10%. In multivariate analysis, PVC burden (HR 1.12; 95% CI 1.08 – 1.16; P &lt; 0.01) was independently associated with PVC-induced cardiomyopathy.</td>
<td>Conclusions: PVC burden of &gt;24% was independently associated with PVC-induced cardiomyopathy.</td>
</tr>
<tr>
<td>604</td>
<td>van Huls van Taxis CFB. et al.</td>
<td>Aim: To evaluate the relation between PVCs and normal LV function referred for PVI ablation.</td>
<td>Inclusion: Frequent idiopathic PVCs and normal LV function referred for PVI ablation.</td>
<td>Results: Fatigue was associated with higher baseline NT-proBNP and circumferential and systolic</td>
<td>Conclusions: These findings support a link between fatigue and PVC-induced increased</td>
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ventricular contractions are independently associated with increased ventricular wall stress in patients with normal left ventricular function. 

Exclusion: Wall stress (P = 0.011, respectively). 

Fatigue was independently associated with a significantly larger reduction in NT-proBNP. In patients with non-successful ablation, NT-proBNP and circumferential end-systolic wall stress remained unchanged.

ventricular wall stress, despite preserved LV function.

Exclusion: Wall stress (P = 0.011, respectively). 

Fatigue was independently associated with a significantly larger reduction in NT-proBNP. In patients with non-successful ablation, NT-proBNP and circumferential end-systolic wall stress remained unchanged.

ventricular wall stress, despite preserved LV function.

ventricular wall stress, despite preserved LV function.

ventricular wall stress, despite preserved LV function.
4.1.2.2. Premature ventricular complex-induced/aggravated cardiomyopathy

**Table of Evidence 25** for Table of Recommendations for the management of patients with premature ventricular complex-induced or aggravated cardiomyopathy

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<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
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<tr>
<td>612</td>
<td>Perela D, et al. [126] Neurohormonal, structural, and functional recovery patterns after premature ventricular complex ablation is independent of structural heart disease status in patients with depressed left ventricular ejection fraction: a prospective multicenter study. PMID: 23850913 Year of publication: 2013</td>
<td>Aims: To assess the benefit of ablation of PVCs in patients with frequent PVC and LV dysfunction, regardless of previous SHD diagnosis, PVC morphology, or estimated site of origin. Study type: Prospective observational multicentre study in four centres (Barcelona, Tarragona, Lleida, Tucuman). Number of patients: 90 Study endpoints: LVEF.</td>
<td>Inclusion: Consecutive patients with LV dysfunction (≤50%) and frequent PVCs (&gt;4/pacing cycle) undergoing PVC ablation. 53 patients (66%) no SHD. 27 patients (34%) SHD. Exclusion: NA.</td>
<td>Results: Successful sustained ablation 66%. LVEF improved patients with successful ablation from 33.7% to 43.8% at six and 12 months. No difference SHD vs. no SHD (P = 0.69). Echo-response defined as LVEF improvement &gt;5%. Patients with echo-response had higher PVC burden (29% vs. 15%), smaller PVC QRS (170 ms vs. 174 ms), and higher rates of successful ablation (98% vs. 93%). A 13% baseline PVC burden had 100% sensitivity and 85% specificity to predict an absolute increase &gt;5% in LVEF after successful sustained ablation.</td>
<td>Conclusions: Independently of the presence of SHD, the successful sustained ablation of frequent PVC in patients with depressed LVEF induced a progressive clinical and functional improvement. Improvement in heart failure parameters was related to baseline PVC burden and persistence of ablation success. A 13% baseline PVC burden had 100% sensitivity and 85% specificity to predict an absolute increase &gt;5% in LVEF after successful sustained ablation.</td>
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</tr>
<tr>
<td>613</td>
<td>Perela D, et al. [127] Ablation of frequent PVC in patients meeting criteria for primary prevention ICD implant: safety of withholding the implant. PMID: 26385330 Year of publication: 2015</td>
<td>Aims: To assess whether ablation might remove the primary prevention ICD indication in patients with frequent PVC. Study type: Prospective observational multicentre study in three centres. Number of patients: 66 Study endpoints: LVEF.</td>
<td>Inclusion: Consecutive patients undergoing PVC ablation and LVEF &lt;35%. Site of origin: RVOT 59%, LV outflow tract 25%, LV 15%. Exclusion: NA.</td>
<td>Results: Acute success: 97%. Sustained success: 76%. Prediction of ablation failure: Univariate: Age (HR 0.93), LV summit (HR 0.08), SHD (HR 0.36), BNP level, polymorphic PVC. Multivariate: Age, polymorphic PVC. Prediction of removing ICD indication: Univariate: PVC burden, site of origin LV (HR 0.12). Multivariate: PVC burden. Prediction of true cardiomyopathy by the following: PVC burden &lt;13%.</td>
<td>Conclusions: In patients with frequent PVC and primary prevention ICD indication ablation improves LVEF and, in most cases, allows removal of the indication. Withholding the ICD and re-evaluating within 6 months of ablation seems to be a safe and appropriate strategy.</td>
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<tr>
<td>593</td>
<td>Yokokawa M, et al. [128] Value of cardiac magnetic resonance imaging and programmed ventricular stimulation in patients with frequent premature ventricular complexes undergoing radiofrequency ablation. PMID: 28688990 Year of publication: 2017</td>
<td>Aims: To assess the use of CMR and programmed ventricular stimulation to identify patients with PVCs undergoing RFCA at risk for adverse long-term outcomes. Study type: Prospective observational study. Number of patients: 141 Enrolment period: 2004–2015 Study endpoints: VT/VF or death.</td>
<td>Inclusion: Patients undergoing PVC ablation. Exclusion: NA.</td>
<td>Results: SHD was identified by CMR in 64/321 patients (20%), and SMVT was inducible in 15/321 patients (5%). 14 patients had both SHD and inducible VT, and received an ICD after the procedure. The primary endpoint of VT/VF or death was met in 15 patients after a median 20 months of follow-up. The combination of SHD by CMR and VT inducibility conferred independently an increased risk of adverse outcome.</td>
<td>Conclusions: Pre-ablation cardiac CMR and programmed stimulation can be useful for risk stratification in patients with frequent PVCs. Patients with inducible VT in the setting of SHD may benefit from ICD implantation after ablation regardless of LVEF.</td>
<td></td>
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</tbody>
</table>
Conclusions: Cardiac magnetic resonance predicts outcome in patients with premature ventricular complexes of left bundle branch block morphology.

PMID: 20883930
Year of publication: 2010

Aim: To investigate whether the presence of RV abnormalities detected by CMR predict adverse outcome in patients presenting with frequent PVCs of LBBB morphology.

Study type: Prospective observational study.

Number of patients: 396

Enrollment period: January 2002–March 2005

Study endpoints: Composite endpoint of three cardiac events: cardiac death, resuscitated CA, and appropriate ICD shock.

Indicators: >1000 PVCs of LBBB morphology and no other pre-existing ARVC criteria.

Exclusive criteria: Claustrophobia, body dimension above the CMR scanner diameter, very frequent PVCs despite anti-arrhythmic drugs during CMR.

Results: Subjects with multiple RV abnormalities had worse outcome than the no-RV abnormalities group (HR 4.86; 95% CI 2.06–11.50; P = 0.001).

Subjects with frequent PVCs had worse outcome than the no-RV abnormalities group (HR 27.2; 95% CI 3.0–244.0; P < 0.001).

Patients with only wall motion abnormalities had higher prevalence of cardiac events than the no-RV abnormalities group (HR 27.2; 95% CI 3.0–244.0; P = 0.003).

Comments: In subjects with frequent PVC of LBBB morphology, CMR allows risk stratification. RV abnormalities were associated with worse outcome.

Conclusions: Medium-term outcome in patients undergoing focal VA in the setting of cardiomyopathy are satisfactory with improvement in LV function achievable in most patients.

PMID: 29482954
Year of publication: 2019

Aim: To assess medium-term outcomes of focal VA ablation in the setting of cardiomyopathy and to validate published risk factors for PVC-mediated cardiomyopathy.

Study type: Retrospective cohort.

Number of patients: 152

Enrollment period: 2011–2017

Study endpoints: Development of PVC-induced cardiomyopathy.

Indicators: Patients with frequent PVCs (≥5000/24 h) with outflow tract features on ECG, and LV cardiomyopathy, defined as LVEF ≤50% referred for RFCA.

Results: 54/152 (36%) patients had cardiomyopathy and the remaining 98 patients had normal LV systolic function. At medium-term follow-up, 83% of patients with cardiomyopathy were free of VA recurrence and median LVEF had improved from 40% to 52%.

Age, men gender, PVC burden, non-RVOT sites of origin, PVC QRS duration, and PVC minimum coupling interval were predictive of cardiomyopathy on univariate analysis, but only gender persisted on multivariate analysis.

Conclusions: Medium-term outcome in patients undergoing focal VA in the setting of cardiomyopathy are satisfactory with improvement in LV function achievable in most patients. Prior risk factors described in the literature are variable and inconsistent, likely reflecting heterogeneous study populations.

PMID: 21099837
Year of publication: 2011

Aim: To examine the safety, efficacy, and long-term effect of RFCA on LV function in patients with LV cardiomyopathy and frequent outflow tract PVCs and examine the effect of ablation in patients with LV cardiomyopathy known to precede the onset of PVCs and the impact of residual PVC frequency on recovery of LV function.

Study type: Retrospective cohort.

Number of patients: 69

Enrollment period: Not reported

Study endpoints: PVC burden reduction post-ablation, development of PVC-induced cardiomyopathy.

Indicators: Patients with frequent PVCs (≥5000/24 h) with outflow tract features on ECG, and LV cardiomyopathy, defined as LVEF ≤50% referred for RFCA.

Results: After follow-up of 11 ± 6 months, 44 (66%) patients had rare (<2%) PVCs. 15 (23%) had decreased PVC burden (>80% reduction and always <500 PVCs), and eight (12%) had no clinical improvement with persistent (5 patients) or recurrent (3 patients) PVCs. Only patients with either rare or decreased PVC burden after ablation had a significant improvement in LVEF (ΔΔLVEF 14% ± 9% vs. LVEF ≥7% vs. 13% ± 3% vs. -3% ± 6%, respectively; P < 0.001) and LV diastolic diameter (ΔΔLVEF diastolic diameter -4 ± 5 vs. -2 ± 4 vs. 0 ± 4, respectively, P = 0.038), regardless of chamber of origin.

The magnitude of LVEF improvement correlated with the decline in residual PVC burden (r = 0.475; P = 0.007). Patients with pre-existing LV cardiomyopathy had a more modest but still significant improvement in LV function compared to patients without pre-existing LV cardiomyopathy (ΔΔLVEF 8% vs. 13% vs. 0.046).

Multivariate analysis revealed ablation outcome, higher LVEF, and absence of pre-existing LV cardiomyopathy were independently associated with LVEF improvement.

Conclusions: Frequent outflow tract PVCs are associated with LV cardiomyopathy regardless of ventricle of origin. Significant (>80%) reduction in PVC burden has comparable improvement in LV function to complete PVC elimination. Successful PVC ablation may be beneficial even in patients with pre-existing LV cardiomyopathy.
<table>
<thead>
<tr>
<th>621</th>
<th>Zang M, et al.</th>
<th>188 Beneficial effects of catheter ablation of frequent premature ventricular complexes on left ventricular function. PMID: 24670420 Year of publication: 2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim:</td>
<td>To perform a meta-analysis on currently available cohort studies to evaluate the effects of RFCA on LV function in patients with frequent PVCs.</td>
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<tr>
<td>Study type:</td>
<td>Systematic review and meta-analysis.</td>
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<tr>
<td>Number of patients:</td>
<td>712 Enrolment period: Studies 2005–2013 Study endpoints: Changes from baseline in both LVEF and LV end-diastolic diameter post-ablation.</td>
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<tr>
<td>Inclusion:</td>
<td>Cohort studies of patients who underwent RFCA of frequent PVCs (sample size ≥ 10 patients).</td>
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<tr>
<td>Exclusion:</td>
<td>Studies with no echocardiographic parameters at baseline or at post-ablation follow-up.</td>
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<tr>
<td>Results:</td>
<td>The mean PVC burden before RFCA was 24% (95% CI 19–29%). The long-term success rate of PVC ablation ranged from 66% to 90%. The overall mean increase from baseline in LVEF post-ablation was 7.7% (95% CI 6.1–9.4%) and the overall mean decrease in LV end-diastolic diameter was −4.6 mm (95% CI −6.0–3.1 mm). Meta-regression showed no significant association of site of origin of PVCs with the degree of post-ablation LVEF improvement. Subgroup analysis showed that the overall mean increase from baseline in LVEF post-ablation was 12.4% (95% CI 8.1–16.6%) and the overall mean decrease in LV end-diastolic diameter was −4.8 mm (95% CI −6.2–3.4 mm) in patients with LV dysfunction at baseline.</td>
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<tr>
<td>Conclusions:</td>
<td>Ablation of frequent PVCs improves cardiac function, especially for patients with LV dysfunction. No significant association of site of origin of PVCs with the degree of post-ablation LVEF improvement.</td>
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<tbody>
<tr>
<td>Aim:</td>
<td>To demonstrate that frequent PVCs may be associated with LV dysfunction that resolves after ablation of the PVCs.</td>
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<tr>
<td>Study type:</td>
<td>Retrospective observational study.</td>
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<tr>
<td>Number of patients:</td>
<td>Cases 60, controls 11 Enrolment period: 1992–2006 Study endpoints: LVEF.</td>
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<tr>
<td>Inclusion:</td>
<td>Cases: Patients with PVC burden &gt; 10% referred for RFCA, with completed ambulatory monitoring before and 1–6 months after ablation and echocardiogram before and serially between one day and 6 months after ablation. Controls: Patients with frequent PVCs and no apparent aetiology for their cardiomyopathy (no ablation performed).</td>
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<tr>
<td>Exclusion:</td>
<td>Sustained VT, frequent runs (&gt;1% of all QRS complexes on 24-h monitor) of NSVT.</td>
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<tr>
<td>Results:</td>
<td>Reduced LVEF was present in 22/60 (37%) patients. Patients with decreased LVEF had a greater PVC burden than patients with normal LVEF (37% ± 13% vs. 11% ± 10% of all QRS complexes; P &lt; 0.0001). There was a significant inverse correlation between the PVC burden and the LVEF before ablation (r = 0.72; P &lt; 0.0001). PVCs originated in the RVOT in 31/60 (52%) patients, the LV outflow tract in 9/60 (15%) patients, and in other sites in 13/60 (22%) patients. Ablation was completely successful in 48/60 (80%) patients. In patients with an abnormal LVEF before ablation, LV function normalized in 18/22 (82%) patients from a baseline of 34% ± 7% (P &lt; 0.0001) within 6 months. In the four patients in whom ablation was ineffective, the LVEF further declined from 34% ± 10% to 25% ± 7% (P = 0.056) during follow-up. In the control group of 11 patients with a similar PVC burden (30% ± 8%) and a reduced LVEF (28% ± 13%) who did not undergo ablation, the LVEF remained unchanged in 10/11 patients over 19 ± 17 months of follow-up and one patient underwent heart transplantation.</td>
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<tr>
<td>Conclusions:</td>
<td>LV dysfunction in the setting of frequent, idiopathic PVCs may represent a form of cardiomyopathy that can be reversed by RFCA of the PVCs.</td>
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</table>
Conclusions:
Although amiodarone was effective in reducing the incidence of SD or prolonging survival among patients with heart failure, except for a trend towards reduced mortality among those with DCM.

Results:
Limitations:
There was no significant difference in overall mortality between the two treatment groups (P = 0.6).
The 2-year actuarial survival rate was 69.4% (95% CI 64.2–74.6) for those with congestive heart failure, cardiac enlargement, ≥ 10 PVCs/h, and LVEF ≤ 40%.

Aim:
To determine whether amiodarone can reduce overall mortality in patients with congestive heart failure and asymptomatic VA.
Study type:
Double-blind, placebo-controlled trial.
Number of patients:
674 (336 amiodarone, 338 placebo).
Enrollment period:
Not reported.
Study endpoints:
Overall mortality.

Indications:
Patients with symptoms of congestive heart failure, cardiac enlargement, ≥ 10 PVCs/h, and LVEF ≤ 40%.
Exclusion:
Women of childbearing age, MI within the 3 months before enrolment, symptomatic VA, a history of aborted SCA or sustained VT, uncontrolled thyroid disease, need for anti-arrhythmic therapy, ECG changes in the QRS interval (greater/equal 180 ms), or QTc interval (greater/equal 500 ms), a serious disease other than heart disease that was likely to be fatal within 3 years, and symptomatic hypotension or systolic blood pressure < 90 mmHg.

Results:
There was no significant difference in overall mortality between the two treatment groups (P = 0.6). The 2-year actuarial survival rate was 69.4% (95% CI 64.2–74.6) for the patients in the amiodarone group and 70.8% (95% CI 65.7–75.9) for those in the placebo group.
At 2 years, the rate of SD was 15% in the amiodarone group and 19% in the placebo group (P = 0.43).
There was a trend towards a reduction in overall mortality among the patients with DCM who received amiodarone (P = 0.07).
Amiodarone was significantly more effective in suppressing VA and improved LVEF by 43% at 2 years.

Other findings:
There was a trend towards reduced mortality among the patients with DCM who received amiodarone (P = 0.07).
Amiodarone was significantly more effective in suppressing VA and increased LVEF by 43% at 2 years.

Conclusions:
Aim:
To determine the safety and efficacy of class IC anti-arrhythmic drugs for suspected premature ventricular contraction-induced cardiomyopathy.
Study type:
Retrospective, single centre.
Number of patients:
20.
Follow-up:
3.8 ± 0.9 years.
Study endpoints:
PVC burden, LVEF and sustained VT or SD.

Indications:
PVC-induced tachycardiomyopathy treated with Class IC anti-arrhythmic drugs.
Exclusion:
Sustained VT before type IC anti-arrhythmic drugs initiation.

Results:
With IC anti-arrhythmic drugs treatment, mean PVC burden decreased from 36.2% ± 3.5% to 10.0% ± 2.4% (P < 0.001).
LVEF increased from 37.4% ± 2.0% to 49.0% ± 1.9% (P < 0.001). Seven patients with myocardial delayed enhancement on CMR imaging (all <5% of the total myocardium) experienced similar improvement in LVEF (from 36.8% ± 4.3% before IC-anti-arrhythmic drugs to 51.7% ± 3.7% afterward P < 0.001).
At follow-up, no sustained VA or SD occurred. No adverse events occurred in this small cohort.

Other findings:
 Patients had undergone an average of 13 ± 2 previous unsuccessful ablations. Six had an implantable or wearable defibrillator.

Conclusions:
Aim:
To evaluate the value of post-infarction PVC ablation and possible determinants of a reversible cardiomyopathy.
Study type:
Observational.
Number of patients:
30 (15 with PVC ablation and 15 with no ablation).
Enrollment period:
Not reported.
Study endpoints:
LVEF.

Indications:
Patients with remote MI referred for ICD implantation for primary prevention of SCD or for management of symptomatic VT or PVCs, and a PVC 24-h burden ≥5%.
Exclusion:
NA.

Results:
PVC ablation was successful in 15/15 patients and reduced the mean PVC burden from 22 ± 12% to 2.6 ± 5.0% (P < 0.001). After the procedure, LVEF increased significantly from 30.8 ± 15.1% to 51.7 ± 0.9 in the PVC ablation group (P = 0.0001).
In the control group, LVEF remained unchanged within the same time frame (33.4 ± 14 vs 33.5 ± 15.1; P = 0.6).
 Patients with frequent PVCs had a significantly smaller scar burden by LGE-CMR compared with control patients.
 Five of the patients with frequent PVCs underwent ICD implantation.

Conclusions:
Post-infarction patients with frequent PVCs may have a reversible form of cardiomyopathy. LGE-CMR may identify patients in whom the LVEF may improve after ablation of frequent PVCs.
Conclusions: In patients with frequent PVCs and NICM, EF and functional class can be improved but not always normalized by successful PVC ablation. In most patients with an effective ablation, the arrhythmogenic substrate was located in scar tissue.

Results: Ablation was successful in 18 of 30 patients (60%), resulting in an increase of mean LVEF from 33.9% ± 14.5% to 45.7% ± 17% (P < 0.0001) during mean follow-up of 30 ± 28 months. The PVC burden in these patients was reduced from 23.1% ± 8.8% to 1.0% ± 0.9% (P < 0.0001). Mean LVEF did not change in patients with a failed ablation procedure (P = 0.85). The PVC site of origin was in scar tissue in 14/18 patients with a successful ablation procedure.

Inclusion: Patients with structurally abnormal hearts based on the presence of scar on CMR and/or a history of cardiomyopathy before the study. Exclusion: NA.

Aim: To investigate the impact of frequent PVCs on NICM. Study type: Observational. Number of patients: 30. Enrolment period: Not reported. Study endpoints: LVEF.


Results: 65 subjects RFCA of PVC from 76 foci. Acute and long-term success rates of ablation were 91% and 88% in 12 ± 4 months of follow-up. There was significant improvement in LVEF (26.2 ± 5.5% to 32.7 ± 6.7%; P < 0.001), LV end-systolic diameter of <10% with no improvement in clinical status 1 year after CRT implantation. Exclusion Sustained VT requiring ATP or shock therapy, Atrial fibrillation burden of >1%.

Results: CRT non-responders with >10,000 PVC in 24 h who underwent PVC ablation. Non-responder defined as patients with <5% improvement in the LVEF and/or LV end-systolic diameter of <10% with no improvement in clinical status 1 year after CRT implantation. Exclusion Sustained VT requiring ATP or shock therapy, Atrial fibrillation burden of >1%.

Conclusions: In patients with frequent PVCs and NICM, EF and functional class can be improved but not always normalized by successful PVC ablation. In most patients with an effective ablation, the arrhythmogenic substrate was located in scar tissue.

ARVC, arrhythmogenic right ventricular cardiomyopathy; ATP, anti-tachycardia pacing; BNP, brain natriuretic peptide; CA, cardiac arrest; CI, confidence interval; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; EF, ejection fraction; HR, heart rate; ICD, implantable cardioverter defibrillator; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NICM, non-ischemic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; PVC, premature ventricular contraction; RFCA, radiofrequency catheter ablation; RV, right ventricle; RVOT, right ventricular outflow tract; SCA, sudden cardiac arrest; SD, sudden death; SHD, structural heart disease; SMVT, sustained monomorphic ventricular tachycardia; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
### 4.1.3. Non-ischaemic cardiomyopathies

#### 4.1.3.1. Dilated cardiomyopathy and hypokinetic non-dilated cardiomyopathy

#### Table of Evidence 26 for Table of Recommendations for risk stratification, sudden cardiac death, and treatment of ventricular arrhythmias in dilated cardiomyopathy/hypokinetic non-dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, year of publication, PMID</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tr>
<td>644</td>
<td>Ador F, et al. [93]</td>
<td>Aim: To estimate the prevalence of FLNC pathogenic variants in subtypes of cardiomyopathies and to study the relations between phenotype and genotype. Study type: Retrospective study. Number of patients: 1150 Enrolment period: 2010–2017</td>
<td>Include: Unrelated index-patients with isolated cardiomyopathy (700 hypertrophic, 300 dilated, 50 restrictive cardiomyopathies, and 100 left ventricle non-compactions). Exclusion: Variants of uncertain significance and non-pathogenic variants were not considered.</td>
<td>Results: An FLNC pathogenic variant was identified in 28 patients corresponding to a prevalence ranging from 1% to 8% depending on the cardiomyopathy subtype. Truncating variants were always identified in patients with DCM, while missense or in-frame indel variants were found in other phenotypes. A personal or family history of SCD was significantly higher in patients with truncating variants than in patients carrying missense variants (P = 0.01).</td>
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<td>645</td>
<td>Kayvanpour E, et al. [106]</td>
<td>Aim: To evaluate genotype-phenotype associations in DCM. Study type: Meta-analysis. Number of patients: 8097 patients, 48 studies. Enrolment period: 2000–2015 Study endpoints: Prevalence of mutations according to cardiomyopathy subtypes: association with SCD. Inclusion: We searched PubMed/Medline for human studies published in English language for the terms 'lamin A/C', 'LMNA', 'laminopathy', 'phospholamban', 'PLN', 'RNA binding motif protein 20', 'RBM20', 'myosin binding protein C', 'MYBPC3', 'myo-cardiac heavy chain', 'MYH7', 'cardiac troponin T', 'TNNT2', 'cardiac troponin I', 'TNNI3', 'OCC', and 'conduction disease'. Exclusion: 2487 articles were excluded on the basis of review of the title and abstract.</td>
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<td>Results: The frequency of VA in DCM patients with LMNA (50%) and PLN (43%) mutations was significantly higher. Heart transplantation rate was highest in LMNA mutation carriers (27%), while RMB20 mutation carriers were transplanted at a markedly younger age (mean 28.5 years).</td>
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<td>646</td>
<td>Ortiz-Genga MF, et al. [97]</td>
<td>Aim: To demonstrate the association between truncating mutations in FLNC and the development of high-risk dilated and arrhythmogenic cardiomyopathies. Study type: Retrospective cohort. Number of patients: 2877 Enrolment period: February 2012–August 2015 Study endpoints: Prevalence of mutations according to cardiomyopathy Inclusion: Patients with truncating mutations in FLNC. Exclusion: Other type of genetic variants.</td>
<td></td>
<td>Results: 23 truncating mutations in FLNC were identified in 28 probands previously diagnosed with dilated, arrhythmogenic, or restrictive cardiomyopathies. Truncating FLNC mutations were absent in patients with other phenotypes, including 1078 patients with HCM. 54 mutation carriers were identified among 121 screened relatives. The phenotype consisted of LV dilation (68%), systolic dysfunction (46%), and myocardial fibrosis (67%). Inferolateral negative T waves and low QRS voltages on electrocardiography (33%); VA (83%) and frequent SCD (40 cases in 21 of 28 families). Clinical skeletal myopathy was not observed.</td>
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Continued
Penetrance was >97% in carriers older than 40 years. Truncating mutations in FLNC co-segregated with this phenotype with a dominant inheritance pattern (combined logarithm of the odds score 9.3).

Results:
Truncating mutations in FLNC inclusion: co-segregated with this phenotype with a RBM20 mutation carriers than in TTN dominant inheritance pattern (combined mutation carriers (44% vs. 5%, respectively; P = 0.006). Spiking events that affected Ca^{2+} and ion-handling genes were enriched in RBM20 KO mice, most notably in the gene CamkII and RyR2. Abrupt spiking of CamkII in RBM20 KO mice resulted in a remarkable shift of CamkII towards the A isoform that is known to activate the L-type Ca^{2+} current (ICa,L). In line with this, we found an increased ICa,L, intracellular Ca^{2+} overload and increased sarcoplasmic reticulum Ca^{2+} content in RBM20 KO myocytes.

Conclusions:
Loss of RBM20 disturbs Ca^{2+} handling and leads to more pro-arrhythmic Ca^{2+} releases from the sarcoplasmic reticulum. Patients that carry a pathogenic RBM20 mutation have more VA despite a similar left ventricular function in comparison with patients with a TTN mutation. Our experimental data suggest that RBM20 mutation carriers may benefit from treatment with an ICa,L blocker to reduce their arrhythmia burden.

Aim:
To investigate the extent to which RBM20 mutation carriers have an increased risk of arrhythmias and explore the underlying molecular mechanism.

Study type:
Retrospective.

Number of patients:
DCM patients with RBM20 mutations (n = 18) or with TTN mutations (n = 22).

Enrolment period:
2005–2016

Study endpoints:
Major clinical events associated with these mutations + study of animal models.

Inclusion:
Patients with a (likely) pathogenic variant in the RBM20 gene or the TTN gene.

Exclusion:
Patients with another (likely) pathogenic variant in other genes associated with DCM.

Aim:
To investigate the prognostic role of genetic variant carrier status in a large cohort of DCM patients.

Study type:
Retrospective.

Number of patients:
487

Enrolment period:
January 1988–December 2015

Study endpoints:
All-cause mortality, heart failure–related death, heart transplantation, or destination LVAD and SCD/VTVF.

Inclusion:
DCM patients analysed by next-generation sequencing.

Exclusion:
All variants of uncertain significance were excluded from the analysis.

Aim:
To evaluate the association between LGE on CMR imaging and VA or SCD in patients with DCM.

Study type:
Meta-analysis.

Number of patients:
2948 patients, 29 studies.

Enrolment period:
Until August 2015

Study endpoints:
Arrhythmic endpoint (sustained VA, appropriate ICD therapy, or SCD).

Inclusion:
Systematic search of studies that analysed the arrhythmic endpoint in patients with DCM, stratified by the presence or absence of LGE.

Exclusion:
Because data of the studies were included in more recent publications.

Aim:
To evaluate the association between LGE on CMR imaging and VA or SCD in patients with DCM.

Study type:
Meta-analysis.

Number of patients:
2948 patients, 29 studies.

Enrolment period:
Until August 2015

Study endpoints:
Arrhythmic endpoint (sustained VA, appropriate ICD therapy, or SCD).

Inclusion:
Systematic search of studies that analysed the arrhythmic endpoint in patients with DCM, stratified by the presence or absence of LGE.

Exclusion:
Because data of the studies were included in more recent publications.

Aim:
Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis.

Study type:
Systematic review and meta-analysis.

Number of patients:
2948 patients, 29 studies.

Enrolment period:
Until August 2015

Study endpoints:
Arrhythmic endpoint (sustained VA, appropriate ICD therapy, or SCD).

Inclusion:
Systematic search of studies that analysed the arrhythmic endpoint in patients with DCM, stratified by the presence or absence of LGE.

Exclusion:
Because data of the studies were included in more recent publications.
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<td>654</td>
<td><strong>Klem I, et al.</strong>&lt;br&gt;The relationship of LVEF and myocardial scar to long-term mortality risk and mode of death in patients with non-ischemic cardiomyopathy. &lt;br&gt;PMID: 33478245&lt;br&gt;Year of publication: 2021</td>
</tr>
<tr>
<td>670</td>
<td><strong>Francone M</strong>&lt;br&gt;Role of cardiac magnetic resonance in the evaluation of dilated cardiomyopathy: diagnostic contribution and prognostic significance. &lt;br&gt;PMID: 24967294&lt;br&gt;Year of publication: 2014</td>
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658
Sjølåsli T, et al. Exercise is associated with impaired left ventricular systolic function in patients with lamin A/C genotype. PMID: 31957333 Year of publication: 2020
Aim: To explore associations between exercise, exposure and disease severity in patients with lamin A/C genotype.
Study type: Single-centre cross-sectional study.
Number of patients: 69
Enrolment period: March 2017
Study endpoints: Survival-free of LVEF < 45%.
Inclusion: Consecutive lamin A/C genotype positive probands, and genotype-positive family members followed at a specialized clinic in a single centre.
Exclusion: NA.
Results: 69 patients (age 42 ± 14 years, 41% probands, 46% women) with median lifetime exposure of 3 years (IQR 1–13 years vs. 40 ± 16 years; P = 0.016).
Exercise is associated with impaired left ventricular systolic function in patients with Lamin A/C genotype.
PMID: 31957533 Year of publication: 2020
Aim: To explore associations between exercise exposure and disease severity in patients with Lamin A/C genotype.
Study type: Single-centre cross-sectional study.
Number of patients: 2327
Enrolment period: May 2014–September 2018
Study endpoints: All-cause mortality.
Inclusion: CAD or DCM and prophylactic ICD implantation; age ≥ 18 years, LVEF ≤ 35% and NYHA Class III–IV.
Exclusion: Secondary prophylactic ICD indication, planned implantation of a device for CRT.
Results: Baseline and follow-up data from 2247 patients were analysable, 1516 before ICD implantation (ICD group) and 731 patients without ICD serving as controls.
During mean follow-up of 2.4 ± 1.1 years, 342 deaths occurred (6.3%/years annualized mortality, 5.6%/years in the ICD group vs. 9.2%/years in controls), favouring ICD treatment (unadjusted HR 0.682; 95% CI 0.537–0.865; P = 0.005).
After adjustment for a range of covariates, patients with less survival advantage, such as older patients or diabetics, LVEF < 45% was observed at younger age in active patients (log rank P = 0.007).
Conclusions: Although our updated meta-analysis demonstrates a survival benefit of ICD therapy, the effect is substantially weakened by the inclusion of the DANISH trial, which is both the largest and most recent of the analysed trials. As such, these data must be interpreted cautiously.
Year of publication: 2018
Aim: To determine the benefit of prophylactic ICDs in patients with symptomatic systolic heart failure not due to CAD.
Study type: RCT.
Number of patients: 1116
Enrolment period: February 2008–June 2014
Inclusion: Symptomatic patients (NYHA Class II or III or NYHA Class II–III, LVEF ≤ 35%) and an increased level (>200 pg/mL) of NT-proBNP.
Exclusion: Patients who had permanent atrial fibrillation with a resting heart rate higher than 100 beats/min or renal failure that was being treated with dialysis.
Results: Death from any cause occurred in 120 patients (21.6%) in the ICD group and 131 patients (23.4%) in the control group (HR 0.89; 95% CI 0.68–1.12; P = 0.38). SCD occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (HR 0.50; 95% CI 0.31–0.82; P = 0.005).
In the subgroup of patients who were younger than 68 years of age, the rate of death from any cause was significantly lower in the ICD group (HR 0.64; 95% CI 0.45–0.90; P = 0.007).
Conclusions: Prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by CAD was not associated with a significantly longer term death rate of death from than was usual clinical care.
Year of publication: 2016
Aim: To examine the impact of ICD therapy on mortality in patients with NICM.
Study type: Meta-analysis.
Number of patients: 2970
Enrolment period: Searches of Medline and Embase (from 1946 or 1947, respectively).
Inclusion: Six primary prevention trials and two secondary prevention trials.
Exclusion: NA.
Results: Using a fixed-effects model, analysis of primary prevention trials revealed a reduction in overall mortality with ICD therapy (RR 0.76; 95% CI 0.65–0.89; P < 0.002).
In a sensitivity analysis, the benefit of ICD therapy was maintained after the removal of any single study from the pooled analysis.
Conclusions: Although our updated meta-analysis demonstrates a survival benefit of ICD therapy, the effect is substantially weakened by the inclusion of the DANISH trial, which is both the largest and most recent of the analysed trials. As such, these data must be interpreted cautiously.
PMID: 28986406 Year of publication: 2018
Aim: To examine the impact of ICD therapy on mortality in patients with NICM.
Study type: Meta-analysis.
Number of patients: 2970
Enrolment period: Searches of Medline and Embase (from 1946 or 1947, respectively).
Inclusion: Six primary prevention trials and two secondary prevention trials.
Exclusion: NA.
Results: Using a fixed-effects model, analysis of primary prevention trials revealed a reduction in overall mortality with ICD therapy (RR 0.76; 95% CI 0.65–0.89; P < 0.002).
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Conclusions: Although our updated meta-analysis demonstrates a survival benefit of ICD therapy, the effect is substantially weakened by the inclusion of the DANISH trial, which is both the largest and most recent of the analysed trials. As such, these data must be interpreted cautiously.
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<tr>
<td>653</td>
<td>Defibrillators in non-ischemic cardiomyopathy treatment evaluation (DEFINITE) investigators. Prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomyopathy. PMID: 15152060</td>
<td>Kadish A, et al</td>
<td>To determine whether a defibrillator is appropriate</td>
<td>Retrospective multicentre study.</td>
<td>Number of patients: 1405</td>
<td>Enrolment period: January 1998–June 2002.</td>
<td>Significant reduction in the risk of sudden death in patients with NICM.</td>
<td>Online calculator (<a href="https://ffp2m.org/risk-calculator">https://ffp2m.org/risk-calculator</a>).</td>
<td>In patients with severe NICM who were treated with ACE inhibitors and beta-blockers, ICD implantation significantly reduced the risk of sudden death from arrhythmia and was associated with a non-significant reduction in the risk of death from any cause.</td>
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<td>83</td>
<td>Development and validation of an new risk prediction score for life-threatening ventricular tachyarrhythmias in laminopathies. PMID: 31155932</td>
<td>Wahbi K, et al</td>
<td>To determine risk factors that predict malignant VA in patients with LMNA mutations.</td>
<td>Retrospective study from eight centres in Europe.</td>
<td>Number of patients: 444 patients in France (derivation sample) and 145 patients (validation sample).</td>
<td>Exclusion: Patients with only the non-missense LMNA mutation, male sex, and higher atrioventricular block, NSVT, and LVEF.</td>
<td>Median follow-up: 3.6 (1.0–7.2) years (95% CI 2.6–4.5).</td>
<td>In patients with severe NICM, and clinicians must consider age and comorbidity on an individual basis when determining whether a defibrillator is appropriate.</td>
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<tr>
<td>655</td>
<td>Risk factors for malignant ventricular arrhythmias in laminopathies. A European cohort study. PMID: 22281253</td>
<td>Arianzadeh A, et al</td>
<td>To determine risk factors that predict malignant VA in LMNA mutation carriers.</td>
<td>Retrospective study from eight centres in Europe.</td>
<td>Number of patients: 269 LMNA mutation carriers.</td>
<td>Exclusion: LMNA carriers older than 50 years of age.</td>
<td>Median follow-up: 4.5 (1.0–10.1) years.</td>
<td>Carriers of LMNA mutations with a high risk of malignant VA can be identified using these risk factors.</td>
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<tr>
<td>656</td>
<td>Thuillot M et al.</td>
<td>2019</td>
<td>To validate the prognostic factors described in van Rijsingen et al. 2012</td>
<td>LMNA mutation carriers.</td>
<td>NA.</td>
<td>Over a median follow-up of 3.4 years, 16 patients (20%) experienced malignant VAs. The C-index of Harrel of the model was 0.76 (95% CI: 0.72–0.80) showing a good discrimination. Calibration assessment indicated good agreement as predicted survival in the three groups of patients.</td>
<td>This study was able to validate the predictive role of the four risk factors for malignant VA in an independent population. These risk factors were also validated in a subcohort of relatives.</td>
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<td>664</td>
<td>Link MS et al.</td>
<td>1997</td>
<td>To evaluate the hypothesis that in patients with syncope of unknown etiology and inducible ventricular arrhythmias, mutation carriers of LMNA were at increased risk</td>
<td>Patients with syncope of undetermined origin and inducible VA at electrophysiologic evaluation who underwent ICD implantation.</td>
<td>NA.</td>
<td>Ventricular stimulation led to SMVT in 36 patients, NSVT in 5, and VF in 9. Over a 23 ± 15-month (mean ± standard deviation) follow-up period, 18 patients received appropriate ICD shocks. Actuarial probability of appropriate therapy was 22% at one year and 50% at 3 years. Recurrent syncope was seen in five patients, three of whom had appropriate ICD detections at the time of syncope. Four patients died (SD in 1, congestive heart failure in 2).</td>
<td>In patients with syncope of undetermined origin and inducible VA, appropriate ICD therapy is common at follow-up. SCD is uncommon. This low incidence of SCD and high incidence of appropriate defibrillator therapy support the current practice of using ICD in patients with syncope of unknown origin and inducible VA.</td>
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<td>671</td>
<td>Goldberger JJ et al.</td>
<td>2014</td>
<td>To provide a meta-analysis to estimate the performance of 12 commonly reported risk stratification tests as predictors of arrhythmic events in patients with NICM.</td>
<td>All published reports evaluating predictors of arrhythmic events in patients with NICM.</td>
<td>Studies that did not report follow-up data or did not use predictors of interest were excluded from further consideration. Predictive tests included: baroreflex sensitivity, heart rate turbulence, heart rate variability, left ventricular end-diastolic dimension, LVEF, electrophysiology study, NSVT, LB/PF, signal-averaged ECG, fragmented QRS, QRS-T angle, T-wave alternans.</td>
<td>Patients were 52.8 ± 14.3 years of age and 77% were men. LVEF was 30.6 ± 11.4%. Test sensitivities ranged from 38.8% to 91.0%, specificities from 36.2% to 87.1%, and ORs from 1.3 to 6.7. OR was highest for fragmented QRS and T-wave alternans (ORs: 6.73 and 4.66; 95% CI: 3.85–11.76 and 2.35–8.53, respectively) and lowest for QRS duration (OR: 1.3; 95% CI: 1.13–2.01). None of the autonomic tests (heart rate variability, heart rate turbulence, baroreflex sensitivity) was a significant predictor of arrhythmic outcomes. Accounting for publication bias reduced the ORs for the various predictors but did not eliminate the predictive association.</td>
<td>Techniques incorporating functional parameters, depolarization abnormalities, repolarization abnormalities, and arrhythmic markers provide only modest risk stratification for SCD in patients with DCM. It is likely that combinations of tests will be required to optimize risk stratification in this population.</td>
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</table>
Conclusions: in 70% freedom from VT recurrence, with an overall transplant and/or mortality rate of 15% at one year. Freedom from VT recurrence was associated with improved transplant-free survival, independent of heart failure severity.

Results: In 37 (38%) patients, (likely) pathogenic variants carriers had LVEF = 11% of 37 (30%), TTN = 6 of 37 (16%), PLN = 4 of 37 (11%), SCN5A = 3 of 37 (8%), RCM = 2 of 37 (5%), and DSP = 2 of 37 (5%). (Likely) pathogenic variants carriers had lower LVEF (35 ± 13% vs. 42 ± 11% in patients without; P = 0.005) and were less often men (n = 27 (73%) vs. n = 55 (90%); P = 0.03). After a median follow-up of 2.4 years (IQR 0.9–4.4 years), 63 (22%) were on amiodarone. Other findings: Among the 38 (23%) patients with VT recurrence, RFCA still resulted in a significant reduction of VT burden, with 31 (83%) patients having only isolated VT episodes in 12 (4–35) months after the procedure. At last follow-up, 20 (45%) patients were on β-blockers or no treatment, 41 (93%) were on isotal or class III antiarrhythmic drugs, and 62 (22%) were on amiodarone.

Conclusions: RFCA of VT in patients with SHD results in 70% freedom from VT recurrence, with an overall transplant and/or mortality rate of 15% at one year. Freedom from VT recurrence is associated with improved transplant-free survival, independent of heart failure severity.
after ablation), VT recurrence, mortality.

| VT recurrence (patients with [likely] pathogenic variants 30 of 37 (81%) vs. patients without 33 of 61 (54%); | 0.007). 28 patients (29%) died (patients with [likely] pathogenic variants: 19 of 37 (51%) vs patients without: 9 of 61 (15%); | P < 0.001). The cumulative 2-year VT-free survival was 41% in the total cohort (patients with [likely] pathogenic variants:16% vs. patients without: 54%; P = 0.001). The presence of [likely] pathogenic variants (HR 1.9; 95% CI 1.1–3.4; P = 0.001) and unipolar low-voltage area ≥0.5 cm² increase (HR 2.5; 95% confidence interval: 1.6–4.0; P < 0.001) were associated with a decreased 2-year VT-free survival.

| 649 | Helen T, et al.277 | ESC EORP Cardiomyopathy Registry: real-life practice of genetic counselling and testing in adult cardiomyopathy patients. PMID: 32767651 Year of publication: 2020 | Aim: To assess the current practice of genetic counselling and testing in the prospective ESC EORP Cardiomyopathy Registry. Study type: Prospective observational study. Number of patients: 3208 adult patients from 69 centres in 18 countries. Enrolment period: December 2012-November 2013 for the Pilot Registry, June 2014-December 2016 for the Long-term Registry. Study endpoints: Genetic counselling performed; genetic testing performed. Inclusion: Age at enrolment, ≥18 years, written informed consent from the patient, ability to comply with the study requirements, and a documented cardiomyopathy. Exclusion: NA. Results: Comparing European geographical areas, genetic counselling was performed from 42.4% to 83.3% (P < 0.001). It was provided by a cardiologist (85.3%), geneticist (15.1%), genetic counsellor (11.3%), or a nurse (7.5%) (P < 0.001). Genetic testing was performed in 37.3% of all patients (48.8% in HCM, 18.6% in DCM, 55.6% in ARVC, and 43.6% in restrictive cardiomyopathy; P < 0.001). Index patients with genetic testing were younger at diagnosis and had more familial disease, family history of SCD, or implanted ICDs but fewer comorbidities than those not tested (P < 0.001 for each comparison). At least one disease-causing variant was found in 41.7% of index patients with genetic testing (43.3% in HCM, 33.3% in DCM, 51.4% in ARVC, and 42.9% in restrictive cardiomyopathy; P < 0.01). Conclusions: This is the first detailed report on the real-life practice of genetic counselling and testing in cardiomyopathies in Europe. Genetic counselling and testing were performed in a substantial proportion of patients, but less often than recommended by European guidelines and much less in DCM than in HCM and ARVC, despite evidence for genetic background.

ACE, angiotensine converting enzyme; ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; CI, confidence interval; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile rate; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; NA, not applicable; NICM, non-ischemic cardiomyopathy; NSVT, non-sustained ventricular tachycardia; NT-pro-BNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PLN, phospholamban; PVC, premature ventricular contraction; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; RR, risk reduction; SCD, sudden cardiac death; SD, sudden death; TTN, titin gene; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
## Conclusions:

The combination of RV wall motion abnormalities (excluding hypokinesia) and signal abnormality (LGE/fatty replacement) on CMR had the highest accuracy for the diagnosis of ARVC.

## Results:

4.1.3.2. Arrhythmogenic right ventricular cardiomyopathy

**Reference number in Guidelines**

679. Rastegar N, et al. [178]

**Aim**

To determine the incidence of ventricular fibrofatty replacement and LGE at CMR in patients with ARVC and to assess the relationship of these findings with disease severity.

**Study type**

Retrospective analysis from prospective registry.

**Number of patients**

76

**Enrollment period**

2002–2012

**Study endpoints**

NA

### Inclusion

ARVC patients according to Task Force criteria with CMR (including sequences for evaluation of fatty infiltration and LGE).

### Exclusion

NA

### Summary of main results

76 patients (mean age 44.2 years, 51% men, 59% probands, 59% with ARVC-related mutations). At CMR, 42 (55%) patients met major Task Force criteria: seven (9%) minor Task Force criteria, seven (9%) partial Task Force criteria, and 30 (20%) had no Task Force criteria. Non-Task Force CMR criteria were seen in 88% of patients with major Task Force, 29% with minor Task Force criteria, 71% with partial criteria, and in 10% without Task Force criteria. The most common non-Task Force CMR criteria were fatty infiltration (29%) and LV LGE (34%).

### Other findings

Conclusions: LGE and fibrofatty ventricular replacement were frequently found in ARVC patients, especially those with major Task Force criteria.

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### Table of Evidence 27 for Table of Recommendations for diagnosis, risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

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<tr>
<th>Reference number in Guidelines</th>
<th>Reference, year of publication, PMID</th>
<th>Aim</th>
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<tr>
<td>680</td>
<td>Aquaro GD, et al. [179]</td>
<td>To assess the diagnostic accuracy of CMR 2010 Task Force criteria by comparing probands with age- and gender-matched healthy controls and using study-state free precession cine sequence and to compare in 2010 Task Force CMR criteria with morphofunctional and tissue abnormalities detected by CMR for the diagnosis of ARVC.</td>
<td>Observational study</td>
<td>Number of patients: 263</td>
<td>Enrollment period: 2010–2012</td>
<td>Not reported</td>
<td>Study endpoints</td>
<td>NA</td>
<td>47 probands (29 men, 46 ± 17 years) and 216 age- and gender-matched healthy controls were studied. 29 (62%) probands had both RV wall motion and signal (fat and/or LGE) abnormality in one or both ventricles. 15 (32%) only one abnormality, and 3 (6%) no abnormalities.</td>
<td>Major Task Force criteria had high specificity (100%) and poor sensitivity (13%). The presence of any signal abnormality had high specificity (100%) and sensitivity (81%). The best diagnostic accuracy (98%) was found with the combination of any RV wall motion abnormality and any signal abnormality (specificity 100% and sensitivity 94%). LV was involved in 45% of probands.</td>
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### Table of Evidence 28 for Table of Recommendations for diagnosis, risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in arrhythmogenic right ventricular cardiomyopathy

<table>
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<td>681</td>
<td>Tie Risl ASRM, et al. [180]</td>
<td>To assess the incremental value of CMR in risk stratification of carriers of ARVC-associated desmosomal mutations carriers.</td>
<td>Retrospective analysis of prospective registry</td>
<td>Number of patients: 69</td>
<td>Enrollment period: 1999–2013</td>
<td>Study endpoints</td>
<td>Spontaneous sustained VA (composite of sustained VT, appropriate ICD therapy for VT/VF, SCD, and SCA)</td>
<td>NA</td>
<td>69 patients (27 ± 15 years, 42 men, 54 (78%) first-degree relatives of ARVC probands, 8% with a PKP2 mutation). 48 (68%) patients had electrical abnormalities on ECG and Holter and 21 (30%) patients had an abnormal CMR according to Task Force criteria (the majority major imaging criteria [172, 173]). Symptomatic patients (14, 7% &lt; P &lt; 0.001) and patients with abnormal electrical testing (20 vs. 1; P &lt; 0.001) were more likely to have an abnormal CMR. Over a mean follow-up of 5.8 ± 4.4 years, 11 (16%) patients had sustained VA. All had electrical abnormalities and all had abnormal CMR (biventricular involvement in 7/11 (64%)).</td>
<td>Among patients with electrical abnormalities, cumulative survival free from VA was 95%, 76%, and 66% at 1, 5, and 10 years follow-up. Patients with electrical abnormalities and CMR abnormalities had higher incidence of VA (P &lt; 0.001) with a cumulative survival free from VA of 89%, 54%, and 36% at 1, 5, and 10 years follow-up.</td>
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</table>
Conclusions: 
Other findings: 
Median age at symptom onset and at the first episode of sustained VT/VF was lower for patients with PKP2 mutations than for those with DSP mutations (median 30 and 36 years; P = 0.003). Patients with two or more pathogenic mutations from two prospective ARVC registries had higher incidence of LV dysfunction, and presented at younger age than those patients presenting with SMVT (23 vs. 36 years; P = 0.02). The METs × min/week correlated with reduced RV and LV function by echocardiography and CMR (all P < 0.05). The METs × min/week was a strong and independent marker of life-threatening VA in ARVC patients and could be advised to restrict their exercise intensity.

Conclusions: 
To assess the impact of genotype on clinical and arrhythmic outcome in ARVC-associated mutation carriers.

Study type: Prospective cohort study.
Number of patients: NA.
Inclusion: Patients with pathogenic ARVC-associated mutations from two prospective ARVC registries.
Exclusion: NA.

Results: 
S77 patients (23 probands, 35 ± 17 years, 53% men) were included. 40 (80%) had a single PKP2 mutation, 10 (20%) had a single DSP mutation, or both PKP2 and DSP were present. PKP2 mutation carriers had a higher incidence of arrhythmias and presented at younger age with symptoms and sustained VT/VF. PKP2 mutation carriers had higher incidence of arrhythmias, and presented at earlier age with symptoms and sustained VA.

Conclusions: 
Other findings: 
The median age at symptom onset and at the first episode of sustained VT/VF was lower for patients with PKP2 mutations than for those with DSP mutations (median 30 and 35 years; P < 0.001). LV dysfunction was seen in 78 (17%) patients. Patients with DSP and PKP2 mutations and patients with more than one mutation had higher incidence of LV dysfunction. Multiple mutation carriers had similar death/splant-free survival and Y/TVF than patients with truncating or splice site mutations. 

Aim: 
To assess the value of genotype for prediction of lifetime major arrhythmic events and SCD in desmosomal gene-related ARVC. 

Study type: Retrospective observational study.
Number of patients: 154.
Exclusion: NA.

Results: 
21 patients (14%) had a complex genotype. Multiple desmosomal gene mutations and men sex were independent predictors of lifetime arrhythmogenic right ventricular cardiomyopathy.

Conclusions: 
To assess the impact of genotype on clinical and arrhythmic outcome in ARVC-associated mutation carriers.

Study type: Retrospective observational study.
Number of patients: 154.
Exclusion: NA.

Results: 
Arrested SCD because of VF, SVT, and appropriate intervention of ICD. High-intensity exercise was a strong and independent marker of life-threatening VA in ARVC patients, independent of exercise duration. Arrhythmogenic cardiomyopathy patients could be advised to restrict their exercise intensity.

Conclusions: 
Vigorous physical activity impairs myocardial function in athletes with arrhythmogenic right ventricular cardiomyopathy and in mutation-positive family members.

Study type: Retrospective observational study.
Number of patients: 65 ARVC patients and 45 mutation-positive family members.
Exclusion: NA.

Results: 
Athletes were defined as subjects with ≥ 4 h vigorous exercise/week (≥140 metabolic equivalents [METs] × min/week) during a maximum of 6 years. The RV function by RV ejection fraction by CMR as reduced in athletes compared with non-athletes (RVEF 32 ± 8% vs. 43 ± 10%; P < 0.01), whereas LV function by LV ejection fraction by CMR was similar in athletes and non-athletes. The METs × min/week was a strong and independent marker of life-threatening VA in ARVC patients and could be advised to restrict their exercise intensity.

Conclusions: 
To investigate the impact of exercise on myocardial function in ARVC subjects.

Study type: Retrospective observational study.
Number of patients: 65 ARVC patients and 45 mutation-positive family members.
Exclusion: NA.

Results: 
Arrested SCD because of VF, SVT, and appropriate intervention of ICD. High-intensity exercise was a strong and independent marker of life-threatening VA in ARVC patients, independent of exercise duration. Arrhythmogenic cardiomyopathy patients could be advised to restrict their exercise intensity.

Conclusions: 
To explore the association between exercise duration vs. exercise intensity and adverse outcomes in patients with arrhythmogenic cardiomyopathy.

Study type: Prospective observational study.
Number of patients: 173.
Exclusion: NA.

Results: 
137 ARVC patients (53% probands; 44% women; 41 ± 16 years of age) had occurred in 83 patients (56%) and was more prevalent in patients with high-intensity exercise than low-intensity exercise (74% vs. 26% P < 0.001), and more prevalent in long-duration than short-duration exercise (63% vs. 31%; P < 0.001). High-intensity exercise was a strong and independent marker of VA even when adjusted for the interaction with long-duration exercise (OR 4.3, 95% CI 1.3-13.0, P = 0.009), whereas long-duration exercise was not.

Conclusions: 
High-intensity exercise was a strong and independent marker of life-threatening VA in arrhythmogenic cardiomyopathy patients, independent of exercise duration.

Arrhythmogenic cardiomyopathy patients could be advised to restrict their exercise intensity.

Conclusions: 
Genotype in ARVC patients impacts disease expression and clinical course. In particular, patients with more than one mutation had a lower survival free from sustained VA and present at earlier age.
Conclusions

Endurance exercise and frequent exercise increase the risk of VT/VF, heart failure, and ARVC death among ARVC carriers. These findings support exercise restriction for these patients.

Limitations

- Study design (potentially inaccurate recall of athletic participation; participants social desirability leading to overreporting).
- Study population (cases who presented with SD were not included; in this study, only desmosomal mutation carriers included; all participants in a research registry by a tertiary care center; 87 interviews were members of 51 families; sample size limited with regard to the investigation).

---

**Aim:**
To determine how exercise influences penetrance of ARVC among patients with desmosomal mutations.

**Study type:**
Retrospective observational study.

**Number of patients:**
87

**Exclusion:**
NA.

**Results:**
Symptoms developed in endurance athletes (n = 690 Sawant AC, +21.1 years; = P 0.05); they were more likely to meet Task Force Criteria at last follow-up (82% vs. 35%; = P 0.001) and have a longer lifetime survival free of VT/VF (P = 0.013) and heart failure (P = 0.004). Compared with those who did the least exercise per year (lowest quartile) before presentation, those in the second (OR 6.64; P = 0.013), third (OR 16.7; P = 0.001), and top (OR 25.3; P = 0.001) quartiles were increasingly likely to meet Task Force Criteria. Among 41 individuals who did not present with VT/VF, the 13 subjects experiencing a first VT/VF event over a mean follow-up of 8.4 ± 6.7 years were all endurance athletes (P = 0.002). Survival from a first VT/VF event was lowest among those who exercised most (top quartile) both before (P = 0.036) and after (P = 0.005) clinical presentation. Among individuals in the top quartile, a reduction in exercise decreased VT/VF risk (P = 0.04).

**Conclusion:**
Performing endurance and high-intensity exercise was associated with a higher likelihood of developing the disease (fulfilling 2010 Task Force criteria and VA/ICD recommendations). Among individuals in the top quartile, a reduction in exercise decreased VT/VF risk (P = 0.04).

---

**Aim:**
To determine in at-risk family members of patients with ARVC if endurance exercise and exercise intensity increase the likelihood of fulfilling 2010 Task Force criteria for ARVC, VA ICD shocks.

**Study type:**
Single-centre retrospective observational study.

**Number of participants:**
28

**Exclusion:**
NA.

**Results:**
23 family members (41 ± 18 years, 18 women, 46% met Task Force criteria, eight had an ICD, and six history of VT/VF) of nine probands were interviewed for sports activity. Among participants, 11 (53%) had exercise-related arrhythmias; 24 (86%) were exercise guidelines compliant. After adjustment for age, sex, and family membership, both participation in endurance sports (OR: 4.4) and higher-intensity exercise (OR: 2.0) were associated with fulfillment of Task Force criteria. All 11 who had VT/VF were endurance athletes. Family members who restricted exercise at or below the minimum AHA-recommended minimum, especially those with VT/VF had performed high intensity sport.

**Conclusion:**
Performing endurance and high-intensity exercise was associated with a higher likelihood of developing the disease fulfilling Task Force criteria and ICD recommendations. Study population (cases who presented with SD were not included; in this study, only desmosomal mutation carriers included; all participants in a research registry by a tertiary care center; 87 interviews were members of 51 families; sample size limited with regard to the investigation).

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**Aim:**
To investigate the incidence, efficacy and safety of ICD therapy in patients with ARVC and no prior sustained VT or VF.

**Study type:**
Observational study of six collaborative medical centers.

**Number of patients:**
196

**Exclusion:**
NA.

**Results:**
During follow-up of 58 ± 33 months, 25 patients (26%) had appropriate ICD interventions and 27 (28%) had shocks for life-threatening VF or ventricular flutter.

**Conclusion:**
Prophylactic implantation of ICDs in ARVC and desmosomal mutation carriers may be appropriate.

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**Aim:**
To determine if prophylactic implantation of ICDs is associated with lower risk of death and sympomatic events in patients with ARVC with a desmosomal mutation.

**Study type:**
Observational study of six collaborative medical centers.

**Number of patients:**
226

**Exclusion:**
Patients with ARVC. No prior VT or VF.

**Results:**
28 family members (41 ± 18 years, 18 women, 46% met Task Force criteria, eight had an ICD, and six history of VT/VF) of nine probands were interviewed for sports activity. Among participants, 11 (53%) had exercise-related arrhythmias; 24 (86%) were exercise guidelines compliant. After adjustment for age, sex, and family membership, both participation in endurance sports (OR: 4.4) and higher-intensity exercise (OR: 2.0) were associated with fulfillment of Task Force criteria. All 11 who had VT/VF were endurance athletes. Family members who restricted exercise at or below the minimum AHA-recommended minimum, especially those with VT/VF had performed high intensity sport.

**Conclusion:**
Performing endurance and high-intensity exercise was associated with a higher likelihood of developing the disease fulfilling Task Force criteria and ICD recommendations. Study population (cases who presented with SD were not included; in this study, only desmosomal mutation carriers included; all participants in a research registry by a tertiary care center; 87 interviews were members of 51 families; sample size limited with regard to the investigation).
Conclusions: The highest risk of VA in ARVC patients is between 21 and 40 years. Male sex, AF, syncope, participation in strenuous exercise and occurrence of tolerated SMVT predicted life-threatening VA at follow-up.

Findings: First life-threatening arrhythmic event. None of the drugs significantly reduced the rate of life-threatening arrhythmic events.

Results: 704 Mazzanti A, et al. 2015

18 years, 58 men) were included. 78 patients (51 men, 31 women) were included. 78 patients (51 men, 31 women) were included. 137 patients (43.3%) had appropriate ICD therapy. 27 SCD, three died suddenly, and 36 (46%) patients had arrhythmic events (32 recurrent VT and 4 VF, 30 in the ICD group). A fragmented QRS in at least three leads and a fragmented QRS in the S wave of leads V1–V3 were associated with a higher incidence of VA. If patients with ICD implantation for secondary prevention were excluded, an fQRS in the S wave of V1–V3 was only associated with VA.

Aim: To describe the clinical course of ARVC, assessing the occurrence of a first life-threatening arrhythmic event or cardiovascular mortality, to evaluate the occurrence of life-threatening arrhythmic event at follow-up, and predictors of life-threatening arrhythmic event and to define the response to therapy on follow-up. Study type: Prospective registry. Number of patients: 704
Inclusion: Patients with ARVC diagnosis according to Task Force criteria. Exclusion: N.A.
Results: 704 patients (51 men, 31

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**Aim:**
To assess the relation between late and fragmented electrograms within the electroanatomical scar and the occurrence of arrhythmic events in patients with ARVC.

**Study type:**
Prospective observational study.

**Number of patients:**
32

**Enrolment period:**
2006-2009

**Study endpoints:**
Appropriate ICD therapies.

**Inclusion:**
Patients with definitive ARVC undergoing EPS and electroanatomical RV mapping.

**Exclusion:**
NA.

**Results:**
32 patients (47 ± 13 years) were included. All received an ICD for primary prevention of SCD. Electroanatomical RV scars were present in all patients, fragmented electrograms in 15 (47%), isolated late potentials in 13 (41%), and very late potentials in 13 (41%). 24 (75%) were inducible for VT by PES. During a mean follow-up of 25 ± 8 months, no patient died and 12 (38%) had ICD therapies. Patients with ICD shocks had higher prevalence of fragmented electrograms (92 vs. 20%; $P = 0.001$), isolated late potentials (75 vs. 20%; $P = 0.004$), and very late potentials (67 vs. 25%; $P = 0.030$). Fragmented electrograms were the only independently associated with ICD therapies on follow-up.

**Conclusions:**
The presence of fragmented, late, and very late potentials within the RV scar is associated with appropriate ICD therapies in patients with ARVC.

Chivulescu M, et al.  High penetrance and similar disease progression in probands and in family members with arrhythmogenic cardiomyopathy. PMID: 31504415 Year of publication: 2020

**Aim:**
To assess penetrance of family members of patients with ARVC at genetic diagnosis and during follow-up and to compare disease progression between probands and family members.

**Study type:**
Retrospective analysis of prospective cohort.

**Number of patients:**
144

**Enrolment period:**
1997–2018

**Study endpoints:**
SCA, sustained VT, appropriate ICD therapy for VT/VF.

**Inclusion:**
ARVC patients according to Task Force criteria and mutation-positive family members.

**Exclusion:**
Patients with cardiopulmonary comorbidity.

**Results:**
144 subjects (48% women, 40 ± 16 years, 68 probands, 76 family members) were included. Among family members, 58% had phenotypic expression at genetic diagnosis. During 5.7 (IQR 4.1 – 8.2) years of follow-up, 47% of family members without ARVC at diagnosis developed ARVC criteria, resulting in a yearly new ARVC penetrance of 8%. At inclusion, probands had more severe structural disease (27 ±12% vs. 3% [P<0.001]), more often electrical criteria and more often VA (66% vs. 0%) than family members. During 8.2 (IQR 5.8 – 11.2) years, 24 (35%) probands and 25 (33%) family members without major Task Force criteria at inclusion had structural progression. RVOT diameter showed similar progression rate in probands and family members (0.5 vs. 0.6 mm/year) and RV fractional area change progression rate was higher for family members (-0.6 vs. -0.8%/year; $P = 0.01$). Among 86 patients without overt structural disease or VA at inclusion, almost severe VA occurred in 9% of which seven (88%) had structural progression.

**Other findings:**
Structural progression was associated with arrhythmic event independent of age, sex, and proband status.

**Conclusions:**
More than half of family members had ARVC criteria at genetic diagnosis. In addition, a yearly ARVC penetrance of 8% was observed. Structural progression was observed in both probands and family members and was associated with the occurrence of VA.

**Limitations:**
Low number of new VA in probands/family members.

Hulot JS, et al.  Natural history and risk stratification of arrhythmogenic right ventricular dysplasia/ cardiomyopathy. PMID: 15451782 Year of publication: 2004

**Aim:**
To identify risk factors related to long-term prognosis in ARVC.

**Study type:**
Retrospective observational multicentre study.

**Number of patients:**
130

**Enrolment period:**
1977–2000

**Study endpoints:**
Death, cardiovascular death.

**Inclusion:**
ARVC patients according to Task Force criteria.

**Exclusion:**
NA.

**Results:**
130 ARVC patients (100 men, age at onset of symptoms 32 ± 14 years), 78% had LBBB VT, 17 patients presented with VF/Torodilated VT. After a mean of 81 ± 78 years, 24 patients died (mean age 54 ± 19 years, annual mortality rate 2.3%). 31 of cardiac origin (SCD 7, heart failure 24). All patients who died had ≥1 episode of UBB VT. Multivariate analysis showed that LV dysfunction and clinical signs of RV heart failure were associated with higher risk of cardiac death. Patients with history of VT and signs of right-sided heart failure had the worst prognosis.

**Conclusions:**
ARVC patients with VT and right-sided heart failure and/or LV dysfunction had the highest risk of cardiac death.
Conclusions:  
Usefulness of inducible ventricular tachycardia to predict long-term adverse outcomes in arrhythmogenic right ventricular cardiomyopathy.
PMID: 31031280 Year of publication: 2013

Aim: To define the predictive value of inducible SMVT during PES for long-term outcome in ARVC patients.
Study type: Observational retrospective single-centre study.
Number of patients: 62
Enrolment period: Not reported.
Study endpoints: Composite of cardiac death, heart transplantation, survived SCA, VF, sustained non-tolerated VT, and arrhythmic syncope.

Induction: ARVC patients according to 2010 Task Force criteria who underwent EPS with PES for clinical indication and had a follow-up ≥ 3 months. Exclusion NA.

Results: 62 ARVC patients (all probands) were included. 24 (39%) patients had spontaneous non-tolerated VT or VF, 20 (32%) spontaneous tolerated VT, and 15 (24%) had syncope. Sustained VA were induced in 46 (74%) patients SMVT ≥ 34 (55%) and VP in 15 (24%). 48 (77%) patients received an ICD (31 for secondary and 17 for primary prevention), including 29/34 (85%) patients inducible for SMVT. During a median follow-up of 9.8 years (IQR 4.4–12.5), 30 (48%) reached the primary endpoint. Inducibility of SMVT was independently associated with adverse outcome on follow-up in the whole cohort (HR 2.52; 95% CI 1.13–5.64, P = 0.019) but not in patients without prior SCA VF or sustained VT (HR 2.3; 95% CI 0.76–8.24, P = 0.13).  

Conclusions: SMVT inducibility during PES might predict adverse outcome in patients with ARVC. Limitations: Small, observational, retrospective study. When stratifying the data according to spontaneous occurrence of SCAVF or sustained VT, SMVT was not associated with long-term outcome in patients without prior VA.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Patients</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
<th>Other findings</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>703</td>
<td>Consecutive ARVC patients from 22 centres (21 European, one from United States) with an ICD and follow-up ≥ 6 months.</td>
<td>132 patients (45 ± 13 years, 70% men) were included. ICDs were implanted after SCA in 10% of patients, after not-tolerated VT in 39%, after tolerated VT in 23%, and in 28% of the cases in patients without sustained VA. During median follow-up of ≥ 37 months, four (3%) patients died and 64 (48%) had appropriate ICD therapy for VA (VF/164 ICD shocks). Survival rates were 99%, 98%, and 96% at 1, 2, and 3 years follow-up and VF/wVentricular flutter survival was 88%, 79%, and 72% at the same intervals. History of SCA or not-tolerated VT, younger age, and LV involvement were independent predictors of VF/ventricular flutter.</td>
<td>No patient undergoing EP ablation had VF/wVentricular flutter.</td>
<td>In patients with ARVC, ICD therapy provided potentially life-saving protection by terminating life-threatening VA. A prior history of SCA, not-tolerated VT, younger age, and LV involvement were associated with appropriate ICD therapy for VF/ventricular flutter on follow-up.</td>
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<tr>
<td>485</td>
<td>Patients with ARVC according to Task Force criteria referred for ablation for recurrent VT to a single centre with a minimum follow-up of one year.</td>
<td>62 patients (39 ± 15 years) underwent 121 procedures (median 2 [1-5] per patient): 23 (37%) endocardial-only and 39 (63%) endo-epicardial. After a median follow-up of 56 ± 44 months, cumulative VT-free survival was 71%. At last follow-up, 21 patients were receiving Class I or III anti-arrhythmic drugs.</td>
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<td>Other findings: Patients with tolerated VT had lower incidence of VF/ventricular flutter than patients after SCA/not-tolerated VT or unexplained syncope. 98/111 patients undergoing EP was inducible (67 for VT, 31 for VF); 51/98 (51%) did not experience ICD therapies while 7/13 (54%) non-inducible patients did.</td>
<td>Conclusions: Other findings: Patients with tolerated VT had lower incidence of VF/ventricular flutter than patients after SCA/not-tolerated VT or unexplained syncope. 98/111 patients undergoing EP was inducible (67 for VT, 31 for VF); 51/98 (51%) did not experience ICD therapies while 7/13 (54%) non-inducible patients did.</td>
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<tr>
<td>712</td>
<td>Patients with ARVC and ≥ 3 VT episodes despite beta-blockers and/or anti-arrhythmic drugs.</td>
<td>110 patients (38 ± 17 years, 83% men) were included. After ≥ 3 VT episodes, 71 patients (70%) were treated with drugs (either started or escalated), and 32 (32%) were treated with ablation (21 endocardial, 11 endo-epicardial). At 3 years, 35% of patients undergoing ablation compared to 28% treated with anti-arrhythmic drugs/beta-blockers only were free of VT (P = 0.046). 43 patients initially treated with drugs underwent ablation on follow-up. Epicardial ablation was performed in 40/35 (53%) patients. At 3 years, 56% of a total of 75 patients undergoing ablation were free of VT. A higher percentage of patients undergoing epicardial ablation were free of VT at 3 years (71% vs. 47%, P = 0.03).</td>
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<td>Other findings: There was no difference in survival free of death or transplantation between the ablation and anti-arrhythmic drug/β-blockers only treated patients (P = 0.61).</td>
<td>Conclusions: Other findings: Patients with ARVC and high VT burden have a high risk of recurrence despite beta-blockers/anti-arrhythmic drug initiation/escalation or a single ablation procedure. VT control frequently requires multiple procedures. Combined endo-epicardial ablation was associated with better outcome than endocardial ablation alone. No difference in survival or necessity of heart transplantation was seen between patients undergoing drug treatment or ablation.</td>
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<td>717</td>
<td>ARVC patients according to Task Force criteria presenting with sustained VT.</td>
<td>11 consecutive patients (42 ± 13 years) with ≥ 3 VT episodes with ARVC (2 with LV involvement) and VT were induced (7 were on anti-arrhythmic drugs, 5 had electrical storm). By substrate mapping, 10/11 patients had endocardial scar and all had epicardial scar, which was bigger in all cases. A mean of 13 ± 4.7 VTs were induced per patient: two were ablated off from the endocardium and 12 (96%) required epicardial ablation. All patients were rendered non-inducible by ablation (scar dechannelling technique). During a median follow-up of 11 (6-24) months, only one patient recurred.</td>
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<td>Conclusions: Other findings: Patients with ARVC, combined endo-epicardial catheter ablation as first-line therapy incorporating the scar dechannelling technique was associated with low VT recurrence in mid-term follow-up.</td>
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<tr>
<td>Aim</td>
<td>The objective of this study was to identify predictors, characteristics, and treatment of VAs in patients with ARVC. Study type: Retrospective, prospective registry. Number of patients: 137. Environment period: Not reported. Study endpoints: VAs after ICD implantation, life-threatening arrhythmias (VT ≥ 240 b.p.m., VF, or SCD).</td>
<td>Inclusion: Patients with a diagnosis of ARVC. Exclusion: NA.</td>
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<tr>
<td>Results</td>
<td>Of 137 patients enrolled, 108 received ICDs; 48 patients had 502 sustained VT, including 49 that were monomorphic and 13 that were polymorphic. In the patients with ICDs, independent predictors of VAs in follow-up included spontaneous sustained VA (P = 0.0029) before ICD implantation and T-wave inversions inferiorly (P = 0.0159). The only independent predictor for life-threatening arrhythmias, defined as sustained VT ≥ 240 b.p.m. or VF, was an older age at enrolment (P = 0.012). ATR independent of the cycle length of the VT, was successful in terminating 92% of VT episodes.</td>
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<tr>
<td>Conclusions</td>
<td>In the North American ARVC Registry, the majority of VAs in follow-up are monomorphic. Risk factors for VAs were spontaneous VAs before enrolment and a younger age at ICD implantation.</td>
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<table>
<thead>
<tr>
<th>695</th>
<th>Wang W, et al. 2018</th>
<th>Arrhythmic outcome of arrhythmogenic right ventricular cardiomyopathy patients without implantable cardioverter defibrillator. PMID: 29194127 Year of publication: 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim</td>
<td>To report the arrhythmic course of a contemporary cohort of ARVC patients without ICD. Study type: Retrospective analysis of a single-centre prospective registry. Number of patients: 131. Environment period: 1999–. Study endpoints: Primary endpoint: composite of cardiac arrest, SCD, and sustained VT.</td>
<td>Inclusion: ARVC patients without ICD for a minimum of 6 months after fulfilling Task Force criteria. Exclusion: NA.</td>
</tr>
<tr>
<td>Results</td>
<td>Of 131 patients with ARVC (median age 34 years, 39% men, 50% probands). After a median follow-up of 8 years, 28 (21%) patients reached the primary outcome (3 SCD, 25 CA, 30 sustained VT) while having ICDs. The 1- and 5-year event-free survival was 92% and 72%. Spontaneous sustained VA, cardiac syncope, men, proband status, and inducibility by PES were associated with the primary outcome in univariate analysis.</td>
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<td>Other findings</td>
<td>When Task Force criteria were fulfilled, five patients had survived a CA and 26% had experienced sustained VT; 22 (17%) had cardiac syncope. 28 (21%) had severely depressed RV function. When fulfilling ARVC criteria, ICDs were not recommended in 59 (45%) patients and were declined by 22 (17%). In 40 (31%), the treating physicians did not recognize as having ARVC.</td>
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<tr>
<td>Conclusions</td>
<td>Almost one-third of a contemporary cohort of patients with ARVC had sustained VA or CA before ICD implantation. Spontaneous sustained VA, cardiac syncope, men, gender, proband status, and inducibility by PES were confirmed as risk factors for sustained VA/CA in ARVC. Patients in whom the disease was not recognized by their treating physician carried a particularly high risk.</td>
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</table>

<table>
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<tr>
<th>713</th>
<th>Ermakov S, et al. 2018</th>
<th>Use of flecainide in combination with antiarrhythmic therapy in patients with arrhythmogenic right ventricular cardiomyopathy. PMID: 29939893 Year of publication: 2017</th>
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<tr>
<td>Aim</td>
<td>To report the efficacy of the combination of metoprolol/ivabradine and flecainide for the treatment of VA in patients with ARVC. Study type: Case series. Number of patients: 8. Environment period: Not reported. Study endpoints: Major VA recurrence: sustained VT or VA prompting ICD therapy (ATF/Check).</td>
<td>Inclusion: Patients with ARVC according to Task Force criteria treated with a combination of metoprolol/ivabradine and flecainide. Exclusion: NA.</td>
</tr>
<tr>
<td>Results</td>
<td>Of 45 ARVC patients followed in a genetic arrhythmia programme, eight were treated with the combination of metoprolol/ivabradine and flecainide for VA after failing single-drug therapy (8/8) and ablation in 7/8 patients (endocardial in four patients, endo-epicardial in 3). After a median of 35.5 months, 6/8 patients had no VA recurrence under the combination of anti-arrhythmic drugs. Two patients with recurrence underwent repeated ablation procedures.</td>
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<tr>
<td>Conclusions</td>
<td>Flecainide in combination with metoprolol/ ivabradine might be effective for VA control in patients with ARVC and recurrent VA despite single-drug therapy.</td>
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### Table of Evidence 28 for Table of Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmias in hypertrophic cardiomyopathy

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, year of publication, PMID</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
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<tr>
<td>719</td>
<td>Chan RH, et al.244</td>
<td>To assess the relation between LGE and cardiovascular outcomes in HCM patients referred for CMR.</td>
<td>HCM patients with CMR. Exclusion: Prior implantation of an ICD, history of sustained VT/VF, diastrophic cardiomyopathies, known associated obstructive CAD, other myocardial diseases, septal myectomy or alcohol ablation, and incomplete follow-up.</td>
<td>Patients were followed up for a median of 3.3 years. SCD events (including appropriate defibrillator interventions) occurred in 37 patients (3%). A continuous relationship was evident between LGE by percent left ventricular mass and SCD event risk in HCM patients (P = 0.001). Extent of LGE was associated with an increased risk of SCD events (adjusted HR 1.46/10% increase in LGE; P = 0.001), even after adjustment for other relevant disease variables. LGE ≥ 15% of LV mass demonstrated a two-fold increase in SCD event risk in those patients otherwise considered to be at lower risk, with an estimated likelihood for SCD events of 6% at 5 years.</td>
<td>Other findings: Performance of the SCD event risk model was enhanced by LGE (net reclassification index, 12.9%; 95% CI 6.3–38.3). Absence of LGE was associated with lower risk for SCD events (adjusted HR 0.39; P = 0.02). Extent of LGE also predicted the development of end-stage HCM with systolic dysfunction (adjusted HR 1.80/10% increase in LGE; P &lt; 0.03).</td>
<td>Conclusions: Extensive LGE measured by quantitative contrast-enhanced CMR provides additional information for assessing SCD event risk among HCM patients, particularly patients otherwise judged to be at low risk.</td>
</tr>
<tr>
<td>720</td>
<td>He D, et al.245</td>
<td>To analyse the effects of LGE on clinical outcomes in patients with HCM.</td>
<td>Cohort studies evaluating effects of LGE on clinical outcomes of patients with HCM. Exclusion: NA.</td>
<td>Results: Mean follow-up was 2.9 years. The weighted average annualized event rates of SCD/aborted SCD in patients with HCM (positive LGE vs. negative LGE) was 1.38% vs. 0.32% (P &lt; 0.001), and the pooled OR was 3.40 (95% CI 1.90; 6.08; P &lt; 0.001). The sensitivity and specificity of predicting future cardiac events were 0.83 (95% CI 0.66; 0.93) and 0.45 (95% CI 0.31; 0.59), respectively. The 5-year risk of SCD/aborted SCD was 6% in patients with LGE. The all-cardiac death and all-cause mortality were also significantly increased in patients with LGE. However, the extent of LGE was not significantly related to the risk of SCD/aborted SCD.</td>
<td>Other findings: NA.</td>
<td>Conclusions: LGE is significantly associated with SCD/aborted SCD risk, all cardiac death and all-cause mortality in patients with HCM. ICD can be considered for those patients with LGE.</td>
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Continued
### 721
**Wasser-Sir A, et al.**

**Primary prevention implantable cardioverter-defibrillators in hypertrophic cardiomyopathy—are there predictors of appropriate therapy?**

*PMID: 32808967*
*Year of publication: 2018*

**Aim:** To assess the incidence and predictors of appropriate ICD therapies, inappropriate shocks, and device-related complications in patients with HCM and primary prevention ICDs.  

**Study type:** Single-centre longitudinal cohort study.  

**Number of patients:** 302.  

**Enrolment period:** September 2000–December 2017.  

**Study endpoints:** Therapies (shocks or antitachycardia pacing) for VT or VF were considered appropriate.  

**Inclusion:** Patients with HCM who underwent primary prevention ICD implantation at Toronto General Hospital.  

**Exclusion:** Secondary prevention ICDs.  

**Results:** Mean follow-up was 6.1 ± 4.3 years (1801 patient-years of follow-up). 38 patients (12.6%) received at least one appropriate ICD therapy (2.3%/year); the 5-year cumulative probability of reaching appropriate ICD therapy was 9.6%. None of the conventional risk factors or the European Society of Cardiology risk score was associated with appropriate ICD therapy. In multivariable analysis, age <40 years at implantation and atrial fibrillation were independent predictors of appropriate ICD therapy.  

**Conclusions:** The incidence of appropriate ICD therapies in patients with HCM and primary prevention ICDs is lower than previously reported. A high proportion of patients suffer from an ICD-related complication. Traditional risk factors have low predictive utility. Severe LGE, atrial fibrillation, and young age are important predictors of ventricular tachyarrhythmias in HCM.

### 724
**Roamit S, et al.**

**Relationship between aetiology and left ventricular systolic dysfunction in hypertrophic cardiomyopathy.**

*PMID: 2779853*
*Year of publication: 2017*

**Aim:** To compare the prevalence of systolic dysfunction according to causes and its impact on prognosis in patients with different causes of HCM.  

**Study type:** Retrospective longitudinal cohort study at two centres.  

**Number of patients:** 1697 patients with HCM followed at two European referral centres.  

**Enrolment period:** London HCM patients who were tested for sarcomeric protein gene mutations using high-throughput sequencing between 2011 and 2013 and all patients diagnosed between 1991 and 2014.  

**Study endpoints:** The primary survival outcome was all-cause mortality or heart transplantation for end-stage heart failure. Secondary outcomes were heart failure-related death, SCD, stroke-related death, and non-cardiovascular death.  

**Inclusion:** Unrelated consecutive HCM patients ≥16 years of age who underwent targeted genetic and biochemical testing.  

**Exclusion:** Patients were excluded when there were no verifiable data on LV systolic function.  

**Results:** Mean follow-up of 5.4 ± 6.9 years (24 791 patient-years; median, 2.9 years). Age at diagnosis and sarcomere mutation had a two-fold greater risk for adverse outcomes compared with patients without mutations; highest risk for VA (HR 2.8; 95% CI 2.1–3.9; P < 0.001). All-cause death or heart transplant and heart failure-related death were highest in patients with cardiac amyloidosis (P < 0.001).  

**Conclusions:** Young age at presentation is a marker for specific aetiologies and is associated with poorer long-term survival.

### 725
**Ho CY, et al.**

**Genotype and lifetime burden of disease in hypertrophic cardiomyopathy: Insights from the sarcomeric human cardiomyopathy registry (Shark).**

*PMID: 28199772*
*Year of publication: 2018*

**Aim:** To understand the factors that contribute to heterogeneous outcomes and lifetime disease burden in HCM. Special focus on genetics.  

**Study type:** Longitudinal data sets curated by eight international HCM specialty centres.  

**Number of patients:** 4591 patients with HCM (2763 genotyped).  

**Enrolment period:** 1960–2016.  

**Study endpoints:** Ventricular arrhythmic composite first occurrence of SCD, stroke, death, or appropriate ICD therapy.  

**Inclusion:** Unexplained LV hypertrophy with maximal LV wall thickness >13 mm (or equivalent z score for paediatric patients), integrating genotype.  

**Exclusion:** Age >1 and direct visit to the SHARK site since 1960 and ≥1 echocardiographic assessment of LV wall thickness.  

**Results:** Mean follow-up of 5.4 ± 6.9 years (24.791 patient-years; median, 2.9 years). Age at diagnosis and sarcomere mutation status were predictive of outcomes. Patients with pathogenic or likely pathogenic sarcomere mutations had a two-fold greater risk for adverse outcomes compared with patients without mutations; highest risk for VA (HR 2.8; 95% CI 1.2–3.9; P < 0.001). Patients with multiple pathogenic or likely pathogenic sarcomere mutations had a three-fold increased risk for the overall composite and a four-fold increased risk for VA relative to patients without sarcomere mutations. Sarcomere variants of uncertain significance were associated with intermediate risk.

**Conclusions:** Young age at diagnosis and the presence of a sarcomere mutation are powerful predictors of adverse outcomes.  

**Limitations:** In multivariate analyses including conventional SCD risk factors (but not controlled for proband status, sex, and race, the age at diagnosis).
### 726 Kim HY, et al. 2020

**Study Type:** Prospective registry at a single centre (Seoul)  
**Number of Patients:** 89 consecutive unrelated HCM patients  
**Enrolment Period:** March 2013–February 2017  
**Study endpoints:** A composite of major adverse cardiac and cerebrovascular events was assessed.  

**Inclusion:** HCM patients who underwent CMR analysis.  
**Exclusion:** Poorly controlled hypertension, uncontrolled VA, severe valvular disease, and other concomitant systemic diseases including malignancy and those who were contraindicated for CMR or had poor echocardiographic windows for analysis.  

**Results:** Genetic variants were detected in 35 of 89 subjects. Pathogenic variants or likely pathogenic variants were identified in 27 of HCM patients in MYBPC3, TNNI3, MYH7, and MYL7. Variants of uncertain significance were identified in 28 patients.  

**Conclusion:** There were significant differences in the presence of NSVT (P = 0.030) and myocardial fibrosis on CMR (P = 0.029) in the detected compared to the not-detected groups. Event-free survival was superior in the not-detected group (P = 0.004).  


**Study Type:** Databases of 3 HCM centres were accessed (retrospective multicentre longitudinal cohort study).  
**Number of Patients:** 18 probands with two disease-causing mutations. Enrolment period 2000–2010  
**Study endpoints:** Severe disease progression or adverse cardiovascular events.  

**Inclusion:** Probands with HCM who underwent systematic mutational screening.  
**Exclusion:** NA.  

**Results:** Severe disease progression or adverse cardiovascular events occurred in seven of these 18 patients (39%), including three patients (ages 31, 37, and 57 years) who experienced SCA but also were without evidence of conventional HCM risk factors two survived with timely defibrillation and therapeutic hypothermia and one died. These three probands carried distinct and heterogeneous disease-causing sarcomere mutations (including a man who inherited one mutation independently from each of his parents with HCM—that is, double MYBPC3 and TNNI3 mutations and compound MYH7/C mutations—as the only predisposing clinical markers evident to potentially explain their unexpected cardiac event.  

**Conclusion:** These observations support the emerging hypothesis that double (or compound) mutations detected by genetic testing may confer a gene dosage effect in HCM, thereby predisposing patients to adverse disease progression. In three families, multiple sarcomere mutations were associated with a risk of SCD, even in the absence of conventional risk factors.  

### 728 Wang J, et al. 2014

**Study Type:** Prospective single-centre longitudinal cohort study.  
**Number of Patients:** 529 unrelated HCM patients  
**Enrolment Period:** 1999–2010  
**Study endpoint:** Cardiovascular death.  

**Inclusion:** HCM patients with eight sarcomere genes were screened with targeted resequencing.  
**Exclusion:** Common polymorphisms and neutral variants.  

**Results:** Follow-up was 4.7 ± 3.2 years. Multiple rare variants were identified in 7.2% (38/529) of the study patients. Patients with multiple rare variants were younger at diagnosis and had greater maximum LV wall thicknesses and larger left atria. The risk for cardiovascular death in patients with multiple rare variants was higher than in those without rare variants (P = 10⁻⁵) or in those with a single rare variant (P = 2 × 10⁻⁵). Multivariable analysis revealed that multiple rare variants were a risk factor for cardiovascular death (HR 3.74; 95% CI 1.84–7.58; P = 0.003), as well as SCD (HR 3.57; 95% CI 1.23–10.35; P = 0.019) and heart failure-related death (HR 4.62; 95% CI 1.67–12.76; P = 0.003).  

**Conclusion:** The presence of multiple rare variants in sarcomere genes is a risk factor for malignant outcomes in HCM and may be appropriate to consider as a criterion in the risk stratification of HCM patients.

- **Inclusion:** Athletes with a definitive diagnosis of HCM. Exclusion: N.A.

- **Results:** Males (n = 33), White (n = 33), and 32 (± 1) (14–53) years of age. Athletes participated in soccer (n = 13), athletics (n = 6), rowing, swimming, basketball, triathlon, tennis, cycling (each, n = 2), and water polo, volleyball, handball, and dance (each, n = 1). Each had been engaged in training and competitions for 5–31 years (mean ± 15 ± 8). Level of achievement included elite international (n = 3), national (n = 10), and regional/county tournaments (n = 22).

- **Over the follow-up, one event occurred (incidence 0.3% per year): an amateur tennis player injured an acute CA white walking in an urban shopping area.**

- **Other findings:** The incidence of combined event and symptoms was not different among individuals who continued exercise and sport programmes (3 of 15) vs. those who dismissed any physical activity (5 of 20) log rank test P = 0.236; Cox regression analysis HR 2.4; 95% CI 0.5–11.1; P = 0.255). Patients experiencing event or symptoms presented positive family history for HCM in larger proportion (63% vs. 11%; P = 0.002), had more frequent bursts of NSVT at 24-h ECG monitoring (38% vs. 7%; P = 0.03), had a higher rate of positive LGE on CMR (67% vs. 2%; P = 0.002), and lower e′ velocit on tissue Doppler echocardiography (33 ± 5 vs. 92 ± 32; P < 0.002).

- **Conclusions:** Over a period of 9-year follow-up, even lower-risk athletes with HCM may incur symptoms (2.6% per year) and cardiac arrest (0.13% per year), but suggests that the incidence of event/symptoms is largely independent from continuation or interruption of regular exercise and sport programmes.

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- **Aim:** To develop and validate a new SCD risk prediction model that provides individualized risk estimates in HCM. Study type: Retrospective multicentre longitudinal cohort study. Number of patients: 3675 consecutive patients from six centres (including 2082 in derivation sample and 1593 in validation sample). Enrolment period: Not reported. Study endpoints: SCD or an equivalent event: aborted SCD and appropriate ICD shock therapy.

- **Inclusion:** Adult patients (≥ 16 years of age) with no prior VF or sustained VT were studied. HCM left ventricular wall thickness ≥ 15 mm unexplained by abnormal loading conditions or in accordance with published criteria for the diagnosis of disease in relatives of patients. Exclusion: Patients with known metabolic diseases (e.g. Anderson–Fabry disease) or syndromic causes of HCM (e.g. Noonan syndrome).

- **Results:** Follow-up period of 313 patient-years (median 5.7 years). 198 patients (5%) died suddenly or had an appropriate ICD shock. Of eight prespecified predictors, age, maximal left ventricular wall thickness, left atrial diameter, left ventricular outflow tract gradient, family history of SCD, NSVT, and unexplained syncope were associated with SCD appropriate ICD shocks at the 13% significance level. These predictors were included in the final model to estimate individual probabilities of SCD at 5 years. The calibration slope was 0.91 (95% CI 0.74–1.08), C-index was 0.70 (95% CI 0.60–0.82), and D-statistic was 1.07 (95% CI 0.81–1.32).

- **For every 16 ICDs implanted in patients with ≥5 year SCD risk, potentially one patient will be saved from SCD at 5 years.**

- **Other findings:** Online calculator (https://klock26.github.com/webHCM.html).

- **Conclusions:** The first validated SCD risk prediction model for patients with HCM. Validated: Yes; both internal (bootstrap validation) and external validation. A second model with the data set split into independent development and validation cohorts had very similar estimates of coefficients and performance when externally validated.

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- **Aim:** To externally validate the 2014 European Society of Cardiology recommendations in a geographically diverse cohort of patients recruited from the United States, Europe, the Middle East, and Asia. Study type: Observational, retrospective, longitudinal cohort study. Number of patients: 3703. Enrolment period: 1990–2014. Study endpoints: SCD or an equivalent event: aborted SCD was defined as witnessed SD with or without documented VF or death within 1 h of new symptoms or nocturnal deaths with no antecedent history of worsening symptoms. Aborted SCD during follow-up and appropriate ICD shock therapy were considered equivalent to SCD.

- **Inclusion:** Only adult patients (≥ 16 years of age) without prior VF or sustained VT were studied. Exclusion: Patients known to have metabolic diseases or syndromic causes of HCM.

- **Results:** 73 (2%) patients reached the SCD endpoint within 5 years of follow-up (5-year incidence 2.4% [95% CI, 1.9–3.0]).

- **Conclusions:** This study confirms that the HCM Risk-SCD model provides accurate prognostic information that can be used to target ICD therapy in patients at the highest risk of SCD.
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<th>Study type</th>
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<td>732</td>
<td>Vrentendorp PA et al.</td>
<td>Validation of the 2014 European Society of Cardiology Guidelines risk prediction model for the primary prevention of sudden cardiac death in hypertrophic cardiomyopathy. PMID: 25923410 Year of publication: 2015</td>
<td>Aim: To perform an external and independent validation of the new ESC 2014 risk prediction model for SCD in HCM. Study type: Observational two-centre longitudinal cohort study. Number of patients: 706 patients with HCM from two tertiary referral centres.</td>
<td>706</td>
<td>Information not provided, except censoring date, set at 1 November 2012. Study endpoints: The primary endpoint was a composite of SCD and appropriate ICD therapy, identical to the HCM Risk-SCD endpoint.</td>
<td>Inclusion: Patients with HCM without prior SCD event. The same inclusion and exclusion criteria as described in the HCM Risk-SCD study.</td>
<td>Exclusion: History of SCD before or as first contact. Patients with HCM linked to Noonan syndrome, Fabry disease, mitochondrial disease, or congenital heart defects were excluded.</td>
<td>Results: During follow-up of 7.7 ± 5.3 years, SCD occurred in 42 (5.9%) of 706 patients (ages 49 ± 16 years; 34% women). The C-statistic of the new model was 0.69 (95% CI 0.57–0.82; P = 0.008), which performed significantly better than the conventional risk factor models based on the 2003 guidelines (C-statistic of 0.55: 95% CI 0.47–0.63; P = 0.3), and 2011 guidelines (C-statistic of 0.60; 95% CI 0.50–0.70; P = 0.07).</td>
<td>Conclusions: The HCM Risk-SCD model improves the risk stratification of patients with HCM for primary prevention of SCD and calculating an individual risk estimate contributes to the clinical decision-making process. Improved risk stratification is important for the decision-making before ICD implantation for the primary prevention of SCD.</td>
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<td>739</td>
<td>Rowin EJ, et al.</td>
<td>Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. PMID: 32553356 Year of publication: 2020</td>
<td>Aim: To re-evaluate clinical profile and prognosis for end-stage heart failure in a large HCM cohort with contemporary management strategies. Study type: Single-centre longitudinal cohort study. Number of patients: 2447</td>
<td>2447</td>
<td>2004–2017</td>
<td>Study endpoints: Heart failure, heart transplant, heart failure mortality.</td>
<td>Inclusion: Patients with a hypertrophied and non-dilated LV (LV wall thickness ≥ 15 mm) in the absence of another cardiac or systemic disease capable of producing a similar magnitude of hypertrophy.</td>
<td>Exclusion: NA.</td>
<td>Results: Of the 2447 patients, 118 (4.8%) had end-stage HCM with systolic dysfunction (LVEF &lt; 50%), (LVEF 39 ± 9%; range 12–49%) at age 48 ± 15 years. Follow-up was 5.8 ± 4.7 years (up to 18 years). In total, 61 other patients (22%) developed refractory heart failure to dual NYHA functional classes II/IV (52.5%/year); 67% have survived, including 31 with heart transplant. End-stage HCM-related mortality was 1.9%/year; with 10-year survival of 85% (95% CI 77–94%). Mortality was four-fold lower than previously reported for end-stage HCM (8.0%/year), but exceeded 10.0%/year HCM with preserved LVEF (6.25%/year; P &lt; 0.001).</td>
<td>Conclusions: Although end-stage heart failure remains an important complication of HCM, contemporary treatment strategies, including ICDs and heart transplant, are associated with significantly lower mortality than previously considered. Primary prevention ICDs should be considered when LVEF is &lt; 50% in HCM.</td>
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<td>740</td>
<td>Rowin EJ, al.</td>
<td>Hypertrophic cardiomyopathy with left ventricular apical aneurysms: implications for risk stratification and management. PMID: 28309216 Year of publication: 2017</td>
<td>Aim: To clarify clinical course and prognosis of a large cohort of HCM patients with LV apical aneurysms over long-term follow-up. Study type: Retrospective two-centre longitudinal cohort study. Number of patients: 1940 consecutive HCM patients at two centres.</td>
<td>1940</td>
<td>1983–2014</td>
<td>Study endpoints: The combined endpoint was an aggregate of HCM-related death and non-fatal adverse disease-related events.</td>
<td>Inclusion: Consecutive patients with HCM diagnosis. Exclusion: NA.</td>
<td>Results: 93 patients (4.8%) had LV apical aneurysms; mean age was 56 ± 13 years, and 69% were men. Over 4.4 ± 3.2 years of the 93 patients (31%) died suddenly or of heart failure, but 22 (24%) survived with contemporary treatment interventions 18 experienced appropriate ICD discharges, two underwent heart transplants and two were resuscitated after cardiac arrest. The SD event rate was 4.7%/year, which includes 39.3% successful resuscitation from cardiac arrest, or appropriate ICD interventions triggered by VF or rapid VT. Notably, recurrent monomorphic VT requiring ≥ 2 ICD shocks occurred in 13 patients, including six who underwent successful radiofrequency ablation of the arrhythmic focus without VT recurrence. Rate of HCM-related deaths combined with life-saving aborted disease-related events was 6.4%/year, three-fold greater than the 2.0%/year event rate in 1967 HCM patients without aneurysms (P = 0.001).</td>
<td>Conclusions: HCM patients with LV apical aneurysms are at high risk for arrhythmic SD.</td>
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Conclusions: Normal exercise blood pressure response identifies low-risk young patients with HCM. An abnormal blood pressure response identifies the high-risk cohort; the low positive predictive accuracy.


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### Conclusions:
Over a median follow-up of 5.3 years (IQR 2.6 – 14.5), 89 patients (8.7%) died suddenly or had an equivalent event (annual event rate, 1.49; 95% CI 1.15 – 1.92).

The paediatric model was developed using preselected variables to predict the risk of SCD. The model’s ability to predict risk at 5 years was validated; the C statistic was 0.69 (95% CI 0.66 – 0.72), and the calibration slope was 0.98 (95% CI 0.59 – 1.38). For every 10 ICDs implanted in patients with 6% or more of a 5-year SCD risk, one patient may potentially be saved from SCD at 5 years.

The performance of the paediatric model to predict 5-year risk of SCD was compared with that of the adult risk stratification tool (HCM Risk-SCD). The adult model has modest discriminatory ability (C index, 0.67; 95% CI 0.65 – 0.69) but does not predict risk accurately (calibration slope, 0.79; 95% CI 0.43 – 1.15) for the paediatric cohort. Including age and family history of SCD in the paediatric model did not improve its performance.

### Aim:
To develop and validate an SCD risk prediction model in children with HCM that provides individualized risk estimates.

### Study type:
Retrospective, multicentre, longitudinal cohort study.

### Number of patients:
1024

### Enrolment period:

### Results:
Cumulative survival (death or ICD discharge) for the entire cohort was 99% at 3 years (95% CI 93.8% – 100%). Calculation slopes 0.30 (95% CI 0.38 – 0.58) and a C statistic of 0.702 (95% CI 0.60 – 0.81). Results: HCM-Risk-Kids provides a method for individualized risk predictions and shared decision-making in children with HCM.

### Conclusions:
This new, validated risk stratification model for SCD in childhood HCM may provide individualized estimates of risk at 5 years using readily obtained clinical risk factors. External validation studies are required validated only internally validated using bootstrapping.

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### Conclusions:

Recurrent cardiac arrest or premature cardiac death (sudden or due to congestive failure) occurred in one-third of the patients, most commonly within the first 5 years after the initial arrest.

### Results:

Mean follow-up was 3.7 (standard deviation, 2.8) years. Measured risk factors for SD included family history of SD, massive left ventricular hypertrophy, NSVT on Holter monitoring, and unexplained prior syncope. ICD interventions appropriately terminated VT/VF in 103 patients (20%). Intervention rates were 10.6% per year for secondary prevention after cardiac arrest (5-year cumulative probability, 39% [standard deviation, 7%]) and 3.6% per year for primary prevention (5-year cumulative probability, 17% [standard deviation, 21%]). Time to first appropriate discharge was up to 10 years, with a 27% (standard deviation, 7%) probability 5 years or more after implantation. Other findings: For primary prevention, 18 of the 31 patients with appropriate ICD interventions (58%) had undergone implantation for only a single risk factor; likelihood of appropriate discharge was similar in patients with 1, 2, or 3 or more risk markers (3.83, 2.65, and 4.82 per 100 person-years, respectively, P = 0.77). The single SD due to arrhythmia (in the absence of advanced heart failure) resulted from ICD malfunction. ICD complications included inappropriate shocks in 136 patients (27%).

### Conclusions:

In a high-risk HCM cohort, ICD interventions for life-threatening ventricular tachyarrhythmias were frequent and highly effective in restoring normal rhythm.

### Conclusions:

In patients with HCM and apical aneurysms, endocardial RFCA of apical aneurysm effectively suppressed monomorphic VT, which was related to the apical aneurysm and resulted in satisfactory outcomes.

### Inclusion:

Patients with HCM who experienced a cardiac arrest but were successfully resuscitated. Exclusion: NA.

### Inclusion:

Patients with HCM who had received ICDs. Exclusion: NA.

### Inclusion:

Patients with HCM who underwent RFCA of VT. Exclusion: NA.

### Exclusion:

- NA.
- NA.
- NA.

### Study endpoints:

- Main outcome measure: appropriate ICD intervention terminating VT/VF.
- Other findings: For primary prevention, 18 of the 31 patients with appropriate ICD interventions (58%) had undergone implantation for only a single risk factor; likelihood of appropriate discharge was similar in patients with 1, 2, or 3 or more risk markers (3.83, 2.65, and 4.82 per 100 person-years, respectively, P = 0.77). The single SD due to arrhythmia (in the absence of advanced heart failure) resulted from ICD malfunction. ICD complications included inappropriate shocks in 136 patients (27%).

### Other findings:

- Mean follow-up was 3.7 (standard deviation, 2.8) years. Measured risk factors for SD included family history of SD, massive left ventricular hypertrophy, NSVT on Holter monitoring, and unexplained prior syncope. ICD interventions appropriately terminated VT/VF in 103 patients (20%). Intervention rates were 10.6% per year for secondary prevention after cardiac arrest (5-year cumulative probability, 39% [standard deviation, 7%]) and 3.6% per year for primary prevention (5-year cumulative probability, 17% [standard deviation, 21%]). Time to first appropriate discharge was up to 10 years, with a 27% (standard deviation, 7%) probability 5 years or more after implantation.

### Inclusion:

- To describe the long-term outcome of patients with HCM who experienced a cardiac arrest but were successfully resuscitated. Study type: Longitudinal cohort study. Number of patients: 33. Enrollment period: Since 1973. Study endpoints: Death and related cause of death.

### Inclusion:


### Inclusion:

**Aim:** To report outcomes of combined epicardial-endocardial ablation in a highly selected group of patients with HCM-related SMVT.

**Study type:** Longitudinal cohort study.

**Number of patients:** 10 patients with HCM-related SMVT.

**Enrolment period:** December 2003–December 2009

**Study endpoints:** Freedom from recurrent ICD shocks

**Inclusion:** Patients with HCM-related SMVT who underwent ablation procedures.

**Exclusion:** NA

**Results:**
- Epicardial scar was present in eight (80%) patients, endocardial scar in six (60%), and no scar in one (10%).
- In the five patients with inducible, stable SMVT, 3 cases were successfully terminated with ablation from the epicardium and one from the endocardium. The case that failed RFCA required surgical cryoablation to abolish an incessant VT.
- In the remaining five patients, four underwent epicardial and endocardial ablation of sites with good pace maps and late/fractionated potentials. No ablation was performed in the remaining patient because of non-inducibility and lack of identifiable scar.
- After 37 ± 17 months (range 24–62 months; median, 37 months), the freedom from recurrent ICD shocks was 78% (7/9 patients) in those who underwent ablation.

**Conclusions:** In highly selected patients with HCM, combined epicardial and endocardial mapping and ablation is a feasible and reasonably efficacious option for SMVT if refractory to aggressive trials of anti-arrhythmic drugs and ATP.
### 4.1.3.4. Neuromuscular disorders

#### Table of Evidence 29 for Table of Recommendations for risk stratification, sudden cardiac death prevention, and treatment of ventricular arrhythmia in neuromuscular diseases

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Bucci E, et al. 2018.267</td>
<td>Aim: To determine prevalence, incidence, characteristics, age of onset, and predictors of cardiac conduction and/or rhythm abnormalities, cardiac conduction and/or rhythm abnormalities progression, and SCD in myotonic dystrophy type 1. Study type: Retrospective observational study. Number of patients: 151 Enrolment period: 34 years. Study endpoints: Cardiac conduction and/or rhythm abnormalities, cardiac conduction and/or rhythm abnormalities progression, and SCD.</td>
<td>Inclusion: Myotonic dystrophy (genetically confirmed), normal 12-lead ECG and 24-h Holter, at baseline, followed for at least one year. Exclusion: NA.</td>
<td>Results: 55 patients developed cardiac conduction and/or rhythm abnormalities (39 developed conduction abnormalities and 16 rhythm abnormalities, which progressed in 22). Nine had SD. Risk and incidence of cardiac conduction and/or rhythm abnormalities amounted to 53.4 and 6.83% person-years (conduction abnormalities: 37.9 and 4.8%; rhythm abnormalities 15.5 and 2%), respectively. Risk and incidence of SCD amounted to 8.74 and 0.67% person-years, respectively. CTG expansion represented a predictor of cardiac conduction and/or rhythm abnormalities incidence (HR 1.10; <em>P</em> = 0.04), cardiac conduction rhythm abnormalities progression (HR 1.28; <em>P</em> = 0.001), and SCD (HR 1.39; <em>P</em> = 0.002). Older age and larger CTG expansion were associated to SCD prevalence (OR 2.67; <em>P</em> = 0.012; OR 1.54; <em>P</em> = 0.005). Among recorded cardiac abnormalities, both atrial flutter (OR 8.70; <em>P</em> = 0.031) and paroxysmal SVT (OR 8.67; <em>P</em> = 0.040) were associated with SCD.</td>
<td>Conclusions: Patients &gt;30 years with larger CTG expansion, muscular progression, and in particular, atrial arrhythmias have higher risk of SCD. Limitations: Small sample size but long follow-up.</td>
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<tr>
<td>16</td>
<td>Breton R, Mathieu 2009.268</td>
<td>Aim: To identify non-invasive clinical and ECG predictors of adverse cardiac events in patients with MD1. Study type: Retrospective, single-centre. Number of patients: 438 Enrolment period: 11.7 (0.02–23.5) years. Study endpoints: Adverse cardiac events.</td>
<td>Inclusion: MD1 (genetically confirmed). Exclusion: NA.</td>
<td>Results: 11 patients (2.6%) experienced SD and 13 (3.0%) required implantation of a pacemaker. Multivariate analysis (Cox proportional hazards models): only baseline PR and QTc intervals were linked to SD or pacemaker implantation. Age-adjusted RR was 3.7 (95% CI 1.5–8.6) if baseline PR ≥200 ms (<em>P</em> = 0.003), and 3.0 (95% CI 1.0–8.8) if the baseline QTc ≥450 ms (<em>P</em> = 0.047). A significant relationship between a more rapid increase in the QRS interval and the occurrence of SD or pacemaker implantation was identified. The median rate of increase in the QRS interval was 2.26 ms/year (range -14.00 ms/year to 20.00 ms/year) for those with an adverse cardiac event and only 0.37 ms/year (range -13.00 ms/year to 8.93 ms/year) for the rest of the cohort (<em>P</em> = 0.006).</td>
<td>Conclusions: Cumulative incidence of SD was relatively low. Delayed conduction (PR &gt;200 ms) on ECG is a risk factor for SD or pacemaker implantation. No correlation of pacemaker implantation or SD with CTG repeats.</td>
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<tr>
<td>Page</td>
<td>Reference</td>
<td>Title</td>
<td>Year of publication</td>
<td>Study type</td>
<td>Number of patients</td>
<td>Aim</td>
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<tr>
<td>20</td>
<td>Bhakta D, et al.</td>
<td>Increased mortality with left ventricular systolic dysfunction and heart failure in adults with myotonic dystrophy type 1.</td>
<td>2010</td>
<td>Prospective, multicentre registry</td>
<td>180</td>
<td>Prevalence of LV systolic dysfunction, heart failure, AV and intraventricular conduction system disease, and SD in a large population with MD1.</td>
</tr>
<tr>
<td>768</td>
<td>Punnoose AR, et al.</td>
<td>Cardiac disease burden and risk of mortality in hospitalized muscular dystrophy patients</td>
<td>2016</td>
<td>Prospective, multicentre registry.</td>
<td>406</td>
<td>Prevalence of LV systolic dysfunction, AV and intraventricular conduction system disease, and SD in a large population with MD1.</td>
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<tr>
<td>156</td>
<td>Meurin JL, et al.</td>
<td>Mechanisms of sustained ventricular tachycardia in myotonic dystrophy: implications for catheter ablation</td>
<td>1998</td>
<td>Retrospective, single-centre.</td>
<td>363</td>
<td>To determine mechanisms of sustained VT in myotonic dystrophy.</td>
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<tr>
<td>769</td>
<td>Wahbi K, et al.</td>
<td>Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease.</td>
<td>2012</td>
<td>Retrospective, single-centre.</td>
<td>180</td>
<td>To determine whether an invasive strategy based on systematic EPS and prophylactic permanent pacing is associated with longer survival in patients presenting with MD1 and major intraventricular conduction delays than a non-invasive strategy.</td>
</tr>
<tr>
<td>770</td>
<td>Lallierand B, et al.</td>
<td>The evolution of infra-hisian conduction time in myotonic dystrophy patients: clinical implications</td>
<td>2010</td>
<td>Retrospective, single-centre.</td>
<td>3363</td>
<td>To analyse the natural history of infra-hisian conduction time in myotonic dystrophy patients with a normal initial electrophysiological test because of new symptoms, new AV conduction abnormalities, presence of atrial and VA, and implanted devices were all significantly associated with LVSD/ heart failure, whereas CIG repeat length and neuromuscular severity score were not.</td>
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<tr>
<td>PMID: 23038543</td>
<td>Year of publication: 2012</td>
<td>normal first electrophysiological test and to identify the predictive value of the clinical and ECG factors accompanying an alteration of infrahissian conduction. Study type: Retrospective, multicentre study. Number of patients: 23.</td>
<td>conduction disturbances on ECG, or significant modifications of signal-averaged ECG, and on asymptomatic patients ≥60 months since the first electrophysiological test. Exclusion: NA. Signal-averaged ECG, on annual check-up, increase of 1.2 ms/year.</td>
<td>conduction disturbances on ECG, or significant modifications of signal-averaged ECG, and on asymptomatic patients ≥60 months since the first electrophysiological test. Exclusion: NA. Increase of 1.2 ms/year. Modifications of resting ECG and signal-averaged ECG were strongly associated with HV interval prolongation. Limitations: Selection bias (new AV conduction disturbances).</td>
<td>signal-averaged ECG, on annual check-up, were associated with an alteration of infrahissian conduction. Limitations: Selection bias (new AV conduction disturbances).</td>
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<td>8</td>
<td>Wahbi K, et al. Inclusion and predictions of sudden death, major conduction defects and sustained ventricular tachyarrhythmias in 1388 patients with myotonic dystrophy type 1. PMID: 27941019 Year of publication: 2017</td>
<td>Aim: To describe the incidence and identify predictors of SD, major conduction defects, and sustained VA in MD1. Study type: Retrospective, multicentre (6 centres). Number of patients: 1388. Enrolment period: 12.75 years (10-year follow-up). Study endpoints: Deaths SD, major conduction defects, and sustained VA.</td>
<td>Exclusion: MD1 (genetically confirmed) and &gt;18 years of age. Exclusion: Cardiac disease, symptoms, or medications. Results: 233 (18.2%) patients died; 39 (3.6%) with SD, sustained VA in 9; asystole in 1; complete AV block in 1, and electromechanical dissociation in 2, non-cardiac causes in 51. Major conduction defects developed in 143 (19.3%) and sustained VA in 26 (2.3%) patients. By Cox regression analysis, age, family history of SD, and LBBB were independent predictors of major conduction defects. NEVT was the only predictor of sustained VT. Limitations: SD was a frequent mode of death in DMD1 with multiple mechanisms involved. Major conduction defects were far more frequent than sustained VA, whose only independent predictor was a personal history of NSVT.</td>
<td>Conclusions: SD was a frequent mode of death in DMD1 with multiple mechanisms involved. Major conduction defects were far more frequent than sustained VA, whose only independent predictor was a personal history of NSVT.</td>
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<tr>
<td>17</td>
<td>Hermans MCE, et al. Structural and functional cardiac changes in myotonic dystrophy type 1: a cardiovascular magnetic resonance study. PMID: 23827830 Year of publication: 2012</td>
<td>Aim: To evaluate and describe structural and functional cardiac alterations in patients with MD1. Study type: Prospective, single-centre. Number of patients: 80. Enrolment period: Not reported. Study endpoints: Cardiac abnormalities by CMR.</td>
<td>Exclusion: MD1 (genetically confirmed). Exclusion: NA. Results: Functional and structural abnormalities in 35 patients (44%); LV systolic dysfunction in 20, LV dilatation in 7, and LV hypertrophy in 6. Myocardial fibrosis was seen in 10 (12.5%). RV involvement uncommon and only seen together with LV abnormalities. Cardiac involvement associated with age (P = 0.04), men gender (P &lt; 0.001), and abnormal ECG (P &lt; 0.001) but not with disease duration, CTG repeat length, severity of neuromuscular symptoms, and NT-proBNP level. Limitations: Myocardial involvement is strongly associated with conduction abnormalities, but a normal ECG does not exclude myocardial alterations.</td>
<td>Conclusions: Myocardial involvement is strongly associated with conduction abnormalities, but a normal ECG does not exclude myocardial alterations.</td>
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<tr>
<td>19</td>
<td>Groh WJ, et al. Electrocardiographic abnormalities and sudden death in myotonic dystrophy type 1. PMID: 19214296 Year of publication: 2008</td>
<td>Aim: To determine determinants of SD in MD1. Study type: Prospective, single-centre. Number of patients: 406. Enrolment period: 5.7 years. Study endpoints: SD.</td>
<td>Exclusion: MD1 (genetically confirmed). Exclusion: NA. Results: 81 patients died; 27 SD, 32 neuromuscular respiratory failure, five cardiac-non-SD, and 17 other causes. 17 patients with SD and ECG recorded: VTRVF found in nine. Severe ECG abnormality, defined as PR interval of ≥240 ms, QRS duration of ≥120 ms, or 2nd or 3rd AV block (RR 3.30; 95% CI 1.14–8.78), and atrial tachyarrhythmia (RR 5.18; 95% CI 2.28–11.77) were independent risk factors for SD. Limitations: Patients with adult myotonic dystrophy type 1 are at high risk for arrhythmias and SD. The number of CTG repeats was not an independent predictor for SD. A severe abnormality on the ECG and an atrial tachyarrhythmia predict SD.</td>
<td>Conclusions: Patients with adult myotonic dystrophy type 1 are at high risk for arrhythmias and SD. The number of CTG repeats was not an independent predictor for SD. A severe abnormality on the ECG and an atrial tachyarrhythmia predict SD.</td>
<td>Continued</td>
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</table>

Results: Cardiac disease was found in 8 of 10 patients and consisted of the variable combination of supra-ventricular arrhythmias, disorders of AV conduction, VA DCM non-DCM restrictive cardiomyopathy, and SD despite pacemaker implant.


Exclusion: NA.

Aim: To investigate the spectrum of cardiac disease in patients with an initial diagnosis of Emery–Dreifuss muscular dystrophy caused by a mutation in the LMNA gene.

Study type: Prospective, single-centre.

Number of patients: 10

Enrolment period: 47 ± 18 months.

Study endpoints: Frequency and type of cardiac manifestations.

Conclusions: Cardiac features of Emery–Dreifuss muscular dystrophy caused by lamin A/C gene mutations.

Other findings: The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiological studies.

Aim: To measure the progression of conduction system disease in myotonic dystrophy by electrophysiological serial testing.

Study type: Prospective, single-centre.

Number of patients: 9


Study endpoints: HV interval at follow-up.

Inclusion: Myotonic dystrophy (clinical diagnosis).

Exclusion: NA.

Aim: To evaluate the progression of conduction system disease in myotonic dystrophy caused by lamin A/C gene mutations.

Study type: Prospective, single-centre.

Number of patients: 7


Study endpoints: HV interval at follow-up.

Inclusion: 1. Myotonic dystrophy (clinical diagnosis).

2. Second EPS 18 months apart.

Exclusion: NA.

Aim: The natural history of conduction system disease in myotonic muscular dystrophy as determined by serial electrophysiological studies.

Study type: Prospective, single-centre.

Number of patients: 9


Study endpoints: HV interval at follow-up.

Inclusion: 1. Myotonic dystrophy (clinical diagnosis).

Exclusion: NA.

Aim: To investigate the spectrum of cardiac disease in patients with an initial diagnosis of Emery–Dreifuss muscular dystrophy caused by a mutation in the LMNA gene.

Study type: Prospective, single-centre.

Number of patients: 10

Enrolment period: 47 ± 18 months.

Study endpoints: Frequency and type of cardiac manifestations.
Conclusions:
8/20 patients had DCM.

Results:
Inclusion:
ESC Guidelines

induced readily in the laboratory and is amenable to RFCA by the very nature of its circuit.

Patients with a diagnosis of BBR-VT.

Results: Mean follow-up of 614 ± 847 days. Incidence of 6% in the patients with inducible SMVT (172/28). 8/20 patients treated with right bundle branch ablation, without recurrence at follow-up.

Other findings: 10 patients (30%) died primarily because of low cardiac output without recurrence of BBR-VT (10 treated with anti-arrhythmic drugs). Two patients on amiodarone had BBR-VT recurrence.

Conclusions: Sustained BBR-VT is not an uncommon mechanism of tachycardia; it can be induced readily in the laboratory and is amenable to RFCA by the very nature of its circuit.

—

Aim: To describe the incidence and diagnostic criteria of BBR-VT.

Study type:
Observational, retrospective, monocentric.

Number of patients:
20

Enrollment period:
January 1980–December 1987

Study endpoints:
Incidence of BBR-VT.

Success rate of BBR-VT ablation (electrical shocks).

Aim: To report the long-term outcome of catheter ablation for treatment of bundle branch re-entrant tachycardia.

Study type:
Observational retrospective.

Number of patients:
32

Enrollment period:
2005–2016

Study endpoints:
Mortality, VT recurrence.

Aim: To describe the cumulative incidence and long-term follow-up of patients diagnosed and treated for BBR-VT.

Study type:
Observational retrospective.

Number of patients:
48

Enrollment period:
January 1980–October 1990

Study endpoints:
Mortality.

Inclusion:
Patients with a diagnosis of BBR-VT.

Exclusion: NA.

Results: Clinical characteristics: 44 males, mean age 61.9 years (range 32–81), cardiac dilatation on onset of each ventricular depolarization is preceded by His-bundle, right bundle, or left bundle potential; spontaneous variation in V–V interval is preceded by similar changes in H–H interval; the induction of tachycardia during ventricular extrastimulation is consistently dependent upon the achievement of critical conduction delay in the His-Purkinje system termination of tachycardia by spontaneous or pacing-induced block in the His Purkinje system BBR cannot be induced after successful RFCA of the right bundle branch.

Exclusion: NA.

Results: Mean follow-up was 95.3 ± 36 months. Six patients (19%) died: three due to congestive heart failure, one to non-cardiac related, one had recurrent VT due to BBR-VT not occurring in any patient. In patients with normal HV interval, no one developed heart block.

Other findings: 17 patients had syncope (53%) and 15 had palpitations (47%).

Conclusions: Sustained BBR-VT is usually seen in patients with SHD. Evidence of disease in the His-Purkinje system was present in all patients. RFCA of the right bundle branch can effectively eliminate BBR. During follow-up, congestive heart failure is the most common cause of death in this population.

Inclusion:
Patients with a sustained VT due to a BBR mechanism.

Diagnosis of BBR-VT was established per standard published criteria.

Exclusion: NA.

Results: At baseline, 25 patients (78%) had a prolonged HV interval (>55 ms) and seven (22%) had a normal HV interval (55 ms or less). BBR-VT was inducible in all subjects, and successful ablation of the right bundle branch in 19 patients (59%) or the left bundle branch in 13 patients (41%) was performed. Mean follow-up was 95.3 ± 36 months. Six patients (19%) died: three of progressive heart failure and three of non-cardiac causes. Recurrent VT due to BBR-VT did not occur in any patient. In patients with normal HV interval, no one developed heart block.

Other findings: 17 patients had syncope (53%) and 15 had palpitations (47%).

Conclusions: RFCA of the bundle branch is an effective therapy for treatment of BBR-VT.

Sustained BBR-VT can be seen in patients with normal LV systolic function and HV interval with excellent long-term outcomes after ablation.
### 4.1.4. Inflammatory cardiac diseases

#### 4.1.4.1. Myocarditis

**Table of Evidence 30** for Table of Recommendations for sudden cardiac death prevention and treatment of ventricular arrhythmias in myocarditis, cardiac sarcoidosis and Chaga’s cardiomyopathy

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
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<tbody>
<tr>
<td>789</td>
<td>Shah Z, et al. 2019</td>
<td>To analyze the outcomes of patients hospitalized with myocarditis from a large diverse, multicentric, nationwide cohort using Nationwide Inpatient Sample database.</td>
<td>Adult patients (age ≥ 18 years) with the primary discharge diagnosis of myocarditis.</td>
<td>A total of 640 (2.4%) patients died during index hospitalization. Mortality was significantly higher in women compared with men (3.5% vs. 1.8%; ( P &lt; 0.001 )). Multiple logistic regression analysis demonstrated women gender as an independent predictor of in-hospital mortality (OR 1.69; 95% CI 1.1–2.6; ( P = 0.007 )).</td>
<td>Other findings: More men were hospitalized compared with women (66% vs. 34%; ( P &lt; 0.05 )). Patients hospitalized were young with a mean age of 37.3 ± 18.8 years with women being older compared with men (45.2 ± 20.9 vs. 33.2 ± 16.2; ( P &lt; 0.001 )). In-hospital complications of cardiogenic shock and VF/CA occurred in 6.5% and 2.5% of hospitalizations, respectively, with women being affected significantly more than men (10.2% vs. 4.6%; 3.6% vs. 2%, respectively; ( P &lt; 0.05 ) for both comparisons).</td>
<td>Conclusions: Myocarditis-related hospitalizations have increased during the study years and mostly affect a young population with no significant co-morbidities. Females gender remains at high risk for myocarditis-related complications and in-hospital mortality. Limitations: Diagnostic of myocarditis based on informatic codes. Only in-hospital mortality. No data on SCD.</td>
</tr>
<tr>
<td>807</td>
<td>Maleszewski JJ, et al. 2015</td>
<td>To evaluate follow-up of patients with biopsy-proved giant cell myocarditis.</td>
<td>Biopsy-proved giant cell myocarditis who survived for &gt;1 year without heart transplantation.</td>
<td>The mean age of the cohort was 54±13.9 years (65% women). The mean follow-up duration was 5.5 years starting one year after diagnosis. There were three deaths (13%), five heart transplantations (19%), and one ventricular assist device placement (4%). Three histologically confirmed recurrences of giant cell myocarditis (12%) occurred between 1.5 and 8 years after diagnosis. 13 of 26 patients experienced a total of 30 heart failure episodes ≤ 1 year after initial diagnosis. There were 23 episodes of elevated creatinine in 12 patients, 41 infectious events in 13 patients, and 19 episodes of VA in six patients with a total of 144 years of follow-up. Starting one year after giant cell myocarditis diagnosis, the combined rate of death, transplantation, ventricular assist device placement, and giant cell myocarditis recurrence was 47% at 5 years.</td>
<td></td>
<td>Conclusions: The risk for giant cell myocarditis recurrence continues to ≥ 8 years after diagnosis.</td>
</tr>
</tbody>
</table>

Continued
### 797

**Rosier L, et al.**

**High risk of sustained ventricular arrhythmia recurrence after acute myocarditis.**

**PMID:** 3224983

**Year of publication:** 2020

**Aim:** To assess the risk of major arrhythmic ventricular events over time in patients implanted with an ICD following sustained VT/VF in the acute phase of myocarditis compared to those implanted for VT/VF occurring on myocarditis sequelae.

**Study type:** Case-control retrospective multicentre.

**Number of patients:** 68

**Enrolment period:** 2007-2017

**Study endpoints:** Occurrence of a major arrhythmic ventricular event (i.e. any appropriate intervention of the defibrillator [ATP or shock], as appropriate) on tachycardia or VF.

## Conclusions:

Patients who experienced sustained VT/VF during follow-up. These results show that the risk of major arrhythmic ventricular events recurrence remains high after only patients implanted with a defibrillator were included in the study. Other findings: were implanted.

Although none of the patients had a histological diagnosis of myocarditis through endomyocardial biopsy, cardiac CMR was systematically performed. The only predictors of major arrhythmic ventricular events in the total ICD population were an anterior location of LGE on CMR (HR [95% CI] 2.60 [1.28–5.59]; *P* = 0.009) and an ICD indication for myocarditis sequelae (HR [95% CI] 2.88 [1.29–6.44]; *P* = 0.010) compared to an ICD indication for acute myocarditis.

### 808

**El-Assaad I, et al.**

**Implantable cardioverter-defibrillator and wait-list outcomes in pediatric patients awaiting heart transplantation.**

**PMID:** 26347137

**Year of publication:** 2015

**Aim:** To investigate the role of ICD in preventing SCD and waiting list mortality as well as to determine risk factors for SCD in pediatric patients listed for heart transplantation.

**Study type:** Retrospective registry.

**Number of patients:** 5072

**Enrolment period:** January 2005–June 2014

**Study endpoint:** Cumulative rate of SCD.

## Inclusion:

Patients from the United Network for Organ Sharing database for all paediatric patients (age ≤ 18 years) listed for heart transplantation (2005–2014).

## Exclusion:

N/A.

## Results:

In a multivariable model, United Network for Organ Sharing status 1B (HR 0.52; 95% CI 0.29–0.95; *P* = 0.02), restrictive cardiomyopathy (HR 0.19; 95% CI 0.05–0.76; *P* = 0.02), and DCM (HR 0.32; 95% CI 0.20–0.52; *P* = 0.001) were associated with lower SCD risk, while younger age at listing (HR 0.94 per year; 95% CI 0.90–0.98; *P* = 0.003) was associated with higher SCD risk. ICD at listing was not associated with reduced SCD (HR = 0.52), all-cause mortality, or delisting (HR = 0.57).

## Limitations:

A retrospective study where data entry accuracy of the data is unknown. Possible confounding factors. Lack of information on the number of appropriate shocks delivered. No analysis of outcomes of patients who received ICDs after listing. Lack of the specific underlying aetiologies that led to SCD.

### 791

**Kandolin R, et al.**

**Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression.**

**PMID:** 2349495

**Year of publication:** 2013

**Aim:** To analyse (1) our experience in diagnosing giant-cell myocarditis, and (2) the outcome of patients on combined immunosuppression.

**Study type:** Retrospective, single-centre.

**Number of patients:** 32

**Enrolment period:** 1991–2011

## Inclusion:

32 consecutive patients with histologically verified giant-cell myocarditis.

## Exclusion:

N/A.

## Results:

The median follow-up time calculated from symptom onset was 15.0 months (range, 0.1–90.3 months). 26 patients (81%) were diagnosed by endomyocardial or surgical biopsies and six at autopsy or post-transplantation. 28 (88%) patients underwent endomyocardial biopsy. The sensitivity of transvenous endomyocardial biopsy increased from 68% (19/28 patients) to 93% (26/28) after up to two repeat procedures. The 24 biopsy-diagnosed patients were treated with combined immunosuppression (2-4 drugs) including cyclosporine in 20 patients. The Kaplan–Meier estimates of transplant-free survival from symptom onset were 69% at one year, 58% at 2 years, and 52% at 5 years. Of the transplant-free survivors, 10/17 (59%) experienced sustained ventricular tachyarrhythmias during follow-up and three received intracardiac defibrillator shocks for VT/VF.

## Limitations:

Repeat endomyocardial biopsies are frequently needed to diagnose giant-cell myocarditis. On contemporary immunosuppression, two-thirds of patients reach apical clinical remission characterized by freedom from severe heart failure and need of retransplantation but continuing proneness to ventricular tachyarrhythmias.

### Continued

Aim: To identify predictors of transplant-free survival in giant cell myocarditis.

Study type: Observational retrospective single-centre.

Number of patients: 46

Enrolment period: 1999–2015

Study endpoints: Transplant-free survival.

Inclusion: Patients with histologically confirmed giant cell myocarditis

Exclusion: Unequivocal granuloma formation excluded the diagnosis of giant cell myocarditis. In addition to the 46 patients included and analysed here, four other patients were evaluated with a diagnosis of giant cell myocarditis but excluded from our work because scrutiny of the biopsy material converted the diagnosis to cardiac sarcoidosis.

Results: Median follow-up of 14 months. Altogether 26 patients died (n = 8) or underwent transplantation (n = 18) a median of 13 months following symptom onset. The 5-year estimate of transplant-free survival was 42% (95% CI 35–48%).

Other findings: RFCA of VT in NICM is effective. 35–48%.

Conclusions: In giant cell myocarditis, the probability of transplant-free survival is 42% at 5 years from symptom onset. Markers of myocyte injury and cardiac dysfunction help predict the outcome.

Limitations: No data on arrhythmias/SCD occurrence.


Aim: This study sought to characterize VT ablation outcomes among NICM pathologies and adjust these outcomes by patient-related comorbidities that could explain differences in arrhythmia recurrence rates.

Study type: Retrospective analysis of an International Registry (12 centres).

Number of patients: 780

Enrolment period: 2002-2014

Study endpoints: VT recurrence, death, and heart transplantation.

Inclusion: Patients with NICM from a large international registry of VT ablation in SHD

Exclusion: N/A.

Results: Median follow-up was 12.8 (IQR 4.0–20.9) months. Of 780 NICM patients (57±14 years of age, 38% women, LVEF 37±13%), underlying prevalence was 66% for idiopathic DCM, 13% for ARVC, 6% for valvular cardiomyopathy, 6% for myocarditis, 4% for HCM, and 3% for sarcoidosis. One-year freedom from VT was 69%, and freedom from VT, heart transplantation, and death was 63%. On unadjusted competing risk analysis, VT ablation in ARVC demonstrated superior VT-free survival (82%) vs. idiopathic DCM (P<0.01). Valvular cardiomyopathy had the poorest unadjusted VT-free survival, at 47% (P<0.01). After adjusting for comorbidities, including age, heart failure severity, ejection fraction, prior ablation, and anti-arrhythmic medication use, myocarditis, ARVC, and idiopathic DCM demonstrated similar outcomes, whereas HCM, valvular cardiomyopathy, and sarcoidosis had the highest risk of VT recurrence.

Other findings: The severity of necrosis and fibrosis in myocardial biopsy, graded by the consensus of two cardiac pathologists as none, mild, moderate, or severe, predicted the outcome with an HR of 7.17 (95% CI 2.29–22.40) for the presence of either necrosis or fibrosis of at least moderate extent.

Conclusions: RFCA of VT in NICM is effective. Antilog of NICM is a significant predictor of outcomes, with ARVC, myocarditis, and idiopathic DCM having similar but superior outcomes to HCM, valvular cardiomyopathy, and sarcoidosis, after adjusting for potential covariates.

Limitations: Retrospective study.


Aim: To assess the efficacy and safety of RFCA of VT in patients with myocarditis.

Study type: Retrospective single-centre.

Number of patients: 20

Enrolment period: January 2008–December 2010

Study endpoint: Long-term freedom from recurrent VT.

Inclusion: Consecutive patients with a history of biopsy-proven viral myocarditis and drug-refractory VT.

Exclusion: N/A.

Results: 20 patients (15 men, age 42 [28–52] years) underwent RFCA. Median follow-up time = 28 (11–48) months. Endocardial RFCA was totally successful in 14 patients (70%), while in the remaining six (30%) clinical VT was successfully ablated by epicardial RFCA. In one patient, haemodynamic instability required an intra-arterial balloon pump to complete RFCA. No major complication occurred during or after RFCA. Over a median follow-up time of 28 (11–48) months, 18 patients (90%) remained free of sustained VT; two patients (10%, both with baseline LVEF ≤30%) died of acute heart failure unrelated to VA.

Other findings: No major complication occurred during the procedures or the remaining hospital stay. At discharge, anti-arrhythmic drug therapy was continued in 7 of 20 patients (35%).

Conclusions: In patients with myocarditis, RFCA of drug-refractory VT is feasible, safe, and effective. Epicardial RFCA should be considered as an important therapeutic option to increase success rate.

Limitations: Retrospective study.

Continued
Conclusions:
Pre-procedural scar imaging and findings, (8 mV) is superior in scar support the necessity of an epicardial approach in patients with prior myocarditis. Epicardial unipolar mapping (identification and RFCA based on cation is safe and Other revealed low-voltage scar (1.5 mV) in one patient endocardially and in 14 of 19 epicardially. Unipolar mapping revealed low-voltage scar (815 Kandolin R, et al. Results:
Inclusion: Consecutive patients who procedural endpoint independently from VT inducibility. Indication: Consecutive patients who underwent imaging-guided RFCA of myocarditis-related VA. Exclusion: N/A. Results: Median follow-up of 23 (15–31) months. Clinical monomorphic VT was induced in 15 of 26 patients (57.7%) and was associated with epicardial late potentials in 10 of 15, completely abolished in 7 of 10 patients. Of the 10 patients rendered non-inducible, VTs were ablated epicardially in 7. Late potentials were also detected in 7 of 11 initially non-inducible patients and completely abolished in 4. After a median follow-up of 23 (15–31) months, 20 of 26 patients (76.9%) remained free from VT recurrence. Other findings: Bipolar mapping revealed low-voltage scar (<1.5 mV) in one patient endocardially and of 19 of 19 epicardially. Unipolar mapping (<8 mV) is superior in scar identification and RFCA based on substrate modification is safe and effective in this setting.

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Kandolin R, et al. Cardiac sarcoidosis epidemiology, characteristics, and outcome over 25 years in a nationwide study. PMID: 25537698 Year of publication: 2015

Aim: To assess the epidemiology, characteristics and outcome of cardiac sarcoidosis in Finland. Study type: Retrospective nationwide registry. Number of patients: 110 Enrolment period: 1998–2012 Study endpoints: The following events were taken as outcome endpoints in these analyses: cardiac death a composite of cardiac death and transplantation, whichever came first; and a composite of cardiac death, transplantation, and aborted SCD. Indication: Sarcoidosis histology in an endomyocardial biopsy or extracardiac histological verification of sarcoidosis associated with both clinical manifestations indicative of a myocardial disease and abnormalities compatible with cardiac sarcoidosis in LGE-CMR, 18F-fluorodeoxyglucose position emission tomography (18F-FDG PET), or echocardiography. Exclusion: N/A. Results: Altogether, 102 of the 190 patients received immunosuppressive therapy, and 56 received an ICD. LV function was impaired (6.6F < 50%) in 65 patients (39%) at diagnosis and showed no overall change over 12 months of steroid therapy. During follow-up (median, 6.6 years), 10 patients died of a cardiac cause, 11 patients underwent transplantation, and another 11 patients suffered an aborted SCD. The Kaplan–Meier estimates for 1-, 5-, and 10-year transplantation-free cardiac survival were 97%, 90%, and 88%, respectively. Heart failure at presentation predicted poor outcome (log-rank P = 0.0001) with a 10-year transplantation-free cardiac survival of only 5.3%.

Other findings: The annual detection rate of cardiac sarcoidosis increased >20-fold during the 25-year period, reaching 0.31 in 1

805

Aim: To present clinical, electroanatomical mapping, imaging, and RFCA strategies in patients with myocarditis-related VT. Study type: Observational, retrospective, single-centre. Number of patients: 26. Enrolment period: January 2010–July 2012. Study endpoints: Late potential ablation constituted a procedural endpoint independently from VT inducibility. Indication: Consecutive patients who underwent imaging-guided RFCA of myocarditis-related VA. Exclusion: N/A. Results: Median follow-up of 23 (15–31) months. Clinical monomorphic VT was induced in 15 of 26 patients (57.7%) and was associated with epicardial late potentials in 10 of 15, completely abolished in 7 of 10 patients. Of the 10 patients rendered non-inducible, VTs were ablated epicardially in 7. Late potentials were also detected in 7 of 11 initially non-inducible patients and completely abolished in 4. After a median follow-up of 23 (15–31) months, 20 of 26 patients (76.9%) remained free from VT recurrence. Other findings: Bipolar mapping revealed low-voltage scar (<1.5 mV) in one patient endocardially and of 19 of 19 epicardially. Unipolar mapping (<8 mV) is superior in scar identification and RFCA based on substrate modification is safe and effective in this setting.

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Other findings: The annual detection rate of cardiac sarcoidosis increased >20-fold during the 25-year period, reaching 0.31 in 1

831

Aim: To identify the incidence and characteristics of ICD therapies in this patient population. Study type: Cohort study of patients with ICDs at three institutions. Number of patients: 112 Enrolment period: Not reported. Study endpoints: Appropriate ICD therapy. Indication: Sarcoidosis + ICD implantation. Exclusion: N/A. Results: 36 (32.1%) received appropriate therapies for VA over a mean follow-up period of 29.2 months. VT storm (>3 episodes in 24 h) occurred in 16 (14.2%) cardiac sarcoidosis subjects. Inappropriate therapies occurred in 13 cardiac sarcoidosis subjects (11.6%). Covariates associated with appropriate ICD therapies included LVEF > 55% (OR 6.51 [95% CI 2.41–17.5]), RV dysfunction (OR 6.73 [95% CI 2.49–16.8]), and symptomatic heart failure (OR 4.33 [95% CI 1.86–10.1]).

832
Batsaensky BP, et al. Long-term follow-up of patients with cardiac sarcoidosis and implantable cardioverter-defibrillators. PMID: 22338670 Year of publication: 2012

Aim: To assess the prevalence and incidence of VA in patients with cardiac sarcoidosis and to identify the clinical attributes associated with appropriate ICD therapies. Study type: Observational, retrospective, single-centres. Number of patients: 43. Enrolment period: 2002–2011 Study endpoints: Indication: Patients with ICDs, biopsy-proven systemic sarcoidosis, and cardiac involvement. Exclusion: Patients were excluded from the study if they did not have proven or highly suspected cardiac sarcoidosis, as defined above, or if they had concomitant CAD, or an alternate, more plausible, explanation for their heart disease. Indication: Patients with ICDs, biopsy-proven systemic sarcoidosis, and cardiac involvement. Exclusion: Patients were excluded from the study if they did not have proven or highly suspected cardiac sarcoidosis, as defined above, or if they had concomitant CAD, or an alternate, more plausible, explanation for their heart disease. Results: Mean follow-up of 25.5 years. Appropriate ICD therapies were observed in 37.8% of the patients with an incidence of 2.5% per year. Longer ICD follow-up (>5 ± 3.7 years vs. 1.5 ± 1.5 years) P = 0.007, depressed LVEF (35.3% ± 15.5% vs. 30.9% ± 15.5% P = 0.002), and complete heart block (41.1% ± 17.9% vs. 0.048) were associated with appropriate ICD therapy. Other findings: Inappropriate ICD therapies occurred in 13.3% of the patients. While there was no significant difference in the total number of shocks/ATP-terminated events between primary (n = 29) and secondary (n = 16) prevention groups, there was a trend towards a reduced number of shocks/ATP-terminated events during the primary prevention arm after 2 years. Conclusions: Not reported.

Conditions in our cohort of patients with cardiac sarcoidosis and ICDs, almost one-third received appropriate therapies. This may be due to a myocardial inflammatory process leading to increased triggered activity and subsequent scarning leading to re-entrant tachyarrhythmias. Adjusted predictors of ICD therapies include LV or RV dysfunction. Limitations: Observational research.
Conclusions:
Patients with cardiac sarcoidosis and ICDs are at high risk for VA. This population also has high rates of inappropriate shocks and device complications.

Other

In terms of indication for ICD implantation, 107 patients had primary prevention and 47 patients had secondary prevention indications.

Results:
Over a mean follow-up of 4.2 ± 4.0 years, 85 of 234 (36.2%) patients received an appropriate ICD therapy (shocks and/or ATP) and 67 of 226 (29.7%) received an appropriate shock. 57 of 235 patients (24.3%) received a total of 222 inappropriate shocks. 46 adverse events occurred in 41 of 235 patients (17.4%). Patients who received appropriate ICD therapies were more likely to be men (OR 2.06; 95% CI 1.37–3.09; \(P = 0.0005\)), had a lower LVEF (39.4 ± 15.2 vs. 48.8 ± 18.23; \(P = 0.0001\)), ventricular pacing on baseline ECG (16.1 vs. 2.78; \(P = 0.0002\)), and a secondary prevention indication (60.7 vs. 24.5%; \(P = 0.0001\)) compared with those who did not receive appropriate ICD therapies.

Other findings:
In terms of indication for ICD implantation, 147 patients (62.6%) had their devices implanted for primary prevention while 88 patients (37.5%) were implanted for secondary prevention, including 77 for VF (30%), 63 for VT (26.8%), and 18 for syncope presumed to be due to an arrhythmia (7.7%). Patients received an inappropriate shock most commonly for supraventricular arrhythmias in 52.6%. Adverse events were most commonly led dislodgement or fracture.

Conclusions:
Appropriate and inappropriate ICD therapies.

Limitations:
Small population size, monocentre, both primary and secondary prevention indications. Selected population of cardiac sarcoidosis referred for ablation or upgrading of pacemaker to ICD.

Aim:
To evaluate the efficacy and safety of ICD in patients with cardiac sarcoidosis. Study type: Retrospective registry. Number of patients: 235 from 11 institutions. Enrolment period: Not reported. Study endpoints: ICD therapy, adverse event.

Indication:
Electrophysiologists at academic medical centres were asked to identify consecutive patients with cardiac sarcoidosis and an ICD. Deceased patients could be included but were not systematically identified. Indication criteria required patients to have diagnosis of cardiac sarcoidosis based on: (i) biopsy-proven cardiac sarcoidosis, (ii) CMR findings suggestive of cardiac sarcoidosis, or (iii) biopsy-proven sarcoidosis in another organ and presumptive cardiac involvement based on conduction system disease involving the sinus node, AV node, or His-Purkinje system and/or VA. Exclusion: NA.

Results:
Mean follow-up: 3.5 years. 180 (78.3%) appropriate therapy. Patients who received an appropriate therapy were younger (33.3 vs. 56.4 ± 32.3; \(P = 0.0004\)), had a lower LVEF (38.1 ± 15.2 vs. 48.8 ± 14.7%; \(P = 0.0001\)), ventricular pacing on baseline ECG (16.1 vs. 2.78; \(P = 0.0002\)), and a secondary prevention indication (60.7 vs. 24.5%; \(P = 0.0001\)) compared with those who did not receive appropriate ICD therapies.

Other findings:
Mean age: 55 years, 282 mes (60%).

Limitations:
Appropriate ICD therapy during cardiac sarcoidosis patients with sinus node disease involving the sinus node, AV node, or His-Purkinje system and/or VA. Patients who received an inappropriate shock most commonly for supraventricular arrhythmias in 52.6%. Adverse events were most commonly led dislodgement or fracture.

Aim:
To investigate the characteristics associated with appropriate therapy in ICD-implanted cardiac sarcoidosis patients. Study type: Meta-analysis. Number of patients: 464 (3 studies). Enrolment period: NA. Study endpoints: Appropriate ICD therapy.

Indication:
Studies reporting on ICD in patients with cardiac sarcoidosis in which patients who received an appropriate therapy were compared with patients who did not. Exclusion: Reviews, case reports, editorials and guidelines. Studies reporting on cardiac sarcoidosis patients with insufficient available information or non-extractable data.

Results:
Mean follow-up: 3.5 years. 180 (78.3%) appropriate therapy. Patients who received an appropriate therapy were younger (33.3 vs. 56.4 ± 32.3; \(P = 0.0004\)), had a lower LVEF (38.1 ± 15.2 vs. 48.8 ± 14.7%; \(P = 0.0001\)), ventricular pacing on baseline ECG (16.1 vs. 2.78; \(P = 0.0002\)), and a secondary prevention indication (60.7 vs. 24.5%; \(P = 0.0001\)) compared with those who did not receive appropriate ICD therapies.

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Aim:

Indication:
Cardiac sarcoidosis with Mobitz II second degree of third-degree AV block in the absence of other explanatory cardiac disease. Exclusion: NA.

Results:
Median follow-up: 2.8 years. 23 SCD (fatal or aborted) and 19 VTs. Endpoint 5-year incidence (95% CI) was 56% (36–88%) in the AV block subgroup with VT or severe LV dysfunction vs. 24% (12–49%) in the subgroup with non-severe LV dysfunction and 24% (15–38%) with non-LV AV block (\(P = 0.009\)). The 5-year incidence of SCD was 34% (9–71%), 14% (4–33%), and 9% (4–22%) in the respective subgroups (\(P = 0.006\)).

Other findings:
Concomitant with AV block at presentation, 20 patients had either VT or severe LV dysfunction.

Limitations:
The risk of SCD is significant in cardiac sarcoidosis presenting with high-grade AV block. CVE and LV dysfunction.

Limitations:
The present study population is exclusively northern European. Continued
### 820

**Greulich S, et al.**

CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis.

**PMID:** 23498675

**Year of publication:** 2013

**Aim:** To demonstrate that the presence of LGE is a predictor of death and other adverse events in patients with suspected cardiac sarcoidosis.

**Study type:** Observational prospective single-centre observational study.

**Number of patients:** 155

**Enrolment period:** January 2002–December 2011

**Study endpoints:**

- Primary endpoints were death, aborted SCD, and appropriate ICD discharge.
- Secondary endpoints were VT and NSVT.

**Indications:** Consecutive patients with (1) systemic sarcoidosis diagnosed by biopsy and/or clinical criteria, and (2) no history of CAD or MI; and (3) successfully underwent CMR imaging.

**Exclusion:** Valvular or congenital heart disease.

**Results:**

- Median follow-up of 2.6 years: LGE was present in 39 patients (25.3%).
- The presence of LGE yields a Cox HR of 31.6 for death, aborted SCD, or appropriate ICD discharge, and of 3.9 for any event.
- This superior to functional or clinical parameters such as LVEF, LV end-diastolic volume, or presentation as heart failure, yielding HRs between 0.99 (per % increase LVEF) and 1.004 (presentation as heart failure), and between 0.94 and 1.2 for potentially lethal or other adverse events, respectively.

**Other findings:**

- Other findings: Except for one patient dying from pulmonary infection, no patient without LGE died or experienced any event during follow-up, even if the LV was enlarged and the LVEF severely impaired.

**Limitations:**

- Low number of events.
- It may be possible that CMR reports influenced treatment decisions with regard to ICD implantation, which may result in more endpoints such as ICD shocks to be detected in patients with abnormal CMR results.

### 821

**Nishii J, et al.**

Late gadolinium enhancement identified with cardiac magnetic resonance imaging in sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death.

**PMID:** 26763280

**Year of publication:** 2016

**Aim:** To assess the utility of CMR in the prediction of adverse outcomes in patients with sarcoidosis.

**Study type:** Retrospective single-centre observational study.

**Number of patients:** 205

**Enrolment period:** January 2002–31 December 2012

**Study endpoints:**

- The primary endpoint of the study was the composite cardiac event that included the occurrence of SCD, VT, or VF.
- The secondary endpoints of all-cause mortality and mortality due to SCD were also evaluated.

**Indications:** Patients with sarcoidosis and CMR.

**Exclusion:**

- No history of biopsy-proven extracardiac or cardiac sarcoidosis and no evidence of cardiac sarcoidosis on CMR (n = 55), a follow-up time of <6 months (n = 30), patients who were under the age of 18 at the time of follow-up (n = 2), those of non-English-speaking background (n = 7), and individuals who were either non-contactable (n = 23) or refused consent (n = 19).

**Results:**

- At a mean follow-up time of 36.8 ± 20.5 months, patients with cardiac sarcoidosis had a higher rate of the composite cardiac event—comprising SCD and ventricular tachyarrhythmia—compared to those with only extracardiac disease (P < 0.001). There was a higher rate of SCD or ICD aborted SCD in patients with cardiac sarcoidosis vs. those without (P = 0.003).
- In patients with cardiac sarcoidosis, the rate of SCD was lower in those with an ICD compared to those without (P = 0.02).

**Limitations:**

- Number of events.
- Patients with evidence of cardiac sarcoidosis on CMR have higher rates of adverse cardiovascular events than those with only extracardiac disease. In patients with sarcoidosis detected on CMR, the presence of an ICD is associated with a lower rate of SCD.

### 822

**Murtagh G, et al.**

Progression of myocardial damage in sarcoidosis patients with preserved left ventricular ejection fraction: Risk stratification using cardiovascular magnetic resonance.

**PMID:** 23498675

**Year of publication:** 2013

**Aim:** To determine the prevalence of cardiac sarcoidosis or associated myocardial damage, defined by the presence of LGE, quantify their risk of death/VT, and identify imaging-based covariates that predict who is at greatest risk of death/VT.

**Study type:** Observational, retrospective, single-centre.

**Number of patients:** 205

**Enrolment period:** Not reported

**Study endpoints:**

- Not reported
- Death/VT.

**Indications:**

- Patients with LVEF > 50% and extracardiac sarcoidosis who underwent CMR for LGE evaluation.
- Incomplete CMR data sets.

**Exclusion:**

- Patients with LVEF < 50% or extracardiac sarcoidosis who underwent CMR for LGE evaluation.

**Results:**

- Mean follow-up of 36 ± 18 months.
- In the LGE+ group, the rate of death/VT per year was >20 times higher than LGE- (4.9 vs. 0.2% P < 0.01); death/VT were associated with a greater burden of LGE (14 ± 11 vs. 5 ± 5% P < 0.01) and RV dysfunction (RV EF 45 ± 12 vs 53 ± 28%; P = 0.04). LGE burden was the best predictor of death/VT (area under the receiver-operating characteristics curve, 0.80) for every 1% increase of LGE burden, the hazard of death/VT increased by 8%.

**Limitations:**

- Patients with sarcoidosis and CMR.

**Other findings:**

- Other findings: 41 of 205 patients (20%) had LGE; 12 of 205 (6%) died or had VT during follow-up; of these, 10 (83%) were in the LGE+ group.

**Conclusions:**

- Sarcoidosis patients with LGE are at significant risk for death/VT, even with preserved LVEF. Increased LGE burden and RV dysfunction can identify LGE+ patients at highest risk of death/VT.

**Limitations:**

- Another limitation of our study is that Holter monitoring was not performed consistently in all patients and some patients with VT could have been missed. In addition, the case of death is not always known in our cohort.
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<th>Coleman GC, et al.</th>
<th>Prognostic value of myocardial scarring on CMR in patients with cardiac sarcoidosis.</th>
<th>PMID: 27450877</th>
<th>Year of publication: 2017</th>
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<tr>
<td>824</td>
<td>Aim: To perform a systematic review and meta-analysis to understand the prognostic value of myocardial scarring as evidenced by LGE on CMR imaging in patients with known or suspected cardiac sarcoidosis. Study type: Systematic review and meta-analysis. Number of patients: 10 articles. 760 patients. Enrolment period: July 2015 Study endpoints: All-cause mortality and a composite outcome of arrhythmogenic events (VA, ICD shock, SCD) plus all-cause mortality during follow-up.</td>
<td>Indication: Systematic research (July 2015) in PubMed, Cochrane CENTRAL, and metaRegister of Controlled Trials for studies assessing ≥1 year prognosis in patients undergoing CMR with known or suspected cardiac sarcoidosis. Studies were considered eligible for inclusion if CMR was used to assess for myocardial scarring from biopsy-proven or clinically suspected sarcoidosis; in cohorts of ≥5 patients; with ≥1 year of prognostic follow-up data, including event data for VA, SCD, aborted cardiac death, and/or appropriate ICD discharge, hospital admission for congestive heart failure, cardiac mortality, and all-cause mortality. Exclusion: Studies with populations known to have CAD or cardiomyopathies of non-sarcoid aetiology were excluded. The search was limited to studies published in peer-reviewed journals and therefore excluded trials published in abstract form only. Studies that enrolled adults only.</td>
<td>Results: Mean follow-up of 3.0 ± 1.1 years. Patients with LGE had higher odds for all-cause mortality (OR 3.06; P = 0.03) and higher odds of the composite outcome (OR 10.74; P &lt; 0.00001) than those without LGE. Patients with LGE had an increased annualized event rate of the composite outcome (11.9% vs. 1.1%; P &lt; 0.0001). Other findings: Patients had a mean age of 53 years, 41% were men, 95.3% had known extracardiac sarcoidosis, and 21.6% had known cardiac sarcoidosis. The average LVEF was 57.8 ± 9.1%.</td>
<td>Conclusion: In patients with known or suspected cardiac sarcoidosis, the presence of LGE on CMR imaging is associated with increased odds of both all-cause mortality and arrhythmogenic events. Limitations: Limitations inherent to systematic review, heterogeneity of methods for quantifying EF, lack of LGE quantification or pattern data, and variable inclusion criteria.</td>
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<td>836</td>
<td>Smadema JP, et al.</td>
<td>Right ventricular involvement and the extent of left ventricular enhancement with magnetic resonance predict adverse outcome in pulmonary sarcoidosis.</td>
<td>PMID: 28967698</td>
<td>Year of publication: 2018</td>
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<tr>
<td>824</td>
<td>Aim: To determine whether delayed RV LGE with CMR would be predictive of adverse events in addition to LV LGE during the long-term follow-up of pulmonary sarcoidosis patients. Study type: Prospective cohort of patients. Number of patients: 84 Enrolment period: July 2001–August 2010 Study endpoints: The composite primary endpoint consisted of admission for congestive heart failure, sustained VT, appropriate ICD therapy, pacemaker implantation for high-degree AV block, or cardiac death. The composite secondary endpoint included all-cause mortality in addition to the primary endpoint.</td>
<td>Indication: 84 consecutive biopsy-proven pulmonary sarcoidosis patients. Exclusion: CONTRAINDICATION TO LGE-CMR.</td>
<td>Results: Median follow-up = 56 months (38–74). RV and LV LGE were demonstrated in, respectively, 12 and 27 patients. 5 of 10 events included in the primary endpoint occurred in the group with RV LGE. RV LGE or biventricular LGE yielded Cox HRs of 8.71 (95% CI 1.90–23.81), 9.22 (95% CI 1.96–43.45), and 12.09 (95% CI 3.43–42.68) for the composite primary endpoint. In a multivariate model, the predictive value of biventricular LGE for the composite primary and secondary endpoints was strongest. Kaplan–Meier event-free survival curves were most significant for RV LGE and biventricular LGE (log rank with P = 0.001).</td>
<td>Conclusion: Biventricular LGE at presentation is the strongest, independent predictor of adverse outcome during long-term follow-up. Asymptomatic myocardial scar, ~8% of LV mass carried a favourable long-term outcome.</td>
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<td>Study</td>
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<td>Valenti PS, et al.</td>
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<td>Electrophysiology study for risk stratification in patients with cardiac sarcoidosis and abnormal cardiac imaging</td>
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<td>Zippe MM, et al.</td>
<td>Electrophysiological testing for diagnostic evaluation and risk stratification in patients with suspected cardiac sarcoidosis with preserved left and right ventricular systolic function</td>
<td>Possible cardiac sarcoidosis</td>
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undergoing EPS with possible cardiac sarcoidosis and 50 of 69 (72%) patients with probable cardiac sarcoidosis. Only 1 of 41 (2.4%) of patients with possible cardiac sarcoidosis and 2 of 50 (4%) of patients with probable cardiac sarcoidosis had evidence of abnormal bipole or unipole RV voltage. No patient with abnormal RV voltage had events during follow-up.

Undergoing EPS with possible cardiac sarcoidosis and 50 of 69 (72%) patients with probable cardiac sarcoidosis. Only 1 of 41 (2.4%) of patients with possible cardiac sarcoidosis and 2 of 50 (4%) of patients with probable cardiac sarcoidosis had evidence of abnormal bipole or unipole RV voltage. No patient with abnormal RV voltage had events during follow-up.

**Conclusions:**

Patients with cardiac sarcoidosis and VT exhibit ventricular substrate characterized by confluent RV scarring and patchy left ventricular scarring capable of sustaining a large number of re-entrant circuits. RFCA is effective in terminating VT storm and eliminating ≥1 inducible VT in the majority of patients, but recurrences are common. Ablation in conjunction with anti-arrhythmic drugs can help palliate VT in this high-risk population.

**Limitations:**

Limited number of patients.
### 844

**Jelic D, et al.**<sup>309</sup>  
Role of radiofrequency catheter ablation of ventricular tachycardia in cardiac sarcoidosis: report from a multicenter registry.  
*PMID: 19187909*  
*Year of publication: 2009*

**Aim:** To assess the response of VT in patients with cardiac sarcoidosis to medical therapy and RFCA.  
**Study type:** Retrospective registry.  
**Number of patients:** 42  
**Enrollment period:** 2004–  
**Study endpoint:** VT recurrence.

**Inclusion:** Consecutive patients from the arrhythmia clinic at the University of Michigan who had cardiac sarcoidosis based on the Japanese Health and Welfare Ministry criteria, and another five patients from other centres who were enrolled in a multicentre registry of cardiac sarcoidosis.  
**Exclusion:** N/A.

**Results:** When VT occurred, a stepwise approach was used: ICD placement, immunosuppressive agents, anti-arrhythmic medications, then RFCA. In nine patients, VT was not controlled by medical therapy, and radiofrequency ablation was performed. A total of 44 VTs were induced. Endocardial radiofrequency ablation was performed in eight patients (RV in 5, LV in 3) and epicardial radiofrequency ablation in one patient. In 4 of 5 patients with RV VTs, a peri-tricuspid circuit was identified. Critical areas were identified for 21 (48%) of 44 VTs, resulting in elimination of 31 (70%) of 44 VTs. The most frequent VT circuit was re-entry in the peri-tricuspid area. This type of VT was eliminated in all patients. Arrhythmic events decreased from 271 ± 363 episodes pre-ablation to 4.0 ± 9.7 post-ablation. All patients had either a decrease (n = 5) or complete elimination (n = 5) of VT during mean follow-up of 19.8 ± 19.6 months.

**Other findings:** 21 (50%) of the 42 patients developed sustained VT/VF during follow-up (including the 12 peri-tricuspid re-entry). Patients who presented with sustained VA and required anti-arrhythmic therapy in addition to steroid therapy.

**Limitations:** Therefore, future well-designed RCTs or large-scale registries are required.

**Conclusions:** RFCA of VT in patients with cardiac sarcoidosis refractory to medical therapy is effective in eliminating VT or markedly reducing the VT burden. The disease process in cardiac sarcoidosis often involves a specific area in the basal right ventricle predisposing to peri-tricuspid re-entry.  

**Epidemiology and demographics:** Critical areas were identified for 21 (48%) of 44 VTs, resulting in elimination of 31 (70%) of 44 VTs. The most frequent VT circuit was re-entry in the peri-tricuspid area. This type of VT was eliminated in all patients. Arrhythmic events decreased from 271 ± 363 episodes pre-ablation to 4.0 ± 9.7 post-ablation. All patients had either a decrease (n = 5) or complete elimination (n = 5) of VT during mean follow-up of 19.8 ± 19.6 months.

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**Aim:** To review the available data regarding the efficacy and safety of VT ablation in patients with cardiac sarcoidosis.  
**Study type:** Meta-analysis of five published studies.  
**Number of patients:** 83  
**Enrollment period:** A systematic search was performed on PubMed, EMBASE, and Cochrane database (from inception to September 2016).  
**Study endpoint:** The primary outcome measure was VT recurrence post ablation. Procedural success was defined as freedom of VT (at the end of follow-up after a single ablation procedure). Other outcomes included freedom from VT recurrence or reduction of arrhythmia burden, mortality, and heart transplant during follow-up. Assessed procedural complications were procedural death, stroke, cardiac tamponade, acute MI, major vascular complications, and other life-threatening complications, assessed on a study-by-study basis.

**Inclusion:** In order to be included, studies needed to provide a minimum of information about the sample of cardiac sarcoidosis patients undergoing RFCA of VT, namely age, gender, VT cycle length, and number of morphologies, as well as information on the cardiac sarcoidosis diagnosis criteria, and baseline medication. Observational non-controlled case series required a minimum of five patients to be considered eligible.  
**Exclusion:** Review articles, editorials and case reports, not considered eligible for the purpose of this review. Patients with granulomatous diseases but without a confirmed diagnosis of sarcoidosis were excluded from the analysis.

**Results:** The mean follow-up period for three of the studies was 19.6 ± 13.3 months, while the remaining two studies had a median follow-up of 27 months. The mean age of patients was 50 ± 8 years, 53/30 (mens/womens) with a maximum of 56 patients receiving immunosuppressive therapy, mean LVEF was 39.1 ± 3.1% and 94% had an ICD in situ. The median number of VTs was three (3.6–4.9/patient), mean cycle length of 360 ms (326–400 ms). 100% of VTs received endocardial ablation, and 18% required epicardial ablation. The complication rates were 4.7–6.3%. Relapse occurred in 45 (54.2%) patients with an incidence of relapse 0.3 (95% CI 0.108–0.55) P < 0.004. Employing a less stringent endpoint (i.e. freedom from arrhythmia or reduction of VA burden), 61 (78.4%) patients improved following ablation.

**Conclusions:** These data support the utilization of RFCA in selected cardiac sarcoidosis cases resistant to medical treatment. However, data are derived from observational non-controlled case series with low/methodological quality. Therefore, future well-designed RCTs or large-scale registries are required.

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**Continued**
### 860

**Title:** Amiodarone for arrhythmia in patients with Chagas cardiomyopathy: a systematic review and individual patient data meta-analysis.  
**PMID:** 30125291  
**Year of publication:** 2018

**Aim:** To assess the effect of amiodarone in patients with Chagas cardiomyopathy.  
**Type of study:** Meta-analysis (96 studies).  
**Number of patients:** 365  
**Enrolment period:** Up to January 2018  
**Study endpoints:** VA burden.

**Indication:** Clinical trials, cross-over studies, case series, and before-after studies assessing the effects of amiodarone on symptoms in patients with Chagas disease.  
**Exclusion:** Case-control studies, reviews, letters, and editorials.

**Results:** In 2443 Hotter, amiodarone reduced the number of VT episodes in 99.9% (95% CI 99.8–100%), PVCs in 91.5% (95% CI 82.9–94%), and the incidence of ventricular couplets in 79% (RR 0.21; 95% CI 0.11–0.39).  
**Other findings:** Amiodarone was associated with corneal microdopias (6.1%; 95% CI 190.9–113; five studies), gastrointestinal events (16.1%; 95% CI 66.3–34; three studies), sinus bradycardia (12.7%; 95% CI 3.7–35.5; six studies), dermatological events (10.6%; 95% CI 47.7–21; nine studies), and drug discontinuation (7.4%; 95% CI 4.1–17.5; five studies).

**Conclusions:** Amiodarone is effective in reducing VA, but there is no evidence for hard endpoints (SD, hospitalization).  
**Limitations:** All included studies were published from 1980–1990.

### 862

**Title:** Ventricular tachycardia in the setting of Chagasic cardiomyopathy: use of voltage mapping to characterize endo-epicardial nonischemic scar distribution.  
**PMID:** 2913179  
**Year of publication:** 2017

**Aim:** To assess usefulness of unipolar endocardial electroanatomical mapping to identify epicardial scar Chagasic cardiomyopathy.  
**Study type:** Retrospective analysis of consecutive patients with Chagas cardiomyopathy.  
**Number of patients:** 19  
**Enrolment period:** July 2007–February 2015  
**Study endpoints:** NA.

**Indication:** Chagasic cardiomyopathy and endo-epicardial voltage mapping.  
**Exclusion:** Patients with a prior VT ablation were excluded. No other arrhythmic ablation in the coronary arteries and no other cause of cardiomyopathy.

**Results:** Basal lateral LV scar involvement was observed in 18 of 19 patients. Bipolar voltage mapping demonstrated larger epicardial than endocardial scar and pattern (≤0.3-mV scar areas [28–30–34] vs. [15–26] and [21–24] vs four [0–7] cm²; \( P = 0.049 \) and \( P = 0.004 \), respectively). Bipolar epicardial and endocardial voltages within scar were low (0.4 [0.2–0.55] and 0.34 [0.23–0.87] mV, respectively) and confluent, indicating a dense/transmural scarring process in Chagasic cardiomyopathy. The endocardial unipolar voltage value (with a newly proposed bipolar scar \( < -0.001 \) mV) predicted the presence and extent of epicardial bipolar scar.

**Conclusions:** Chagasic cardiomyopathy causes a unique VT substrate concentrated to the basal lateral LV, with marked epicardial predominance. The scar pattern is particularly dense and transmural as compared with the more erratic/patchy scar patterns seen in other NICM. Endocardial unipolar voltage mapping serves to characterize epicardial scar in this setting.

### 863

**Title:** Efficacy and safety of combined endo-epicardial catheter ablation for ventricular tachycardia in Chagas disease: a randomized controlled study.  
**PMID:** 3208736  
**Year of publication:** 2020

**Aim:** To evaluate the efficacy and safety of combined epicardial ablation in patients with Chagas disease.  
**Study type:** Single-centre, open-label, RCT.  
**Number of patients:** 30  
**Enrolment period:** April 2014–July 2017  
**Study endpoints:** VT inducibility and all-VA recurrence.

**Indication:** Chagasic cardiomyopathy, ICD, and recurrent SM/VF with at least four episodes in the prior 6 months despite anti-arrhythmic drug therapy. Patients without ICD were eligible after two episodes of sustained VT.  
**Exclusion:** NA.

**Results:** 10 patients were enrolled, and most were men. The median age was 67 (Q1: 58; Q3: 70) years in the endo group and 58 (Q1: 43; Q3: 66) years in the endo-epicardial group. The LV EF was 33% ± 9.5% and 35.2% ± 11.5%, respectively; \( P = 0.13 \). Acute success (non-reinducibility of clinical VT) was obtained in 13 patients (86%) in the endo-epicardial group and in six patients (40%) in the endo-only group (\( P = 0.08 \)). There were 12 patients with VT recurrence (80%) in the endo-only group and six patients (40%) in the endo-epicardial group (\( P = 0.02 \)) by intention-to-treat analysis. Epicardial ablation was ultimately performed in nine patients (60%) in the endo-only group because of an absence of endocardial scar or maintenance of VT inducibility. There was no difference in complications between the groups.

**Conclusions:** Combining endo-epicardial VT RFA in patients with Chagas disease significantly increases short- and long-term freedom from all-VA. Epicardial access did not increase peri-procedural complication rates.

### 854

**Title:** Systematic review and meta-analysis of clinical outcome after implantable cardioverter-defibrillator therapy in patients with Chagas heart disease.  
**PMID:** 31664742  
**Year of publication:** 2019

**Aim:** To pool data from published studies on outcomes after ICD therapy in patients with Chagas heart disease.  
**Study type:** Systematic review and meta-analysis.  
**Number of patients:** 1041 patients.  
**Enrolment period:** 11 studies.

**Indication:** Studies prospective or retrospective observational, in the absence of randomized controlled trials) in which the primary objective was to analyze the impact of ICD therapy on outcomes in patients with Chagas heart disease. Studies were considered eligible if they fulfilled two criteria (1) original articles, published between

**Results:** Overall, the annual all-cause mortality rate was 9% (95% CI 6.9–11.7), 2.8 ± 1.9 years of follow-up, and the annual sudden death rate was 2% (95% CI 1.3–3.1) in 2.6 ± 1.9 years. In addition, in 2484 (95% CI 157.3–370) of patients received one or more appropriate interventions (shocks or ATP), 4.7% (95% CI 3.2–6.9) received

**Other findings:** There were 1041 patients (mean age at implantation 57 ± 11 years; 64% men), most of whom (92%) received an ICD for secondary prevention. Anti-arrhythmic medication consisted of amiodarone (79%) and beta-blockers (44%).

**Conclusions:** In patients with an ICD, annual all-cause mortality rate was 9%. Appropriate ICD interventions and electric storms were frequent, occurring at a rate of 25% and 9% per year, respectively. Inappropriate ICD shocks were not infrequent (5% per year). The benefits and risks of ICD therapy in patients with Chagasic heart disease should be carefully weighed until
Inappropriate shocks, and 9.1% (95% CI 5.3–14.7) had electric storms annually. Data from better studies become available.

Limitations: Most studies did not have data on losses to follow-up, significant publication bias in the rate of inappropriate ICD shocks, heterogeneity in the rate of appropriate ICD interventions and electric storms between included studies.

**857**


**Aims:** To assess the efficacy of ICD in patients with Chagas' heart disease and identify the clinical predictors of mortality and ICD shock during long-term follow-up.

**Type of study:** Retrospective cohort.

**Number of patients:** 116

**Enrolment period:** June 2000–June 2008

**Study endpoints:** Mortality, ICD shocks.

**Indication:** Chagas’ heart disease, diagnosed by positive serological tests, and an ICD implanted for secondary prevention of SCD, according to the Brazilian guidelines.

**Exclusion:** Age <18 years old, advanced atrioventricular block, or previous pacemaker or CRT device at ICD implantation.

**Results:** Follow-up was 45 ± 12 months. 58 patients (30%) had appropriate shocks and 13 (11%) had inappropriate therapy. A total of 31 patients died (7.1% annual mortality rate). NYHA II (HR 3.09; 95% CI 1.37–6.96; P = 0.0064) was a predictor of a worse prognosis. The LVEF (HR 0.97; 95% confidence interval 0.94–0.99; P = 0.042) and low cumulative RV pacing (HR 0.23; 95% CI 0.11–0.49; P = 0.0001) were predictors of better survival. The left ventricular diastolic diameter was an independent predictor of appropriate shock (HR 1.03; 95% CI 1.00–1.06; P = 0.033).

**Other findings:** Mean LVEF was 42 ± 16% at implantation.

**Conclusions:** ICD efficacy for secondary SCD prevention in patients with Chagas’ heart disease was marked by a favourable annual rate of all-cause mortality (7.7%); 50% of the cohort received appropriate shock therapy. NYHA Class III and LVEF were independent predictors of worse prognosis, and low cumulative RV pacing defined better survival.

**Exclusion:** Patients with Chagas heart disease and sustained VT treated with ICD implantation or with amiodarone.

**Study endpoints:** LVEF < 40% and LVEF ≥ 40%.

**Number of patients:** 104

**Enrolment period:** May 1996–December 2011

**Study endpoints:** VA arrhythmia and all-cause mortality.

**Indication:** Patients with Chagas heart disease and VA.

**Exclusion:** N/A.

**Results:** Mean follow-up was 33 ± 16 months for the ICD group and 35 ± 17 months for the control group (P = 0.22). Higher use of beta-blockers in the ICD group (P = 0.0001). Amiodarone was used in 90% of the ICD group. Therapy with ICD plus amiodarone resulted in a 72% reduced risk of all-cause mortality (P = 0.007) and a 95% reduced risk of SD (P = 0.006) compared with amiodarone-only therapy.

**Other findings:** The survival benefit of ICD was greatest in patients with LVEF < 40% (P = 0.07) and was not significant in those with LVEF ≥ 40% (P = 0.15). Survival-free of appropriate ICD therapy was not different between patients with LVEF < 40% and LVEF ≥ 40% (P = 0.07).

**Conclusions:** Superiority of ICD therapy plus amiodarone in reducing all-cause mortality in Chagas heart disease patients with sustained VAs, as compared with amiodarone or the therapy alone. Secondly, the benefit from ICD therapy resulted from the significant decrease in the risk of SD. Thirdly, patients with LVEF 40% derived the most survival benefit from ICD. Limitations: Difference of use of beta-blockers among the two groups.

859


**Aims:** To assess the efficacy of the ICD for secondary prevention in patients with Chagas heart disease, comparing mortality as the primary outcome of patients treated with ICD with those treated with amiodarone.

**Type of study:** Review and meta-analysis.

**Number of patients:** 598

**Enrolment period:** Not reported

**Study endpoints:** All cause mortality.

**Indication:** Patients with Chagas heart disease and sustained VT treated with ICD implantation or with amiodarone.

**Exclusion:** N/A.

**Results:** Six observational studies were included, totaling 115 patients in amiodarone group and 483 patients in ICD group. The mortality outcome in the ICD population was 9.7 per 100 patient-years of follow-up (95% CI 5.7–13.7) and 9.6 per 100 patient-years in the amiodarone group (95% CI 6.7–12.4; P = 0.95). Meta-regression did not show any association with LVEF (P = 0.32), age (P = 0.4), beta-blocker (P = 0.33), or angiotensin-converting enzyme inhibitors (P = 0.096) usage.

**Conclusions:** The best available evidence derived from small observational studies suggests that ICD therapy in secondary prevention of SD (VT or resuscitated SCD) is not associated with lower rate of all-cause mortality in patients with Chagas heart disease.
<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Study type</th>
<th>Aim of the study</th>
<th>Study endpoints</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>874</td>
<td>Eckart RE, et al. 2007</td>
<td>Retrospective, single-centre</td>
<td>To define the characteristics of SMVT after valve surgery.</td>
<td>Study period: 2000–2005</td>
<td>Sustained VT was inducible in 17 patients. Of the 14 patients who were inducible during electrophysiology study had clinical recurrence that necessitated ablation.</td>
<td>Of the 20 patients, 13 (65%) had VT during electrophysiology study. Two patients (10%) had VT during electrophysiology study.</td>
<td>Ablation abolished 41 (98%) of the 42 targeted VTs.</td>
</tr>
<tr>
<td>875</td>
<td>Liang JJ, et al. 2019</td>
<td>Retrospective, single-centre</td>
<td>To investigate the substrate, procedural strategies, safety, and outcomes of RFCA for VT in patients with aortic valve replacement.</td>
<td>Study period: 2004–2016</td>
<td>Clinical VT circuit(s) involved the periaortic region in 10 patients (34%), two (7%) had bundle branch reentry-VT, and 17 (59%) had substrate unrelated to aortic valve replacement. There were two major complications (both related to vascular access). Only two patients (9.1%) had VT recurrence. Over median follow-up of 12.8 months, 11 patients died (none as a result of recurrent VT).</td>
<td>Of the 29 patients, 23 (79%) had VT during electrophysiology study.</td>
<td>Bundles branch reentry should be seriously considered as the VT mechanism. Ablation can be safely performed with excellent long-term VT elimination.</td>
</tr>
<tr>
<td>884</td>
<td>Narasimhan C, et al. 1997</td>
<td>Retrospective, single-centre</td>
<td>To define the characteristics of SMVT after valve surgery.</td>
<td>Study period: 1993–1995</td>
<td>Sustained VT was inducible in 17 patients. Of the 14 patients who were inducible during electrophysiology study had clinical recurrence that necessitated ablation.</td>
<td>Of the 20 patients, 13 (65%) had VT during electrophysiology study. Two patients (10%) had VT during electrophysiology study.</td>
<td>Ablation abolished 41 (98%) of the 42 targeted VTs.</td>
</tr>
</tbody>
</table>

Table of Evidence 31 for Table of Recommendations for sudden cardiac death prevention and treatment of ventricular arrhythmia in valvular heart disease.
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Aim:</strong></td>
<td>To describe outcomes of valvular cardiomyopathy patients referred for ICD implantation for primary prevention compared to patients with CAD or DCM.</td>
<td></td>
</tr>
<tr>
<td><strong>Study type:</strong></td>
<td>Retrospective, multicentre (15 centres).</td>
<td></td>
</tr>
<tr>
<td><strong>Number of patients:</strong></td>
<td>73 out of 1174 consecutive.</td>
<td></td>
</tr>
<tr>
<td><strong>Enrolment period:</strong></td>
<td>2010–2011</td>
<td></td>
</tr>
<tr>
<td><strong>Study endpoints:</strong></td>
<td>All-cause mortality and cardiovascular mortality.</td>
<td></td>
</tr>
<tr>
<td><strong>Inclusion:</strong></td>
<td>Patients referred for ICD implantation for primary prevention.</td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion:</strong></td>
<td>Channelopathies, ARVC, HCM, and congenital heart disease.</td>
<td></td>
</tr>
<tr>
<td><strong>Results:</strong></td>
<td>During a follow-up of 38.1 ± 21.3 months: 197 patients (16.7%) died, without significant differences among the groups (19.2% in the valvular cardiomyopathy group, 15.8% in the ischaemic cardiomyopathy group, and 17.9% in the DCM group; P = 0.2); 136 died of cardiovascular causes (11.6%), without significant differences among the groups (12.3%, 10.5%, and 13.1%, respectively; P = 0.1).</td>
<td></td>
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<tr>
<td><strong>Other findings:</strong></td>
<td>No differences in the proportion of appropriate ICD interventions (13.7%, 17.9%, and 18.8%; P = 0.4). Differences in inappropriate interventions (8.2%, 7.1%, and 12.0%, respectively; P = 0.03).</td>
<td></td>
</tr>
<tr>
<td><strong>Conclusions:</strong></td>
<td>All-cause and cardiovascular mortality in patients with valvular cardiomyopathy were similar to those in other patients referred for defibrillator implantation. They also had similar rates of appropriate interventions. These data suggest that defibrillator implantation in this patient group confers a similar benefit to that obtained by patients with CAD or DCM.</td>
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</tbody>
</table>

**ARVC, arrhythmogenic right ventricular cardiomyopathy; CAD, coronary artery disease; DCM, dilated cardiomyopathy; EF, ejection fraction; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; NA, not applicable; RFCA, radiofrequency catheter ablation; SMVT, sustained monomorphic ventricular tachycardia; VT, ventricular tachycardia.**
### 4.1.6. Congenital heart disease

#### Table of Evidence 32 for Table of Recommendations for risk stratification and primary prevention of sudden cardiac death in congenital heart disease and secondary prevention of sudden cardiac death and treatment of ventricular arrhythmias in congenital heart disease

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>888</td>
<td>Gallego P. et al. 2012</td>
<td>To determine incidence and risk factors for SCA in a study population of 936 adults with previously repaired congenital heart disease who had completed follow-up at a single tertiary centre during a mean period of 9 ± 7 years.</td>
<td>Retrospective observational study.</td>
<td>936</td>
<td>1990–2010</td>
<td>SCD, SCA, ICD, shock for VF.</td>
<td>Adults with reparative intervention before age 20. TOF 23%. Coarctation 17%. Double transposition 10%. Aortic Stenosis 9%. Pulmonary Stenosis 9%. ASD 8%. VSD 7%.</td>
<td>NA.</td>
<td>SCD: 62 (25%). Median follow-up 9 ± 7 years.</td>
<td>NA.</td>
<td>Severe subaortic ventricular systolic dysfunction is a dominant multivariate predictor of SCA in an unselected population of adult survivors after surgery for congenital heart disease. This supports the consideration of primary prevention strategies in these patients.</td>
</tr>
<tr>
<td>889</td>
<td>Ghali A. et al. 2002</td>
<td>To determine if LVEF was also a predictor of SCD in adults with repaired TOF.</td>
<td>Retrospective case-control.</td>
<td>125</td>
<td>1980–2010</td>
<td>SCD, SCA, ICD, shock for VF.</td>
<td>Adults repaired TOF patients. Echo and follow-up available. SCD cases. Controls: 125 out of 310 in database. Age at surgical correction: 5 years Age at last follow-up: 45 years. Time from repair: 20–25 years.</td>
<td>NA.</td>
<td>Observed differences (SCD vs. controls): Severe pulmonary regurgitation 92% vs. 51%, P = 0.002. History of sustained VT: 42% vs. 6%, P &lt; 0.001. ORS ≥ 180: 56% vs. 13%, P &lt; 0.02. LVEF &lt; 40%: 42% vs. 9%, P &lt; 0.001. No difference: AF/atrial flutter, RV dilatation.</td>
<td>NA.</td>
<td>Conclusions: Severe subaortic ventricular systolic dysfunction is a dominant multivariate predictor of SCA in an unselected population of adult survivors after surgery for congenital heart disease. This supports the consideration of primary prevention strategies in these patients.</td>
</tr>
<tr>
<td>890</td>
<td>Khairy P. et al. 2004</td>
<td>To test the diagnostic and predictive value of PVS in repaired TOF patients.</td>
<td>Observational.</td>
<td>252</td>
<td>1983–2002</td>
<td>SCD, SCA, ICD, shock for VF.</td>
<td>Patients with repaired TOF undergoing PVS in the six centres. Age at surgical correction: 5 years.</td>
<td>NA.</td>
<td>Median follow-up after PVS: 63 ± 43 years.</td>
<td>NA.</td>
<td>Conclusions: Programmed ventricular stimulation is of diagnostic and prognostic value in risk stratifying patients with rTOF. Inducible sustained polymorphic VT should not be disregarded as non-specific. Limitations: Pre-selected group of higher-risk patients.</td>
</tr>
</tbody>
</table>
Conclusions:

A risk stratification scheme, based on clinical history (incl. time of repair) and non-invasive testing allows categorization of TOF patients at high risk of malignant arrhythmia. A multicentre prospective evaluation of the accuracy of this scoring system is now being planned.

Limitations:

Retrospective, no validation of decision tree.

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892

Abdallah J, et al.

Ventricular arrhythmia and life-threatening events in patients with repaired Tetralogy of Fallot.

PMID: 32793337

Year of publication: 2020

Aim:

To ascertain factors associated with life-threatening arrhythmic events in repaired TOF.

Study type: Retrospective case-control

Number of patients:

Cases: n = 72
SCD: n = 9
CA: n = 15
Sustained VT: n = 41
Appropriate ICD-shock: n = 7
Controls: n = 216
Number of centres: 13
Enrolment period: 1980–2010
Study endpoints: SCD.

Incidence:

Repaired TOF (96%).
TOF-like repairs for double outlet right ventricle, d-transposition of the great arteries.
Complete repair.
Age at surgical correction: 6.5 years.
Age at last follow-up: 33 years.
Exclusion: N/A.

Results:

Oberved differences (cases vs. controls):

Arrhythmic symptoms:
Pallorations: 53% vs. 17%; P < 0.001
Dizziness: 29% vs. 7%; P < 0.001
Syncope: 22% vs. 3%; P < 0.001
LVEF < 45%: 15% vs. 2%; P < 0.001
QRS > 180 ms (P = 0.055).
Habar sustained or non-sustained VT n (P = 0.055).
Echo: Moderate–severe PR, RV dilatation, Moderate–severe RV dysfunction (all P < 0.05), EPS (only subset): inducibility 55% vs. 12% (P < 0.001).
< 1980
Symptoms and LV dysfunction:
Plus: RV-dysfunction and age at repair < 6.5 preceded by shunt.
> 1980
Symptoms and LV dysfunction.
Plus low risk: transannular patch.
Decision-tree derived.

Other findings:

Aim:

Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries.

PMID: 15337224

Year of publication: 2004

Aim:

To identify predictors for SD in patients with transposition of the great arteries who have undergone repair.

Study type: Retrospective case-control study

Number of patients:

Cases: n = 140
Mustard or Senning repair performed at one centre.
Age at event: 12 years.
Exclusion: 11.1 years.

Incidence:

Mustard or Senning operation performed at one centre.
Audit at event: 12 years.
Age at surgery: 1.1 years.
Exclusion: N/A.

Results:

Oberved differences (SD vs. controls):

History of AF/atrial flutter: HR 5.2
Arrhythmia symptoms:
HR 2.16
Heart failure symptoms:
HR 4.4
Severly impaired RV function: 26% vs. 3%.

Other findings:

Aim:

To ascertain factors associated with life-threatening arrhythmic events in repaired TOF.

Study type: Retrospective case-control

Number of patients:

Cases: n = 72
SCD: n = 9
CA: n = 15
Sustained VT: n = 41
Appropriate ICD-shock: n = 7
Controls: n = 216
Number of centres: 13
Enrolment period: 1980–2010
Study endpoints: SCD.

Incidence:

Repaired TOF (96%).
TOF-like repairs for double outlet right ventricle, d-transposition of the great arteries.
Complete repair.
Age at surgical correction: 6.5 years.
Age at last follow-up: 33 years.
Exclusion: N/A.

Results:

Oberved differences (cases vs. controls):

Arrhythmic symptoms:
Pallorations: 53% vs. 17%; P < 0.001
Dizziness: 29% vs. 7%; P < 0.001
Syncope: 22% vs. 3%; P < 0.001
LVEF < 45%: 15% vs. 2%; P < 0.001
QRS > 180 ms (P = 0.055).
Habar sustained or non-sustained VT n (P = 0.055).
Echo: Moderate–severe PR, RV dilatation, Moderate–severe RV dysfunction (all P < 0.05), EPS (only subset): inducibility 55% vs. 12% (P < 0.001).
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Results:

Oberved differences (SD vs. controls):

History of AF/atrial flutter: HR 5.2
Arrhythmia symptoms:
HR 2.16
Heart failure symptoms:
HR 4.4
Severly impaired RV function: 26% vs. 3%.
### Conclusions:

- Sustained VT/SCD in adults after a Mustard operation for transposition of the great arteries are more common than previously described.
- Age, systemic ventricular function, and QRS duration are interrelated and are associated with VT/SCD.
- History of AT/AF not associated with VT/SCD, contradictory to other studies. May be due to small sample size.

### Results:

- Inclusion: Patients who had ICDs implanted before 2010 in 10 centres for primary prevention. Age at ICD implantation: 37 ± 12 years, 72% men.
- Exclusion: Patients with documented NSVT and symptoms of palpitations or (near) collapse are at risk for appropriate ICD shocks.

### Limitations:

- Small cohort (n = 36).
- Holter data for NSVT only in 58% of patients available (only 21 patients). The paper suggests that the symptoms are related to the NSVT. The method section does not provide details of symptoms at the time of Holter or at any time.

### Aims:

- To examine the prevalence of sustained VT and SCD in adults with atrial repair of transposition of the great arteries and to determine associated risk factors.

### Variables:

- Prior shunt, inducible sustained VA, QRS ≥ 180 ms, ventricular incision, NSVT, moderate–severe LV dysfunction.

### Findings:

- Median follow-up: 9 ± 6 years.
- Events: n = 13 (9%).
- Sustained VT n = 2.
- Median follow-up: 9 ± 6 years.
- Events: n = 13 (9%).
- Sustained VT n = 5.

### Other findings:

- Surgical era: Before 1980
- Small cohort (n = 36).

### Conclusions:

- Sustained VT/SCD in adults after a Mustard operation for transposition of the great arteries are more common than previously described.
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<tr>
<td>908</td>
<td>Kayak Z, et al. [13] Implantable cardioverter defibrillator therapy in adults with congenital heart disease: who is at risk of shocks?</td>
<td>2012</td>
<td>Observational</td>
<td>To identify rates of appropriate and inappropriate ICD shocks in patients with congenital heart disease and to identify risk factors for appropriate shocks.</td>
<td>Study type: Observational. Number of patients: 136 (10 centres). Enrolment period: 32 years. Study endpoints: (1) appropriate ICD shocks, (2) inappropriate ICD shocks. (3) ICD-related complications.</td>
<td>Results: Median follow-up 4.6 years. 39 patients (29%) at least one appropriate ICD therapy. 41 patients (30%) at least one inappropriate ICD shock. 40 patients (29%) ICD-related complications. Predictors of appropriate ICD shock: Secondary prevention indication HR 3.6; Pe = 0.009. CAD HR 2.7; Pe = 0.042. NSVT HR 9.1; Pe = 0.001. Predictors of appropriate ICD shock in one prevention patient: NSVT HR 3.0; P = 0.02.</td>
<td>Predictors of appropriate ICD shock: Secondary prevention indication HR 3.6; Pe = 0.009. CAD HR 2.7; Pe = 0.042. NSVT HR 9.1; Pe = 0.001. Predictors of appropriate ICD shock in one prevention patient: NSVT HR 3.0; P = 0.02.</td>
<td>Conclusions: Congenital heart disease patients with ICDs for primary and secondary prevention experience high rates of appropriate shocks. Symptomatic NSVT is independently associated with ICD shocks in primary and secondary prevention ICD recipients. Limitations: Selection bias for primary prevention indication. Event rate very high, but ICD programming (time-to-detection) unknown.</td>
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<tr>
<td>909</td>
<td>Cochet H, et al. [132] Focal scar and diffuse myocardial fibrosis are independent imaging markers in repaired tetralogy of Fallot.</td>
<td>2019</td>
<td>Case-control</td>
<td>To identify the correlates of focal scar and diffuse fibrosis in patients with history of TOF repair.</td>
<td>Study type: Case-control. Number of patients: TOF cases: n = 103. n = 82 no history of VA. n = 21 with history of VA 10 frequent PVCs. Six NSVT. Five sustained VT. Enrolment period: 2015–2017. Study endpoints: Correlates between fibrosis on CMR and occurrence of VA.</td>
<td>Results: Observed differences (VA vs. no VA):</td>
<td>Correlates between LGE on CMR and occurrence of VA. Correlates between fibrosis on CMR and occurrence of VA.</td>
<td>Other findings: Surgical era: Mostly after 1980 Transannular patch 73%.</td>
<td>Conclusions: Other findings: Surgical era: Mostly after 1980 Transannular patch 73%. Correlates between LGE on CMR and occurrence of VA. Other findings: Surgical era: Mostly after 1980 Transannular patch 73%. Correlates between LGE on CMR and occurrence of VA.</td>
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<td>910</td>
<td>Babu-Narayan SV, et al. [133] Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot: and its relationship to adverse markers of clinical outcome.</td>
<td>2006</td>
<td>Cross-sectional</td>
<td>To test whether LGE after repaired TOF relates to ventricular dysfunction and clinical outcomes including arrhythmias.</td>
<td>Study type: Cross-sectional observational. Number of patients: Repaired TOF Cases: n = 93. n = 16 clinical arrhythmia/syncope (11 SVT, 3 VT, two syncope). Enrolment period: 2002–2005. Study endpoints: Correlates between LGE on CMR and occurrence of VA.</td>
<td>Results: Observed differences (Arrhythmia vs. no Arrhythmias): RV LGE Score is a predictor of ‘arrhythmia’ (but mainly SVT).</td>
<td>Results:</td>
<td>Conclusions: RV and LV LGE were common after TOF repair and were related to adverse clinical markers, including ventricular dysfunction, exercise intolerance, and neurohumoral activation. Furthermore, RV LGE was significantly associated with clinical arrhythmia. Limitations: Only cross-sectional analysis. Only 3 of 16 ‘arrhythmia’ with VT, rest SVT.</td>
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<td>Patients had their surgery before 1980: techniques have changed and with new techniques, VA substrate is very different.</td>
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**Inclusion:** Repaired TOF patients seen in Mayo Clinic, 1990-2017:
- Age at surgical correction ≥ 5 years
- Age at enrolment ≥ 37 years

**Exclusion:**
- AF on ECG (HR 4.8).
- No fragmented QRS (HR 2.0).
- QRS > 180 ms (HR 2.63).
- AF on ECG (HR 4.8).

**Primary endpoint:** all-cause mortality.
**Secondary endpoint:** Clinical VA.

### Mechanism and risk factors for death in adults with tetralogy of Fallot

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- AF on ECG (HR 4.8).

**Primary endpoint:** all-cause mortality.
**Secondary endpoint:** Clinical VA.
Conclusions:
Pre-pulmonary valve replacement induced VT in 53% of TOF patients.

Other findings:
The unexpected high rate of inducibility of 50% is probably related to selection of patients with a high risk for VA. Overall low event numbers.

Surgical ablation seems to reduce VA post-pulmonary valve replacement.

Mostly before 1980

Surgical era:
Transannular patch: 62%. Prior ventriculotomy: 36%.

Aim:
To study the optimal evaluation for and management of VT in patients with repaired TOF patients at the time of pulmonary valve replacement.

Study type: Retrospective observational registry study.

Number of patients: 205
Enrollment period: 1988–2010

Study endpoints: Composite of VT recurrence, OMCA, appropriate ICD therapy, and SCID post-pulmonary valve replacement.

Results:
 Patients undergoing pulmonary valve replacement:
Age at pulmonary valve replacement: 33 years.
Age at initial repair: 4.7 years.
Prior VT: n = 16 (8%)
Pre-operative PES in 40 patients: 33% inducible for VT.
Surgical cryoablation n = 22
Exclusion: N/A.

Follow-up: 6.7 years.

Events during follow-up: 19
SCID n = 5
ICD therapy: 7
OMCA n = 3
Clinical VT: n = 4
Events rates during follow-up:
5 years: 5%.
10 years: 10%.
15 years: 21%.

Surgical cryoablation in 22 patients:
Ablation vs. no ablation:
History of VT 18% vs. 7%.
ICD 23% vs. 5%.
Age at pulmonary valve replacement: 42 vs. 31
Events ablation vs. no ablation:
Ablation: 1 of 22 (4.5%).
No ablation: 18 of 183 (10%).

Other findings:
Surgical era: Mostly before 1980
Transannular patch: 63%
Prior ventriculotomy: 36%.

Conclusions:
PES pre-pulmonary valve replacement induced VT in 53% of TOF patients.

Composite endpoint for subsequent VT after pulmonary valve replacement is rather rare. Surgical ablation seems to reduce VA post-pulmonary valve replacement.

Limitations:
The unexpected high rate of inducibility of 50% is probably related to selection of patients with a high risk for VA. Overall low event numbers.

Aim:
In repaired TOF patients presenting with tachyarrhythmias (SVT and VT), 32% required haemodynamic intervention for tachycardia To study the optimal evaluation for and management of VT in patients with repaired TOF at the time of pulmonary valve replacement.

Study type: Retrospective observational registry study.

Number of patients: 205
Enrollment period: 1988–2010

Study endpoints: Complete rhythm control or failure with and without haemodynamic intervention.

Results:
Complete rhythm control 69%.
Partial rhythm control 13%.
Failure 18%.

Aim:
To assess management strategies (haemodynamic intervention, anti-arrhythmic drugs, ablation) in repaired TOF patients presenting with tachyarrhythmias (SVT and VT).

Study type: Retrospective observational study.

Number of patients: 66

Study endpoints: Complete rhythm control, partial rhythm control or failure with and without haemodynamic intervention.

Results:
Management without haemodynamic intervention:
Complete rhythm control 69%.
Partial rhythm control 13%.
Failure 18%.

Management with haemodynamic intervention:
Complete rhythm control 38%.
Partial rhythm control 33%.
Failure 29%.

Aim:
To identify risk factors for VT and to describe the management and outcome of VT in repaired TOF patients.

Study type: Retrospective case-control study.

Number of patients: n = 210
Cases (sustained VT) n = 18
Controls (no sustained VT) n = 192
Enrollment period: 1990–1994

Study endpoints: VT occurrence.

Results:
Patients with VT had:
More frequent PVC (40 of 9 vs. 21 of 105).
Lower cardiac index (mean 6 standard deviations) 2.4 6 0.4 vs. 3.0 6 0.8.
More structural abnormalities of the RV (outflow tract aneurysms and pulmonary or tricuspid regurgitation).
Management:
14 of 18 VT patients underwent surgery:
PV replacement n = 10, PV repair n = 3, RVOT Taneuneumyectomy n = 9.
VT inducible intra-operatively in 10 patients → cryoablation in all.
Follow-up:
14 patients who required reoperation, VT has recurred in three, 80% of patients with cryoablation free of recurrence.

Other findings:
Surgical era: Likely before 1980

Conclusions:
Most patients with VT late after repair of TOF have outflow tract aneurysms or pulmonary regurgitation, or both.

These patients have a greater frequency of ventricular ectopic beats than arrhythmia-free patients after repair of TOF.

A combined approach of correcting significant structural abnormalities (pulmonary valve replacement or RV aneurysmectomy, or both) with intra-operative electrophysiologically guided ablation may reduce the potential risk of deterioration in ventricular function and enable arrhythmia management to be optimized.
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<td>902</td>
<td>Zyl M van et al.</td>
<td>Retrospective cohort study</td>
<td>Repaired TOF patients and other patients with repaired congenital heart disease</td>
<td>Age at surgical correction: first VT: 31 years. Age at ablation: 5.4 years.</td>
<td>Ablation outcome (acute success and conduction block across A-V); Post-ablation outcome; Composite of ICD shock, OHCA, in-hospital arrhythmic death.</td>
<td>In-hospital arrhythmic death.</td>
<td>Catheter-based VT ablation in patients with repaired congenital heart disease is associated with a low rate of VT recurrence.</td>
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<td>903</td>
<td>Larrodo M et al.</td>
<td>Observational cohort study</td>
<td>TOF patients undergoing VT ablation in Paris.</td>
<td>Age at surgical correction: 3.4 years.</td>
<td>Ablation outcome (acute success); Post-ablation outcome; Composite of VT recurrence and death.</td>
<td>Complete success 33 of 34 patients.</td>
<td>Ten-year outcomes of monomorphic ventricular tachycardia catheter ablation in repaired tetralogy of Fallot.</td>
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<td>904</td>
<td>Kapel GRL et al.</td>
<td>Observational</td>
<td>Congenital heart disease patients undergoing VT ablation at two institutions. TOF n = 28 Transposition great arteries n = 2 Ventricular septal defect n = 2 Atrial septal defect n = 1 Pulmonary stenosis n = 1</td>
<td>Procedure success (non-inducibility and transection of the anatomical isthmus) was achieved in 23 (74%) patients. During long-term follow-up (46 ± 29 months), all patients with procedural success (18/25 with internal cardiac defibrillators) were free of VT recurrence, but 7 of 18 experienced internal cardiac defibrillator-related complications. None of the 18 patients (12/18 with internal cardiac defibrillators) with complete success and preserved cardiac function experienced any VA. In contrast, VT recurred in 4 of 9 patients without procedural success. Four patients died from non-arrhythmic causes.</td>
<td>Procedural success; VT during follow-up.</td>
<td>In patients with repaired congenital heart disease with preserved ventricular function and isthmus-dependent re-entry, VT isthmus ablation can be curative.</td>
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Continued
Khairy P, et al.343
Sudden death and defibrillators in transposition of the great arteries with intraventricular baffles: a multicenter study.
PMID: 19808416
Year of publication: 2008

Aim:
To study rates of appropriate and inappropriate shocks and tachycardia mechanisms in dextro-transposition of the great arteries patients with ICDs.

Study type:
Multicentric observational registry study.

Number of patients:
37

Enrolment period:
Before 2006

Number of centres:
Seven (Canada, United Kingdom, USA).

Study endpoints:
Appropriate ICD shocks, inappropriate ICD shocks, subgroup: subclassification of VT mechanism.

Inclusion:
ICDs implanted in dextro-transposition of the great arteries. Patients implanted before 2006.

Follow-up:
3.6 years.

Exclusion:
NA.

Results:
Events:
Five patients with a total of 47 appropriate ICD shocks.
Nine patients with 92 inappropriate ICD shocks.

Subanalysis of 18 appropriate shocks:
Coexisting SVT in 9 cases = 50%.

Conclusions:
In dextro-transposition of the great arteries patients with an ICD receiving ICD shocks, 50% have coexisting SVT that precedes VT in at least half of the patients.

Limitations:
Small sample and event size.

Kapel GFL, et al.344
Arrhythmogenic anatomical isthmuses identified by electroanatomical mapping are the substrate for ventricular tachycardia in repaired tetralogy of Fallot.
PMID: 28182233
Year of publication: 2017

Aim:
To identify specific electroanatomical characteristics of anatomical isthmuses related to VT which may allow for individualized risk stratification and tailored ablation.

Study type: Observational.

Number of patients:
74

Enrolment period: 2005–2013

Study endpoints:
VT inducibility; presence of slow conducting anatomical isthmus; VT during follow-up.

Inclusion:
Repaired TOF patients, who were considered at risk for VT or had documented VT referred for electrophysiological evaluation and treatment between 2005 and 2013.

Age at surgical correction:
6 years.

Age at EP study:
40 years.

Exclusion:
NA.

Results:
Slow conducting anatomical isthmuses are related to VT inducibility.
Patients with absent or eliminated slow conducting anatomical isthmuses did not have VT recurrence during 50 months of follow-up.

Other findings:
Surgical era:
Likely mostly before 1980.

Transannular patch:
≏ 49%.

Conclusions:
In repaired TOF, slow conducting anatomical isthmuses identified by electroanatomical mapping during sinus rhythm are the dominant substrate for VT allowing individualized risk stratification and preventive ablation.

AF, atrial fibrillation; AI, anatomical isthmus; ARVC, arrhythmogenic right ventricular cardiomyopathy; ASD, atrial septal defect; CA, cardiac arrest; CAD, coronary artery disease; CI, confidence interval; CMR, cardiac magnetic resonance; ECG, electrocardiogram; EF, ejection fraction; EPS, electrophysiological study; HCM, hypertrophic cardiomyopathy; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IQR, interquartile rate; LGE, late gadolinium enhancement; LV, left ventricle; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NA, not applicable; NSVT, non-sustained ventricular tachycardia; NT-pro-BNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; PES, programmed electrical stimulation; PET, positron emission tomography; PVC, premature ventricular contraction; RCT, randomized controlled trial; RFCA, radiofrequency catheter ablation; RA, risk reduction; RV, right ventricle; SCD, sudden cardiac death; SD, sudden death; SHD, structural heart disease; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
4.2. Primary electrical disease

4.2.1. Idiopathic VF

Table of Evidence 33 for Table of Recommendations for the management of patients with idiopathic ventricular fibrillation

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<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
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<th>Summary of main results</th>
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<td>252</td>
<td>Mellor G, et al.136</td>
<td>Aim: To characterize the role of genetic testing in cardiac arrest survivors without a definite clinical phenotype. Study design: CASPER registry. Number of patients: 174 patients with genetic testing.</td>
<td>Study endpoints</td>
<td>29 (17%)</td>
<td>Pathogenic variants were identified in 29 (17%) patients (60% channelopathy-associated and 40% cardiomyopathy-associated genes).</td>
<td>Exclusion: 70 (43%)</td>
<td>Pathogenic variants were identified in 29 (17%) patients (60% channelopathy-associated and 40% cardiomyopathy-associated genes).</td>
<td>Clinical = targeted genetics yield: SADS 35%, unexplained cardiac arrest 48%.</td>
<td>Conclusions: Pathogenic variants are demonstrated in phenotype-negative unexplained cardiac arrest survivors. Genetic testing identifies a pathogenic variant in a significant proportion of unexplained cardiac arrest survivors. Multiphenotype testing revealed the highest frequency of pathogenic variants in phenotype-negative patients.</td>
</tr>
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<td>281</td>
<td>Kumar S, et al.136</td>
<td>Aim: Yield in screening in SD and cardiac arrest survivors. Number of patients: 302. Study design: Retrospective, single-centre.</td>
<td>Inclusion criteria (patients)</td>
<td>32 (18%)</td>
<td>SADS yield 18%; LQTS in young ≤30 years; Brugada syndrome in age ≥40 years.</td>
<td>Exclusion: NA</td>
<td>Pathogenic variants were identified in 32 (18%) patients.</td>
<td>Clinical = targeted genetics yield: SADS 35%, unexplained cardiac arrest 48%.</td>
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<td>915</td>
<td>Leenhardt A, et al.137</td>
<td>Aim: To describe a new entity that they proposed be called 'short-coupled variant of torsade de pointes'. Study design: Retrospective, observational, single-centre. Number of patients: 14.</td>
<td>Inclusion criteria (patients)</td>
<td>14 patients included. Mean follow-up 7 years: five deaths (4 sudden), nine alive of whom six were treated with verapamil alone.</td>
<td>Exclusion: NA</td>
<td>Pathogenic variants were identified in 14 (7%) patients.</td>
<td>Clinical = targeted genetics yield: SADS 18%.</td>
<td>Conclusions: Pathogenic variants are demonstrated in phenotype-negative unexplained cardiac arrest survivors. Genetic testing identifies a pathogenic variant in a significant proportion of unexplained cardiac arrest survivors. Multiphenotype testing revealed the highest frequency of pathogenic variants in phenotype-negative patients.</td>
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<td>916</td>
<td>Eisenberg S, et al.138</td>
<td>Aim: To describe 15 patients with polymorphic VT and normal QT intervals. Study design: Retrospective case series, observational, single-centre. Number of patients: 15.</td>
<td>Inclusion criteria (patients)</td>
<td>15 patients included. Mean follow-up 7 years: five deaths (4 sudden), nine alive of whom six were treated with verapamil alone.</td>
<td>Exclusion: NA</td>
<td>Pathogenic variants were identified in 15 (7%) patients.</td>
<td>Clinical = targeted genetics yield: SADS 35%, unexplained cardiac arrest 48%.</td>
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Continued
Conclusions: Cardiac genetic testing is positive in nearly 2/3 of patients with suspected cardiac phenotypes.

Results: 60 patients included. 32 pathogenic or likely pathogenic variants found in 27 (45%). In 24 patients with detectable 'cardiac phenotypes' after SCA, 16 (67%) had mutations congruent with suspected phenotype vs. 17% in those without phenotypes.

Inclusion: Patients with SCA presenting to Bern University Hospital for genetic testing between January 2014 and May 2018. Patients with CAD, myocarditis, sarcoidosis, systemic diseases affecting the heart, secondary cardiomyopathies, reversible cases of SCA.

Results: Authors advise against routine analysis of 1 of 33 patients was found to have a likely pathogenic mutation. Added yield of genetic testing with NGS of 179 additional genes = 3%.

Inclusion: In 15% of patients, ≥ 1 variants of uncertain clinical significance detected.

Exclusion: Patients who had NGS of 34 genes already performed. If initial NGS of 34 genes negative, NGS of 179 additional genes requested.

Conclusions: Excellent survival rate among survivors of VF with minimal or no SHD, occurrence of (infrequent) ICD discharges suggests that ICDs can be of overall benefit. Limitations: True idiopathic ventricular fibrillation in out-of-hospital cardiac arrest survivors in the Swiss Canton Ticino prevalence, clinical features, and long-term follow-up.

Prompting the patient to participate is critical to the success of cardiac rehabilitation programs. This is a self-contained text, focusing on the importance of patient engagement in cardiac rehabilitation programs to achieve desired outcomes. The text emphasizes the patient's active role in their rehabilitation process, which is essential for successful recovery and maintenance of cardiovascular health.

Conclusions: Cardiac genetic testing is positive in nearly 2/3 of patients with suspected cardiac phenotypes and in 1/6 without evident cardiac phenotypes.

Examining the patient’s genetic profile is crucial to identifying potential risk factors. This is a comprehensive analysis, highlighting the importance of genetic screening in cardiovascular conditions. The examination covers various genetic markers, including familial susceptibility, genetic predispositions, and the impact of genetic testing on patient management.

Conclusions: Cardiac genetic testing is positive in nearly 2/3 of patients with suspected cardiac phenotypes and in 1/6 without evident cardiac phenotypes.

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<table>
<thead>
<tr>
<th>Document ID</th>
<th>Title</th>
<th>Authors</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Inclusion</th>
<th>Methods</th>
<th>Results</th>
<th>Conclusions</th>
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<tbody>
<tr>
<td>925</td>
<td>Conclusions: Quinidine use is rare in Canada, but is associated with ↓ VA in patients with Brugada syndrome, ERS, IVF with minimal toxicity. Access to quinidine should be improved.</td>
<td>Mathi N, et al.</td>
<td>2020</td>
<td>Retrospective cohort</td>
<td>Number of patients: 46</td>
<td>To determine nature of quinidine use and accessibility. Study design: Retrospective cohort. Number of patients: 9</td>
<td>Inclusion: Patients aged ≥ 18 years taking quinidine for prevention or treatment of VA identified using the Hearts in Rhythm Organization (HiRO), including CASPIR. Exclusion: NA.</td>
<td>Results: In population of 36 million (Canada), 46 patients are currently prescribed quinidine (Brugada syndrome 5%, ERS 13%, IVF 46%). ICD shocks before vs. after quinidine initiation: 7.47 ± 1.3 in 34 ± 46 months vs. 0.86 ± 1.69 in 44 ± 42 months. Conclusions: Quinidine use is rare in Canada, but is associated with ↓ VA in patients with Brugada syndrome, ERS, IVF with minimal toxicity. Access to quinidine should be improved.</td>
</tr>
<tr>
<td>926</td>
<td>Conclusions: Quinidine guided by EP studies was effective in suppressing recurrent VF in IVF cases with and without SC-PVC. Quinidine represents a valuable long-term alternative to ICD therapy.</td>
<td>Belhassen B, et al.</td>
<td>2009</td>
<td>Retrospective cohort</td>
<td>Number of patients: 23</td>
<td>To determine nature of quinidine use and accessibility. Study design: Retrospective, single-centre. Number of patients: 9</td>
<td>Inclusion: No SHD, normal QT, EP testing with quinidine showing no inducible sustained VA, long-term treatment with quinidine following first EPS, repeat EPS ≥ 1 year after first EPS. Exclusion: NA.</td>
<td>Results: Nine patients included (5 with Brugada syndrome, 4 with IVF). All patients had inducible VF at baseline that was prevented by quinidine. Repeat EPS at mean of 9.8 years: all patients still non-inducible with no recurrent documented VA. Conclusions: Quinidine guided by EP studies was effective in suppressing recurrent VF in IVF cases with and without SC-PVC. Quinidine represents a valuable long-term alternative to ICD therapy.</td>
</tr>
<tr>
<td>927</td>
<td>Conclusions: Quinidine was effective in suppressing recurrent VF in IVF cases with and without SC-PVC.</td>
<td>Belhassen B, et al.</td>
<td>1987</td>
<td>Retrospective cohort</td>
<td>Number of patients: 5</td>
<td>To determine nature of quinidine use and accessibility. Study design: Case series. Number of patients: 5</td>
<td>Inclusion: No known cardiac disease, referred for EPS for documented IVF. Exclusion: NA.</td>
<td>Results: Five patients included. Programmed stim could induce VA in all patients (2 on amiodarone), but were non-inducible after oral quinidine or oral disopyramide. Long-term use of acutely effective anti-arrhythmic drugs associated with asymptomatic mean follow-up of 32 months. Conclusions: Quinidine was effective in suppressing recurrent VF in IVF cases with and without SC-PVC.</td>
</tr>
<tr>
<td>929</td>
<td>Conclusions: EP-guided therapy with Class IA antiarrhythmic drugs is safe and effective for long-term management of patients with idiopathic ventricular fibrillation.</td>
<td>Belhassen B, et al.</td>
<td>1999</td>
<td>Prospective study</td>
<td>Number of patients: 23</td>
<td>To determine nature of quinidine use and accessibility. Study design: Prospective study. Number of patients: 23</td>
<td>Inclusion: Patients with IVF/Brugada syndrome with initially inducible polymorphic VT or VF rendered non-inducible with class IA anti-arrhythmic drugs treated with these agents long-term. Exclusion: N.A.</td>
<td>Results: 23 patients included, none of whom died over a mean follow-up of 9.1 years. Other findings: Two deaths occurred in patients without inducible polymorphic VT/VF at baseline who were treated empirically. Conclusions: EP-guided therapy with class IA antiarrhythmic drugs is safe and effective for long-term mgt of IVF.</td>
</tr>
<tr>
<td>930</td>
<td>Conclusions: VAs originating from the moderator band may present with VF. RFCA is effective, although risk of requiring ≥2 procedure may be higher than for other sites.</td>
<td>Sadik M, et al.</td>
<td>2015</td>
<td>Retrospective cohort</td>
<td>Number of patients: 10</td>
<td>To determine nature of quinidine use and accessibility. Study design: Single-centre observational. Number of patients: 10</td>
<td>Inclusion: 10 patients with VAs mapped to moderator band in RV undergoing RFCA. Exclusion: NA.</td>
<td>Results: VF was the clinical arrhythmia in seven patients and monomorphic VT in three patients. Six patients required repeat procedure. Mean follow-up 21.5 ± 11.6 months: all patients free of sustained VAs, with only one patient requiring anti-arrhythmic drug therapy and one patient having isolated PVCs no longer inducing VF. No procedural complications. Conclusions: VAs originating from the moderator band may present with VF. RFCA is effective, although risk of requiring ≥2 procedure may be higher than for other sites.</td>
</tr>
<tr>
<td>Page</td>
<td>Title</td>
<td>Authors</td>
<td>Year of publication</td>
<td>Study type</td>
<td>Aim</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Results</td>
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<tr>
<td>931</td>
<td>Catheter ablation of ventricular fibrillation importance of left ventricular outflow tract and papillary muscle triggers.</td>
<td>Van Herendael H, et al.</td>
<td>2014</td>
<td>Retrospective, observational.</td>
<td>To describe and characterize sites of origin of VPDs triggering VF and polymorphic VT (polymorphic VT).</td>
<td>Number of patients: 30</td>
<td>Referral for ablation for VA and VF/polymorphic VT.</td>
<td>Freedom from recurrent VF at long-term follow-up.</td>
</tr>
<tr>
<td>932</td>
<td>Ventricular fibrillation triggered by PVCs from papillary muscles: clinical features and ablation.</td>
<td>Santoro F, et al.</td>
<td>2014</td>
<td>Retrospective, observational.</td>
<td>To investigate the role of papillary muscle PVCs as triggers for VF and the safety and feasibility of RFCA in these patients.</td>
<td>Number of patients: 6</td>
<td>History of VF resulting in repetitive ICD shocks despite anti-arrhythmic drug therapy.</td>
<td>Freedom from VF recurrence at 3 months.</td>
</tr>
<tr>
<td>933</td>
<td>Catheter ablation of polymorphic ventricular tachycardia/fibrillation in patients with and without structural heart disease.</td>
<td>Nakamura T, et al.</td>
<td>2019</td>
<td>Retrospective, observational.</td>
<td>The purpose of this study was to characterize the electrophysiological findings and ablation outcomes for patients with polymorphic VT/VF and SHD compared to those with IVF. Study type: Retrospective, observational.</td>
<td>Number of patients: 32</td>
<td>Data from 32 consecutive patients (13 IVF, 19 SHD) with recurrent polymorphic VT/VF.</td>
<td>Freedom from recurrent polymorphic VT/VF episodes/shocks at 3 months.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARVC, arrhythmogenic right ventricular cardiomyopathy; BB, beta-blocker; CAD, coronary artery disease; CI, confidence interval; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; EP, electrophysiological; EPS, electrophysiological stimulation; ER, early repolarization; ERP, early repolarization pattern; ERS, early repolarization syndrome; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, interquartile range; IVF, idiopathic ventricular fibrillation; LQTS, long QT syndrome; LV, left ventricle; NA, not applicable; OHCA, out of hospital cardiac arrest; OR, odds ratio; PVC, premature ventricular complex; RFCA, radiofrequency catheter ablation; RV, right ventricle; SADS, sudden arrhythmic death syndrome; SCA, sudden cardiac arrest; SC-SCD, sudden cardiac death; SC-PVC, short-coupled premature ventricular complex; SD, sudden death; SHD, structural heart disease; SMVT, sustained monomorphic ventricular tachycardia; SUD, sudden unexplained death; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
### 4.2.2. Long QT syndrome (including acquired long QT syndrome)

#### Table of Evidence 34 for Table of Recommendations for the management of patients with long QT syndrome

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tbody>
<tr>
<td>85</td>
<td>Priori S, et al. [363]</td>
<td>Aim: To define the cumulative probability of a first cardiac event (defined as syncope, cardiac arrest, or SD) before therapy (i.e. the natural history of the disease) and to analyze the complex interplay among the genetic locus, sex, and the duration of repolarization, which determines the probability of cardiac events in long QT syndrome. Study type: Prospective cohort study. Number of patients: 647 patients in 193 families. Enrolment period: Not reported. Follow-up: Mean 28 years. Study endpoints: Cardiac arrest or SD before the age of 40 years and before the initiation of any treatment related to long QT syndrome. Inclusion: Genotyped LQT1, LQT2, or LQT3 patients and genotype-positive family members. Exclusion: NA. Results: The incidence of a first cardiac event before the age of 40 years and before the initiation of therapy was lower among patients with a mutation at the LQT1 locus (30%) than among those with a mutation at the LQT2 locus (46%) or those with a mutation at the LQT3 locus (43%) (P &lt; 0.001). Multivariate analysis showed that the genetic locus and the QTc, but not sex, were independent predictors of risk. Other findings: The genotype affects the clinical course of long QT syndrome and modulates the effects of the QTc and sex on clinical manifestations. The authors propose an approach to risk stratification based on these variables.</td>
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<tr>
<td>140</td>
<td>Churet M, et al. [364]</td>
<td>Aim: To evaluate the diagnostic reliability of the epinephrine provocative test for LQTS diagnosis, taking into consideration intra- and interobserver variability in the interpretation of the test. Study type: Retrospective analysis. Number of participants: 79 Enrolment period: 2010–2017 Study endpoints: QT and RR intervals at rest and at each dose, as well as final operator interpretation of the test. Inclusion: Tests performed for family screening or individual suspicion of LQTS. Exclusion: Tests carried out for suspicion of CPVT. Results: Epinephrine was administered following a standardized protocol at two doses: 0.05 and 0.10 μg kg⁻¹ min⁻¹. ECG were blindly read twice by three different operators at ≥1-week intervals. QT and RR intervals were collected at rest and at each dose, as well as final operator interpretation of the test. There was a high interobserver reproducibility of corrected QT measurements with an intraclass correlation (ICC) of 0.74 (95% CI 0.66–0.80) but a low interobserver reproducibility on the final interpretation with a κ of 0.31. Intraobserver reproducibility of corrected QT was very good (ICC 0.93; 0.91–0.95) but still resulted in only moderate intraobserver agreement in the interpretation of the epinephrine provocative test for LQTS is poor to moderate. Complexity in interpretation varies from one case to the next. The low reliability of this test encourages a reconsideration of its importance in the clinical management of patients with suspected LQTS. Strength: Results were compared between the first to the second readings (intraobserver reproducibility) and between operators (interobserver reproducibility). Limitations: Single-centre and retrospective.</td>
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</table>
### Conclusions:
The study provides a table with estimators of risk of LAEs in LQTS that allows a granular estimate of 5-year data have been validated in an independent cohort: submitted. A calculator is available and could be provided as an addition to the document.

### Strength:
Arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS.

### Limitations:
Not blind, not randomized.

The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes.

### Results:
Inclusion: LQTS patients who underwent LCSD.
Exclusion: NA.

**Results:**
- After LCSD, 46% remained asymptomatic Syncpe occurred in 31%, aborted cardiac arrest in 16%, and 3D in 7%.

Conclusions: LCSD was associated with a significant reduction in the incidence of aborted cardiac arrest and syncpe in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD was not entirely effective in preventing cardiac events including SCD during long-term follow-up.

### Results:
Inclusion: Carriers of a single mutation in one of the major LQT genes: KCNQ1, KCNH2, or SCN5A.
Exclusion: Carriers of double mutations or genetic variants adjudicated as benign or likely benign according to the criteria proposed by the American College of Medical Genetics and Genomics.

**Results:**
The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes. Intergenotype comparison showed that the risk for patients with LQT2 and LQT3 increased by 100% and 157% at any QTc duration vs. patients with LQT1. Only nadolol reduced the arrhythmic risk in all genotypes significantly (by 62%) compared with no therapy (HR 0.38; 95% CI 0.15–0.93; P = 0.001 in cohort; RR 0.39; P = 0.001 in ITS). Neither propranolol (HR 0.79; 95% CI 0.35–1.77; P = 0.56) nor the selective beta-blockers (HR 0.79; 95% CI 0.35–1.77; P = 0.56) conferred a significant reduction in the risk of LAEs at follow-up.

Conclusions: LCSD was associated with a significant reduction in the incidence of aborted cardiac arrest and syncpe in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD was not entirely effective in preventing cardiac events including SCD during long-term follow-up.

<table>
<thead>
<tr>
<th>Study</th>
<th>Aim</th>
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<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>544</td>
<td>Schwartz P, et al.</td>
<td>Left cardiac sympathetic denervation in the management of high-risk patients affected by long QT syndrome.</td>
<td>LCSD in a group of high-risk LQTS patients. Study type: Retrospective. Number of patients: 147 Enrollment period: 1990–2002.</td>
<td>Indication: LQTS patients who underwent LCSD. Exclusion: NA.</td>
<td>Results: After LCSD, 46% remained asymptomatic Syncpe occurred in 31%, aborted cardiac arrest in 16%, and 3D in 7%.</td>
<td>LCSD was associated with a significant reduction in the incidence of aborted cardiac arrest and syncpe in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD was not entirely effective in preventing cardiac events including SCD during long-term follow-up.</td>
</tr>
<tr>
<td>943</td>
<td>Mazzanti A, et al.</td>
<td>Interplay between genetic substrate, QTc duration, and arrhythmia risk in patients with long QT syndrome.</td>
<td>LCSD in a group of high-risk LQTS patients. Study type: Prospective cohort study. Number of patients: 1710 Enrollment period: Up to 2016 Follow-up: Median: 7.1 years (IQR 2.7–13.4). Study endpoints: 5-year risk of life-threatening arrhythmic events (LAEs) including SCD, aborted cardiac arrest, haemodynamically non-tolerated polymorphic VT.</td>
<td>Indication: Carriers of a single mutation in one of the major LQT genes: KCNQ1, KCNH2, or SCN5A. Exclusion: Carriers of double mutations or genetic variants adjudicated as benign or likely benign according to the criteria proposed by the American College of Medical Genetics and Genomics.</td>
<td>Results: The estimated risk of LAEs increased by 15% for every 10-ms increment of QTc duration for all genotypes. Intergenotype comparison showed that the risk for patients with LQT2 and LQT3 increased by 100% and 157% at any QTc duration vs. patients with LQT1. Only nadolol reduced the arrhythmic risk in all genotypes significantly (by 62%) compared with no therapy (HR 0.38; 95% CI 0.15–0.93; P = 0.001 in cohort; RR 0.39; P = 0.001 in ITS) and 130% and 157% at any QTc duration vs. patients with LQT1. Only nadolol reduced the arrhythmic risk in all genotypes significantly (by 62%) compared with no therapy (HR 0.38; 95% CI 0.15–0.93; P = 0.001 in cohort; RR 0.39; P = 0.001 in ITS). Neither propranolol (HR 0.79; 95% CI 0.35–1.77; P = 0.56) nor the selective beta-blockers (HR 0.79; 95% CI 0.35–1.77; P = 0.56) conferred a significant reduction in the risk of LAEs at follow-up.</td>
<td>The study provides a table with estimators of risk of LAEs in LQTS that allows a granular estimate of 5-year arrhythmic risk and demonstrate the superiority of nadolol in reducing the risk of LAEs in LQTS.</td>
</tr>
<tr>
<td>946</td>
<td>Schwartz P, et al</td>
<td>Genotype-phenotype correlation in long QT syndrome gene-specific triggers for life-threatening arrhythmias.</td>
<td>LCSD in a group of high-risk LQTS patients. Study type: Retrospective analysis. (International LQTS Registry). Number of patients: 670 LQTS patients. Enrollment period: Before 2001 Study endpoints: Clinical characteristics, medication treatment, death, syncope, and aborted cardiac arrest.</td>
<td>Indication: LQTS patients with a known genotype in LQTS 1–3. Exclusion: NA.</td>
<td>Results: LQT1 patients experienced the majority of their events (62%) during exercise, and only 3% occurred during rest/sleep. These percentages were almost reversed among LQT2 and LQT3 patients, who were less likely to have events during exercise (13%) and more likely to have events during rest/sleep (29% and 39%).</td>
<td>Life-threatening arrhythmias in LQTS patients tend to occur under specific circumstances in a gene-specific manner.</td>
</tr>
<tr>
<td>948</td>
<td>Ahn J, et al.</td>
<td>Effectiveness of beta-blockers depending on the genotype of congenital long QT syndrome: a meta-analysis.</td>
<td>Patients with a genetic diagnosis of LQTS. Beta-blockers prescribed in treated group.</td>
<td>Indication: Patients with a genetic diagnosis of LQTS.</td>
<td>Results: Use of beta-blocker was associated with significant risk reduction of all cardiac events (HR 0.49; P &lt; 0.001 in cohort) and serious cardiac events (aborted cardiac arrest or SCD) (HR 0.47; P &lt; 0.001 in cohort). Among the beta-blockers, nadolol had the greatest effect in reducing the risk of serious cardiac events.</td>
<td>Effectiveness of beta-blockers on reduction of cardiac events in LQTS was different depending on LQT genotype, suggesting that nadolol could be considered first-line therapy, and that a genotype-guided strategy for the use of other beta-blockers can improve the clinical outcomes in patients with LQTS.</td>
</tr>
<tr>
<td>Study ID</td>
<td>Author(s)</td>
<td>Year of publication</td>
<td>Aim</td>
<td>Inclusion</td>
<td>Exclusion</td>
<td>Results</td>
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<tr>
<td>949</td>
<td>Priori S, et al</td>
<td>2004</td>
<td>To describe cardiac events among LQTS patients treated with beta-blockers.</td>
<td>Genotyped LQT1, LQT2, or LQT3 patients treated with long-term beta-blocker therapy.</td>
<td>NA</td>
<td>Cardiac events occurred in 19 of 187 (10%) LQT1 patients, 27 of 120 (23%) LQT2 patients, and nine of 28 (32%) LQT3 patients.</td>
</tr>
<tr>
<td>951</td>
<td>Mazzanti A, et al</td>
<td>2016</td>
<td>To determine whether mexiletine prevents arrhythmic events in patients with long QT syndrome type 3 treated with beta-blockers.</td>
<td>LQT3 mutation carriers.</td>
<td>NA</td>
<td>Mexiletine significantly shortened QTc (by 61 ± 6 ms; P &lt; 0.0001) and reduced the percentage of patients with arrhythmic events (from 22% to 3%; P = 0.031), the mean number of arrhythmic events per patient (from 0.43 ± 0.17 to 0.03 ± 0.03; P = 0.007), and the annual rate of arrhythmic events (from 10.3% to 0.7%; P = 0.0097).</td>
</tr>
<tr>
<td>955</td>
<td>Moss A, et al</td>
<td>2000</td>
<td>To evaluate risk factors for syncope, aborted cardiac arrest, and death during prescribed beta-blocker therapy.</td>
<td>LQTS probands and affected family members.</td>
<td>NA</td>
<td>After initiation of beta-blockers, there was a significant (P &lt; 0.001) reduction in the rate of cardiac events in probands (0.67–0.31 events per year) and in affected family members (0.26–0.13 events per year). During 5-year matched periods on-therapy surveillance analysis revealed that patients with cardiac symptoms before beta-blockers (n = 598) had an HR of 5.8 for recurrent cardiac events (syncope, aborted cardiac arrest, or death) during beta-blocker therapy compared with asymptomatic patients.</td>
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</table>

**Exclusions:**
- NA.

**Gene-specific therapy with mexiletine reduces arrhythmic events in patients with long QT syndrome type 3.**

<table>
<thead>
<tr>
<th>Year of publication</th>
<th>Enrolment period</th>
<th>Follow-up</th>
<th>Study endpoints</th>
<th>Study type</th>
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<tbody>
<tr>
<td>2004</td>
<td>2000</td>
<td>35 months (IQR 19–64)</td>
<td>Median: 35 months (IQR 19–64)</td>
<td>Prospective cohort study</td>
</tr>
<tr>
<td>2016</td>
<td>2000</td>
<td>35 months (IQR 19–64)</td>
<td>Median: 35 months (IQR 19–64)</td>
<td>Prospective cohort study</td>
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<tr>
<td>2000</td>
<td>2000</td>
<td>35 months (IQR 19–64)</td>
<td>Median: 35 months (IQR 19–64)</td>
<td>Retrospective analysis, International LQTS Registry</td>
</tr>
</tbody>
</table>
Conclusions:
Life-threatening events.

Results:
The lowest risk was found in patients with only one syncope occurring before the start of beta-blocker. In contrast, patients experiencing syncope after starting beta-blocker had a 3.6-fold increase in the risk of severe arrhythmic events (P < 0.001) relative to the low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker were associated with an intermediate risk (HR: 1.8; P < 0.001). The risk of syncope during beta-blocker therapy is high during childhood in both sexes, but is higher in women than in men (HR: 2.3; P < 0.001).

Inclusion:
LQTS patients with a corrected QT interval ≥ 450 ms presenting with syncope as a first symptom.
Exclusion:
N/A.

Limitations:
Reliance on patient reporting and lack of objective measures, no validated questionnaire was suitable for this study cohort, possible discordance between responses of parents and children (but an ordinal logistic regression excluding parental data to minimize this issue was performed), follow-up is variable and <1 year in 23% of the cohort, a time when side effects are more pronounced.

Strengths:
NA.

Conclusions:
Patients with syncope during beta-blocker are at high risk of life-threatening events.

Aim:
To identify risk factors for fatal arrhythmias in LQTS patients presenting with syncope.
Study type:
Retrospective analysis (International LQTS Registry).
Number of patients:
1059
Enrollment period:
Before 2010
Study endpoints:
Severe arrhythmic events comprising aborted cardiac arrest, appropriate ICD therapy, and SCD.

Inclusion:
LQTS patients with a corrected QT interval ≥ 450 ms presenting with syncope as a first symptom.
Exclusion:
N/A.

Results:
The lowest risk was found in patients with only one syncope occurring before the start of beta-blocker. In contrast, patients experiencing syncope after starting beta-blocker had a 3.6-fold increase in the risk of severe arrhythmic events (P < 0.001) relative to the low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker were associated with an intermediate risk (HR: 1.8; P < 0.001). The risk of syncope during beta-blocker therapy is high during childhood in both sexes, but is higher in women than in men (HR: 2.3; P < 0.001).

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The lowest risk was found in patients with only one syncope occurring before the start of beta-blocker. In contrast, patients experiencing syncope after starting beta-blocker had a 3.6-fold increase in the risk of severe arrhythmic events (P < 0.001) relative to the low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker were associated with an intermediate risk (HR: 1.8; P < 0.001). The risk of syncope during beta-blocker therapy is high during childhood in both sexes, but is higher in women than in men (HR: 2.3; P < 0.001).

Conclusions:
Patients with syncope during beta-blocker are at high risk of life-threatening events.

Aim:
To investigate the safety and efficacy of video-assisted thoracoscopic (VATS) LCSD in patients with LQTS and CPVT.
Study type:
Retrospective, observational study.
Number of patients:
15 (4 men, 11 LQTS, 1 CPVT).
Enrollment period:
2010–2015
Follow-up:
Mean 927 ± 330 days.
Study endpoints:
Complications including Horner syndrome, bleeding, pneumothorax, severe pain.
Acute anti-arrhythmic efficacy (epinephrine test). Cardiac events including SCD, aborted cardiac arrest, syncope.

Inclusion:
Diagnosis of LQTS or CPVT and treated with VATS-LCSD between November 2010 and January 2015 for hereditary VA syndromes at Kyungpook National University Hospital.
Exclusion:
NA.

Results:
Six and one patients developed ventricular tachyarrhythmia during pre-procedural and postprocedural epinephrine test, respectively (P = 0.063). No serious complications such as Horner syndrome, pneumothorax, or bleeding developed after LCSD. Mean hospital stay after VATS-LCSD was 3.7 ± 1.5 days. One LQTS patient and one CPVT patient, neither of whom manifested tachyarrhythmia during post-LCSD epinephrine test, developed torsade de points and syncope respectively. The annual event rates of six patients who were symptomatic during the period preceding LCSD decreased from 0.97 to 0.19 events/year (P = 0.045).

Conclusions:
VATS-LCSD was a safe and effective procedure for patients with hereditary VT syndrome, with no serious adverse events and with short hospital stay.
Strength:
Long follow-up.
Safety of technology.
Limitation:
Only six patients were symptomatic before the procedure.

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To investigate the safety and efficacy of video-assisted thoracoscopic (VATS) LCSD in patients with LQTS and CPVT.
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VATS-LCSD was a safe and effective procedure for patients with hereditary VT syndrome, with no serious adverse events and with short hospital stay.
Strength:
Long follow-up.
Safety of technology.
Limitation:
Only six patients were symptomatic before the procedure.

Aim:
To identify risk factors for fatal arrhythmias in LQTS patients presenting with syncope.
Study type:
Retrospective analysis (International LQTS Registry).
Number of patients:
1059
Enrollment period:
Before 2010
Study endpoints:
Severe arrhythmic events comprising aborted cardiac arrest, appropriate ICD therapy, and SCD.

Inclusion:
LQTS patients with a corrected QT interval ≥ 450 ms presenting with syncope as a first symptom.
Exclusion:
N/A.

Results:
The lowest risk was found in patients with only one syncope occurring before the start of beta-blocker. In contrast, patients experiencing syncope after starting beta-blocker had a 3.6-fold increase in the risk of severe arrhythmic events (P < 0.001) relative to the low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker were associated with an intermediate risk (HR: 1.8; P < 0.001). The risk of syncope during beta-blocker therapy is high during childhood in both sexes, but is higher in women than in men (HR: 2.3; P < 0.001).

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Conclusions:
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Severe arrhythmic events comprising aborted cardiac arrest, appropriate ICD therapy, and SCD.

Inclusion:
LQTS patients with a corrected QT interval ≥ 450 ms presenting with syncope as a first symptom.
Exclusion:
N/A.

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Conclusions:
Life-threatening events.

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The lowest risk was found in patients with only one syncope occurring before the start of beta-blocker. In contrast, patients experiencing syncope after starting beta-blocker had a 3.6-fold increase in the risk of severe arrhythmic events (P < 0.001) relative to the low-risk group and displayed a risk of severe arrhythmic events similar to that of patients not treated with beta-blockers. Multiple syncopal episodes occurring before initiation of beta-blocker were associated with an intermediate risk (HR: 1.8; P < 0.001). The risk of syncope during beta-blocker therapy is high during childhood in both sexes, but is higher in women than in men (HR: 2.3; P < 0.001).

Conclusions:
Patients with syncope during beta-blocker are at high risk of life-threatening events.
Aim: To evaluate the effect of LCSD on heart rate, cardiac contractility, and cardiopulmonary fitness in human subjects. Study design: Retrospective. Number of patients: 55 (39 Females, 36 LQT1, 15 LQT2). Enrolment period: 2006–2017 Follow-up: 5.1 ± 2.5 years. Study endpoints: Differences in cardiopulmonary fitness and response between testing pre- and post-LCSD (mean peak heart rate, mean peak oxygen consumption, mean peak respiratory exchange ratio, time to peak heart rate, heart rate recovery), differences in cardiac contractility pre- and post-LCSD (left ventricle end-diastolic volume, left ventricle ejection fraction). Inclusion: Patients with LQTS who underwent LCSD between 2006 and 2017 and who had both pre- and post-LCSD cardiopulmonary exercise stress tests performed at Mayo Clinic, Rochester, Minnesota. Exclusion: Patients who underwent bilateral sympathetic denervation.

Results: Mean peak heart rate before LCSD was 143 ± 23 b.p.m., mean peak oxygen consumption (VO2) was 32 ± 10 mL/kg/min, and mean peak respiratory exchange ratio was 1.14 ± 0.12. There was no difference in peak heart rate, peak VO2, peak QTc, or respiratory exchange ratio pre- and post-LCSD. To evaluate the isolated effect of LCSD, the study performed a subset analysis of patients with LCSD monotherapy (n = 10) or no change in beta-blockers dose (n = 12). Patient-matched pre- and post-LCSD exercise testing showed no difference in heart rate, VO2, or left ventricular function following LCSD.

Conclusions: LCSD provides increased protection from an LQTS-triggered event without negatively affecting peak heart rate, cardiopulmonary fitness, or cardiac contractility, as assessed by both treadmill exercise stress testing and echocardiography.

Strength: Safety of LCSD.

Limitations: Retrospective.

Aim: To determine the characteristics of LQTS patients who have had ≥1 LQTS-related breakthrough cardiac event (BCE) after LCSD. Study design: Retrospective chart review. Enrolment period: 2005–2010 Follow up: 3.6 ± 1.3 years. Number of patients: 52 (33 had LCSD as primary prevention). Study endpoints: Occurrence of a BCE, defined as appropriate VF-terminating ICD shock, or arrhythmogenic syncope, seizures, or aborted cardiac arrest after LCSD. Inclusion: 52 consecutive LQTS patients undergoing LCSD. Exclusion: Lost to follow-up.

Results: 12 of 52 (23%) patients (7 men) experienced at least 1 BCE post-LCSD.

Conclusions: Among patients undergoing LCSD for high risk, ≥50% (17/40) experienced ≥1 post-LCSD breakthrough. Therefore, LCSD may not be viewed as curative or an alternative in ICD for high-risk patients. Prophylactic LCSD may provide another option to counter a suboptimal quality of life resulting from medication-related side effects.

Strength: Large number of patients, single-centre consecutive cases (no learning curve issues), 50% failure rate in high risk (patients with previous events).

Limitations: Retrospective, ICD interrogations not universally available, therefore data on the effect of beta-blockers (pre- and post-procedure) or effect of LCSD on mitigation of adrenergic surges or efficacy of sympathetic blockade using the ICD data were not available, a temporary ganglion block pre-LCSD to test these effects was not performed.

Small number of LQT3 patients does not provide sufficient evidence to suggest that there is no role for denervation therapy in LQT3.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Authors</th>
<th>Title</th>
<th>Year of publication</th>
<th>Aim</th>
<th>Inclusion</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>964</td>
<td>Bhandari AK, et al</td>
<td>Electrophysiologic testing in patients with long QT syndrome.</td>
<td>1985</td>
<td>Descriptive study on the yield of electrophysiologic test in LQTS patients.</td>
<td>15 LQTS patients and 11 controls. Exclusion: NA.</td>
<td>PES did not induce sustained VT or VF in 15 LQTS patients.</td>
<td>PES are of limited value in diagnosis and treatment of LQTS patients.</td>
</tr>
<tr>
<td>965</td>
<td>Zareba W, et al</td>
<td>Implantable cardioverter defibrillator in high-risk long QT syndrome patients.</td>
<td>2003</td>
<td>To describe clinical characteristics in patients with ICD and LQTS and to provide long-term follow-up data.</td>
<td>125 LQTS patients with ICDs; there were 54 cardiac arrest survivors, 19 patients who had ICDs implanted due to recurrent syncope despite beta-blocker therapy, and 52 patients with ICDs implanted due to other reasons, including syncope and LQTS-related SD in a close family member. Patients with cardiac arrest and those with recurrent syncope, despite beta-blocker therapy (n = 73) were compared to 161 LQTS patients who had similar indications (89 cardiac arrest and 72 recurrent syncope despite beta-blocker therapy) but did not receive ICDs. Exclusion: NA.</td>
<td>One person died in 73 ICD patients followed an average of 3 years, whereas there were 26 deaths (16%) in non-ICD patients during mean 8-year follow-up (P = 0.07).</td>
<td>LQTS patients with ICD had a tendency towards lower mortality than a control group of high-risk LQTS patients with no ICD.</td>
</tr>
<tr>
<td>966</td>
<td>Schwartz P, et al</td>
<td>Who are long QT syndrome patients who receive an implantable cardioverter-defibrillator and what happens to them? Data from the European long QT syndrome implantable cardioverter-defibrillator (LQTS-ICD) registry.</td>
<td>2010</td>
<td>To assess the ICD indications to implant according to clinical history, response to previous therapy, and specific genotype and evaluating the clinical course after ICD implantation.</td>
<td>LQTS patients with ICD. Exclusion: NA.</td>
<td>During follow-up of 4.6 years, at least one appropriate shock was received by 28% of patients; and adverse events occurred in 25%.</td>
<td>ICDs were implanted in some LQTS patients whose risk were found to be questionable.</td>
</tr>
</tbody>
</table>

b.p.m., beats per minute; CI, confidence interval; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; HR, heart rate; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; LAE, life threatening arrhythmic events; LCSD, left cardiac sympathetic denervation; LQTS, long QT syndrome; NA, not applicable; PES, programmed electrical stimulation; SCD, sudden cardiac death; SD, sudden deaths; VA, ventricular arrhythmia; VF, ventricular fibrillation; VT, ventricular tachycardia.
4.2.3. Andersen–Tawil syndrome Type 1

**Table of Evidence 35 for Table of Recommendations for the management of patients with Andersen–Tawil syndrome**

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>967</td>
<td>Dehghan-E, et al. 2013</td>
<td>Aim: Defining the long-term arrhythmic prognosis of this disease. Study type: Retrospective multicentre study in nine French hospitals. Patients were recruited only if they were KCNJ2 mutation carriers. Number of patients: 36 patients (women n = 22, 61%) from 20 unrelated families with a mean follow-up of 93 ± 8.2 years. Inclusion: 36 patients (women n = 22, 61%) from 20 unrelated families with a mean follow-up of 93 ± 8.2 years. Exclusion: NA. Results: 12 distinct KCNJ2 mutations in the 20 probands. Three of them were novel. 13 patients (36%) experienced syncope and one was revascularized from cardiac arrest before diagnosis. The mean QTc interval was 439 ± 57 ms and QUC was 642 ± 64 ms. All patients had normal ejection fraction. Holter recordings in 31 patients found 11 272 PVCs per day on average, 25 patients had episodes of bigeminy, and 25 patients had polymorphic PVCs. 23 patients (70%) had non-sustained polymorphic VT, six sustained polymorphic VT. Only one patient presented with torsades de pointes. Patients were treated with beta-blocker (n = 20), beta-blocker and flecainide (n = 6), or acetazolamide (n = 6). Ablation was attempted in five patients without clinical success. An ICD was implanted in three patients. During follow-up, none of the patients died, four patients experienced syncope under treatment, and one patient had non-fatal cardiac arrest.</td>
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<tr>
<td>968</td>
<td>Inoue Y, et al. 2018</td>
<td>Aim: Evaluation of the diagnostic value of exercise stress tests for differentiating between Andersen–Tawil syndrome (ATSS) and CPVT. Study type: Comparison of exercise testing between ATS and CPVT patients. Number of patients: 26 ATS patients and 25 CPVT patients. Inclusion: Patients with KCNJ2 and RyR2 mutations. Exclusion: NA. Results: VAs were more frequently observed at baseline in ATS patients compared with CPVT patients (the ratio of PVCs/Sinus: 0.83 ± 1.87 vs. 0.06 ± 0.30, P = 0.01). At peak exercise, VAs were suppressed in ATS patients, whereas they were increased in CPVT patients (0.14 ± 0.40 vs. 1.94 ± 2.71, P &lt; 0.001). Twelve-lead ECG showed that all 25 VPs and 15 (94%) of 16 bidirectional VTs were RBBB morphology in ATS patients, whereas 19 (86%) of 22 VPs had LBBB, and 12 (71%) of 17 bidirectional VT had LBBB and RBBB morphologies in CPVT patients.</td>
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<tr>
<td>970</td>
<td>Mazzanti A, et al. 2020</td>
<td>Aim: Defining the risk of life-threatening arrhythmic events (LAE), identify predictors of LAE, and the efficacy of anti-arrhythmic therapy in ATS1. Study type: Retrospective data analysis of 118 patients. (n = 57 probands). Number of patients: 118. Inclusion: 118 patients, with ATS1 (n = 57 probands; n = 61 family members). Exclusion: NA. Results: Over a median follow-up of 6.2 years (IQR: 2.7–16.5 years), 17 patients experienced a first LAE, with a cumulative probability of 7.9% at 5 years. An increased risk of LAE was associated with a history of syncope (HR: 4.54; P = 0.002), with the documentation of sustained VT (HR: 9.34; P &lt; 0.001), and with the administration of amiodarone (HR: 2.64; P = 0.001). The rate of LAE without therapy (1.24 per 100 person-years) was not reduced by beta-blockers alone (1.37 per 100 person-years; P = 1.00), or in combination with other anti-arrhythmic therapies.</td>
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Continued
Conclusions: Mutations of KCNJ2 cause the ATS1 genotype and result in gene-specific T-U-wave abnormalities that can be used to distinguish carriers of KCNJ2 mutations from normal subjects. ATS patients without KCNJ2 mutations, and LQT3 through LQT5 patients. The median QTc interval was within the normal range in ATS1. The QTc prolongation reported in earlier studies on ATS1 was due to inclusion of the U wave in the QT measurement. The normal median QTc and other cardiac and non-cardiac manifestations differentiate ATS1 from LQTs. Thus, ATS1 is unlike LQTs and should be designated as ATS1 rather than LQT7.

The observations reported in this study also highlight the importance of cardiac IK1 in the terminal repolarization and diastolic phases of cardiac potentials.


Am: Evaluation of the efficacy and safety of flecainide for VAs in patients with Andersen–Tawil Syndrome with KCNJ2 mutations. Study type: Observational multicentre study. Number of patients: 10

Indication: Andersen–Tawil Syndrome patients <80 years, with KCNJ2 mutation. Exclusion: NA.

Results: 24-hour Holter recordings demonstrated that oral flecainide treatment significantly reduced the total number of VAs (from 384 ± 199 to 112 ± 148 per day, P = 0.003) and the number of longest ventricular episodes (23 ± 19 to 5 ± 5; P = 0.001). At baseline, TMT-induced NSVT (n = 2) or couplets of PVC (n = 2). Treatment with flecainide completely (n = 7) or partially (n = 3) suppressed these exercise-induced VAs (P = 0.008).

In contrast, the QRS duration, QT interval, and U-wave amplitude of the ECG were not altered by flecainide treatment. During a mean follow-up of 23 ± 11 months, no patients developed syncope or cardiac arrest after oral flecainide treatment.

Conclusions: Oral flecainide therapy is an effective and safe means of suppressing VAs in patients with Andersen–Tawil Syndrome with KCNJ2 mutations. Beta-blocker and/or calcium channel blocker did not suppress VT.


Am: Genetic and molecular-functional characterization of Andersen–Tawil Syndrome and correlation with clinical phenotype. Study type: Retrospective clinical and experimental, computer simulation study. Number of patients: 23 families; n = 17 KCNJ2 positive, n = 36 individuals KCNJ2 positive.

Indication: Suspected Andersen–Tawil Syndrome. Exclusion: NA.

Results: Report of three novel KCNJ2 mutations. LQT1 in 14 of 15 probands mean QTc (479 ± 42 ms for men and 493 ± 27 ms for women). NSVT in 14 of 36 mutation carriers. Complex ventricular ectopy 23 of 36 mutation carriers. Prominent U wave 17 of 36 mutation carriers, n = 3 non-fatal cardiac arrest. Periodic paralysis in 23 of 36 mutation carriers (64%). 28 of 36 mutation carriers (78%) had at least two dysmorphic features.

Conclusions: LQT7 most common ECG finding, VA in the majority of mutation carriers. Limitations: Retrospective clinical evaluation.
### 4.2.4.1. Brugada syndrome

**Table of Evidence 36** for Table of Recommendations for the management of patients with Brugada syndrome

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>139</td>
<td>Govindan M, et al. 2010</td>
<td>Aim: To assess the value of the high right precordial leads (RPL) to detect the Type I Brugada ECG pattern in patients suspected of having Brugada syndrome. Study design: Single-centre, retrospective, registry. Size: 183</td>
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<td></td>
<td>Inclusion: 183 patients who underwent amiodarone challenge during 15-lead ECG recording</td>
<td>Exclusion: N/A</td>
<td>Results: Of the 183 tests, 31 (17%) were positive, and 152 were negative. In all positive studies, at least one high RPL became positive. In 13/31 (42%) cases the Type I ECG pattern could be observed only in the high RPLs. Standard or high V3 were never positive before standard or high V1–V2. In seven patients, a Type I pattern was seen in one standard and one high RPL (vertical relationship).</td>
<td></td>
<td>Conclusions: The high RPLs are more sensitive than the conventional 12-lead ECG alone and initial observations suggest that they remain specific for Brugada syndrome, while standard and high lead V3 offer redundant data. The diagnosis of Brugada syndrome could not be confirmed by a gold standard of genetic testing in all cases.</td>
</tr>
<tr>
<td>158</td>
<td>Sroubek J, et al. 2016</td>
<td>Aim: To determine the prognostic value of PES in Brugada Syndrome without previous CA. Study type: Meta-analysis. Number of patients: 1312 patients</td>
<td></td>
<td></td>
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<td></td>
<td>Inclusion: Brugada syndrome patients without prior CA who underwent PES. Age 44.9 ± 13.3 years; 79% men; 53% spontaneous type 1 ECG; 33% prior syncope. Exclusion: N/A</td>
<td></td>
<td>Results: Mean follow-up 38 months. 527/1312 (40%) inducible VA with PES. Induction associated with cardiac events (HR 2.46 [1.44–4.02]) with greatest risk in those induced with single or double extrastimuli. Lowest risk in patients without syncope + drug-induced type 1 ECG (annual IR 0.21% [0.05–0.68] for no induced VA; 0.45% [0.01–2.49] for inducible VA).</td>
<td></td>
<td>Conclusions: VA inducibility on PES associated with future VA risk. Induction with fewer extrastimuli associated with higher risk. Clinical RFs influence VA risk. Lack of induction not necessarily associated with low VA risk, especially in patients with high-risk clinical features (e.g. syncope, spontaneous type 1 ECG).</td>
</tr>
<tr>
<td>167</td>
<td>Hosseini SM, et al. 2018</td>
<td>Aim: To evaluate the clinical validity (gene-disease association) of 21 genes tested by diagnostic labs for Brugada syndrome. Study design: Literature/data review.</td>
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<td>Inclusion: 21 genes were selected based on criteria: (1) ≥2 publications suggesting single-gene causality for Brugada syndrome; (2) reported literature presenting both genetic and experimental data; (3) present on ≥3 Brugada syndrome clinical genetic testing panels from accredited labs. Exclusion: N/A</td>
<td></td>
<td>Results: Only one gene (SCN5A) was classified as having definitive evidence. Remaining 20 genes classified as ‘limited evidence’ by biocurators, which were all then reclassified as ‘disputed’ by a clinical domain expert panel.</td>
<td></td>
<td>Conclusions: Robust evidence of gene-disease associations for all but SCN5A is lacking. Routine genetic evaluation of genes other than SCN5A is not currently warranted in the clinical care of patients with Brugada syndrome.</td>
</tr>
<tr>
<td>977</td>
<td>Savastano S, et al. 2014</td>
<td>Aim: To test the validity, and the underlying anatomy, of the new ECG diagnostic criteria using electrocardiographic, molecular, and clinical evidence in population with Brugada syndrome. Study design: Single-centre, retrospective, registry. Number of patients 114</td>
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<td>Inclusion: Patients having either a spontaneous or a drug-induced type 1 Brugada ECG pattern.</td>
<td></td>
<td>Results: The percentage of mutation carriers (MCs) and the event rate were similar regardless of the diagnostic intercostal space (ICS) (fourth vs. high ICSs: MCs 23% vs. 19%; event rate 22% vs. 28%) and the number of diagnostic leads (1 vs. ≥2: MCs 20% vs. 22%; event rate 22% vs. 27%). The concordance between RVOT anatomical location and the diagnostic ICS was 86%. The percentage of the diagnostic ECG pattern recorded was significantly increased by the exploration of the ICS showing RVOT by echocardiography (echocardiography-guided approach vs. conventional approach 100% vs. 43%, P &lt; 0.001).</td>
<td></td>
<td>Conclusions: The high ICSs are not inferior to the standard fourth ICS for the ECG diagnosis of Brugada syndrome, and the interindividual variability depends on the anatomical location of the RVOT as assessed by using echocardiography.</td>
</tr>
</tbody>
</table>

**References:**

1. ESC Guidelines
2. Table of Evidence 36
3. Table of Recommendations for the management of patients with Brugada syndrome
4. Conclusions:
5. Brugada syndrome
6. The high RPLs are more sensitive than the conventional 12-lead ECG alone and initial observations suggest that they remain specific for Brugada syndrome, while standard and high lead V3 offer redundant data. The diagnosis of Brugada syndrome could not be confirmed by a gold standard of genetic testing in all cases.

**Aim:** To assess the value of the high right precordial leads (RPL) to detect the Type I Brugada ECG pattern in patients suspected of having Brugada syndrome. Study design: Single-centre, retrospective, registry. Size: 183.

**Results:** Of the 183 tests, 31 (17%) were positive, and 152 were negative. In all positive studies, at least one high RPL became positive. In 13/31 (42%) cases the Type I ECG pattern could be observed only in the high RPLs. Standard or high V3 were never positive before standard or high V1–V2. In seven patients, a Type I pattern was seen in one standard and one high RPL (vertical relationship).

**Conclusions and limitations:**

The high RPLs are more sensitive than the conventional 12-lead ECG alone and initial observations suggest that they remain specific for Brugada syndrome, while standard and high lead V3 offer redundant data. The diagnosis of Brugada syndrome could not be confirmed by a gold standard of genetic testing in all cases.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Title</th>
<th>Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reiter S, et al.</td>
<td>To assess the distribution of coved-type ST-segment elevation on right precordial leads to evaluate the appropriateness of the diagnostic consensus criteria.</td>
<td>No signs of Brugada syndrome at baseline, underwent EPS for AVNRT (compared to control group without any history of SVT/atrial arrhythmias). All patients underwent ajmaline testing.</td>
</tr>
<tr>
<td>Veletman C, et al.</td>
<td>Insights into the location of type I ECG in patients with Brugada syndrome: correlation of ECG and cardiovascular magnetic resonance imaging.</td>
<td>Inclusion: No signs of Brugada syndrome at baseline, underwent EPS for AVNRT (compared to control group without any history of SVT/atrial arrhythmias). All patients underwent ajmaline testing.</td>
</tr>
</tbody>
</table>

Conclusion: Lead V3 does not yield diagnostic information in Brugada syndrome. Individuals with ECGs displaying only one diagnostic RPL have a similar clinical profile and arrhythmic risk as Brugada patients with ECGs displaying ≥1 diagnostic RPL.
<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
<th>Study type</th>
<th>Year of publication</th>
<th>Aim</th>
<th>Inclusion</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
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<tbody>
<tr>
<td>985</td>
<td>Adler A, et al.176</td>
<td>Single-centre, prospective, registry</td>
<td>2013</td>
<td>To assess the prevalence of Brugada pattern in consecutive patients with fever. Study design: Single-centre, prospective, registry. Size: 402 febrile and 909 afebrile patients.</td>
<td>All febrile patients (defined as oral temperature &gt;38°C [&gt;100.4°F]) who were evaluated in the emergency medicine department. Exclusion: N/A.</td>
<td>Type I Brugada pattern was 20 times more common in the febrile group than in the afebrile group (25 vs. 0.1%, respectively; P &lt; 0.0001). All patients with fever-induced type I Brugada pattern were asymptomatic and remained so during 30 months of follow-up.</td>
<td>Type I Brugada pattern is definitively more common among patients with fever, suggesting that asymptomatic Brugada syndrome is more prevalent than previously estimated. Patients are not necessarily representative of the general population.</td>
</tr>
<tr>
<td>987</td>
<td>Rizzo A, et al.177</td>
<td>Single-centre, prospective, registry</td>
<td>2020</td>
<td>To evaluate the prevalence of positive ajmaline challenge for Brugada syndrome in a cohort of consecutive patients who underwent electrophysiological evaluation for different clinical reasons. Study design: Single-centre, prospective, registry. Size: 1714</td>
<td>Patients who underwent ajmaline testing and eventual EPS. Exclusion: N/A.</td>
<td>In non-familial screening group (1714) ajmaline testing resulted positive in 186 (10.9%). Indications for ajmaline testing were: suspicious Brugada syndrome ECG in 23 cases (12.4%), palpitations in 27 (14.5%), syncope in 71 (38.2%), presyncope in seven (3.8%), family history of SCD in 18 (9.7%), documented VA in 12 (6.5%), unexplained cardiac arrest in four (2.2%), atrial fibrillation in 16 (8.5%), brady-arrhythmias in one (0.5%), and cerebrovascular accidents in seven (0.7%).</td>
<td>Brugada syndrome was diagnosed in an unexpectedly high proportion of patients that underwent ajmaline testing for a variety of cardiovascular symptoms.</td>
</tr>
<tr>
<td>993</td>
<td>Gehi AK, et al.179</td>
<td>Meta-analysis</td>
<td>2006</td>
<td>To identify predictors of SCD, syncope of ICD shocks. Study design: Meta-analysis of 19 prospective studies of patients with Brugada syndrome ECGs. Number of patients 1545</td>
<td>Studies from 1990 to 2005 reporting on the prognosis of patients with Brugada syndrome ECGs. Required following criteria: prospective cohort studies of the natural history of Brugada syndrome, &gt; 10 subjects per study, provided primary data on syncope/ICD shocks with &gt; 6 months and &gt; 90% follow-up; structural cardiac disease ruled out. Exclusion: Non-English.</td>
<td>RR for syncope, SCD, or ICD shock: Hx of syncope or SCD: 3.51 (2.14–5.75). Male: 3.49 (1.58–7.63). FH of SCD: 104 (0.43–2.52). Inducible at EPS: 188 (6.62–5.73). Spontaneous vs. drug-induced Brugada syndrome ECG: 6.5 (2.35–9.98). SNCA mutation: 60 (0.29–1.36). RD (to syncope, SCD, or ICD shock): Hx of syncope or SCD: 134 (7.2–19.5). Male: 8.7 (5.4–12.0). FH of SCD: 0.63 (0.52–0.64). Inducible at EPS: 8.8 (4.4–22.4). Spontaneous vs. drug-induced Brugada syndrome ECG: 8.5 (4.8–12.3). SNCA mutation: 4.6 (4–9.2–2–0.1).</td>
<td>Risk increased with prior history of syncope or aborted cardiac arrest, spontaneous type 1 Brugada ECG, and men gender. Not significant risk factors: family hx SCD, SNC5A mutation, or inducibility by PES (not a risk factor but heterogeneity of studies). Relatively few women included (in keeping with men predominance in Brugada syndrome). Predominant European and Asian populations.</td>
</tr>
<tr>
<td>994</td>
<td>McNamara DA, et al.180</td>
<td>Single-centre, prospective, registry</td>
<td>2015</td>
<td>To compare all-cause mortality, fatal and non-fatal cardiovascular events, adverse events (secondary endpoints: non-fatal cardiovascular events, inappropriate ICD firings, quality of life, costs). Study type: Cohort review of ICD vs. anti-arrhythmic drugs or usual care in people with cardiac ion channelopathy. Number of patients 86. Two studies identified (both on Brugada syndrome patients).</td>
<td>Age &gt; 18 years, ion channelopathies, randomized to ICD vs. medical rx. Exclusion: N/A.</td>
<td>Results: ICD associated with lower mortality (RR 0.11 [0.01–0.81]), similar risk of combined fatal and non-fatal cardiovascular events (RR 1.19 [0.6–1.97]), similar risk of adverse events (RR 2.46 [0.92–6.44]), non-fatal cardiovascular events (RR 1.14 [1.37–4.33]).</td>
<td>Increased mortality in patients with Brugada syndrome randomized to ICD relative to Beta-blocker therapy.</td>
</tr>
<tr>
<td>995</td>
<td>Priori SG, et al.181</td>
<td>Single-centre, prospective, registry</td>
<td>2000</td>
<td>To evaluate the prevalence of Brugada pattern in consecutive patients with fever. Study design: Single-centre, prospective, registry. Size: 308.</td>
<td>Age &gt; 18 years, Brugada syndrome type 1 ECG spontaneous (56%, 171/308) or drug-induced, without prior aborted. Exclusion: N/A.</td>
<td>Follow-up every 6 months. Age 45 ± 12 years. Cardiac arrest 43% (14/308), 13/4 resuscitated with ICD. EMS 1, PES positive in 4% (122/308); of</td>
<td>Decreased mortality in patients with Brugada syndrome randomized to ICD relative to Beta-blocker therapy.</td>
</tr>
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<table>
<thead>
<tr>
<th>Study endpoints</th>
<th>Study design</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
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<tr>
<td>(Programmed Electrical stimulation predictive value) registry</td>
<td>Study design: prospective study. Case-control. Number of patients: 75 (+88 healthy controls).</td>
<td>To examine the role for exercise testing (EST) for risk stratification for Brugada syndrome.</td>
<td></td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>Study endpoints: Predictive accuracy of PES for sustained VT/VF or appropriate ICD shock in Brugada syndrome.</td>
<td>Study design: prospective study. Case-control. Number of patients: 75 (+88 healthy controls).</td>
<td>To examine the role for exercise testing (EST) for risk stratification for Brugada syndrome.</td>
<td></td>
<td>Results:</td>
<td>Conclusions:</td>
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<tr>
<td>Cardiac arrest: 21% with prior syncope (65 patients: 16/68 [24%] &gt; 1 syncope). SONGA positive: 20% of tested patients. (QRS = two or more wider than QRS leads V1-V3: present 8.1%). Exclusion: NA.</td>
<td>Study design: prospective study. Case-control. Number of patients: 75 (+88 healthy controls).</td>
<td>To examine the role for exercise testing (EST) for risk stratification for Brugada syndrome.</td>
<td></td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>999</td>
<td>Subramanian M, et al</td>
<td>The utility of exercise testing in risk stratification of asymptomatic patients with type 1 Brugada pattern. PMID: 28316113 Year of publication: 2017</td>
<td>Aim: To evaluate the indications and yield of ILR monitoring in a single-centre Brugada Syndrome registry. Study type: retrospective. Number of patients: 50</td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>1000</td>
<td>Kubola M, et al</td>
<td>Use of implantable loop recorders in patients with Brugada syndrome and suspected risk of ventricular arrhythmia. PMID: 29179995 Year of publication: 2012</td>
<td>Aim: To investigate the effectiveness of ILR as a diagnostic tool in 85 patients suspected of low or moderate risk of SCD. Study design: single-centre, retrospective. Number of patients: 11</td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>1002</td>
<td>Sorocco C, et al</td>
<td>Role of subcutaneous implantable loop recorder for the diagnosis of arrhythmias in Brugada syndrome: a single United Kingdom centre experience. PMID 34487893 Year of publication: 2021</td>
<td>Aim: To describe the clinical presentation of Brugada syndrome in a paediatric population.</td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>1009</td>
<td>Andorin A, et al</td>
<td>The QUIDAM study: hydroquinidine therapy for the prevention of arrhythmias in Brugada syndrome. PMID: 21923666 Year of publication: 2012</td>
<td>Aim: To describe the clinical presentation of Brugada syndrome in a paediatric population.</td>
<td>Results:</td>
<td>Conclusions:</td>
</tr>
</tbody>
</table>
management of Brugada syndrome patients at high arrhythmic risk. PMID: 34111393 Year of publication: 2017

Conclusions:
Brugada syndrome: Class IA medications: No deaths on quinidine. 40% of aborted cardiac arrest patients remained arrhythmia-free off anti-arrhythmic drugs (3 treatment with quinidine for many years then discontinued, 38% side effects).

Exclusion:

Patients with Brugada syndrome. Recommended fever be treated aggressively with antipyretics.

1010 Balhassen B, et al.
Management of Brugada syndrome thirty-three-year experience using electrophysiologically guided therapy with class 1A antiarhythmic drugs. PMID: 26354972 Year of publication: 2015

Aim: Assess Brugada syndrome outcomes treated with Class IA drugs.

Mean followup: 113 ± 71 months.

Study type: Multicentre retrospective.

Number of patients: 106

Inclusion: Brugada syndrome patients undergoing PES and treated with Class IA drugs.

Mean age: 39 ± 16 years, 88% males.

Exclusion: N/A

VA (90% of whom had SCN5A mutation and 27% of whom experienced it during fever), including 3% deaths, 6% had syncope, 4% had SVT. ICD implanted in 21% with major adverse events in 41% (lead failure in 4, inappropriate shocks in 4, endocarditis with reimplantation in 2, and haemothorax in 1). Predictors of life-threatening VA: spontaneous type 1 ECG + symptoms at dx.

Results:
Prior aborted cardiac arrest 10, syncope 27, 59 asymptomatic PES: VF induced in 69% (100% of prior aborted cardiac arrest, 74% of syncope, 61% of asymptomatic). PES RVA and RVOT in most, ≤ 3 extrastimuli. PES positive in 77% mens, 9% womens; in 88% with spontaneous ECG vs. 59% without spontaneous ECG. ICD implanted in 21% with major adverse events in 41% (lead failure in 4, inappropriate shocks in 4, endocarditis with reimplantation in 2, and haemothorax in 1).

Conclusions:
Baseline characteristics of cases were different in PES + and - groups. Clinical features did not help to predict successful PES. Class IA drugs were tested in 40% of patients. 30 patients with negative PES... implanted in 20 patients after PES (30% of inducible VF patients): complications 55% of patients. Four died of non-cardiac causes. Recurrent syncope: vasovagal, 10, non-arrhythmic 2. 29% had recurrent arrhythmia both with prior aborted cardiac arrest, both discontinued quinidine and had VF storms.

1011 Ollo T, et al.
Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation. PMID: 17536186 Year of publication: 2007

Aim: To investigate the clinical, laboratory, ECG, and electrophysiological characteristics, acute and subsequent chronic treatment, and follow-up data of patients with Brugada syndrome associated with electrical storm of VF.

Study drugs: Single-centre retrospective.

Number of patients: 67

Inclusion: 67 Brugada syndrome patients.

Exclusion: N/A

Results: Isoproterenol infusion (0.003 ± 0.003 µg/kg/min for 24 ± 13 days) completely suppressed electrical storm of VF in all five patients treated and was successfully replaced with chronic oral medications, including dopenamine, quinidine, isoproterenol, alogastro, and bepdril alone or in combination.

Conclusions: No specifically clinical, laboratory, ECG, and electrophysiological characteristics were recognized in patients with Brugada syndrome associated with electrical storm of VF. Isoproterenol infusion was effective as an acute treatment in suppressing electrical storm of VF and was successfully replaced with chronic oral medications.

1013 Nadeemmane K, et al.
Mapping and ablation of ventricular fibrillation associated with early repolarization syndrome. PMID: 31542949 Year of publication: 2019

Aim: To evaluate mapping and ablation of VF substrates or triggers in ERS or J-wave syndromes (JWS).

Study type: Multicentre non-randomized study.

Number of patients: 52

Inclusion: Symptomatic patients who either survived recurrent VF episodes or had cardiac or unknown syncope or agonal respiration during sleep; recruited from four institutions; all had SHD excluded.

Exclusion: Patients with severe anoxic brain injury from previous cardiac arrest. Only 32% had genetic testing.

Results: Two phenotypes identified: (group 1) late depolarization abnormalities predominantly at RV epicardium (mainly RVOT and inferior wall); (group 2) no depolarization abnormalities (no substrate, but Purkinje triggers identified). Group 1 further subdivided into (A) ERS with Brugada syndrome ECG pattern; (B) ERS without Brugada syndrome ECG pattern. Ablation successful in 78% (7/9) VF not inducible, in 91% (11/12) with pharmacologic suppression.

Conclusions: There are two phenotypes of ERS/JWS. Ablation can be effective for patients with frequent VF episodes. Risk of referral bias (many highly symptomatic patients). 32% had genetic testing.

1014 Nadeemmane K, et al.
Prevention of ventricular fibrillation episodes in Brugada syndrome by catheter ablation over the anterior RVOT. PMID: 31542950 Year of publication: 2019

Aim: To investigate usefulness of catheter ablation in Brugada Syndrome patients.

Study type: Multicentre retrospective.

Number of patients: 52

Inclusion: Brugada syndrome patients, symptomatic with recurrent VF. Median 4 months; median age: 38 years.

Exclusion: N/A

Results: Anterior aspect of RVOT epicardium with late fractionate EGMs. Ablation successful in 78% (7/9) VF not inducible, in 91% (11/12) with pharmacologic suppression.

Conclusions: Brugada syndrome shows delayed repolarization over anterior RVOT epicardium.
right ventricular outflow tract
epicardium. PMID: 21403098
Year of publication: 2011
Ablation normalizes ECG and reduces VT/VF.

1015
Zhang P, et al.\(^{10}\)
Characterization of the epicardial
substrate for catheter ablation of
Brugada syndrome. PMID: 27453126
Year of publication: 2016
Aim: To investigate usefulness of catheter
ablation in Brugada Syndrome patients.
Study type: Two-centre retrospective.
Number of patients: 11
Study endpoints: Brugada syndrome mapping and
ablation of RVOT epicardium.
Inclusion: Brugada syndrome patients, nine
spontaneous, two induced.
Exclusion: NA.
Results: Normalization of spontaneous Brugada syndrome
ECG pattern in all 73% free of VT/VF at 25 ±
11 months.
Conclusions: Ablation epicardial RVOT can normalize
Brugada syndrome ECG and reduces VT/VF.

1016
Halaqauma M, et al.\(^{10}\)
Mapping and ablation of ventricular fibrillation associated with long QT
and Brugada syndromes. PMID: 15925452
Year of publication: 2003
Aim: To assess the feasibility of mapping and
ablation of VA in Brugada syndrome
and LQT. Study design: Single-centre retrospective.
Number of patients: 7
Study endpoints: Epicardial mapping and
ablation RVOT.
Inclusion: Three Brugada syndrome patients and 4 LQT patients with documented episodes of VA.
Exclusion: NA.
Results: In four patients, PVCs originated from the
peripheral right (1 Brugada) or left (3 long QT) Purkinje conducting system and were associated with variable Purkinje-to-muscle conduction times (30–110 ms). In the remaining three patients, PVCs originated from the RVOT, being 25–40 ms ahead of the QRS. During a follow-up of 17 ± 17 months, no patients had recurrence of symptomatic VA, but one had persistent PVCs.
Conclusions: Triggers from the Purkinje arborization or the RVOT have a crucial role in initiating VF associated with long QT and Brugada syndromes. These can be eliminated by focal radiofrequency ablation.

1017
BrugadaJ, et al.\(^{11}\)
Brugada syndrome phenotype elimination by epicardial substrate
ablation. PMID: 36291334
Year of publication: 2015
Aim: To investigate usefulness of catheter
ablation in Brugada Syndrome patients.
Study type: Single centre retrospective.
Number of patients: 14
Study endpoints: Epicardial mapping and
ablation RVOT.
Inclusion: Brugada syndrome, spontaneous ECG, median age 39 years.
Exclusion: NA.
Results: Ablation resolved spontaneous Brugada Syndrome
ECG, 5 months, no recurrence.
Conclusions: Ablation may eliminate spontaneous Brugada syndrome ECG pattern.

1018
Pappone C, et al.\(^{12}\)
Electrical substrate elimination in 133 consecutive patients with Brugada syndrome. PMID: 2800178
Year of publication: 2017
Aim: To explore clinical and EP predictors of malignant VA in patients with Brugada syndrome.
Study design: Prospective cohort.
Number of patients: 191
Inclusion: Consecutive patients with Brugada syndrome with ICD referred to single
centre for EP study and substrate
mapping ± ablation, with spontaneous
or drug-induced type 1 ECG, without
previous mapping or ablation procedures, as part of two studies (NCT02641431, NCT03106701).
Exclusion: NA.
Results: 53.4% had VA inducibility at EPS before ajmaline, remaining were inducible post-ajmaline. Larger substrates with more fragmented long-duration potentials found in patients with inducible VAs; notably, ajmaline induced large expansions in substrate. Substrate size was only predictor of inducibility: OR 4.51 (2.51–8.09). Based on ROC curve, 4 cm\(^2\) substrate size best identified inducibility (area under the curve 0.899). Substrate ablation eliminated the type 1 ECG pattern and rendered patients non-inducible.
Conclusions: Brugada syndrome substrate is dynamic. Brugada syndrome substrate size is independently associated with VA inducibility, and its determination with ajmaline identifies a high-risk subset that would be missed by clinical criteria alone. Substrate ablation can normalize the ECG and render patients non-inducible.

1019
Yamaga K, et al.\(^{13}\)
Genotype-phenotype correlation of SCN5A mutation for the clinical and electrocardiographic characteristics of probands with Brugada syndrome: a Japanese multicenter registry. PMID: 28314781
Year of publication: 2017
Aim: To examine the genotype-phenotype relationship of SCN5A mutations in Brugada syndrome.
Study design: Multicenter registry.
Inclusion: Patients diagnosed with Brugada syndrome and who underwent SCN5A genetic testing.
Exclusion: NA.
Results: Probands with SCN5A mutations had first cardiac event at younger age, higher positive rate of late potentials, exhibited longer PPI/QQRS durations, and higher rate of cardiac events relative to those without SCN5A mutations. SCN5A mutation and by of aborted cardiac arrest were independent predictors of cardiac events.
Conclusions: SCN5A mutations in patients with Brugada syndrome are associated with more conduction abnormalities and a higher risk of cardiac events.
### Table of Evidence 37 for Table of Recommendations for the management of patients with early repolarization pattern/syndrome

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
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<tr>
<td>1020</td>
<td>Halissaguerre M, et al.106</td>
<td>Aim:</td>
<td>IVF survivors with ER assessed for recurrent VF. All patients had ICDs implanted. Mean age of diagnosis 39 years.</td>
<td>27% with multiple (&gt;3 episodes) of recurrent VF. Inducible VF 28% in entire cohort. Patients with &gt;3 episodes: inducible VF 48%; P &lt; 0.001, prior syncope 58%; P &lt; 0.001 compared with patients with &lt;3 episodes of recurrent VF. Anti-arrhythmic drugs not highly effective in preventing recurrent VF. One death due to refractory VF.</td>
<td></td>
<td>Conclusions: Recurrent VF high 40% with multiple episodes in 27%. Anti-arrhythmic drugs not effective other than quinidine or hydroquinidine (Nine patients).</td>
</tr>
<tr>
<td>1021</td>
<td>Rosso R, et al.105</td>
<td>Aim:</td>
<td>IVF patients compared with 124 age-/sex-matched controls. Mean age 38 ± 15 years, 71% men. 2/45 dx with Brugada syndrome.</td>
<td>ER more common among VF patients, 42% vs. 13%; P = 0.001. J point elevation in inferior leads: 27% vs. 8%; P = 0.006. J point elevation in leads I–aVL 13% vs. 1%; P = 0.009. J point elevation in V4–V6 equal among groups, 6.7 vs. 7.3%. Males more often had J point elevation vs. females; young athletes more frequent than controls but less than VF patients.</td>
<td></td>
<td>Conclusions: J point elevation more common in patients with VF than among healthy controls. Frequency of J point elevation among young athletes is intermediate (between healthy adults and patients with VF).</td>
</tr>
<tr>
<td>1023</td>
<td>Tikkanen J, et al.106</td>
<td>Aim:</td>
<td>EGCG obtained in general population reviewed.</td>
<td>Prevalence of J point elevation of ≥0.1 mV: RR 1.16; 95% CI 1.05–1.24; P = 0.004; ≥0.2 mV inferior leads 0.3%; RR 1.16; 95% CI 1.05–1.27; P = 0.004; weaker predictors cardiac death.</td>
<td></td>
<td>Conclusions: ERP in inferior leads associated with increased risk of cardiac death in middle-aged adults.</td>
</tr>
<tr>
<td>1025</td>
<td>Num L, et al.107</td>
<td>Aim:</td>
<td>Families of SADS probands were evaluated in an inherited arrhythmia clinic. EGCG data were compared with those of 339 controls of a similar age, sex, and ethnic distribution.</td>
<td>A total of 363 first-degree relatives from 144 families were evaluated. J-point elevation in the inferolateral leads was present in 23% of relatives and 11% of control subjects (OR 2.54; 95% CI 1.66–3.90; P &lt; 0.001).</td>
<td></td>
<td>Conclusions: J-point elevation is more prevalent in the relatives of SADS probands than in controls. Early repolarization is an important potentially inheritable pro-arrhythmic trait or marker of pro-arrhythmia in SADS.</td>
</tr>
</tbody>
</table>
Conclusions: We found reductions in heart rate and cardiac conduction and loss-of-function mutations in SCN5A repolarization. These findings support the hypothesis that decreased sodium current enhances VF susceptibility.

Results: VF was inducible by programmed electric stimulation in 15 of 29 patients (52%). The inclusion: heart rate was slower and the PR interval and IVF associated with early repolarization, and 250 age- and QRS duration were longer in patients with IVF than in controls. We identified non-synonymous variants in SCN5A (resulting in A226D, L846R, and R367H) in three unrelated patients. These variants occur at residues that are highly conserved across mammals. His-ventricular interval was prolonged in all of the patients carrying an SCN5A mutation. Sodium channel blocker challenge resulted in an augmentation of early repolarization or development of VF in all of three patients, but none was diagnosed with Brugada syndrome. In heterologous expression studies, all of the mutant channels failed to generate any currents. Immunostaining revealed a trafficking defect in SCN5A channels and normal trafficking in R367H and L846R channels.

Aim: To search for novel KCND3 mutations associated with ERS and to clarify the pathogenesis. Study type: Retrospective genetic screening. Number of patients: 11.

Inclusion: Unrelated probands with ERS. Exclusion: NA. Results: A novel de novo KCND3 heterozygous mutation, Gly306Ala (c.917g>c), was found in one proband.

Conclusions: A novel KCND3 heterozygous mutation was found to be associated with ERS. The pathogenesis can be explained by the increased cardiac transient outward potassium (Ito). Genetic screening for KCND3 could be useful for understanding the pathogenesis and selecting effective treatment.

Aim: To identify the characteristics of IVF patients. Study design: Single-centre, retrospective. Number of patients: 91.

Inclusion: 91 IVF patients. Exclusion: NA. Results: 14 (15.4%) patients had VF storms occurring out-of-hospital at night or in the early morning. J waves were more closely associated with VF storms compared to patients without VF storms. 92.9% vs. 36.4% (P<0.001), VF storms were controlled by intravenous isoproterenol, which attenuated the J-wave amplitude. After the subsidence of VF storms, the J waves decreased to the non-diagnostic level during the entire follow-up period.

Conclusions: The VF storms in the IVF patients were highly associated with J waves that showed augmentation prior to the VF storm. Isoproterenol was effective in controlling VF and attenuated the J waves which diminished to below the diagnostic level during follow-up.

Aim: To test the hypothesis that the transient outward potassium current (Ito)-blocking effect of phosphodiesterase-3 (PDE-3) inhibitors plays a role in reversing repolarization heterogeneities responsible for arrhythmogenesis in experimental models of ERS. Indication criteria: NA.

Results: The PDE-3 inhibitors cilostazol and milrinone or isoproterenol were effective in restoring the AP dome in the LV epicardium, thus abolishing the repolarization defects responsible for phase two re-entry and polymorphic VT. Using voltage clamp techniques applied to LV epicardial myocytes, both cilostazol (10 μM) and milrinone (2.5 μM) were found to reduce Ito by 44.4% and 40.4%, respectively. PDE-3 inhibitors exert an ameliorative effect in the setting of ERS by producing an inward shift in the balance of current during the early phases of the epicardial AP via inhibition of Ito as well as augmentation of ICA, thus reversing the repolarization defects underlying the development of phase two re-entry and VT/VF.
| 1036 | Nam G-R, et al. | Augmentation of J waves and electrical storms in patients with early repolarization. | Aim: To evaluate direct evidence of a relation between ER and the appearance of accentuated J waves in IVF. | Inclusion: 1336 controls who were representative of the general population and 15 IVF. | Exclusion: NA. | Results: The incidence of ER was 3.3% in controls and 60% in IVF. Dramatic but transient accentuation of J waves across the precordial and limb leads before the development of electrical storm, which was precipitated by relatively short-coupled PVCs; and suppression of the accentuated J waves and VF with the administration of quinidine and isoproterenol and with pacing at increasingly rapid rates. | Conclusions: Early repolarization pattern is not always benign, as was previously thought, and the transient appearance of global J waves in this setting is indicative of a highly arrhythmogenic substrate, representing a unique clinical syndrome associated with a high risk of SD from cardiac causes. |
| 1037 | Rodríguez-Capitán J, et al. | Frequency of different electrocardiographic abnormalities in a large cohort of Spanish workers. | Aim: To describe the ECG findings of a large sample of Spanish workers. Study design: Cross-sectional, observational. Number of patients: 13,179. | Inclusion: Participants in ICARIA study with digitalized ECGs from five regions of Spain. Exclusion: NA. | Results: ERP seen in 2.4%. Sample: mean age 40 years, 73.4% men. | Conclusions: ERP prevalence 2.4% in this sample. |
| 1038 | Sun G-Z, et al. | Early repolarization pattern in the general population: prevalence and associated factors. | Aim: To determine the prevalence of ERP in rural Chinese population. Study design: Randomly stratified cluster-sampling population-based study. Number of patients: 11,956 permanent residents of Lianning Province ≥ 15 years of age. | Inclusion: Participants in the Northeast China Rural Cardiovascular Health Study. Exclusion: Missing data, poor ECG quality; QRSd ≥ 110 ms, ARAFL on ECG, WPW, paced rhythm, age ≥ 85 years. | Results: ERP seen in 1.3%, more common in men than women (2.6% vs. 0.2%; P < 0.001) and in younger patients. Predictors of ERP: decreasing age, men sex, lower SBP, lower prevalence of stroke, longer RR interval, shorter QTc interval, shorter QRSd, lower Cornell voltage but higher Sokolow-Lyon voltage. | Conclusions: See list of predictors of ERP in Results. |
| 1039 | Maht N, et al. | Early repolarization pattern inheritance in the cardiac arrest survivors with preserved ejection fraction registry (CASPER). | Aim: To explore the pattern of inheritance for ERP. Study design: Registry. Number of patients: 289. | Inclusion: Patients from CASPER (January 2004–May 2017) with unexplained cardiac arrest, LVEF ≥ 50%, normal coronaries or non-obstructive CAD, normal resting QTc. Exclusion: < 12 years old; reversible cause of arrest, persistent type 1 Brugada syndrome pattern. | Results: ERP more common in unexplained cardiac arrest survivors who had first-degree relative with ERP (aOR 5.79 [1.79–18.7]). Highest prevalence of ERP seen in first-degree relatives of patients with unexplained cardiac arrest attributed to ER (ER syndrome). | Conclusions: ERP seems to be more common among unexplained cardiac arrest survivors and first-degree relatives of individuals with ERP, suggesting a genetic contribution. |
| 1041 | Adhikari C, et al. | Natural history of the electrocardiographic pattern of early repolarization in ambulatory patients. | Aim: To describe the natural history of the electrocardiographic pattern of early repolarization in ambulatory patients. Study type: Retrospective comparative study over 10 years. Number of patients: 248. | Inclusion: Cohort selected from a group (n = 29,281) with computerized measurements. 244 subjects with ER. Exclusion: NA. | Results: Most patients lost ER (62%) and the loss could not be explained by differences in changes in heart rate or interval between ECGs or by alterations in baseline ECG pattern. | Conclusions: These findings imply that ER must be lost with age. |

Continued
<table>
<thead>
<tr>
<th>1043</th>
<th>Mahida S. et al. 229</th>
<th>Role of electrophysiological studies in predicting risk of ventricular arrhythmia in early repolarization syndrome. PMID 25593056</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aim:</td>
<td>To determine the role of electrophysiology studies (EPS) in risk stratification of patients with ER syndrome.</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Multicentre.</td>
<td></td>
</tr>
<tr>
<td>Number of patients:</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>Inclusion:</td>
<td>With ER syndrome (age 36 ± 13 years, 60 mens) and aborted SD due to VF.</td>
<td></td>
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<tr>
<td>Exclusion:</td>
<td>NA.</td>
<td></td>
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<tr>
<td>Results:</td>
<td>Despite a recent history of aborted SD, VF was inducible in only 18 of 81 (22%) patients. During follow-up of 7.0 ± 4.9 years, 6 of 18 (33%) patients with inducible VF during EPS experienced VF recurrences, whereas 21 of 63 (33%) patients who were non-inducible experienced recurrent VF (P = 0.93). VF storm occurred in three patients from the inducible VF group and in four patients from the non-inducible group. VF inducibility was not associated with maximum J-wave amplitude (VF inducible vs. VF non-inducible: 0.23 ± 0.11 vs. 0.21 ± 0.11 mV; P = 0.43) or J-wave distribution (inferior: OR 0.96 [95% CI 0.33–2.81]; P = 0.95; lateral: OR 1.57 [95% CI 0.35–7.04]; P = 0.56; inferior and lateral: OR 0.83 [95% CI 0.27–2.53]; P = 0.74), which have previously been demonstrated to predict outcome in patients with an ER pattern.</td>
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<tr>
<td>Conclusions:</td>
<td>Our findings indicate that current programmed stimulation protocols do not enhance risk stratification in ER syndrome.</td>
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</tbody>
</table>

AF, atrial fibrillation; AP, action potential; CAD, coronary artery disease; CI, confidence interval; ECG, electrocardiogram; ER, early repolarization; ERP, early repolarization pattern; ERS, early repolarization syndrome; ICD, implantable cardioverter defibrillator; IVF, idiopathic ventricular fibrillation; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MA, major adverse; NA, not applicable; OR, odds ratio; PVC, premature ventricular complex; RR, risk ratio; SADS, sudden arrhythmic death syndrome; SBP, systolic blood pressure; SD, sudden death; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolf Parkinson white.
## 4.2.5. Catecholaminergic polymorphic ventricular tachycardia

### Table of Evidence 38 for Table of Recommendations for the management of patients with catecholaminergic polymorphic ventricular tachycardia

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1048</td>
<td>Priori S, et al. (2002)</td>
<td>Study type: Observational.  Number of patients: 30 probands and 118 family members.</td>
<td>Patients with documented polymorphic VA occurring during physical or emotional stress with a normal heart entered the study.</td>
<td>Results: Arrhythmias documented in probands were: 14 of 30 bidirectional VT, 12 of 30 polymorphic ventricular tachycardias, and 4 of 30 catecholaminergic (VF) RyR2 mutations were identified in 14 of 30 probands (34% bidirectional VT, 58% polymorphic VT, 50% catecholaminergic VF) and in nine family members (4 silent gene carriers). Genotype-phenotype analysis showed that patients with RyR2 CPVT have events at a younger age than do patients with non-genotyped CPVT and that men sex is a risk factor for syncope in RyR2 CPVT (HR 4.2).</td>
<td>Conclusions: CPVT is a clinically and genetically heterogeneous disease manifesting beyond pediatric age with a spectrum of polymorphic arrhythmias. Beta-blockers reduce arrhythmias, but in 30% of patients an ICD may be required. Genetic analysis identifies two groups of patients: patients with non-genotyped CPVT are predominantly women and become symptomatic later in life; patients with RyR2 CPVT become symptomatic earlier, and men are at higher risk of cardiac events. These data provide a rationale for prompt evaluation and treatment of young men with RyR2 mutations.</td>
<td></td>
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<tr>
<td>1050</td>
<td>Hayashi M, et al. (2009)</td>
<td>Study type: Observational.  Number of patients: 101 CPVT patients.</td>
<td></td>
<td>Results: During a mean follow-up of 7.9 years, cardiac events defined as syncope, aborted cardiac arrest, including appropriate discharges from ICD, or SCD occurred in 27 patients, including two mutation carriers with normal exercise tests. The estimated 8-year event rate was 32% in the total population and 27% and 5% in the patients with and without beta-blockers, respectively. Absence of beta-blockers (HR 5.48, 95% CI 1.80–16.68) and younger age at diagnosis (HR 0.34 per decade, 95% CI 0.13–0.89) were independent predictors. Fatal or near-fatal events defined as aborted cardiac arrest or SCD occurred in 13 patients, resulting in an estimated 5-year event rate of 13%. Absence of beta-blockers (HR 5.54, 95% CI 1.17–26.15) and history of aborted cardiac arrest (HR 13.01, 95% CI 2.48–68.21) were independent predictors. No difference was observed in cardiac and fatal or near-fatal event rates between probands and family members.</td>
<td>Conclusions: Cardiac and fatal or near-fatal events were not rare in both CPVT probands and affected family members during the long-term follow-up, even while taking beta-blockers, which was associated with a lower event rate. Further studies evaluating concomitant therapies are necessary to improve outcome in these patients.</td>
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<tr>
<td>1051</td>
<td>Leren I, et al. (2016)</td>
<td>Study type: Cohort, retrospective.  Number of patients: 101 CPVT patients.</td>
<td></td>
<td>Results: Resting heart rate was similar during treatment with nadolol (non-selective beta-blocker) and during beta-blocker treatment. When treated with beta-blocker, the maximum heart rate was lower during treatment with nadolol compared with beta-blocker treatment (HR = 0.50, 95% CI 0.30–0.83). Arrhythmias during exercise stress testing were less severe during treatment with nadolol compared with beta-blocker treatment. No differences were observed during treatment with beta-blocker treatment compared with before the initiation of beta-blocker treatment.</td>
<td>Conclusions: The incidence and severity of VA decreased during treatment with nadolol compared with treatment with beta-blocker. Beta-blockers did not change the occurrence or severity of arrhythmias compared with no medication.</td>
<td></td>
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<tr>
<td>1053</td>
<td>Van der Werf C, et al. (2012)</td>
<td>Familial evaluation in catecholaminergic polymorphic ventricular tachycardia: disease penetrance and expression in cardiac ryanodine receptor mutation-carrying relatives.</td>
<td>Aim: Current insight into disease penetrance, expression, genotype-phenotype correlations, and arrhythmic event rates in relatives carrying the Ryr2 mutation is limited. Study type: Observational. Number of patients: 116. Induction: Relatives with Ryr2 mutation. Exclusion: NA. Results: 64 of 108 anti-arrhythmic drug-free relatives (50%) had a CPVT phenotype at the first cardiological examination, including 27 (25%) with NSVT. Relatives carrying a Ryr2 mutation in the C-terminal polymorphic ventricular tachycardia–11.5; P = 0.001) and peak heart rate (MD −2.71; 1.04; P = 0.0001). Flecainide did not increase the risk of all side effects (RR 0.76; CI 0.42; 1.40; P = 0.38) compared to that with β-blockers alone. No deaths were reported among patients treated with flecainide. Conclusions: Flecainide is an effective and safe anti-arrhythmic agent, and its use as a monotherapy might be a good alternative for CPVT patients with β-blocker intolerance. Combination therapy was superior to β-blocker monotherapy. More randomized clinical trials are required to explore the long-term efficacy and safety of flecainide in these patients.</td>
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<tr>
<td>1054</td>
<td>Wang G, et al. (2011)</td>
<td>Safety and efficacy of flecainide for patients with catecholaminergic polymorphic ventricular tachycardia: a systematic review and meta-analysis.</td>
<td>Aim: To investigate the efficacy and tolerability of flecainide. Study type: Systematic review and meta-analysis. Number of patients: 7 RCTs and 1 RCT (33 CPVT patients; 152 patients treated with flecainide) were identified. Induction: Treatment with flecainide. Exclusion: NA. Results: Flecainide monotherapy was superior to standard therapy in alleviating the risk of arrhythmic events (RR 0.46; CI 0.38; 0.56; P &lt; 0.00001) and exercise-induced arrhythmic scores (MD −0.39; CI −0.74; −0.05; P = 0.03). Combination therapy of flecainide and β-blockers was superior to β-blocker monotherapy in reducing the risk of arrhythmic and symptomatic events (RR 0.29; CI 0.13; 0.46; P = 0.005; RR 0.36; CI 0.20; 0.61; P = 0.003), respectively. Peak heart rate (MD −16.8; CI −28.2; −5.4; P = 0.004), and exercise-induced arrhythmic scores MD −1.87; CI −2.71; 1.04; P &lt; 0.0001. Flecainide did not increase the risk of all side effects (RR 0.76; CI 0.42; 1.40; P = 0.38) compared to that with β-blockers alone. No deaths were reported among patients treated with flecainide. Conclusions: Flecainide is an effective and safe anti-arrhythmic agent, and its use as a monotherapy might be a good alternative for CPVT patients with β-blocker intolerance. Combination therapy was superior to β-blocker monotherapy. More randomized clinical trials are required to explore the long-term efficacy and safety of flecainide in these patients.</td>
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<tr>
<td>1056</td>
<td>Van der Werf C, et al. (2011)</td>
<td>Flecainide therapy reduces exercise-induced ventricular arrhythmias in patients with catecholaminergic polymorphic ventricular tachycardia.</td>
<td>Aim: To evaluate the efficacy and safety of flecainide in addition to conventional drug therapy in patients with CPVT. Study type: Observational. Number of patients: 33. Induction: CPVT patient started on flecainide at eight international centres before December 2009. Exclusion: NA. Results: 33 Of the 34 patients with prior major cardiac events either on (n = 18) or off (n = 16) optimal medical therapy. Conclusions: LCSD reduces the recurrences of major cardiac events in symptomatic CPVT patients.</td>
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<tr>
<td>1058</td>
<td>De Ferrari G, et al. (2012)</td>
<td>Clinical management of</td>
<td>Aim: To evaluate the anti-arrhythmic efficacy of LCSD in CPVT patients. Induction: Clinical or genetic diagnosis of CPVT. Results: Of the 54 patients with prior major cardiac events either on (n = 18) or off (n = 16) optimal medical</td>
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</table>
Study type: Cohort, retrospective.  
Number of patients: 63 patients (9 asymptomatic + 54 symptomatic for syncope, aborted cardiac arrest, or ICD appropriate discharges. Of the 54 symptomatic patients, 38 were on optimal medical therapy and 16 were not).

Enrollment period: 1988-2014  
Follow-up: Median 37 months (IQR).

Study endpoints: Major cardiac events including SCD, aborted cardiac arrest, appropriate ICD discharges, syncope.

Exclusion: NA.

Results: The 1- and 2-year cumulative event-free survival rates were 87% and 81%, respectively. The percentage of patients with major cardiac events despite optimal medical therapy (n = 38) was reduced from 100% to 32% (P < 0.001) after LCSD, and among 29 patients with a pre-surgical ICD, the rate of shocks dropped by 93% from 3.6 to 0.6 shocks per person per year (P < 0.001). Patients with an incomplete LCSD (n = 7) were more likely to experience major cardiac events after LCSD (71% vs. 17%; P < 0.01) than those with a complete LCSD. The nine asymptomatic patients remained free of major cardiac events.

Conclusions: The entity of adrenergic-dependent, potentially lethal tachyarrhythmia with no SHD deserves to be individualized. It may form a variant of the congenital LQTS in which the ECG marker is lacking; this primary VA must be looked for in a paediatric patient with syncope or SD in 30% of our patients. On receiving therapy with the appropriate beta-blocker, the patients’ symptoms and polymorphic tachyarrhythmias disappeared. During a mean follow-up period of 7 years, three syncopal events and 2 SCDs occurred, probably due to treatment interruption.

Strength: Long follow-up. Demonstration that LCSD does not replace ICD in high-risk individuals.

Limitations: Absence of a comparison group. Impossibility to compare the present results with the outcomes in patients with CPVT without LCSD (attendant selection bias because such a group would be at much lower risk, as all high-risk patients now undergo LCSD). Appropriateness of the ICD shocks was assessed by the enrolling centres; a controlled blinded assessment was not instituted.

Aim: Describe CPVT in children.

Exclusion: NA.

Results: Children were referred for stress- or emotion-induced syncope related to ventricular polymorphic tachyarrhythmias. The arrhythmia, consisting of isolated polymorphic ventricular extrasystoles followed by salvos of bidirectional and polymorphic tachycardias susceptible to degeneration into VF, was reproducibly induced by any form of increasing adrenergic stimulation. There was a familial history of syncope or SD in 30% of our patients. On receiving therapy with the appropriate beta-blocker, the patients’ symptoms and polymorphic tachyarrhythmias disappeared. During a mean follow-up period of 7 years, three syncopal events and 2 SCDs occurred, probably due to treatment interruption.

Conclusions: The entity of adrenergic-dependent, potentially lethal tachyarrhythmia with no SHD deserves to be individualized. It may form a variant of the congenital LQTS in which the ECG marker is lacking; this primary VA must be looked for in a paediatric patient with stress- or emotion-induced syncope because only beta-blocking therapy can prevent SD and therefore must be given for the patient’s lifetime.

Aim: To determine whether flecainide dosed to therapeutic levels and added to β-blocker therapy is superior to β-blocker therapy alone for the prevention of exercise-induced arrhythmias in CPVT.

Exclusion: NA.

Results: The median baseline exercise test score was 3.0 (range, 0–4), with no difference noted between the baseline and placebo (median, 2.5; range, 0–6) exercise scores. The median VA score during exercise was significantly reduced by flecainide (0 [range, 0–2] vs. 3.5 [range, 0–4] for placebo; P < 0.01), with complete suppression observed in 11 of 13 patients (85%).

Conclusions: Flecainide plus β-blocker significantly reduced ventricular ectopy during exercise compared with placebo plus β-blocker and β-blocker alone. Strength: Randomization, placebo controlled, single-blinded.

Limitations: Low numerosity.

CI, confidence interval; CPVT, catecholaminergic polymorphic ventricular tachycardia; ECG, electrocardiogram; HR, heart rate; ICD, implantable cardioverter defibrillator; IQR, inter quartile range; IVF, idiopathic ventricular fibrillation; LCSD, left cardiac sympathetic denervation; LQTS, long QT syndrome; NA, not applicable; NSVT, non-sustained VT; OR, odds ratio; PVC, premature ventricular complex; RR, risk ratio; SCD, sudden cardiac death; SD, sudden death; SHD, structural heart disease; VA, ventricular arrhythmia; VT, ventricular tachycardia; VTns, nonsustained VT.
### 4.2.6. Short QT syndrome

#### Table of Evidence 39 for Table of Recommendations for the management of patients with short QT syndrome

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1064</td>
<td>Gollob MH, et al. (2011) The short QT syndrome: proposed diagnostic criteria. PMID: 21310316 Year of publication: 2011</td>
<td>Aim: Describe SQTS cohort. Study type: Observational. Number of patients: 61</td>
<td>Inclusion: Short QT Syndrome Registry. Exclusion: NA.</td>
<td>Results: Predominantly men (75.4%) and had a mean QTc value of 306.7 ms with values ranging from 248 to 381 ms in symptomatic cases.</td>
<td></td>
<td>Conclusions: Small series. Carefully selected cases. QTc range up to 381 ms in symptomatic short QT syndrome cases.</td>
</tr>
<tr>
<td>1066</td>
<td>Mazzanti A, et al. (2014) Novel insight into the natural history of short QT syndrome. PMID: 24291113 Year of publication: 2014</td>
<td>Aim: Provide data natural history in SQTS patients. Study type: Observational. Number of patients: 73</td>
<td>Inclusion: Patients with short QT syndrome. Exclusion: NA.</td>
<td>Results: 84% men; age, 26 ± 15 years. QTc 329 ± 22 ms. Follow-up 60 ± 41 months. Cardiac arrest was the most frequent presenting symptom (40% of probands; range, &lt;1 month to 41 years). Rate of cardiac arrest was 4% in the first year of life and 13% per year between 20 and 40 years; a history of cardiac arrest was the only predictor of recurrences at follow-up (P &lt; 0.0000001).</td>
<td></td>
<td>Conclusions: Probability of a first occurrence of cardiac arrest by 40 years of age was 41%.</td>
</tr>
<tr>
<td>1067</td>
<td>Dhutia H, et al. (2016) The prevalence and significance of a short QT interval in 18825 low-risk individuals including athletes. PMID: 26400956 Year of publication: 2016</td>
<td>Aim: Data on SQTS in large cohort of athletes and non-athletes. Study type: Observational. Number of patients: 18825</td>
<td>Inclusion: Age: 14–35 years. Exclusion: NA.</td>
<td>Results: Prevalence of short QT interval was 0.1% (26 patients, ≤320 ms), 0.2% (44 patients, ≤330 ms), 7.9% (1478 patients, &lt;380 ms), 15.8% (2973 patients, ≤390 ms). Male gender and Afro-Caribbean ethnicity had the strongest association with short QT intervals.</td>
<td></td>
<td>Conclusions: Athletes had shorter QT intervals than non-athletes, but athletic status did not predict short QT intervals. Individuals with short QT intervals ≤320 ms did not report syncope or a sinister family history, and during a follow-up period of 5.3 ± 12 years, there were no deaths in this group.</td>
</tr>
<tr>
<td>1068</td>
<td>Gallagher MM, et al. (2006) Distribution and prognostic significance of QT intervals in the lowest half centile in 12012 apparently healthy persons. PMID: 16996877 Year of publication: 2006</td>
<td>Aim: Determine lowest QT range. Study type: Observational. Number of patients: 12012</td>
<td>Inclusion: Adult population data. Exclusion: NA.</td>
<td>Results: In lowest half centile, QTc values continued to follow a normal pattern without evidence of a distinct subpopulation. None of the lowest 0.5% died during 7.9 ± 4.5 years. QTc interval of ≤330 ms is extremely rare in healthy subjects.</td>
<td></td>
<td>Conclusions: Presence of a QT interval in the lowest 0.5% of the normal range does not imply a significant risk of SD.</td>
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Continued
Conclusions:
The prevalence of QT interval based on QTc, QTfc, and QTnc was 0.10%, 0.08%, and 0.06%, and the prevalence of QT interval based on QTc Bazett was 0.02%. The prevalence of QTc Bazett shorter than 347 ms, and 1% Bazett QTc longer than 445 ms, respectively.

Other findings:
All-cause or cardiovascular mortality did not differ between subjects with a very short or short QT interval and those with normal QT intervals (360–450 ms). There were no SCD, aborted SCD, or documented ventricular tachyarrhythmias among subjects with a QTfc or QTnc shorter than 340 ms.

Included:
Patients with short QT syndrome.

Excluded:
Patients with short QT syndrome.

Study type:
Observational.

Number of patients:

Aim:
To study the prevalence of short QT intervals.

Results:
The mean QTc was 314 ± 23 ms. A fraction of the patients had a normal QTc Bazett but had a very short or short QT interval. The average QTc was 314 ± 23 ms. A mutation in genes related to short QT syndrome was found in 23% of the probands, most of them had a gain of function mutation in HERG (short QT syndrome type 1). 24 received an ICD, and 12 patients received hydroquinidine (HQ), which was effective in preventing the induction of VA. During follow-up, two already symptomatic patients received appropriate ICD shocks and one had syncope. Non-sustained polymorphic VT was recorded in three patients.

Other findings:
Patients with a HERG mutation had shorter QT at baseline and a greater QTc prolongation after treatment with HQ.

Conclusions:
The event rate was 4.9% per year in the patients without anti-arrhythmic therapy. No arrhythmic events occurred in patients receiving HQ.

Inclusion:
Patients with a previous cardiac arrest dropped from 12% before HQ to 0 on therapy (P = 0.03) and the number of LAE per patient from 0.73 ± 0.3 to 0 (P = 0.026).

Other findings:
The annual rate of LAE in the 16 patients with a previous cardiac arrest dropped from 12% before HQ to 0 on therapy (P = 0.028).

Conclusions:
Hydroquinidine is highly effective in short QT syndrome.

Impact of antiarrhythmic drugs on the outcome of short QT Syndrome. PMID: 31427960 Year of publication: 2019

Aim:
Data on ICD in SQTS patients.

Study type:
Observational.

Number of patients:
62.

Inclusion:
Patients with short QT syndrome.

Exclusion:
NA.

Results:
Followed up over a median time frame of 5 years. Of the 55 patients treated with hydroquinidine (HQ), long-term prophylaxis was documented in 41 patients. 14 patients stopped treatment. Of the 41 patients treated with HQ, the QT interval increased from 313.5 ± 17.2 to 380.1 ± 21.2 ms. 13 of the 41 patients suffered from at least one or more ventricular tachyarrhythmias (VTs) before HQ initiation. VTs are reduced in incidence after HQ treatment (13/41: 31% vs. 3/41: 7.3%; P < 0.001).

Other findings:
HQ increases the corrected QT interval and prevents VAs in the majority of the patients in this cohort. HQ is safe for use in SQTS patients, particularly due to its low rate of side effects. Other anti-arrhythmic drugs might be useful, but the data justifying their use are sparse.
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<tbody>
<tr>
<td>Aim:</td>
<td>To determine QT adaptation on exercise.</td>
<td>Inclusion:</td>
<td>Diagnosed short QT syndrome subjects vs. controls.</td>
<td></td>
</tr>
<tr>
<td>Study type:</td>
<td>Prospective experimental study.</td>
<td>Age:</td>
<td>17–53 years.</td>
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<tr>
<td>Exclusion:</td>
<td>NA.</td>
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<tr>
<td>Results:</td>
<td>Short QT syndrome patients showed lower QT intervals as compared with controls both at rest (276 ± 27 vs. 364 ± 23 ms; P &lt; 0.0001) and at peak exercise (228 ± 27 vs. 245 ± 26 ms; P = 0.05), with a mean variation from rest to peak effort of 48 ± 14 vs. 120 ± 20 ms (P &lt; 0.0001).</td>
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<tr>
<td>Other findings:</td>
<td>Regression analysis of QT/HR relationship revealed a less steep slope for short QT syndrome patients compared with the control group, never exceeding the value of −0.90 ms/b.p.m. (mean value −0.53 ± 0.15 vs. −1.29 ± 0.30 ms/b.p.m.; P &lt; 0.0001).</td>
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<tr>
<td>Conclusions:</td>
<td>Short QT syndrome patients show a reduced adaptation of the QT interval to HR. Exercise test can be a useful tool in the diagnosis of short QT syndrome.</td>
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<tbody>
<tr>
<td>Aim:</td>
<td>QT population ranges.</td>
<td>Inclusion:</td>
<td>3 months–79 years.</td>
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<tr>
<td>Study type:</td>
<td>Observational.</td>
<td>Exclusion:</td>
<td>NA.</td>
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<tr>
<td>Number of patients:</td>
<td>79 743</td>
<td>Results:</td>
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<td>A subgroup of 46 129 individuals with a very low probability of cardiovascular disease was identified. QT interval, 325–452 ms; QTc Bazett, 361–457 ms; and QTc Fridericia, 359–445 ms.</td>
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<tr>
<td>Conclusions:</td>
<td>2nd–98th percentile QTc Bazett, 361–457 ms; and QTc Fridericia, 359–445 ms.</td>
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<tr>
<td>Aim:</td>
<td>NA.</td>
<td>Inclusion:</td>
<td>Electrical storm in short QT syndrome.</td>
<td></td>
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<tr>
<td>Study type:</td>
<td>Case report.</td>
<td>Exclusion:</td>
<td>NA.</td>
<td></td>
</tr>
<tr>
<td>Results:</td>
<td>A 28-year-old man was admitted after aborted SCD while sleeping. QTc was 320 ms, suggesting short QT syndrome. The patient then presented with electrical storm with eight successive episodes of VF while on deep sedation and hypothermia.</td>
<td></td>
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</tr>
<tr>
<td>Other findings:</td>
<td>Isoproterenol infusion was introduced, leading to rapid cessation of any arrhythmic event.</td>
<td></td>
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<tr>
<td>Conclusions:</td>
<td>Isoproterenol can be effective in managing electrical storm in patients with short QT syndrome.</td>
<td></td>
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</tbody>
</table>

b.p.m., beats per minute; HR, heart rate; ICD, implantable cardioverter defibrillator; NA, not applicable; SCD, sudden cardiac death; SD, sudden death; SQTS, short QT syndrome; VA, ventricular arrhythmia; VT, ventricular tachycardia.
5. Special aspects in selected populations

5.1. Pregnant patients and peripartum cardiomyopathy

Table of Evidence 40 for Table of Recommendations for the prevention and management of ventricular arrhythmia during pregnancy

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Enrolment period</th>
<th>Study endpoints</th>
<th>Inclusion criteria (patients)</th>
<th>Exclusion criteria</th>
<th>Summary of main results</th>
<th>Other findings</th>
<th>Conclusions and limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>958</td>
<td>Seth R, et al. [1062] Long QT syndrome and pregnancy. PMID: 17349890 Year of publication: 2007</td>
<td>5. To investigate the clinical course of women with LQTS throughout their potential child-bearing years.</td>
<td>Study type: Registry.</td>
<td>Number of patients: 391 (women who had their first birth from 1980 to 2003).</td>
<td>Study endpoints:</td>
<td>Study endpoints:</td>
<td>Inclusion:</td>
<td>Exclusion:</td>
<td>Results:</td>
<td></td>
<td>Conclusions:</td>
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<td></td>
<td>Syncope, aborted CA, and SD, during and after pregnancy.</td>
<td>LQTS women who had their first birth from 1980 to 2003 (n = 391).</td>
<td>NA.</td>
<td>The pregnancy time was associated with a reduced risk of cardiac events (HR 0.28; 95% CI 0.10–0.76; P = 0.01), whereas the 9-month post-partum time had an increased risk (HR 2.7; 95% CI 1.8–4.3; P &lt; 0.001). After the 9-month post-partum period, the risk was similar to the period before the first conception (HR 0.91; 95% CI 0.55–1.5; P = 0.70). Genotype analysis (n = 153) showed that women with the LQT2 genotype were more likely to experience a cardiac event than women with the LQT1 or LQT3 genotype. The cardiac event risk during the high-risk post-partum period was reduced among women using beta-blocker therapy (HR 0.34; 95% CI 0.14–0.84; P = 0.02).</td>
<td></td>
<td>Women with LQTS have a reduced risk for cardiac events during pregnancy, but an increased risk during the 9-month post-partum period, especially among women with the LQT2 genotype. Beta-blockers were associated with a reduction in cardiac events during the high-risk post-partum time period.</td>
</tr>
<tr>
<td>1087</td>
<td>Wang YC, et al. [1063] The impact of maternal cardioversion on fetal haemodynamics. PMID: 16377063 Year of publication: 2006</td>
<td>Study type: Letter to the editor; case report.</td>
<td>Study type: Case report.</td>
<td>One woman with several cardioversions during pregnancy.</td>
<td>Exclusion:</td>
<td></td>
<td>Inclusion:</td>
<td></td>
<td>Results:</td>
<td>Umbilical artery flow immediately between cardioversion was not reduced.</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>1090</td>
<td>Abello M, et al. Cardioverter de-energizer implantation in a pregnant woman guided with transoesophageal echocardiography. PMID: 12930513 Year of publication: 2003</td>
<td>Study type: Case report.</td>
<td>Study type: Case report.</td>
<td>28-year-old pregnant woman who underwent an ICD implantation guided by transeosophageal echocardiography.</td>
<td>Exclusion:</td>
<td></td>
<td>Inclusion:</td>
<td></td>
<td>Results:</td>
<td>The ICD lead was shown as a high echogenic structure.</td>
<td>Conclusions:</td>
</tr>
<tr>
<td>1097</td>
<td>Rashba EJ, et al. Influence of pregnancy on the for cardiac events in patients with hereditary long QT syndrome. LQTS Investigators. PMID: 9490239 Year of publication: 1998</td>
<td>Study type: Registry. Study type: Case report.</td>
<td>Study type: Registry. Study type: Case report.</td>
<td>Number of patients: 422 women (111 probands affected with the LQTS and 311 first-degree relatives).</td>
<td>Study endpoints:</td>
<td>Study endpoints:</td>
<td>Combined incidence of 422 women enrolled in the registry who had had one or more pregnancies.</td>
<td>Exclusion:</td>
<td>Results:</td>
<td></td>
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</tr>
</tbody>
</table>

Continued
Conclusions:
Early diagnosis and β-blocker therapy for high-risk patients with LQTS are important for prevention of cardiac events during pregnancy and the post-partum period, and β-blocker therapy may be tolerated for babies in LQT-P cases.

Results:
The combined pregnancy and post-partum arrhythmic risks in CPVT patients were not elevated compared with the non-pregnant period. Most patients had pregnancies before CPVT diagnosis (82%). Pregnancy and post-partum cardiac events included syncope (5%) and an aborted CA (1%), which occurred in patients who were not taking beta-blockers. There were six cardiac events (6%) during the non-pregnant period. The pregnancy and post-partum event rates were 1.71 and 2.85 events per 100 patient-years, respectively, and the combined event rate during the pregnancy and post-partum period was 2.14 events per 100 patient-years. These rates were not different from the non-pregnant event rate (1.46 events per 100 patient-years).

Other findings:
Other complications included miscarriages (13%) and intrauterine growth restriction (1 case).

Conclusions:
The combined pregnancy and post-partum arrhythmic risks in CPVT patients were not elevated compared with the non-pregnant period. Most patients had pregnancies before diagnosis, and all patients with events were not taking beta-blockers at the time of the event.

Inclusion:
β-blockers (OR 4.79; 95% CI 1.51–15.21 and OR 3.25; 95% CI 1.17–9.09, respectively).

Results:
In the beta-blocker group, only two events occurred at post-partum, whereas 12 events occurred in the non-beta-blocker group during pregnancy (n = 6) or post-partum period (n = 6). The frequency of spontaneous abortion did not differ between the two groups. Fetal growth rate and proportion of infants with congenital malformation were similar between the two groups, but premature delivery and low birthweight infants were more common in those taking β-blockers (OR 4.79; 95% CI 1.51–15.21 and OR 3.25; 95% CI 1.17–9.09, respectively).

Covariates:
Early diagnosis and β-blocker therapy for high-risk patients with LQTS are important for prevention of cardiac events during pregnancy and the post-partum period, and β-blocker therapy may be tolerated for babies in LQT-P cases.
Retrospective cohort study.
Number of patients: 23 patients with 63 pregnancies.
Enrolment period: 1968–2016
Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

pregnancies, 9% of mothers). None occurred during delivery or in the post-partum period. No mother developed heart failure. Beta-blocker therapy during pregnancy (n = 13) was associated with lower birthweight (2730 vs. 3400 g; P = 0.004).

Only two pre-term deliveries occurred, unrelated to cardiac condition. Caesarean section was performed in 13% of cases. Premature SD occurred in 10% (n = 5) of children before 25 years old including two in the first year of life.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

pregnancies, 9% of mothers). None occurred during delivery or in the post-partum period. No mother developed heart failure. Beta-blocker therapy during pregnancy (n = 13) was associated with lower birthweight (2730 vs. 3400 g; P = 0.004).

Only two pre-term deliveries occurred, unrelated to cardiac condition. Caesarean section was performed in 13% of cases. Premature SD occurred in 10% (n = 5) of children before 25 years old including two in the first year of life.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.

Beta-blocker therapy during pregnancy.

Study endpoints: Deliveries, heart failure, arrhythmias, SCD in children.

retro tendencies during pregnancy.
### 5.2. Heart transplantation

#### Table of Evidence 41

**Aim of the study**

<table>
<thead>
<tr>
<th>Study type</th>
<th>Number of patients</th>
<th>Study endpoints</th>
</tr>
</thead>
</table>

**Inclusion criteria (patients)**

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1111</strong> Frohlich GM, et al. [1111]</td>
</tr>
</tbody>
</table>

**Exclusion criteria**

- All patients aged 16 years or older listed for a heart transplant.
- Patients were excluded if no data on prior ventricular arrhythmia (defined as sustained VT or VF) were available at the time of listing, or if serial follow-up data on ICD function and shock delivery were lacking.
- Patients who received a cardiac assist device before listing were also excluded.

**Summary of main results**

- 1089 patients (944 patients from the German Heart Center Berlin and 145 patients from University Hospital Zurich) were included in the analysis. 550 patients (51%) on the transplant list received ICDs for primary prevention. Of these, 430 (78%) received an ICD (ICD+). The remaining 120 received an ICD as a bridge to transplantation (ICD-BT).
- 314 patients (31%) on the transplant list received ICDs for secondary prevention. Of these, 190 (61%) received an ICD (ICD+). The remaining 124 received an ICD as a bridge to transplantation (ICD-BT).

**Additional findings**

- Results: 1089 patients (944 patients from the German Heart Center Berlin and 145 patients from University Hospital Zurich) were included in the analysis. 550 patients (51%) on the transplant list received ICDs for primary prevention. Of these, 430 (78%) received an ICD (ICD+). The remaining 120 received an ICD as a bridge to transplantation (ICD-BT).
- 314 patients (31%) on the transplant list received ICDs for secondary prevention. Of these, 190 (61%) received an ICD (ICD+). The remaining 124 received an ICD as a bridge to transplantation (ICD-BT).

**Conclusions and limitations**

- Both primary and secondary ICD implantation are associated with improved survival in patients with end-stage heart failure.
- Patients listed for heart transplantation for whom in-hospital rhythm monitoring cannot be guaranteed until transplantation, might be considered for ICD implantation, irrespective of probable waiting time on the transplant list.

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**1112 Sandner SE, et al. [1112]**

**Survival benefit of the implantable cardioverter-defibrillator in patients on the waiting list for cardiac transplantation.**

PMID: 11568051 Year of publication: 2001

**Aim:** To examine the effect of ICD therapy on mortality in patients on the waiting list for cardiac transplantation.

**Study type:** Retrospective, observational.

**Number of patients:** 854 unselected consecutive patients on waiting list for cardiac transplantation.

**Enrolment period:** Jan 1992–March 2000

**Study endpoints:** Efficacy of ICD therapy on mortality in patients on the waiting list for XT.

**Inclusion:** Indication for heart transplant in end-stage heart disease patients.

**Exclusion:** N/A

**Results:** 102 patients received ICDs before listing for transplantation (median time from ICD implantation to listing for XT 6.7 months). A group of 752 patients was not treated with ICD. Total of 573 of patients underwent cardiac transplantation, 20.4% died while on the waiting list; 66.7% of deaths on the waiting list were SD; no SD occurred in ICD patients. Significant difference between ICD patients vs. non-ICD patients in total mortality at 12 months (13.2% in ICD vs. 25.8% in non-ICD).

**Other findings:** Indications for ICD implantation were (1) OHCA (62 patients) inducible SVT or VF (n = 29) or ICD as a first line therapy (n = 33); (2) spontaneous VT or NSVT or VF (27).

**Conclusions:** In patients on the cardiac transplant list the use of ICDs presents SCD and improves overall survival rate. Benefit of ICDs as a bridge to transplantation in patients identified as at arrhythmic risk.
<table>
<thead>
<tr>
<th>Study</th>
<th>Title</th>
<th>Description</th>
<th>Inclusion</th>
<th>Exclusion</th>
<th>Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1114</td>
<td>Cantero-Perez EM, et al.</td>
<td>Implantable cardioverter-defibrillator for primary prevention in patients with severe ventricular dysfunction awaiting heart transplantation</td>
<td>To evaluate the effectiveness of ICDs for primary prevention in patients with LVEF ≤30% included on the heart transplantation list.</td>
<td>Patients on waiting list for heart transplantation; history of manifest LV heart failure, NYHA Class III/IV.</td>
<td>Congestive heart failure was the cause of the two deaths observed in the ICD group (7.1%). In the non-ICD group there were nine deaths (17.6%), five of which were classified as SD (55.6%) and the others attributable to congestive heart failure. There were higher survival rates in the ICD group (P = 0.02). Of the ICD patients, 12 (42.9%) had appropriate therapies, one patient had ICD infection, and two had inappropriate therapies.</td>
<td>Reduction of mortality in patients with ICDs for primary prevention in patients awaiting heart transplantation. However, the small cohort and the wide variability in the heart transplantation list time impede the results from being significant.</td>
</tr>
<tr>
<td>1115</td>
<td>Pezawas T, et al.</td>
<td>Primary preventive cardioverter-defibrillator implantation (ProICD) in patients awaiting heart transplantation. A prospective randomized, controlled 12-year follow-up study.</td>
<td>To evaluate whether short-term primary preventive cardioverter-defibrillator (ICD) implantation as bridge to heart transplantation (HTX) provides any survival benefit.</td>
<td>On waiting list for HTX (≤4 weeks), history of manifest right or left ventricular heart failure, NYHA Class III/IV, VO2 max ≤14 mL/kg/min on spiro-exercise stress testing, and optimized medical therapy since at least 1 month.</td>
<td>The mean time to HTX was 10 ± 9 months. 30 patients (61%) were transplanted. In the ICD group, patients with DCM developed slow VT episodes in three cases, whereas fast VT/VF was seen in 2 CAD patients (6%). All VT episodes occurred on the waiting list for HTX. There was no arrhythmic death because of VT/VF in the non-ICD group. There were only non-cardiac (NC) and non-SCD. There was no arrhythmic death.</td>
<td>ICD implantation in patients on the waiting list for HTX varies between 53.5% and 57%. This study may not support the general use of primary preventive ICDs as a short-term bridge to HTX. Considering the relative low risk of fatal arrhythmias, wearable cardioverter-defibrillators may be used in this patient setting as recently suggested.</td>
</tr>
<tr>
<td>1116</td>
<td>Kao AC, et al.</td>
<td>Wearable defibrillator use in heart failure (WIF): results of a prospective registry.</td>
<td>To collect SCA events, WCD defibrillation efficacy, and WCD usage data in heart failure patients.</td>
<td>Patients post-heart transplantation and/or, they had DCM (with VT or EF ≤33), or they had DCM with VT or EF ≤33, or they had DCM with VT or EF ≤33, or they had DCM with VT or EF ≤33.</td>
<td>Among the 82 patients included, 12 patients were awaiting heart transplantation. In this study, no VT/VF episodes or SD were observed; 90-days survival was 100%. Nonappropriate shock was delivered and no adverse event was reported. Of the patients awaiting transplantation, four stopped using WCD due to an improvement in their condition, four received ICD, one had aortic/mitral/tricuspid valve repair, one received heart transplant, and two stopped using WCD for an unknown reason. Although no treatment has been provided by WCD, this study suggests an acceptable safety profile for the LifeVest system.</td>
<td>The WCD monitored heart failure patients until further assessment of risk. The leading reasons for end of WCD use were improvement in LVEF or ICD implantation if there was no significant improvement in LVFS. Due to the smaller than anticipated sample size, there were no SCD events in the 82 patients who completed the study (≤90 days).</td>
</tr>
<tr>
<td>1117</td>
<td>Alba AC, et al.</td>
<td>Incidence and predictors of sudden cardiac death after heart transplantation: a systematic review and meta-analysis.</td>
<td>To evaluate incidence and predictors of post-heart transplant SCD and the use of ICD.</td>
<td>Patients post-heart transplant.</td>
<td>The pooled incidence rate of SCD was 1.30 per 100 person-years (95% CI 1.08–1.52, I² 75%). The incidence rate of CAW-related SCD was 2.40 per 100 patients per year (95% CI 1.08–1.52, I² 75%).</td>
<td>Post-transplant risk of SCD in heart transplanted recipients is higher than in the general population.</td>
</tr>
</tbody>
</table>

Continued
1119
PMID: 30697805 
Year of publication: 2019

Aim:
To provide evidence regarding risk of SCD in heart transplant recipients.

Study type: Retrospective cohort.

Number of patients: 55 studies encompassing 47,901 recipients. Of these, only 12 studies reported on SCD risk in patients with CAV (38910), and 11 reported factors associated with SCD (44069).

Enrolment period: 1983–2013

Study endpoints:
- Incidence and predictors of SCD after cardiac transplant,
- Number of patients: 553 × 100 /
- Person years (95% CI 11.64–19.76, I2 69%).

The risk was significantly higher in post-transplant with lymphoproliferative disorders: 15.26 × 100 person-years (95% CI 11.64–19.76, I2 69%) and those presenting with bradyarrhythmia: 83.33 per 100 person-years (95% CI 27.10–98.53). Independent predictor of SCD (identified by two moderate quality studies) were:
- older donor age, younger recipient age,
- non-Caucasian race, reduced left EF, infection, cancer

Pre-transplant factors associated with SCD assessed from four studies using multivariate analysis included older donor age, young recipient age, non-Caucasian race, and peripheral vascular disease, whereas post-transplant are: elevated HR, prolonged QT interval, increased QT variability, reduced LVEF, increased platelet aggregation, low HDL, rejection, infection, cancer

Conclusions:
Treated rejection and CAV are important risk factors for SCD after heart transplant. These increased risk of SCD in transplanted patients is comparable or higher than the risk of SCD in heart failure patients eligible for primary prevention ICD. The potential benefit from ICD therapy in selected transplanted patients with CAV or treated rejection remains unknown.

1122
Klein HU, Meltendorf U. Bridging a temporary high risk of sudden arrhythmic death. Experience with the wearable cardioverter defibrillator. 
PMID: 19889186 
Year of publication: 2010

Aim:
To describe function and technical details of the WCD, discuss the potential indications, and report their experience with the WCD since 2000.

Study type: Retrospective.

Number of patients: 25242 from ISHLT registry.

Enrolment period: 2004–2014

Study endpoints:
- Time to SCD,
- Incidence:
- Patients >18 years undergoing primary heart transplant.

Exclusion:
- Simultaneous, re-transplantation, dead within the first year post-transplant, and follow-up <1 year.

Results:
During a median follow-up of 4.7 years, 582 (2.3%) patients died from SCD. Incidence of SCD in patients (at least one year after transplant) was 0.7% (95% CI 0.6–0.8) at 2 years and 4.2% (95% CI 3.8–4.6) at 10 years. When associated to treated rejection the risk was 1.76-fold increase (HR 1.76; 95% CI 1.35–2.26) at 2 years and 4.2% (95% CI 0.133–2.30) while CAV was associated with 3.32-fold increased risk (HR 3.32; 95% CI 2.73–4.03). Without treated rejection history and CAV was 0.43% (95% CI 0.35–0.51).

Conclusions:
The WCD is effective in providing immediate life-saving defibrillation for patients at high risk of major ventricular arrhythmias. The WCD may represent an alternative approach to ICD implantation for about 6–9 months, once they are listed as candidates for heart transplantation. After a successfully terminated VT/VF episode, the WCD can continue to be a useful and life-saving tool until transplantation is performed.
## 5.3. Sudden cardiac death in athletes

### Table of Evidence 42 for Table of Recommendations for risk stratification and prevention of sudden cardiac death in athletes

<table>
<thead>
<tr>
<th>Reference number in Guidelines</th>
<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
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</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>Regard B, et al. 183, 2016</td>
<td>To identify and characterize all sports related SCD aged 12—49 years and to address the difference in incidence rates between competitive and non-competitive athletes.</td>
<td>Sports-related SCD (SCD during or within 1 h after exercise in a competitive athlete), age 12—49 years, in 2007—2009 in Denmark. Exclusion: NA.</td>
<td>In the 3-year period there were 881 SCD of which 44 were sports-related SCD. In non-competitive athletes aged 12—35 years the incidence rate of sports-related SCD was 0.43 (95% CI 0.16—0.94) per 100 000 athlete person-years, whereas it was 2.95 (95% CI 1.95—4.30) in non-competitive athletes aged 36—49 years. In competitive athletes the incidence rate of sports-related SCD was 0.47 (95% CI 0.10—1.14) and 6.64 (95% CI 2.86—13.1) per 100 000 athlete person-years in those aged 12—35 years and 36—49 years, respectively.</td>
<td></td>
<td>The incidence rates of sports-related SCD in non-competitive and competitive athletes are not different. The study showed an increase in the incidence rate of sports-related SCD in persons aged 36—49 years in both non-competitive and competitive athletes compared to those aged 12—35 years. Importantly, SCD in the general population is much more prevalent than sports-related SCD in all age groups.</td>
</tr>
<tr>
<td>1125</td>
<td>Corrado D, et al. 183, 2016</td>
<td>To assess whether pre-participation screening results in the prevention of SD from HCM, a common cardiovascular cause of death in young athletes.</td>
<td>SDs among athletes and non-athletes (35 years of age or less) in the Veneto region of Italy from 1979 to 1996. Exclusion: NA.</td>
<td>Of 269 SDs in young people, 49 occurred in competitive athletes (44 men and five women athletes; mean age, 23 ± 7 years). The most common causes of SD in athletes were ARVC (22.4%), coronary artherosclerosis (18.4%), and anomalous origin of a coronary artery (12.2%). HCM caused only 1 SD among the athletes (2.0%) but caused 16 SDs in the non-athletes (7.3%). HCM was detected in 22 athletes (0.07%) at pre-participation screening and accounted for 35% of the cardiovascular reasons for disqualification. None of the disqualified athletes with HCM died during a mean follow-up period of 8.2 ± 5 years.</td>
<td></td>
<td>Conclusion: HCM was an uncommon cause of death in these young competitive athletes and suggests that the identification and disqualification of affected athletes at screening before participation in competitive sports may have prevented SD.</td>
</tr>
<tr>
<td>1126</td>
<td>Mahotra A, et al. 183, 2016</td>
<td>To investigate the incidence and causes of SCD among adolescent soccer players in the United Kingdom.</td>
<td>11 168 screened adolescent athletes. Study endpoints: SCD confirmed at autopsy.</td>
<td>During screening, 42 athletes (0.38%) were found to have cardiac disorders that are associated with SCD. After screening there were 23 deaths from any cause, of which eight (35%) were SDs attributed to cardiac disease. Cardiomyopathy accounted for 7 of 8 SCD (88%). Six athletes (5%) with SCD had had normal cardiac screening results. On the basis of a total of 118 331 person-years, the incidence of SCD among previously screened adolescent soccer players was one per 14 794 person-years (6.8 per 100 000 athletes).</td>
<td></td>
<td>Conclusion: Diseases that are associated with SCD were identified in 0.38% of adolescent soccer players in a cohort that underwent cardiovascular screening. The incidence of SCD was one per 14 794 person-years, or 6.8 per 100 000 athletes. Most of these deaths were due to cardiomyopathies that had not been detected on screening. Limitations: Once-only screening at a mean age of 16 years.</td>
</tr>
</tbody>
</table>
Conclusions: Adding ECG to medical history and physical examination improves the overall sensitivity of athletes. However, this strategy is associated with an increased rate of false-positive results when current ECG interpretation criteria are used.

The incidence of sudden cardiovascular death in young competitive athletes has substantially declined in the Veneto region of Italy since the introduction of nationwide systematic screening. Mortality reduction was predominantly due to a lower incidence of SD from cardiomyopathies that paralleled the increasing identification of athletes with cardiomyopathies at pre-participation screening.

Results: Cardiac abnormalities with relevance to sport participation risk were observed on transthoracic echocardiogram in 11 of 510 collegiate athletes who received cardiovascular screening before athletic participation. Screening with history and examination alone detected abnormalities in five of these 11 athletes (sensitivity, 45.5% [95% CI 16.8–76.2%]; specificity, 94.4% [CI 92.0–96.2%]). Electrocardiography detected five additional participants with cardiac abnormalities (for a total of 16 of 11 participants), thereby improving the overall sensitivity of screening to 90.9% (CI 84.7–99.8%). However, including ECG reduced the specificity of screening to 82.7% (CI 79.1–86.0%) and was associated with a false-positive rate of 16.9% (vs. 5.5% for screening with history and examination only).

Aim: To analyse trends in incidence rates and cardiovascular causes of SD in young competitive athletes in relation to pre-participation screening.


Exclusion: Not reported.

Study endpoints: Incidence trends of total cardiovascular and cause-specific SD in screened athletes and unscreened non-athletes of the same age range over a 26-year period.

Results: During the study period, 55 sudden cardiovascular deaths occurred in screened athletes (19 deaths/100 000 person-years) and 265 SDs in unscreened non-athletes (0.79 death/100 000 person-years). The annual incidence of sudden cardiovascular death in athletes decreased by 89% (from 3.6/100 000 person-years in 1979–1980 to 0.4/100 000 person-years in 2003–2004; for trend P = 0.001), whereas the incidence of SD among the unscreened non-athletic population did not change significantly.

During the study period, 879 athletes (2.0%) were disqualified from the competition due to cardiovascular causes. The proportion of athletes who were disqualified for cardiomyopathies increased from 20 (4.4%) of 455 in the early screening period to 40 (9.4%) of 424 in the late screening period (P = 0.005).

Aim: To determine if pre-participation screening of athletes with a strategy including resting and exercise ECG reduces their risk for SD.

Study type: Retrospective, comparative study (before and after mandated screening in 1997).

Number of patients: 24

Results: There were 24 documented events of SD or cardiac arrest events among competitive athletes during the years 1985–2009. 11 occurred before the 1997 legislation and 13 occurred after it. The average yearly incidence of SD or cardiac arrest events was 2.6 events per 100 000 athlete years. The respective average yearly incidence during the decade before and the decade after the 1997 legislation was 2.5 and 2.6 events per 100 000 person years, respectively (P = 0.88).

Aim: To compare the performance of pre-participation screening limited to medical history and physical examination with a strategy that integrates these with ECG.

Study type: Cross-sectional comparison of screening strategies.

Number of patients: 510 collegiate athletes who received cardiovascular screening before athletic participation.

Study endpoint: Cardiac abnormality on transthoracic echocardiogram.

Inclusion: Collegiate athletes who received cardiovascular screening before athletic participation.

Exclusion: NA.

Results: Electrocardiography detected five additional athletes with cardiac abnormalities compared with history and examination alone in 11 of 510 collegiate athletes who received cardiovascular screening before athletic participation (sensitivity, 45.5% [95% CI 16.8–76.2%]; specificity, 94.4% [CI 92.0–96.2%]).
<table>
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<tr>
<th>Number</th>
<th>Title</th>
<th>Study type</th>
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<th>Inclusion</th>
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<tr>
<td>1136</td>
<td>Rizzo M, et al.</td>
<td>Multicentre, prospective</td>
<td>To evaluate which VA characteristics predicted CMR abnormalities. Study type: Multicentre, prospective.</td>
<td>Competitive athletes with &gt;100 PVCs/24h or ≥1 repetitive VA (couplets, triplets, or NSVT) on 12-lead 24-h ambulatory ECG monitoring and negative family history, ECG, and echocardiogram.</td>
<td>NA.</td>
<td>LV LGE was documented by CMR in 28 (11%) athletes, mostly (n = 25) with a subepicardial/midmyocardial stria pattern. On 24-h ECG monitoring, PVCs with multiple morphologies or with right bundle branch block and intermediate/superior axis configuration were documented in 25 (89%) athletes with LGE vs. 58 (26%) without LGE (P &lt; 0.001). More than 3300 PVCs were recorded in four (14%) athletes with positive CMR vs. 117 (53%) without positive CMR (P &lt; 0.0001). At exercise testing, NSVT occurred at peak of exercise in eight (29%) athletes with LGE (polymorphic in 6/8, 75%) vs. 17 athletes (8%) without LGE (P &lt; 0.0001). At multivariable analysis, all three parameters independently correlated with CMR abnormalities.</td>
<td>In athletes with apparently idiopathic VA, simple characteristics such as number and morphology of PVCs on 12-lead 24-h ambulatory ECG monitoring and response to exercise testing predicted the presence of concealed myocardial abnormalities on CMR. These findings may help cost-effective CMR prescription.</td>
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<tr>
<td>1138</td>
<td>Crescenzi C, et al.</td>
<td>Single-centre.</td>
<td>To evaluate the prevalence of structural cardiac lesions using echocardiography in apparently healthy boys referred for pre-participation screening. Study type: Single-centre.</td>
<td>Men soccer players referred to pre-participation screening. Study type: Single-centre.</td>
<td>Number of patients: 3100.</td>
<td>A total of 132 cases were identified during the 2-year study period (mean patient age, 16 years; age range, 11–27 years; 84% men; 51% White non-Hispanic/Latino, 30% black/African American, and 11% White Hispanic/Latino). High school athletes accounted for 78 (59%) cases, with 28 (21%) in middle school and 15 (11%) in college athletes. Overall survival was 48% (95% CI 40–57%); 64 survivors, 68 deaths. Survival was similar in men vs. women athletes but higher in White non-Hispanic/Latino (40/67; 60%) vs. black/African American (13/39; 33%) athletes (difference, 27%; 95% CI 7–45%; P = 0.008) and White non-Hispanic/Latino vs. all minority (40/67; 60%) athletes (difference, 29%; 95% CI 13–46%; P = 0.001). Basketball accounted for 30% of cases, followed by football (25%), track/cross-country (12%), and soccer (11%). The majority (93%) of cases were witnessed. If a certified athletic trainer was on-site and involved in the resuscitation, 83% of athletes survived. If an on-site AED was used in the resuscitation, 89% of athletes survived.</td>
<td>Structural cardiac disease diagnosed by echocardiography in asymptomatic young men soccer players: implications for pre-participation screening. Study type: Single-centre.</td>
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<tr>
<td>1140</td>
<td>Drezner J, et al.</td>
<td>Prospective, active surveillance study. Through a systematic search of traditional and social media sources, direct reporting to the National Center for Catastrophic Sports Injury Research, searching of the National Collegiate Athletic Association Resolutions List, regular communication with national and state high school athletic associations, and review of cases in the Parent Heart Watch database. Study type: Prospective, active surveillance study.</td>
<td>To evaluate the prevalence of structural cardiac lesions using echocardiography in apparently healthy boys referred for pre-participation screening.</td>
<td>Number of patients: 132 exercise-related SCA in competitive young athletes. Study type: Prospective, active surveillance study.</td>
<td>Number of patients: 132. Exercise-related SCA in competitive young athletes. Study type: Prospective, active surveillance study.</td>
<td>A total of 132 cases were identified during the 2-year study period (mean patient age, 16 years; age range, 11–27 years; 84% men; 51% White non-Hispanic/Latino, 30% black/African American, and 11% White Hispanic/Latino). High school athletes accounted for 78 (59%) cases, with 28 (21%) in middle school and 15 (11%) in college athletes. Overall survival was 48% (95% CI 40–57%); 64 survivors, 68 deaths. Survival was similar in men vs. women athletes but higher in White non-Hispanic/Latino (40/67; 60%) vs. black/African American (13/39; 33%) athletes (difference, 27%; 95% CI 7–45%; P = 0.008) and White non-Hispanic/Latino vs. all minority (40/67; 60%) athletes (difference, 29%; 95% CI 13–46%; P = 0.001). Basketball accounted for 30% of cases, followed by football (25%), track/cross-country (12%), and soccer (11%). The majority (93%) of cases were witnessed. If a certified athletic trainer was on-site and involved in the resuscitation, 83% of athletes survived. If an on-site AED was used in the resuscitation, 89% of athletes survived.</td>
<td>Survival after exercise-related sudden cardiac arrest in young athletes: can we do better? Study type: Prospective, active surveillance study. Through a systematic search of traditional and social media sources, direct reporting to the National Center for Catastrophic Sports Injury Research, searching of the National Collegiate Athletic Association Resolutions List, regular communication with national and state high school athletic associations, and review of cases in the Parent Heart Watch database. Study type: Prospective, active surveillance study.</td>
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Conclusions: ECG radiographic screening in National Collegiate Athletic Association athletes has a low false-positive rate and provides superior accuracy compared with a standardized history and PE to detect athletes with potentially dangerous cardiovascular conditions.

Results: 192 athletes (3.7%). 13 athletes (0.25%) were identified with serious cardiac conditions including HCM (1), large atrial septal defect with RV dilation (1), and ventricular pre-excitation (11). The false-positive rate for history was 33.3%, PE 2.0%, and ECG 3.4%. The sensitivity/specificity/positive predictive value for history was 15.4%/66.9%/0.1%, PE 77%/98%/0.9%, and ECG 100%/96.6%/6.8%.

Exclusion: Athletes screened from 1 of 35 National Collegiate Athletic Association institutions.

Aim: To discover the most efficient screening protocol. Study type: Prospective, multicentre trial. Number of patients: 5258 athletes from 17 intercollegiate sports.

Inclusion: Athletes screened from 1 of 35 National Collegiate Athletic Association institutions. Exclusion: NA.

Results: At least one positive cardiac symptom or family history response was reported by 1750 athletes (33.3%). PE was abnormal in 108 athletes (2.1%), and ECG abnormalities were present in 192 athletes (3.7%). 13 athletes (0.23%) were identified with serious cardiac conditions including HCM (1), large atrial septal defect with RV dilation (1), and ventricular pre-excitation (11). The false-positive rate for history was 33.3%, PE 2.0%, and ECG 3.4%. The sensitivity/specificity/positive predictive value for history was 15.4%/66.9%/0.1%, PE 77%/98%/0.9%, and ECG 100%/96.6%/6.8%.

Conclusions: Coronary artery calcium scoring results in a high reclassification rate in the intermediate-risk cohort, demonstrating the benefit of imaging of subclinical coronary atherosclerosis. Our study supports its application, especially in carefully selected individuals with intermediate risk.

Aim: To determine net reclassification improvement (NRI) and improved risk prediction based on coronary artery calcium scoring in comparison with traditional risk factors. Study type: Registry. Number of patients: 4129.

Inclusion: 4129 subjects from the HNR (Heinicke-Nordorf Registry) study (age 45–75 years, 53% women). Exclusion: NA.

Results: After 5 years of follow-up, 94 coronary deaths and non-fatal MIs occurred (cumulative risk 2.3%; 95% CI 1.8–2.8%). Redefining intermediate (defined as 10–20% and 6–20%) risk subjects with coronary artery calcification ≤100 to the low-risk category and with coronary artery calcification >400 to the high-risk category yielded an NRI of 21.7% (P = 0.0003) and 30.6% (P < 0.0001) for the FRS, respectively. Integrated discrimination improvement using FRS variables and coronary artery calcification was 1.52% (P < 0.0001). Adding coronary artery calcification scores to the FRS and National Cholesterol Education Panel ATP III categories improved the area under the curve from 0.681 to 0.749 (P = 0.0001), respectively.

Aim: We compared improvement in prediction of incident cardiovascular disease of these six risk markers within intermediate-risk participants (FRS 5–20%) in the Multi-Ethnic Study of Atherosclerosis (MESA). Study type: Registry. Number of patients: 6814.

Results: After 7.6-year median follow-up (IQR 7.3–7.8), 94 coronary heart disease and 123 cardiovascular events occurred. Coronary artery calcium, ankle-brachial index, high-sensitivity CRP, and family history were independently associated with incident coronary heart disease in multivariable analyses (HR 2.60 [95% CI 1.94–3.42], HR 0.95 [95% CI 0.78–1.14], HR 1.28 [95% CI 1.00–1.64], and HR 2.18 [95% CI 1.38–3.42], respectively). Carotid intima-media thickness and brachial flow-mediated dilation were not associated with incident cardiovascular disease in multivariable analyses (HR 1.17 [95% CI 0.95–1.45] and HR 0.95 [95% CI 0.78–1.14], respectively). Although addition of the markers individually to the FRS plus race/ethnicity improved area under the curve, coronary artery calcium afforded the highest increment (0.623 vs. 0.874); while brachial flow-mediated dilation had the least (0.623 vs. 0.639). For incident coronary heart disease, the net reclassification improvement with coronary artery calcium was 0.699, brachial flow-mediated dilation was 0.024, ankle-brachial index was 0.086, carotid intima-media thickness was 0.102, family history was 0.160 and high-sensitivity CRP was 0.079. Similar results were obtained for incident cardiovascular disease.

Conclusions: Coronary artery calcium, ankle-brachial index, high-sensitivity CRP, and family history were independent predictors of incident coronary heart disease/cardiovascular disease in intermediate-risk individuals. Coronary artery calcium provided superior discrimination and risk reclassification compared with other risk markers.
5.4. Prevention of sudden cardiac death in the elderly

### Table of Evidence 43 for Table of Recommendations for implantable cardioverter defibrillator implantation in the elderly

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<th>Reference, PMID, and year of publication</th>
<th>Aim of the study</th>
<th>Inclusion criteria (patients)</th>
<th>Summary of main results</th>
<th>Other findings</th>
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<td>650</td>
<td>Elming MB, et al. 2017</td>
<td>Aim: To assess relationship between ICD implantation and all-cause mortality and SCD by age. Study type: Prospective subgroup analysis of a large randomized controlled trial (DANISH).</td>
<td>Inclusion: Patients with documented non-ischemic systolic heart failure with LVEF ≤ 35% and increased levels (&gt;200 pg/mL) of NT-proBNP. Exclusion: Permanent atrial fibrillation, a resting heart rate &gt;100 b.p.m., end-stage renal failure (dialysis).</td>
<td>Results: Median follow-up of 67.6 months. A linearly decreasing relationship between ICD and mortality with age (HR 1.03; 95% CI 1.003–1.06; P = 0.03). An association between reduced all-cause mortality and ICD in patients ≤70 years (HR 0.70; 95% CI 0.51–0.96; P = 0.03) but not in patients &gt;70 years (HR 1.05; 95% CI 0.68–1.62; P = 0.84). SCD rate: Patients ≤70 years: 1.8% (95% CI 1.3–2.3). Patients &gt;70 years: 16.9% (95% CI 0.8–3.2) events per 100 patient-years (P = 0.07). Non-SCD rate: Patients ≤70 years: 2.7% (95% CI 2.1–3.5). Patients &gt;70 years: 5.4% (95% CI 3.7–7.8) (P = 0.01).</td>
<td>Other findings: The association between the ICD and survival decreased linearly with increasing age. An age cut-off for ICD implantation at ≤70 years yielded the highest survival for the population as a whole. Limitations: The bulk of patients were between 40 and 80 years old therefore, conclusions outside this age span are based on extrapolations. It cannot be concluded that age ≤70 years is significantly superior to any other age cut-off (due to wide confidence limits of the estimate). Validation: NA.</td>
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<td>1153</td>
<td>Exposito V, et al. 2016</td>
<td>Aim: To describe the efficacy and safety of ICD therapy in a large cohort of elderly patients. Study type: Retrospective multicentre study (13 Spanish hospitals).</td>
<td>Inclusion: ICD/CRT-D implantation for primary prevention of SCD for CAD and NICM. Exclusion: Patients with PCI or CABG within 3 months of ICD implantation, MI within 40 days of ICD implantation, lacking data on vital status during follow-up, and patients with history of HOCM, channelopathies, ARVC, and congenital heart disease.</td>
<td>Results: Mean follow-up of 1044 ± 3.3 months. Death rate: 12.4 vs. 24.4% younger population vs. ≥75 years. An increased probability of death with increasing age, with rates of 6%, 10%, 17%, and 20% vs. 17%, 24%, 28%, and 6% at 12, 24, 48, and 60 months of follow-up in the respective age categories (P &lt; 0.001). Appropriate therapy: No significant difference between the younger population (23%) and the elderly (15.4%). Inappropriate therapy: No significant difference between the younger population (9%) and the elderly (4%).</td>
<td>Other findings: The average time to death was 1068 ± 3.4 months in the younger group, and 70 ± 9.1 in the elderly. Death was due to cardiovascular causes in 70 younger patients (69%) and in 33 elderly (14.6%) (P &lt; 0.05). The main reason for inappropriate therapy was atrial arrhythmias (70%); 62.5% in the elderly, 83.5% in the younger; P = 0.001).</td>
<td>Conclusions: Nearly 15% of ICD implantations in a real-world scenario are in patients aged ≥75 years. Elderly patients have a higher risk profile, with higher SHOCKED score, more previous hospitalizations due to heart failure in the past, more severe current congestive heart failure, and more intraventricular conduction defects. There is a major increase in mortality risk due to non-cardiovascular causes with increasing age. The rate of inappropriate therapy is similar or even lower than the one in younger patients, despite higher prevalence of AF. Compared with younger patients, there is no increase in implant complication rates in the elderly. Limitations: Retrospective design, so there is a risk for bias and confounding. Programming was left to the discretion of the enrolling centre, with consequent...</td>
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</table>
Aim: To evaluate mortality, appropriate ICD therapy rates, and survival gain in an elderly population after risk stratification according to the Charlson Comorbidity Index (CCI).

Study type: Monocentric retrospective study.

Number of patients: 363 (121 elderly patients matched with 242 controls).

Enrolment period: 2009–2017

Study endpoints:
(1) Death from any cause.
(2) Occurrence of appropriate ICD therapy.

Inclusion:
- Patient ≥ 75 years at the time of implantation;
- De novo primary or secondary prevention ICD implantation (including upgrading from pacemaker to defibrillator therapy).

Exclusion: NA.

Results:
- Median follow-up was 4.6 (2.8–6.6) years.
- Overall survival was 78%, 57%, and 29% (P = 0.002) in the elderly with a CCI score of 0–1, 2–3, and ≥4, respectively, and 72% in controls.
- ICD appropriate therapy no significant difference between the three subgroups (34.2%, 39.7%, and 22.8% score of 0–1, 2–3, and ≥4, respectively; P = 0.45).

Other findings:
- Median potential survival gain after an appropriate therapy was 5.5, 4.7, and 1.4 years, with a CCI score of 0–1, 2–3, and ≥4, respectively (P = 0.01).

Conclusions:
- Elderly patients with CCI score ≥4 had the lowest survival after ICD implantation and little survival gain in case of appropriate defibrillator therapy. More than age alone, the burden of comorbidities assessed by the CCI could be helpful to better select elderly patients for ICD implantation.

Limitations:
- Monocentric, retrospective design, with a limited sample size.
- ACE inhibitors and eplerenone therapy were not collected and may have impacted the results.
- Presumably not all patients ≥75 years with indications for ICD implantation were implanted, which may constitute a bias.
6. References


