Clinical course and outcome of patients enrolled in US and non-US centres in MADIT-CRT

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Aims
We aimed to evaluate within the MADIT-CRT database whether different enrollment characteristics between US and non-US centres affected the clinical course of study patients.

Methods and results
We evaluated differences in baseline characteristics, procedure-associated complications, clinical as well as echocardiographic response to cardiac resynchronization therapy with a defibrillator (CRT-D), between patients enrolled in 87 US centres (n = 1271) and 23 non-US centres (n = 549) in MADIT-CRT. Non-US patients displayed significant differences in baseline characteristics from US patients, including a higher frequency of left bundle branch block, a more advanced heart failure (HF) functional class >3 months prior to enrolment, and larger baseline cardiac volumes. Procedure-related complications occurred at a significantly higher frequency among patients enrolled in non-US centres (17%) than among those enrolled in US centres (10%; P < 0.001). During follow-up, CRT-D was associated with 42% (P = 0.003) and 38% (P < 0.001) reductions in the risk of HF or death in the two respective groups (P for the difference = 0.80), and with similar reductions in cardiac volumes (all P > 0.10). Subgroup analysis showed a more pronounced effect of CRT-D among women in the US group, including a significant 71% (P = 0.02) reduction in the risk of death, whereas CRT-D therapy was associated with a significant clinical benefit in men only in the non-US group.

Conclusion
Patients enrolled in US and non-US centres in MADIT-CRT displayed significant differences in baseline clinical and echocardiographic characteristics and in the frequency of procedure-related complications, but experienced an overall similar clinical and echocardiographic response to CRT-D.

Keywords
Cardiac resynchronization therapy • Heart failure • Death • Complications

Introduction
Randomized clinical trials have shown significant morbidity and mortality benefits with cardiac resynchronization therapy with or without a defibrillator (CRT-D/CRT) in patients with advanced heart failure (HF), leading to a class I indication for implantation in both American and European guidelines.1,2 Subsequently, the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) was carried out to explore the possible clinical implication of prior observations, suggesting that CRT might delay disease progression in HF patients with less severe symptoms, supposedly via the left ventricular reverse remodelling process.3–6 The study showed a significant 34% reduction in the risk of HF or death with CRT-D as compared with ICD-only therapy during a mean follow-up of 2.4 years.7 The MADIT-CRT population comprised 1820 patients, of whom 1271 were enrolled in the USA (70%) and 549 outside the USA (30%). In the present study, we aimed to evaluate within the MADIT-CRT database whether clinical differences between
the US and non-US countries at the time of enrollment affected the clinical and echocardiographic outcome of the MADIT-CRT population.

Methods

MADIT-CRT

The design and primary results of MADIT-CRT were recently published. Briefly, the study patients were randomly assigned in a 3:2 ratio to either CRT-D or ICD-only. Patients of either sex aged at least 21 years were enrolled if they had ischaemic (NYHA class I or II) or non-ischaemic cardiomyopathy (NYHA class II only), sinus rhythm, a left ventricular ejection fraction (LVEF) of < 30%, and a QRS duration of > 130 ms. From 22 December 2004 to 23 April 2008, a total of 1820 patients were enrolled, 1271 in the USA and 549 outside the USA (non-US centres). After an average follow-up of 2.4 years, CRT-D was associated with a significant 34% (P < 0.001) reduction in the risk of the primary endpoint of the study, comprising death or a non-fatal HF event.

The present study comprises all 1820 MADIT-CRT participants who were followed up through 31 December 2009.

The protocol was approved by the institutional review board at each participating organization, and each patient provided written informed consent before enrollment.

Echocardiographic studies

Echocardiograms were obtained prior to device implantation (n = 1809), and at 1 year (n = 626 in the ICD-only group; n = 752 in the CRT-D group). Paired echocardiograms from baseline and at 12 months with the CRT-D device turned on were evaluated in 1372 patients.

Echocardiograms were sent to a core laboratory at Brigham and Women’s Hospital where they were screened for quality and for left ventricular, right ventricular, and left atrial measurements. Echocardiographic parameters were measured according to established American Society of Echocardiography protocols. Reproducibility of the primary volumetric measures was assessed by having the primary observer re-analyse 101 random studies. The coefficient of variation for end-diastolic volume, end-systolic volume, and ejection fraction were 5.2, 6.2, and 5.5%, respectively.

Definitions

Centre location

From the 110 participating hospital centres, 1271 patients were enrolled in the USA, 527 in Europe and Israel, and 22 in Canada. For the primary analyses in the present study, centre location was categorized as US centres [comprising all 87 enrolling centres in the USA (n = 1271)] and non-US centres [comprising the 21 European/Israel, and two Canadian enrolling centres (n = 549)]. It should be noted that the number US and non-US centres reported in the present study is different from the original publication (88 and 22, respectively) due to an error in the latter report. For sensitivity analyses that compared the outcome of patients enrolled in US vs. European/Israel centres, the 22 patients who were enrolled in Canada were omitted.

Procedure-related complications

Complications related to implantation were assessed from standardized detailed questionnaires. Complications were defined as procedure-related if they occurred within 90 days of implantation.

These events were further categorized by: (i) the type of device that was implanted (CRT-D or ICD-only) and (ii) the severity of complications, which was pre-specified as major or minor complications.

Echocardiographic response

The primary outcome for the assessment of echocardiographic response was defined as per cent reduction in chamber volumes (including left ventricular end-diastolic and -systolic volumes and left atrial volume) and percent increase in LVEF 1 year after enrollment compared with baseline values.

Clinical response

The primary outcome measure for the assessment of clinical response was defined as a first occurrence of a non-fatal HF event or death, whichever came first, during follow-up. The separate occurrences of non-fatal HF events and all-cause mortality were also assessed as secondary endpoints.

Statistical analysis

The chi-square test was used for the comparison of categorical variables, and the non-parametric Wilcoxon rank-sum test for continuous variables [assessed as mean (± SD) after identifying a normal distribution for each continuous measure]. Best subset logistic regression analysis was used to identify candidate variables (listed in Table 1) associated with risk for procedure-related complications. Kaplan–Meier estimates for HF or all-cause mortality in each treatment group, stratified according to centre location, were determined and statistically compared with the log-rank test. The Cox proportional-hazards regression model was used to evaluate the independent contribution of baseline clinical factors to the development of the endpoint. All models included the following pre-specified covariates: treatment arm, age > 65 years, gender, ischaemic status, QRS > 150 ms, blood urea nitrogen (BUN) > 25 mg/dL, LVEF < 25%, left bundle branch block (LBBB), the presence of advanced HF class (NYHA class III/IV) > 3 months prior to enrollment, the occurrence of procedure-related complications, low centre enrollment (categorized as centres who enrolled <14 patients [lower-quartile] during the study period), and medical therapy with diuretics. The benefit of CRT-D compared with ICD-only therapy in reducing the endpoints by centre location was assessed by including a treatment-by-US/non-US centre interaction-term in the multivariate models. Interaction-term analysis was also used to evaluate the benefit of CRT-D therapy in patient subsets within separate models that comprised US and non-US patients. Pre-specified interactions were categorized by gender, QRS morphology, QRS duration, and the aetiology of cardiomyopathy (i.e. ischaemic/non-ischaemic). All P values were two sided, and a P value < 0.05 was considered significant. Analyses were performed with the use of SAS software (version 9.20).

Results

Baseline characteristics

The baseline clinical characteristics of study patients by centre location are presented in Table 1. Patients who were enrolled in non-US centres showed increased frequency of high-risk clinical characteristics, including more advanced HF functional class (NYHA III/IV) > 3 months prior to enrollment, a higher burden of atrial tachyarrhythmias prior to recruitment (possibly leading to a greater frequency of treatment with amiodarone also observed in this group), a more prolonged QRS, and a higher...
frequency of LBBB. Patients enrolled in US centres were older, were more frequently women, and had an increased body mass index. The frequency of lower enrollment centres (defined as centres who enrolled <14 patients, which was the median number of patients enrolled at each centre for the entire study group) was higher in the USA than outside of the USA. However, the average number of implanting physicians per centre was not significantly different between the two groups (Table 1). Baseline characteristics by treatment arm were similar in both the US and non-US groups (see Supplementary material online, Appendix Tables A and B).

**Procedure-related complications in US and non-US patients**

The occurrences of pre-specified major and minor procedure-related complications are listed in Table 2. Altogether, procedure-related complications for CRT-D as well as for ICD implantation occurred significantly more often in non-US centres (17%) compared with US centres (10%; \( P < 0.001 \)).

The most common complication for both groups was lead dislodgement: 4 and 7% of US and non-US patients, respectively. Pneumothorax (0.5 vs. 3%), pericardial tamponade (0.2 vs. 0.4%) and device infection (0.4 vs. 0.9%) also occurred more frequently in non-US centres, whereas thrombo-embolic events occurred more often in US centres (1 vs. 0.2%). There was no significant difference in the incidence of minor complications between the two groups (Table 2).

Multivariate logistic regression analysis showed that independent predictors of the occurrence of procedure-related complications included enrollment in a non-US centre (odds ratio [OR] = 1.67 [95% CI 1.23–2.27]; \( P = 0.001 \)) and implantation of a CRT-D device (OR = 2.29 [95% CI 1.56–2.99]; \( P < 0.001 \)); a history of advanced HF symptoms >3 months prior to enrollment (OR = 1.74 [95% CI 1.16–2.61]; \( P = 0.008 \)); and a history of atrial tachyarrhythmias requiring therapy >1 month prior to enrollment (OR = 1.89 [95% CI 1.09–3.23]; \( P = 0.02 \)). In contrast, recruitment in a low-volume enrolling centre was not shown to be a significant risk factor for this endpoint (OR = 1.22 [95% CI 0.80–1.66]; \( P = 0.46 \)).

Multivariate Cox proportional hazards regression analysis showed that the occurrence of procedure-related complications was not a significant risk factor for the development of subsequent HF or death (HR = 1.18 [95% CI 0.86–1.62]; \( P = 0.30 \)), but was independently associated with a significant increase in the risk of all-cause mortality (HR = 1.84 [95% CI 1.14–2.96]; \( P = 0.01 \)).

**Echocardiographic response to cardiac resynchronization therapy with a defibrillator in US and non-US patients**

Consistent with the higher frequency of baseline clinical risk factors among patients enrolled in non-US centres, echocardiographic assessment at enrollment showed significantly greater left ventricular- and atrial-volume in this group (Figure 1A). Despite this, echocardiographic evaluation at 1 year showed pronounced improvement in non-US centres (17%) compared with US centres (10%; \( P = 0.001 \)).
Clinical response to cardiac resynchronization therapy with a defibrillator—in US and non-US patients

Kaplan—Meier survival analysis showed that CRT-D was associated with a significant reduction in the rate of HF or death among patients in both groups (Figure 2A and B, respectively). However, among non-US patients separation in the rates of HF or death between the two treatment arms was evident only after 1 year of enrollment (Figure 2B), whereas this separation occurred much earlier (2–3 months after enrollment) in US centre patients (Figure 2A).

Multivariate analysis (Table 3) showed that, after adjustment for baseline clinical factors and the occurrence of procedure-related complications, CRT-D was associated with similar reductions in the risk of HF or death among patients enrolled in US centres (38% risk-reduction; \( P < 0.001 \)) and in non-US centres (42%; risk reduction; \( P = 0.003 \)).

Subgroup analyses showed a significant difference in the benefit of CRT-D for the reduction of HF or death between men and women only among patients enrolled in US centres (Figure 3A). A similar difference existed between LBBB and non-LBBB patients, also more pronounced among patients enrolled in US centres (Figure 3B). When the separate occurrence of all-cause mortality was assessed, treatment with CRT-D was shown to be associated with 71% (\( P = 0.02 \)) and 51% (\( P = 0.01 \)) respective risk reductions among patients with LBBB and women from US centres, whereas no such effects were found in patient who were enrolled in non-US centres (Figure 3B).

Discussion

We have shown that despite identical enrollment criteria in MADIT CRT, patients enrolled in non-US centres displayed clinical and echocardiographic characteristics consistent with more advanced HF prior to enrollment, a fact that may have contributed to the longer time that was required for the separation in event rates between the two treatment arms and the higher complication rate in this group. These differences, however, did not affect the overall significant clinical and echocardiographic response to CRT-D in all the study patients.

Effect of centre location on patient characteristics and response to cardiac resynchronization therapy with a defibrillator

Similar to MADIT-CRT, the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial comprised asymptomatic or mildly symptomatic patients with left ventricular dysfunction who were enrolled in European (n = 262) and North American (n = 348) centres. Only the European cohort was prospectively randomized for 24 months, and its long-term follow-up results showed a statistically significant reduction in the primary endpoint. The Kaplan—Meier curves for the endpoint of HF or death in the REVERSE follow-up were similar to the curves observed among US patients in the present study, possibly due to younger age, lower frequency of ischaemic cardiomyopathy, and higher frequency of treatment with angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers as compared with the non-US group in MADIT-CRT. European patients from both studies derived a similar magnitude of reverse chamber remodelling and improvement in LVEF with CRT-D.

Table 2  Procedure-related complications by centre location*  

<table>
<thead>
<tr>
<th>Type of event</th>
<th>US centres (n = 1271)</th>
<th>Non-US centres (n = 549)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>127 (10)</td>
<td>91 (17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>By device</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Related to a CRT-D implantation, n (%)</td>
<td>96 (8)</td>
<td>68 (12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Related to a ICD implantation, n (%)</td>
<td>31 (2)</td>
<td>23 (4)</td>
<td>0.03</td>
</tr>
<tr>
<td>By typeb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>94 (7)</td>
<td>69 (13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>complications, n (%)</td>
<td>56 (4)</td>
<td>39 (7)</td>
<td></td>
</tr>
<tr>
<td>Lead dislodgement, n (%)</td>
<td>20 (2)</td>
<td>22 (4)</td>
<td></td>
</tr>
<tr>
<td>RA lead</td>
<td>7 (0.6)</td>
<td>5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>RV lead</td>
<td>35 (3)</td>
<td>16 (3)</td>
<td></td>
</tr>
<tr>
<td>LV lead</td>
<td>5 (0.4)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax, n (%)</td>
<td>6 (0.5)</td>
<td>14 (3)</td>
<td></td>
</tr>
<tr>
<td>Tamponade, n (%)</td>
<td>2 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure, n (%)</td>
<td>4 (0.3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Thrombo-embolic event, n (%)</td>
<td>11 (1)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>Wound infection requiring IV antibiotics, n (%)</td>
<td>5 (0.4)</td>
<td>5 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Pocket hematoma requiring evacuation, n (%)</td>
<td>13 (1)</td>
<td>9 (2)</td>
<td></td>
</tr>
<tr>
<td>Other majorc</td>
<td>6 (0.5)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>43 (3)</td>
<td>39 (7)</td>
<td>0.06</td>
</tr>
<tr>
<td>complications, n (%)</td>
<td>2 (0.2)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Transient increase of Creatinine, n (%)</td>
<td>4 (0.3)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Failure to convert during defibrillation</td>
<td>5 (0.4)</td>
<td>4 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Inadvertent tachyarrhythmia</td>
<td>9 (0.7)</td>
<td>2 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Extracardiac stimulation, n (%)</td>
<td>25 (2)</td>
<td>23 (4)</td>
<td></td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter defibrillator; IV, intravenous, other abbreviations as defined in previous tables.

*Device-related complications were reported as adverse events within 90 days of device implantation.

*The total number of individual events may be larger than the overall major and minor complication rates due to small numbers individual complication rates were not compared statistically.

*Includes coronary vein dissection, HF exacerbation associated with device implantation, arterial perforation, permanent AV block, and systemic infection within 30 days of implantation.

*Includes transient lead malfunctions, post-surgical wound discomfort, pocket seroma, venous erosion, pleural effusion, pericardial effusion (without tamponade), and venous occlusion.
therapy, but did not show a significant reduction in the risk of all-cause mortality, most likely due to the relatively short follow-up time of the two trials. This is supported by the recently published data from the RAFT trial, which showed a significantly lower mortality after a mean follow-up time of 40 months.

We showed that despite the existence of differences in important baseline characteristics, similar reverse structural remodelling and prevention of HF progression were achieved. Thus, the increased frequency of factors previously shown to be associated with an unfavourable response to CRT, including higher levels of BUN, prior atrial tachyarrhythmias, and of ischaemic cardiomyopathy did not appear to attenuate the clinical and echocardiographic benefit of CRT-D therapy.

**Centre location and the risk of procedure-related complications**

Complications associated with the device implantation procedure, and with the CRT-D device in particular, occurred more frequently in non-US centres. These differences could be attributed to higher-risk clinical characteristics among non-US patients, including larger cardiac volumes, a higher proportion of patients who were at NYHA classes III/IV at >3 months prior to enrollment, and a higher frequency of atrial tachyarrhythmias at >1 month prior to enrollment (the two latter factors were identified as independently associated with the risk of procedure-related complications in this study). Evidently, lack of device handling experience did not cause more complications, as a lower number of enrolled patients per centre were not associated with increase in the risk of complications and the average number of implanting physicians per centre was not significantly different between the US and the non-US groups. The reported complication rates at MADIT-CRT are similar to those reported at both the REVERSE (overall 16% complication rate and 21% for the European cohort) and RAFT (overall 19.9% in CRT and ICD arms together) trials. The reason for the relatively high incidence of right atrial lead dislodgement in the non-US centres of MADIT-CRT (4 vs. 2% in US patients, Table 2) could be attributed to the significantly higher ventricular and atrial volumes in this group and higher frequency of prior atrial fibrillation, making them possibly more prone for advanced remodelling of the right atrium.

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**Figure 1** Comparison of echocardiographic parameters between US and non-US patients at (A) baseline; and (B) per cent change at 1 year of follow-up. Distribution of echocardiographic parameters was normal. LAV, left atrial volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; US, United States.
Benefit of cardiac resynchronization therapy with a defibrillator in risk subsets

The original MADIT-CRT publication\(^7\) and a recent substudy \(^{19}\) suggest that CRT-D is more effective in women.\(^7\) The reason for this difference is unclear. It is possible that among patients with heart disease, the risk of HF is greater for women,\(^{20}\) resulting in a greater benefit from preventive CRT-D therapy. Furthermore, a recent sub-analysis of the trial has shown that CRT-D was associated with a pronounced reduction in the risk of HF or death.

**Table 3** Multivariate analysis: cardiac resynchronization therapy with a defibrillator vs. cardiac resynchronization therapy-only risk of endpoints by enrollment centre*  

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>US centres</th>
<th></th>
<th>Non-US centres</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
<td>Hazard ratio (95% CI)</td>
<td>P</td>
</tr>
</tbody>
</table>
| Heart failure or death    | 0.62 (0.48–0.80)    | <0.001          | 0.58 (0.41–0.84)     | 0.003           | 0.80  
| Heart failure only        | 0.55 (0.41–0.72)    | <0.01           | 0.56 (0.38–0.81)     | 0.003           | 0.95  
| Death                     | 0.69 (0.44–1.07)    | 0.10            | 1.25 (0.63–2.50)     | 0.52            | 0.15  

*Further adjusted for age >65, gender, ischaemic status, QRS >150, BUN >25 mg/dL, EF <25, LBBB, presence of NYHA class III/IV >3 months prior to enrollment, the occurrence of implantation-related adverse events, centre size, and therapy with diuretics; the CRT-D vs. ICD risk by centre location was assessed by including a location-by-treatment interaction-term in the multivariate models; results were consistent when the comparison with US centres was confined to patients who were enrolled only European centres.
among patients with LBBB, possibly due to more left ventricular dyssynchrony in LBBB than in non-LBBB patients. The results of the present study extend these observations and show a significant difference in the clinical benefit of CRT-D therapy by gender and QRS morphology among patients who were enrolled in US centres. In contrast, among non-US patients, who had a higher risk profile at enrollment, the subgroup differences in CRT-D efficacy were attenuated. Notably, prior studies among patients with more advanced HF symptoms did not demonstrate a significant difference in the benefit of CRT-D between LBBB and non-LBBB patients, suggesting that previously observed subgroup differences in MADIT-CRT pertain mostly to lower-risk patients.

Study limitations
Centre location was not a randomization factor in MADIT-CRT-D. Thus, differences between the baseline characteristics of the patients who were enrolled in US and non-US patients could have affected the response to therapy in the two groups. Nevertheless, the favourable effects of CRT-D persisted after multivariate adjustment for baseline clinical factors and medical therapies, suggesting that these parameters did not affect the overall response to device therapy in the two groups.

The present study shows a higher rate of procedure-related complications in non-US centres. These findings may be due to the higher-risk characteristics of non-US patients. However, we cannot rule additional explanations, including centre-specific operational procedures with CRT. Specifically, despite the fact that the multivariate models were adjusted for the size of enrollment per centre, we did not collect data regarding the total or absolute CRT-D implantation volume per participating centre (not related to specific enrollment) and regarding the type and location of the implantation in each centre (i.e. EP lab vs. operating theatre). Furthermore, despite the fact that the average number of implantation physicians was similar between US and non-US centres in MADIT-CRT, more specific information regarding the composition of the implanting teams were not consistently collected in the study.

Figure 3
Subgroup analysis: cardiac resynchronization therapy with a defibrillator vs. ICD-only adjusted risk in US and non-US patients by gender and QRS morphology for the endpoints of (A) heart failure or death; and (B) all-cause mortality. Models were carried out separately in US and non-US patients; all findings were further adjusted for age >65 years, gender, ischaemic status, QRS > 150 ms, BUN > 25 mg/dL, EF < 25%, left bundle branch block, the presence NYHA class III/IV > 3 months prior to enrollment, the occurrence of implantation-related adverse events, centre size, and medical therapy with diuretics; the cardiac resynchronization therapy with a defibrillator vs. ICD risk in each patient subset was assessed by including a location-by-QRS morphology/gender interaction-term in the US and non-US multivariate models; results were consistent when the comparison with US centres was confined to patients who were enrolled only European centres.
It should also be noted that the overall procedure-related complication rate in the non-US group of MADIT-CRT is well in the range of the reports in all other CRT studies and that the higher rate of procedure-related complications among non-US patients in MADIT-CRT did not have a significant impact on the overall clinical and echocardiographic benefit of CRT-D in this group.

Conclusions

Large randomized trials that enroll patients from worldwide regions with different healthcare systems and clinical settings, as well as potentially different patient behaviour, often contain differing baseline characteristics of enrolled patients mandating specific evaluation in order to assess potential independently contributing factors of baseline characteristics. The present evaluation of the two major groups of US and non-US enrollment centres of the MADIT-CRT study indicates that different baseline characteristics in the context of well-defined trial inclusion criteria do not change the results of CRT-D in patients with no or mild HF symptoms.

Supplementary material

Supplementary material is available at European Heart Journal online.

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References


