Technology Assessment

Technology Assessment Program

Assessment on Implantable Defibrillators and the Evidence for Primary Prevention of Sudden Cardiac Death

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Assessment on Implantable Defibrillators and the Evidence for Primary Prevention of Sudden Cardiac Death

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments. To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. Comments may be sent by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Assessment on Implantable Defibrillators and the Evidence for Primary Prevention of Sudden Cardiac Death

Structured Abstract

Background: Implantable cardioverter–defibrillators (ICDs) are battery-powered implantable devices that monitor heart rhythm and deliver therapy in the form of either electric shock or antitachycardia pacing (ATP) when a life-threatening ventricular arrhythmia is detected. ICDs have been used in patients who survived sustained ventricular arrhythmias to prevent sudden cardiac death (SCD). In recent years, ICDs have also been implanted for primary prevention (prevention of SCD in a patient who has not had yet had sustained ventricular tachyarrhythmia but has risk factors for it). ICDs may also include cardiac resynchronization therapy (CRT) for additional treatment of heart failure in patients with dyssynchronous ventricles.

Objectives: We aimed to examine the clinical effectiveness of ICD use for primary prevention of SCD. Key Question 1 examined ICD versus no ICD, ICD with ATP versus ICD alone, or ICD with CRT versus ICD alone, and differences among subgroups. Key Question 2 examined early and late adverse events and inappropriate shocks after ICD implantation, and differences among subgroups. Key Question 3 examined eligibility criteria and evaluation methods for patients included in comparative studies and the risk of SCD.

Data Sources: MEDLINE® (through December 4, 2012) and the Cochrane Central Trials Registry (through the third quarter of 2012), with no language exclusion.

Review Methods: For Key Questions 1 and 3, we included comparative studies of ICDs for primary prevention. For Key Question 2, we examined reports from ICD registries or other cohort studies with at least 500 patients with ICDs for primary or secondary prevention. Details on design, patients, interventions, outcomes and quality were extracted into standard forms.

Results: There were 14 studies comparing ICD versus no ICD, 3 studies comparing ICD with CRT (CRT-D) versus ICD, and 59 articles contributing data on adverse events after ICD implantation. There is a high strength of evidence for benefit from ICD treatment compared to control treatment without an ICD for reducing all cause mortality. Meta-analysis of seven RCTs comparing ICD versus control yielded a summary hazard ratio (HR) of 0.69 (95% confidence interval [CI] 0.60, 0.79) for death favoring ICD treatment. Across RCTs, the number needed to treat (NNT) to prevent one death ranged from 6.2 (95% CI 4.0, 18) to 22 (95% CI 2.3, infinite) at the longest durations of followup (3 to 7 years). There is a high strength of evidence for benefit from ICD treatment compared to control treatment without an ICD for reducing SCD. Meta-analysis of five studies comparing ICD versus control showed benefit from ICD use for reducing SCD (HR 0.37; 95% CI 0.26, 0.52). Across RCTs, the NNT to prevent one arrhythmic death ranged from about 2 to 3 (approximate 95% CI 1.3, 16) to 11 (95% CI 1.3, infinite).Three other trials in which ICDs were implanted immediately after myocardial infarction (MI) or at the time of coronary artery bypass grafting did not show a benefit for all-cause mortality, but two of the

trials did show a reduction in SCD. Three RCTs of ICD versus no ICD provided low strength of evidence that failed to show a consistent effect of ICD placement on quality of life.

Analyses failed to show statistically significant differences for all-cause mortality or SCD across subgroups by age, sex, and other patient characteristics; however, there may be an indication that ICDs are more effective in patients with more distant coronary revascularization compared with recent surgery. Studies of patients with recent MIs (within 31 or 40 days) had no reduction in all-cause mortality in contrast with studies in patients with more distant MIs. Due to discordant findings among studies, there is insufficient evidence from four RCTs regarding the relative effect on all-cause mortality among patients who receive CRT-D compared to those who receive ICD alone. Heart failure outcomes and related quality of life measures were not reviewed.

Eligibility criteria were reviewed to assess applicability. Comparative studies included individuals with ischemic or nonischemic dilated cardiomyopathy, and left ventricular ejection fraction was ≤35 percent in all but one study. Eligibility criteria regarding heart failure class were variable. The trials of CRT-D used QRS interval data for eligibility; most other trials did not. Most of the RCTs of ICD tested all patients for nonsustained VT, but with different diagnostic tools. Only one RCT reported performing electrophysiology testing in all patients. Only 4 of the 13 RCTs explicitly tested for coronary stenosis, mostly with coronary angiography or exercise testing. Most studies excluded older adults over 70 to 80 years. SCD occurred in 4 to 13 percent of control patients during the 2 to 5 years after randomization.

A high strength of evidence shows early (in-hospital) adverse event rates of approximately 3 percent and serious adverse event rates of approximately 1 percent. Low strength of evidence shows variable, late (out of hospital) rates for device- and lead-related adverse events. Moderate strength evidence shows 3 to 21 percent of patients experience at least one inappropriate shock over 1 to 5 years of followup.

Limitations of the evidence base in some RCTs include lack of blinding of outcome assessors of arrhythmia outcomes or SCD, high attrition rates (>20%), or differential rates of attrition or crossover between study groups and differences in the control treatments or in the rates of concomitant use of beta blockers between the study groups. Nonsignificant findings in subgroup analyses need to be interpreted in the context of studies likely being underpowered to explore differences in effects across subgroups of interest. The quality of the long-term adverse events suffered from a lack of harmonized definitions and systematic ascertainment.

Future research is needed to address comparative effectiveness for quality of life and other patient reported outcomes and to explore treatment heterogeneity according to baseline risk. Consistent reporting of rates of SCD in the non-ICD trial arms would facilitate an assessment of how the mortality benefit may be correlated with the baseline risk.

Conclusions: There is a high strength of evidence that ICD therapy for primary prevention of SCD, versus no ICD therapy, shows benefit with regard to all cause mortality and SCD in patients with reduced left ventricular ejection fraction and ischemic or nonischemic cardiomyopathy beyond the immediate post-MI or coronary revascularization periods. Studies failed to show statistically significant differences for all-cause mortality across subgroups. There is insufficient evidence for all-cause mortality for patients who receive CRT-Ds versus ICD alone for primary prevention. There is high strength of evidence that in-hospital adverse events are infrequent (1-3%) and moderate strength of evidence that up to one-fifth of patients receive inappropriate shocks from the ICDs.

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Introduction

Background

Sudden cardiac death (SCD) is the most common cause of cardiovascular death worldwide, accounting for approximately 300,000 deaths in the United States annually, although estimates have ranged from 200,000 to 450,000 deaths.[1-10] The estimate of prevalence depends on the definition and inclusion criteria used in studies.[6] Operationally, SCD is most frequently defined as a cardiac death that occurred within 1 hour of cardiac symptom onset and without another probable cause of death. Studies from epidemiological cohorts from the 1970s through the 1990s suggest that 88 to 91 percent of deaths that occur within 1 hour of symptom onset are arrhythmic in nature.[11] The temporal definition of SCD strongly influences epidemiological data.[6,12] Increasing the time window to 24 hour since symptom onset to define SCD increases the sensitivity but reduces specificity by reducing the proportion of all sudden natural deaths that are due to cardiac causes.

Approximately three-quarters of cases of SCD are caused by ventricular tachyarrhythmias such as ventricular tachycardia (VT) and ventricular fibrillation (VF).[2,13,14] Sustained ventricular arrhythmias may lead to hemodynamic instability and abrupt loss of consciousness without spontaneous recovery, requiring cardiac resuscitation (i.e., cardiac arrest). With advancements in cardiopulmonary resuscitation and greater availability of automatic external defibrillators, it is possible to "abort" SCD. Nonetheless, only 3 to 10 percent of patients who have an out-of-hospital cardiac arrest are successfully resuscitated.[15] Timely administration of therapy is essential, as the rate of survival for people with VF declines by approximately 10 percent per minute.[5,16] Even for those out-of-hospital arrests who survive to hospitalization, survival to hospital discharge is less than 8 percent.[5,17,18]

Prevention is the primary strategy to lower death from SCD. However, SCD is a particular management challenge because the majority of cases occur in individuals without a prior diagnosis of cardiac disease or other clear risk factors for SCD. The most common underlying cardiovascular diagnosis among people with SCD is coronary artery disease (CAD). Yet, in about half of the cases of SCD, SCD itself is the initial manifestation of CAD.[1,4-6] The clinical strategy to prevent death from SCD involves identification of risk factors for ventricular tachyarrhythmias and SCD, to target individuals for medical and interventional treatments.

Outcomes Adjudication

There is the potential to misclassify SCD; thus, to interpret trial results, it is important that studies clearly define their primary and secondary outcomes and follow rigorous methods of adjudication. The most unambiguous outcome with regard to classification is death from any cause or total mortality; this is therefore a common outcome. Arguably, all-cause death is the principal outcome of interest to patients and their families, even though the goal of ICD implantation is to prevent specifically SCD or death from arrhythmia. SCD is a common secondary outcome in ICD trials. However, determination of cause-specific mortality may be fraught with errors. From the Framingham Heart Study, it is suggested that SCD rates derived from death certificates alone should be interpreted with caution.[19] In clinical trials, adjudication of arrhythmia or SCD can be very involved requiring validation by blinded committees which independently adjudicate all deaths according to algorithms and consensus

Criteria for adjudication of SCD were originally developed by Hinkle and Thaler[20]and

previously validated in the Canadian Implantable Defibrillator Study[21] and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial.[22] These criteria are based on the clinical circumstances of death and do not rely on ICD information. Documentation of the cause of death may further incorporate information obtained from witnesses, relatives and family members, death certificates, hospital records, and autopsy reports where available.

Risk Factors for SCD

Risk factors for SCD are multifactorial, dynamic, and associated with a continuous risk function.[23] Some risk factors are nonmodifiable, such as sex and family history of CAD.[24] The incidence of SCD increases as a function of advancing age. The incidence is 100-fold less in young adults less than 30 years of age as compared with older adults.[6,25-28] In regard to the development of disease processes, the Framingham Heart Study revealed that CAD is associated with a 2.8- to 5.3-fold increase in risk of SCD. Following myocardial infarction, there is a 4-fold higher risk of SCD for women and a 10-fold higher risk of SCD for men.[11] Mortality following ST-segment elevation myocardial infarction (MI), in particular, is high with an especially high risk of SCD in those patients with left ventricle dysfunction in the first 30 days.[29] Modifiable CAD risk factors that have been demonstrated to predict SCD include hypertension, hypercholesterolemia, and diabetes.[11] In regard to hypertension which is both an established risk factor for CAD and SCD, both the electrocardiogram pattern of left ventricular hypertrophy and echocardiographic evidence of left ventricular hypertrophy are associated with a higher proportion of sudden and unexpected cardiac death.[6] There are also meaningful associations between cigarette smoking, obesity, lifestyle and SCD. For instance, in a study of 310 survivors of out-of-hospital cardiac arrest, the recurrent cardiac arrest rate was 27 percent at 3 years of follow-up among those who continued to smoke as compared with 19 percent in those who stopped.[30]

The Framingham Heart Study also showed that congestive heart failure is associated with a 2.6- to 6.2-fold increased risk of SCD.[11,31] Other disease processes that impart a variable risk of SCD are cardiomyopathies such as dilated, hypertrophic, and arrhythmogenic right ventricular cardiomyopathy as well as primary electrical disorders such as long QT syndrome and Brugada syndrome. Population-based studies have demonstrated that electrocardiography criteria such as an elevated resting heart rate,[32] prolonged QRS duration,[33,34] and prolonged QT interval increase SCD risk in the general population.[11,35,36]

Currently, the single most widely used risk stratification criterion, based on multiple randomized controlled trials, is a reduced left ventricular ejection fraction (LVEF), typically a value of $\leq$30 or $\leq$35 percent.[23] From a pathophysiologic standpoint, the presence of scar tissue is known to be a substrate for ventricular tachyarrhythmias. Molecular, cellular and interstitial changes play a role in myocardial remodeling. One of the challenges of better risk stratification is the fact that different pathophysiological processes may lead to ventricular tachyarrhythmias and subsequently SCD. Thus, the predilection toward a ventricular arrhythmia is complex and cannot be entirely defined by a single dichotomous variable such as LVEF. Further, the greatest absolute number of SCD events will occur in people without known risk factors or with SCD as the first manifestation of cardiac disease.[14,37] In one study which examined patients who had a cardiac arrest, approximately 65 percent would not have qualified for a primary prevention ICD prior to the event.[38] Thus, there is a great need for improved risk stratification tools. Attempts have been made to calculate SCD risk score models such as one derived from Multicenter Automatic Defibrillator Implantation Trial (MADIT)II as well as the Duke risk score in patients

with coronary artery disease. The risk scores may be helpful in guiding therapy for a physician but they have not been applied in a prospective manner in clinical trials.[39,40]

An example of an invasive risk stratification tool which has been studied prospectively in Multicenter Unsustained Tachycardia Trial (MUSTT)[41] and MADIT[42] is the electrophysiology study. MUSTT provided evidence that electrophysiologically guided antiarrhythmic therapy with ICDs reduces the risk of SCD in high-risk patients with CAD, LVEF ≤40 percent, spontaneous and unsustained VT, or sustained tachyarrhythmia induced by programmed stimulation. MADIT[42] included patients with CAD and a prior MI, LVEF ≤35 percent, and inducible, sustained VT or VF at electrophysiologic study.[42] Thus, the electrophysiology study has a tailored role in risk prediction.

Medical and Interventional Treatment for Prevention of SCD

Prevention strategies include risk factor modification and treatment of the underlying disease processes of CAD, congestive heart failure, and cardiomyopathy with medical therapy. Medical therapy includes the use of aspirin, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone blockers, and statins. In addition, reperfusion therapies for MI such as tissue plasminogen activators and percutaneous coronary intervention for CAD have resulted in a significant decline in SCD over the past 30 years.[43]

Antiarrhythmic drugs have also been used in an attempt to lower the risk of SCD. These medications can effectively suppress abnormal rhythms; however, suppression of arrhythmias with these drugs has not been found to translate into improved survival. In fact these medications have no effect or can increase the risk of SCD. The Cardiac Arrhythmia Suppression Trial (CAST) showed that suppression of spontaneous ventricular arrhythmias with antiarrhythmic agents in high-risk patients after MI resulted in an excess mortality.[44,45] Studies of other antiarrhythmic drugs such as D-sotalol[46] and dronedarone[47] have also resulted in mortality concerns. Amiodarone has not been associated with improved survival in high-risk patients after MI (in two trials, European Myocardial Infarction Amiodarone Trial [EMIAT][48] and Canadian Amiodarone Myocardial Infarction Arrhythmia Trial [CAMIAT],[22] nor has it resulted in improved survival when compared to an implantable cardioverter–defibrillator (ICD) in patients who had a prior cardiac arrest (in the Cardiac Arrest Study Hamburg [CASH],[49] Canadian Implantable Defibrillator Study [CIDS],[21] and Antiarrhythmics versus Implantable Defibrillators [AVID][50] trials). The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed no survival benefit from amiodarone for primary prevention of SCD when compared with placebo.[51] Furthermore, the use of amiodarone can cause long-term harms involving lung, liver, thyroid, and skin. Given the excess adverse events from antiarrhythmic therapy, antiarrhythmic drugs currently are only selectively administered in some patients to reduce symptoms from recurrent ventricular arrhythmias, without the intention to improve mortality.

In this setting of inadequate medical treatment of ventricular tachyarrhythmias, another treatment option is device therapy. In 1980, Mirowski et al. developed a paradigm of interventional treatment with the development of the ICD,[52] a medical device designed to prevent SCD by terminating ventricular tachyarrhythmias and subsequently aborting cardiovascular collapse and death.

ICD Technology

The ICD is a battery-powered implantable device that consists of a generator and one or more leads capable of sensing a ventricular arrhythmia and delivering therapy in the form of an

electric shock. This electric shock causes defibrillation when a potentially life-threatening arrhythmia is detected, to terminate the arrhythmia and prevent SCD. Over the years, ICD technology has evolved in several ways. Over time, the size of the device, or footprint, has become significantly smaller. With improved technology, large abdominal generators have been replaced by smaller pectoral generators. Furthermore, the ICD lead was initially designed as an epicardial patch, which required opening the chest for surgical implantation. At present, right atrial, right ventricular, and left ventricular leads may all be placed endocardially via a transvenous approach, obviating the need for thoracotomy or sternotomy in most cases.

Over the past decade, there has also been an evolution in ICD technology. ICDs were initially designed as single chamber devices with the sole purpose of providing an electric shock to terminate a lethal ventricular rhythm. These devices can now incorporate pacing capabilities to provide backup ventricular pacing. A dual chamber device (with a lead in the right atrium and a lead in the right ventricle) may be implanted to impart atrial and ventricular synchrony in patients who meet indications for a dual chamber pacemaker (i.e., those with certain types of bradycardia) as well as defibrillator therapy.

Currently, device-based therapy also includes the ability to deliver cardiac resynchronization therapy (CRT) via the addition of a left ventricular lead. CRT may be delivered in the form of a standalone biventricular pacemaker (CRT-P) or in addition to an implantable cardioverter defibrillator (CRT-D). CRT implantation involves the placement of right atrial, right ventricular, and left ventricular leads. The difference between CRT-P and CRT-D relates to the type of right ventricular lead (with or without coils) and the type of generator. The goal of CRT is to improve cardiac output in patients who manifest electrical dyssynchrony and cardiac dysfunction via atrial-synchronized biventricular pacing towards improving congestive heart failure and related symptoms as well as prolonging survival. While patients at increased risk for SCD and those who have dyssynchrony share some characteristics, they are not exactly the same clinical populations. The goals of ICD and CRT therapy overlap in their overall goal to improve meaningful survival, but they are distinct in that the intention of ICD therapy is restoration of normal sinus rhythm in the setting of life-threatening arrhythmias, and the intention of CRT is improvement of functional status and symptoms of heart failure.

Technological advances have taken place not only in the design of the generator and the leads but also in software algorithms. One of the goals of these algorithms is to avoid “inappropriate” shocks, shocks that are delivered when ventricular tachyarrhythmias are not occurring. This can occur when there is a fast rhythm that is actually supraventricular (atrial) in origin rather than ventricular. To prevent these inappropriate shocks, ICD programming has been developed to discriminate among types of tachyarrhythmias and to differentiate atrial from ventricular arrhythmias. An inappropriate shock may also be delivered as a result of electromagnetic interference or a lead or device malfunction.

Further developments that combine pacing capabilities with sophisticated programming algorithms include the ability to treat ventricular tachycardias via antitachycardia pacing (ATP). ATP is achieved by pacing the ventricle at a cycle length faster than the ventricular tachyarrhythmia in an attempt to abort the rhythm. Because ICD shocks are painful and are associated with patient morbidity,[53-55] ATP offers the potential to terminate the abnormal rhythm in a painless manner without the need for an electrical shock. On the other hand, ATP may accelerate a VT resulting in the degeneration of the rhythm into VF. The safety and efficacy of ATP has been evaluated in multiple studies.[56-59] Most recently, MADIT-RIT (Multicenter

Automatic Defibrillator Implantation Trial: Reduce Inappropriate Therapy) examined effect of ICD programming on inappropriate therapy and mortality.[60]

ICD Complications

Any potential benefits have to be balanced against potential harms. Implantating a cardiac electronic device is an invasive procedure with inherent risks. There is the potential for intraoperative or immediate postoperative complications, including but not limited to bleeding, infection, pneumothorax, cardiac tamponade, or lead dislodgement.[61-65] Long-term complications include lead or generator malfunction, thrombosis of the access site, infection, and inappropriate ICD shocks that may have emotional and psychological repercussions. In addition to patient characteristics, physician characteristics such as training and volume may play a role in complications rates.[66,67]

ICD Use for Secondary Prevention of SCD

Persons with sustained VT and survivors of out-of-hospital cardiac arrest have an actuarial incidence of SCD at 2 years of 15 to 30 percent.[11,68] Initial use and testing of ICDs was performed in this group of patients who had already experienced a sustained ventricular tachyarrhythmia or SCD and were at high risk of recurrence. This scenario of preventing SCD recurrence is called secondary prevention of SCD. A meta-analysis of three randomized controlled trials (CASH,[49] CIDS,[21] and AVID[50]) of antiarrhythmic therapy versus ICD in this population revealed a 28 percent reduction in the relative risk of death with the ICD.

The current 2008 joint American College of Cardiology Foundation/American Heart Association guidelines for device-based therapy state that ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained ventricular tachyarrhythmia following exclusion of completely reversible causes.[69]

ICD Use for Primary Prevention of SCD

ICDs have begun to be used in patients with no prior episode of sustained ventricular tachyarrhythmia or SCD but who are considered to be at high risk for SCD. As noted above, the majority of cases of SCD occur in people with no known history of VT or VF. Thus, primary prevention (i.e., preventing a first occurrence) of SCD is of paramount importance.

Current Guidelines

In 2008, a joint task force of the American College of Cardiology Foundation (ACCF)/American Heart Association (AHA)/Heart Rhythm Society in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Cardiac Pacemakers and Antiarrhythmia Devices updated the 2002 guidelines for device-based therapy.[2,70] According to these clinical guidelines, class I indications for ICD therapy for primary prevention of SCD include 1) Patients with LVEF ≤35 percent due to prior MI who are at least 40 days post-MI and are in NYHA Class II or III; 2) Patients with nonischemic dilated cardiomyopathy who have an LVEF ≤35 and who are in NYHA Class II or III. 3) Patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF ≤30 percent, and are in NYHA Class I.[70] These clinical indications correlate with the coverage criteria set by CMS.

This review is focused on primary prevention of SCD and does not provide a comprehensive assessment of the effectiveness of CRT for management of heart failure or dyssynchrony.

However, given overlapping indications for CRT and ICD therapy, it is important to note that in October 2012, a joint ACCF/AHA task force on practice guidelines published a focused update, revising its 2008 guidelines.[71] Recommendations specifically for CRT were updated on the basis of multiple heart failure trials in the 2012 Focused Update for Device-Based Therapy of Cardiac Rhythm Abnormalities; ACC/AHA Guidelines for the Management of Patients with Heart Failure; and ICD Indications.[72-74] New recommendations and modifications focused on heart failure status, QRS duration, left versus non-left bundle branch block, and underlying rhythm (sinus rhythm vs. atrial fibrillation). In addition, the Appropriate Use Criteria have been published based on a 2013 HRS-ACC-AHA Expert Consensus on ICD Indications Outside of Current Guidelines.[75] This document assessed levels of appropriateness for implanting ICDs and CRTs in 369 real-life case scenarios, to provide guidance concerning the decision to implant ICDs and CRT devices in a variety of clinical scenarios where there are gaps in guidelines. The AUC document should be used in conjunction with the ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities and the 2012 Focused Update.

CMS Coverage Decisions for Primary Prevention

CMS issued coverage decisions for ICD implantation for primary prevention which are reviewed here since they have shaped subsequent research and clinical care. In 2003, CMS provided coverage for primary prevention of SCD, primarily on the basis of data from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)[42]—which included patients with CAD and a prior MI, LVEF ≤35 percent, and inducible, sustained VT or VF at electrophysiologic study—and from MADIT II[76]—which included patients with prior MI and, LVEF ≤30 percent.

The 2005 CMS national coverage determination broadened the indications for implantation of ICDs for primary prevention of SCD.[77] In addition to the above criteria, it added the following indications:

- Documented prior MI and a LVEF ≤30 percent
- Ischemic dilated cardiomyopathy, prior MI, New York Heart Association (NYHA) class II or III heart failure, and LVEF ≤35 percent
- Current CMS coverage requirements for a CRT device, together with ambulatory NYHA class IV heart failure
- Nonischemic dilated cardiomyopathy for >3 months, NYHA class II or III heart failure, and LVEF ≤35 percent.

To be covered, a patient must also be receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than 1 year.

As part of its coverage determination, Medicare instituted a requirement for the CMS to establish an ICD registry to collect data on individuals undergoing ICD implantation to be able to assess outcomes after ICD implantation. Thus, the National Cardiovascular Data Registry (NCDR) ICD registry has been active since 2005.

Current Uncertainties

The field of ICD implantation for primary prevention of SCD is evolving as clinicians are challenged by decisions about how to direct it to patients who may derive net benefit. A number of recent developments may have impacted the risk benefit ratio. With the 2005 coverage decision, the pool of patients eligible for implantation has expanded. Selection criteria have

changed with earlier trials selecting patients based on invasive electrophysiological testing, while more recent studies selected patients solely based on clinical selection criteria. Meanwhile, technology has advanced to newer generations of devices. While the risk of SCD is highest in the first few weeks after MI in patients with left ventricular dysfunction, there has been a decrease in the SCD and mortality after MI as a result of medical and percutaneous coronary interventional advances.[29,43] This highlights the need for an updated evaluation of the aggregate data on ICD benefits and harms and how they apply to particular patient subgroups.

Aim of the Technology Assessment

This Technology Assessment examines the state of evidence related to ICD use for primary prevention of SCD. It examines the effectiveness of treatment with an ICD versus control treatment without an ICD. It also examines the effectiveness of combining an ICD with ATP or with CRT versus an ICD alone.

Key Questions

This Technology Assessment considers evidence regarding the following three Key Questions, based on those originally drafted by CMS and refined through discussions with the Agency for Healthcare Research and Quality (AHRQ) and CMS:

Key Question 1

a) In candidates for ICD implantation for primary prevention of SCD, what are the effects of ICD compared with no ICD therapy on clinical outcomes and patient-reported outcomes?
b) In candidates for ICD implantation for primary prevention of SCD, what are the effects of ICD with ATP versus ICD alone, or of ICD with CRT versus ICD alone on clinical outcomes and patient-reported outcomes?
c) How do outcomes vary within the following subgroups?
    i. Different patient characteristics such as varying demographic features, major comorbidities, different risk factors for SCD, or different indications for ICD implantation
    ii. Different ICD characteristics
    iii. Different characteristics of clinicians implanting ICDs—that is, different levels of training and experience
    iv. Different characteristics of facilities where ICDs are implanted

Key Question 2

a) What are the adverse events related to treatment with an ICD for primary prevention of SCD? Specifically:
    i. Early (during hospitalization for implantation)
    ii. Late
    iii. Inappropriate shocks
b) How do adverse events vary within the following subgroups?
    i. Different patient characteristics such as varying demographic features and major comorbidities
    ii. Different ICD characteristics

iii. Different characteristics of clinicians implanting ICDs—that is, different levels of training and experience
iv. Different characteristics of facilities where ICDs are implanted

Key Question 3

Which patients have been included in comparative studies of ICDs for primary prevention of SCD?

a) What were eligibility criteria for patients in studies included for Key Question 1? How were patients evaluated and what diagnostic tests and algorithms were used to select patients?
b) Among patients in studies included for Key Question 1, what was the likelihood of SCD or ventricular tachyarrhythmia, as measured by total shocks for those with ICDs or episodes of SCD for those without ICDs?

Methods

The methods for this Technology Assessment follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter referred to as the Methods Guide; available at www.effectivehealthcare.ahrq.gov/methodsguide.cfm).[78]

AHRQ Task Order Officer

The AHRQ Task Order Officer (TOO) was responsible for overseeing all aspects of this project. The TOO facilitated a common understanding among all parties involved in the project, resolved ambiguities, and fielded all EPC queries regarding the scope and processes of the project. The TOO and other staff at AHRQ reviewed the report for consistency, clarity, and to ensure that it conforms to AHRQ standards.

External Expert Input

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from The Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the Tufts Evidence-based Practice Center: (Contract Number: 290 2007 10055 I).

The Key Questions in this TA were drafted by CMS and refined by the Evidence-based Practice Center (EPC) through discussions with Agency for Healthcare Research and Quality (AHRQ) Task Order Officer and CMS experts

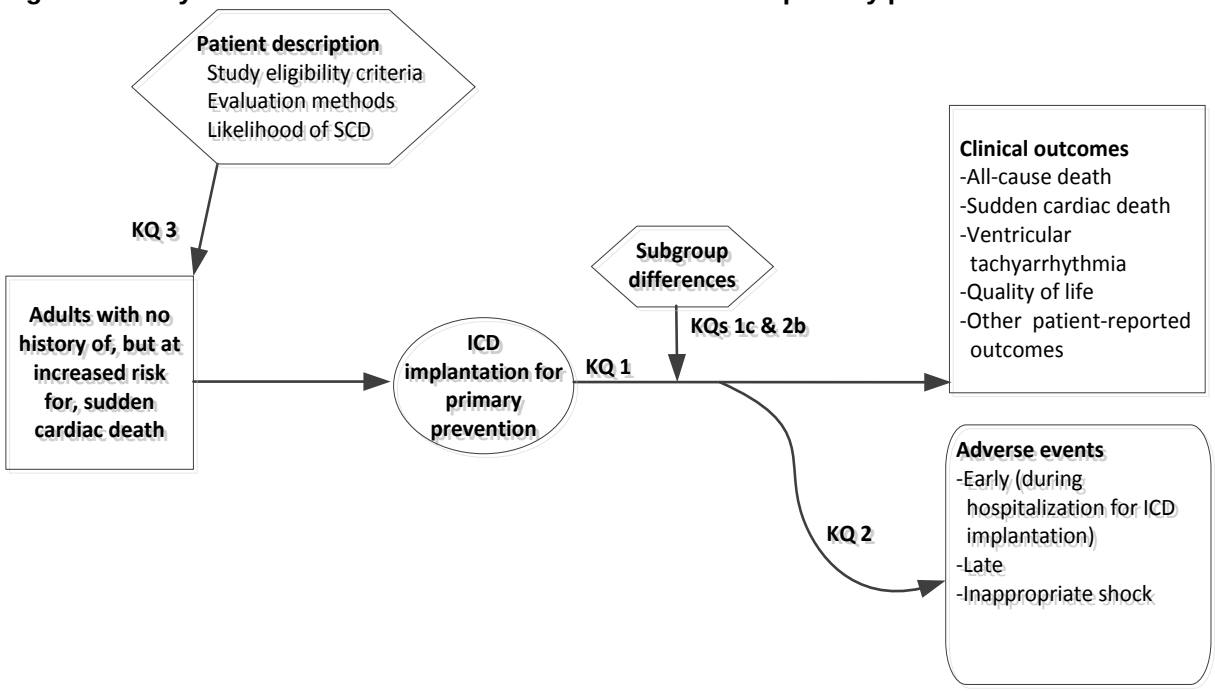
Key Questions

Key Questions were refined to take into account the patient populations, interventions, comparators, outcomes, and study designs that are clinically relevant for the use of ICDs in the primary prevention of SCD. Three Key Questions are addressed in the present report. Key Question 1 pertains to clinical outcomes (benefits) of ICDs for primary prevention of SCD. Key Question 2 pertains to adverse events associated with ICDs. Key Question 3 pertains to the description of patients enrolled in ICD trials for primary prevention. The Key Questions are listed at the end of the Introduction.

Analytic Framework

To guide the development of the Key Questions for the evaluation of ICDs, we developed an analytic framework (**Figure 1**) that maps the specific linkages associating the populations of interest, the interventions, and the outcomes of interest (intermediate outcomes, surrogate outcomes, and clinical outcomes). Specifically, this analytic framework depicts the chain of logic that evidence must support to link the interventions to improved health outcomes.

Figure 1. Analytic framework for the evaluation of ICDs in the primary prevention of SCD



The Key Questions (KQs) are shown within the context of the PICO (Population, Intervention, Comparators, and Outcomes) criteria. The figure illustrates how implantable cardioverter–defibrillator (ICD) implantation for primary prevention of sudden cardiac death affects clinical outcomes and may result in adverse events.

Literature Search and Study Selection

We conducted the literature search in MEDLINE® and the Cochrane Central Register of Controlled Trials with no language restrictions (**Appendix A**). Key words included terms related to the device of interest (ICDs) and terms related to study design. The first search was performed on November 11, 2011, with a final update on December 4, 2012.

Key Question 1

For Key Question 1, randomized controlled trials (RCTs) or comparative longitudinal cohort studies (nonrandomized comparative studies [nRCSs]) were eligible if they provided relevant data directly comparing an ICD to no ICD, including antiarrhythmic drug treatment, or to different ICD interventions and if they included at least 10 participants per study group. For nRCSs, only those studies that used concurrent controls and reported a multivariate analysis were included. The population of interest included adults potentially eligible to receive an ICD for primary prevention of SCD (i.e., adults with no known history of SCD or ventricular tachyarrhythmia). If the study included patients receiving ICDs for secondary prevention, the articles had to provide results by subgroups or specify that the proportion of secondary prevention was less than 20 percent. Participants had to be followed from the time of ICD implantation, not only from some arbitrary time after ICD implantation. There was no minimum followup duration.

For Key Question 1a, comparisons of interest were ICD versus no ICD (i.e., medical management with a designated comparator drug or with concomitant medical therapy). For this review, we included studies comparing CRT-D versus CRT alone as a comparison of ICD versus

no ICD. For Key Question 1b, comparisons of interest were ICD with ATP versus ICD alone, or ICD with CRT CRT versus ICD versus ICD alone. We did not review comparisons of different pacing or shock algorithms.

For Key Question 1c, we examined effect modification in subgroups. In studies eligible for Key Questions 1a and 1b, we examined the results across subgroups for different patient characteristics such as varying demographic features (age, sex, race, and ethnicity), major comorbidities, different risk factors for SCD, or different indications for ICD implantation (including LVEF≥30 versus < 30 percent, duration of QRS interval, NYHA heart failure classification, and type of underlying heart disease [e.g., ischemic vs. nonischemic cardiomyopathy]); time from MI; different numbers of leads; different characteristics of clinicians implanting ICDs—that is, different levels of training and experience; and different characteristics of facilities where ICDs are implanted, such as patient volume and presence or absence of a training program. We planned to evaluate subgroups that were of particular interest to CMS upon setting up the ICD registry: patients with LVEF of 31 to 35 percent, patients with nonischemic cardiomyopathy of less than 9 months' duration, and patients with NYHA class IV heart failure who may benefit from an ICD with CRT. Studies had to report how a difference in the factor affected outcomes of interest (e.g., death rates in subgroups based on age ranges), not the groups' baseline characteristics on the basis of the outcome (e.g., mean ages at ICD implantation among patients who survived or died). We examined whether estimates differed statistically significantly across subgroups.

For all of Key Question 1, outcomes of interest were clinical outcomes including death from SCD, all-cause mortality, sustained ventricular tachyarrhythmia, quality of life (QoL), and other patient-reported outcomes. We excluded heart failure outcomes as well as composite outcomes of death and heart failure. For QoL and other patient-reported outcomes, we gave priority to measurements made with standardized and validated instruments.

Key Question 2

For rates of adverse events, we included longitudinal studies of any design with at least 500 participants. This criterion was set because the rate of adverse events is low and because we were able to use a registry for in-hospital adverse events. Participants had to be followed from the time of ICD implantation, not only from some arbitrary time after ICD implantation. There was no minimum followup duration. For comparison of rates of different ICD devices we reviewed comparative studies with at least 10 patients per arm that were included in Key Question 1b.

The population of interest was adults who received an ICD for primary prevention alone, preferentially, or for either primary or secondary prevention, if not separately reported. A mix of primary and secondary prevention was permitted because we determined that there is little reason to expect adverse events to differ between primary prevention and secondary prevention populations and that the addition of patients with ICDs for secondary prevention would allow for better estimates of adverse event rates. However, studies specifying ICD implantation only for secondary prevention were excluded. We also excluded studies published prior to 2002, because we aimed to focus on harms associated with current devices and implantation methods.

Interventions of interest were the same as those for Key Question 1: single-chamber, dual-chamber, or biventricular ICDs with or without ATP or CRT. The outcomes of interest for adverse events are listed below, divided into those that occur early after ICD implantation (including events that occur during the hospital stay for implantation or up to 30 days postimplantation) and those occurring later:

- Early (during hospitalization for ICD implantation)
    - Any adverse event
    - Any adverse event or death
    - Any serious adverse event
    - Atrioventricular fistula
    - Cardiac arrest
    - Cardiac perforation
    - Cardiac valve injury
    - Cerebrovascular accident/Stroke
    - Conduction block
    - Coronary venous dissection
    - Drug reaction
    - Hematoma
    - Hemothorax
    - Infection related to device
    - Lead dislodgement
    - Myocardial infarction
    - Pericardial tamponade
    - Peripheral embolism
    - Peripheral nerve injury
    - Phlebitis - deep
    - Phlebitis - superficial
    - Pneumothorax
    - Transient ischemic attack
- Late (after hospitalization for implantation)
    - Device malfunction
    - Device or lead revision
    - Lead dislodgement
    - Lead fracture or malfunction
    - Infection related to device
    - Thrombosis
- Inappropriate shocks

For adverse events occurring early after the implantation procedure (during hospitalization), we reviewed and reconciled reports from the NCDR ICD database. This registry was started after the 2005 Medicare coverage decision and provides standardized, comprehensive data on over 90 percent of ICD implantations in the United States with active and passive ascertainment for adverse events during the hospitalization for the implantation.[79] We included all pertinent reports from the registry even though there was overlap in participants across publications.

For adverse events occurring after hospitalization, we included cohort studies with ICD groups, including ICD arms from RCTs. Since the adverse events of interest are unique to the ICD or the implantation procedure, we did not extract data on control arms without ICDs. For information on how adverse events differ across ICD types, we tabulated the adverse events reported in eligible comparative studies from Key Question 2.

We further searched for any information on effect modifiers that might increase or decrease the risk of adverse events. Subgroups or factors of interest were different patient characteristics

(age, sex, race, diabetes, end-stage renal disease), different ICD characteristics (including ATP or CRT features and number of leads), different characteristics of clinicians implanting the ICDs (different levels of training and experience), and different characteristics of facilities where ICDs are implanted. For subgroups, we again included only data reported on the basis of the factor, not on the basis of the outcome, and examined whether estimates differed statistically significantly across subgroups.

Key Question 3

For Key Question 3a, related to the eligibility criteria and prior evaluation of participants, we reviewed the studies used to address Key Question 1 and tabulated the descriptive information about how patients were evaluated prior to enrollment and randomization. For Key Question 3b, we evaluated the studies reviewed for Key Question 1 and captured the number of total shocks and ATP pacing events as an indicator of the underlying severity of disease (i.e., the likelihood of SCD) in patients analyzed in studies to assess treatment heterogeneity across studies. Note that the number of inappropriate shocks, a measure of harm, is covered in Key Question 2.

Article Screening and Data Extraction

We screened titles and abstracts using *Abstrackr* (http://sunfire34.eecs.tufts.edu).[80] Seven researchers double-screened the abstracts after iterative training of all reviewers on several batches of abstracts. Discordant decisions and queries were resolved at group meetings. Full-text articles were retrieved for all potentially relevant abstracts. Studies excluded during full-text screening and the reasons for exclusion are given in **Appendix B**.

Each study was extracted by one experienced methodologist. The extraction for results and quality were reviewed and confirmed by at least one other methodologist. Data extraction was done using the Systematic Review Data Repository (SRDR) database (www.srdr.ahrq.gov).[81] The form was customized to capture all relevant elements for the key question and included elements for population characteristics, sample size, study design, descriptions of the ICD and comparison interventions, outcomes, subgroup factors, and relevant results analyses. We also extracted data on items of particular relevance to Key Question 3, such as eligibility criteria and how patients were evaluated.

For data from survival curves, we extracted both the reported hazard ratio (HR), preferentially the adjusted HR rather than the unadjusted HR, and any reported counts data. We did not digitize figures to estimate counts or percentages of outcomes. We used the maximum duration of the survival curve as the duration of followup for each relevant outcome, unless the article explicitly expressed the HR as applying to a different timepoint. For outcomes with data reported at multiple timepoints, our *a priori* timepoints of interest for clinical outcomes were 1, 2, and 4 years of followup. In our meta-analyses (described below), we also analyzed data from all years of followup with data.

Risk of Bias and Quality of Reporting Assessment

For Key Question 1, we assessed methodological quality of RCTs using eight items derived from the Cochrane risk of bias tool[82] and one additional item created to address participant crossovers during the study period (**Table 1**). Reviewing across all eight risk of bias items, we assigned an overall quality grade of good, fair, or poor to each RCT. We assigned particular weight to risk of bias concerns related to differential attrition or crossover between arms and to

differences other than ICD assignment between the two arms. We downgraded for risk of bias related to outcome assessor blinding only for clinical outcomes other than all-cause mortality. We did not grade nonrandomized comparative studies (nRCS).

For Key Question 2, we assessed the quality of reporting of harms using items adapted from the McMaster Quality Assessment Scale of Harms (McHarm) Tool (**Table 2**).[83,84]

Table 1. Risk of bias items assessed for randomized controlled trials (Key Question 1)

1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?
2. What is the risk of selection bias (biased allocation of interventions) due to inadequate concealment of allocations before assignment?
3. For each main outcome or class of outcomes, what was the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?
4. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?
5. Were all randomized participants analyzed in the group to which they were allocated?
6. Were the groups similar at baseline regarding the most important prognostic indicators?
7. Were co-interventions avoided or similar?
8. Are there other risks of bias? If yes, describe them in Notes.
9. Number of crossovers?

Table 2. Quality of reporting items assessed for adverse event studies (Key Question 2)

1. Were any harms pre-specified (*a priori*) in methods section?
1a. If yes, were any of them pre-specified with *a priori* standardized or precise definitions?
2. Were all pre-specified harms reported?
3. Was the mode of harms collection active (sought to collect information on adverse events)?
4. Was the mode of harms collection passive? (Participants are not specifically asked about or tested for the occurrence of adverse events. Rather, adverse events are identified based on patient reports made on their own initiative.)
5. Did the study specify the timing and/or frequency of collection of harms?
6. Is the number of participants who experience harms provided for each arm?
7. Is the number at risk for harms (denominator) provided for each arm?
8. For comparative studies (those also addressing Key Question 1): Is there statistical analysis of relative harms between groups?

Data Synthesis

We summarized all included studies in narrative form as well as in evidence tables that summarize the important features of the study design, population characteristics, results, study quality, and inclusion criteria. Tables in **Appendix C** provide detailed baseline characteristics of the included patients and cointerventions given at baseline, the qualitative results summary, the quality of each study, and the results for Key Question 3 (See Table of Contents for Appendix C).

For outcomes with at least three RCTs with sufficiently similar comparisons of interventions and comparators (relevant to Key Question 1), we performed DerSimonian & Laird random effects model meta-analyses.[85] We meta-analyzed adjusted HRs, unadjusted HRs (if no adjusted HR was reported), and estimated HRs (if no HR was reported). To estimate the HR, we used the various methods described by Tierney et al. to estimate HR given different types of reported data.[86] For these calculations, only reported counts (events) were used; we did not use digitized

data from figures. For each meta-analysis the statistical heterogeneity was assessed with the I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance.[87,88]

For our primary meta-analyses, we included only studies that included only patients who meet current practice for ICD use for primary prevention, thus excluding studies of patients undergoing ICD implantation immediately after coronary revascularization or early after recent myocardial infarction. We conducted sensitivity analyses in which we added back in the RCTs of these "atypical" patients.

To assess how the effect of ICD versus no ICD changes over time since randomization we drew plots of the difference in cumulative mortality between ICD and no ICD based on the reported Kaplan Meier plots for each trial. At each year timepoint we estimated the cumulative death proportion by digitizing the figure for both ICD and no ICD and subtracted the no ICD cumulative death proportion from the ICD proportion. This calculation measures the vertical distance between the two curves in the Kaplan Meier plots. To roughly estimate the average difference in cumulative death across studies we calculated a weighted mean of the differences at each annual time point based on the numbers of people remaining at risk within each study at each timepoint.

For each RCT of ICD versus no ICD, we calculated the numbers-needed-to-treat (NNT) to prevent one death (all-cause) and to prevent one tacchyarrhythmia death. Since most RCTs reported HRs for death, we estimated the NNT for each trial to prevent one death at each year from reported or estimated HRs. To estimate NNT from HR, we used the method described by Altman et al., which estimates the control and treatment rates from the HR, the survival rate at each year, and the number at risk at each year.[89] Since the control rates across studies varied widely, we did not meta-analyze NNT as the summary NNT value would be uninterpretable without a single value for the control rate as a referent.

In regards to subgroup analyses, for each study that reported odds ratios (or relative risks or hazard ratios) for the same or similar pairs of subgroups (e.g., women vs. men, age≤60 or 65 years vs. >60 or 65 years), we calculated a "relative odds ratio" as the ratio of the odds ratio (or similar metric) of one subgroup to the other subgroup, and its 95 percent confidence interval. When at least three studies reported sufficient data for pairs of similar subgroups, we meta-analyzed these using a random effects model.

Strength of Evidence Grading

We followed the Methods Guide to evaluate the strength of the body of evidence for Key Questions 1 and 2 with respect to four domains: risk of bias, consistency, directness, and precision.[78,90] Briefly, we defined the risk of bias (low, medium, or high) on the basis of the study design and the methodological quality of the studies. Where there was sufficient evidence from RCTs, we determined strength of evidence from these alone, without considering the nRCSs.

For consistency we did not use rigid counts of studies as standards of evaluation (e.g., four of five studies agree, therefore the data are consistent); instead, we assessed the direction, magnitude, and statistical significance of all studies for each specific topic and made a qualitative determination.

Since we examined clinical and patient-reported outcomes (and clinically important adverse events), we expected all analyzed evidence to be "direct." Where applicable, we considered the

degree to which conclusions are based on direct comparisons (within studies) or indirect comparisons across studies).

We assessed the precision of the evidence as precise or imprecise on the basis of the degree of certainty surrounding each effect estimate. A precise estimate is one that allows for a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., both clinically important superiority and inferiority—a situation in which the direction of effect is unknown) and that therefore precludes a conclusion.

We rated the body of evidence on the basis of four strength-of-evidence levels (high, moderate, low, and insufficient[90]) to indicate our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

A high strength of evidence suggests that we are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable.

A moderate strength of evidence suggests that we are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.

A low strength of evidence suggests that we have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.

A ranking of insufficient evidence suggests that we have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding judgment. We graded the body of evidence to be insufficient to assess a strength of evidence if evidence was either unavailable or did not permit estimation of an effect because of lacking or sparse data or if the data were too inconsistent or inconclusive to determine whether there was evidence of a benefit, a harm, or no difference between intervention and comparator. In general, when only one study had been published, the evidence was considered insufficient, unless the study was particularly large, robust, and of good quality.

We reviewed subgroups results for Key Question 1 and 2 for statistically significant differences. Subgroup analyses are by their nature exploratory. Thus we did not grade strength of evidence of the subgroup results.

Applicability

We followed the Methods Guide to evaluate the applicability of included studies to patient populations of interest.[78,90] We highlighted limitations to applicability when comparing the populations in the included studies with the core Medicare population.

Peer Review

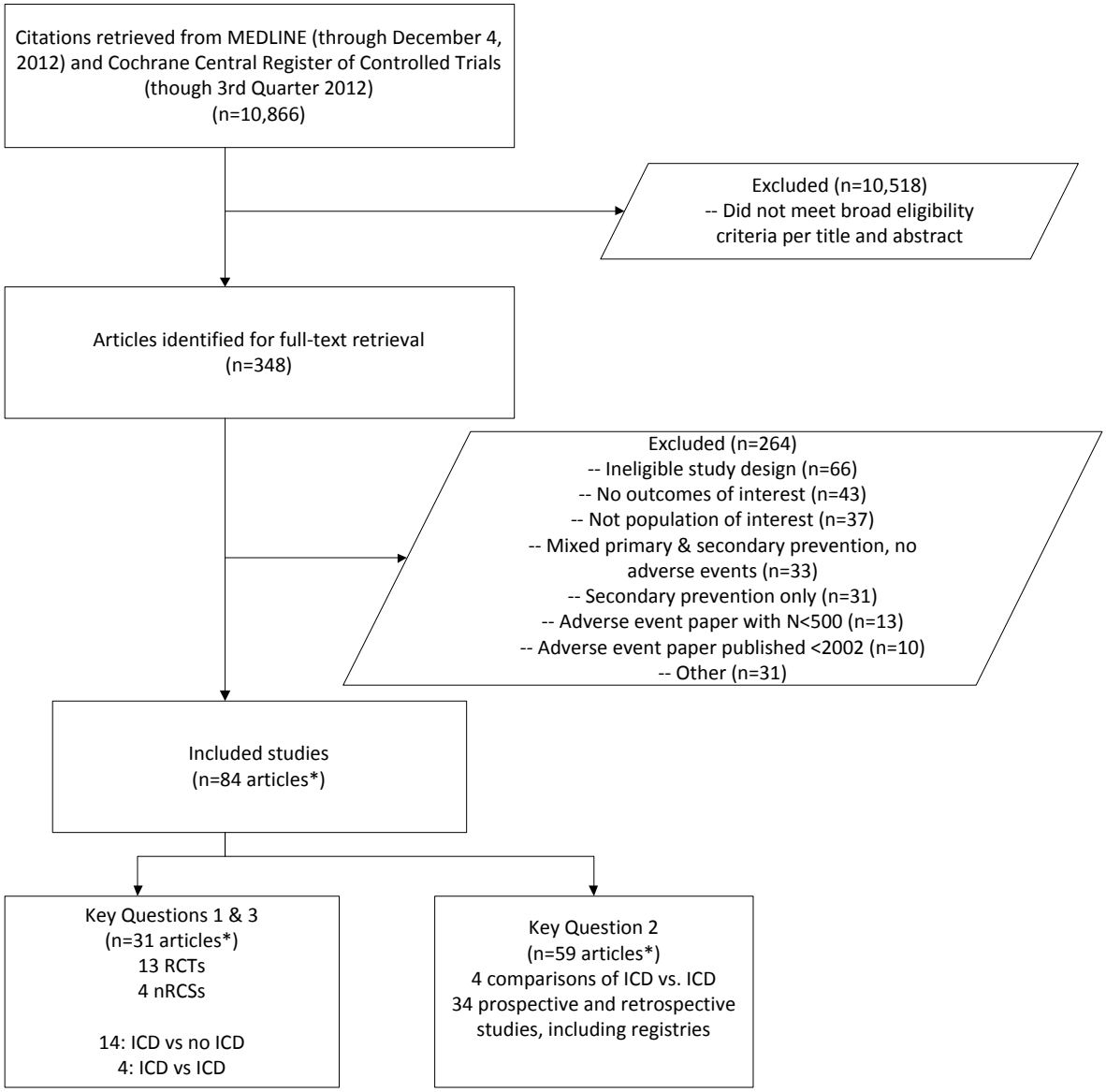
The draft report was prereviewed by the AHRQ TOO. Following revisions, the draft report was sent to invited peer reviewers and simultaneously uploaded to the AHRQ Web site where it was available for public comment for 2 weeks. All reviewer comments (both invited and from the public) were collated and individually addressed. The revised report and the EPC's responses to invited and public reviewers' comments were again reviewed by the TOO prior to completion

of the report. The authors of the report had final discretion as to how the report was revised on the basis of the reviewer comments, with oversight by the TOO.

Results

Our searches identified a total of 10,866 abstracts, of which we screened 348 in full text and included 84 articles (**Figure 2**). **Appendix B** lists the studies that were excluded in full text. There were 31 articles that described 13 randomized controlled trials (RCTs) and 4 nonrandomized comparative studies (nRCSs) that address Key Questions 1 and 3. For Key Question 2, there were 59 articles that included 37 independent study cohorts of patients with ICD, including 4 RCTs that compared different types of ICDs. Six articles (Five studies) were included in both Key Questions 1 and 2.

Figure 2. Literature Flow Diagram



ICD = implanted cardioverter defibrillator, nRCSs = nonrandomized comparative studies, RCTs = randomized controlled trials. Studies could have had more than one reason for exclusion but only one reason for each is listed here.

* Includes multiple publications (articles) derived from the same studies. Five articles on 4 studies provided data for Key Questions 1 and 2.

Of note, under Key Question 1, we have incorporated Key Question 1c (on subgroups) into both Key Questions 1a (ICD vs. no ICD) and 1b (ICD vs. ICD).

The list following this paragraph includes all studies included for Key Question 1, with their acronyms defined. In the Discussion section, we explain why several well-known ICD trials did not meet eligibility criteria.

AMIOVERT	Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia
CABG-Patch	Coronary Artery Bypass Graft Patch Trial
CAT	Cardiomyopathy Trial
Chan 2009	
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
Diab 2011	
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
Fonarow 2000	
IRIS	Immediate Risk Stratification Improves Survival
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MENDMI	Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction Study
Mezu 2011	
OPTIMIZE-HF/GWTG-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure and Get With the Guidelines-Heart Failure
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial

Key Questions 1a & 1c: In Candidates for ICD Implantation for Primary Prevention of SCD, What Are the Effects of ICD Therapy Compared with No ICD Therapy on Clinical Outcomes and Patient-Reported Outcomes? How Do Outcomes Vary Within Subgroups?

For Key Questions 1a and 1c, we included studies that compared ICD use with no ICD use, with or without concomitant CRT or ATP in adults being treated for primary prevention of SCD. Except as noted, we did not distinguish between studies that compared ICD with no ICD (both arms with or without antiarrhythmic drugs) and studies that compared ICD alone with antiarrhythmic drugs. The findings and strength of evidence for outcomes with sufficient evidence for the comparison of ICD versus no ICD are summarized in **Table 3**.

Table 3. Summary of findings for ICD vs. no ICD

Outcome	Study Design: No. Studies (N)	Findings	Strength of Evidence
All-cause mortality	ICD vs. no ICD RCT: 10 (8,606) nRCS: 4 (5,949)	• ICD use as primary prevention for patients who meet the current practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of all-cause mortality over the course of 3 to 7 years after implantation: HR = 0.69 (95% CI 0.60, 0.79). The benefit of ICD appears fairly stable over time. Across trials, the range of NNT to prevent one death was 6.2 to 22 at 3 to 7 years, with wide 95% CIs. • There is indirect evidence across studies that patients with recent MIs (<30-40 days), on average, do not benefit from ICD, in contrast with patients with more distant MIs. • Within-study subgroup analyses fail to support whether the value of ICD placement differs in other subgroups of patients, including by sex or age, or based on different characteristics of facilities where ICDs are implanted.	High
Sudden cardiac death	ICD vs. no ICD RCT: 7 (4,093) nRCS: 2 (1,115)	• ICD use as primary prevention for patients who meet the current practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of SCD over the course of 2 to 6 years after implantation: HR = 0.37 (95% CI 0.26, 0.52). There is insufficient evidence to evaluate the course of the effect over time. Across trials, the range of NNT to prevent one SCD was approximately 2.0 to 11. • Within-study subgroup analyses fail to support whether the value of ICD placement differs in subgroups of patients or based on different characteristics of facilities where ICDs are implanted.	High
Quality of life	ICD vs. no ICD RCT: 3 (1,825)	• The evidence fails to show a consistent effect of ICD placement on quality of life. • There is no evidence regarding subgroups.	Low

CI = confidence interval, CMS = Centers for Medicare and Medicaid Services, HR = hazard ratio, ICD = implantable cardioverter–defibrillator, MI = myocardial infarction, NNT = number-needed-to-treat, No. = number, nRCS = nonrandomized comparative study, RCT = randomized, controlled trial, SCD = sudden cardiac death.

We identified 10 RCTs (reported in 18 articles[42,51,76,91-104]) and 4 nRCSs[105-108] (**Table 4**).

Among the 14 RCTs, 9 were assessed to be of good quality and 5 of fair quality (**Figure 3, Appendix Table 8**); 2 of these trials were further downgraded (to fair or poor quality) for outcomes other than all-cause mortality because outcome assessors were not blinded.[92,94] Methodological concerns included high attrition rates (>20%),[95] differential rates of attrition and/or crossover between study groups,[51,94,95,99] and differences in the rates of use of beta blockers between the two study groups.[51] Of note, all trials conducted intention-to-treat analyses.

We did not explicitly grade the methodological quality of the four nRCSs, though we included only studies that performed multivariable analyses.

The 14 studies were published from 1996 to 2011 and the patients' mean ages ranged from 48 to 86 years. The RCTs enrolled between 103 and 2,521 patients, and the nRCSs analyzed between 147 and 4,685 patients. The majority of patients in these studies were men with LVEF

ranging from 21 to 28 percent. All four New York Heart Association (NYHA) classes were represented in the study samples. Two studies (one RCT[95] and one nRCS[106]) included only patients with NYHA Class III or IV heart failure. The RCT enrolled approximately 84 percent Class III patients and the nRCS enrolled half Class III and half Class IV patients. The percentage of patients with diabetes ranged widely across the studies, from 5 to 63 percent. Additional information about the characteristics of the patients included in the studies is described under Key Question 3.

Of note, two of the trials that met eligibility criteria (IRIS and DINAMIT)[98,102] included patients who would not meet current CMS criteria for an ICD because they were restricted to patients who had a recent MI (within 31 or 40 days). In a third trial, CABG-Patch,[94] ICD implantation took place at the time of coronary artery bypass graft (CABG). These patients would also fall outside of the current clinical guidelines for implantation as well as guidelines for CMS coverage. Thus, the primary meta-analyses of the RCTs exclude these three trials, though they are included in tables, forest plots, and sensitivity analyses.

All-Cause Mortality

All 10 RCTs and 4 nRCSs reported data on long-term all-cause mortality (**Appendix Table 3**). We meta-analyzed the RCT data, as shown in **Figure 4**. The studies followed patients for approximately 3 to7 years (mean followup durations of about 1.3 to 5.5 years). ICD implantation resulted in a lower risk (or hazard) of all-cause death (summary HR 0.69; 95% CI 0.60, 0.79) without statistical heterogeneity. The estimated NNTs to prevent one death for these studies (Table 8) ranged from 6.2 (95% CI 4.0, 18) to 22 (95% CI 2.3, infinite) at the longest durations of followup (3 to 7 years).

It should be noted that two studies—COMPANION[95] and SCD-HeFT[51]—were three-arm studies that each included two non-ICD interventions that could be construed as the comparator of interest. The first study, COMPANION had the following three arms: ICD with CRT (CRT-D), CRT without ICD (CRT-P), and medical therapy. We determined that the medical therapy arm, not the CRT-P arm, was most similar to the comparison arms in other studies. The second study, SCD-HeFT included the following three arms: ICD, medical therapy (not including amiodarone), and medical therapy with amiodarone. The study found no difference in death rates between the amiodarone and no amiodarone groups. We chose the medical therapy without amiodarone as the most relevant control arm.

In sensitivity analyses, including the studies that were the most clinically different from the rest resulted in weaker effect sizes and greater statistical heterogeneity. Including the two studies that included patients with recent MIs (IRIS and DINAMIT) yielded a smaller effect favoring ICD but with statistical heterogeneity (HR 0.76 [95% CI 0.65, 0.91; I^2 = 44%]). Alternatively, including CABG-Patch, which included patients undergoing CABG, yielded a similar effect (HR 0.73 [95% CI 0.62, 0.87; I^2 = 36%]). Including all three atypical studies yielded the smallest effect with the greatest heterogeneity (HR 0.80 [95% CI 0.68, 0.94; I^2 = 51%])

Figure 5 suggests that the reduction in overall mortality imparted by ICD is fairly stable over time from 1 to 7 years. The maximal difference in how many people have died was approximately 10 percent. The MADIT trial may differ from other trials in that the point estimates of the difference in cumulative death was about twice as large favoring ICD than other studies, but again the difference between ICD and no ICD was fairly stable, excluding year 5 when only 3 patients were still at risk of dying in the study (since most patients were not yet followed for that long). As suggested by the wide confidence intervals for HRs of all-cause

mortality for MADIT and other trials (Figure 4), the difference between MADIT and the other studies may be due solely to random chance. The results in AMIOVIRT differed in that the benefit of ICD did not appear until year 3. The three atypical studies (CABG-Patch, DINAMIT, and IRIS; shown in grey in Figure 5), by definition consistent with their larger HRs for death compared with other studies, found no sustained benefit of ICD over time (the differences in cumulative death were near zero or positive, indicating fewer deaths with no ICD).

The four nRCSs all examined the effects of ICD versus no ICD on all-cause mortality (**Appendix Table 3**). There was one prospective cohort study and three retrospective cohort studies. The studies varied in duration of followup from 2 to 5 years. All four provided data on all-cause mortality at 2 to 3 years. All found reduced all-cause mortality with ICD implantation versus no ICD. The range of adjusted HRs was 0.46 (95% CI 0.22, 0.98) to 0.78 (95% CI 0.44, 1.30), favoring ICD use. Three of the four studies found the adjusted HRs to be statistically significant.

Two of the trials (MADIT and CABG-Patch) also reported 30-day mortality data (**Appendix Table 6**). MADIT had no deaths in either group at 30 days. CABG-Patch did not report mortality rates, but noted no significant difference in 30-day mortality rates.

Subgroup Data: All-Cause Mortality

Eight RCTs and two nRCSs (17 publications) provided data on the differential effects of ICD placement (versus no ICD) based on 11 different subgroups.[94] **Table 5** presents subgroup data for subgroup variable pairs that were reported by at least two studies, including by sex, age, NYHA Class, LVEF, presence of heart failure, presence of left bundle branch block, QRS duration, time since myocardial infarction, blood urea nitrogen, and diagnosis of diabetes. **Appendix Table 5** is a more complete version of the table, also including subgroup analyses that were reported by unique studies; this table also includes data based on type of heart disease (ischemic versus nonischemic), prior coronary revascularization, time since coronary revascularization, kidney function, and other specific subgroups not included in Table 5.

Among 76 subgroup analyses across the 10 studies, no significant differences were found in relative all-cause mortality between ICD and no ICD groups for subgroup analyses, with the exception of a comparison of NYHA Class II and III patients in SCD-HeFT (ICD effective in patients with Class II heart failure, but not Class III).[51] Meta-analyses the relative OR of death for women vs. men (**Figure 6**), age subgroups (**Figure 7**), LVEF subgroups, QRS duration subgroups, and diabetes vs. no diabetes were all statistically homogeneous and found no significant difference between the respective subgroups.

SCD-HeFT[51] and COMPANION[95] examined time since coronary revascularization and both found greater, but not significantly different, benefits for ICD use in patients with more distant coronary revascularization. In MADIT II, among patients with revascularization >6 months prior HR=0.64 compared with HR=1.19 with more recent revascularization, but P=0.29.[97] SCD-HeFT found that for patients with CABG >2 years prior HR=0.71 compared with HR=1.40 with more recent CABG (P=0.09), but time since percutaneous coronary revascularization was not associated with ICD benefit.[109] An indirect comparison of ISIS and DINAMIT (which included patients with recent MIs, within 31 or 40 days) versus the remaining trials, suggests that patients with recent MIs may have no reduction in all-cause mortality (HR 1.05 [95% CI 0.86, 1.30]) than patients with more distant or no prior MIs (HR 0.69 [95% CI 0.60, 0.79]). By meta-regression, the difference between IRIS and DINAMIT and the other seven RCTs is statistically significant (P = 0.012).

Evaluation across studies for other indirect comparisons of subgroups did not reveal any additional subgroup differences.

Summary: All-Cause Mortality

Ten RCTs of fair to good quality and four nRCSs that directly compared ICD with no ICD (or amiodarone) provided consistent and precise findings of a significant benefit of ICD to reduce all-cause mortality (**Table 7**). There is a high strength of evidence that ICD use as primary prevention for patients who meet the current CMS practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of all-cause mortality by about 31 percent (95% CI 21, 40) percent over the course of 3 to 7 years after implantation (**Table 3**). The reduction in all-cause mortality appears fairly stable over time across studies. Across RCTs, the NNT to prevent one death ranged from 6.2 (95% CI 4.0, 18) to 22 (95% CI 2.3, infinite) at the longest durations of followup (3 to 7 years). Overall, within-study analyses failed to show statistically significant differences for all-cause mortality across subgroups; however there may be an indication that ICDs are more effective in patients with more distant coronary revascularization or MIs compared with recent surgery (within either 6 months or 2 years) or MI (within 31 or 40 days). There are no data for different characteristics of clinicians implanting ICDs or facilities where ICDs are implanted.

Sudden Cardiac Death (Arrhythmic Death)

Seven RCTs (six good quality, one fair quality) and two nRCSs reported data on SCD (or death from cardiac arrhythmia) (**Appendix Table 7**). We meta-analyzed the RCT data, as shown in **Figure 7**. The studies followed patients for between 2 and 6 years. In general, SCD event rates were low, such that in four of the six RCTs, three or fewer individuals had SCD in one or both study groups during study followup. In the CAT study,[91] no SCD events occurred at 2 years of followup. Nevertheless, in all studies (except CAT), SCD was less common in patients who had an ICD than those without an ICD. The summary HR across the four primary analysis trials (excluding the atypical studies) was 0.37 (95% CI 0.26, 0.52) with no statistical heterogeneity ($I^2 = 0$). However, the lack of heterogeneity can largely be ascribed to the wide CIs within each study. Sensitivity analysis including IRIS and DINAMIT yielded a smaller effect size (summary HR 0.241;95% CI 0.31, 0.54). **Figure 9** suggests that the effect of ICD versus no ICD on SCD proportions over time is fairly stable but may increase beyond 2 or 3 years. Among the four eligible RCTs with adequate data (Table 9), the estimated NNT to prevent one arrhythmic death was1.9 to 3.2 in three trials (approximate 95% CIs 1.3, 16) and 11 (95% CI 1.3, infinite) in the fourth RCT.

The two nRCSs examined the effects of ICD versus no ICD on SCD (**Appendix Table 7**). Fonarow 2000,[106] a retrospective cohort study, followed patients for 2 years; Chan 2009,[105] a prospective cohort study, followed patients for 3 years. Both found lower risk of SCD with ICD implantation (0 vs. 22% actuarial rate over 2 years, P = 0.05; and adjusted HR = 0.65, 95% CI 0.40, 1.03 over 3 years).

Subgroup Data: Sudden Cardiac Death

Subgroup analyses of SCD-HeFT related to time since MI, prior coronary revascularization, and time since revascularization and subgroup analyses of MADIT II related to time since coronary revascularization and presence of kidney disease all failed to find a significant interaction between ICD placement and subgroups (**Table 6**).[96,97,109,110] No other subgroup

analyses have been reported. Indirect comparison across studies fails to show any differences based on patient or other characteristics. There are no data for different characteristics of clinicians implanting ICDs or facilities where ICDs are implanted.

Summary: Sudden Cardiac Death

Seven RCTs of generally good quality and two nRCSs that directly compared ICD with no ICD (or amiodarone) provided consistent and sufficiently precise findings of a significant benefit of ICD to reduce SCD (**Table 7**). There is a high strength of evidence that ICD use as primary prevention for patients who meet the current CMS practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of SCD by about 63 percent (95% CI 48, 74) over the course of 2 to 6 years after implantation (**Table 3**). There is a suggestion across studies that the effect of ICD on SCD over time may increase beyond 2 or 3 years. Across RCTs, the NNT to prevent one arrhythmic death ranged from about 2 to 3 (approximate 95% CI 1.3, 16) to 11 (95% CI 1.3, infinite). The evidence fails to support a difference in the benefit of ICD based on time since MI, coronary revascularization, or kidney disease. There is insufficient evidence to evaluate differential effects of ICD on SCD in other subgroups of patients or based on different characteristics of clinicians implanting ICDs or facilities where ICDs are implanted.

Sustained Ventricular Tachyarrhythmia

No study that directly compared ICD to no ICD (or amiodarone) reported on long-term sustained ventricular tachyarrhythmia. The only study to report any data on sustained ventricular tachycardia was CABG-Patch,[100] which reported event rates postoperatively as an adverse event of CABG surgery with or without ICD placement.

Summary: Sustained Ventricular Tachyarrhythmia

There is insufficient evidence to estimate the effect of ICD placement for primary prevention on the rate of sustained ventricular tachyarrhythmia episodes (**Table 7**).

Quality of Life

Three RCTs (two of good quality, 1 fair) reported on the effect of ICD placement versus no ICD placement on various measures of QoL (**Appendix Table 9**). The three trials each evaluated different QoL measures, including the Health Utility Index 3 (MADIT II[101], a health utility assessing health-related QoL across eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort), the Quality of Well-being Schedule (AMIOVIRT[103], assessing both functional and symptom status, translatable into quality-adjusted life years), the State Trait Anxiety Inventory (AMIOVIRT[103], focusing on the anxiety component of QoL), the Short Form 36 (SF-36) (CABG-Patch[100], evaluating eight health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, mental health, health transition (perceived change in health), and the Perception of Health Transition scale (CABG-Patch[100], where patients assess their current health status relative to 1 year before). No QoL scale was used by more than a single study.

MADIT II[101] and AMIOVIRT[103] found no statistically significant difference in QoL between ICD and control arms according to the Health Utility Index 3, the State Trait Anxiety Inventory, and the Quality of Well-being Schedule. CABG-Patch,[100] which compared CABG plus ICD placement with CABG without ICD, reported on seven of the SF-36 subscales (not vitality)

along with the Perception of Health Transition scale. The trial found no significant difference between the two groups for five of the seven evaluated SF-36 QoL domains, but control patients (those without ICD) reported significantly better QoL for the subscales regarding emotional role functioning and mental health. In addition, control patients had better perception of health transition compared with 1 year prior.

Subgroup Data: Quality of Life

No study reported subgroup analyses for the relative effect of ICD versus no ICD on QoL.

Summary: Quality of Life

Across three RCTs of good and fair quality, only one found that some measures of QoL favored no ICD over ICD (**Table 7**). While the three trials covered a broad range of QoL measures, no specific QoL measure was evaluated by more than a single trial. Furthermore, the single trial that did find a difference (favoring no ICD) for some measures of QoL, is of limited applicability to current practice, both because all patients had CABG and because the trial implanted epicardial ICD systems which are much more invasive and large compared to the transvenous ICDs currently employed. It is unknown to what degree the concurrent CABG or the older technologies may have led to the worse emotional role, mental health, and perception of overall health in those who received ICDs.

Given the sparseness of data on QoL and the lack of consistency across trials, overall, there is a low strength of evidence low strength of evidence that failed to show a consistent effect of ICD placement on QoL (**Table 3**). There is insufficient evidence to evaluate differential effects of ICD on QoL in different populations of patients or based on different characteristics of facilities where ICDs are implanted.

Other Patient-Reported Outcomes

No eligible study reported other patient-reported outcomes of interest. Therefore, there is insufficient evidence to estimate the effect of ICD placement for primary prevention on other patient-reported outcomes (**Table 7**).

Table 4. ICD vs. no ICD: Study characteristics

Study Author Year PMID	Intervention (Control)	NYHA class	Ischemic	Non-ischemic	Non-sustained VT	%LVEF	Total N	Primary outcome	Duration followup	ICD type/No. of leads	Enrollment period
AMIOVIRT Strickberger 2003 12767651	ICD (Amiodarone)	I, II, III	No	Yes	Yes	≤35	103	Death, all-cause	5 y	nd	8/1996-9/2000
CABG-Patch Bigger 1997 9371853	ICD (No ICD)	NYHA not a criterion	Yes	No	No	<36	900	Death, all-cause	4 y mean 32 ± 16 mo (2.67 y)	nd	Pilot began 1990 with full-scale study started in 1993
CAT Bansch 2002 11914254	ICD (Control)	II, III	No	Yes	No	≤30	104	Death, all-cause at 1 y	6 y	nd	5/1991-3/1997
Chan 2009 20031808	ICD (No ICD)	NYHA not a criterion	Yes	Yes	No	≤35	965	Death, all-cause	5 y	nd	3/2001-6/2005
COMPANION Bristow 2004 15152059	ICD + CRT (No ICD)*	III, IV	Yes	Yes	No	≤35	1520	Death from or hospitalization for any cause	1080 d (2.95 y) median 14 mo (weighted average of CRT-D and control groups)	Multi-chamber	1/2000-11/2002
DEFINITE Kadish 2004 15152060	ICD (No ICD)	I, II, III	No	Yes	Yes	<36	458	Death, all-cause	5 y mean 29 ± 14.4 mo (2.42 y)	Single-chamber	1998-2002 (randomization date)
DINAMIT Hohnloser 2004 15590950	ICD (No ICD)	I, II, III	Yes	No	No	≤35	674	Death, all-cause	4 y mean 2.5 y	Single-chamber	1998-nd (last follow-up 9/2003)
Fonarow 2000 10760339	ICD (Control)	III, IV	No	Yes	No	<35	147	nd	mean 22 ± 26 mo	nd	1/1988-1/1997
IRIS Steinbeck 2009 19812399	ICD (No ICD)	I, II, III	Yes	No	Yes	≤40	898	Death, all-cause	6 y mean 37 mo	nd	6/9/1999-10/15/2007

Study Author Year PMID	Intervention (Control)	NYHA class	Ischemic	Non-ischemic	Non-sustained VT	%LVEF	Total N	Primary outcome	Duration followup	ICD type/No. of leads	Enrollment period
MADIT Moss 1996 8960472	ICD (No ICD)	I, II, III	Yes	No	Yes	≤35	196	Death, all-cause	5 y mean 27 mo	Single-chamber	1990-nd (trial stopped in 1996)
MADIT II Moss 2002 11907286	ICD (No ICD)	I, II, III	Yes	No	No	≤30	1232	Death, all-cause	mean 20 mo range 6 d-53 mo	nd	7/11/1997-nd
Mezu 2011 21640321	ICD (No ICD)	I, II, III	Yes	Yes	No	≤35	152	Death, all-cause	4 y mean 2.3 y	nd	1/2000-12/2008
OPTIMIZE-HF and GWTG-HF Hernandez 2010 20009044	ICD (No ICD)	NYHA not a criterion	No	No	No	≤35	4685	Death, all-cause	3 y	nd	2003-2006
SCD-HeFT Bardy 2005 15659722	ICD (no ICD/placebo)[#]	II or III	Yes	Yes	Yes	≤35	2521	Death, all-cause	6 y median (survivors) 45.5 mo	Single-chamber	9/16/1997-7/18/2001 (randomization date)

*The CRT-P arm of COMPANION study was not used for the meta-analysis

The amiodarone arm of SCD-HeFT was not used for the meta-analysis

AMIOVERT = Amiodarone versus Implantable Cardioverter-Defibrillator Randomized Trial, CABG-Patch = Coronary Artery Bypass Graft Patch, CAT = Cardiomyopathy Trial, COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure, CRT = cardiac resynchronization therapy, d = day, DEFINITE = Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation, DINAMIT = Defibrillator in Acute Myocardial Infarction Trial, GWTG-HF = Get With the Guidelines-Heart Failure, ICD = implantable cardiac defibrillator, IRIS = Immediate Risk Stratification Improves Survival, LV = left ventricular, MADIT = Multicenter Automatic Defibrillator Implantation Trial, mo = month, nd = not documented, NYHA = New York Heart Association, OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure, SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial, VT = ventricular tachycardia, y = year

Table 5 Subgroup analysis data and meta-analyses of ICD vs. no ICD for all-cause death

Study, Author, Year, PMID	Subgroup 1 vs. 2	OR* (CI), Subgroup 1	OR* (CI), Subgroup 2	ROR† (CI)	Reported P‡
Sex					
COMPANION, Bristow, 2004, 15152059	Female vs. Male	0.6 (0.3, 1.1)	0.65 (0.4, 0.9)	0.92 (0.43, 1.99)	nd
DEFINITE, Kadish, 2004, 15152060	Female vs. Male	1.1 (0.5, 2.6)	0.49 (0.27, 0.90)	2.24 (0.81, 6.23)	NS
DINAMIT, Hohnloser, 2004, 15590950	Female vs. Male	1.0 (0.5, 2.1)	1.1 (0.7, 1.7)	0.91 (0.39, 2.11)	0.82
Hernandez§, 2010, 20009044	Female vs. Male	0.58 (0.41, 0.83)	0.80 (0.63, 1.01)	0.73 (0.47, 1.11)	0.31
IRIS, Steinbeck, 2009, 19812399	Female vs. Male	1.0 (0.6, 1.7)	1.1 (0.8, 1.5)	0.91 (0.49, 1.67)	0.15
MADIT II, Moss, 2002, 11907286	Female vs. Male	0.6 (0.3, 1.1)	0.7 (0.5, 0.9)	0.86 (0.42, 1.75)	0.85
SCD-HeFT, Russo, 2008 18373605	Female vs. Male	0.90 (0.56, 1.43)	0.71 (0.57, 0.88)	1.27 (0.76, 2.12)	0.54‖
CABG-Patch, Bigger, 1997, 9371853	Female vs. Male	nd	nd	nd	NS
MADIT, Moss, 1996, 8960472	Female vs. Male	nd	nd	nd	>0.2
Meta-analysis:	**I^2=0%**			**0.95 (0.75,1.20)**	
Age					
Chan, 2009, 20031808	<65 vs. 65-74 y	0.74 (0.43, 1.28)	0.76 (0.45, 1.29)	0.97 (0.46, 2.08)	0.43¶
COMPANION, Bristow, 2004, 15152059	≤65 vs. >65 y	0.6 (0.3, 0.95)	0.7 (0.5, 1.0)	0.86 (0.44, 1.68)	nd
DEFINITE, Kadish, 2004, 15152060	<65 vs. 65-84 y	0.7 (0.3, 1.4)	0.6 (0.3, 1.2)	1.17 (0.41, 3.29)	NS
DINAMIT, Hohnloser, 2004, 15590950	<60 vs. 60-80 y	0.9 (0.4, 1.9)	1.2 (0.8, 1.9)	0.75 (0.31, 1.83)	0.46
IRIS, Steinbeck, 2009, 19812399	<65 vs. 65-80 y	0.95 (0.6, 1.5)	1.05 (0.8, 1.5)	0.90 (0.52, 1.58)	0.73
MADIT II, Moss, 2002, 11907286	<60 vs. 60-69 y	0.5 (0.2, 0.9)	0.8 (0.5, 1.3)	0.63 (0.26, 1.52)	NS**
SCD-HeFT, Bardy 2005 15659722	<65 vs. ≥65 y	0.68 (0.52, 0.95)	0.86 (0.65, 1.14)	0.79 (0.55, 1.13)	nd
Meta-analysis:	**I^2=0%**			**0.83 (0.66, 1.05)**	
Chan, 2009, 20031808	65-74 vs. ≥75 y	0.76 (0.45, 1.29)	0.59 (0.39, 0.90)	1.29 (0.66, 2.52)	0.43¶
Hernandez§, 2010, 20009044	65-74 vs. 75-84 y	0.65 (0.47, 0.89)	0.80 (0.62, 1.03)	0.81 (0.54, 1.22)	0.31
MADIT II, Moss, 2002, 11907286	60-69 vs. ≥70 y	0.8 (0.5, 1.3)	0.6 (0.45, 0.95)	1.33 (0.73, 2.45)	NS**
Meta-analysis:	**I^2=17%**			**1.03 (0.73, 1.45)**	
MADIT, Moss, 1996, 8960472	Age, continuous	--	--	nd	>0.2
CABG-Patch, Bigger, 1997, 9371853	Age, continuous	--	--	nd	NS
NYHA Class					
DEFINITE, Kadish, 2004, 15152060	NYHA Class II vs. III	1.0 (0.5, 2.2)	0.37 (0.15, 0.90)	2.70 (0.85, 8.64)	NS‡‡
SCD-HeFT, Bardy 2005 15659722	NYHA Class II vs. III	0.54 (0.41, 0.81)	1.16 (0.87, 1.44)	0.47 (0.32, 0.67)	<0.001

Study, Author, Year, PMID	Subgroup 1 vs. 2	OR* (CI), Subgroup 1	OR* (CI), Subgroup 2	ROR† (CI)	Reported P‡
Left ventricular ejection fraction					
Chan, 2009, 20031808	LVEF ≤25 vs. 26-35%	0.73 (0.51, 1.04)	0.59 (0.37, 0.93)	1.24 (0.69, 2.22)	0.61
DINAMIT, Hohnloser, 2004, 15590950	LVEF <26 vs. 26-35%	1.5 (0.8, 2.7)	0.85 (0.5, 1.5)	1.76 (0.78, 4.00)	0.16
MADIT II, Moss, 2002, 11907286	LVEF ≤25 vs. 25-30%	0.6 (0.5, 0.9)	0.7 (0.4, 1.2)	0.86 (0.46, 1.60)	NS
Meta-analysis:	**I^2=0%**			**1.17 (0.80, 1.70)**	
COMPANION, Bristow, 2004, 15152059	LVEF ≤20 vs. 20-35%	0.6 (0.4, 0.9)	0.7 (0.4, 1.1)	0.86 (0.45, 1.64)	nd
DEFINITE, Kadish, 2004, 15152060	LVEF <20 vs. 20-36%	0.9 (0.4, 2.0)	0.5 (0.3, 0.95)	1.80 (0.67, 4.84)	NS
Heart failure					
CABG-Patch, Bigger, 1997, 9371853	Heart failure vs. No heart failure	nd	nd	nd	NS
Chan, 2009, 20031808	Heart failure vs. No heart failure	0.69 (0.50, 0.93)	0.70 (0.35, 1.41)	0.99 (0.46, 2.11)	0.59
MADIT, Moss, 1996, 8960472	Heart failure vs. No heart failure	nd	nd	nd	>0.2
IRIS, Steinbeck, 2009, 19812399	Heart failure vs. No heart failure	1.0 (0.7, 1.4)	1.2 (0.8, 1.8)	0.83 (0.49, 1.42)	0.56
Left Bundle Branch Block					
COMPANION, Bristow, 2004, 15152059	LBBB vs. No LBBB	0.5 (0.4, 0.8)	0.9 (0.5, 1.6)	0.56 (0.28, 1.09)	nd
MADIT, Moss, 1996, 8960472	LBBB vs. No LBBB	nd	nd	nd	>0.2
MADIT II, Moss, 2002, 11907286	LBBB vs. No LBBB	nd	nd	nd	NS
QRS duration					
DEFINITE, Kadish, 2004, 15152060	QRS <120 vs. ≥120 msec	0.75 (0.4, 1.5)	0.5 (0.2, 1.1)	1.50 (0.51, 4.41)	NS
DINAMIT, Hohnloser, 2004, 15590950	QRS <120 vs. ≥120 msec	0.85 (0.5, 1.4)	1.5 (0.8, 2.9)	0.57 (0.25, 1.29)	0.13
MADIT II, Moss, 2002, 11907286	QRS <120 vs. 120-150 msec	0.7 (0.5, 1.2)	0.6 (0.4, 1.1)	1.17 (0.60, 2.28)	NS††
SCD-HeFT, Bardy 2005 15659722	QRS <120 vs. ≥120 msec	0.84 (0.64, 1.11)	0.67 (0.51, 0.95)	1.25 (0.88, 1.79)	nd
Meta-analysis:	**I^2=0%**			**1.13 (0.82, 1.54)**	
Time since Myocardial Infarction					
MADIT II, Wilber, 2004, 14993128	Time since MI <18 vs. 18-51 mo	0.97 (0.51, 1.81)	0.52 (0.26, 1.05)	1.87 (0.73, 4.79)	NS
SCD-HeFT, Piccini, 2011, 21109025	Time since MI <18 vs. 18-59 mo	0.7 (0.37, 1.31)	0.54 (0.3, 0.98)	1.30 (0.55, 3.08)	0.33||||
MADIT II, Wilber, 2004, 14993128	Time since MI 18-59 vs. 60-119 mo	0.52 (0.26, 1.05)	0.50 (0.26, 0.91)	1.04 (0.41, 2.66)	nd
SCD-HeFT, Piccini, 2011, 21109025	Time since MI 18-51 vs. 52-111 mo	0.54 (0.3, 0.98)	1.47 (0.75, 2.87)	0.37 (0.15, 0.90)	0.33||||
MADIT, Moss, 1996, 8960472	Time since MI <6 vs. ≥6 mo	nd	nd	nd	>0.2
MADIT II, Moss, 2002, 11907286	Time since MI <6 vs. ≥6 mo	nd	nd	nd	NS
Blood Urea Nitrogen					
MADIT, Moss, 1996, 8960472	BUN ≤25 vs. >25 mg/dL	nd	nd	nd	>0.2
MADIT II Moss, 2002, 11907286	BUN ≤25 vs. >25 mg/dL	nd	nd	nd	NS

Study, Author, Year, PMID	Subgroup 1 vs. 2	OR* (CI), Subgroup 1	OR* (CI), Subgroup 2	ROR† (CI)	Reported P‡
Diabetes mellitus					
Chan, 2009, 20031808	DM vs. No DM	0.68 (0.45, 1.03)	0.69 (0.48, 1.01)	0.99 (0.56, 1.72)	0.95
DINAMIT, Hohnloser, 2004, 15590950	DM vs. No DM	0.9 (0.5, 1.5)	1.2 (0.8, 2.0)	0.75 (0.37, 1.53)	0.38
SCD-HeFT, Bardy 2005 15659722	DM vs. No DM	0.95 (0.71, 1.24)	0.67 (0.52, 0.93)	1.42 (0.99, 2.03)	nd
CABG-Patch, Bigger, 1997, 9371853	DM vs. No DM	nd	nd	nd	NS
IRIS, Steinbeck, 2009, 19812399	DM vs. No DM	nd	nd	nd	NS
MADIT II, Moss, 2002, 11907286	DM vs. No DM	nd	nd	nd	NS
Meta-analysis:	**I^2=32%**			**1.12 (0.78, 1.61)**	

The table includes only subgroup comparisons for which at least 2 trials reported analyses for similar subgroups. Meta-analyses were performed only if there were at least 3 such studies with sufficient data for a given subgroup comparison.

BUN = blood urea nitrogen, CI = 95% confidence interval, DM = diabetes mellitus, LBBB = left bundle branch block, LVEF = left ventricular ejection fraction, MI = myocardial infarction, nd = no data reported, NS = nonsignificant, NYHA = New York Heart Association, OR = odds ratio, PMID = PubMed ID, ROR = relative odds ratio. See page 16 for study acronyms.

* Reported odds ratio or relative risk or hazard ratio.

† Relative odds ratios and their confidence intervals calculated from reported odds ratios (etc.) for each subgroup.

‡ The reported P value for the interaction among subgroups.

§ OPTIMIZE-HF and GWTG-H

|| For analysis of ICD vs. amiodarone vs. placebo.

¶ For analysis of <65 y vs. 65-74 y vs. ≥75 y.

** For analysis of <60 y vs. 60-69 y vs. ≥70 y

†† For analysis of <120 msec vs. 120-150 msec vs. ≥150 msec.

‡‡ For analysis of NYHA Class I vs. Class II vs. Class III.

|||| For analysis of <18 mo vs. 18-51 mo vs. 52-111 mo vs. >111 mo.

Table 6. Subgroup analyses of ICD vs. no ICD for sudden cardiac death

Study, Author, Year, PMID	Subgroups HR/RR (95% CI)				P Interaction
SCD-HeFT, Piccini, 2011, 21109025	**Time Since MI**				
	<18 mo:	0.47 (0.16, 1.42)	18-51 mo:	0.28 (0.073, 1.10)	P=0.68
	52-111 mo:	0.24 (0.063, 0.89)	>111 mo:	0.25 (0.065, 0.97)	
SCD-HeFT, Al-Khatib 2008, 18479330	**Prior CABG:**	0.52 (0.26, 1.02)	No CABG:	0.44 (0.23, 0.83)	P=0.94
	Prior PCI:	0.31 (0.08, 1.13)	No PCI:	0.51 (0.31, 0.85)	P=0.53
	Time Since CABG:	nd			P=0.38
	Time Since PCI:	nd			P=0.80
MADIT II, Goldenberg, 2006, 16682305	**Time since CR**				
	≤6 mo:	2.01 (0.18, 22.22)	>6 mo:	0.34 (0.19, 0.61)	P=0.16
	7-60 mo:	0.27 (0.11, 0.66)	>60 mo:	0.40 (0.19, 0.86)	nd
MADIT II Goldenberg, 2006, 16893702	**Kidney Disease**				
	eGFR<35:	0.95 (0.23, 4.00)	eGFR ≥35:	0.34 (0.20, 0.56)	P=0.19
	eGFR 35-59:	0.37 (0.19, 0.74)	eGFR≥60:	0.32 (0.15, 0.69)	nd

CABG = coronary artery bypass graft, CI =confidence interval, CR = coronary revascularization, eGFR = estimated glomerular filtration rate (in mL/min/m^2), HR = hazard ratio, ICD = implantable cardiac defibrillator, MI = myocardial infarction, mo = month, nd =no data, PCI = percutaneous coronary revascularization, PMID = PubMed ID, Revasc = revascularization, RR = risk ratio. See page 16 for study acronyms

Table 7. ICD vs. no ICD for primary prevention of SCD: Strength of evidence domains

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding and Strength of Evidence
All-cause mortality (≥1 y)	RCT: 10 (8,606) nRCS: 4 (5,949)*	Low RoB (6 good, 4 fair) Not graded	Direct	Consistent	Precise	Undetected		High ICD reduces all-cause mortality in patients meeting current practice criteria (no recent MI, no concurrent coronary revascularization) HR = 0.69 (95% CI 0.60, 0.79)
All-cause mortality (30 d)	RCT: 2 (1096)	Low RoB (1 good, 1 fair)	Direct	Consistent	Imprecise	Undetected	0 deaths in 1 applicable RCT	Insufficient Unknown difference in 30-day mortality
Sudden cardiac death (arrhythmic death)	RCT: 7 (4,093) nRCS: 2 (1,115)*	Low RoB (6 good, 1 fair) Not graded	Direct	Consistent	Precise	Undetected		High ICD reduces SCD in patients meeting current practice criteria (no recent MI, no concurrent coronary revascularization) HR = 0.24 (95% CI 0.11, 0.56)
Sustained ventricular tachyarrhythmia	0							Insufficient
Quality of life	RCT: 3 (1,825)	Low RoB (2 good, 1 fair)	Direct	Inconsistent	Imprecise	Undetected		Low ICD may not affect quality of life
Other patient-reported outcomes	0							Insufficient

CI = confidence interval, HR = summary hazard ratio, ICD = implanted cardiac defibrillator, nRCS = nonrandomized comparative study, RoB = risk of bias, RCT = randomized controlled trial, SCD = sudden cardiac death.

* The nRCSs are not included in the determination of the strength of evidence

Table 8. ICD vs. no ICD: Number-needed-to-treat (95% confidence interval) to prevent one death, by study

Study	Year:	1	2	3	4	5	6	7
MADIT, Moss 1996		3.6	3.7	4.0	4.3	7.2		
8960472		(2.2, 14)	(2.4, 14)	(2.7, 14)	(2.9, 15)	(5.0, 23)		
COMPANION, Bristow 2004		6.4	6.2	6.2				
15152059		(3.8, 20)	(3.9, 18)	(4.0, 18)				
MADIT II, Moss 2002		9.7	7.6	7.4	7.5			
11907286		(4.8, 58)	(4.1, 41)	(4.2, 38)	(4.3, 37)			
DEFINITE, Kadish 2004		9.8	7.2	6.7	6.5	6.4		
15152060		(3.7, inf)	(3.2, inf)	(3.1, inf)	(3.1, inf)	(3.2, inf)		
SCD-HeFT, Bardy 2005		11	12	11	10	10		
15659722		(6.0, 77)	(6.3, 85)	(5.8, 71)	(5.7, 68)	(5.8, 67)		
CAT, Bansch 2002		17	12	8.6	8.4	8.2	8.0	8.1
11914254		(3.5, inf)	(3.0, inf)	(2.6, inf)	(2.6, inf)	(2.6, inf)	(2.8, inf)	(2.9, inf)
AMIOVIRT, Strickberger 2003		29	26	25	22			
12767651		(2.4, inf)	(2.4, inf)	(2.4, inf)	(2.3, inf)			

inf = infinite. See page 16 for study acronyms.

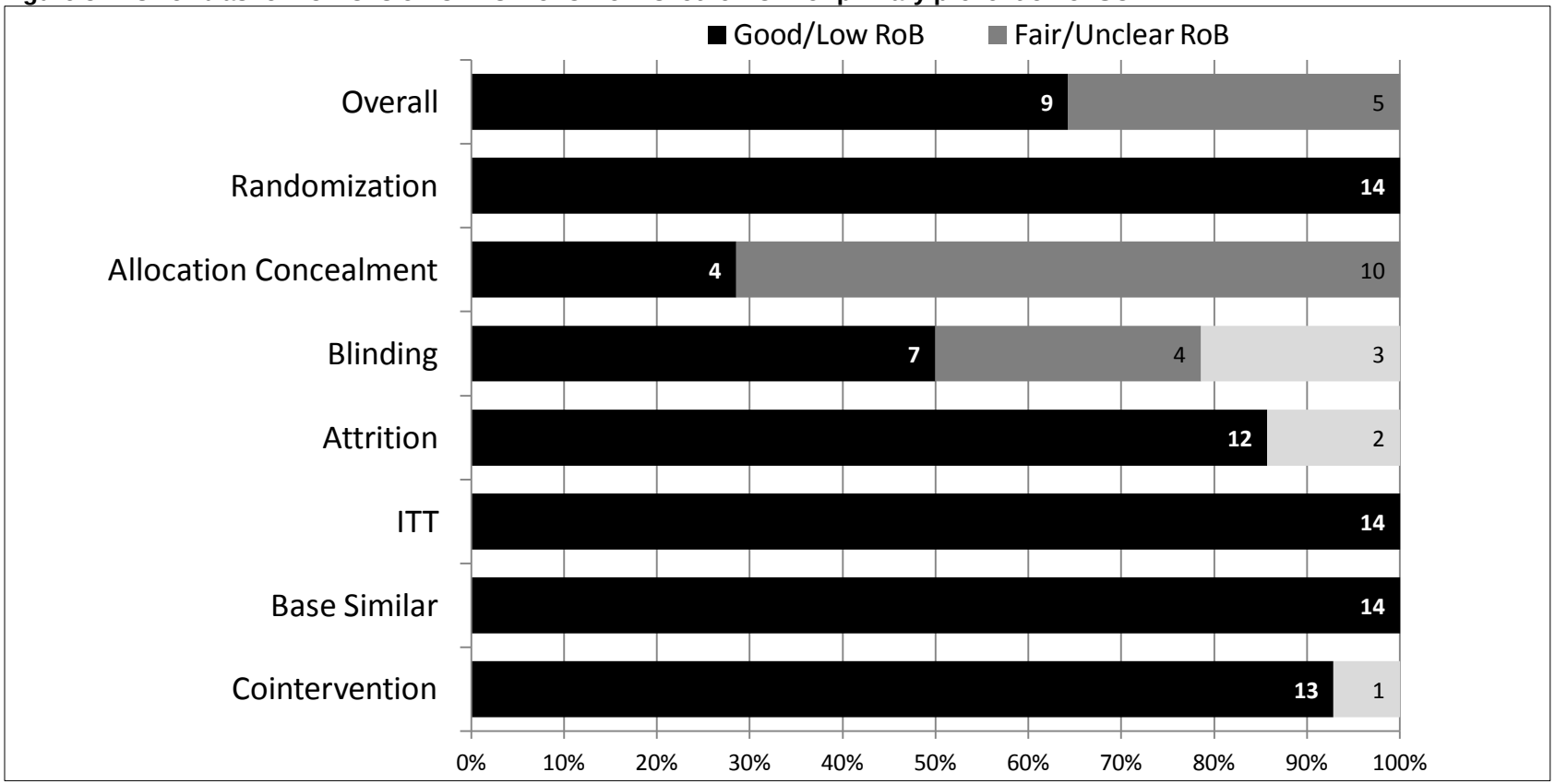
Table 9. ICD vs. no ICD: Number-needed-to-treat (95% confidence interval) to prevent one tachyarrhythmia death, by study*

Study	Year:	1	2	3	4	5
MADIT, Moss 1996			2.0			
8960472			(1.4, 16)			
DEFINITE, Kadish 2004		2.6	2.0	1.9	1.9	1.9
15152060		(1.3, 36)	(1.3, 13)	(1.3, 12)	(1.3, 11)	(1.3, 11)
AMIOVIRT, Strickberger 2003			11			
12767651			(1.3, inf)			
SCD-HeFT, Bardy 2005		4.2	3.5	3.4	3.2	3.2
15659722		(2.6, 9.1)	(2.3, 6.9)	(2.3, 6.4)	(2.3, 6.0)	(2.2, 5.8)

inf = infinite. See page 16 for study acronyms.

* There were no tachyarrhythmia deaths in CAT by 2 years, therefore this study is not included.

Figure 3. Risk of bias for 13 RCTs of ICD vs. no ICD or vs. other ICD for primary prevention of SCD



The numbers within the bars represent the number of studies within each category.

Overall: Good, fair, or poor quality study

Randomization: What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence?

Allocation Concealment: What is the risk of selection bias (biased allocation to interventions) due to inadequate concealment of allocations before assignment?

Blinding: Outcome Assessor Blinding—or each main outcome or class of outcomes, what was the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)?

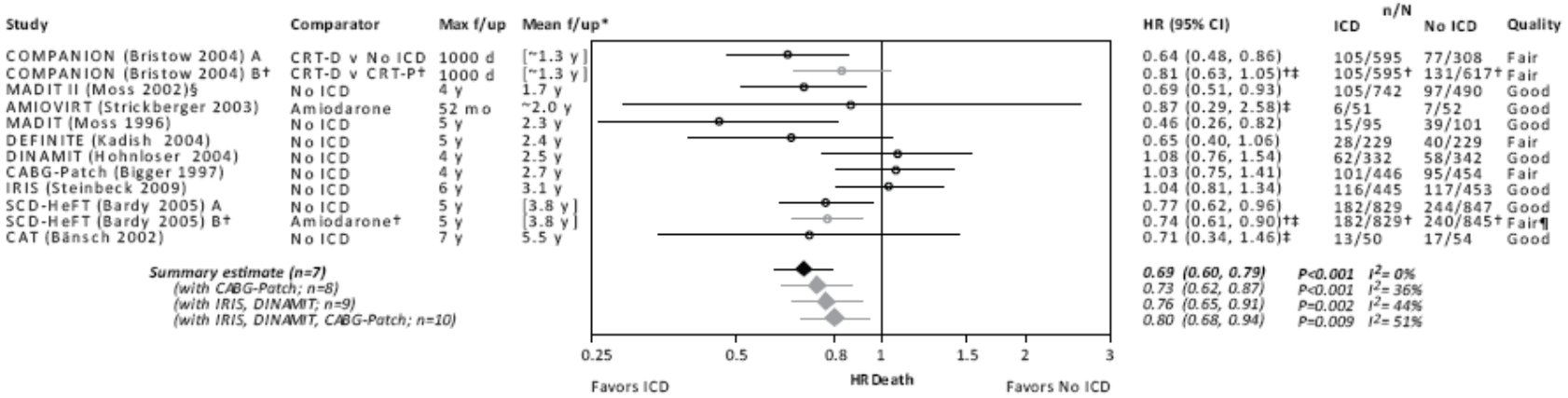
Attrition: For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data?

ITT: Intention-to-Treat—Were all randomized participants analyzed in the group to which they were allocated?

Base Similar: Groups Similarity—Were the groups similar at baseline regarding the most important prognostic indicators?

Cointervention: Were co-interventions avoided or similar?

Figure 4. Random effects model meta-analysis of ICD vs. no ICD for all-cause mortality



CI = confidence interval; CRT-D = cardiac resynchronization therapy with a defibrillator; CRT-P = cardiac resynchronization therapy with a pacemaker (without a defibrillator); f/up = followup; HR = hazard ratio; ICD = implantable cardiac defibrillator; n/N = total events (deaths)/total analyzed. See page 16 for study acronyms.

* Values in brackets are medians; ~ signifies approximate.

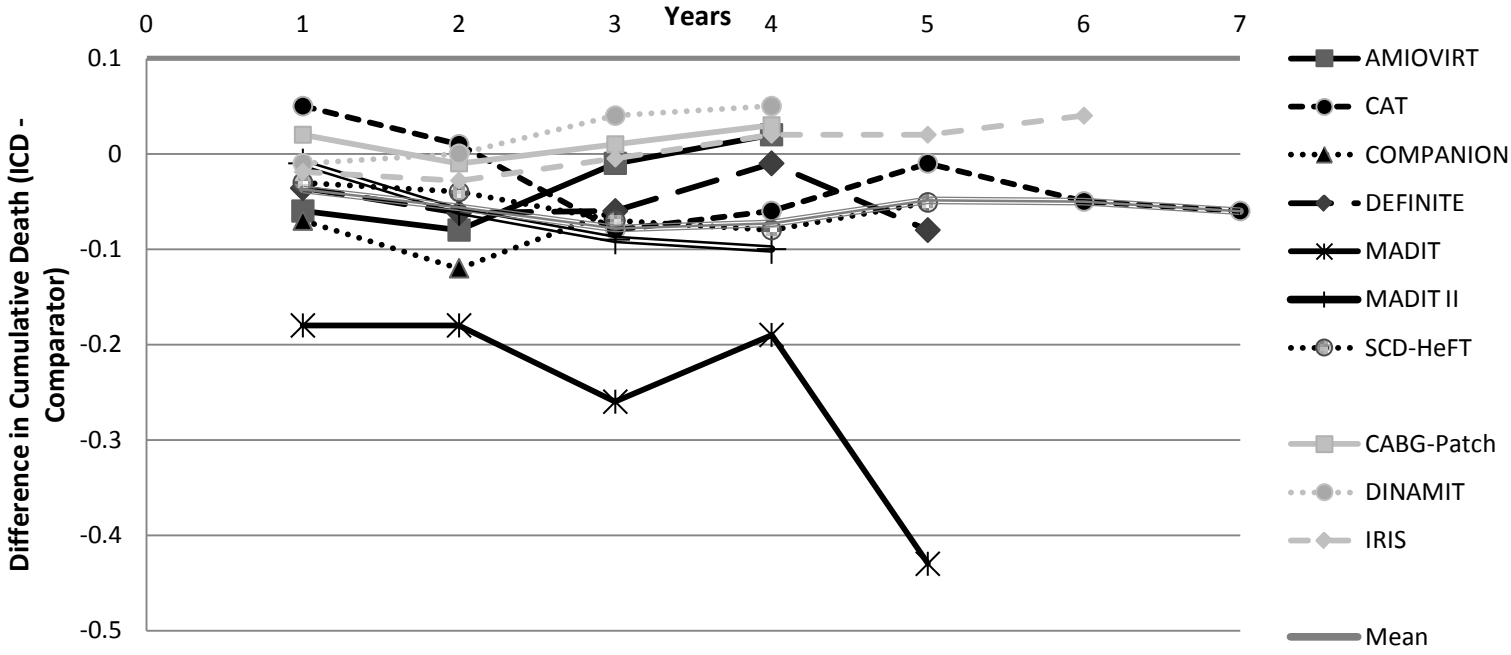
† Not included in meta-analyses (the alternative comparison for each study was the only comparison included in meta-analyses).

‡ Hazard ratio and confidence interval estimated from reported data.

§ The 8-year (maximum) followup of MADIT II (Barsheshet 2011) excluded because it analyzed an arbitrary subgroup of ICD group only.

¶ Differential use of beta blockers between ICD and amiodarone groups (but not between ICD and no ICD groups).

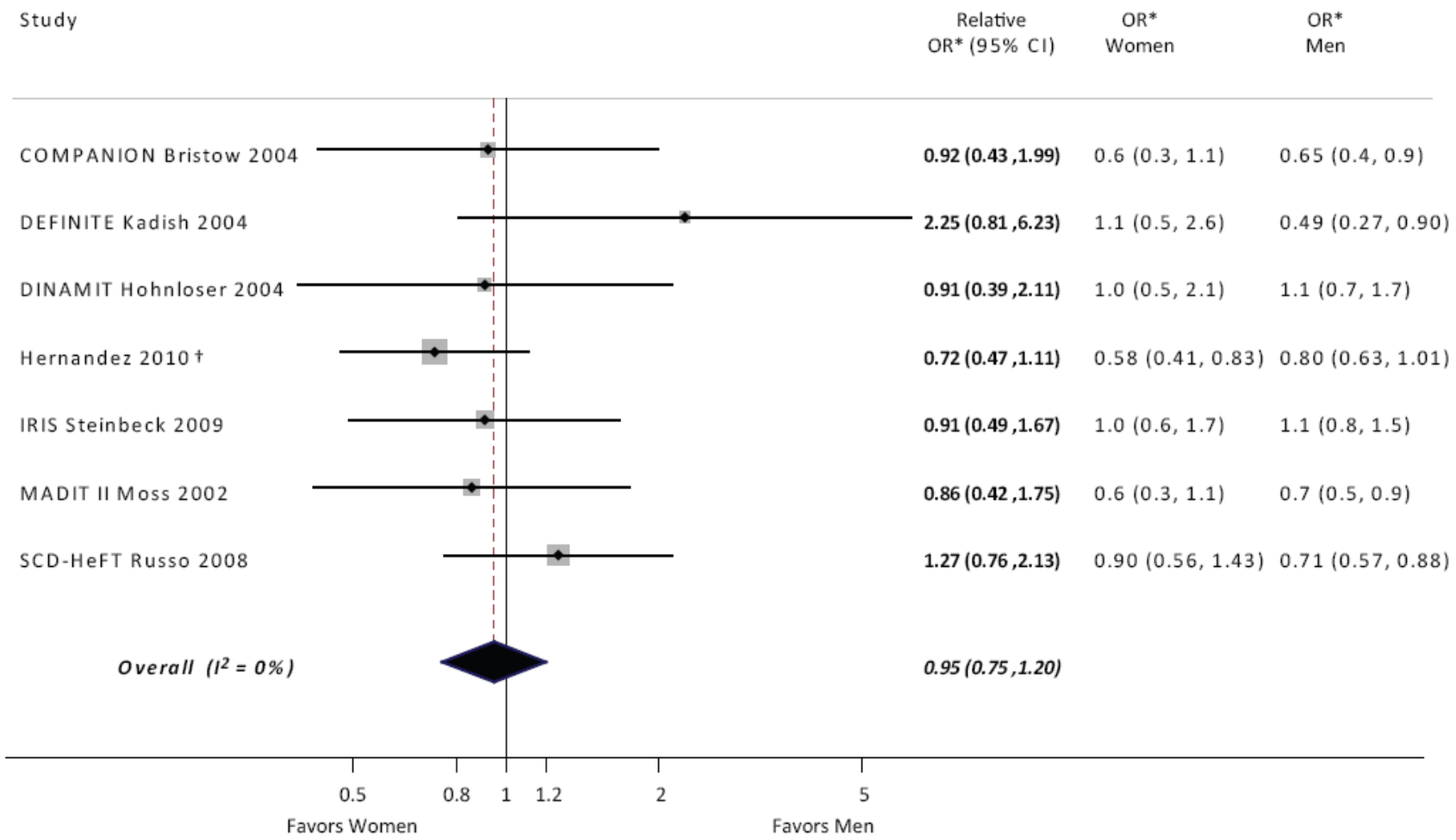
Figure 5. Differences in cumulative death proportions between ICD and no ICD, by year



Study	No. at Risk						Total Deaths (Proportion)		ICD	Comparator	Mean Followup
AMIOVIRT	103	nd	nd	nd	nd				6 (0.11)	7 (0.13)	~2.0 y
CAT	104	98	96	89	81	67	49	28	13 (0.26)	17 (0.31)	5.5 y
COMPANION	903*	606†	205‡	3§					105 (0.17)	77 (0.25)	~15 mo (median)
DEFINITE	458	428	271	144	73	nd			28 (0.12)	40 (0.17)	29 mo
MADIT	196	147	101	60	34	3			15 (0.15)	39 (0.38)	27 mo
MADIT II	1232	832	444	175	12				105 (0.14)	97 (0.19)	20 mo
SCD-HeFT	1674	1560	1448	985	584	200			182 (0.21)	240 (0.28)	46 mo (median)
CABG-Patch	900	783	621	412	138				101 (0.22)	95 (0.2)	32 mo
DINAMIT	674	504	428	247	56				62 (0.19)	58 (0.18)	30 mo
IRIS	898	746	610	437	288	157	76		116 (0.26)	117 (0.25)	37 mo

ICD = implanted cardiac defibrillator, mo = months, y = years. See page 16 for study acronyms.
Data derived from digitized Kaplan-Meier curves. The mean difference curve is a rough average, weighted by number at risk or its imputed estimate, of studies excluding CABG-Patch, DINAMIT, and IRIS.

Figure 6. Random effects model meta-analysis of relative odds ratio of ICD vs. no ICD for arrhythmic death between women and men

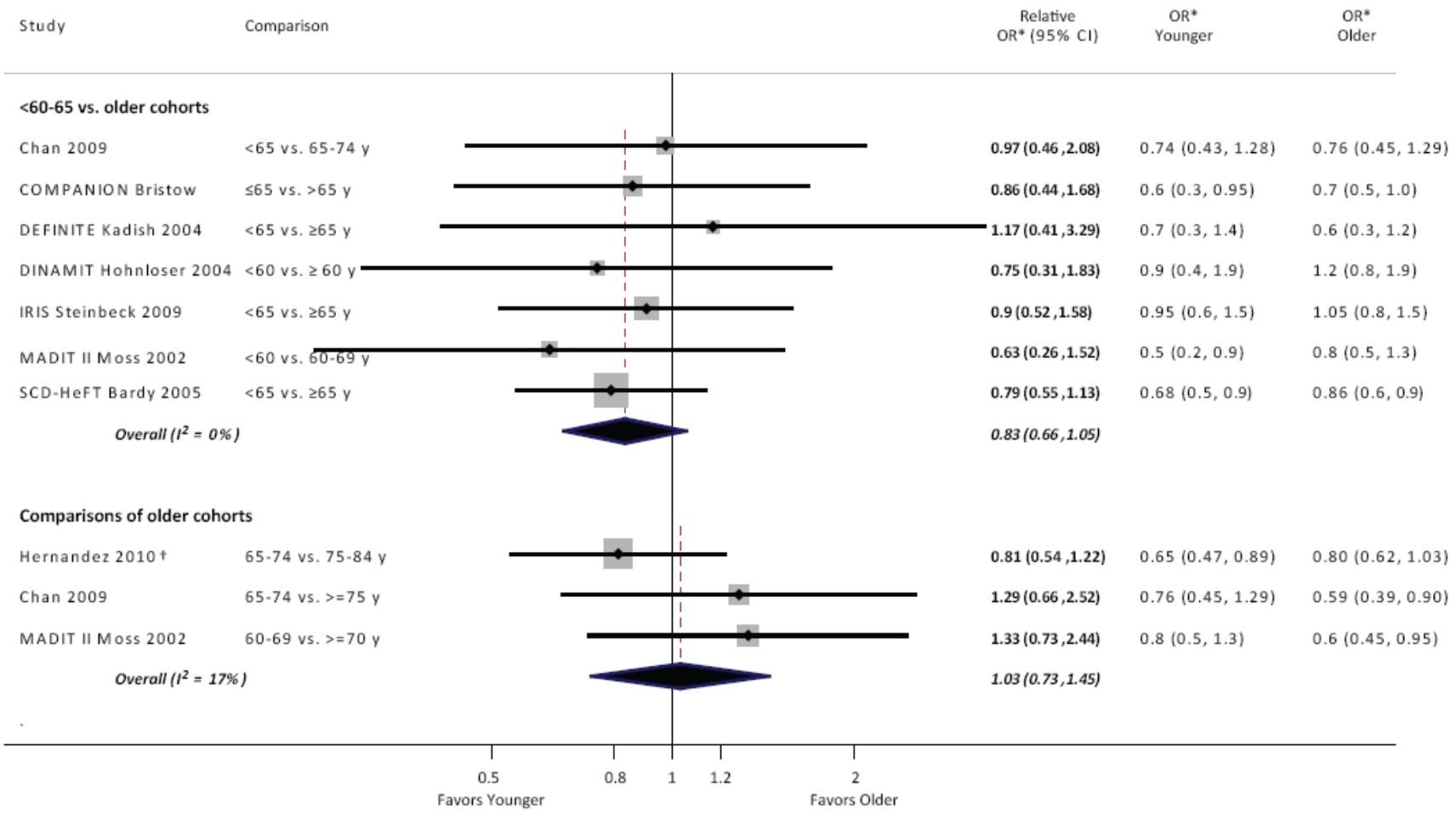


OR = odds ratio. See page 16 for study acronyms.

* Relative odds ratio or risk ratio or hazards ratio, as reported by studies.

† OPTIMIZE-HF and GWTG-H

Figure 7. Random effects model meta-analysis of relative odds ratio of ICD vs. no ICD for arrhythmic death between younger and older subgroups

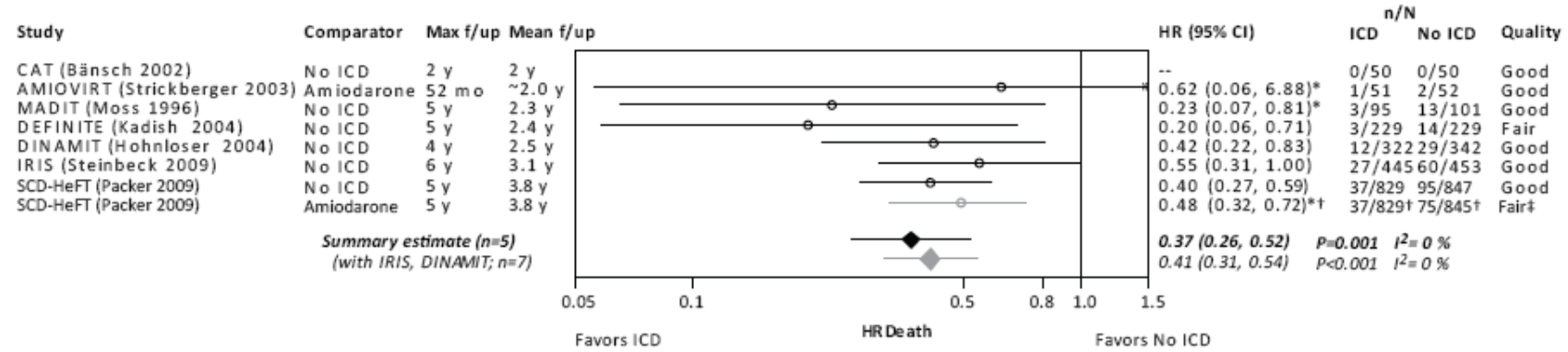


OR = odds ratio. See page 16 for study acronyms.

* Relative odds ratio or risk ratio or hazards ratio, as reported by studies.

† OPTIMIZE-HF and GWTG-H

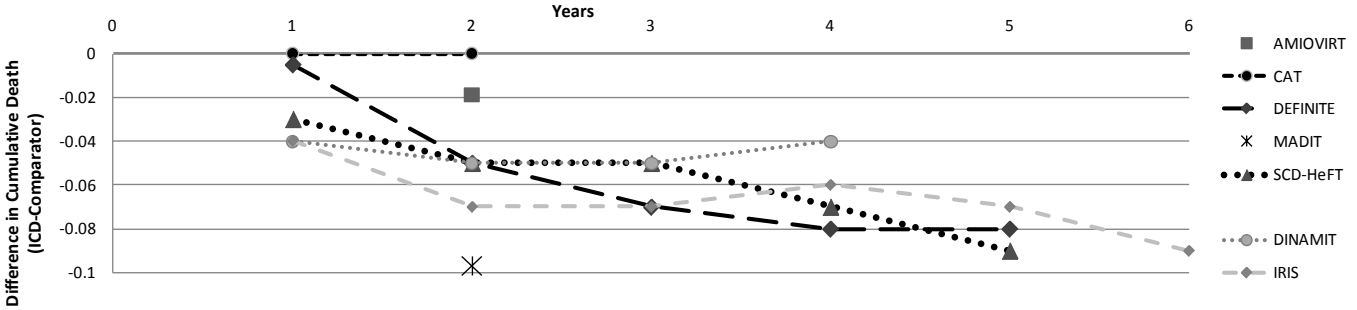
Figure 8. Random effects model meta-analysis of ICD vs. no ICD for arrhythmic death



~ = approximately; CI = confidence interval; f/up = followup; HR = hazard ratio; ICD = implantable cardiac defibrillator; n/N = total events (deaths)/total analyzed. See page 16 for study acronyms.

* Hazard ratio and confidence interval estimated from reported data.
† Not included in meta-analyses (the alternative comparison for each study was the only comparison included in meta-analyses).
‡ Differential use of beta blockers between ICD and amiodarone groups (but not between ICD and no ICD groups).

Figure 9. Differences in cumulative sudden cardiac/arrhythmia death proportions between ICD and no ICD, by year



Study	No. at Risk							Total SCD (Proportion): ICD	Comparator	Mean Followup
AMIOVIRT	103							1 (0.01)	2 (0.03)	~2.0 y
CAT	104	98						0	0	5.5 y
DEFINITE	458	428	271	144	73	nd		3 (0.01)	14 (0.06)	29 mo
MADIT	196							3 (0.03)	13 (0.12)	27 mo
SCD-HeFT	1676	1575	1457	1006	608	192		37 (0.04)	95 (0.11)	3.8 y
DINAMIT	674	504	428	247	56			12 (0.03)	29 (0.09)	30 mo
IRIS	898	746	610	437	288	157	76	27 (0.06)	60 (0.13)	37 mo

ICD = implanted cardiac defibrillator, mo = months, SCD = sudden cardiac death, y = years. See page 16 for study acronyms.
Data derived from digitized Kaplan-Meier curves, where available. AMIOVIRT, CAT, and MADIT did not report Kaplan Meier curves. CAT reported data for years 1 and 2.
AMIOVIRT and MADIT reported only total numbers of death; the points for these two studies are plotted at their approximate mean duration of followup.

Key Questions 1b & 1c:
In Candidates for ICD Implantation for Primary Prevention of SCD, What Are the Effects of ICD with ATP versus ICD alone, or of ICD with CRT versus ICD alone on Clinical Outcomes and Patient-Reported Outcomes?
How Do Outcomes Vary Within Subgroups?

We searched for studies that examined the effect of ATP added to ICD, or the effect of CRT added to ICD, versus ICD alone. We did not include comparisons of shock algorithms or algorithms pertaining to pacing for bradycardia, different manufacturers of equivalent ICDs, or different numbers of leads used *per se* (except as required for CRT). The findings and strength of evidence for outcomes with sufficient evidence for the comparison of CRT-D versus ICD are summarized in **Table 8**.

No study examined the effect of adding ATP in patients undergoing ICD implantation for predominantly primary prevention. Four studies that met eligibility criteria directly compared ICD with CRT versus ICD alone (**Table 10**).[73,111,112] All focused on congestive heart failure outcomes, which were not outcomes of interest for this review. We did not meta-analyze the studies since there were only two sufficiently large studies to analyze death and meta-analysis would not provide a better estimate of the effect size than evaluating the two large trials separately.

Table 10. Summary of findings for CRT-D vs. ICD

Outcome	Study Design: No. Studies (N)	Findings	Strength of Evidence
All-cause mortality	CRT-D vs. ICD RCT: 4 (3,743)	• The 2 larger trials found either no difference (HR = 1.00) or a significant benefit with CRT-D (HR = 0.75). No differences in effect were found between patients with ischemic or nonischemic heart disease or with NYHA Class II or III cardiomyopathy • There was no evidence regarding the comparison of CRT-D and ICD in subgroups of patients or based on different characteristics of facilities where ICDs are implanted.	Insufficient

Abbreviations: CI = confidence interval, CRT-D = cardiac resynchronization therapy-defibrillator, HR = hazard ratio, ICD = implantable cardioverter–defibrillator, No. = number, NYHA = New York Heart Association, RCT = randomized, controlled trial

Studies

MADIT-CRT

MADIT-CRT[73] compared the combination of CRT plus ICD (CRT-D) with ICD alone in patients with ischemic or nonischemic cardiomyopathy, an LVEF <30 percent, and QRS duration >130 ms. We assessed the study to be of good quality. Patients' mean age was 64 years and three-quarters of them were men. Their mean LVEF was 24 percent. About 15 percent of patients had NYHA Class I ischemic heart disease, 40 percent had Class II ischemic heart

disease, and 45 percent had Class II nonischemic heart disease. This distribution reflects the study's eligibility criteria. About 65 percent had a QRS duration≥150 ms. About 30 percent had diabetes.

After 5 years of followup, 74 of 1089 patients (6.8%) who received CRT-D died and 53 of 731 (7.3%) patients with ICD only died. The HR for all-cause death with CRT-D versus ICD only was 1.00 (95% CI 0.69, 1.44). The effects of adding CRT in either patients with ischemic or with nonischemic cardiomyopathy were similar and not statistically significantly different between populations. For patients with ischemic heart disease (NYHA Class I or II), the HR was 1.06 (95% CI 0.68, 1.64); for patients with nonischemic heart disease (NYHA Class II only), the HR was 0.87 (95% CI 0.44, 1.70). MADIT-CRT did not evaluate other outcomes of interest to this review or other subgroups of interest for all-cause mortality.

In a comparison of patients who had and who did not have coronary revascularization prior to ICD placement,[113] the frequency of combined ventricular tachyarrhythmia or death did not differ among patients with CRT-D or ICD, regardless of coronary revascularization history or time since coronary revascularization.

RAFT

RAFT compared CRT-D with ICD alone in patients with NYHA Class II or III heart failure, LVEF≤30 percent, QRS duration ≥200 msec, sinus rhythm or controlled atrial fibrillation, and planned ICD implantation.[74] The study was not restricted to patients receiving ICDs for primary prevention, but only 14 percent had a history of a prior SCD episode. We assessed the study to be of good quality. Patients' mean age was 66 years and 83 percent were men. Their mean LVEF was 23 percent and 80 percent had NYHA Class II heart failure; the remainder had Class III heart failure. Their mean QRS duration was 158 ms. About one-third had diabetes.

During a total of 6 years of followup (mean 40 months), 236 of 904 (26%) patients who had received ICD alone died and 186 of 894 (21%) with CRT-D died; thus the HR for all-cause death was 0.75 (95% CI 0.64, 0.87), favoring CRT-D. No difference in effect size was found for patients with Class II or Class II heart failure. The HR for all-cause death among those with Class II heart failure was 0.71 (0.56, 0.91) and for those with Class III heart failure 0.79 (0.58, 1.08).

Diab 2011

In the only RCT of ICD for primary prevention without an acronym name, Diab 2011 compared CRT-D with ICD alone in patients with NYHA Class III or IV heart failure, LVEF <35 percent, and QRS duration ≥120 ms, but with echocardiographic evidence of no mechanical dyssynchrony.[112] We assessed the study to be of good quality, although underpowered for clinical outcomes. Patients' mean age was 66 years and 89 percent were men. Their mean LVEF was 26 percent. Almost 90 percent had NYHA Class III heart failure. Their mean QRS duration was 138 ms. The percentage of patients with diabetes was not reported.

After 6 months of followup, 2 of 22 (9%) patients who received ICD alone died, but none of 24 patients with CRT-D died. One patient in each group was hospitalized for surgical lead implantation or repositioning. No other outcomes of interest and no subgroup analyses were reported.

MENDMI

MENDMI compared CRT-D with ICD alone in patients with a recent MI (within 3 to 16 days), LVEF ≤35 percent, and a wall motion abnormality on echocardiogram in >5 of 16 cardiac segments.[111] Based on their recent MIs, current guidelines would not recommend ICD in these patients. We assessed the study to be of fair quality, having differential attrition rates. It was also underpowered for clinical outcomes. Patients' mean age was 57 years and 75 percent were men. Their mean LVEF was 28 percent. About two-thirds had NYHA Class II or III heart failure. Their mean QRS duration was 88 ms. Before a protocol revision, diabetes had been an exclusion criterion, so only 8 percent of patients had diabetes.

In the trial, 42 patients received CRT-D and 38 received ICD alone. Within 1 year of followup, one patient died in each arm. The only hospitalization postimplantation occurred after a failed ICD induction, but it was not reported which ICD the patient had.

Summary

Four RCTs compared CRT-D with ICD alone, one of which included patients with very recent MIs (within 2 weeks) (**Table 11**). The two large trials had discordant findings, such that MADIT-CRT found no difference in death between CRT-D and ICD alone in patients with ischemic NYHA Class I cardiomyopathy or ischemic or nonischemic NYHA Class II cardiomyopathy, while RAFT found a statistically significant 25 percent reduction in death with CRT-D in patients with Class II or III ischemic or nonischemic cardiomyopathy. The other two RCTs were greatly underpowered for clinical outcomes and therefore adds little to the evidence base for outcomes of interest to this review. The evidence is insufficient to determine whether there is a difference in death between CRT and ICD alone for primary prevention or whether there may be a subpopulation of patients (captured by RAFT) who may benefit from CRT-D (**Table 8**). Both large trials found no difference in effect between either patients with ischemic or nonischemic heart disease or patients with Class II or III cardiomyopathy. There is insufficient evidence for all other outcomes and comparisons of interest, including differential effects of CRT-D and ICD on all-cause mortality for other populations of patients or different characteristics of facilities where ICDs are implanted; the effect of CRT-D versus ICD on SCD, sustained ventricular tachyarrhythmia, general QoL, or other general patient-reported outcomes. No study examined the effect of adding ATP in patients undergoing ICD implantation for predominantly primary prevention.

Table 11. ICD vs. CRT-D: Study characteristics

Study Author Year PMID	Intervention (Control)	NYHA class	Ischemic	Non-ischemic	Non sustained VT	% LVEF	Total N	Primary outcome	Duration followup	ICD type/No. of leads	Enrollment period
Diab 2011 21700757	ICD (CRT-D)	III, IV	Yes	Yes	nd	≤35	73	Peak oxygen consumption	6 mo	nd	2007-2009
MADIT-CRT Moss 2009 19723701	ICD (CRT-D)	I, II	Yes	Yes	No	≤30	1820	All-cause death or nonfatal heart failure event	4 y mean 2.4 y	Single-, dual-chamber vs. biventricular	12/22/2004-4/23/2008
MENDMI Chung 2010 20852059	ICD (CRT-D)	I, II, III	nd	Yes	NR	≤35	80	Change in LV end-diastolic volume at 12 mo	12 mo	Single-, dual-chamber vs. biventricular	2005-2008
RAFT Tang, 2010 21073365	ICD (CRT-D)	II, III	Yes	Yes	nd	≤30	1798*	Death or hospitalization for heart failure	40 mo mean 3.3 y	nd	1/2003-2/2009

CRT-D = cardiac resynchronization therapy defibrillator, ICD = implantable cardiac defibrillator, LV = left ventricular, MADIT-CRT = Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy, MENDMI = Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction Study, mo = month, nd = not documented, NYHA = New York Heart Association, VT = ventricular tachycardia, y = year

* 20% of patients had ICDs implanted for secondary prevention of sudden cardiac death.

Table 11. CRT-D vs. ICD for primary prevention of SCD: Strength of evidence domains

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Finding and Strength of Evidence
All-cause mortality (≥1 y)	RCT: 4 (3,743)	Low RoB (3 good, 1 fair)	Direct	Inconsistent	Precise	Undetected		Insufficient The 2 larger trials found either no difference (HR = 1.00) or a significant benefit with CRT-D (HR = 0.75) No differences in effect were found between patients with ischemic or nonischemic heart disease or with NYHA Class II or III cardiomyopathy
All-cause mortality (30 d)	0							Insufficient
Sudden cardiac death (arrhythmic death)	0							Insufficient
Sustained ventricular tachyarrhythmia	0							Insufficient
Quality of life	0							Insufficient
Other patient-reported outcomes	RCT: 1 (46)	Low RoB (1 good)	Direct	Consistent	Imprecise	Undetected		Insufficient Unclear whether rates of hospitalization for surgical lead implantation or repositioning differ

CI = confidence interval, CRT-D = cardiac resynchronization therapy with defibrillator, HR = summary hazard ratio, ICD = implanted cardiac defibrillator, nRCS = nonrandomized comparative study, NYHA = New York Heart Association, RoB = risk of bias, RCT = randomized controlled trial.

Key Question 2a: What are the adverse events related to treatment with an ICD for primary prevention of SCD?

Key Question 2b: How do adverse events vary within subgroups?

Although this report is focused on primary prevention, for our review of adverse events, we also included studies of mixed populations of patients with ICDs for either primary or secondary prevention. This was done not only to enrich the evidence base but also because many adverse events are related to ICD placement rather than the indication for the device and thus are likely to be more similar than different across populations with primary and secondary indications.

We identified a total of 59 articles contributing data on adverse events, 14 with results for early adverse events, i.e. adverse events occurring during hospitalization for ICD implantation or up to 30 days after implantation, 33 studies contributing data for late adverse events and 22 studies on inappropriate shock. The findings and strength of evidence for adverse events related to ICD are summarized in **Table 12**.

Table 12. Summary of findings regarding adverse event

Outcome	Study Design: No. Studies (N)	Findings	Strength of Evidence
Early AEs (In-hospital)	RCT: 3 (3,867) Observational: 11 (356,515*) [overlapping cohorts]	During hospitalization, 2.8–3.6% of patients had any adverse event. Serious adverse events occurred in 1.2–1.35% after ICD placement. The most common specific adverse events were lead dislodgement (0.7–1.2%) and hematoma (0.8–1.1%). Other in-hospital adverse events occurred in ≤0.5% of patients receiving ICDs Based on within-study subgroups analyses, there may be higher rates of adverse events among patients receiving dual-chamber ICDs, CRT-D, among older patients, women, and those with ESRD. Physicians and hospitals with lower volume of implantation and operators other than electrophysiologists may have more adverse events.	High
Late AEs (Out of hospital)	RCT: 3 (2,149) Observational: 28 reports of 22 independent cohorts (99,725†)	Device-related adverse events occurred in <0.1–6.4% of ICD patients during 2–49 month followup. Other relatively common adverse events included lead malfunction (<0.1–3.9% during 1.5–40 month followup), infection (0.2–3.7% for 1.5–49 month followup), and thrombosis (0.2–2.9% for 1.5–49 month followup). Based on within-study subgroup analyses, there may be more lead-related adverse events in women. There was no apparent difference in adverse events between CRT-D and ICD or between dual and single chamber ICDs.	Low
Inappropriate shock	RCT: 1 (249) Observational: 21 reports of 17 independent cohorts (212,063‡)	Inappropriate shock occurred in 3–21% of patients during 1–5 year followup. Based on within-study subgroup analyses, there may be more inappropriate shocks among younger patients Evidence on the difference in inappropriate shocks between dual and single chamber ICDs was inconsistent. Limited data show no apparent difference in inappropriate shocks between CRT-D and ICD.	Moderate

Abbreviations: AE = adverse event, CRT-D = cardiac resynchronization therapy-defibrillator, ESRD = end stage renal disease, ICD = implantable cardioverter–defibrillator, No. =number, RCT = randomized, controlled trial

* Largest independent N

† Largest independent N. Two large cohorts: N=38,992 (PMID 21795298), N=15,387 (PMID 19925609).

‡ Largest independent N. One large cohort: N=185,778 (PMID 21098452)

Figure 10 and **Appendix Table 11** shows the quality of reporting for harms across the comparative and cohort studies according to the questions shown in the legend. All reports from one database (i.e., the NCDR ICD Database and the EPD-Vision Database) were graded jointly. Most studies prespecified at least one adverse event in the Methods section, and many used a standardized or precise definition. It seemed that all prespecified harms were reported. Most studies reported the active collection of harms, although some did not comment on ascertainment. Very few studies explicitly stated whether passive (patient-initiated) ascertainment was used (as either the primary or supplementary mode of collection). Most studies described the timing of adverse event

collection at regularly scheduled postimplantation visits. Our review only included studies providing the number of patients experiencing harms (numerator) and the total number at risk (denominator).

Overall, our screening and selection criteria enriched the database for studies with purposeful reporting of adverse events. The strength of evidence for early (in-hospital) adverse events is high as they are derived from a registry with standard definitions, wide capture, and a large number of patients. The strength of evidence for late adverse events is low because there are only a few studies for each outcome and outcome definitions and ascertainment varied. The strength of evidence for inappropriate shocks was moderate with good data ascertainment but imprecise rates across studies.

Early Adverse Events from the NCDR ICD Registry

We identified 11 studies reporting harms ascertained in the NCDR ICD registry (**Appendix Table 12)**.[62,66,67,114-121] These studies ranged in size from 44,805 to 356,515 patients; the patients overlapped to a large degree across studies; therefore the patient populations are not independent. The percentage of patients receiving an ICD for primary prevention in the individual studies ranged from 68 to 100 percent (with one study not reporting the proportion). Although the NCDR ICD registry is a comprehensive database with purposeful data collection, it is restricted to the data capture during the hospitalization for ICD implantation and may not capture all early adverse events.

Appendix Table 13 shows the range of rates for each adverse event category across the 10 reports reporting rates.[62,66,67,114-118,120,121] One additional study provided subgroup data only.[119] **Table 13** presents a summary of the early adverse event rates across studies. The percentage of patients with any adverse events ranged from 2.77 to 3.55 percent across cohorts. Wei 2011[121] reported a substantially higher adverse event percentage (4.6%) than other studies, so we did not include it in the range. The higher rates of adverse events in Wei 2011 most likely occurred because the study involved patients who were at higher risk; namely, it included patients who had a B-type natriuretic peptide value at baseline, a laboratory test that which is tested in patients evaluated for heart failure. This study also did not focus on patients with a first ICD.

The most commonly reported specific early adverse events were lead dislodgement (0.73-1.2% of patients) and hematoma (0.84-1.1% of patients). All other specific adverse events occurred in less than 0.51 percent of patients.

Subgroup Analyses

All 11 studies using the NCDR ICD database reported subgroup analyses (**Appendix Table 14**). Statistical tests were not always provided for comparison of adverse event rates in subgroups, but 7 of the 11 studies reported statistical comparisons for at least one subgroup.

The rate of any adverse events was consistently and significantly higher in groups with dual-chamber ICDs and CRT-Ds (vs. single-chamber), older age, female sex, end-stage renal disease (ESRD), and implantation either by physicians or at hospitals with a low volume of implantations performed. The findings from analyses for specific adverse events were consistent with these subgroup effects or were not statistically significant. The only exception is a study showing a lower, rather than higher, risk of coronary

venous dissection in patients with ESRD,[114] but the overall rate of this complication was low at 0.15 percent.

Other results of subgroup analyses were variable. Findings from two analyses (Tsai 2011 and Cheng 2010) for race and ethnicity were inconsistent.[62,120] Results for diabetes were non-significant in two studies. Haines 2011[117] found no statistically significant difference in the risk of an adverse event or death in patients who had received an ICD for primary prevention versus those who received an ICD for secondary prevention.

Four studies used the NCDR database to ascertain the rates of adverse events according to physician training.[62,66,67,120] In general, electrophysiologists had the lowest (or among the lowest) rates of adverse events. Tsai 2011[120] found a statistically higher odds ratio (OR) for any adverse event or death associated with surgeons (OR 1.49, P<0.001), nonelectrophysiologist cardiologists (OR 1.20, P<0.001), or other specialists (OR 1.18, P<0.05) rather than board-certified electrophysiologists. Cheng 2010[62] reported a higher risk of lead dislodgement in association with physicians trained under alternative pathways (HR 1.23; 95% CI 1.07, 1.45), and a trend for surgery board–certified physicians (HR 1.22; 95% CI 0.95, 1.56) as compared with electrophysiologists. Freeman 2012[67] reported the lowest rates of any adverse event for electrophysiologists but did not report statistical comparisons among physician groups. Finally, Curtis 2009[66] compared the rates of adverse events across electrophysiologists, nonelectrophysiologist cardiologists, thoracic surgeons, and other specialists. The percentages of any complication and of any major complication differed statistically significantly across the four groups, with the lowest percentages in the electrophysiologist group. Among common, specific adverse events, electrophysiologists had the lowest rates of hematoma, lead dislodgement, pneumothorax, and cardiac arrest. Other outcomes occurred in 0.1 percent or less of patients, with zero to five events in at least one subgroup; thus the estimates are not reliable.

Comparative Studies

There is limited comparative evidence on early adverse events for ICDs with different device features or numbers of leads (**Appendix Table 15 and Appendix Table 16**). MADIT-CRT[73] compared in-hospital and 30-day rates of adverse events in ICD and CRT-D recipients, which were as follows: coronary venous dissection with pericardial effusion (0% [ICD] vs. 0.5% [CRT-D]), pneumothorax (0.8 vs. 1.7%), infection (0.7 vs. 1.1%), and pocket hematoma requiring evacuation (2.5 vs. 3.3%). 30-day adverse events comparing ICD with CRT-D were also reported by RAFT: coronary sinus dissection (0 vs. 1.2%), hemothorax or pneumothorax (0.9 vs. 1.2%), pocket infection requiring intervention (1.8 vs. 2.4%), pocket hematoma requiring evacuation (1.2 vs. 1.6%) and lead dislodgement requiring revision (0.1 vs. 0.5%).[74] Neither study reported between-group statistical findings, but there was a trend toward higher percentages in the CRT-D arm than in the ICD arm.

ADRIA (A+ versus DR Clinical Investigation of Arrhythmia Discrimination)[122] compared in-hospital adverse events associated with receipt of a single-lead ICD with integrated atrial sensing rings versus a dual-chamber ICD. No statistical differences were found for pneumothorax (0.8% for both ICDs) or ventricular perforation (0 vs. 0.8%, respectively).

Late Adverse Events from Cohort Studies

We identified 28 studies of 500 or more patients that reported late adverse events occurring 30 or more days after ICD implantation (**Appendix Table 17**).[76,123-149] This includes ICD arms from MADIT II[76]) and SCD-Heft[145] as well as four studies derived from one database, the Leiden University Medical Center Cardiology Information System (EPD-Vision)[124,128,139,141] **Table 14** presents a summary of the late adverse event rates across studies.

In contrast with the studies in the NCDR ICD database, the literature overall had no standardization of outcome definitions across long-term studies. We tabulated device- and lead-related adverse events as they were reported (**Appendix Table 19**). Eight studies provided data on device-related events, namely malfunction requiring replacement or revision or dislocation.[127,130,132,134,139,140,142,146] The duration of followup was 2.6 to 70 months. The percentage of patients with malfunction or dislocation ranged from <0.1 to 6.4 percent.

One study reported that 6.1 percent of patients with recalled ICD devices experienced device-related adverse events with a 70 month followup.[146] (**Appendix Table 20**).

Sixteen studies provided data on lead-related adverse events, such as malfunction, failure, dislodgement, fracture, need for replacement, or revision or repositioning (**Appendix Table 20**).[76,124,125,127,129-132,135-137,140-143,149] The rates of these events ranged from <0.1 to 19 percent. Twelve studies reported rates from <0.1 to only 3.9 percent and had followup of 1.5 to 86 months. One study, by Morrison, reported reported a 4-year lead survival rate of 98.7 percent.[136] Four studies reported higher rates and had long followup periods (35 months, 43 months, 49 months and 8 years). Lead dysfunction was reported in 16.5 percent of patients at 35 months,[129] and lead revisions, in 19 percent at 43 months.[125] These two studies may have overlapping patient populations. High voltage lead defects were reported in 7.0 percent of patients with 49 month followup.[143] In addition, van Rees 2012, which reported 3.9 percent lead failure at 41 months, reported a cumulative 11.5 percent rate of lead failure at 8 years, the longest followup time reported for this outcome.[141]

Seven studies provided data on lead-related adverse events for the recalled Sprint Fidelis leads with followup ranging from 32 to 86 months (**Appendix Table 20**). Five of these studies reported a failure or a malfunction rate of between 7.1 and 8.4 percent.[123,126,131,144,147] The sixth study reported a 4-year lead survival rate of 87 percent,[136] which corresponds at most to a 13 percent failure rate. A *post hoc* analysis of patients in RAFT who received Sprint Fidelis leads reports 5.5 percent of patients had lead failure over 39 months and a lead fracture rate of 1.65 percent per year.[149]

Twelve studies provided data on infection, with followup periods of 1.5 to 49 months (**Appendix Table 21**).[76,124,127,128,130,132-134,138-141] The definition of infection varied across the studies, as did the severity and consequence of the observed cases. Additionally, it was not always possible to ascertain whether the infections reported in cohort studies included post-operative infection. Across all studies, the rate of infection ranged from 0.2 to 3.7 percent.

Four studies reported the rates of thrombosis (**Appendix Table 21**).[133,134,143,145] Among patients in SCD-HeFT without atrial fibrillation or flutter at baseline 2.9 percent experienced a thromboembolic event.[145] Three studies reported deep vein thrombosis rates of 0.2 to 1.0 percent with 1.5 to 49 month followup.[133,134,143]

Subgroup Analyses

We identified 12 articles that reported subgroup analyses of late (out of hospital) adverse events in ICD recipients (**Appendix Table 22**).[123,126,132,134,135,138,142,144,147,149-151] Of these, 11 studies reported statistical comparisons among subgroups for at least one outcome. Five studies compared rates of adverse events between patients receiving ICDs for primary prevention versus those with ICDs for secondary prevention.[123,132,142,144,147] No statistically significant differences were found between the two groups for surgical revision, lead dislodgement, recalled lead failure, or infection.

Four studies found statistically significantly higher rates of lead-related adverse events among women compared with men.[123,126,135,144] For other outcomes and subgroups, the evidence is sparse, with only one study addressing each subgroup comparison or two or more studies showing inconsistent findings.

Comparative Studies

There is limited comparative evidence on late (out of hospital) adverse events for ICDs with different device features or numbers of leads (**Appendix Table 15 and Appendix Table 16)**. These studies have limited followup which may under-appreciate the rate of adverse events. Two RCTs report rates of late adverse events in ICD groups versus CRT-D groups.[73,111] MADIT-CRT reported the rates of total device-related adverse events as 5.2 vs. 4.5 per 100 device-months in ICD and CRT-D groups, respectively (without statistical comparison provided).[73] In the MENDMI study of 80 patients, after 1 year of followup, the composite adverse event was 42 percent with ICD and 52 percent with CRT-D (not statistically significant).[111] This prespecified composite outcome included LV lead dislodgement, postimplantation LV lead repositioning, permanent failure to deliver biventricular pacing, ventricular tachyarrhythmia, hospitalization due to cardiac causes and all-cause mortality.

ADRIA compared adverse events in patients who received a single-lead ICD with integrated atrial sensing rings to those with a dual-chamber ICD. At 1 year, ventricular lead–related adverse events were not statistically significantly different at 5.6 percent and 4.0 percent, respectively.[122]

Inappropriate Shock

We identified fifteen studies which provided data on inappropriate shocks in a cohort of at least 500 patients receiving ICDs.[51,125,129,130,135,136,152-160] Baseline information about these studies can be found in **Appendix Table 17**. The duration of followup ranged from 1 to 5 years. The percentage of patients experiencing inappropriate shocks was 3 to 21 percent overall (**Table 14, Appendix Table 18**). In four studies with 12 months of followup, percentages were 3 to 16 percent. For the other studies with 18 to 60 months followup, the percentage ranged from 8 to 21 percent. One study reported rates per year and found 2.4 percent of patients per year had inappropriate or unadjudicated shocks.[51] MADIT-RIT found that programming of ICD therapies for tachyarrhythmias of $\geq$200 beats per minute or with a prolonged delay in therapy at $\geq$170 beats per minute, as compared with conventional programming, was associated with reductions in inappropriate shock.[60]

Subgroup Analyses

We identified 13 articles that reported subgroup analyses of inappropriate shock in ICD recipients (**Appendix Table 22**).[93,125,129,135,148,150,151,153-155,159,161,162] All of these studies reported statistical comparisons for at least one subgroup comparison. Five studies compared rates of inappropriate shock between patients receiving ICDs for primary prevention versus those with ICDs for secondary prevention.[129,148,153,159,162] Only one of these found a statistically significant difference with fewer shocks in the primary prevention group.[153]

Five studies found lower rates of inappropriate shocks in older patients.[125,141,153,155,162] Age cut-offs varied between studies (more than 66.4 [the cohort mean age], 70, or 75 years, or per 10-year increase). In four of these, the difference was statistically significant. The fifth study did not report a statistical comparison. There was mixed data regarding the subgroup effect on inappropriate shock for single- vs. dual-chamber ICDs and for diabetes.

Comparative Studies

We identified one RCT and one nRCS that compare inappropriate shock in patients implanted with ICDs with different device features or numbers of leads (**Appendix Table 15 and Appendix Table 16**).[122,156] ALTITUDE (the acronym is undefined) reported a 5-year rate of inappropriate shock as 16 percent among ICD recipients and 17 percent among CRT-D recipients (no statistical comparison provided).[156] ADRIA (described above) reported rates of inappropriate shock as 5.6 percent in both single- and dual-chamber ICD groups.[122]

Summary

The rates of adverse events captured early in the NCDR ICD database range from 2.8 to 3.6 percent and the serious adverse event rates ranges from 1.2 to 1.35 percent (**Table 15**). The most common early adverse events are lead dislodgement (in 0.7 to 1.2 percent of patients) and hematoma (in 0.8-1.1 percent). Other early in-hospital adverse events occur in 0.5 percent of patients or less. The strength of evidence for early adverse events is high (**Table 12**).

Higher rates of early adverse events have been shown in the following subgroups: patients implanted with dual-chamber ICDs or CRT-Ds (vs. single-chamber ICDs); patients who are older, female, or have ESRD; patients implanted by physicians with a lower implantation volume or by nonelectrophysiologists; and patients implanted at hospitals with a lower implantation volume.

Regarding late adverse events which were captured usually after the initial hospitalization for implantation, the percentage of patients with device-related adverse events with variable definitions ranged from <0.1 to 6.4 percent for followup durations of 2 to 49 months. For lead-related adverse events (malfunction, failure, dislodgement, fracture, or need for replacement or revision, or repositioning) the rates ranged from <0.1 to 3.9 percent of patients with followup durations from 1.5 to 40 months, but studies with longer followup times (35 to 96 months) reported rates of 7.0 to 19 percent. Failure of the Sprint Fidelis lead was reported in approximately 6 to 8 percent of patients followed for up to 7 years. Infections, variably defined, were reported in 0.2 to 3.7 percent of patients with followup of 1.5 to 49 months. There are limited data on thrombosis in long-term

followup:one study reported a rate of thromboemolic events of 2.9 percent, with a 46 month followup, and three studies reported deep vein thrombosis rates of 0.2 and 1 percent, with followup periods of 1.5 to 49 months. Given the limited number of studies for each outcome and the variable definitions and methods of ascertainment, the strength of evidence for late adverse events is low. Subgroup analyses show female sex to be associated with more lead-related adverse events.

The percentage of patients who experience at least one inappropriate shock ranged from 3 to 21 percent for followup between 1 and 5 years. The strength of evidence for inappropriate shocks was moderate with good data ascertainment but imprecision due to varying percentages across studies. Subgroup analyses show older age to be associated with fewer inappropriate shocks.

The data from five comparative studies for early and late adverse events and inappropriate shock fail to show differences across ICDs with different device features.

Table 14. Percentage of patients with early (in-hospital) adverse events in NCDR ICD database

Outcomes	No. Studies* (Largest N)	Adverse Event Range
Any adverse event	8 (356,515)	2.77–3.55
Any serious adverse event	5 (356,515)	1.17–1.35
Any adverse event or death	2 (268,701)	1.5–3.37
Arteriovenous fistula	6 (268,701)	<0.1
Cardiac arrest	9 (356,515)	0.26–0.34
Cardiac perforation	7 (268,701)	0.06–0.1
Cardiac valve injury	4 (268,701)	<0.1
Conduction block	6 (268,701)	0.03–0.1
Coronary venous dissection	6 (356,515)	0.08–0.15
Drug reaction	6 (268,701)	0.09–0.11
Hematoma	8 (356,515)	0.84–1.1
Hemothorax	8 (268,701)	0.07–0.1
Infection related to device	6 (268,701)	<0.1
Lead dislodgement	8 (356,515)	0.73–1.2
Myocardial infarction	6 (268,701)	<0.1
Pericardial tamponade	6 (268,701)	0.07–0.1
Peripheral embolism	6 (268,701)	<0.1
Peripheral nerve injury	4 (268,701)	<0.1
Phlebitis, deep	5 (268,701)	<0.1
Phlebitis, superficial	6 (268,701)	0.04–0.1
Pneumothorax	9 (356,515)	0.42–0.51
Stroke/cerebrovascular accident	6 (268,701)	0.05–0.1
Transient ischemic attack	6 (268,701)	<0.1

* Data from Wei, 2011 PMID 21487093 are outliers and are not included. All patients in this study had B-type natriuretic peptide (BNP) measurement which may represent patients with heart failure. Also the study did not explicitly exclude patients with prior ICD.

Table 15. Percentage of patients with late (out of hospital) adverse events and inappropriate shocks (excluding studies of recalled leads or devices)

Outcomes	No. Studies/Cohorts* (N)	Adverse Event Range
Device- and lead-specific adverse events		
Total device-related adverse event	2 (1,820)	4.5-5.2/100 device-mo
ICD mechanical complications	1 (38,992)	4.2%
ICD replacement	3 (5,593)	<0.1-2.6%; 0.1/100 pt-yr
ICD revision	2 (42,245)	2.2-6.4%; 5.2/100 pt-yr
ICD mechanical complication	1 (38,992)	4.2%
Lead-related adverse event, total	3 (15,636)	3.6-5.6%
Lead malfunction	3 (20,242)	2.4-3.9%; 1.14-1.2/100 pt-yr
Lead (high voltage) defect	1 (903)	7.0%
Lead problem requiring surgery	1 (742)	1.8%
Lead failure	3 (4,246)	0.2-3.8%; 1.4/100 pt-yr
Lead fracture requiring revision	1 (1,060)	3.4%
Lead fracture requiring ICD explants	1 (1,339)	<0.1%; 0.07/100 pt-yr
Lead dislodgement	5 (27,084)	0.6-3.1%; 1.4-2.8/100 pt-yr
Lead replacement	3 (15,697)	0.4-1.0%; 0.34-3.4/100 pt-yr
Lead revision or repositioning	5 (12,995)	0.3-19%; 0.8/100 pt-yr
Infection		
Infection, general	2 (199,207)	1.2-2.7%
Infection of ICD device	2 (10,561)	0.9%; 4.2/100 pt-yr
Infection requiring ICD removal	4 (531,959)	0.5-3.7%; 0.7/100 pt-yr
Infection of lead requiring antibiotics	1 (1,060)	0.5%
Infection requiring surgery, nonfatal	1 (742)	0.7%
Pocket infection	1 (667)	1.0%; 1.2/100 pt-yr
Pocket infection requiring debridement	1 (3,340)	1.0%
Sepsis/severe infection	2 (12,868)	0.2% 1st yr: 98.8/100 pt-yr Following: 63.9/100 pt-yr
Thrombosis		
Deep vein thrombosis	1 (38,992)	1.0%
Subclavian vein thrombosis	2 (4,243)	0.2-0.9%
Thromboembolic event, any	1 (681)	2.9%
Inappropriate shocks		
Inappropriate shocks	21 (212,312)	3-21%

ICD = implanted cardiac defibrillator, mo = months; N = number of patients, pt-yr = patient-years.

* Single cohort studies and cohorts (study arms) from comparative studies are counted individually

Table 16. ICDs for Primary Prevention of SCD: Strength of evidence domains

Outcome	Study Design: No. Studies (N)	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Other Issues	Strength of Evidence and Findings
Major outcomes								
Early (in-hospital) AE		Low	Direct	Consistent	Precise	Low	None	High
• Any AE	Registry: 9 (356,515*)							Any AE: 2.8-3.6%
• Serious AE	Registry: 7 (356,515*)							Serious AE: 1.2-1.35%
• Lead dislodgement	RCT:1, Registry: 9 (358,313*)							Lead dislodgement: 0.7-1.2%
• Hematoma	RCT:2, Registry: 9 (360,133*)							Hematoma: 0.8-1.1%
• Multiple†								All other AE: <0.5%
Late (out of hospital) AE		Low	Direct	Inconsistent	Imprecise	Suspected	None	Low
• Total AE‡	RCT: 1 (80)							Total AE§: ICD vs. CRT-D 42% vs. 52% (NS) for 1 yr F/U
• Device-related AE	Cohort: 9 (64,174)							Device-related AE: <0.1-6.4% for 2-49 mo F/U
• Lead-related AE	RCT: 1, Cohort: 23 (57,234*)							Lead-related AE: <0.1–3.9% for 1.5-41 mo F/U
• Infection	Cohort: 15 (65,449*)							Infection: 0.2–3.7% for 1.5-49 mo F/U
• Thrombosis	Cohort: 5 (45,789)							Thrombosis: 0.2–2.9% for 1.5–49 mo F/U
Inappropriate shock	RCT: 1, Cohort: 21 (212,312*)	Low	Direct	Consistent	Imprecise	Low	None	Moderate Inappropriate shock: 3-21% for 1-5y F/U

Abbreviations: AE=adverse event; DVT=Deep vein thrombosis; F/U=followup; ICD: implantable cardioverter-defibrillator; mo=month; No.=Number; RCT=randomized, controlled trial; SCD=sudden cardiac death; y=year.

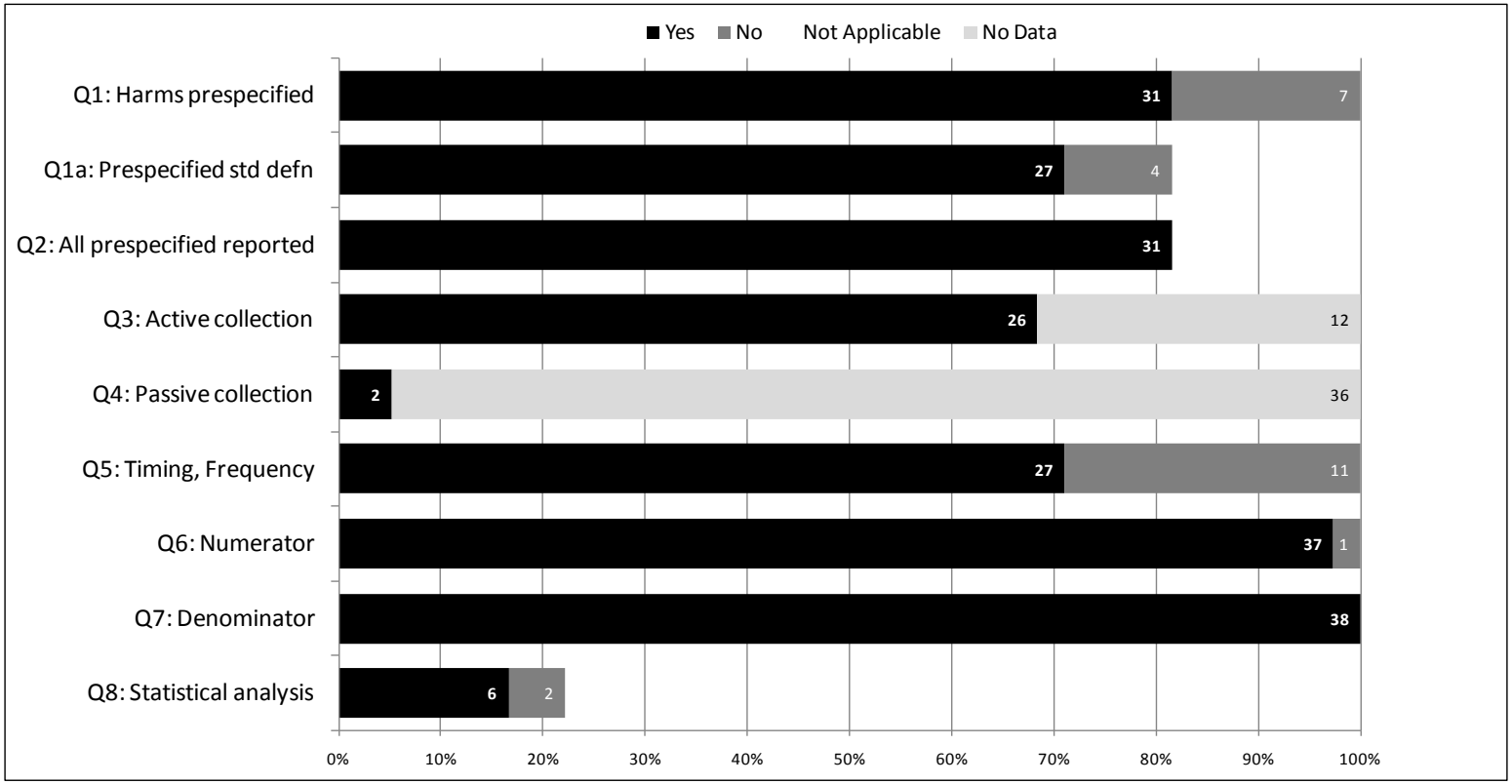
*Largest independent N

† Study design is registry unless otherwise noted. Outcome: No. of studies (largest independent N): Any AE or death: 2 (268,701), Arteriovenous fistula: 7 (268,701), Cardiac arrest: 10 (356,515), Cardiac perforation: 1 RCT, 8 Registry (268,950), Cardiac valve injury: 4(268,701), Conduction block: 7 (268,701), Coronary venous dissection: 2 RCT, 7 Registry (360,133), Drug reaction: 7 (268,701), Hematoma: 1 RCT, 9 Registry (358,335), Hemothorax: 9 (268,701),Hemothorax or pneumothorax: 1 RCT (1798), Infection related to device: 2 RCT, 8 registry (272,319), Myocardial infarction: 7 (268,701), Pericardial tamponade: 7 (268,701), Peripheral embolism: 7 (268,701), Peripheral nerve injury: 5(268,701), Phlebitis – deep: 6(268,701), Phlebitis – superficial: 7 (268,701), Pneumothorax: 2 RCT, 10 Registry (358,584), Pocket problems requiring revision: 1 RCT (1798), Stroke/CVA: 7 (268,701), Transient ischemic attack: 7 (268,701).

‡ Outcome of interest for comparative studies.

§ Left ventricular lead dislodgement, postimplantation left ventricular lead repositioning, permanent failure to deliver biventricular pacing, ventricular tachyarrythmia, hospitalization due to cardiac causes and all-cause mortality.

Figure 10. McHarms quality measures for 38 independent studies reporting adverse event data



The numbers within the bars represent the number of studies within each category.

Q1. Were any harms prespecified (*a priori)* in Methods section?
Q1a. If yes, were any of them prespecified with *a priori* standardized or precise definitions?
Q2. Were all prespecified harms reported?
Q3. Was the mode of harms collection ACTIVE (sought to collect information on AEs)?
Q4. Was the mode of harms collection PASSIVE? (Participants are not specifically asked about or tested for the occurrence of adverse events. Rather, adverse events are identified based on patient reports made on their own initiative.)
Q5. Did the study specify the TIMING and/or FREQUENCY of collection of harms?
Q6. Is the number of participants who experience harms provided for each arm?
Q7. Is the number at risk for harms (denominator) provided for each arm?
Q8. For studies comparing adverse events across two or more arms: Is there a STATISTICAL analysis of relative harms between groups?

Key Question 3: Which Patients Have Been Included in Comparative Studies of ICDs for Primary Prevention of SCD?

For Key Question 3, we reviewed the eligibility criteria for all 18 studies contributing data to Key Question 1.

Key Question 3a: What Were Eligibility Criteria for Patients in Studies Included for Key Question 1? How Were Patients Evaluated and What Diagnostic Tests and Algorithms Were Used to Select Patients?

Eligibility Criteria

We categorized the studies according to whether they included only a) patients with ischemic cardiomyopathy and MIs that occurred at least 30 days before ICD implantation (henceforth called "remote MIs"), b) patients with nonischemic cardiomyopathy only, c) patients with either ischemic or nonischemic cardiomyopathy and remote MIs, and d) patients with ischemic cardiomyopathy and either MIs that occurred more recently than 30 days before ICD implantation (henceforth called "recent MIs") or coronary revascularization (i.e., patients who would not meet current CMS criteria for ICD implantation for primary prevention of SCD). Note that a study was considered to address remote MI only if all patients had their MI at least 30 days before ICD placement; if the range of timing of MI included some time points of less than 30 days before implantation, the population was considered to have recent MI. **Table 17** provides an overview of the eligibility criteria across studies.

Studies of Patients with Ischemic Cardiomyopathy and Remote MI (>30 days before ICD)

MADIT and MADIT II compared ICD versus no ICD in patients with ischemic cardiomyopathy and remote MI (**Appendix Table 23**).[42,76] Both studies were conducted in the US and Europe. MADIT included adults aged 25 to 80 years; MADIT II included adults over 21 years. Both enrolled only patients in NYHA Classes I, II, and III. The LVEF inclusion criterion for the original MADIT was ≤35 percent. MADIT II was more restrictive, including only those with an LVEF ≤30 percent.

Studies of Patients with Nonischemic Cardiomyopathy

Four studies enrolled patients with nonischemic cardiomyopathy (**Appendix Table 23**).[91,99,103,106] Two RCTs (DEFNITE and CAT) and one nRCS (Fonarow 2000)compared ICD versus no ICD (**Appendix Table 23**).[91,99,106] The third RCT (AMIOVIRT) compared ICD versus amiodarone.[103] The studies of ICD versus no ICD were conducted in the US, and the single study of ICD versus amiodarone was conducted in Germany.

Two studies (CAT and AMIOVIRT) enrolled adults over 18 years of age, but in the CAT study, the upper limit for age was 70 years. The other studies did not set an age restriction for enrollment.

Two RCTs (DEFINITE and AMIOVIRT) enrolled patients in NYHA Classes I, II, and III. The single nRCS (Fonarow 2000) included only those with Classes III and IV. The CAT study restricted its inclusion to those with Classes II and III only.

Two studies (DEFINITE, AMIOVIRT) enrolled only patients with an LVEF≤35 percent; Fonarow 2000 included patients with LVEF <35 percent. The CAT study was restricted to those with an LVEF ≤30 percent.

Studies of Patients with Mixed Ischemic and Nonischemic Cardiomyopathy

Five RCTs (COMPANION, SCD-HeFT, MADIT-CRT, RAFT and Diab 2011) and three nRCSs (Chan 2009, OPTIMIZE-HF/GWTG-HF, and Mezu 2011) enrolled a mixed population of ischemic and nonischemic cardiomyopathy (**Appendix Table 23**).[51,73,95,105,107,108,112,149] The three nRCSs (Chan 2009, OPTIMIZE-HF/GWTG-HF and Mezu 2011) examined the comparison of ICD versus no ICD,[105,107,108] while a single RCT (SCD-HeFT) compared ICD vs. amiodarone.[7] Another RCT (COMPANION) compared CRT-D versus a control[95] and three additional RCTs (MADIT-CRT, RAFT, and Diab 2011) looked at the comparison of ICD versus CRT-D.[73,112,149] The studies of ICD or CRT-D versus no ICD or amiodarone were conducted in the US. Of the three studies examining ICD versus CRT-D, one was conducted in the US, Canada, and Europe, another in Europe, Canada and Australia, and the third was conducted in the United Kingdom.

One (Chan 2009) of the three nRCSs comparing ICD versus no ICD enrolled patients over 18 years of age. OPTIMIZE-HF/GWTG-HF included patients aged 65 to 84 years while Mezu 2011 restricted its enrollment to only those over 80 years of age. Only one of the RCTs (MADIT-CRT) examining ICD versus CRT-D reported an inclusion criterion for age (> 21 years). COMPANION, RAFT, and SCD-HeFT also did not set an age restriction.

Of the four studies reporting on ICD or CRT-D versus no ICD, two (Chan 2009 and OPTIMIZE-HF/GWTG-HF) did not have an inclusion criterion regarding NYHA class. The remaining two (COMPANION, Mezu 2011) included those with only NYHA Classes III and IV, or Classes I, II, and III respectively. SCD-HeFT included only Classes II and III. One study (MADIT-CRT) of ICD versus CRT-D enrolled only patients in NYHA Classes I and II, while the another enrolled those in NYHA Classes II and III (RAFT), and a third (Diab 2011) enrolled only those in Classes III and IV. In all but two studies, the cutoff for the LVEF was≤35 percent. The remaining studies (MADIT-CRT and RAFT) were restricted to only patients with an LVEF ≤30 percent. Two RCTs of ICD versus no ICD (COMPANION and Chan 2009) required the patients to have a QRS interval >120 ms. All studies of ICD versus CRT-D set a limit on the QRS interval for enrollment; two (in RAFT and Diab 2011) were≥120 ms while the other (in MADIT-CRT) was ≥130 ms.

Studies of Patients with Ischemic Cardiomyopathy and Recent MI (<30 days before ICD) or Revascularization

Three RCTs (DINAMIT, IRIS, and MENDMI) enrolled patients with ischemic cardiomyopathy and recent MI (<30 days before ICD implantation)[98,102,111] and a fourth trial (CABG-Patch) enrolled patients with ischemic cardiomyopathy who were undergoing coronary revascularization.[94] The four studies were conducted in multiple countries, including the US and Germany (**Appendix Table 23**). Three (DINAMIT, IRIS, CABG-Patch) had an age restriction as part of their inclusion criteria, enrolling only those younger than 80 years of age.

The three trials of patients with recent MIs (i.e., with at least one patient, but not necessarily all, who had an MI less than 30 days before ICD placement) included those whose MIs occurred either between 6 and 40 days before ICD implantation, 5 and 31 days before, and 3 and 14 days before.

Two studies (DINAMIT and MENDMI) restricted their enrollment by NYHA Class I, II, and III. Three studies (DINAMIT, MENDMI, and CABG-Patch) required an LVEF ≤35 percent, another study (IRIS) included patients with an LVEF≤40 percent. Two studies specified an inclusion criterion for QRS interval: one (CABG-Patch) set its cutoff at ≥114 ms; the other (MENDMI), <120 ms.

Summary: Eligibility

The two studies of patients with ischemic cardiomyopathy whose MIs occurred at least 30 days prior to ICD implantation included adults with NYHA Class I, II, or III with an LVEF either ≤30 percent or ≤35 percent.

The four studies of patients with nonischemic cardiomyopathy included adults (though one study was restricted to adults 70 years or younger) with a variety of NYHA class criteria. Two RCTs included patients with NYHA Classes I, II, and II; one RCT included only those with Classes II and III; and the nRCS restricted enrollment to Classes III and IV. Three of the studies included patients with LVEF either less than or less than or equal to 35 percent. One trial restricted to LVEF ≤30 percent.

The plurality of studies (five RCTs and two nRCSs) included both patients with ischemic and nonischemic cardiomyopathy. The RCTs included essentially all eligible adults. The two nRCSs, on the other hand, were restricted to older adults, either aged 65 to 84 years or over 80 years. The studies were heterogeneous as to which NYHA Classes were included (I-IV, I-III, I and II, II and III, or III and IV). All but two studies included patients with LVEF either less than or less than or equal to 35 percent; two trial restricted to LVEF ≤30 percent. Four of the trials used QRS interval eligibility criteria of either greater than or greater than or equal to 120 ms or, for one trial, ≥130 ms.

Four trials had eligibility that clearly would not meet current CMS criteria for ICD use for primary prevention of SCD. Three trials included patients with recent MIs, either ≤40, ≤31, or ≤14 days since their MI. The fourth trial was restricted to patients undergoing CABG.

Diagnostic Tests and Algorithms Used to Select Patients

Table 18 displays the diagnostic tests that were used in the RCTs to select patients. No trial explicitly used an algorithm (other than electrophysiology testing, which is described below). All trials used LVEF criteria for eligibility and measured LVEF with a variety of tests, though usually echocardiography; other tests included angiography and radionuclide scanning. All studies except CABG-Patch determined the patients' NYHA class of heart failure. The CRT-D studies and CABG-Patch used QRS intervals on 12-lead electrocardiograms (ECGs) or signal-averaged ECGs; other ICD trials did not.

Six of the 10 ICD versus no ICD trials tested patients for nonsustained VT, most frequently with 24-hour ambulatory Holter monitoring, but also with telemetry, 12-lead ECG, or exercise ECG (stress testing). Only MADIT reported using electrophysiology testing. MADIT II specifically addressed whether electrophysiology testing could be avoided when determining whether ICD placement would be of value.

Only four of the 10 ICD versus no ICD trials and one of the three CRT-D versus ICD trials explicitly tested for coronary stenosis, mostly with coronary angiography or exercise testing. A few trials used other unique diagnostic tests, as listed in **Table 17**.

Summary: Tests Used

There was heterogeneity regarding which diagnostic tests were used to determine study eligibility across trials. (**Table 18**) All RCTs used LVEF criteria, but the studies used different specific tests (though most were based on echocardiography). NYHA class was also determined in all patients (except in one older trial). The trials of CRT-D used QRS interval data for eligibility; most other trials did not. Most of the RCTs of ICD versus no ICD tested all patients for nonsustained VT, but with different specific diagnostic tests. Only one RCT reported performing electrophysiology testing in all patients. Only 4 of the 13 RCTs explicitly tested for coronary stenosis, mostly with coronary angiography or exercise testing.

Key Question 3b: Among Patients in Studies Included for Key Question 1, What Was the Likelihood of SCD or Ventricular Tachyarrhythmia, as Measured by Total Shocks for Those with ICDs or Episodes of SCD for Those without ICDs?

Five RCTs[42,51,94,99,103] and one nRCS (Fonarow 2000[106]) provided data for total shocks or appropriate shocks in patients with an ICD. Some studies provided the data as total number of shocks; others, as number of patients receiving any shock or patients receiving only inappropriate shocks. The data are summarized in **Table 19**. In the first year after ICD implantation, between about one-quarter and one-half of patients had a shock. The percentage of patients who had a shock rose consistently with time since ICD implantation. Four of the studies that reported numbers of shocks (SCD-HeFT, Fonarow 2000, MADIT, CABG-Patch) described the percentage of patients receiving shocks over time and found progressively increasing percentages. Two of the trials (MADIT and CABG-Patch) report survival curves showing that about 50 percent of patients have a shock within the first year, after which the rate of patients having their first shock slows but continues to rise to approximately 70 percent at 4 years (CABG-Patch) and approximately 90 percent at 5 years (MADIT). The studies that reported appropriate shocks revealed similar patterns as for total shocks, though, as expected, with lower rates of appropriate shocks than total shocks.

Six RCTs reported on the episodes of SCDs in patients without an ICD.[42,91,98,99,102,103] CAT reported no SCDs at 1 year. At 2 years, DEFINITE reported episodes in 6.1 percent of patients while MADIT reported episodes in 13 percent. At 3 years, DINAMIT and IRIS reported SCDs in 8.5 and 13 percent of their non-ICD patients, respectively. The study with the longest followup (5 years), AMIOVIRT, reported SCD in only 4 percent of patients at the end of followup. There was no clear trend for increasing likelihood of SCD with longer followup time across the six studies, but within the three RCTs that presented survival curves (DINAMIT, IRIS, and DEFINITE), there appeared to be fairly steady rates of SCD for about 3 to 6 years after randomization.

Summary: Risk of SCD

The six studies that provided data for total or appropriate ICD shocks found that patients in these trials were very likely to have a shock during followup. The majority of the first episodes

of being shocked appear to occur within the first year after ICD implantation. The six RCTs that reported SCD in patients without an ICD included with a likelihood of SCD between about 4 and 13 percent during the 2 to 5 years after randomization. Rates of SCD over time appeared to be fairly steady.

Table 17. Eligibility criteria in comparative study

Study Author Year	IDCM & Documented MI	NIDCM >3 mo	NYHA II/III	NYHA IV/CRT	LVEF ≤35%	No MI <40 d	No Revasc <3 mo	No shock / hTN	Revasc not indicated	No brain damage	Exp Surv >1 y
ICD vs. No ICD											
AMIOVIRT Strickberger 2003	--	**Yes** (no time*)	No (also Class I)	--	**Yes**	**Yes** (implied)	**Yes** (implied)	nd	**Yes**	nd	nd
CABG-Patch Bigger 1997	No (MI not required)	--	nd	nd	**Yes**	nd	No	nd	*No (al having CABG)*	nd	**Yes**
CAT Bänsch 2002	--	No (≤9 mo)	**Yes**	--	**Yes**	**Yes**	**Yes** (implied)	nd	**Yes**	nd	nd
Chan 2009	**Yes**	**Yes**	nd	nd	**Yes**	No (No MI <30 d)	**Yes** (no time*)	nd	nd	nd	**Yes**
COMPANION Bristow 2004	No (MI not required)	**Yes** (no time*)	**Yes**	**Yes**	**Yes**	nd	nd	nd	nd	nd	nd
DEFINITE Kadish 2004	--	**Yes** (no time*)	No (also Class I)	--	**Yes**	**Yes** (implied)	**Yes** (implied)	nd	**Yes**	nd	nd
DINAMIT Hohnloser 2004	**Yes**	--	No (also Class I)	--	**Yes**	*No (All MI ≤40 d)*	**Yes** (implied)	nd	**Yes**	nd	**Yes** ("limited")
Fonarow 2000	--	**Yes** (no time*)	**Yes**	Maybe (nd re: CRT)	**Yes**	**Yes**	**Yes** (implied)	nd	nd	nd	nd
IRIS Steinbeck 2009	**Yes**	--	No (also Class I)	--	No (≤40%)	*No (All MI ≤31 d)*	nd	nd	**Yes**	nd	**Yes** ("severe")
MADIT Moss 1996	**Yes**	--	No (also Class I)	--	**Yes**	No (No MI <21 d)	No (<2 mo)	nd	**Yes**	**Yes**	**Yes**
MADIT II Moss 2002	**Yes**	--	No (also Class I)	--	**Yes**	No (No MI <1 mo)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Mezu 2011	No (MI not required)	**Yes (no time*)**	No (also Class I)	--	**Yes**	No (any time)	No (implied)	nd	No (implied)	No	No
OPTIMIZE-HF / GWTG-HF Hernandez 2010	No (MI not required)	**Yes (no time*)**	nd	nd	**Yes**	nd	nd	nd	nd	nd	nd
SCD-HeFT Bardy 2005	No (MI not required)	**Yes** (no time*)	**Yes**	--	**Yes**	nd	nd	nd	nd	nd	nd
ICD vs. CRT-D											
Diab 2011	No (MI not required)	**Yes** (no time*)	**Yes**	**Yes**	**Yes**	nd	nd	nd	**Yes**	nd	No (>6 mo)
MADIT-CRT Moss 2009	**Yes**	**Yes**	No (also Class I)	--	**Yes**	**Yes**	**Yes**	nd	**Yes**	**Yes**	**Yes**
MENDMI Chung 2010	**Yes**	--	No (also Class I)	--	**Yes**	No *(all MI ≤14 d)*	**Yes**	nd	nd	nd	No (>6 mo)

Study Author Year	IDCM & Documented MI	NIDCM >3 mo	NYHA II/III	NYHA IV/CRT	LVEF ≤35%	No MI <40 d	No Revasc <3 mo	No shock / hTN	Revasc not indicated	No brain damage	Exp Surv >1 y
RAFT Tang, 2010 21073365	No (MI not required)	**Yes**	**Yes**	--	**Yes**	nd	nd	nd	nd	nd	nd

Explanation of headers:
IDCM & Documented MI: Ischemic dilated cardiomyopathy and documented prior myocardial infarction
NIDCM >3 mo: Nonischemic dilated cardiomyopathy >3 months (with or without prior myocardial infarction)
NYHA II/III: New York Heart Association Class II or III heart failure
NYHA IV/CRT: NYHA Class IV heart failure and meet all current CMS coverage requirements for a cardiac resynchronization therapy device
LVEF ≤35%: Left ventricular ejection fraction ≤35%
No MI <40 d: No acute myocardial infarction within the past 40 days
No Revasc <3 mo: No coronary artery revascularization (coronary artery bypass graft or percutaneous transluminal coronary angioplasty) within the past 3 months
No shock / hTN: No cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm
Revasc not indicated: No clinical symptoms or findings that would make them a candidate for coronary revascularization
No brain damage: No irreversible brain damage from preexisting cerebral disease
Exp Surv >1 y: No disease, other than cardiac disease (e.g. cancer, uremia, liver failure), associated with a likelihood of survival <1 year

Abbreviations: -- = this factor was not part of inclusion criteria (e.g., AMIOVIRT trial excluded patients with ischemic dilated cardiac disease), CABG = coronary artery bypass graft, CRT-D = cardiac resynchronization therapy and implanted cardioverter defibrillator, ICD = implanted cardioverter defibrillator, nd = not documented.

* Eligibility criteria did not include duration of NIDCM or time since revascularization

Table 18. Diagnostic tests used to select patients (RCTs only)*

Study	LVEF Measured (Test)	QRS Measured	NYHA Class Determined	NSVT	EP Study	Coronary Stenosis (Test)	Other
ICD vs. No ICD							
AMIOVIRT Strickberger 2003	Yes (nd)	No	Yes	Yes (multiple†)	No	Yes, implied (nd)	No
CABG-Patch Bigger 1997	Yes (nd)	Yes (SA ECG)	No	No	No	Yes, implied (angiography)	No
CAT Bänsch 2002	Yes (angiography)	No	Yes	Yes (Holter)	No	Yes (angiography)	No
COMPANION Bristow 2004	Yes (echo)	Yes (ECG)	Yes	No	No	No	No
DEFINITE Kadish 2004	Yes (nd)	No	Yes	Yes (Holter or telemetry)	No	Yes (angiography or ETT)	No
DINAMIT Hohnloser 2004	Yes (multiple‡)	No	Yes	No	No	No	RR interval (Holter)
IRIS Steinbeck 2009	Yes (echo)	No	Yes	Yes (Holter)	No	No	No
MADIT Moss 1996	Yes (multiple‡)	No	Yes	Yes (multiple§)	Yes	No	No
MADIT II Moss 2002	Yes (multiple‡)	No	Yes	No	No	No	No
SCD-HeFT Bardy 2005	Yes (nd)	No	Yes	Yes (Holter)	No	No	6 min walk, CXR
ICD vs. CRT-D							
Diab 2011	Yes (echo)	Yes (nd)	Yes	No	No	Yes (ETT)	Mech dyssynch (echo or TDI) LVEDD (echo)
MADIT-CRT Moss 2009	Yes (echo)	Yes (nd)	Yes	No	No	No	No
MENDMI Chung 2010	Yes (echo)	Yes (ECG)	Yes	No	No	No	WMA (echo)
RAFT Tang, 2010 21073365	Yes (nd)	Yes (nd)	Yes	No	No	No	6-min walk

6 min walk = 6 minute walk test, CRT-D = cardiac resynchronization therapy with defibrillator, CXR = chest radiography, ECG = electrocardiography, Echo = echocardiography, EP = electrophysiology, ETT = exercise tolerance test (stress test), Holter = 24-hour Holter monitor, ICD = implanted cardiac defibrillator, LVEDD = left ventricle end-diastolic diameter, LVEF = left ventricle ejection fraction, nd = not documented, Mech dyssynch = mechanical ventricular dyssynchrony, NSVT = nonsustained ventricular tachycardia, NYHA = New York Heart Association, SA ECG = signal averaged ECG, RR interval = time between R waves on ECG, TDI = tissue Doppler imaging, WMA = left ventricular wall motion abnormality.

* Excluding laboratory tests, symptoms, past medical history, or physical examination findings.
† ECG, telemetry or Holter monitor
‡ Angiography, radionuclide scanning, or echocardiography
§ ECG, Holter, or exercise ECG.

Table 19. Patients with any shock from ICD and sudden cardiac deaths (with no ICD)

Study Author, Year PMID, Country	Intervention (Control)	Patients with an ICD who received any shock [appropriate shocks]	Patients with no ICD with SCD
5 y			
AMIOVIRT Strickberger, 2003 12767651, US	ICD (Amiodarone)	nd total [31% [16/51) appropriate]	3.8% (2/52)
4 y			
SCD-HeFT Bardy, 2005 15659722, US	ICD (Amiodarone)	31% (259/829) any shock; 7.5%/y [21% (177/829) appropriate; 5.1%/y]	nd
3 y			
DINAMIT Hohnloser, 2004 15590950, Multi	ICD (No ICD)	nd	8.5%; 3.5%/y (29/342)
IRIS Steinbeck, 2009 19812399, Germany	ICD (No ICD)	nd	13.2% (60/453)
2 y			
CABG-Patch Bigger, 1997 9371853, US and Germany	ICD (No ICD)	57% actuarial risk (N=428) any shock	nd
DEFINITE Kadish, 2004 15152060, US	ICD (No ICD)	nd any shock* [18% (41/229) appropriate]	6.1% (14/229)
Fonarow, 2000 10760339, US	ICD (Control)	nd any shock† [40% (10/25) appropriate (55% actuarial risk)]	nd
MADIT Moss, 1996 8960472, US and EU	ICD (No ICD)	60% (54/90) any shock	12.9% (13/101)
1 y			
CAT Bänsch, 2002 11914254, Germany	ICD (Control)	nd	0% (0/50)
CABG-Patch Bigger, 1997 9371853, US and Germany	ICD (No ICD)	50% actuarial risk (N=428) any shock	nd
Fonarow, 2000 10760339, US	ICD (Control)	27% actuarial risk (N=25) any shock	nd

1°=primary, CABG=coronary artery bypass graft, EU=Europe, ICD=implantable cardiac defibrillator, LVEF=left ventricular ejection fraction, MI=myocardial infarction, nd=not documented, NYHA=New York Heart Association, RCT=randomized controlled trial, UK, United Kingdom, US=United States.

* 49 patients received inappropriate shocks; no data on how many patients in any shock received shocks.
† 3 patients received inappropriate shocks; no data on how many patients in any shock received shocks.

Discussion

Key Findings and Strength of Evidence

We identified 14 studies comparing ICD versus no ICD, 4 studies comparing CRT-D versus ICD, and 59 studies contributing data on adverse events after ICD implantation. The summary of key findings and strength of evidence is shown in **Table 20**. This table is an amalgamation of Tables 3, 7, and 10, plus outcomes with insufficient evidence.

Table 20. Summary of findings

Outcome	Study Design: No. Studies (N)	Findings	Strength of Evidence
All-cause mortality	ICD vs. no ICD RCT: 10 (8,606) nRCS: 4 (5,949)	• ICD use as primary prevention for patients who meet the current practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of all-cause mortality over the course of 3 to 7 years after implantation: HR = 0.69 (95% CI 0.60, 0.79). The benefit of ICD appears fairly stable over time. Across trials, the range of NNT to prevent one death was 6.2 to 22 at 3 to 7 years, with wide 95% CIs. • There is indirect evidence across studies that patients with recent MIs (<30-40 days), on average, do not benefit from ICD, in contrast with patients with more distant MIs. • Within-study subgroup analyses fail to support whether the value of ICD placement differs in other subgroups of patients, including by sex or age, or based on different characteristics of facilities where ICDs are implanted.	High
	CRT-D vs. ICD RCT: 4 (3,743)	• The 2 larger trials found either no difference (HR = 1.00) or a significant benefit with CRT-D (HR = 0.75)No differences in effect were found between patients with ischemic or nonischemic heart disease or with NYHA Class II or III cardiomyopathy • There was no evidence regarding the comparison of CRT-D and ICD in subgroups of patients or based on different characteristics of facilities where ICDs are implanted.	Insufficient
Sudden cardiac death	ICD vs. no ICD RCT: 7 (4,093)nRCS: 2 (1,115)	• ICD use as primary prevention for patients who meet the current practice criteria (no recent MI, no concurrent coronary revascularization) reduces the risk of SCD over the course of 2 to 6 years after implantation: HR = 0.37 (95% CI 0.26, 0.52). There is insufficient evidence to evaluate the course of the effect over time. Across trials, the range of NNT to prevent one SCD was approximately 2.0 to 11. • Within-study subgroup analyses fail to support whether the value of ICD placement differs in subgroups of patients or based on different characteristics of facilities where ICDs are implanted.	High

Outcome	Study Design: No. Studies (N)	Findings	Strength of Evidence
Sustained ventricular tachyarrhythmia	0	• There is no evidence	Insufficient
Quality of life	ICD vs. no ICD RCT: 3 (1,825)	• The evidence failed to show a consistent effect of ICD placement on quality of life. • There is no evidence regarding subgroups.	Low
Early AEs (In-hospital)	RCT: 3 (3,867) Observational: 11 (356,515†) [overlapping cohorts]	• During hospitalization, 2.8–3.6% of patients have any adverse event. Serious adverse events occurred in 1.2–1.35% after ICD placement. • The most common specific adverse events were lead dislodgement (0.7–1.2%) and hematoma (0.8–1.1%). Other in-hospital adverse events occurred in ≤0.5% of patients receiving ICDs • Based on within-study subgroups analyses, there may be higher rates of adverse events among patients receiving dual-chamber ICDs, CRT-D, among older patients, women, and those with ESRD. Physicians and hospitals with lower volume of implantation and operators other than electrophysiologists may have more adverse events.	High
Late AEs (Out of hospital)	RCT: 3 (2,149) Observational: 28 reports of 22 independent cohorts (99,725‡)	• Device-related adverse events occurred in <0.1–6.4% of ICD patients during 2–49 month followup. • Other relatively common adverse events included lead malfunction (<0.1–3.9% during 1.5–40 month followup), infection (0.2–3.7% for 1.5–49 month followup), and thrombosis (0.2–2.9% for 1.5–49 month followup). • Based on within-study subgroup analyses, there may be more lead-related adverse events in women. There was no apparent difference in adverse events between CRT-D and ICD or between dual and single chamber ICDs.	Low
Inappropriate shock	RCT: 1 (249) Observational: 21 reports of 17 independent cohorts (212,063§)	• Inappropriate shock occurred in 3–21% of patients during 1–5 year followup. • Based on within-study subgroup analyses, there may be more inappropriate shocks among younger patients. There were mixed data on the difference in inappropriate shocks between dual and single chamber ICDs. Limited data show no apparent difference in inappropriate shocks between CRT-D and ICD, or between dual and single chamber ICDs.	Moderate

AE = adverse event, CI = confidence interval, CMS = Centers for Medicare and Medicaid Services, CRT-D = cardiac resynchronization therapy-defibrillator, ESRD = end stage renal disease, HR = hazard ration, ICD = implantable cardioverter–defibrillator, MI = myocardial infarction, No. =number, nRCS = nonrandomized comparative study, NYHA = New York Heart Association, RCT = randomized, controlled trial, SCD = sudden cardiac death.

† Largest independent N

‡ Largest independent N. Two large cohorts: N=38,992 (PMID 21795298), N=15,387 (PMID 19925609).

§ Largest independent N. One large cohort N=185,778 (PMID 21098452)

Overall, there is a high strength of evidence, with the RCTs and nRCSs showing a consistent and precise benefit of all-cause mortality reduction in selected patients undergoing ICD implantation for primary prevention of SCD compared to those being treated without ICD. The

patients who benefit have a combination of reduced LVEF, nonischemic cardiomyopathy and heart failure or a combination of reduced LVED, ischemic cardiomyopathy and at least 30 to 40 days after a MI or 3 months after revascularization. Meta-analysis of seven RCTs yielded a HR of 0.69 (95% CI 0.60, 0.79) for death. Followup ranged from 3 to 7 years. The reported Kaplan Meier curves generally found that the reduction in all-cause mortality with ICD was fairly stable over time. Across RCTs, the NNT to prevent one death at ranged from 6.2 (95% CI 4.0, 18) to 22 (95% CI 2.3, infinite) at the longest durations of followup (3 to 7 years). Three studies of patients who were not in the selected populations because their ICDs were implanted immediately after MI (IRIS[102] and DINAMIT[98]) or were undergoing CABG (CABG-Patch[163]) did not show a benefit with respect to all-cause mortality. Regarding the outcome SCD, meta-analysis of five studies (again excluding IRIS and DINAMIT) showed benefit from ICD use for reducing SCD (HR 0.37; 95% CI 0.26, 0.52) over the course of 2 to 6 years after implantation. Across RCTs, the NNT to prevent one arrhythmic death ranged from about 2 to 3 (approximate 95% CI 1.3, 16) to 11 (95% CI 1.3, infinite). The evidence suggests that the effect of ICD versus no ICD on SCD over time may increase beyond 2 or 3 years. The finding of a large benefit on SCD, which increased over time, contrasts with a smaller benefit for all-cause mortality, which remained constant over time. This suggests that there are competing risks for mortality in this population limiting the effectiveness of ICDs to reduce death.

Three RCTs of ICD versus no ICD examined QoL with a broad range of QoL measures, but no specific QoL measure was evaluated by more than a single trial. Two of the trials found no difference in QoL with various QoL tools (Health Utility Index 3, Quality of Well-being Schedule, and the State Trait Anxiety Inventory). The third trial found differences favoring no ICD for 2 out of 7 specific components of SF-36 and for perception of health transition. However, this latter trial is of limited applicability to current practice, both because all patients had CABG and because the trial implanted epicardial ICD systems which are much more invasive compared to the transvenous ICDs currently employed. Thus, given the sparseness of data on QoL and the lack of consistency across trials, overall, there is a low strength of evidence low strength of evidence that failed to show a consistent effect of ICD placement on QoL. There is insufficient evidence to evaluate differential effects of ICD on QoL in different populations of patients or based on different characteristics of facilities where ICDs are implanted.

Our analyses failed to show statistically significant differences for all-cause mortality or SCD across subgroups, including by meta-analysis. This contrasts with conclusions by others who proposed differential effects by age and sex. Two prior reviews have proposed no or less benefit from ICDs in women.[164,165] One other review concluded that ICDs may be less effective in older adults.[172] We believe that these conclusions were based on an over-reliance of within subgroup findings despite nonsignificant interaction tests, study selection (the MUSTT trial included in the review by Ghanbari was unfavorable for women), and lower precision due to women constituting only 23 percent of the study populations.[164,166] Our Table 5 and Figures 6 and 7 indicate that the studies consistently found no significant difference in effect between men and women (or other subgroups of patients). However there may be an indication that ICDs are more effective in patients with more distant coronary revascularization compared with recent surgery. Indirect review across studies suggests that patients with recent MIs (within 31 or 40 days) have no reduction in all-cause mortality in contrast with patients with more distant MIs. The evidence fails to support a difference in the benefit of ICD based on time since MI, coronary revascularization, or kidney disease. There is insufficient evidence to evaluate differential effects of ICD on all-cause mortality or SCD in based on different characteristics of clinicians

implanting ICDs or facilities where ICDs are implanted. Four RCTs examined the effect of adding CRT to ICD versus ICD alone. Two trials were too small to yield meaningful conclusions regarding death.[111,112] MADIT-CRT[167] found no difference in all-cause death in patients with ischemic or nonischemic cardiomyopathy. In contrast, RAFT found a significant 25 percent reduction in all-cause death with CRT-D in patients with NYHA Class II or III cardiomyopathy (but no difference in effect between Class II and III).[149] Given the inconsistencies between the two studies, there is insufficient evidence regarding how CRT-D and ICD alone compare to prevent all-cause death. Our review examined whether the addition of CRT to ICD impacts mortality. It is important to note that we did not include the review of other outcomes that may be affected by CRT, such as heart failure and related hospitalizations.

We found no study specifically examining the effect of ICD with ATP versus ICD alone for primary prevention. A prior trial compared ICDs with and without ATP for primary or secondary prevention patients and showed benefit for QOL.[57] ATP is now a standard software feature available in all modern transvenous ICD systems and can be readily activated by a clinician if deemed appropriate for any given patient. Thus the question of ATP versus no ATP is not as relevant. Instead the more important programming features which have been elucidated by MADIT-RIT are those of rate cut-off and detection delay in addition to the use of ATP.[168] MADIT-RIT is discussed in detail below in the section on excluded studies.

We reviewed study eligibility criteria and how the criteria compare to current CMS coverage criteria. Several trials excluded older adults (>70 years to 84 years), whereas two nRCSs included only older adults 65 to 84 years or ≥80 years. All studies used a LVEF criterion but different methods of ascertainment of the EF. IRIS[102] included patients with a LVEF <40 percent, but all other studies included only those with LVEF≤35 percent . The actual mean LVEF at baseline in all studies was below 30 percent. The studies were heterogeneous as to which NYHA Classes (I-IV) were included. The three trials comparing CRT-D versus ICD used QRS interval criteria which varied from≥130 ms in MADIT -CRT[167] ≥120 ms in Diab[112] 2011 and <120 ms in MENDMI.[111] Other approaches to risk stratification for SCD prior to ICD implantation varied across studies. MADIT was the only study that used formal electrophysiological testing.

Although this report's Key Questions did not cover the comparison of the patients in the eligible trials and patients enrolled in the National Cardiovascular Data Registry ICD Registry (NCDR), a recent publication partially does so for patients undergoing primary prevention ICD placement.[169] Masoudi et al. provide baseline characteristics data for NCDR, MADIT II, and SCD-HeFT. Although, they did not conduct direct comparisons, notable differences between the trials and NCDR include less frequent NYHA Class III (MADIT II 25% and SCD-HeFT 30%; NCDR 52%), less frequent hypertension (MADIT II 53% and SCD-HeFT 55%; NCDR 75%), less common LBBB (MADIT II 19%; NCDR 29%), and more digoxin use (MADIT II 57% and SCD-HeFT 67%; NCDR 29%). Compared to NCDR, the patients in the trials also had lower mean age (MADIT II 64 years and SCD-HeFT 60 years; NCDR 68 years), lower percentage of women (MADIT II 16% and SCD-HeFT 23%; NCDR 27%), and LVEF (MADIT II 23% and SCD-HeFT 24%; NCDR 25%),.

Six RCTs reported SCD in the control groups that were not assigned to ICD. They found SCD occurring in 4 to 13 percent of patients during 2 to 5 years after randomization. There was no clear trend for increasing rates of SCD with longer followup.

The benefits of ICDs have to be weighed against the risks. A high strength of evidence shows overall early in-hospital adverse event rates ranging from 2.8 to 3.6 percent and serious adverse

event rates ranging from 1.2 to 1.35 percent. The most common early adverse events are lead dislodgement (in 0.73 to 1.2% of patients) and hematoma (in 0.84 to 1.1% of patients). Higher rates of in-hospital adverse events have been shown in the following subgroups: patients implanted with dual-chamber ICDs or CRT-Ds (vs. single-chamber ICDs); patients who are older, female, or have ESRD; patients implanted by physicians with a lower implantation volume or by nonelectrophysiologists; and patients implanted at hospitals with a lower implantation volume.

Regarding late (out of hospital) adverse events, there is low strength of evidence that device-related adverse events (with variable definitions) occurred in <0.1 to 6.4 percent of patients for followup durations of 2 to 49 months. Lead-related adverse events occurred in <0.1 to 3.9 percent of patients with followup durations from 1.5 to 40 months, but in 7.0 to 19 percent of patients during longer followup (35 to 96 months). Based on moderate strength evidence, the percentage of patients who experienced at least one inappropriate shock ranged from 3 to 21 percent for followup between 1 and 5 years.

Generally, these risks from ICD identified in this review appear low. However, it is possible there is underreporting for hospital based complications, and a gross underestimation of complications after hospital discharge which are not systematically captured.

Comparison With Current Knowledge

Our findings for benefit from ICD implantation for primary prevention of SCD are consistent with those in the literature. A prior meta-analysis of the same seven RCTs we combined in our main analysis found a HR of 0.74 (95% CI 0.67, 0.83).[170] This estimate differs slightly from our estimate due to selecting different control arms from COMPANION[95] and SCD-HeFT.[51] Another meta-analysis restricted to five trials in individuals with nonischemic cardiomyopathy found a HR for mortality of 0.69 (95% CI 0.55, 0.87).[171]

The studies in our review failed to find statistically significant differences in effects across subgroups. Two prior reviews concluded that ICDs were ineffective or less effective in women and older adults.[164,165,172] However, these conclusions are based on a faulty reliance on nonstatistically significant findings in *post hoc* subgroups with relatively small sample sizes (women and older adults).

A retrospective cohort study of Medicare beneficiaries hospitalized with heart failure and LVEF ≤35 percent who were selected for ICD therapy had lower risk-adjusted long-term mortality compared with those who did not receive an ICD.[107] This study is susceptible to bias by indication.

Supplementary Evidence in Excluded Studies

Additional studies that did not meet inclusion criteria for our review supplement our findings. MUSTT was not included in the review, as it was not designed with the specific intention to test ICD therapy versus no ICD therapy for the primary prevention of SCD.[41] It compared treatment administered according to a risk stratification algorithm with electrophysiological testing, followed by antiarrhythmic therapy or ICD in those who failed antiarrhythmic therapy versus routine medical management without antiarrhythmic therapy. The risk of cardiac arrest or death from arrhythmia among the patients who received an ICD was significantly lower than that among the patients receiving no antiarrhythmic therapy (adjusted risk ratio [RR] 0.27; 95% CI 0.15, 0.47). The risk of death from all-causes was also significantly lower in patients who received an ICD than in those who received no antiarrhythmic therapy (adjusted RR 0.45; 95%

CI 0.32, 0.63). Those receiving medical antiarrhythmic therapy had the highest risk of all-cause mortality and SCD. The trial provided evidence that electrophysiologically guided antiarrhythmic therapy with ICDs reduces the risk of SCD in high-risk patients with CAD, LVEF ≤40 percent, spontaneous and unsustained VT, or sustained tachyarrhythmia induced by programmed stimulation.

Another study in individuals undergoing ICD implantation for primary prevention, MADIT-RIT, did not meet criteria for inclusion in Key Question 1, as it assessed the effect of different programming algorithms to avoid inappropriate ATP or shock therapy.[60] However, the trial's data on inappropriate shocks were included in the evidence base for Key Question 2. MADIT-RIT compared three arms with different programming approaches: one with higher rate cutoffs (with a 2.5 second delay before the initiation of therapy at a heart rate of ≥200 beats per minute), one of programming with longer delays (with a 60 second delay at 170 to 199 beats per minute, a 12 second delay at 200 to 249 beats per minute, and a 2.5 second delay at ≥250 beats per minute), and one of conventional programming (with a 2.5 second delay at 170 to 199 beats per minute and a 1.0 second delay at ≥200 beats per minute). The primary outcome measure was time to the first occurrence of inappropriate therapy, either inappropriate ATP or shock, and the secondary outcomes were all-cause mortality and syncope. The trial showed that programming a higher rate cutoff or a longer delay prior to ATP or shock therapy resulted in a lower rate of inappropriate therapy compared with conventional programming. Both interventional arms also had lower mortality for high-rate therapy versus conventional therapy (HR 0.45; 95% CI 0.24, 0.85 for high-rate therapy vs. conventional therapy; and HR 0.56; 95% CI 0.30, 1.02 for delayed therapy versus conventional therapy).

With regard to trials of CRT-D versus ICD, we did not include the Multicenter InSync ICD Randomized Clinical Evaluation trial (MIRACLE ICD),[173] the cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias trial (CONTAK-CD),[88] since these trials were not exclusively primary prevention trials. Although the Cardiac-Resynchronization Therapy in Heart Failure with Narrow QRS Complexes trial (RETHINQ) evaluated CRT-D versus ICD therapy, it was also not included in our review as there were no outcomes of interest.[174]

Applicability

The review of the eligibility criteria shows that the findings are applicable to selected individuals in the US and other high-resource countries, in particular individuals with nonischemic or ischemic cardiomyopathy and reduced LVEF (<30 to 35%). For patients with ischemic cardiomyopathy, the finding of benefit from ICD applies to those more than 30 to 40 days after MI and at least 3 months after revascularization.

Compared with the population of primary prevention therapy in the NCDR, the RCT populations of key trials were younger, less often women, and had had a lower burden of comorbidity.[169] The subgroup analyses showed no evidence to suggest different efficacy of ICDs in women or older adults. Nevertheless, how representative the trial findings are to the larger eligible Medicare population is an important question. Five out of seven comparative studies in the review provided subgroup data for those over 65 years. They showed that about a third to half of patients were 65 years or older, while the proportion in NCDR is well over 42%.[175] One cohort study followed Medicare Beneficiaries (median age 75 years) after primary ICD implantation and found a mortality at 3 years of follow up of 31%.[176] This was higher than in the major primary ICD trials SCD-HEFT (mean age 60 years, 3 year mortality 16%) and MADIT-II

(mean age 64 years, three year mortality 22%). However, almost half of the Medicare patients did not have previous heart failure hospitalizations and received an ICD on the admission day suggesting they were electively admitted for the procedure. In this subgroup, the mortality of 22% was similar to that of the large trials, despite the difference in mean ages. While most trials did not specify that patients were electively admitted for ICD implantation, this is assumed to be the case.[176] This suggests that the trial findings may apply to a sizeable proportion of Medicare patients.

The estimates for adverse events derive from studies with mixed populations (i.e., patients who received ICDs for primary or secondary prevention). One study found no statistically significant difference in the risk of an adverse event or death between patients with ICDs for primary and those with ICDs for secondary prevention, supporting the notion that the rate of procedure-related adverse events, which contribute the majority of adverse events, may be similar across primary and secondary populations.[117]

Limitations

Limitations of the evidence base in some RCTs include lack of blinding of outcome assessors of arrhythmia outcomes or SCD, high attrition rates (>20%), or differential rates of attrition and/or crossover between study groups and differences in the control treatments or in the rates of concomitant use of beta blockers between the study groups. Of note, all trials conducted intention-to-treat analyses. Nonsignificant subgroup analyses need to be interpreted in the context of studies likely being underpowered to explore differences in effects across subgroups of interest. At the same time, positive treatment effects within subgroups may represent spurious findings from multiple testing. The quality of the long-term adverse events suffered from a lack of harmonized definitions and systematic ascertainment. This review does not provide a complete assessment of the effectiveness of CRT. The intention of ICD therapy is restoration of normal sinus rhythm in the setting of life-threatening arrhythmias, and the intention of CRT is improvement of functional status and symptoms of heart failure. We did not include heart failure outcomes, which were primary outcomes of interest for the studies comparing CRT-D versus ICD as the focus of our review was prevention of SCD rather than management of heart failure. It is important to point out that study populations in ICD trials and CRT trials have overlapping characteristics but are not exactly the same. Research Gaps

The gaps in our current knowledge are large with regard to knowing which patients should be offered ICD with the expectation of improving meaningful survival. The rates of SCD in the non-ICD trial arms were not consistently reported. Consistent reporting would facilitate an assessment of how the mortality benefit may be correlated with the baseline risk. There is a great need for better risk stratification tools and their validation to better identify those patients who are most likely to benefit from ICD therapy. Some risk scores have been developed in clinical trials and may be used going forward towards reducing the risk of unnecessary ICD implantation. However, since most sudden deaths are not in patients with previously identified risk factors, there is a need explore risk prediction tools that extend beyond currently used trial inclusion criteria.

While it is beyond the scope of the current report, additional risk stratification tools are continually being examined, including measures of autonomic function such as T-wave alternans. This latter modality has been formally studied in a comparative analysis with EP testing in the ABCD (Alternans Before Cardioverter Defibrillator) Trial.[177] In addition, advances in magnetic resonance imaging (MRI) or genetic testing may be useful in the future.

Similarly, analyses of subgroups of patients who may particularly benefit (or derive no benefit) from ICD use are needed, especially when the etiology, pathophysiology and competing risks for death differ.To date, the analyses of subgroups are underpowered and inconclusive. A patient-level meta-analysis across major trials may be able to provide the power to adequately evaluate subgroups. Future trials should focus on elderly, women, who constitute only a minority in clinical ICD trials, and on patients with chronic kidney disease. We found no eligible studies in children, pointing to this group also requiring future study.

A research gap also exists in the area of primary prevention of SCD in familial or inherited conditions as well as less common cardiomyopathies including but not limited to long-QT syndrome, Brugada syndrome, catecholaminergic polymorphic VT, hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia, cardiac sarcoidosis, and left ventricle noncompaction. These disease states are less prevalent than ischemic cardiomyopathy and nonischemic dilated cardiomyopathy and were, in large part, implicitly or explicitly excluded from the studies in this review. In particular, patients with channelopathies have structurally normal hearts (i.e., those with normal LVEFs) but nonetheless, may have an elevated risk of SCD. Patients with hypertrophic cardiomyopathy generally have hyperdynamic ventricles until they reach the end stage of the disease process. Thus, many or most of these patients would have also been excluded in the RCTs to date. While there are research gaps for these patient groups, the low prevalence of some of these diseases presents challenges for conducting RCTs. The NCDR ICD database provides an opportunity to track these patients and describe their outcomes.

As mentioned above, the intent of this review was to address sudden cardiac death outcomes rather than heart failure outcomes. Since one of the primary goals of chronic resynchronization therapy is the improvement of heart failure, this issue was not completely addressed. Thus, a comparative effectiveness review of CRT warrants a separate review in order to address outcomes related to heart failure and mortality. In order to be comprehensive, CRT-P and CRT-D studies have to be included.

While there is robust information on adverse events immediately post implantation in the hospital, there are also large gaps in the knowledge about adverse events after the hospitalization for implantation and the impact on patient reported outcomes. This includes information on likelihood of lead complications needing revision, likelihood of both appropriate and inappropriate shocks, resulting distress from ICD shocks and impact on QoL. Another crucial issue that is uncertain is the impact of ICD on the quality of death, and the challenge to approach ICD inactivation to avoid undesired shocks at the end of life.

In an era of fast-paced technological advances, it is imperative to critically reevaluate the incremental net benefit and cost of evolving medical and device therapies. On September 28, 2012, the US Food and Drug Administration approved the first subcutaneous ICD, which incorporates a generator and a lead that is implanted below the skin along the bottom of the rib cage and breast bone, removing the need for fluoroscopic guidance and direct vascular or cardiac access. Data in support of the approval were from a 33-center trial involving 321 patients who underwent ICD implantation or were undergoing replacement for a transvenous ICD.[178] A postmarket study will follow 1,616 patients for 5 years.

Evolution in programming algorithms may also alter the benefits harms balance.[179] As discussed above, MADIT-RIT showed mortality benefit for programming algorithms which may be additive to the benefit of an ICD alone.

Conclusions

There is a high strength of evidence that ICD therapy for primary prevention of SCD, versus no ICD therapy, shows benefit with regard to mortality and SCD in selected patients with reduced LVEF and ischemic or nonischemic cardiomyopathy. There is low strength of evidence that the risk of all-cause mortality is similar for patients who receive CRT-Ds versus ICD alone for primary prevention. A high strength of evidence shows overall early in-hospital adverse event rates of approximately 3 percent and serious adverse event rates of approximately 1 percent. Low strength of evidence shows variable late adverse events. Moderate strength of evidence shows inappropriate shocks are experienced by 3 to 21 percent of patients over 1 and 5 years of followup.

Acronyms

ADRIA	A+ versus DR Clinical Investigation of Arrhythmia Discrimination
AHRQ	Agency for Healthcare Research and Quality
AMIOVERT	Amiodarone Versus Implantable Cardioverter-Defibrillator: Randomized Trial in Patients With Nonischemic Dilated Cardiomyopathy and Asymptomatic Nonsustained Ventricular Tachycardia [trial]
AVID	Antiarrhythmics Versus Implantable Defibrillators [trial]
ATP	antitachycardia pacing
CABG	coronary artery bypass grafting
CABG-Patch	Coronary Artery Bypass Graft Patch [trial]
CAD	coronary artery disease
CAMIAT	Canadian Amiodarone Myocardial Infarction Arrhythmia Trial
CASH	Cardiac Arrest Study Hamburg
CAST	Cardiac Arrhythmia Suppression Trial
CAT	Cardiomyopathy Trial
CI	Confidence interval
CIDS	Canadian Implantable Defibrillator Study
CMS	Centers for Medicare and Medicaid Services
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure [study]
CRT	cardiac resynchronization therapy
CRP-D	CRT with a biventricular defibrillator
CRT-P	CRT with a biventricular pacemaker (without a defibrillator)
DEFINITE	Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
ECG	Electrocardiograms
EMIAT	European Myocardial Infarction Amiodarone Trial
ESRD	End stage renal disease
EPC	Evidence-based Practice Center
GWTG-HF	Get With the Guidelines-Heart Failure [study]
HR	hazard ratio
ICD	implantable cardioverter–defibrillator
IRIS	Immediate Risk Stratification Improves Survival [trial]
ITT	Intention-to-Treat
LV	left ventricular
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MADIT II	Multicenter Automatic Defibrillator Implantation Trial II
MADIT-CRT	Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MENDMI	Prevention of Myocardial Enlargement and Dilation Post Myocardial Infarction [study]
MI	myocardial infarction
ms	millisecond(s)
NCDR	National Cardiovascular Data Registry
NNT	Number needed to treat
nRCS	nonrandomized comparative study
NYHA	New York Heart Association
OPTIMIZE-HF	Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure [study]
OR	odds ratio
QoL	quality of life
PCI	Percutaneous coronary intervention
RAFT	Resynchronization-Defibrillation for Ambulatory Heart Failure Trial

RCT	randomized controlled trial
RR	risk ratio
SA ECG	Signal Averaged ECG
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SRDR	Systematic Review Data Repository
TOO	Task Order Officer
VF	ventricular fibrillation
VT	ventricular tachycardia

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