Clinical value of cardiovascular magnetic resonance in patients with MR-conditional pacemakers


NIHR Cardiovascular Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust and Imperial College, Sydney Street, London SW3 6NP, UK

Received 25 May 2015; accepted after revision 22 October 2015; online publish-ahead-of-print 20 November 2015

Aims

Magnetic resonance (MR) conditional pacemakers are increasingly implanted into patients who may need cardiovascular MR (CMR) subsequent to device implantation. We assessed the added value of CMR for diagnosis and management in this population.

Methods and results

CMR and pacing data from consecutive patients with MR conditional pacemakers were retrospectively reviewed. Images were acquired at 1.5 T (Siemens Magnetom Avanto). The indication for CMR and any resulting change in management was recorded. The quality of CMR was rated by an observer blinded to clinical details, and data on pacemaker and lead parameters were collected pre- and post-CMR. Seventy-two CMR scans on 69 patients performed between 2011 and 2015 were assessed. All scans were completed successfully with no significant change in lead thresholds or pacing parameters. Steady-state free precession (SSFP) cine imaging resulted in a greater frequency of non-diagnostic imaging (22 vs. 1%, P < 0.01) compared with gradient echo sequences (GRE). Right-sided pacemakers were associated with less artefact than left-sided pacemakers. Late gadolinium enhancement imaging was performed in 59 scans with only 2% of segments rated of non-diagnostic quality. The CMR data resulted in a new diagnosis in 27 (38%) of examinations; clinical management was changed in a further 18 (25%).

Conclusions

CMR in patients with MR conditional pacemakers provided diagnostic or management-changing information in the majority (63%) of our cohort. The use of gradient echo cine sequences can reduce rates of non-diagnostic imaging. Right-sided device implantation may be considered in patients likely to require CMR examination.

Keywords

cardiovascular magnetic resonance • CMR • pacemaker • conditional • PPM

Introduction

Cardiovascular magnetic resonance (CMR) allows accurate volumetric assessment and tissue characterization, and indications for CMR have steadily increased over the past decade.1,2 Patients with conventional pacemakers have generally been excluded from CMR due to safety concerns; however, over half of these patients have clinical indications for magnetic resonance imaging.3

Potential hazards of CMR in a patient with a conventional pacemaker include induction of currents in the pacing leads causing local heating; changes in device programming; and pacing-induced arrhythmias.4,5 MR conditional pacemakers are designed to minimize these risks, with a reduction in ferromagnetic material and the use of a Hall rather than a reed switch to reduce the potential of pacing inhibition.6 However, MR may currently only be performed at 1.5 T or lower field strength, and the devices remain ‘conditional’ rather than MR-safe, indicating that the device must be used within specified conditions as laid down by the manufacturer and approved by the regulatory authorities.7

CMR requires both the device and leads to be in the centre of the magnet with the greatest radiofrequency (RF) deposition in the region where the pacemaker is situated. Patients who are pacing dependent are a particular challenge in the event of device failure as immediate evacuation to a safe location for resuscitation would be required. Additional challenges in image interpretation result from artefact from the generator and leads and limitations on total RF energy dosage.

* Corresponding author. Tel: +44 0207 352 8121; Fax: +44 020 7351 8816. E-mail: craphael@rbht.nhs.uk; claireraphael@gmail.com

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: journals.permissions@oup.com.
Safe scanning under carefully supervised conditions has been demonstrated in both MR conditional and conventional pacemakers. However, many centres still do not perform MR in pacemaker patients due to safety concerns. The American Heart Association (AHA) and European Society of Cardiology (ESC) guidance remain cautious regarding CMR in patients with pacemakers, suggesting other imaging modalities should be used if they can answer the clinical question in preference to CMR. In particular, the AHA recommends that pacemaker-dependent patients should only be scanned with a strong clinical indication and where the benefits clearly outweigh the potential risks of the procedure.

While previous work has largely focused on safety, the clinical impact and utility of CMR in patients with pacemakers have received relatively little attention. We therefore assessed the added value of CMR in a cohort of patients with MR conditional pacemakers at a single, tertiary institution.

**Methods**

Consecutive patients referred for CMR at our institution with an MR conditional pacemaker had a CMR scan according to an agreed protocol between 2011 and 2015 (Figure 1).

**Assessment prior to CMR**

Patients were first reviewed by a clinician to assess for the presence of a bonefide indication for CMR. All patients underwent a chest radiograph to identify any abandoned leads or additional devices. The device and leads were confirmed to be CMR conditional on both chest radiograph and pacing assessment. The underlying rhythm, lead thresholds, sensitivity, and impedance were recorded and the device programmed to the manufacturer CMR conditional mode with an appropriate pacing mode; DOO/VOO for pacemaker-dependent patients and VVI/DDI for non-pacemaker-dependent patients.

Patients with additional non-conditional leads, any suspicion of lead fracture, or a break in insulation (impedance < 200 Ω or >1000Ω) were excluded. Devices implanted < 6 weeks prior to CMR were not excluded if the indication was felt to be appropriate and urgent.

**CMR protocol**

CMR was acquired at 1.5 T scanners with an eight-channel, phased-array receiver coil (Siemens Magnetom Avanto). The patient had continuous ECG monitoring with regular assessment of symptoms and haemodynamic status. CMR was protocolled for each patient to ensure that the most clinically important sequences were performed first. Scans were supervised by a cardiologist.

Typically, free breathing multiple slice half-Fourier spin echo (HASTE) sequences were used for anatomical imaging. Patients referred for assessment of aortic dimensions had both black-blood and bright-blood sequences performed.

Cine imaging was initially performed using a retrospectively gated balanced steady-state free precession (SSFP) sequence. If the pacemaker produced significant artefact, a gradient echo sequence (GRE) was used instead. Breath-hold cine images were obtained in three long-axis planes, followed by a contiguous stack of short-axis slices through the ventricles. T2-weighed (STIR) imaging was performed if cardiac inflammation was suspected.

Late enhancement images were acquired 10–20 min after injection of Gadovist (Bayer-Schering, Berlin, Germany, 0.1 mmol/kg) with an inversion recovery-prepared segmented turbo fast, low-angle shot sequence. Inversion times were optimized to null normal myocardium.

**Assessment of image quality**

The quality of cardiac cine, gadolinium, and STIR imaging was rated by two observers experienced in CMR and blinded to clinical details. Grading was performed based on the level of artefact produced by either the leads or the pacing box. The long-axis images were divided into 6 segments and the short-axis images into 16 segments according to the AHA classification system. Each segment was graded using a point scale from 5 (excellent image quality) to 1 (non-diagnostic).

Grade 5 indicated very good image quality with no artefacts affecting cardiac anatomy; 4—good image quality with minor artefact affecting cardiac anatomy but with no impact on diagnostic quality; 3—moderate effect of artefacts on cardiac anatomy but no impact on diagnostic quality; 2—artefact moderately affecting cardiac anatomy causing some impact on diagnostic quality; and 1—poor image quality with significant impact of artefact on cardiac anatomy, i.e. non-diagnostic imaging (Figure 2).

The ventricular blood to myocardium contrast ratio (BMCR) and contrast to noise ratio (CNR) were calculated. A region of interest was drawn in the anterior and inferior walls at mid-ventricular level in the two-chamber view and in the centre of the left ventricle at end-diastole. For inversion recovery images, the region of interest was drawn in the anterior wall in a region of healthy myocardium (no fibrosis).

$$BCMR = \frac{S_{\text{blood}}}{S_{\text{myocardium}}}$$

$$CNR = \frac{2 \times (S_{\text{blood}} - S_{\text{myocardium}})}{SD_{\text{blood}} - SD_{\text{myocardium}}}$$
Assessment of impact of CMR on diagnosis and management

The indication for referral for CMR was recorded for all patients. The additional utility of the CMR scan in diagnosis or management of the patient was assessed by two independent consultants through examination of the patients notes prior to CMR and following CMR examination.

CMR was considered to result in a new diagnosis if a diagnosis not previously suspected was made by CMR, or if a diagnosis that was suspected through clinical history, examination, and cardiac investigations was confirmed. CMR was considered to lead to a change in management if it resulted in referral for cardiac surgery, revascularization, a change in medication, or if it obviated the need for invasive coronary assessment. Conditions with serial CMR follow-up, e.g. aortic dimensions were considered to change management providing the CMR scan was of diagnostic quality, as stable vessel dimensions allowed less frequent follow-up visits, whereas increasing aortic dimensions required closer follow up or consideration for surgery.

Statistical analysis

Statistical analysis was performed using SPSS (version 17.0, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD) for normally distributed data and as medians with interquartile ranges for non-parametric data. Differences between
parametric continuous variables were assessed using Student’s t-test. Categorical data were presented as frequencies and percentages. Differences between categorical variables were assessed using the χ² test. All tests were two tailed, and P-value of < 0.05 was considered significant. The agreement between operators for scoring of image quality was assessed using a weighted Kappa test.

Results

 Seventy-two CMR scans of 69 serial patients with MR conditional devices were performed. One patient who was unable to undergo CMR due to severe kyphoscoliosis was not included in the study. Three patients had repeat imaging for serial follow-up of aortic dimensions (2) and cardiac sarcoidosis (1). All patients gave written informed consent. Sixty-four patients had a left-sided and 5 a right-sided pectoral device. One patient had a pacemaker inserted 3 weeks prior to CMR, while all other patients had a period of at least 6 weeks between pacemaker insertion and CMR. The most common indication for pacing was complete heart block, and 30% of patients were pacing dependent at the time of CMR examination (Table 1).

Studies were safely performed in all cases with a mean examination duration of 45 ± 10 min. There was no electrical pacemaker reset, reports of pain or heating over the device site, or symptoms that might indicate arrhythmia. One patient went into atrial fibrillation following adenosine was admitted for observation and cardioverted spontaneously 3 h after the CMR. There were no other complications.

There was no significant change in lead impedance or sensing thresholds between the pre- and post-procedure checks. There was also no evidence of battery voltage depletion following CMR (Table 2).

Assessment of impact of CMR on diagnosis and management

Indications for CMR and the impact on clinical management are summarized in Table 3. Twenty-seven (38%) of the scans resulted in a new diagnosis or confirmation of a suspected diagnosis. A further 18 CMR scans (25%) resulted in a change in clinical management.

For patients with suspected cardiomyopathy, the most common diagnosis was myocarditis (Figure 4, bottom panel). Fifteen percent of patients referred had pulmonary sarcoidosis with either known (8) or suspected (2) cardiac sarcoid, on the basis of ECG findings and new conduction abnormalities. Of the six patients referred for serial assessment of aortic dimensions, three had stable aortic dimensions, and two had increased dimensions meeting criteria for aortic surgery.

Assessment of image quality

Twenty-nine patients had cine imaging of diagnostic quality with SSFP sequences alone, 9 had GRE cine imaging alone, and 32 patients required both SSFP and GRE cine imaging due to the presence of artefact on SSFP. Overall, the image quality was rated excellent or good (score 5 or 4) in 1596/1848 (86%) of segments with a mean score of 4.2 ± 0.8 using the 5-point scoring system.

Non-diagnostic imaging was more common using SSFP sequences (246/2378 segments) compared with GRE sequences (10/1148 segments, P < 0.001); however, when SSFP sequences were not significantly affected by artefact (27/66 patients), image quality assessed using the 5-point system was significantly better compared with GRE for both the LV (4.6 ± 0.88 vs. 4.2 ± 0.98, P < 0.001) and the RV (4.1 ± 0.9 vs. 3.6 ± 1.6, P = 0.009). Overall, artefact resulting in non-diagnostic imaging was more common in anterior segments compared with non-anterior segments (28/648 vs. 2/1378 segments, P < 0.001, Figure 3).

Gadolinium imaging was performed in 59 (82%) of examinations and was of significantly better quality than cine imaging (mean score 4.5 ± 0.8, P < 0.0001) with 1442/1568 (92%) of segments rated excellent or good quality. 30/1568 (2%) of segments were...

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient and device characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age/years</td>
<td>51 ± 16</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>41 (59)</td>
</tr>
<tr>
<td>% pacing dependent</td>
<td>21 (30)</td>
</tr>
<tr>
<td>Time since device implantation/years</td>
<td>0.88 ± 0.90</td>
</tr>
<tr>
<td>Indication for device</td>
<td>Complete heart block 31 (45%) 2nd degree AV block 15 (22%) Sinus node dysfunction 13 (19%) Syncope with evidence of conduction disease 7 (11%) Atrial fibrillation and bradycardia 3 (5%)</td>
</tr>
<tr>
<td>Device characteristics</td>
<td></td>
</tr>
<tr>
<td>Generator</td>
<td>Medtronic Ensura 25 (36%) Medtronic Advanta Sure Scan 23 (33%) St Jude/Accent 13 (19%) Boston Guidant Advantio MRI 8 (12%)</td>
</tr>
<tr>
<td>Leads</td>
<td>Medtronic Capsure 39 (57%) Medtronic Other (CMR conditional) 10 (14%) St Jude Tendril 10 (14%) St Jude Other (CMR conditional) 3 (4%) Boston Guidant Ingevity MRI 7 (10%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Pacing parameters prior to and immediately after CMR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-CMR</td>
</tr>
<tr>
<td>A lead threshold/mV</td>
<td>0.73 ± 0.57</td>
</tr>
<tr>
<td>A lead sensing/V</td>
<td>3.6 ± 1.9</td>
</tr>
<tr>
<td>A lead Impedance/Ω</td>
<td>446 ± 121</td>
</tr>
<tr>
<td>V lead threshold at pulse width 0.4 ms/mV</td>
<td>0.67 ± 0.23 mV</td>
</tr>
<tr>
<td>V lead sensing/V</td>
<td>10.4 ± 6.0</td>
</tr>
<tr>
<td>V lead Impedance/Ω</td>
<td>524 ± 85</td>
</tr>
<tr>
<td>Battery longevity/V</td>
<td>3.0 ± 0.06</td>
</tr>
</tbody>
</table>
### Table 3  Indications for CMR examination and impact on subsequent management

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>New diagnosis</th>
<th>Change in management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocarditis</td>
<td>7</td>
<td>5 (7%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Suspected cardiomyopathy</td>
<td>5</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac sarcoid</td>
<td>11</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Investigation of complete heart block</td>
<td>13</td>
<td>3 (4%)</td>
<td>8 (11%)*</td>
</tr>
<tr>
<td>Investigation of syncope</td>
<td>7</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Aortic dimensions</td>
<td>6</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Aetiology of heart failure</td>
<td>5</td>
<td>4 (6%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Assessment of valvular disease</td>
<td>2</td>
<td>1 (1%)</td>
<td></td>
</tr>
<tr>
<td>Assessment of LV function</td>
<td>4</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assessment for ischaemia</td>
<td>4</td>
<td>1 (2%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Haemachromatosis</td>
<td>1</td>
<td></td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Suspected cardiac amyloid</td>
<td>1</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

| Totals                                 | 72  | 27 (38%)      | 18 (25%)             |

*CMR-guided treatment decisions with steroid and steroid sparing agents.
*increase in aortic dimensions meeting criteria for surgery.

### Figure 3  Image quality per segment for long- and short-axis cine imaging using SSFP (40%) and GRE sequences (60%). Black segments have an image quality of 4.1 or greater and grey segments have an image quality of 3.1–4.0. The mean score for image quality is numerically displayed per segment. Anterior and apical segments were more affected by artefact than basal and non-anterior segments, although overall the image quality remained of good quality.
non-diagnostic. STIR imaging was performed in 25 patients and was of similar quality to cine imaging (mean score for image quality 4.4 ± 0.9, P = 0.08). There were no non-diagnostic segments using STIR sequences.

Although the number of right-sided pectoral devices was small, they were associated with significantly better cine imaging than left-sided devices (mean score 4.5 ± 0.8 vs. 4.3 ± 1.0, P = 0.03) and no non-diagnostic segments. There was no significant difference in image quality for gadolinium imaging (4.5 ± 0.6 vs. 4.5 ± 0.8, P = 0.57).

The BCMR was higher for SSFP compared with GRE in both the anterior (3.5 ± 1.2 vs. 2.2 ± 1.4, P = 0.001) and inferior (3.5 ± 0.8 vs. 1.9 ± 0.3, P < 0.001) walls with a similar CNR. BCMR was highest for IR sequences (10.2 ± 6.5) and CNR was similar. The linear weighted Kappa between operators for assessment of image quality was 0.43 (95% confidence intervals 0.4–0.44), indicating a moderate level of agreement.

**Discussion**

As indications for CMR increase, the number of studies performed in patients with MR conditional pacemakers will also increase. Limited data exist regarding the clinical utility of these examinations. In our cohort, the majority of CMR examinations resulted in a new diagnosis (38%) or a clinically significant change in management (25%). These data indicate that CMR is valuable in well-selected patients with MR conditional pacemakers and also that CMR is safe and well tolerated. This single-centre experience adds substantially to the limited existing reports on CMR in MR conditional pacemaker patients.

While we and others9,16,17 have reported no significant adverse events while following the recommended protocol for CMR in patients with MR conditional devices, experience of performing CMR in these patients is still limited.10,16 The ESC and ACR guidelines suggest that MR should only be performed after assessment of the risks and potential benefits of examination.12,18 In our series, CMR usually led to a change in management, a new diagnosis or allowed rule out of clinically important conditions. Conditions such as cardiac sarcoid and myocarditis may be suspected on other non-invasive imaging such as echocardiography. Gadolinium imaging allowed confirmation of these diagnoses and therefore instigation of appropriate treatment.

While some questions may be appropriately answered with alternative modalities such as transoesophageal echocardiography, stress echocardiography, or computerized tomography (CT), for tissue characterization, CMR remains the gold standard. Reflecting the tertiary nature of our institution, 15% of patients referred for CMR had cardiac sarcoid (Figure 4, top panel), with implantation of a CMR-conditional device in anticipation of the need for CMR. CMR allows imaging of oedema as well as fibrosis and aids decisions
regarding use of steroid and steroid sparing agents and subsequent assessment of treatment response.

For cardiomyopathy, CMR offers additional diagnostic\textsuperscript{19,20} and prognostic\textsuperscript{21,22} data with assessment of fibrosis and disease severity. Aetiology of syncope or conduction disease was another common indication for CMR in our cohort. Of the 20 patients referred on this basis, a new diagnosis was made in 20\%. While the majority of this cohort had a normal CMR, this was an important negative finding as coupled with appropriate serology (e.g. for autoimmune and Lyme disease) it may allow discharge of the patient from routine follow-up by a physician following pacemaker implantation.

CMR allows reproducible measurement of aortic dimensions without ionising radiation\textsuperscript{23} (\textbf{Figure 5}). Although the protocol for patient assessment and scanning is more time and resource consuming than CT, for younger patients who are likely to require lifelong aortic surveillance, the lack of ionising radiation is attractive and our centre routinely implants MR conditional devices in such patients.

\textbf{CMR protocol for safe scanning in pacemaker patients}

Each CMR scan was protocollled to ensure that the most clinically important sequences were acquired at the beginning of the study in case of a need to prematurely terminate the examination. Increased monitoring is required compared with routine CMR examination. We found no significant change in pacing parameters between the pre- and post-CMR assessment. Other groups have shown small, statistically but not clinically significant changes in lead parameters following CMR in patients with MR conditional devices.\textsuperscript{24} In contrast to previous studies, we did not exclude patients with a device in situ for < 6 weeks if urgent CMR was required. For the one patient who was scanned in under 6 weeks, CMR was safely performed with no evidence of lead displacement or significant change in lead parameters. CMR of MR conditional devices scanned according to protocol appears to have a good safety protocol, and requirement for cardiologist supervision may be obviated with increased publication of safety data.

The pacing mode was determined following a pacemaker check with assessment of the underlying rhythm and indication for pacemaker. Patients who were pacemaker dependent were programmed to DOO or VOO modes, whereas non-pacemaker-dependent patients were programmed to VVI or DDI mode. This allowed minimization of pacing in patients who were not pacemaker dependent, which although generally well tolerated, may result in altered haemodynamic parameters and an atypical assessment of ventricular function.\textsuperscript{25}

\textbf{Image quality and sequence selection in CMR imaging of patients with CMR conditional pacemakers}

The quality of images varied considerably between patients (\textbf{Figure 2}). In keeping with previous work,\textsuperscript{26,27} SSFP sequences were more likely to result in non-diagnostic imaging than GRE sequences. While GRE sequences produce less RF heating, the BCMR was higher with SSFP, so we recommend a trial of SSFP initially with conversion to GRE if significant artefact occurs. Previous work by Sasaki, largely focusing on CMR artefacts from ICDs, suggested that inversion recovery sequences were particularly susceptible to artefact.\textsuperscript{26} However, in our series and in the 15 patients with pacemakers in their series, image quality was less affected by artefact in gadolinium imaging compared with cine imaging. Use of wideband CMR techniques may further improve LGE image quality in device patients.\textsuperscript{28,29}

Although absolute numbers were small, we demonstrated significantly less artefact with right-sided pectoral devices compared with left sided. Cardiologists may therefore consider right-sided implantation in patients likely to require future CMR examinations and

\textbf{Figure 5} Transverse (left) and sagittal (right) imaging of a Marfan patient with previous aortic valve and root replacement. The ascending aorta is severely dilated. Artefact from the left-sided pacemaker is indicated with an arrow.
unlikely to require upgrade to a complex device. Upgrade to a biventricular pacemaker is typically more technically challenging from a right-sided approach, due to unfavourable angles for both coronary sinus and left ventricular lead placement. Therefore, a left-sided approach may be more appropriate if device upgrade in the future is anticipated.

**Study limitations**

The referral patterns for our tertiary centre population may differ from other institutions. While no adverse events were detected in our series or others, data on MR conditional devices are still limited. We did not assess late changes in lead parameters; however, there were no reports of device-related complications in the 3–6 months following CMR examination. We did not compare CMR to alternative diagnostic modalities as CMR was considered the gold standard test in the majority of cases. Data were collected at 1.5 T and cannot be extrapolated to 3 T.

**Conclusion**

CMR in patients with MR conditional pacemakers frequently led to a new diagnosis or change in clinical management. Patients with pacemakers should be assessed on a risk/benefit basis before referral for CMR. CMR examination can be safely performed with a low rate of non-diagnostic imaging but requires closer monitoring and appropriate pacemaker checks.

**Conflict of interest:** D.J.P. is a consultant to Siemens Healthcare, and a Director and stockholder in Cardiovascular Imaging Solutions. No other authors have any relevant disclosures.

**Funding**

C.E.R. is supported by the British Heart Foundation. This work is supported by the NIHR Cardiovascular Biomedical Research Unit at the Royal Brompton Hospital

**References**

23. Burkhardt JD, Wilkoff BL. Interventional electrophysiology and cardiac resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association; Eur Heart J 2013;34:3281–329.