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CLINICAL RESEARCH
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# Association between myocardial substrate, implantable cardioverter defibrillator shocks and mortality in MADIT-CRT

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**Objective** The aim of the present study was to assess a possible association between myocardial substrate, implantable cardioverter defibrillator (ICD) shocks, and subsequent mortality.

**Methods** Within the multicentre automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) population ($n = 1790$), we investigated the association between myocardial substrate, ICD shocks and subsequent mortality using multivariate Cox regression analyses and landmark analyses at 1-year follow-up.

**Results** The 4-year cumulative probability of ICD shocks was 13% for appropriate shock and 6% for inappropriate shock. Compared with patients who never received ICD therapy, patients who received appropriate shock had an increased risk of mortality [HR = 2.3 (1.47–3.54), $P < 0.001$], which remained increased after adjusting for echocardiographic remodelling at 1 year (HR = 2.8, $P = 0.001$). Appropriate anti-tachycardia pacing (ATP) only was not associated with increased mortality ($P = 0.42$). We were not able to show an association between inappropriate shocks ($P = 0.53$), or inappropriate ATP ($P = 0.10$) and increased mortality. Advanced myocardial structural disease, i.e. higher baseline echocardiographic volumes and lack of remodelling at 1 year, was present in patients who received appropriate shocks but not in patients who received inappropriate shocks or no shocks.

**Conclusion** In the MADIT-CRT study, receiving appropriate ICD shocks was associated with an increased risk of subsequent mortality. This association was not evident for appropriate ATP only. These findings, along with advanced cardiac structural disease in the patients who received appropriate shocks, suggest that the compromised myocardium is a contributing factor to the increased mortality associated with appropriate ICD shock therapy.

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**Keywords** ICD therapy • MADIT-CRT • Mortality • Shocks • Anti-tachycardia pacing

## Introduction

Several large randomized trials have substantiated the preventive effect of implantable cardioverter defibrillators (ICD) on sudden cardiac death (SCD) by delivery of anti-tachycardia pacing (ATP) and/or shock therapy.[1–6] Although ICD shocks save lives, they have been associated with progression in heart failure[7,8] and non-arrhythmic death.[8,9] Some studies have reported increased mortality irrespective of the type of shock (appropriate, inappropriate, both),[8–13] while others only report increased mortality with appropriate shocks and no increase in mortality with inappropriate shocks,[14,15] or appropriate ATP.[16,17] When looking into the

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underlying cause of the inappropriate shock, studies have suggested that only inappropriate shocks due to atrial tachyarrhythmias (ATs) are associated with an increased mortality.[13,16] Inappropriate shocks secondary to T-wave oversensing[16] and lead noise are not associated with an increased risk of mortality.[13]

Although appropriate and inappropriate ICD shocks have been correlated with development of heart failure, ischaemic events, lower ejection fraction, and atrial fibrillation,[7,8,18,19] data on shocks causing direct myocardial damage are still limited and conflicting.[20–23]

Many questions remain unanswered. Are shocks a marker of advanced heart failure, associated co-morbid conditions and advanced structural myocardial disease, or are shocks themselves harmful? Are all shocks equally harmful and does the delivery of ATP play a role?

The present study was designed to investigate the role of altered myocardial substrate in the association of ICD shocks on subsequent mortality. We hypothesized that ICD shocks are associated with increased mortality only when advanced myocardial structural disease is present.

# Methods

## Multicentre automatic defibrillator implantation trial-cardiac resynchronization therapy study design

The design and primary results of the multicentre automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial have been previously published.[24,25] Briefly, the MADIT-CRT was a randomized multicentre trial, involving 110 centres from the USA, Canada, and Europe. The trial was designed to determine whether implantation of a cardiac resynchronization therapy with a defibrillator (CRT-D) device would reduce the risk of death or non-fatal heart failure events (HFE) in patients with mild heart failure symptoms [New York Heart Association (NYHA) I–II], a left ventricular ejection fraction (LVEF) $\leq$30% and wide QRS complex (QRS $\geq$130) when compared with ICD therapy. The study randomized 1820 patients in a 3:2 fashion for a CRT-D or ICD device. The trial was carried out from 22 December 2004 to 22 June 2009. Complete data collection and adjudication of HFE and mortality was continued throughout 2010. Thus, the present study provides extended follow-up data for all MADIT-CRT participants through 10 September 2010.The present study included 1790 of the 1820 patients in the MADIT-CRT cohort, since we excluded 30 patients who never received a device.

## Device programming and interrogation

Commercially available transvenous devices (Boston Scientific, Natick, MA, USA) were used in the trial. All devices were programmed according to a pre-specified study protocol,[24] with a therapy zone for ventricular tachycardia (VT) from 180 to 210 beats per minute (b.p.m.) and ventricular fibrillation (VF) zone >210 b.p.m. Nominal detection was programmed as 2.5 s for the VT zone and 1.0 s for the VF zone. Recommended programming for the first therapy in the VT zone was burst-type ATP with eight pulses per burst at 88% of the cycle length with a 10 ms decrement between bursts followed by the second therapy shock at a defibrillator threshold testing level shock energy of +10 J followed by maximum shock energy. The VF zone was programmed for maximum shock. Further ATP programming, including ATP during charging, was left to the discretion of the implanting physician. All shocks were biphasic and supraventricular tachycardia-discriminators were nominally programmed at 'on'-mode. Sensitivity was set at the physician's discretion.

The devices were interrogated at 1 month after randomization and thereafter quarterly. All interrogation discs were sent to an independent central core laboratory where an arrhythmia adjudication committee adjudicated all arrhythmias and therapies according to pre-defined definitions.

## Events and therapy

The primary endpoint of the present study was defined as all-cause mortality. All deaths were adjudicated centrally by an assigned heart failure and mortality committee. Secondary analysis included baseline and 1-year echocardiographic data.

Appropriate therapy was defined as ATP or shock rendered for VT or VF. Ventricular tachycardia was defined as ventricular rate in the range 180–210 b.p.m.; VF was defined as ventricular rate faster than 210 b.p.m.

Inappropriate therapy was defined as ATP or shocks rendered when VT or VF was not present. The arrhythmia adjudication committee categorized the underlying cause/rhythm of the inappropriate therapy. Inappropriate therapy rendered for ATs included supraventricular tachyarrhythmias, atrial fibrillation/flutter, and sinus tachycardia.

## Echocardiographic methods

According to study-specific protocol, echocardiograms were obtained before device implantation and at 1-year follow-up. In the present study population of 1790 patients, paired echocardiograms at baseline and after 1 year were available for 1374 patients. Echocardiographic parameters were measured in the core echocardiography laboratory according to the established American Society of Echocardiography protocol.[26] Left ventricular volumes were measured by Simpson's method of discs in the apical four- and two-chamber views and averaged.

## Statistical methods

For *Table 1*, comparing baseline characteristics, we divided the population into four mutually exclusive groups comprising patients who received the following: only appropriate shock; only inappropriate shock; both appropriate and inappropriate shock; or no shock, constituting patients who never had any therapy and patients who only received appropriate or inappropriate ATP. Baseline characteristics were compared between the groups using the $\chi^2$ test for categorical variables and the Kruskal–Wallis test or Wilcoxon rank-sum, where appropriate, for continuous variables.

To assess changes in echocardiographic parameters from baseline to 1-year follow-up within each group, we used the paired *t*-test only including patients who had paired baseline and 12-month echocardiographic measurements. Changes in echocardiographic measures are reported as median with inter-quartiles ranges as they did not follow a normal distribution, with differences in percentage change between all four groups analysed by the Kruskal–Wallis test and differences between two specific groups by the Wilcoxon rank-sum test.

The cumulative probability of ICD shock and death was displayed by the method of Kaplan–Meier. To determine whether ICD therapy was associated with a higher mortality, we used multivariate Cox proportional hazard regression models incorporating time-dependent variables of ICD therapy. For the multivariate model, we defined the first occurrence of ICD shock as a shock event whether or not it was preceded by ATP. Appropriate ATP only and inappropriate ATP only groups were defined as patients who only received ATP without ever receiving an appropriate or inappropriate shock, respectively. Therefore, patients who never received any ICD therapy were always used as a reference group. Stepwise selection and best subset analyses were used to determine the covariates included in the multivariate model. Setting the limit for entry into the model at $P < 0.05$, the following variables entered the

**Table 1 Baseline characteristics**

| Clinical characteristics | Appropriate shock only ($n = 198$) | Inappropriate shock only ($n = 95$) | Appropriate shock and Inappropriate shock ($n = 28$) | No shock ($n = 1469$) |
|---|---|---|---|---|
| Female | 22 (11)† | 16 (17)† | 8 (29) | 398 (27)* |
| Age at enrolment (years) | 62.0 ± 10.1† | 61.4 ± 12.7† | 60.2 ± 13.5 | 65.0 ± 10.5* |
| QRS (ms) | 157.8 ± 23.9 | 157.1 ± 19.0 | 156.3 ± 15.2 | 158.3 ± 19.3 |
| Heart rate (b.p.m.) | 67.9 ± 10.7 | 67.8 ± 10.6 | 70.0 ± 12.9 | 67.7 ± 10.9 |
| BMI (kg/m$^2$) | 29.0 ± 5.0 | 29.1 ± 5.5 | 28.4 ± 6.3 | 28.6 ± 5.3 |
| BUN (mg/dL) | 21.3 ± 8.1 | 20.5 ± 7.7 | 20.8 ± 6.3 | 21.6 ± 9.2 |
| Creatinine (mg/dL) | 1.15 ± 0.27 | 1.12 ± 0.33 | 1.16 ± 0.21 | 1.17 ± 0.37 |
| Systolic blood pressure (mmHg) | 121.2 ± 17.7 | 119.3 ± 17.8† | 119.5 ± 13.8 | 123.1 ± 17.3* |
| Diastolic blood pressure (mmHg) | 71.0 ± 11.1 | 72.2 ± 9.8 | 71.9 ± 9.2 | 71.7 ± 10.3 |
| Ischaemic NYHA class I | 37 (19) | 14 (15) | 3 (11) | 206 (14) |
| Ischaemic NYHA class II | 89 (45) | 31 (33) | 12 (43) | 590 (40) |
| Non-ischaemic NYHA class II | 72 (36)† | 50 (53) | 13 (46) | 673 (46)* |
| NYHA >II <3 month prior to enrolment | 19 (10) | 11 (12) | 2 (7) | 149 (11) |
| CRT-D assigned treatment | 99 (50)† | 57 (60) | 13 (46) | 909 (62)* |
| PR interval (ms) | 197 ± 31 | 198 ± 31 | 194 ± 39 | 197 ± 33 |
| Left bundle brach block | 121 (61)† | 67 (71) | 17 (61) | 1059 (72)* |
| Medical history | | | | |
| Hospitalizations in prior year | 80 (41) | 53 (57) | 17 (61) | 677 (47)* |
| Prior hospitalizations for CHF | 71 (36) | 39 (44) | 11 (39) | 548 (38) |
| Prior CABG | 67 (34) | 21 (22) | 6 (21) | 427 (29) |
| Prior non-CABG revascularization | 50 (25) | 22 (23) | 4 (14) | 408 (28) |
| Diabetes | 52 (26) | 24 (25) | 10 (36) | 457 (31) |
| Hypertension | 122 (62) | 53 (56) | 16 (57) | 946 (65) |
| Prior myocardial infarction | 109 (56)† | 35 (37) | 14 (52) | 604 (42)* |
| History of atrial arrhythmias | 28 (14) | 10 (11) | 7 (25) | 163 (11) |
| History of ventricular arrhythmias | 34 (17)† | 7 (7) | 7 (25)† | 76 (5)* |
| Pharmacotherapy at baseline | | | | |
| ACE inhibitor or ARB | 190 (96) | 91 (96) | 28 (100) | 1402 (95) |
| Beta-blocker excl. Sotalol | 183 (92) | 92 (97) | 23 (82) | 1372 (93) |
| Amiodarone | 22 (11)† | 4 (4) | 5 (18)† | 96 (7)* |
| Digitalis | 67 (34)† | 26 (27) | 9 (32) | 357 (24)* |
| Diuretic | 138 (70) | 70 (74) | 21 (75) | 982 (67) |
| Statins | 140 (71) | 56 (59) | 13 (46)† | 1000 (68)* |
| Echocardiographic measurements at baseline | | | | |
| LVEF (%) | 27.8 ± 3.4† | 28.4 ± 3.4† | 28.5 ± 2.8 | 29.2 ± 3.4* |
| LVEDV indexed by BSA (mL/m$^2$) | 132.9 ± 34.2† | 125.4 ± 34.0 | 124.9 ± 29.0 | 122.0 ± 26.8* |
| LVESV indexed by BSA (mL/m$^2$) | 96.6 ± 28.0† | 90.2 ± 27.2 | 89.6 ± 22.5 | 86.8 ± 21.6* |
| LAV indexed by BSA (mL/m$^2$) | 49.4 ± 10.3† | 47.5 ± 10.5 | 50.2 ± 10.5† | 46.1 ± 9.9 |

*$P < 0.05$ for overall comparisons between the four groups.
†$P < 0.05$ for comparisons between the specific group and others.
Data are presented as crude numbers and percentage or means ± standard deviation.
ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy; CRT-D, cardiac resynchronization therapy-defibrillator; LVEF, left ventricular ejection fraction; CHF, congestive heart failure; Revasc proc, revascularization procedure; ACE-I, angiotensin-converting enzyme inhibitor; BUN, blood urea nitrogen; BSA, body surface area; BMI, body mass index.

model: diabetes, ischaemic cardiomyopathy, age ≥65 years, creatinine ≥1.4 mg/dL, baseline left atrial volume (LAV) indexed by the body surface area, prior hospitalizations for congestive heart failure, NYHA class III within 3 months prior to enrolment. In addition assigned treatment (ICD vs. CRT-D), left bundle branch block (LBBB) morphology, and treatment–LBBB interaction were forced into the model, based on randomization and imbalances between the groups at baseline.

Using landmark analysis, starting follow-up at 1 year after enrolment, another multivariate model was fitted assessing risk of mortality in each ICD therapy subgroup, taking differences in left ventricular end-

systolic volume (LVESV) percentage change from baseline to 1-year follow-up into account. Given the high correlation (≈0.9) between the echocardiographic parameters of LVEF, LAV, LVESV, and left ventricular end-diastolic volume (LVEDV), we were not able to enter more than one echocardiographic parameter into the model.

Hazard ratios (HRs) with their 95% confidence intervals (CIs) and two-sided *P*-values were reported. A two-tailed *P*-value $<0.05$ was considered statistically significant. Analyses were performed using the SAS statistical system 9.3 version (SAS institute, Cary, NC, USA).

# Results

Baseline characteristics of the 1790 patients in the present study are presented in *Table 1*. Patients who received ICD shock therapy were significantly younger but had a lower LVEF at baseline compared with patients without shock therapy. Compared with patients who never experienced an ICD shock, patients who received an appropriate shock, were more often assigned to ICD treatment and had QRS morphology other than LBBB. They were more often male, had a significantly higher rate of past ventricular arrhythmias, past myocardial infarction, and ischaemic cardiomyopathy and were more often taking antiarrhythmics. Furthermore, they had higher baseline LAVs and LVEDV and LVESV. The history of atrial tachyarrhythmia was similar across all groups. The usage of heart failure medication was high and similar across all groups (*Table 1*). Baseline values between patients who experienced shock, those who experienced ATP only and those who never had any ICD therapy, are presented in Supplementary material online, Appendix A.

During a mean follow-up of 3.3 ± 1.1 years, 189 out of 1790 (11%) patients died.

The cumulative probability of ICD shock therapy at 4 years was 21% for any ICD shock, 13% for appropriate ICD shock, 6% for inappropriate ICD shock, and 2% for receiving both appropriate and inappropriate shocks (*Figure 1*). A total of 123 patients received an inappropriate shock, with 95 of these (77%) secondary to ATs.

## Implantable cardioverter defibrillator therapy and mortality

The 3-year cumulative probability of death was 23% in patients who experienced first appropriate shock and 16% in patients who experienced first inappropriate shock (*Figure 2*). Patients who received appropriate shock had a significant 2.3-fold increased risk of death compared with those who never received ICD therapy and patients who experienced both an appropriate and an inappropriate shock had the highest risk of death with a HR of 5.1 (*Table 2*). Patients who only received appropriate ATP and never received an appropriate shock were not at an increased risk of death (*Table 2*).

We were not able to show an association between inappropriate shocks and mortality; however, we observed borderline significant increased risk of death in patients who received inappropriate ATP (*Table 2*). The cause for inappropriate ATP was ATs in 166 out of 203 patients (82%).

Similar results were found when additional adjustments were made for variables that were significantly different between the four groups (*Table 1*) at baseline (results not shown).

The relationship between different ICD therapies and subsequent mortality was not significantly different in ICD and CRT-D patients (likelihood ratio interaction *P*-value, with 5 degrees of freedom = 0.745). This was also true for the subgroup of LBBB (likelihood ratio interaction *P*-value, with 5 degrees of freedom = 0.791) and for NYHA class (likelihood ratio interaction *P*-value, with 5 degrees of freedom = 0.183) (Supplementary material online, Appendices B–D).

When looking at ICD therapy by heart rate ranges, we observed that the majority of the ICD therapy rendered $<200$ b.p.m. was ATP only, whereas ICD shocks with or without prior ATP dominated in the heart rate range $>220$ b.p.m. (*Figure 3*).

## The impact of shock and anti-tachycardia pacing burden on mortality

During the follow-up, the total number of appropriate and inappropriate shocks rendered amounted to 1013 and 503, respectively.

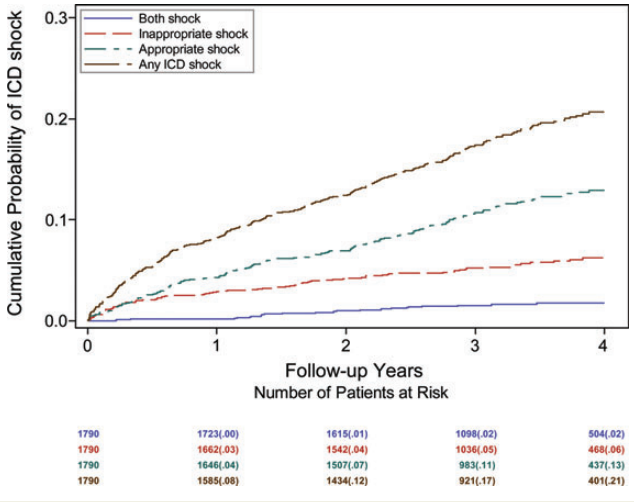


**Figure 1** Cumulative probability of implantable cardioverter defibrillator shock therapy over time. Kaplan–Meier plot showing the cumulative incidence of implantable cardioverter defibrillator shocks over time.

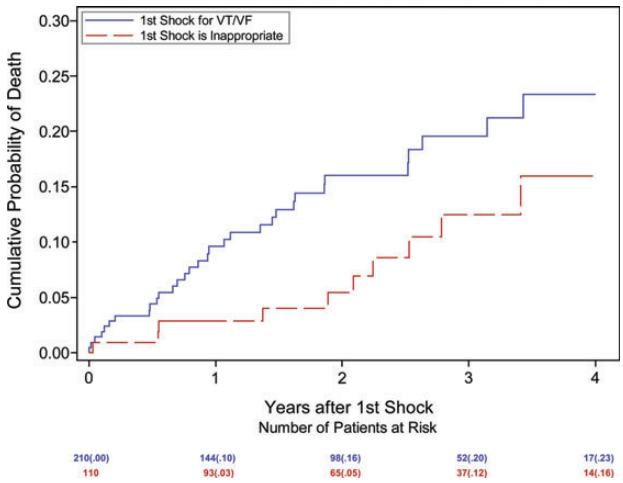


**Figure 2** Probability of death after first implantable cardioverter defibrillator shock therapy. Cumulative probability of death by the type of first implantable cardioverter defibrillator shock therapy, starting follow-up at the time of the first implantable cardioverter defibrillator shock.

**Table 2 Multivariate analysis of type of implantable cardioverter defibrillator therapy and risk of mortality**

| Type of therapy | Hazard ratio | 95% confidence intervals | *P*-value |
|---|---|---|---|
| Appropriate ICD shock | 2.28 | 1.47–3.54 | <0.001 |
| Inappropriate ICD shock | 1.28 | 0.59–2.77 | 0.527 |
| Both shock | 5.10 | 2.34–11.12 | <0.001 |
| Appropriate ATP only | 1.25 | 0.72–2.17 | 0.425 |
| Inappropriate ATP only | 1.65 | 0.92–2.97 | 0.095 |

Always using 'no ICD therapy' as a reference group.
Adjusted for age ≥65 years, diabetes, ischaemic cardiomyopathy, prior hospitalizations for congestive heart failure, NYHA class III within 3 months prior to enrolment, creatinine ≥1.4 mg/dL, baseline left atrial volume index, assigned treatment (CRT-D:ICD), LBBB morphology and treatment–LBBB interaction. ATP, anti-tachycardia pacing; ICD, implantable cardioverter defibrillator.

Multivariate analysis revealed a higher and more significant mortality risk when two or more appropriate shocks were given than when one shock was delivered (*Table 3*). Patients receiving only appropriate ATP did not have significantly increased risk of mortality whether one or more appropriate ATPs were rendered. The same was true for inappropriate shocks, although we observed a significantly increased risk of mortality in patients receiving two or more inappropriate shocks or inappropriate ATPs (*Table 3*).

## Echo analyses

Within the CRT-D subgroup, comparisons of baseline and 1-year echocardiographic volume measurements between patients who received appropriate ICD shock only, inappropriate ICD shock only, both appropriate and inappropriate ICD shocks, or no ICD shock revealed a significant echocardiographic response in each of the four groups, with significant reductions in both LVEDV and LVESV and LAV ($P < 0.001$) (*Table 4*). However, comparisons between the four groups showed significantly less echocardiographic response in patients who experienced an appropriate shock or those who experienced appropriate and inappropriate shock compared with patients who did not experience an ICD shock (*Table 4* and *Figure 4A*). CRT-D patients who received inappropriate shock had similar improvement in echocardiographic structural parameters compared with the no shock group (*Table 4* and *Figure 4A*). No significant reverse remodelling was seen in the ICD patients (*Table 4* and *Figure 4B*).

In the CRT-D patients LVEF was significantly improved at 1-year follow-up compared with baseline ($P < 0.001$) within all four groups. However, when comparing the groups against each other, patients in the appropriate shock group and the both shock group had significantly less improvement than the no shock group (*Table 4* and *Figure 4A*). No significant improvement in LVEF was seen in the ICD patients (*Table 4* and *Figure 4B*).

Overall, CRT-D patients in the appropriate and both shock groups showed similar patterns of echocardiographic response within 1 year, with significantly less echocardiographic response compared with the no shock group (*Table 4* and *Figure 4A*).

## Assessing the impact of changes in echocardiographic parameters on the risk of mortality given different implantable cardioverter defibrillator therapies

This analysis, including 1373 patients, started follow-up at 1 year after enrolment and included patients who had paired baseline and 1-year echocardiographic measurements. Over a mean follow-up of 2.3 ± 0.9 years from the 1-year echo (landmark analysis), a total of 96 patients died. In multivariate Cox proportional hazard regression analysis, experiencing an appropriate shock was associated with an increased risk of mortality after adjusting for changes in LVESV

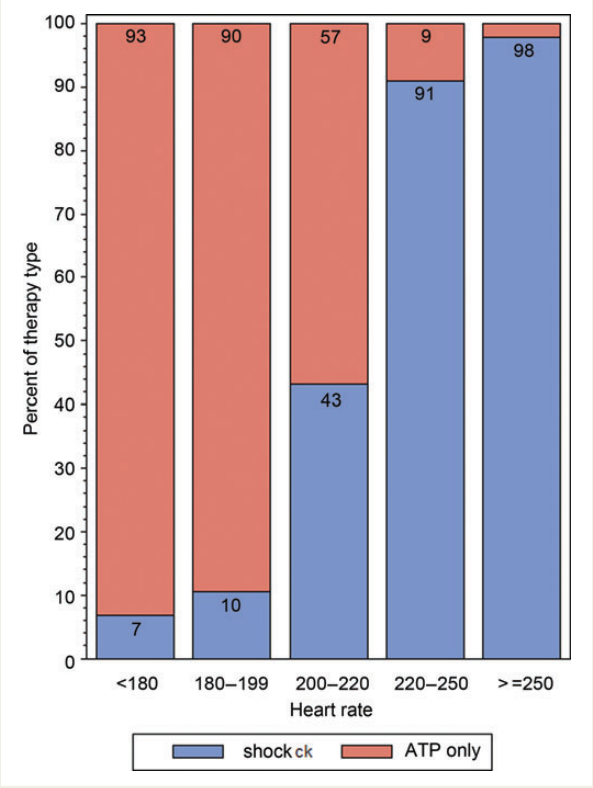


**Figure 3** Implantable cardioverter defibrillator therapy by heart rate ranges divided into anti-tachycardia pacing only and shocks. The majority of the implantable cardioverter defibrillator therapies for rhythms <200 b.p.m. was rendered as anti-tachycardia pacing only, whereas implantable cardioverter defibrillator therapies for rhythms >220 were rendered as shocks with or without prior anti-tachycardia pacing.

from baseline to 1-year follow-up (*Table 5*). The same was true for patients who received both appropriate and inappropriate shocks. We were not able to show a significant association between inappropriate shocks alone and mortality; however, we were limited in power by few events (*Table 5*).

Interestingly, when adjusting for changes in echocardiographic volumes, patients who received inappropriate ATP had a significant three-fold increased risk of death (*Table 5*). Appropriate ATP was not associated with increased mortality (*Table 5*). The results were similar when adjusting for changes in LAV or LVEDV from baseline to 1-year follow-up and when additional adjustments were made for variables that were significantly different at baseline, including past ventricular arrhythmias, prior myocardial infarction, gender, and medical therapy with digitalis or amiodarone.

## Discussion

We found a significantly increased risk of mortality in patients who received appropriate shock alone or in combination with inappropriate shock after adjusting for relevant clinical variables including type of device (ICD vs. CRT-D). This association was not seen in patients who only received appropriate ATP, suggesting dissociation between the underlying VT/VF and the increased risk of mortality.

We were not able to show an association between inappropriate shock and increased mortality, probably because of limited number of events. Although there was a significant two-fold increased risk of death in patients who received more than two inappropriate shocks or more than two inappropriate ATPs. After adjusting for changes in echocardiographic parameters, inappropriate ATP was associated with a three-fold increased risk of mortality.

We further explored the causal relationship between mortality and shocks, using changes in echocardiographic parameters from baseline to 1 year. CRT-D patients who received only appropriate

**Table 3 Impact of therapy burden on mortality**

| Type of therapy | Number | Hazard ratio | 95% confidence interval | *P*-value |
|---|---|---|---|---|
| Appropriate shocks | 1013 | | | |
| 1 shock: no shock | | 2.47 | 1.42–4.28 | 0.001 |
| ≥2 shock: no shock | | 2.70 | 1.63–4.50 | <0.001 |
| Inappropriate shock | 503 | | | |
| 1 shock: no shock | | 1.98 | 0.86–4.53 | 0.107 |
| ≥2 shock: no shock | | 2.13 | 1.03–4.41 | 0.041 |
| Appropriate ATP | 3129 | | | |
| 1 ATP: no ATP | | 1.03 | 0.48–2.22 | 0.939 |
| ≥2 ATP: no ATP | | 1.55 | 0.74–3.26 | 0.243 |
| Inappropriate ATP | 1826 | | | |
| 1 ATP: no ATP | | 0.90 | 0.33–2.47 | 0.844 |
| ≥2 ATP: no ATP | | 2.66 | 1.32–5.37 | 0.006 |

Adjusted for age ≥65 years, diabetes, ischaemic cardiomyopathy, prior hospitalizations for congestive heart failure, NYHA class III within 3 months prior to enrolment, creatinine ≥1.4 mg/dL, baseline left atrial volume index, assigned treatment (CRT-D:ICD), LBBB morphology, treatment–LBBB interaction and the respective type of ICD therapies not investigated. ATP, anti-tachycardia pacing; ICD, implantable cardioverter defibrillator.

**Table 4 Changes in echocardiographic parameters from baseline to 1-year follow-up**

| Clinical characteristics | Appropriate shock only | Inappropriate shock only | Appropriate shock and inappropriate shock | No shock | Overall *P*-value |
|---|---|---|---|---|---|
| CRT-D patients | | | | | |
| LVEDV % reduction | 14.0 (10.0–20.3)† | 20.8 (11.5–29.4) | 10.5 (5.9–14.9)† | 20.5 (13.6–29.2) | <0.001 |
| LVESV % reduction | 24.8 (16.9–30.9)† | 34.3 (22.3–43.1) | 17.5 (11.6–24.8)† | 33.8 (24.1–43.8) | <0.001 |
| LAV % reduction | 22.3 (13.5–31.2)† | 25.1 (21.1–36.0) | 18.9 (9.9–21.9)† | 29.0 (21.6–36.9) | <0.001 |
| LVEF increase | 8.3 (5.8–10.9)† | 10.9 (8.5–14.5) | 5.8 (4.2–8.3)† | 11.5 (8.2–15.0) | <0.001 |
| ICD patients | | | | | |
| LVEDV % reduction | 5.0 (2.6–8.2) | 5.8 (2.5–9.6) | 3.1 (2.0–6.6) | 5.8 (3.1–8.7) | 0.182 |
| LVESV % reduction | 9.0 (4.9–14.4) | 10.4 (6.6–14.6) | 8.2 (1.7–12.5) | 10.5 (5.4–15.6) | 0.285 |
| LAV % reduction | 9.1 (5.0–12.6) | 10.2 (5.2–15.5) | 7.5 (2.4–10.6) | 9.7 (5.4–14.6) | 0.450 |
| LVEF increase | 3.1 (1.6–5.1) | 3.4 (2.1–5.2) | 3.4 (0.3–4.8) | 3.2 (1.6–5.2) | 0.724 |

All numbers are shown as median and inter-quartile ranges.
†$P < 0.01$ between the specific group and no shock group.
LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAV, left ventricular atrial volume; LV mass, left ventricular mass; LVEF, left ventricular ejection fraction.

**Table 5 Landmark multivariate Cox analysis showing risk of mortality given different implantable cardioverter defibrillator therapies when adjusting for left ventricular end-systolic volume change from baseline to 1-year follow-up**

| Type of therapy | Hazard ratio | 95% confidence intervals | *P*-value |
|---|---|---|---|
| Appropriate ICD shock | 2.8 | 1.51–5.27 | 0.001 |
| Inappropriate ICD shock | 1.9 | 0.58–6.29 | 0.29 |
| Both shock | 7.7 | 2.69–22.12 | <0.001 |
| Appropriate ATP only | 0.74 | 0.26–2.07 | 0.56 |
| Inappropriate ATP only | 3.3 | 1.54–7.05 | 0.002 |

Always using 'no ICD therapy' as a reference group. Adjusted for change in LVESV from baseline to 1-year follow-up, diabetes, ischaemic cardiomyopathy, age ≥65 years, creatinine ≥ 1.4 mg/dL, basline left atrial volume index, prior hospitalizations for congestive heart failure, NYHA class III within 3 months prior to enrolment, assigned treatment, LBBB morphology and treatment–LBBB interaction.
LVESV, left ventricular end-systolic volume; ATP, anti-tachycardia pacing; ICD, implantable cardioverter defibrillator.

shock or both appropriate and inappropriate shocks had significantly lower reductions in left ventricular volumes compared with CRT-D patients who never received shocks. CRT-D patients who received inappropriate shocks alone had similar changes in echocardiographic volumes compared with CRT-D patients who never received a shock.

These findings prompted the question—is higher mortality in the appropriate shock group simply reflective of patients with more advanced myocardial disease, or does the shock itself contribute to mortality? To attempt to answer this question, we undertook landmark analyses; assessing the risk of mortality in each subgroup of ICD therapy, starting follow-up at 1 year, and adjusting for changes in LVEDV from baseline to 1-year follow-up. The increased risk of mortality persisted in patients who experienced an appropriate shock or both appropriate and inappropriate shocks during the follow-up, whereas we were not able to establish an association between increased risk of mortality in patients who received appropriate ATP or inappropriate shocks only.

Previous studies have presented conflicting data on association of ICD shocks and mortality. Some studies have reported increases in mortality with any ICD shock[9–11,13] and some only with appropriate but not inappropriate ICD shocks or ATP.[14,15,17] A recent review of 17 randomized trials showed no effect on mortality with a decrease in an incidence of ICD shocks.[27] However, this review only included 25% primary prevention ICD patients and is, therefore, not representative for this patient population. Furthermore, only 73% were on beta-blockers and the mean follow-up in most of the trials was only 1–2 year. These factors may explain the lack of survival benefit reported by this review.

The increased risk of mortality observed in patients receiving appropriate ICD shocks may be a consequence of several factors. Direct myocardial damage due to ICD shock may be a contributing factor, but there is conflicting evidence for this conclusion.[20–23] Animal and human data suggest that clinically delivered shock energy is much lower than that required for shock-related myocardial injury.[23] Also, no increased risk of mortality has been shown in patients receiving ICD shock as part of routine defibrillator threshold testing.[14,28] Tereshchenko *et al.* have reported increased risk of heart failure and death in patients receiving appropriate ICD shock, only if associated with local injury current, leading them to suggest that appropriate shocks do not cause death, but rather, unveil the risk of future HFE and death.[22] Similarly, we were able to demonstrate advanced baseline echocardiographic myocardial structural disease and diminished left ventricular remodelling in patients who received appropriate shocks alone or in combination with inappropriate shocks.

We did not find a relationship between appropriate ATP only and increased mortality. This lack of increased risk persisted despite adjusting for echocardiographic changes.

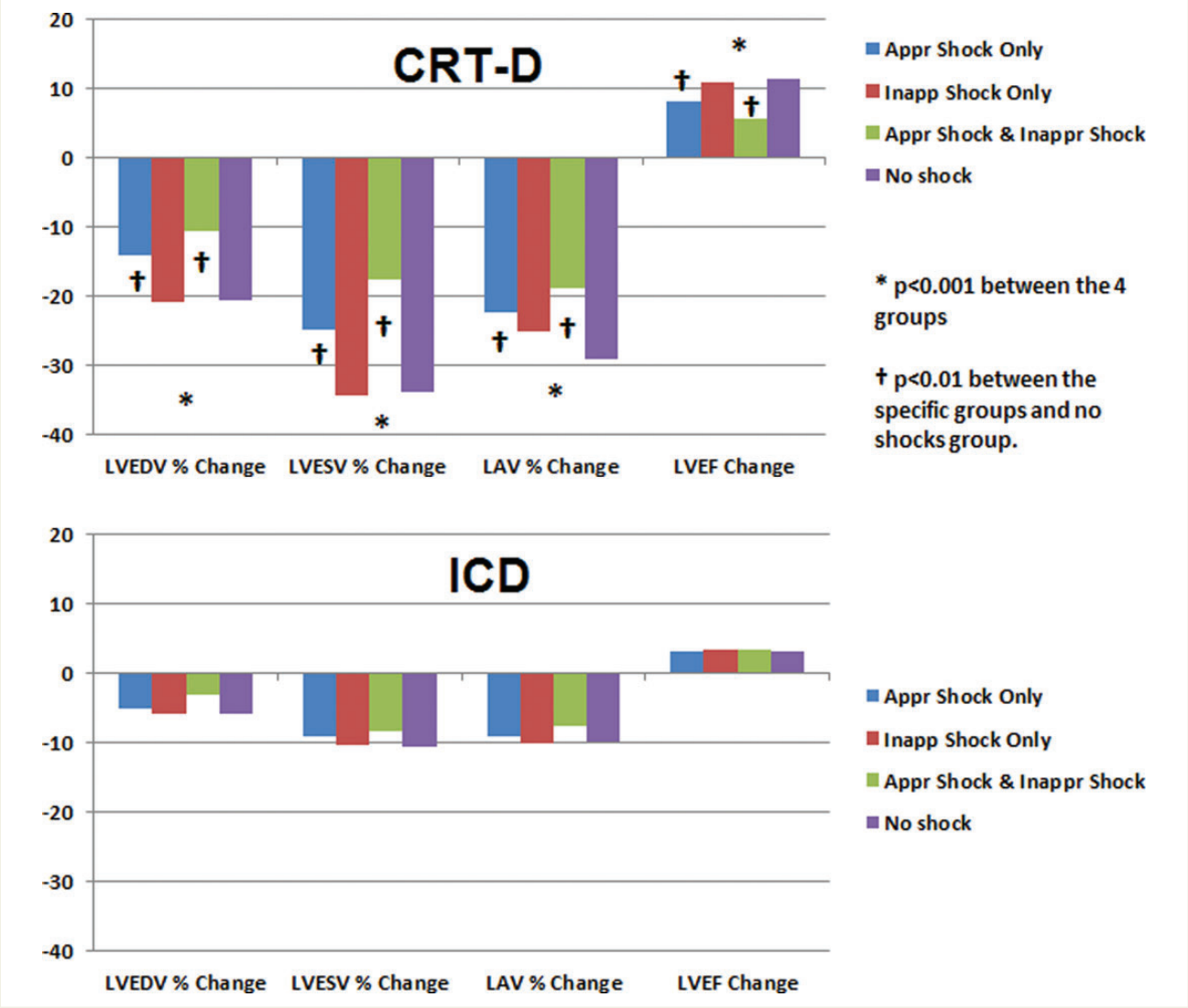


**Figure 4** Echocardiographic response within 1 year for cardiac resynchronization therapy-defibrillator (*A*) and implantable cardioverter defibrillator (*B*) patients. Bar graph showing percentage change in left ventricular end-diastolic volume, left ventricular end-systolic volume, left atrial volume, and left ventricular ejection fraction from baseline to 1-year follow-up. Cardiac resynchronization therapy-defibrillator patients who received an appropriate shock or both an appropriate and an inappropriate shock had significantly less echocardiographic remodelling at 1-year compared with cardiac resynchronization therapy-defibrillator patients who never received an implantable cardioverter defibrillator shock. Whereas cardiac resynchronization therapy-defibrillator patients who only received an inappropriate implantable cardioverter defibrillator shock had comparable remodelling to the cardiac resynchronization therapy-defibrillator patients who never received an implantable cardioverter defibrillator shock. No significant echocardiographic changes were seen in implantable cardioverter defibrillator patients at 1-year follow-up. The Kruskal–Wallis test was used to compare echocardiographic changes overall between all four groups (*), whereas Student's *t*-test was used to compare changes between two specific groups (†). LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume. LAV, left atrial volume; LVEF, left ventricular ejection fraction.

We were not able to show an association between inappropriate shocks and mortality in overall analysis or after adjusting for echocardiographic remodelling at 1 year. However, it seemed like the amount of inappropriate therapy (shocks and ATP) influenced the risk of mortality. Previously, the MADIT-II[10] and SCD-HeFT[9] studies have reported increased risk of mortality with inappropriate ICD shocks. However, there are important differences in the patient population of these studies compared with our study. Patients in SCD-HeFT and MADIT-II had a higher baseline incidence of AT (23% SCD-HeFT[9] and 18% MADIT-II[10] vs. 11% MADIT-CRT) and there was a lower utilization of beta-blockers in MADIT-II and SCD-HeFT compared with MADIT-CRT. Furthermore, the MADIT-CRT study only included patients in NYHA class I and II, whereas SCD-HeFT included patients in NYHA class II and III. All these factors might have contributed to a higher mortality and a higher rate of inappropriate shocks in MADIT-II and SCD-HeFT when compared with our results.

Interestingly, we found a borderline significant increased mortality risk in patients receiving inappropriate, but not appropriate ATP. After adjusting for echocardiographic changes at 1-year follow-up, this increased risk of mortality became highly significant ($P = 0.002$). Furthermore, the mortality risk associated with inappropriate ATP and shocks was significantly influenced by the amount of inappropriate therapies rendered. The majority of inappropriate therapies was rendered secondary to ATs. We find it likely that the increased risk of mortality seen in association with inappropriate ATP may be a surrogate marker of the independent association between the incidence of AT and mortality.[19,29] Therefore, we speculate that a higher atrial tachyarrhythmia burden may account for an increased risk of mortality seen in patients receiving >1 inappropriate ATP or shock, although clinical characteristics and medications were similar in this group compared with the rest of the cohort. Atrial tachyarrhythmia burden, catheter ablation, mean heart rate during atrial tachyarrhythmia, or/and advanced heart failure could also explain this association. Unfortunately, we do not have data available for these variables and are therefore not able to fully elucidate this association. However, we cannot eliminate the possibility of a harmful effect of the ATP and/or the shock in itself. During an episode atrial tachyarrhythmia, inappropriate ATP and /or shocks are often rendered multiple times in an already vulnerable myocardium, which might have a deleterious effect on the myocardium that has yet to be shown. Further studies are needed to study this association in detail. The recent MADIT-RIT[30] study revealed a dramatic reduction in both mortality and inappropriate therapy with simple ICD programming changes. Although, not yet reported, one can speculate that the reduction in mortality may have been associated with the reduction seen in inappropriate therapy, which would be consistent with our results.

We also investigated whether ICD shock burden was associated with increased mortality, as reported in a recent study.[12] We found a higher and more significant mortality risk, when two or more appropriate shocks were given than when one appropriate shock was delivered.

Thus, in this study we showed that appropriate ICD shocks are associated with an increased mortality. Appropriate ATP was not associated with an increased risk of mortality. However, the majority of the ATPs rendered was for rhythms with heart rates <200, suggesting that the underlying rhythm of the appropriate therapy is not the reason for the increased mortality, but the rate of the rhythm may contribute to a more vulnerable myocardium. Furthermore, advanced myocardial structural disease, i.e. higher baseline echocardiographic volumes and lack of remodelling at 1 year, was present only in patients who received appropriate shocks alone or in combination with inappropriate shocks. The association between increased mortality and appropriate ICD shocks remained after adjustments for these parameters. Therefore, we postulate that ICD shocks have a deleterious effect on mortality only when vulnerable myocardium is present. We speculate that the association of ICD shocks and mortality is multifactorial and involves advanced structural myocardial disease, co-morbid conditions, and possibly deleterious effects from ICD shocks themselves.

The current study is limited by the *post hoc* nature of our analyses. However, this study is the first to provide data on myocardial substrate in patients receiving ICD shocks and we consider this to be a hypothesis generating study. Randomized controlled trial evaluating both myocardial substrate and clinical outcomes in patients receiving ICD shocks is required to solve this long debated topic in our field.

## Clinical implications

Increased risk of mortality seen in ICD-treated patients with heart failure and cardiomyopathy may be a combination of structural myocardial disease, remodelling, and effect of shocks. Given the psychological and economical impact of ICD shocks, ICD programming to avoid appropriate and inappropriate shocks and *a priori* identification and treatment of early decompensated heart failure, atrial fibrillation, and other clinical predictors is of utmost importance in reducing ICD therapy and improving quality of life and survival in patients with cardiomyopathy and heart failure.

## Limitations

This was a *post hoc* analysis of the MADIT-CRT study, which might contribute to potential bias and our results should be interpreted thereafter. The groupings used in the current study were not according to the original randomization and therefore, imbalances between the groups were present. Differences in baseline characteristics between the groups were taken into account in multivariate analyses, but other unmeasured confounders might affect the results in an unknown fashion.

Since the MADIT-CRT study only included NYHA class I and II patients, these results may not relate to patients with more advanced heart failure.

In the landmark analysis, we acknowledge that the results may be biased by (i) the fact that we do not know the 12 months clinical characteristics of the patients and (ii) since the landmark analysis only included patients with paired baseline and 12 months echocardiographic measurements, patients who died within the first year are not included and may therefore bias the results.

# Conclusion

In the MADIT-CRT study, receiving appropriate ICD shocks was associated with an increased risk of mortality. This was not observed in patients who only experienced appropriate ATP. These findings, along with advanced cardiac structural disease in the patients who received appropriate shocks, suggest a correlation between appropriate ICD shocks, advanced myocardial structural disease, and increased mortality, indicating that compromised myocardium is a contributing factor to the increased mortality associated with appropriate ICD shock therapy, and that ICD shocks only have a deleterious effect on mortality when vulnerable myocardium is present.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

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