Systematic review for the 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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BACKGROUND Although large randomized clinical trials have found that primary prevention use of an implantable cardioverter-defibrillator (ICD) improves survival in patients with cardiomyopathy and heart failure symptoms, patients who receive ICDs in practice are often older and have more comorbidities than patients who were enrolled in the clinical trials. In addition, there is a debate among clinicians on the usefulness of electrophysiological study for risk stratification of asymptomatic patients with Brugada syndrome.

AIM Our analysis has 2 objectives. First, to evaluate whether ventricular arrhythmias (VAs) induced with programmed electrostimulation in asymptomatic patients with Brugada syndrome identify a higher risk group that may require additional testing or therapies. Second, to evaluate whether implantation of an ICD is associated with a clinical benefit in older patients and patients with comorbidities who would otherwise benefit on the basis of left ventricular ejection fraction and heart failure symptoms.

METHODS Traditional statistical approaches were used to address 1) whether programmed ventricular stimulation identifies a higher-risk group in asymptomatic patients with Brugada syndrome and 2) whether ICD implantation for primary prevention is associated with improved outcomes in older patients (>75 years of age) and patients with significant comorbidities who would otherwise meet criteria for ICD implantation on the basis of symptoms or left ventricular function.

RESULTS Evidence from 6 studies of 1138 asymptomatic patients were identified. Brugada syndrome with inducible VA on electrophysiological study was identified in 390 (34.3%) patients. To minimize patient overlap, the primary analysis used 5 of the 6 studies and found an odds ratio of 2.3 (95% CI: 0.63–8.66; p=0.2) for major arrhythmic events (sustained VAs, sudden cardiac death, or appropriate ICD therapy) in asymptomatic patients with Brugada syndrome and inducible VA on electrophysiological study versus those without inducible VA.

Ten studies were reviewed that evaluated ICD use in older patients and 4 studies that evaluated unique patient populations were identified. In our analysis, ICD implantation was associated with improved survival (overall hazard ratio: 0.75; 95% confidence interval: 0.67–0.83; p<0.001). Ten studies were identified that evaluated ICD use in patients with various comorbidities including renal disease, chronic obstructive pulmonary disease, atrial fibrillation, heart disease, and others. A random effects model demonstrated that ICD use was associated with reduced all-cause mortality (overall hazard ratio: 0.72; 95% confidence interval: 0.65–0.79; p<0.0001), and a second "minimal overlap" analysis also found that ICD use was associated with reduced all-cause mortality (overall hazard ratio: 0.71; 95% confidence interval: 0.61–0.82; p<0.0001). In 5 studies that included data on renal dysfunction, ICD implantation was associated with reduced all-cause mortality (overall hazard ratio: 0.71; 95% confidence interval: 0.60–0.85; p<0.001).

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Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, based on systematic methods to evaluate and classify evidence, provide a cornerstone of quality cardiovascular care. In response to reports from the Institute of Medicine [1,2] and a mandate to evaluate new knowledge and maintain relevance at the point of care, the ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) modified its methodology.[3–5]

Evidence Review

The Task Force recognizes the need for objective, independent evidence review committees (ERCs) that include methodologists, epidemiologists, clinicians, and biostatisticians who systematically survey, abstract, and assess the evidence to address systematic review questions posed in the PICOTS format (P=population, I=intervention, C=comparator, O=outcome, T=timing, S=setting).[2,4–6] Practical considerations, including time and resource constraints, limit the ERCs to evidence that is relevant to key clinical questions and lends itself to systematic review and analysis that could affect the strength of corresponding recommendations. Recommendations developed by the writing committee on the basis of the systematic review are marked "SR".

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The Task Force avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities (RWI). All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant RWI (Appendix 1). For transparency, ERC members' comprehensive disclosure information is available online, as is comprehensive disclosure information for the Task Force.

Glenn N. Levine, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

Part 1: For Asymptomatic Patients With Brugada Syndrome, What Is the Association Between an Abnormal Programmed Ventricular Stimulation Study and Sudden Cardiac Death and Other Arrhythmia Endpoints?

Introduction: Part 1

Brugada syndrome was first described in 1992 after the identification of a cohort of patients with recurrent episodes of sudden cardiac death (SCD) with characteristic electrocardiographic features including a right bundle-branch block and persistent ST elevation in leads V_1 to V_2–V_3.[7] Since this finding, diagnostic criteria for Brugada syndrome have been established.[8] Because of the arrhythmias observed in this syndrome, it has been suggested that electrophysiological study with programmed ventricular stimulation may be used to assess inducibility of ventricular arrhythmias (VA).[9] The potential use of electrophysiological study for risk stratification has been of interest for asymptomatic patients with typical electrocardiographic features but without documented arrhythmias or syncope. Early studies have suggested that electrophysiological study is useful in identifying those at risk for VA. However, more recent studies have suggested that there is limited value to performing an electrophysiological study in asymptomatic patients.[9–16] The implication is that for those patients with higher risk, an implantable cardioverter-defibrillator (ICD) would be suggested; however, ICD implantation is associated with procedural complications, post-procedural complications, and problems such as inappropriate therapy.[17] The indication for performing electrophysiological study in asymptomatic patients a priori remains controversial.[18] The objective of this study is to ascertain the prognostic value of electrophysiological study in asymptomatic patients with Brugada syndrome.

Methods: Part 1

A literature search of MEDLINE (via PubMed/OVID) and EMBASE (via OVID) was performed, with limits including publication dates from 1966 to 2016, English language, and human subjects, by Doctor Evidence, LLC (Santa Monica, CA). Study selection included these criteria: Asymptomatic patients with a diagnosis of Brugada syndrome who underwent electrophysiological study were included. All the studies based the diagnosis of Brugada Syndrome by electrocardiographic criteria and absence of structural heart disease. Patients defined as symptomatic, patients with syncope, patients who experienced SCD, patients with sustained VA, and patients with hypertrophic cardiomyopathy were

excluded. Patients with inducible VA on electrophysiological study were compared with those without inducible VA. The primary outcome was any major arrhythmic event (includes documented VA, SCD, and appropriate ICD therapy). Secondary outcomes included specifically appropriate shocks and SCD. Patients with <3 months of follow-up were excluded. Studies included were prospective and retrospective observational studies, case series, randomized controlled clinical trials (RCTs), and systematic reviews/meta-analyses. Case reports were excluded. Initial screening for meeting inclusion criteria was performed by Doctor Evidence. Manuscripts were then screened by 2 independent adjudicators to determine relevancy, and mutually agreed on studies were included for meta-analysis.

Meta-analysis was performed using the DOC Data 2.0 advanced web-based platform (Doctor Evidence: DOC Data, Version 2.0, Santa Monica, CA). All studies were summarized by raw rates (number of events and denominators). The primary analysis was performed using the Random Effect model, with 0.1 continuity correction. The Mantel-Haenszel and PETO methods were also used.

Results: Part 1

The literature search identified 236 titles and abstracts through MEDLINE/EMBASE database, using various combinations of identifiers for Brugada syndrome, right bundle-branch block, ST-segment, sudden death, electrophysiology, programmed ventricular stimulation, SCD, sustained VA, and ICD therapy. Seventy-two studies were selected for full-text analysis, of which another 66 were excluded (1 population not of interest; 1 intervention not of interest; 19 looking at other parameters on electrophysiological studies; 1 nonclinical study; 10 inadequate number of participants; 8 publications with shared data; and 25 outcome stratification not of interest) and 1 was exchanged for a more recent update on the patient population[14,19] (see Figure 1.1 for details of selection). In the end, 6 studies were selected for the meta-analysis.[10–14,16] To avoid potential duplication of data, we excluded 1 study [10] because part of this study's population was also included in a subsequent retrospective analysis [15] that is included in our analysis. However, because an unspecified proportion of their study population was not included in subsequent studies, a second meta-analysis including this study was also performed.

In the final 6 studies used for the analysis,[10–14,16] there were 1138 asymptomatic patients with Brugada syndrome, with inducible VA on electrophysiological study in 390 (34.3%) patients (Data Supplement 1). Of the patients with inducible VA, 13 total arrhythmic events occurred (3.3% of the patients with inducible VA). In asymptomatic patients with Brugada syndrome, 748 patients did not have inducible VA on electrophysiological study. There were 12 total arrhythmic events in this population (1.6% of the patients with noninducible VA). This results in an odds ratio (OR) of 2.3 (95% confidence interval [CI]: 0.63 to 8.66; p=0.20) for major arrhythmic events in asymptomatic patients with Brugada syndrome and inducible VA on electrophysiological study (Figure 1.2). Due to the small number of events, specific analyses of secondary outcomes could not be performed.

Including the original registry study of Brugada syndrome from 2003,[10] which may introduce duplication of patients, there were a total of 1,401 patients of whom 481 had inducible VA on electrophysiological study (34.3%). In this cohort, there were 24 arrhythmic events in the patients with inducible VA (5.0%). Among patients with noninducible VA, there were 14 arrhythmic events (1.5%). This results in an OR of 3.3 (95% CI: 1.03 to 10.4; p=0.04) for major arrhythmic events in asymptomatic patients with Brugada syndrome and inducible VA on electrophysiological study (Figure 1.3).

Two studies[20,21] were examined that specifically looked at long-term results in patients who underwent ICD implantation. A multicenter study [21] followed 166 asymptomatic patients with Brugada syndrome for 85 ± 36 months after ICD implantation. They reported 7% appropriate ICD shocks and 28% inappropriate shocks, and 1 death related to inappropriate shock–induced ventricular fibrillation. A recent analysis from another registry[20] described 13% appropriate shocks and 15% inappropriate shocks among 46 asymptomatic patients with Brugada syndrome over a 20-year period.

Discussion: Part 1

The role of inducibility of VA in electrophysiological study for risk stratification of asymptomatic Brugada syndrome has been a source of great debate.[8,22] A large observational study[10] had shown an extremely high incidence of spontaneous ventricular fibrillation (28%) in patients with inducible VA on electrophysiological study, as opposed to only 2% in patients with noninducible VA. Similarly, in a 20-year experience of patients with Brugada syndrome, inducibility of VA on electrophysiological study in asymptomatic patients had 75.0% sensitivity, 91.3% specificity, positive predictive value 18.2%, and negative predictive value 98.3% for spontaneous VA or ICD shocks.[23] However, this study included 137 patients that had been included in earlier Brugada syndrome registries.

Interestingly, the overall inducibility rate (symptomatic and asymptomatic patients) decreased from 49% to 18%, which also reflects the findings of a similar cohort.[10,23] Among asymptomatic patients in that cohort, the rates decreased from 34.6% to 10%.[10,15] Similarly, the annual event rate for VA or ICD shock decreased from 4.5% to 0.9%. These studies suggest that these findings might be related to an earlier selection bias as initial reports included patients at higher risk. These findings still differ widely from the PRELUDE (Programmed Electrical Stimulation Predictive Value) [12] and the FINGER (France, Italy, Germany) [14] registries of Brugada syndrome patients. In the PRELUDE registry [12], which included 273 asymptomatic patients, there was no significant difference in event rates between patients with inducible and noninducible VA. The more recent and larger FINGER registry [14] of 654 asymptomatic patients found a higher event rate in the patients with inducible VA (both symptomatic and asymptomatic), which was nonsignificant on multivariable analysis, with an overall low incidence of 0.5% in asymptomatic patients. Both the PRELUDE and FINGER registries had shorter median follow-up duration.[15] The 3 other studies included in our meta-analysis,[11,13,16] also showed no difference in event rates between asymptomatic patients with inducible and noninducible VA, with an extremely low overall event rate.

There was a wide range of inducibility of VA on electrophysiological study as outlined in Table 1. This may have been secondary to the patient population or the differences in the technical aspects of the ventricular stimulation protocol, also outlined in Table 1. Although some have suggested that a less aggressive ventricular stimulation strategy limited to the right ventricular apex might improve the specificity of electrophysiological study in prognostication of asymptomatic Brugada syndrome, this hypothesis remains untested.[23] A study assessing the impact of a number of extrastimuli in electrophysiological study [24] suggested that a less aggressive protocol limited to single or double extrastimuli resulted in a better positive predictive value and negative predictive value compared with triple extrastimulus testing (<3 extrastimuli: positive predictive value: 36%; negative predictive value: 87% versus 3 extra-stimuli: positive predictive value: 23%; negative predictive value: 81%). However, VA induction specifically from the right ventricular apex was not predictive of subsequent cardiac events.

The relatively high incidence of inappropriate ICD shocks in patients with Brugada syndrome [20,21] could be related to the relatively younger age of this population or programming strategies. One study demonstrated that the combination of R-wave amplitude >5 mV at implantation, optimal programming (long interval to detection duration, single high ventricular fibrillation zone >210 to 220 bpm), and close follow-up with remote monitoring was associated with lower rate of inappropriate shocks (0.7%/year compared with 3.7%/year in the general Brugada syndrome population).[21]

Our meta-analysis shows that for the outcome variables of VA and appropriate ICD shocks, there was no significant difference between asymptomatic patients with Brugada syndrome with or without inducible VA on electrophysiological study. However, inclusion of the additional study,[10] potentially leading to double counting patients, led to a modestly significant increased OR for arrhythmia in this population ($p=0.044$). In observing the Forest plot, the concern of patient overlap between the 2 studies[10,15] is quite evident. Only these 2 studies show positive significance for the inducible group with OR above unity. To evaluate whether there may have been a link between study size and treatment effect and to screen for any reporting bias, Funnel plots were performed and are shown in Figure 1.4 and Figure 1.5, both with and without inclusion of the additional study that could lead to potential double counting.

To summarize, our meta-analysis of relevant studies for the role of electrophysiological study in asymptomatic patients with Brugada syndrome suggests that inducibility of VA in asymptomatic patients does not predict higher VA or ICD shocks. In fact, the extremely low overall event rate in the asymptomatic population in almost all studies suggests that this population is at low risk for future cardiac events.

Limitations: Part 1

This meta-analysis is limited by a small number of events. This precludes subanalyses within the asymptomatic Brugada population, including patients with spontaneous type I patterns or other electrocardiographic patterns and those with family history of arrhythmic events. Although every effort was made to avoid duplication of populations, this remains a potential confounder, especially when adding the 2003 study.[10] The exact protocol for electrophysiological study could also not be evaluated given the small numbers and nature of reporting in the studies as this may influence inducibility.

Figures and Table

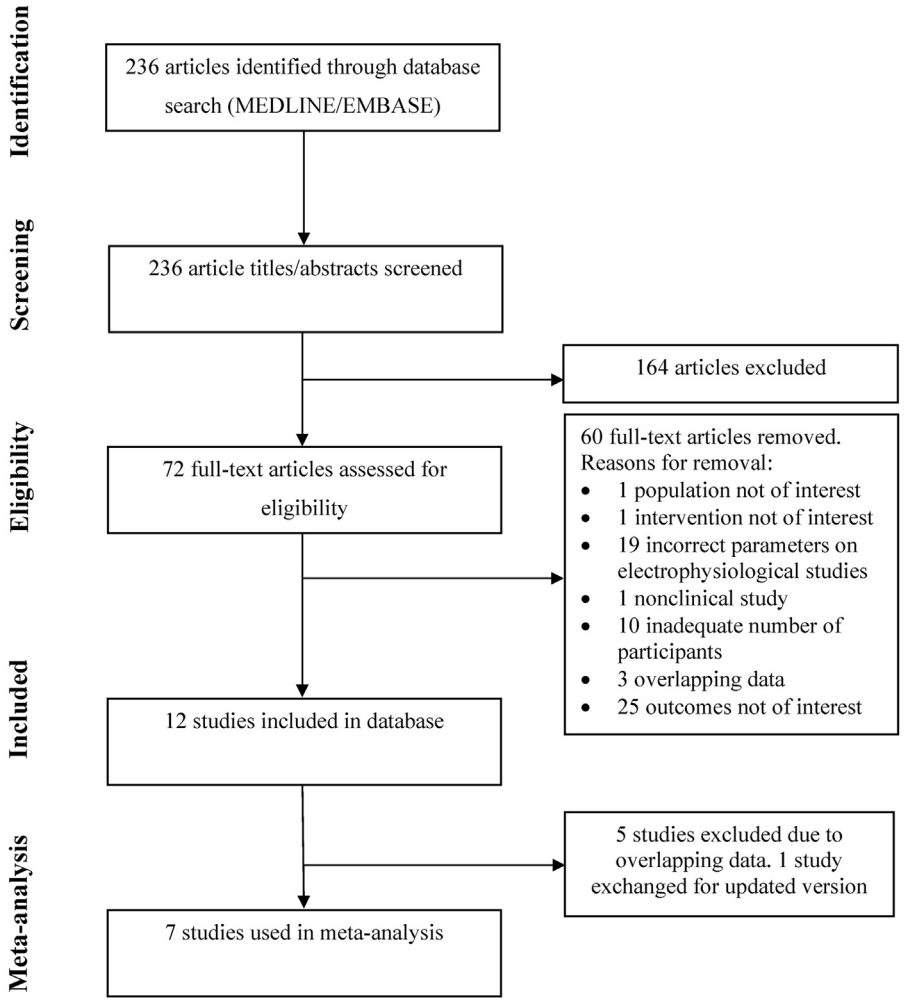

Figure 1.1 PRISMA Diagram Demonstrating Selection of Studies Included in the Meta-analysis.

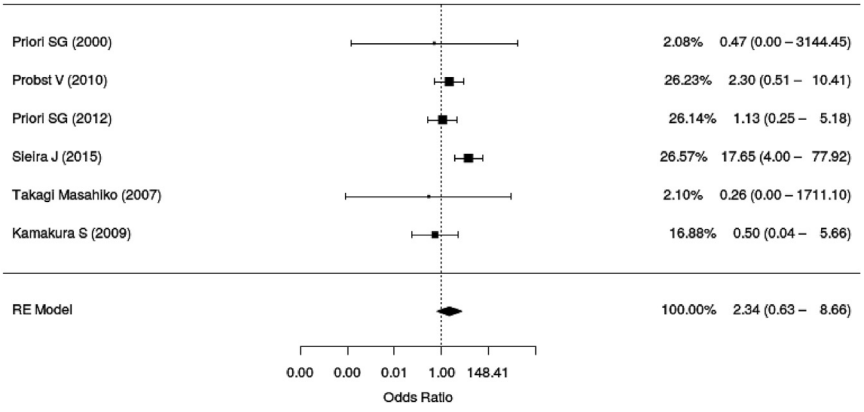

Figure 1.2 Forest Plot for Risk of All Arrhythmic Events Excluding Brugada et al. (2003).[10] RE = random effects.

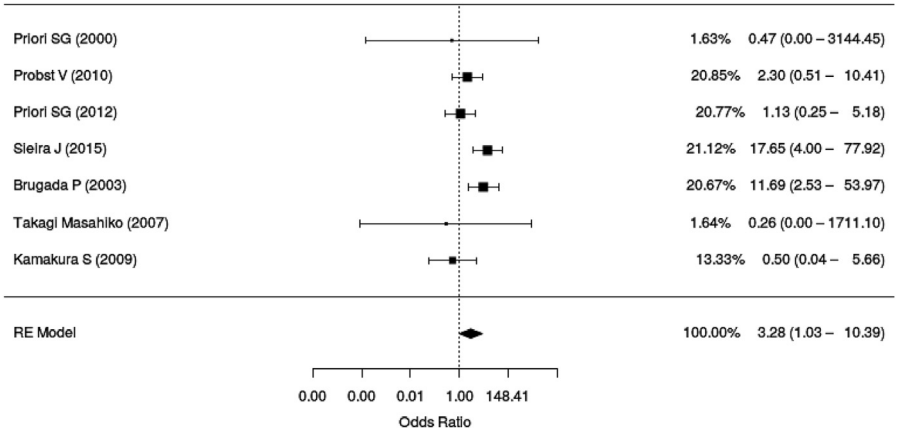

Figure 1.3 Forest Plot for Risk of All Arrhythmic Events Including Brugada et al. (2003).[10] RE = random effects.

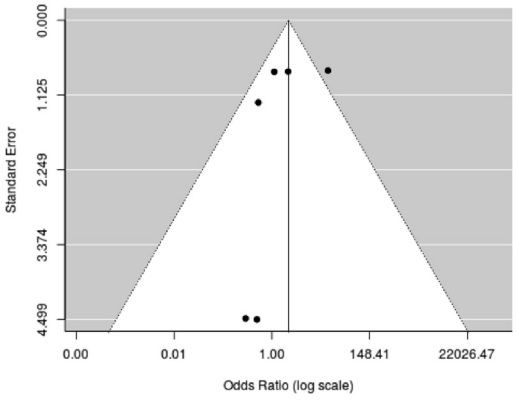

Figure 1.4 Funnel Plot for Risk of All Arrhythmic Events Excluding Brugada et al. (2003).[10]

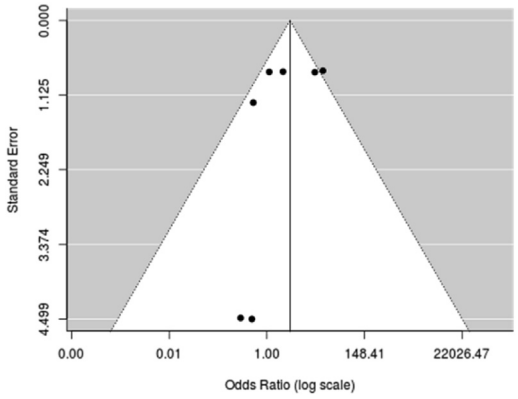

Figure 1.5 Funnel Plot for Risk of All Arrhythmic Events Including Brugada et al. (2003).[10]

Table 1 Summary of Electrophysiological Study Protocols and Inducibility Rates by Study Included

Study, Year, Reference	Positive EP Study	Protocol
Sieira, et al 2015 [15]	32/241 (13%)	Single site, 3 cycle lengths, 3 ES (≥200 ms)
Priori 2012, et al [12]	97/243 (40%)	2 sites (RVA, RVOT), 2 cycle lengths, 3 ES (≥200 ms)
Kamakura 2009, et al [11]	61/123 (50%)	2 sites (RVA, RVOT), 2 cycle lengths, 3 ES (does not mention a minimum CL)
Takagi, et al 2007 [16]	50/63 (79%)	Unspecified in the methods
Probst, et al 2010 [14]	137/369 (37%)	2 sites (unspecified), 2 cycle lengths, 3 ES (≥200 ms for a "positive" study)
Priori, et al 2000 [12]	6/19 (32%)	Unspecified in the methods but several sites and up to 3 ES (not uniformly specified by the protocol)
Brugada, et al 2003 [10]	91/263 (35%)	Single site (not RVOT), 2 cycle lengths, ≥2 ES (VERP)

EP = electrophysiological; ES = extrastimulus; RVA = right ventricular apex; RVOT = right ventricular outflow tract; VERP = ventricular effective refractory period.

Part 2: What Is the Impact of ICD Implantation for Primary Prevention in Older Patients and Patients With Significant Comorbidities?

Introduction: Part 2

Several RCTs have clearly established the mortality benefit of ICDs placed for primary prevention.[25–27] In general, candidates for ICD implantation for primary prevention of SCD are patients with heart failure (HF) and a left ventricular ejection fraction <30% to 40% as long as optimal medical therapy and a reasonable expectation of meaningful survival (>1 year) are present.[25–30] In this cohort including patients with ischemic and nonischemic cardiomyopathy, the reduction in mortality from the ICD ranges from 23% to 55%.[31,32] Similar benefit has also been described for subcutaneous ICD.[33,34] As such, with expanding indications and technological advances, the rate of implantation of the devices continues to rise.[32,35]

However, there are a number of RCTs demonstrating that certain subgroups do not clearly benefit from primary prevention ICD implantation. Patients with a recent myocardial infarction (within the past 40 days) and patients with revascularization by coronary artery bypass grafting [36,37] show no survival advantage with an ICD in place. Furthermore, a number of patient populations were not well studied in many of the landmark ICD RCTs and it is uncertain whether these subgroups also benefit from ICD implantation.[31,32]

Patients enrolled in many of the landmark RCTs may not be representative of patients who are evaluated and referred for ICD implantation in real-world practice. For example, the mean or median age of patients enrolled in pivotal trials ranged between 58 and 67 years (MUSTT [Multicenter Unsustained Tachycardia Trial],[28] MADIT-I [Multicenter Automatic Defibrillator Implantation Trial I],[26] MADIT-II [Multicenter Automatic Defibrillator Implantation Trial II],[27] SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial],[25] CABG-PATCH [Coronary Artery Bypass Graft Patch] Trial,[36] DEFINITE [Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation] Trial,[29] DINAMIT [Defibrillator in Acute Myocardial Infarction Trial],[37] and the IRIS [Immediate Risk Stratification Improves Survival] study,[30] and patients >75 years of age only accounted for 11% of the patients in MUSTT, MADIT-I, MADIT-II, and SCD-HeFT.[38] By contrast, a recent analysis of the National Cardiovascular Data Registry (NCDR) ICD Registry showed a large number of patients >70 years of age.[39] In addition to older age, these patients often have comorbidities such as renal disease, chronic obstructive pulmonary disease (COPD), and frailty. Also in these patients, it is unclear if ICD therapy has any significant benefit for mortality.

Methods: Part 2

Selection and Characteristics of Studies

Screening was performed against the predefined PICOTS (Population, Intervention, Comparator, Outcome, Timing, Setting) selection criteria using the Doctor Evidence Library Management System.

A literature search of MEDLINE (through PubMed/OVID), EMBASE (via OVID), and Cochrane Central Database of Controlled Trials (via CENTRAL) was performed with limits including publication dates from 1996 to 2016, English language, and human subjects.

Studies were included if they met these eligibility criteria: adults ≥18 years of age, left ventricular systolic dysfunction ≤40% with or without defined HF, renal failure, frailty (defined by Charlson Comorbidity Index[40] or Elixhauser Comorbidity Indices,[41] and pulmonary disease/smoking. Exclusion criteria were those patients with any of these: syncope, prior SCD, sustained VAs, and/or hypertrophic cardiomyopathy. The intervention of interest was implantation of a transvenous or subcutaneous ICD with no cardiac resynchronization therapy (CRT). Those studies with CRT implants were excluded (to eliminate any potential effect from CRT on outcomes) as were studies evaluating ICDs placed for secondary prevention. The primary outcome was mortality. Secondary outcomes included SCD, and complications and adverse events from the intervention including periprocedural issues, inappropriate tachyarrhythmic therapy, hospitalizations, and post-procedure device complications. Studies with <3 months of follow-up were excluded. Studies included were RCTs, prospective and retrospective observational cohort studies with concurrent controls that report outcomes of interest in a multivariate model, nonrandomized controlled trials with concurrent controls that report outcomes of interest in a multivariate model, case series, uncontrolled observational studies, and systematic reviews/meta-analyses. Case reports and conference abstracts were excluded. Unpublished studies and abstracts were not sought.

The Doctor Evidence Library Management System is a web-based software platform featuring key word emphasis (coloring or bolding of key words), search, and ranking functionalities as well as ability to assign and manage reasons rejected for all references at all stages of screening. Studies that met the inclusion criteria based on the population, intervention, and study design reported in the article's title/abstract were included for full-text review. Articles title/abstract screening was performed by a single reviewer with subsequent quality control by an independent reviewer. All quality control was performed using the tools and functions available in the library management system. The references of individual studies were also back-checked for relevant studies.

Members of the ERC were divided into pairs and performed dual independent review of full-text articles in the DOC Library software platform. Disagreements were resolved through discussion between the 2 reviewers and then by the ERC chair.

After a comprehensive screening process, 18 studies that met the criteria were identified.[29,42–58] All studies addressed the question of whether there is a survival benefit from prophylactic ICD implantation compared with no-device therapy in 3 specific groups: 1) older (≥75 years of age) patients, 2) patients with coexistent significant

comorbidities, and 3) patients with renal dysfunction. Eight studies[29,43,45,47,51,52,55,56] used patient level data from ≥1 published RCTs. Three studies[49,50,54] were single-center retrospective observational studies. Six studies[42,44,48,53,57,58] were retrospective cohort studies in which patients were drawn mainly from 2 major national registries: 1) the NCDR ICD Registry of the American College of Cardiology Foundation and the Heart Rhythm Society; and 2) the Get With The Guidelines-Heart Failure (GWTG-HF) database derived from OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) study. Two studies derived their patient cohorts from existing institutional (single or multicenter) registries.[46,50] Given that multiple studies have drawn patients from common registries, we recognized the potential for patients being included in >1 study. The characteristics of the studies, comparators, outcomes and adjustments are summarized in Data Supplement 2.

Data Extraction and Quality Assessment

Quality assessment was performed on the included studies. All studies showed intermediate-to-high pertinence regarding their study population, intervention, and outcome measures. Studies that were performed on patient level data from RCTs had low risk of bias since they administered independent and blind assessment of outcomes. Studies of retrospective design had intermediate overall risk of bias due to the lack of implementation of blind assessment of outcomes.

Data extraction and meta-analyses were performed with the DOC Data 2.0 software platform using a universal electronic extraction form and guided by a data configuration protocol that specifies the characteristics and outcomes and associated metadata (variables that characterize numerical data points) to extract. Data points and metadata were extracted from the articles and input manually into the database, and with automated quality control features to prevent incorrect data-type entry into incompatible fields. Each collected data point was verified manually against the source article by an independent reviewer (i.e., single extraction with sequential quality control). Using an ontology management tool within the platform, the naming of outcomes of similar type—based on the author-reported outcome name as well as author-reported definitions—was managed for consistency. Statistical tests for heterogeneity suggested low-to-moderate heterogeneity (I^2: 0% to 27%), and funnel plots did not provide convincing evidence for the presence of publication bias.

The final search plan and workflow of inclusion of studies is described in PRISMA Figures 2.1 and 2.2.

Results: Part 2

ICD Implantation in Older Patients

Description of Individual Studies

A 2007 study[47] examined a subgroup of previously published RCT patients (n=204) who were ≥75 years of age. The mean age of this subgroup was 79 ± 3 years, and 128 of them were randomized to undergo ICD implant surgery. The HR for the mortality risk in patients assigned to ICD therapy compared with those assigned to conventional therapy was 0.56 (95% CI: 0.29 to 1.08; p=0.08) after a mean follow-up of 17.2 months.

A pooled analysis of 5 previously published RCTs (MADIT-I, MUSTT, MADIT-II, DEFINITE, and SCD-HeFT) examined the relationship of patient's age on the risks of death and rehospitalization after primary prevention ICD implantation.[45] In the 390 patients (58% of whom were randomized to receive an ICD) who were ≥75 years of age, the HR for risk of mortality (ICD versus non-ICD recipients) was 0.54 (95% CI: 0.37 to 0.78) after a median follow-up duration of 2.6 years.

The DEFINITE study[29] examined the benefit of prophylactic ICD to prevent SCD in patients with nonischemic cardiomyopathy by randomizing 458 patients to receive standard medical therapy or standard medical therapy plus single-chamber ICD and following these patients for a mean duration of 29 months. Among the subgroup of patients (n=157) who were ≥65 years of age, the HR for risk of mortality was approximately 0.61 (95% CI: 0.32 to 1.18).

In a retrospective single-center analysis,[49] 99 patients ≥80 years of age who received a primary prevention ICD were compared with a cohort of similar patients ≥80 years of age who did not receive an ICD (n=53). During the mean follow-up period of 2.3 ± 2.0 years, the adjusted HR for risk of mortality (ICD versus non-ICD) was 0.78 (95% CI: 0.44 to 1.30; p=0.312). In this study, only age (p=0.043) and glomerular filtration rate[59] (p=0.006) predicted survival.

In an analysis of the GWTG-HF registry linked with data from the Centers for Medicare and Medicaid Services, 430 women with HF (median age, 76 years) who received a primary prevention ICD were propensity score matched to 430 women (median age, 76 years) who did not.[58] Median follow-up period was 3.4 years versus 3.0 years, respectively. After adjusting for multiple covariates, the risk of mortality in women with an ICD compared with those without an ICD was significantly lower (HR: 0.75; 95% CI: 0.63 to 0.90; p=0.002). In a parallel comparison, 859 men (median age, 75 years) who received a primary prevention ICD were propensity score matched to 859 men (median age, 75 years) who did not receive an ICD. Median follow-up period was 3.9 years versus 2.9 years, respectively. After adjusting for multiple covariates, the risk of mortality in men with an ICD compared with those without an ICD was also significantly lower (HR: 0.76; 95% CI: 0.67 to 0.87; p<0.001).

In a large multiple registry–based study, 1487 patients (mean age, 75 years) admitted with HF who received a primary prevention ICD (from NCDR ICD Registry) were matched in 1:1 manner to 1487 patients (mean age, 75 years) who did not receive an ICD (from GWTG-HF registry linked with Medicare claims) and studied with a median follow-up period of 4.5 years.[48] The 3-year adjusted mortality rate was lower in the ICD group versus the non-ICD group

(46.7% versus 55.8%; adjusted HR: 0.76; 95% CI: 0.69 to 0.83; p<0.0001).

In a study from the NCDR ICD Registry,[42] 408 patients (median age, 76 years) with left ventricular ejection fraction 30% to 35% who received a primary prevention ICD were propensity score matched and compared with 408 similar patients (median age, 75 years) from the GWTG-HF database who did not receive an ICD. Median follow-up period was 4.4 years. The 3-year adjusted mortality rate was lower in the ICD group versus the non-ICD group (47.1% versus 58.0%; adjusted HR: 0.83; 95% CI: 0.69 to 0.99; p=0.04).

In another study from the NCDR ICD Registry,[51] 179 patients from the NCDR ICD Registry who were ethnic minorities (nonwhite race or Hispanic) were propensity score matched and compared with 121 similar patients from the GWTG-HF database who did not receive an ICD. Median follow-up period was 3.1 years. The 3-year adjusted mortality rate was lower in the ICD group versus the non-ICD group (adjusted HR: 0.79; 95% CI: 0.63 to 0.98; p=0.034). In the same study, 490 white, non-Hispanic patients with prophylactic ICD were propensity score matched and compared with 303 similar patients without an ICD. The 3-year adjusted mortality rate was lower in the ICD group versus the non-ICD group (adjusted HR: 0.75; 95% CI: 0.67 to 0.83; p<0.0001).

In a study from the merged registries of OPTIMIZE-HF and GWTG-HF, 188 patients (75 to 84 years of age) with ICDs were compared with 2,458 similar patients without an ICD from the same registries.[44] During the follow-up period of 3 years, the inverse probability-weighted adjusted HR for mortality was 0.80 (95% CI: 0.62 to 1.03; p=not reported).

In a study from the NCDR ICD Registry, 490 women (≥65 years of age) who received an ICD during a hospitalization for HF from January 1, 2006, through December 31, 2007, were propensity score matched to 490 ICD-eligible women without an ICD hospitalized for HF in the GWTG-HF database from January 1, 2006, through December 31, 2009.[57] After a median follow-up of 4.6 years versus 3.2 years (ICD versus non-ICD), the survival of women with an ICD was significantly longer than that of women without an ICD (adjusted HR: 0.79; 95% CI: 0.66 to 0.95; p=0.013). In a parallel comparison from the same study, men (≥65 years of age) with an ICD had lower mortality than men without an ICD (adjusted HR: 0.73; 95% CI: 0.65 to 0.83; p<0.0001).

Collective Data Analysis

An initial analysis of all the studies[29,42,44,45,47–49,51,57,58] described is shown in Figure 2.3 and Figure 2.4. Given that several articles used patients from common registries, some patients were included in >1 study. To eliminate patient duplication, a "minimal overlap" meta-analysis was performed using 4 of the studies[44,45,48,49] that included patients from 4 exclusively different databases. A survival advantage of ICD versus no ICD was seen with an overall HR of 0.75 (95% CI: 0.67 to 0.83; p<0.001) (Figure 2.5). The studies reported data using different age ranges. In an attempt to best answer the systematic review question, age ranges of 70 to 84 years,[48] 75 to 84 years,[44] 79 to 90 years,[49] and ≥75 years[45] were used. Out of the included registries only SCD-HeFT[25] had patients >80 years of age. To examine whether there may have been a link between study size and treatment effect and to screen for any reporting bias, a Funnel plot was performed and is shown in Figure 2.6.

ICD Implantation in Patients With Significant Comorbidities

Description of Individual Studies

A post hoc analysis of MADIT-II[56] examined the interaction between ICD therapy and diabetes mellitus. The HR for the risk of death in patients treated with ICD compared with those treated with conventional therapy was similar in patients with diabetes mellitus (HR: 0.61; 95% CI: 0.38 to 0.98) as in patients without diabetes mellitus (HR: 0.71; 95% CI: 0.49 to 1.05).

A retrospective, single-center study[54] evaluated potential survival benefit of ICD in patients with COPD. In a pool of 100 patients with a COPD diagnosis (30 with and 70 without ICD), it was found that the patients with an ICD had lower total corrected mortality rate compared with those without an ICD (2-year survival of 88% vs. 59%; p=0.016). In a multivariate model using the propensity score, the ICD was protective against death (HR: 0.20; 95% CI: 0.06 to 0.59; p=0.004).

A retrospective, single-center study[49] that sought to examine whether octogenarians and nonagenarians derive a survival benefit from ICDs implanted in the primary prevention setting also performed another analysis that focused on comorbidities using the Charlson Comorbidity Index. During the follow-up period of 2.3 ± 2.0 years, 93 patients died (58 in the ICD group and 35 in the non-ICD group). ICD recipients had better 1-year survival compared with those with no ICD (72% versus 52%; p=0.014). However, after the adjustment for other comorbid factors, such as left ventricular ejection fraction, glomerular filtration rate (GFR), age, and Charlson Comorbidity Index, ICD implantation did not confer survival benefit (HR: 0.78; 95% CI: 0.45 to 1.34; p=0.312) in a multivariate model for which only age and GFR were independently associated with survival.

Four RCTs (MADIT-I, MADIT-II, DEFINITE and SCD-HeFT)[25–27,29] have been analyzed together using patient-level data with a focus on the effect of comorbidities.[55] A total of 3,348 patients were assessed with respect to these comorbidities: smoking, pulmonary disease, diabetes mellitus, peripheral vascular disease, atrial fibrillation, ischemic heart disease, and chronic kidney disease (CKD); 75% of the patients had ≥2 comorbidities. The unadjusted HR for death

in patients with an ICD versus without ICD was significantly lower. However, this effect was attenuated in patients with ≥2 comorbidities (unadjusted HR: 0.71; 95% CI: 0.61 to 0.84) compared with those with <2 comorbidities (unadjusted HR: 0.59; 95% CI: 0.40 to 0.87). After adjustment, the survival benefit of an ICD decreased with increasing number of comorbidities (p=0.004).

An analysis of the NCDRs ICD Registry and the GWTG-HF registry linked with Medicare claims evaluated the modulating effect of comorbidities on ICD implant.[48] They examined the survival outcomes associated with primary prevention ICD compared with no ICD among patients with HF, and found that ICD implantation was associated with better survival both in patients with ≤3 comorbidities (HR: 0.77; 95% CI: 0.69 to 0.87) and in those with >3 comorbidities (HR: 0.77; 95% CI: 0.64 to 0.93).

A post hoc analysis of MADIT-II [27] evaluated the survival outcome of patients with an ICD implant and correlated with the degree of renal dysfunction as quantitated by estimated GFR (eGFR).[43] Multivariate analysis in patients treated conventionally (i.e., without an ICD) showed that for each 10-unit reduction in eGFR, the risk of all-cause mortality increased by 16% (p=0.005). In comparison, ICD therapy was associated with a survival benefit in each eGFR category of >35 mL/min/1.73 m^2 (overall risk reduction for all-cause mortality 32%; p=0.001). This beneficial effect was lost for an eGFR <35 mL/min/1.73 m^2 (all-cause mortality HR: 1.09; p=0.84).

Cumulative data on patients who were enrolled in 2 registries and had history of end-stage renal disease, left ventricular systolic dysfunction, and ICD implantation have been analyzed in a retrospective study.[46] The median survival durations in the ICD group versus non-ICD group were 8.0 years and 3.1 years, respectively. The multivariate analysis showed that the ICD group had significantly less all-cause mortality compared with the non-ICD group (HR: 0.40; 95% CI: 0.19 to 0.82; p=0.013).

A meta-analysis of 3 large RCTs (MADIT-I, MADIT-II, and SCD-HeFT)[25–27] evaluated 2,867 patients of whom 36.3% had eGFR <60 mL/min/1.73 m^2.[52] The probability of death during the follow-up period was 43.3% for 1,334 patients assigned to receive the usual care versus 35.8% for 1,533 patients who were assigned to the ICD group. After adjustment for baseline differences, there was evidence that the survival benefit associated with ICDs compared with usual care was dependent on eGFR. ICD was associated with survival benefit for patients with eGFR ≥60 mL/min/1.73 m^2 (adjusted HR: 0.49), but not for patients with eGFR <60 mL/min/1.73 m^2 (adjusted HR: 0.80).

A retrospective study [53] identified 108 patients on dialysis who received a primary prevention ICD from the NCDR ICD Registry and compared them with a similar set of 195 patients drawn from the GWTG-HF registry without an ICD. Using the propensity score technique, they matched the ICD recipients to non-ICD patients, and the overall survival was compared between the 2 groups. Three-year mortality was 68.8% in the ICD cohort compared with 75.7% in the non-ICD cohort. There was no significant survival advantage associated with an ICD (HR: 0.87; 95% CI: 0.66 to 1.13; p=0.29). After propensity score matching, the analysis included 86 ICD patients and 86 controls. The 3-year mortality was 74.0% in the ICD group and 76.6% in the control group (HR: 0.94; 95% CI: 0.67 to 1.31, p=0.71).

A single-center registry of patients with CKD has been studied to examine the benefit of ICDs placed for primary prevention.[50] A total of 1,053 patients with an ICD were matched to 631 control patients without an ICD. During the median follow-up of 2.9 years, the HR of death among propensity score matched patients was 0.69 (95% CI: 0.59 to 0.82) for the ICD group compared with the non-ICD group. A statistically significant interaction was found between ICDs and eGFR (p=0.04). Specifically, ICD was associated with a lower risk of death among those with eGFR of 45 to 59 mL/min/1.73m^2 (HR: 0.58; 95% CI: 0.44 to 0.77) and those with eGFR of 30 to 44 mL/min/1.73m^2 (HR: 0.65; 95% CI: 0.50 to 0.85), but not among those with eGFR <30 mL/min/1.73 m^2 (HR: 0.98; 95% CI: 0.71 to 1.35).

Collective Data Analysis

The first meta-analysis included all 10 studies [43,46,48–50,52–56] to determine whether ICDs implanted for primary prevention is associated with improved survival in patients with significant comorbidities. Comorbid conditions were defined as various combinations of renal disease, COPD, atrial fibrillation, heart disease, and others. Random effects model demonstrated that all-cause mortality was improved with ICD implantation compared with without ICD implantation (overall HR: 0.72; 95% CI: 0.65 to 0.79; p<0.0001) (Figure 2.7). A second "minimal overlap" meta-analysis was performed using only 5 of the studies[46,50,52,53,55] so that the potential for patient duplication across multiple studies could be minimized. Random effects model found that all-cause mortality was improved with ICD implantation compared with without ICD implantation (overall HR: 0.71; 95% CI: 0.61 to 0.82; p<0.0001) (Figure 2.8). To examine whether there may have been a link between study size and treatment effect and to screen for any reporting bias, Funnel plots were performed (Figures 2.9 and 2.10).

ICD Implantation in Patients With Renal Disease

Five of these 10 comorbidity studies[43,46,50,52,53] included data specifically on patients with varying degree of renal dysfunction. We conducted a meta-analysis using these 5 studies[43,46,50,52,53] to assess whether there is an overall

mortality benefit with the implantation of primary prevention ICD in patients with renal disease. Random effects model demonstrated that all-cause mortality was improved with ICD implantation compared with without ICD implantation (overall HR: 0.71; 95% CI 0.60 to 0.85; p<0.001) (Figure 2.11). To examine whether there may have been a link between study size and treatment effect and to screen for any reporting bias, a Funnel plot was performed (Figure 2.12). The definition of renal disease varied dramatically among the 5 studies with only 2 studies[46,53] specifically studying ICD implant in patients with end-stage renal disease.

Discussion: Part 2

Although numerous studies have resulted in demonstrating the survival benefits of ICDs for primary prevention of SCD, certain groups of patients have unclear benefit. The life expectancy, at any given age, is not <1 year until a person reaches 113 years of age (https://www.ssa.gov/oact/STATS/table4c6.html).[60] However, with the presence of a depressed ejection fraction among other conditions, there are attenuating circumstances on expected survival for most patients being considered for an ICD. As such, 2 main groups of patients, older patients and those patients with significant comorbidities, such as renal dysfunction, COPD, or diabetes mellitus, may not benefit from ICD implantation and are the focus of this review. The analyses performed in this review sought to determine whether there is a survival benefit associated with primary prevention ICD implantation compared with no-device therapy in those patients who are older age and those with significant comorbidities.

In this meta-analysis, in older patients (≥75 years of age), primary prevention ICD implantation is associated with benefit, with an HR reduction of 24% for death compared with those patients without ICD implantation. However, the data are derived from retrospective observational studies and significant uncertainty still remains on the potential benefit of ICD implant in older patients. Age itself remains a predictor of mortality with higher mortality rates occurring in these older patients than seen in the landmark clinical trials.[61,62] However, the HR reduction in death from ICD implantation in older individuals appears consistent with the reduction seen in younger persons. These individual studies that do not show survival benefit in older patients are likely underpowered.[29,44,47,49]

Even with the presence of comorbidities, an ICD implant is associated with benefit in these older patients. Looking at patients with ≤3 comorbidities (chronic lung disease, prior atrial fibrillation, ischemic heart disease, diabetes mellitus, and renal disease) versus >3 comorbidities, ICDs are associated with improved survival in both groups with HR of 0.77 (95% CI: 0.69 to 0.87) and HR of 0.77 (95% CI: 0.64 to 0.93), respectively.[48]

Prior studies also suggest that the benefit of ICD implantation increases as the ejection fraction decreases below 35%.[63] Thus, if the patients' ejection fraction was closer to 35%, these older patients may derive less or no benefit. However, using the NCDR ICD Registry with similar patients from the GWTG-HF database, survival in patients who had an ejection fraction of 30% to 35% was improved with an HR of 0.83 (95% CI: 0.69 to 0.99; p=0.04). Those older patients with ejection fraction <30% had a larger mortality reduction with an HR of 0.72 (95% CI: 0.65 to 0.81; p<0.001).[42]

The applicability of these primary prevention ICDs to underrepresented groups, such as women and minorities, also remains largely unknown. Most of the clinical trials are comprised of men as the majority of the study population, with women comprising only 8% to 29% of the cohorts (MUSTT, MADIT-I, MADIT-II, SCD-HeFT, CABG-PATCH, DEFINITE, DINAMIT, IRIS).[25–30,36,37] Minorities accounted for a similarly low percentage as noted in MUSTT and SCD-HeFT.[25,28] From the NCDR ICD Registry and GWTG-HF registry, there are suggestions that older women still benefit from ICD implantation. Data analysis from those registries showed that older women with an ICD had a lower mortality rate at 1- and 3-year follow-up, with adjusted HR of 0.79 (95% CI: 0.66 to 0.95) compared with those without primary prevention ICD.[57] In another analysis of the same registries, minorities (Hispanic, Black, Asian, American Indian, Alaska Native, Native Hawaiian, and Pacific Islander) also had lower overall mortality with an adjusted HR of 0.79 (95% CI: 0.63 to 0.98; p=0.034).[51]

Similar benefit is seen with primary prevention ICD implantation in patients with significant comorbidities. In the past, regarding clinically complex patients with multiple comorbidities, studies performed to determine the benefit of ICDs have been limited, inadequately powered, and largely observational.[55] Additionally, some of these studies have looked at specific comorbidities in isolation, as opposed to accounting for patients with several comorbidities that influence mortality, as is typically seen in day-to-day clinical practice.

In patients with CKD, the risks and benefits of primary prevention ICD therapy are unclear. Observational studies have described decreased overall survival and increased complication rates in patients with primary prevention ICDs and CKD compared with patients without CKD. However, the patients who have received ICDs have not consistently been compared with a control group with CKD that did not receive primary prevention ICD using a prospective

randomized trial design.[52] This has made it a challenge to determine whether these specific patients derive benefit from ICD therapy. Also, within this subgroup of patients of CKD, the degree of renal insufficiency likely influences survival benefit, as indicated by some of the individual studies included in our meta-analysis.[43,50,52]

We conducted a meta-analysis that included all 10 studies of patients with comorbidities, including renal disease.[30,43,46,48–50,52–54,56] A separate specific analysis of the 5 studies[16,43,46,50,52,53] that explored renal dysfunction was also done. In both cases, a random effects model demonstrated that all-cause mortality was improved compared with no ICD implantation. Six of the 10 studies were retrospective observational studies.[46,48–50,52,53] The 4 studies that incorporated data from 4 RCTs in total were MADIT-I, MADIT-II, DEFINITE, and SCD-HeFT.[25–27,29] Most patients, ≈62% and ≈65% in the overall analysis and the renal disease analysis, respectively, were drawn from observational studies. There was significant overlap in the patient populations as the retrospective observational studies predominantly drew patients from the NDCR ICD Registry and the GWTG-HF registry. This was especially the case in the studies that used data from RCTs. For example, the 2 studies in the renal disease analysis that used patient level data from RCTs overlapped in their inclusion of patients from MADIT-II.[27]

Our analyses indicate that patients with comorbidities, including renal dysfunction, derive a survival benefit from primary prevention ICD implantation. In the model assessing all 10 studies of patients with comorbidities, the overall HR of 0.72 (95% CI: 0.65 to 0.79; $p<0.001$) (Figure 2.7). In the meta-analysis of patients with renal disease, there was evidence of an overall benefit to ICD implantation compared with no ICD therapy (HR: 0.71; 95% CI: 0.60 to 0.85; $p<0.001$) (Figure 2.11). However, it is difficult to draw conclusions regarding the role of ICD in end-stage renal disease because these patients comprised a very small percentage of the total number of patients with CKD.

Among the studies that looked at patients with significant comorbidities, patients had a range of comorbidities including atrial fibrillation, pulmonary disease, renal disease, ischemic heart disease, diabetes mellitus, peripheral vascular disease, and cerebrovascular disease. A single-center, retrospective[49] study assessed comorbid conditions using the Charlson Comorbidity Index,[40] which includes an even wider range of comorbidities in addition to the aforementioned medical conditions.

Prior landmark clinical trials have demonstrated the survival benefit of ICD therapy for primary prevention of SCD, although many of these patients were younger and had less comorbidity when compared with the typical patient encountered in clinical practice. The average age of the patients in our meta-analysis of significant comorbidities was generally older (Data Supplement 2) when compared with patients enrolled in the landmark clinical trials that were designed to evaluate ICD therapy for primary prevention of SCD.[25–27] As such, our meta-analysis is more applicable to the average patient seen by practicing physicians. We hope to lend support to better decision-making surrounding ICD implantation since these studies incorporate a wider variety of comorbidities and draw most patients from large registries that include older patients. The present meta-analysis suggests that primary prevention ICD therapy is associated with benefits in older patients and those with significant comorbidities.

Limitations: Part 2

Our analysis does carry limitations. One important confounder is the type of cardiomyopathy in these patients; most had an ischemic etiology limiting the applicability to nonischemic patients. A RCT has suggested that ICDs are only beneficial in younger patients with nonischemic cardiomyopathy.[64] Also, medication usage and adherence, which are known to improve cardiac function and ejection fraction, were not analyzed. We also did not include CRT, which carries additional benefit in selected patients who also meet primary prevention ICD eligibility criteria. After discussion, we elected not to report absolute risk or benefit of ICD use or number needed to treat in our analysis because of concerns for introducing assumptions that would decrease the value and reliability of any calculated results. Although we looked specifically at survival in our analysis, we could not assess other pertinent factors, such as quality of life and complications related to device implantation, which may play a significant role in the shared decision-making for patients considering a primary prevention ICD. In addition, much of the data used in the meta-analysis is derived from observational and retrospective studies, some with a small sample size and wide CIs. Several substudies of the NCDR ICD Registry and GWTG-HF registry were used to determine benefit of prophylactic ICD implantation, and the potential overlap of patients may be a significant confounder in our analysis despite our efforts to limit this effect. In addition, these analyses used propensity scoring to adjust for confounding that may be insufficient for identifying similar patient populations.[65] Of note, other strategies such as decision analysis modeling may provide information on the potential use of any therapy such as ICD in the setting of competing comorbidities[66,67] Finally, with much of the data being from nonrandomized data sources, we can state there is an association of primary prevention ICD implantation and reduction in mortality seen in both older patients and those with significant comorbidities, but a cause-and-effect cannot be established. None of the observational studies included in our analyses used strategies such as prespecified falsification analysis to identify spurious correlations.[68] Even if such statistical methods were used, selection bias and unidentified confounding biases can be potentially addressed but never fully adjusted for.

Figures

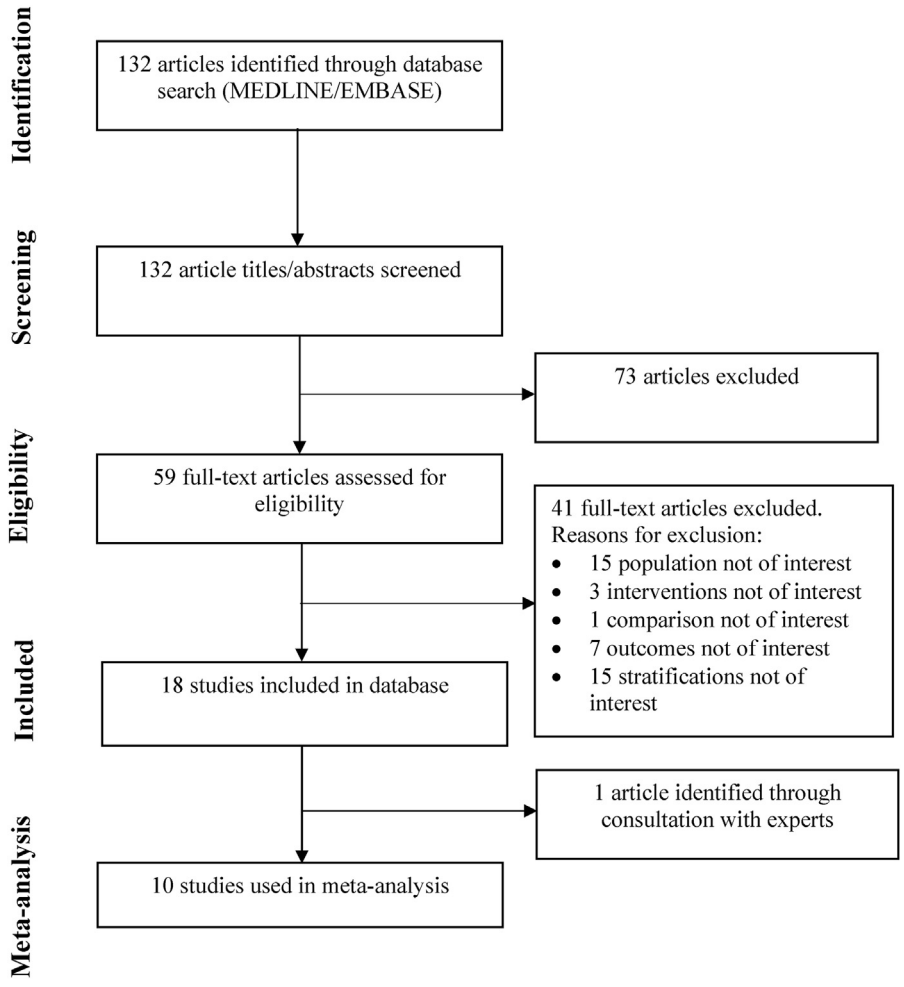

Figure 2.1 PRISMA Diagram for ICD Prevention in Older Patients.

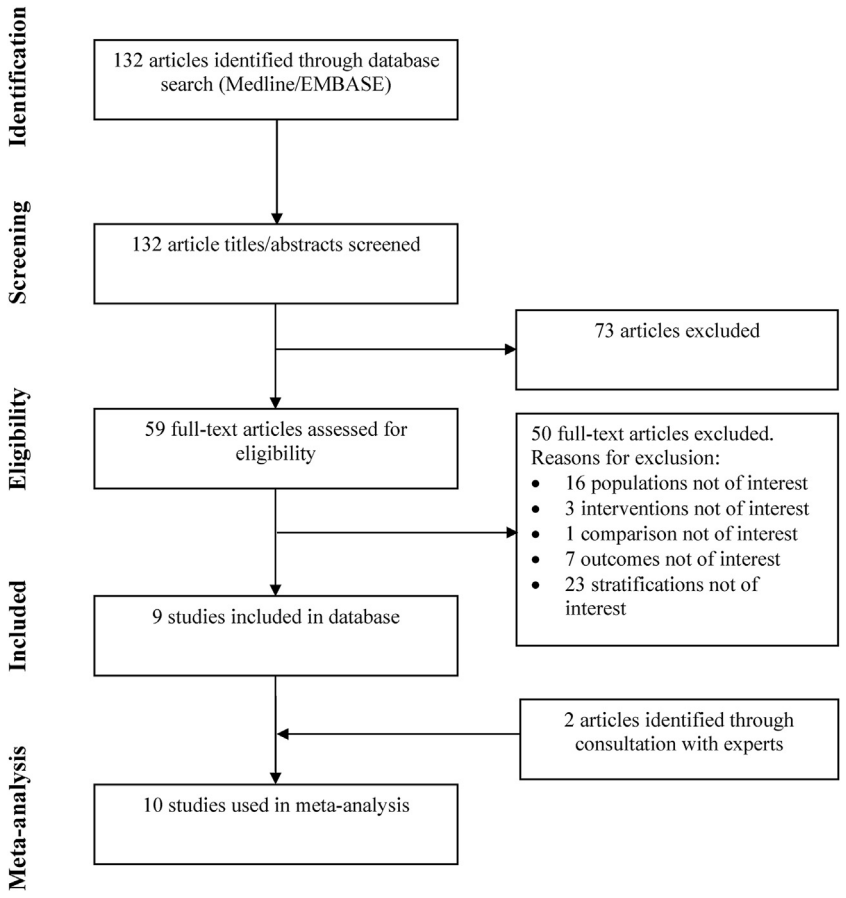

Figure 2.2 PRISMA Diagram for ICD Prevention in Patients With Significant Comorbidities (Including Renal).

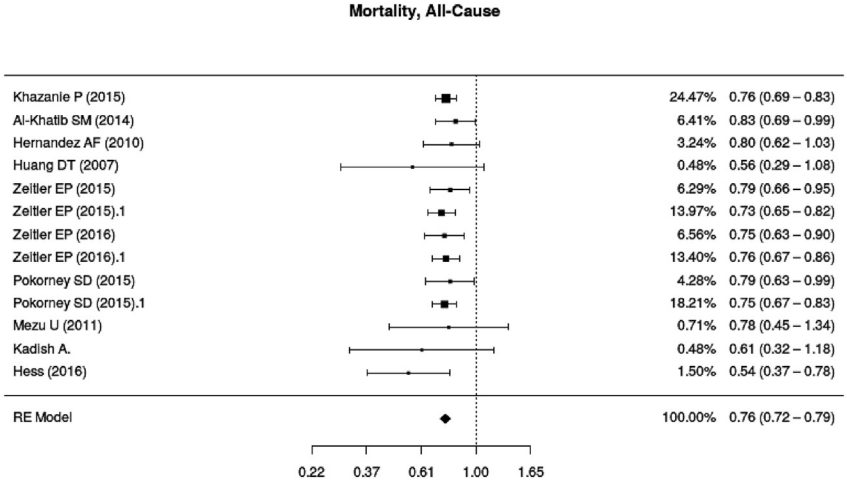

Figure 2.3 Forest Plot for ICD Implantation in Older Patients. ICD = implantable cardioverter-defibrillator; RE = random effects.

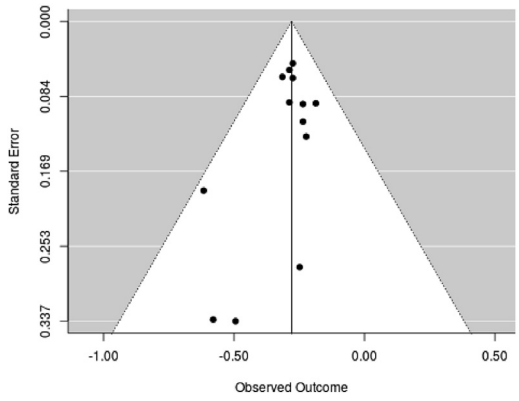

Figure 2.4 Funnel Plot for ICD Implantation in Older Patients. ICD = implantable cardioverter-defibrillator.

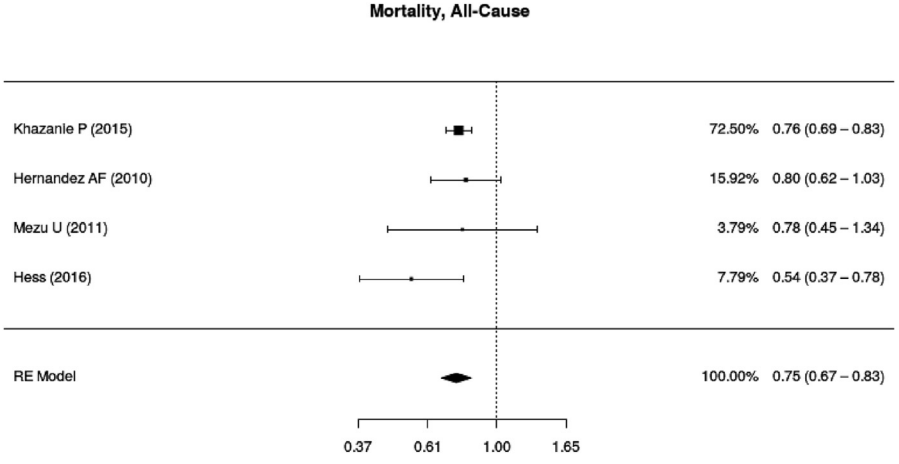

Figure 2.5 Forest Plot for ICD Implantation in Older Patients (Minimal Overlap). ICD = implantable cardioverter-defibrillator; RE = random effects.

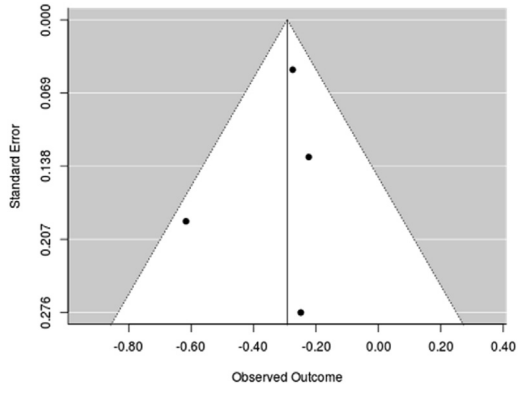

Figure 2.6 Funnel Plot ICD Implantation in Older Patients (Minimal Overlap). ICD = implantable cardioverter-defibrillator.

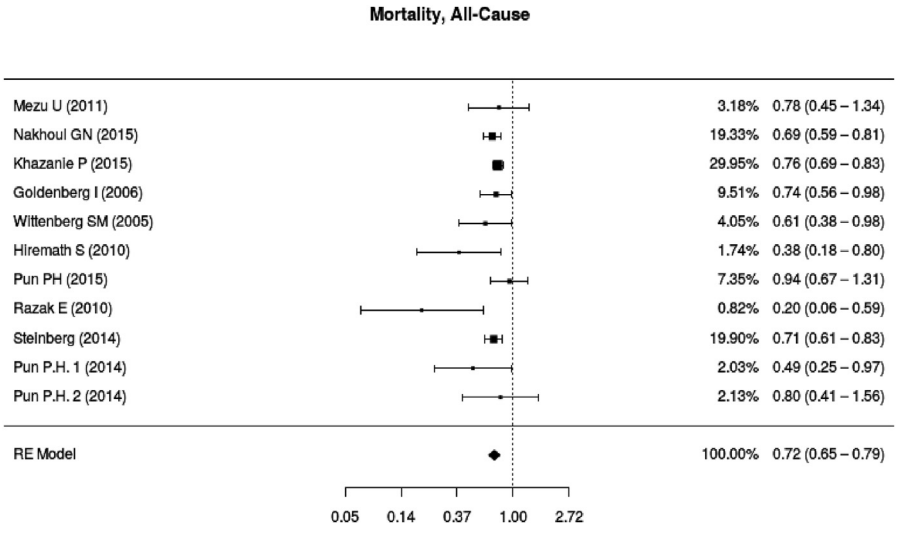

Figure 2.7 Forest Plot for ICD Implantation in Patients With Significant Comorbidities. ICD = implantable cardioverter-defibrillator; RE = random effects.

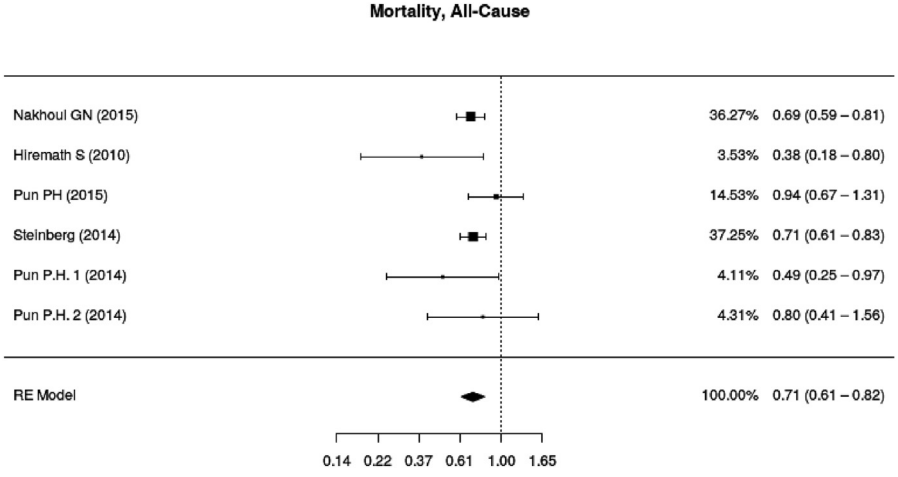

Figure 2.8 Forest Plot for ICD Implantation in Patients With Significant Comorbidities (Minimal Overlap). ICD = implantable cardioverter-defibrillator; RE = random effects.

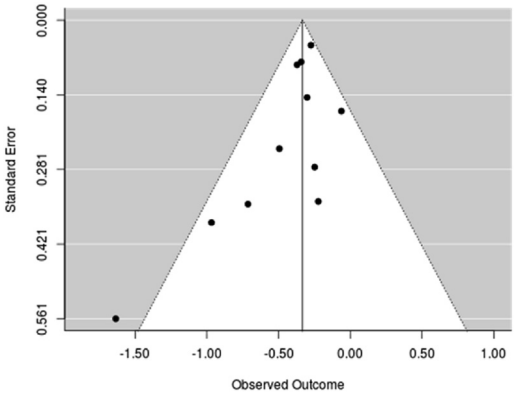

Figure 2.9 Funnel Plot for ICD Implantation in Patients With Significant Comorbidities. ICD = implantable cardioverter-defibrillator.

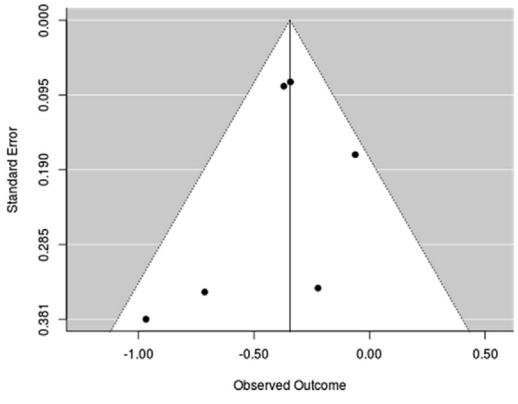

Figure 2.10 Funnel Plot for ICD Implantation in Patients With Significant Comorbidities (Minimal Overlap). ICD = implantable cardioverter-defibrillator.

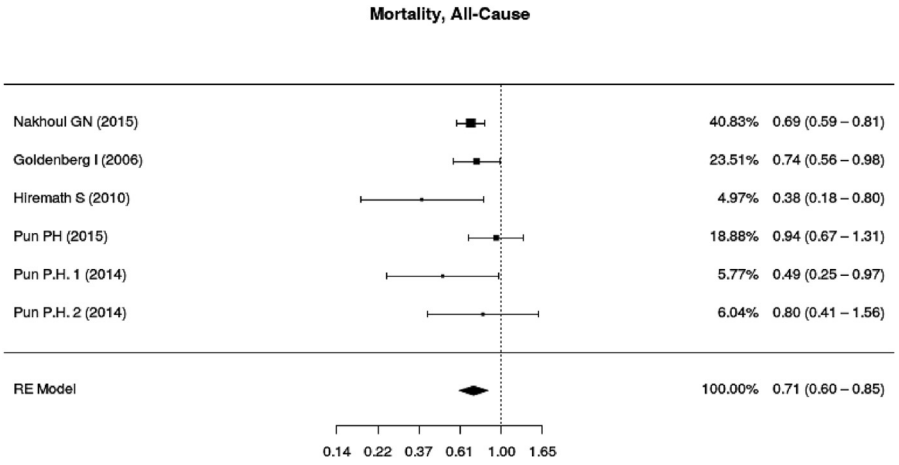

Figure 2.11 Forest Plot for ICD Implantation in Patient With Renal Comorbidities. ICD = implantable cardioverter-defibrillator; RE = random effects.

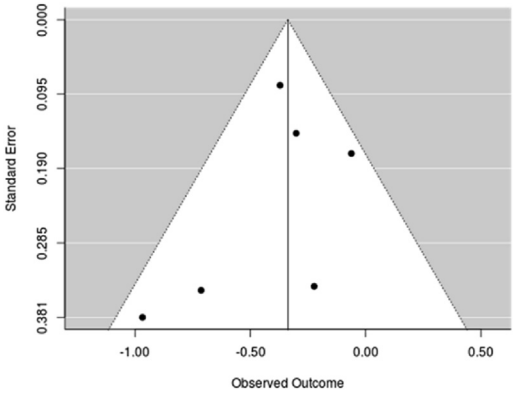

Figure 2.12 Funnel Plot for ICD Implantation in Patient With Renal Comorbidities. ICD = implantable cardioverter-defibrillator.

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Appendix

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hrthm.2017.10.037

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Appendix 1 Evidence Review Committee Relationships With Industry and Other Entities* (Relevant)—Systematic Review for the 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (October 2017)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational or Other Financial Benefit	Expert Witness
Fred M. Kusumoto *(Chair)*	Mayo Clinic—Director, Pacing and Electrophysiology Service	None	None	None	None	None	None
Kent R. Bailey *(Vice Chair)*	Mayo Clinic—Professor, Health Sciences Research	None	None	None	None	None	None
Ahmad Sami Chaouki	Northwestern University Feinberg School of Medicine—Assistant Professor, Department of Pediatrics, Division of Cardiology	None	None	None	None	None	None
Abhishek J. Deshmukh	Mayo Clinic—Senior Associate Consultant, Associate Professor	None	None	None	None	None	None
Sandeep Gautam	University of Missouri Health Care—Assistant Professor of Clinical Medicine, Division of Cardiovascular Medicine	None	None	None	None	None	None
Robert J. Kim	University of Florida; Health Science Center Jacksonville—Assistant Professor of Medicine	None	None	None	None	None	None
Daniel B. Kramer	Harvard Medical School— Assistant Professor of Medicine	None	None	None	None	None	None
Litsa K. Lambrakos	University of Miami, Miller School of Medicine—Assistant Professor of Medicine	None	None	None	None	None	None
Naseer H. Nasser	South Bend Clinic—Attending Cardiac Electrophysiologist	None	None	None	None	None	None
Dan Sorajja	Mayo Clinic Arizona Cardiovascular Diseases—Assistant Professor of Medicine	None	None	None	None	None	None

This table represents the relationships of evidence review committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of $\geq$5% of the voting stock or share of the business entity, or ownership of $\geq$$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the document; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the document or makes a competing drug or device addressed in the document; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the document.

ACC = American College of Cardiology; AHA = American Heart Association; HRS = Heart Rhythm Society.

*For transparency, the ERC members' comprehensive disclosure information is available as an online supplement.

Appendix 2 Abbreviations

CKD = chronic kidney disease
CRT = cardiac resynchronization therapy
COPD = chronic obstructive pulmonary disease
ECG = electrocardiogram
eGFR = estimated glomerular filtration rate
ERC = evidence review committee
GFR = glomerular filtration rate
HF = heart failure
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
OR = odds ratio
RCT = randomized control trial
SCD = sudden cardiac death
VA = ventricular arrhythmias