Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials

Matthew J. Shun-Shin, Sean L. Zheng, Graham D. Cole, James P. Howard, Zachary I. Whinnett*, and Darrel P. Francis

Imperial College London, National Heart and Lung Institute, Hammersmith Hospital Campus, B Block, 2nd floor, NHLI - Cardiovascular Science, Du Cane Road, W12 0NN London, UK

Received 7 November 2016; revised 21 November 2016; editorial decision 11 January 2017; accepted 13 January 2017; online publish-ahead-of-print 21 February 2017

See page 1747 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx096)

Aims
Primary prevention implantable cardioverter defibrillators (ICDs) are established therapy for reducing mortality in patients with left ventricular systolic dysfunction and ischaemic heart disease (IHD). However, their efficacy in patients without IHD has been controversial. We undertook a meta-analysis of the totality of the evidence.

Methods and results
We systematically identified all RCTs comparing ICD vs. no ICD in primary prevention. Eligible RCTs were those that recruited patients with left ventricular dysfunction, reported all-cause mortality, and presented their results stratified by the presence of IHD (or recruited only those with or without). Our primary endpoint was all-cause mortality. We identified 11 studies enrolling 8567 participants with left ventricular dysfunction, including 3128 patients without IHD and 5439 patients with IHD. In patients without IHD, ICD therapy reduced mortality by 24% (HR 0.76, 95% CI 0.64 to 0.90, P = 0.001). In patients with IHD, ICD implantation (at a dedicated procedure), also reduced mortality by 24% (HR 0.76, 95% CI 0.60 to 0.96, P = 0.02).

Conclusions
Until now, it has never been explicitly stated that the patients without IHD in COMPANION showed significant survival benefit from adding ICD therapy (to a background of CRT). Even before DANISH, meta-analysis of patients without ischaemic heart disease already showed reduced mortality. DANISH is consistent with these data. With a significant 24% mortality reduction in both aetiologies, it may no longer be necessary to distinguish between them when deciding on primary prevention ICD implantation.

Keywords
Implantable cardiac defibrillators • Meta-analysis • Ischaemic heart disease • Cardiomyopathy • Non-ischaemic • Heart failure

Introduction
Implantable cardiac defibrillators (ICD) are established as preventing death in patients with left ventricular dysfunction and ischaemic heart disease (IHD).\(^1\) In patients without IHD, however, ICDs are already considered controversial,\(^2\) and recent trial data have been interpreted as indicating that they are not beneficial.\(^3\)
We set out to analyse the totality of RCT data of ICD vs. no ICD therapy in primary prevention of mortality in patients with left ventricular dysfunction.

Methods

Eligibility and search strategy
We identified all reports of studies of the use of ICD therapy against no ICD therapy for primary prevention in patients with left ventricular systolic dysfunction, in which outcome data was available stratified by the presence of IHD, or recruited only one of these two groups. We included cardiac resynchronization therapy (CRT) RCTs that included a defibrillator arm (CRT-D) and a cardiac resynchronization pacing only arm (CRT-P). We did not include comparisons between CRT-D and no device.

Pubmed (1st January 1946 to 18th December 2016), EMBASE (1st January 1974 to 18th December 2016), and the Cochrane Central register for randomized controlled trials used the search strategy detailed in Supplementary material online, Appendix S1. Only articles in English were considered. Reference lists and relevant systematic reviews were hand-searched for additional publications. No published protocol exists for this systematic review and meta-analysis.

Data abstraction
Data was independently extracted by two authors (SZ, MJS), including year, participants, intervention, and outcomes. Disagreements were resolved by discussion with a third reviewer (DPF). The risk of bias was independently assessed by two authors (SZ, MJS). We sought data on the primary outcome measure of all-cause mortality. Secondary outcome measures included cardiovascular mortality and sudden cardiac death. We also collected data on specific ICD associated complications including inappropriate shocks and device-related infections. We abstracted reported hazard ratios with confidence intervals, and appropriately transformed them for meta-analysis. If hazard ratios or their confidence intervals were not available, but Kaplan-Meier plots were available, we extracted the underlying data using Digitizer and converted to hazard ratios and their standard errors. If a trial randomized patients to control, CRT-Defibrillator, and CRT-Pacemaker; and only presented data stratified by aetiology for the CRT-Defibrillator vs. control, and CRT-Pacemaker vs. control comparisons; the effect of the defibrillator component was determined by indirect comparison of the CRT-Defibrillator vs. the CRT-Pacemaker arms. The steps used to calculate the hazard ratio effect of the defibrillator component, and derive its confidence interval, for the groups with and without IHD separately, are shown in Supplementary material online, Appendix S2, and are based on formulae from Tierney et al.

If hazard ratio data were unavailable we extracted risk ratios.

Risk of bias assessment
We used the Cochrane Risk of Bias Tool to assess all trials for bias across six domains (selection, performance, detection, attrition, reporting, and other).

Data analysis
Where appropriate, we quantitatively synthesised the extracted hazard ratios and risk ratios using a random-effects meta-analyses with the Restricted Maximum Likelihood (REML) estimator. We calculated the annualized mortality rate across for each aetiology by dividing the overall mortality rate in the control group by the mean follow-up time, and weighting by study size. The $I^2$ statistic was used to measure heterogeneity of trial results. We carried out a sensitivity analysis for patients without IHD by omitting each of the trials in turn and repeating the meta-analysis. Publication bias was graphically assessed using Funnel plots, with Egger’s test for asymmetry. Data were analysed using “R” and the package “metafor”. The PRISMA checklist is included as Supplementary Data.

Results

The primary study yielded 2698 records, which were processed as shown in the study flow chart (Figure 1). Full-text was independently reviewed for 219 articles and 11 trials of ICD therapy for primary prevention were included. Three additional articles reported secondary outcomes for included trials. Two trials enrolled patients with left ventricular dysfunction regardless of aetiology, six eight four trials enrolled patients exclusively without IHD, nine 9–12 three exclusively with chronic IHD,12,13,14 and two trials exclusively after an acute myocardial infarction.15,16 One trial used amiodarone as the comparator, all other trials continued prescribed therapy.

Three trials7–9 were excluded as they recruited patients resuscitated from an arrhythmic cardiac arrest, with an ICD inserted as secondary prevention. One trial30 was excluded as, whilst it was a randomized controlled trial, allocation to insertion of an ICD was not randomized.

A total of 8567 participants were enrolled (4371 ICD therapy, 4196 control), 3128 without IHD and 5439 with IHD (Table 1, study characteristics).

Risk of bias assessment
Trial quality was assessed using Cochrane risk of bias tool (Table 2). There was no effective blinding of therapy in any of the trials. We assessed our primary end-point of all-cause mortality as having a low risk of bias. End-points requiring clinical judgement, such as sudden cardiac death and cardiovascular death, are at risk of bias if assessors are not blinded. Only five of the eleven trials reported on procedures to blind end-point assessment. Secondary outcomes were poorly reported, and often used different statistical measures to the primary outcome.

Populations studied
Across the 11 trials, the mean age was 63.1 years. Most trials enrolled patients with an EF ≤ 35%; two trials enrolled those with an EF ≤ 30%19,20 and one enrolled those with an LVEF ≤ 40%.26 All trials included patients with NYHA Class III symptoms. In 5 trials only patients who were NYHA Class II and III were included. Three trials included patients with NYHA Class IV symptoms, but these accounted for only a small proportion of patients (14%, 4%, 1%). One trial6 did not recruit NYHA Class II patients. 5 trials included NYHA Class I patients.

The electrophysiology inclusion criteria varied between the trials with 6 trials enrolling based on previous NSVT or ectopics, and 5 having no specific electrophysiological inclusion criteria. In one trial,21 ICDs were placed with epicardial leads during coronary artery bypass grafting (CABG) surgery. In one trial,24 47% were placed with epicardial leads and 53% placed with transvenous leads.
In all other studies transvenous leads were used. The studies enrolling patients with chronic IHD recruited patients at least 3 weeks after previous MI; those enrolling patients with acute MI within 31 days or 40 days of an MI. Baseline characteristics, inclusion, and exclusion criteria are detailed in Table 1.

**Effect on all-cause mortality**

**Left ventricular dysfunction without ischaemic heart disease**

Across the 3128 patients without ischaemic heart disease, there was a significant reduction in all-cause mortality with minor heterogeneity (HR 0.76, 95% CI 0.64 to 0.90, \( P = 0.001 \), \( I^2 = 3\% \). Figure 2). The annualized mortality rate in control patients was 5.4%.

A sensitivity analyses, carried out by omitting each of the trials in turn, in each case shows a statistically significant consensus reduction in mortality (see Supplementary material online, Appendix S4). A funnel plot did not show any significant asymmetry (Egger’s test \( P = 0.2 \), Supplementary material online, Appendix S5).

**Left ventricular dysfunction with ischaemic heart disease**

Across the 3867 patients in all trials of primary prevention ICD therapy with ischaemic heart disease and no recent MI, there was a non-significant reduction in all-cause mortality (pooled HR 0.81, 95% CI 0.65 to 1.03, \( P = 0.08 \), Figure 3A). However, there was substantial heterogeneity (\( I^2 = 62\% \)). One trial was unique in inserting the ICD at the time of CABG surgery. There was a 16% higher infection rate in the ICD group, with 4.3% requiring removal. Current practice is to minimize infection risk by implanting the cardiac device separately from any open surgery. Running the analysis for the trials that tested this approach showed a significant reduction in mortality (HR 0.76, 95% CI 0.60 to 0.96, \( P = 0.02 \), \( I^2 = 52\% \), Figure 3B). The annualized mortality rate in the control patients was 11.3%. A funnel plot did not show any significant asymmetry (Egger’s test \( P = 0.2 \), Supplementary material online, Appendix S5).

**Left ventricular dysfunction with acute myocardial infarction**

In the 2 trials that enrolled 1572 patients after an acute MI, ICD therapy did not cause a significant reduction in mortality (HR 1.05, 95% CI 0.86 to 1.30, \( P = 0.6 \), \( I^2 = 0\% \), Figure 4). The annualized event rate in the control patients was 7.6%. Supplementary material online, Appendix S5 contains the funnel plot.

**Effect on secondary outcomes**

Secondary outcomes were inconsistently reported with not all trials presenting data. Some data were presented as raw counts from which risk ratios could be derived, and some as hazard ratios. ICD therapy was consistently associated with a statistically significant
### Table 1: Study characteristics

| Trial | CABG-Patch | MADIT I | MADIT II | CAT | AMIOVIRT | DEFINITE | DINAMIT | COMPANION | SCD-HeFT | IRIS | DANISH |
|-------|------------|---------|----------|-----|----------|----------|---------|-----------|----------|------|--------|
| Year  | 1996       | 1996    | 2002     | 2003| 2004     | 2004     | 2005    | 2009      | 2016     |
| Author| Bigger     | Moss    | Moss     | Bianschi| Strickberger| Kadish  | Hohnloser| Birswig   | Bardsy   | Stanbæk| Kober  |
| Intervention | ICD | ICD    | ICD     | ICD | ICD      | ICD      | ICD    | ICD       | ICD      | ICD   | ICD    |
| Control | SMT | SMT    | SMT     | SMT | SMT      | SMT      | SMT    | SMT       | SMT      | SMT   | SMT    |
| LVIF cut-off | <35% | <30%   | <30%    | <35%| <35%     | <35%     | <35%   | <40%      | <35%     | <35%  | <35%   |
| Randomized (N) | 900 | 196    | 1232    | 104 | 103      | 458      | 674    | 1520      | 1676     | 898   | 1116   |
| Without IHD | –   | –      | 100%     | (n = 104) | 100%     | (n = 458) | 100%   | 100%      | 100%     | 100%  | 100%   |
| With IHD | 100% (n = 900) | 100% (n = 196) | 100% (n = 1232) | – | –       | 100% (n = 103) | 100% (n = 458) | 100% | 100% (n = 1116) | – |
| ICD group N | 446 | 95     | 742      | 50  | 51       | 229      | 332    | 359       | 829      | 445   | 536    |
| Follow-up (months) | 32 | 27     | 20       | 66  | 24       | 29       | 30     | 15.8      | 45.5     | 37    | 67.6   |
| Primary outcome | ACM | ACM    | ACM      | ACM | ACM      | ACM      | ACM    | ACM       | ACM      | ACM   | ACM    |
| Inclusion criteria | Undergoing CABG, abnormal ECG, MI, NYHA 1–3 Recent DCM diagnosis, NYHA 1–3, asymptomatic | | | | Symptomatic DCM, recent HF hospitalization | | | NYHA class 2–3, OMST | | | NYHA 2–4, raised NT-proBNP |
| Exclusion criteria | Sustained VT or VF Cardiac arrest, syncope, VT, MI within 1 month | | | | | Syncope | NYHA 4, familial cardiomyopathy | | NYHA 4, ventricular arrhythmia before or ≥48 h after | |
| EP inclusion criteria | QRS ≥ 114 or other signal averaged ECG abnormalities | | | | | VE | Excluded VT, VF, asymptomatic | | None | None |
| IHD definition | Undergoing CABG Q wave or cardiac enzyme positive MI | | | | | | | | \| | No significant CAD on invasive or CT angiogram, or normal MPS. Allowed 2 stenosed coronaries if felt not significant. |
| Time after MI | – | >3 weeks | >1 month | NA | NA | NA | 6–40 days | – | – | 5–31 days | NA |
| ICD type | Epicardial | Epicardial 47% Transvenous Transvenous Transvenous Transvenous Transvenous Transvenous Transvenous Transvenous | | | | | | | | |
| CRT implantation permitted | – | – | – | – | – | – | – | – | – | – | Yes |
| Age (mean±sd) | 64±9 | 63 | 65±10 | 52±11 | 59±12 | 58 (range 20–84) | 62±11 | 67 | 60 | 63±11 | 64 |
| Male | 84% | 92% | 85% | 80% | 70% | 71% | 76% | 68% | 77% | 77% | 73% |
| ACEi/ARB | 54% | 62% | 70% | 86% | 97% | 95% | 89% | 96% | 82% | 97% |
| BB | 21% | 23% | 70% | 4% | 52% | 83% | 87% | 68% | 69% | 98% | 92% |
| CRT | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% | 0% |
| LVIF | 27% (Mean) | 26% (Mean) | 23% (Mean) | 24% (Mean) | 23% (Mean) | 21% (Mean) | 28% (Mean) | 21% (Median) | 25% (Median) | 35% (Mean) | 25% (Median) |
reduction in hazard ratio and risk ratios for all three groups (without IHD, with IHD, and acute MI) for sudden cardiac death (without IHD HR 0.4 RR 0.29; with IHD HR 0.38 RR 0.41; acute MI HR 0.49, RR 0.57, Supplementary material online, Appendix S3).

Discussion

Based on high-quality data from RCTs, this meta-analysis finds that primary prevention ICDs reduce all-cause mortality in patients with left ventricular dysfunction both with and without IHD. No benefit from ICDs is seen in the setting of acute myocardial infarction. These findings are consistent with the current ESC guideline recommended management.31,32

Patients without ischaemic heart disease

There has been controversy over the utility of ICDs in patients without IHD. Many of the published guidelines make a distinction between the aetiologies with respect to the level of evidence on which their recommendations are made. The 2015 European Society of Cardiology (ESC) ventricular arrhythmia guidelines,31 and the 2016 ESC heart failure guideline32 give ICDs for primary prevention a 1A recommendation for an ischaemic aetiology, and 1B for a non-ischaemic aetiology. Indeed, this uncertainty was the stimulus for conducting the recent DANISH study. Subsequent commentary3 has added to the uncertainty.

Part of this uncertainty may have arisen as mortality rate in patients without IHD is lower than those with IHD (5.4%/year vs. 11.3%/year, respectively), and consequently the confidence intervals are wider for individual trials.

However, all the point estimates lie in the range 0.55 to 0.87, and the trials showed minimal heterogeneity ($I^2 = 3\%$). The group without IHD in COMPANION was, even on its own, statistically significant for a reduction of all-cause mortality with ICD (see Supplementary material online, Appendix S2), although this was not the chosen central message of the COMPANION primary publication.

Our meta-analysis confirms a statistically significant reduction in all-cause mortality by primary prevention ICD in patients without IHD. Whilst only one trial was individually significant, the point estimates from all 6 trials were in the same direction, suggestive of benefit. Furthermore, even omitting both COMPANION and the recent DANISH trial from the meta-analysis still produces a statistically significant consensus reduction in mortality (see Supplementary material online, Appendix S4).

Patients with ischaemic heart disease

This meta-analysis supports the current consensus that ICDs reduce all-cause mortality in left ventricular dysfunction with IHD, in the trials that use the current clinical convention of a dedicated device implant procedure. Interestingly, the reduction in hazard ratio is numerically the same (24%) in patients with and without IHD. Consequently, when considering ICD therapy, distinctions between the two groups may be unnecessary.

In acute myocardial infarction, however, there is no indication of a reduction in all-cause mortality.
| Trial | CABG-Patch | MADIT I | MADIT II | CAT | AMIOVIRT | DEFINITE | DINAMIT | COMPANION | SCD-HeFT | IRIS | DANISH |
|-------|------------|---------|----------|-----|----------|----------|---------|-----------|----------|------|--------|
| Year  | 1996       | 1996    | 2002     | 2002| 2003     | 2004     | 2004    | 2005      | 2009     | 2016 | 2016   |
| Author| Bigger     | Moss    | Moss     | Bansch| Strickberger| Kadish   | Hohnloser| Bristow   | Brady    | Steinbeck | Køber   |
| Random sequence generation (selection bias) | Low risk | Mass | Unclear–not reported | Mass | Undisclosed | Low risk–central randomization | Low risk–central | Undisclosed | Low risk | Low risk | Low risk |
| Allocation concealment (selection bias) | Unclear | Unclear–not reported | Unclear–not reported | Low risk–“closed envelope with the assigned study group were sent to each centre … envelopes were opened when a patient was enrolled” | Unclear–not reported | Unclear–not reported | Low risk–“patients, physicians … were not blinded to the treatment assignments” | Low risk–“steering committee and endpoint committee were unaware of the treatment assignments” | Low risk | Low risk | Low risk |
| Blinding of participants and personnel (performance bias) | High–“nature of the intervention precluded the blinding of investigators or patients” | High-risk | High-risk | High-risk | High-risk | High-risk | High-risk | High-risk | High-risk | High-risk | High-risk |
| Blinding of outcome assessment (performance bias) | Unclear–“accumulating data were reviewed by an independent Data and Safety Monitoring Board”, but no report of whether outcome assessments were blindly assessed | Unclear–“two member-endpoint subcommittee reviewed information on the causes and circumstances of death”, but no report of whether blinded | Undisclosed | Undisclosed | Low–“events committee determined the cause of death” … “independently evaluated all information available” and “to assure a blinded review, all references to amiodarone or ICD therapy was removed from the reviewed documents” | Low–“cause of death was determined by an events committee” … “unaware of patients’ treatment assignment” | Low–“ascertainment of the cause of death was the responsibility of the local investigators”, but a “blinded central validation committee independently reviewed information on all deaths” | Low–“steering committee and endpoint committee were unaware of the treatment assignments” | Low–“adverse-event committee that was unaware of the treatment assignments classified the causes of death” | Low–“endpoint classification committee, the members of which were unaware of the treatment assignments, used prespecified criteria to adjudicate all prespecified clinical outcomes” | Low–“endpoint classification committee” | Low–“endpoint classification committee” |
| Incomplete outcome data (attrition bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Selective reporting (reporting bias) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Other bias | Trial funded by CPI/Guidant who supplied devices, but had no role in design, analysis, interpretation or writing | Trial funded by CPI/Guidant who supplied devices, but had no role in design, analysis, interpretation or writing | Trial funded by CPI/Guidant who supplied devices, but had no role in design, analysis, interpretation or writing | Supported in part by an unrestricted research grant from the Guidant Corporation | Trial funded by St Jude who supplied devices, but had no role in design, analysis, interpretation or writing | Trial funded by St Jude who supplied devices, but had no role in design, analysis, interpretation or writing | Trial funded by Guidant who supplied devices, but had no role in design, analysis, interpretation or writing | Trial funded by Medtronic who supplied devices and had access to the final pre-submission manuscript | Trial funded by Medtronic who supplied devices and had access to the final pre-submission manuscript | Trial funded by Medtronic, St Jude, TrygFonden, but had no role in design, analysis, interpretation or writing | Trial funded by Medtronic, St Jude, TrygFonden, but had no role in design, analysis, interpretation or writing |
Difference between this meta-analysis and previous meta-analyses

Our meta-analysis is the first to include the results of the patients without IHD from the COMPANION and DANISH trials. Other meta-analyses have omitted COMPANION, presumably because the paper did not display the hazard ratio explicitly. However, the hazard ratio and its confidence interval can be calculated from the steps shown in Supplementary material online, Appendix S2. The current meta-analysis therefore provides important new information regarding the role of ICD therapy in patients with left ventricular dysfunction without IHD.

Study limitations

Any meta-analysis can only examine studies that have actually been carried out. Different studies took different approaches to recruitment. However, it is notable that all six non-ischaemic trial results were concordant not only in the direction of effect, but also the approximate magnitude, with the $I^2$ statistical test showing minor heterogeneity.

In the case of the COMPANION trial, the hazard ratio was calculated using the information published in the primary publication by steps shown in Supplementary material online, Appendix S2. The original publication did not comment on this hazard ratio. It is wise to be cautious of results of sub-group analyses, because many such analyses are possible and some will be positive by chance alone. However, the single most important dichotomy in current guidelines for primary prevention ICDs in left ventricular systolic dysfunction is the presence vs. absence of ischaemic heart disease. Therefore, this sub-group analysis need not be assumed to be a random result selected from many possible sub-groups analyses. Moreover, all six groups of patients without ischaemic heart disease showed the same direction of effect. Furthermore, the finding is stable to the removal of any one trial (see Supplementary material online, Appendix S4).

Background medical therapy has improved over the time-course of these trials, with only 4% treated with beta-blockers in the CAT (2002), but 92% in DANISH (2016). Whilst the relative mortality-reduction effect size has remained remarkably consistent over time this will reduce the absolute effect size (when analysed over a fixed time window) of ICDs for primary prevention.

Our study could not consider the degree to which comorbidities might affect results. It has been noted that patients recruited into trials often have fewer comorbidities than those in the general population. The external validity of RCTs is always challenged by this, particularly in conditions such as heart failure where comorbidities may be frequent and severe. Furthermore, whilst this meta-analysis finds that stratifying by the presence or absence of ischaemic heart disease does not influence the mortality benefit of ICDs in primary prevention, other factors might. Supplementary material online, Appendix S4 includes data stratified by the presence or absence of CRT, but this analysis is hindered by the limited data in CRT group which is derived from COMPANION and a sub-group of DANISH. The 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy similarly recognize that limited RCT data is available for the comparison between CRT-P and CRT-D. The guidelines suggest clinical conditions such as advanced or end-stage cardiac or renal disease may favour CRT-P over CRT-D.

Clinical implications

The challenge facing clinical trials, as highlighted by McMurray, is that skilful modern treatment algorithms have reduced event rates down to low levels in the types of patients who would be eligible for, and willing to enter, randomized controlled trials; the annualized rate is...
5.4% in patients without IHD. In light of this perhaps, we should pay maximal attention to information that RCTs give us.

The low event rate in the trials is why viewing multiple trials is necessary to see the survival benefit. However, the 24% risk reduction is as sizable as one might realistically hope for, for any intervention. This meta-analysis provides strong support for the role of primary prevention ICDs in patients with left ventricular dysfunction. A 24% risk reduction in all-cause mortality is comparable with other therapies which we recommend in heart-failure such as candesartan or an angiotensin-neprilysin inhibitor (HR 0.77, 0.84, respectively).

**Conclusions**

In patients with left ventricular dysfunction, primary prevention ICDs reduce mortality. ICDs reduce mortality by 24% in both patients with (P = 0.03) and without IHD (P = 0.0023).
When deciding on ICD therapy, classification of heart failure by aetiology may therefore not be useful.

**Supplementary material**

Supplementary material is available at European Heart Journal online.

**Funding**

This work was supported by the British Heart Foundation [grant numbers FS/14/27/30752 (MJS), FS/12/12/29294 (GC), FS/13/44/30291 (ZW), FS/10/038 (DPF)].

**Conflict of interest**

M.J.S., S.Z., J.P.H., G.C., and D.P.F. declare no conflict of interest. ZW has received speaker fees from St. Jude, and a recent grant unrelated to this work from Medtronic.

**References**

1. Bets TR, Sadarmin PP, Tomlinson DR, Rajappan K, Wong KCK, Bono JP, D. Bashir Y. Absolute risk reduction in total mortality with implantable cardioverter defibrillators: analysis of primary and secondary prevention trial data to aid risk/benefit analysis. European 2013;15:813–819.

2. Kasumoto FM, Calhoun H, Boehmer J, Buxton AE, Chung MK, Gold MR, Hohnloser SH, Indik J, Lee R, Mehra MR, Monen V, Page RL, Shen W-K, Slotwiner DJ, Stevenson LW, Varoy PD, Weiskovitch L, HRS/LACCI/AHA expert consensus statement on the use of implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials. Circulation 2014;130:94–125.

3. McMurray JJV. The ICD in heart failure—time for a rethink? N Engl J Med 2016;375:1283–1284.

4. Plot Digitizer [Internet]. Available from: http://plotdigitizer.sourceforge.net/. (24 January 2017).

5. Strickberger SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, Bitar J. Absolute risk reduction in total mortality with implantable cardioverter-defibrillator in patients with coronary disease at high risk for ventricular arrhythmias and the prevention of sudden cardiac death: the task force of the European Society of Cardiology (ESC). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Available from: https://www.R-project.org/. (24 January 2017).

6. Stroicklerberg SA, Hummel JD, Bartlett TG, Frumin HI, Schuger CD, Beau SL, Bitar C, Morady F. AMIOVIRT Investigators. Amiodarone versus implantable cardioverter-defibrillator: randomized trial in patients with nonischemic dilated cardiomyopathy and asymptomatic nonsustained ventricular tachycardia–AMIOVIRT. J Am Coll Cardiol 2003;41:1707–1712.

7. Higgins JPT, Altman DG, Gøtzsche PC, Juni P, Moher D, Oxman AD, Sterne JA. Cochrane Bias Methods Group, Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

8. Higgins JPT, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.

9. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.

10. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

11. Bigger JT, Whang W, Rottman JN, Kleger RE, Gottlieb CD, Namerow PB, Steinman RC, Estes NA. Mechanisms of death in the CABG Path trial: a randomized trial of implantable cardiac defibrillator prophylaxis in patients at high risk of death after coronary artery bypass graft surgery. Circulation 1999;99:1416–1421.

12. Reeder GS, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. MADIT-II Investigators. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43:1459–1465.
A meta-analysis of 8567 patients in the 11 trials

Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Europace 2015;17:1601–1687.

32. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, Gonzalez-Juanatey JR, Harjola VP, Jankowska E, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, Meer P, van der. Authors/Task Force Members. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016;37:2129–2200.

33. Colquitt JL, Mendes D, Clegg AJ, Harris P, Cooper K, Picot J, Bryant J. Implantable cardioverter defibrillators for the treatment of arrhythmias and cardiac resynchronisation therapy for the treatment of heart failure: systematic review and economic evaluation. Health Technol Assess 2014;18:1–560.

34. Boriani G, Berti E, Belotti LMB, Biffi M, Palma R, De Malavasi VL, Bottoni N, Rossi L, Maria E, De Mantovan R, Zardini M, Casali E, Marconi M, Bandini A, Tomasi C, Boggian G, Barbato G, Toselli T, Zennaro M, Sassone B. RERAI (Registry of Emilia Romagna on Arrhythmia Interventions) Investigators. Cardiac device therapy in patients with left ventricular dysfunction and heart failure: “real-world” data on long-term outcomes (mortality, hospitalizations, days alive and out of hospital). Eur J Heart Fail 2016;18:693–702.

35. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt O-A, Cleland J, Deharo-J-C, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–2329.

36. Granger CB, McMurray JJV, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Solomon SD, Swedberg K, Zile MR. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.