Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

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<thead>
<tr>
<th>Policy Number:</th>
<th>Current Effective Date:</th>
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<tbody>
<tr>
<td>MM.06.025</td>
<td>December 20, 2019</td>
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<table>
<thead>
<tr>
<th>Lines of Business:</th>
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<tr>
<td>HMO; PPO; QUEST Integration</td>
<td>July 01, 2015</td>
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<thead>
<tr>
<th>Place of Service:</th>
<th>Precertification:</th>
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<tbody>
<tr>
<td>Inpatient, Outpatient</td>
<td>Not Required</td>
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I. Description
An implantable cardioverter defibrillator (ICD) is a device designed to monitor a patient's heart rate, recognize ventricular fibrillation or ventricular tachycardia, and deliver an electric shock to terminate these arrhythmias to reduce the risk of sudden death. A subcutaneous ICD (S-ICD), which lacks transvenous leads, is intended to reduce lead-related complications.

Transvenous ICDs
For individuals who have a high-risk of sudden cardiac death (SCD) due to ischemic or nonischemic cardiomyopathy in adulthood who receive transvenous ICD (TV-ICD) placement for primary prevention, the evidence includes multiple well-designed and well-conducted randomized controlled trials (RCTs) as well as systematic reviews of these trials. The relevant outcomes are overall survival (OS), morbid events, quality of life (QOL), and treatment-related mortality and morbidity. Multiple, well-done RCTs have shown a benefit in overall mortality for patients with ischemic cardiomyopathy and reduced ejection fraction. RCTs assessing early ICD use following recent myocardial infarction did not support a benefit for immediate vs delayed implantation for at least 40 days. For nonischemic cardiomyopathy, there is less clinical trial data, but pooled estimates of available evidence from RCTs enrolling patients with nonischemic cardiomyopathy and from subgroup analyses of RCTs with mixed populations have supported a survival benefit for this group. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a high-risk of SCD due to hypertrophic cardiomyopathy (HCM) in adulthood who receive TV-ICD placement for primary prevention, the evidence includes several large registry studies. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. In these studies, the annual rate of appropriate ICD discharge ranged from 3.6% to 5.3%. Given the long-term high-risk of SCD in patients with HCM, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of ICDs in patients with HCM. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a high-risk of SCD due to an inherited cardiac ion channelopathy who receive TV-ICD placement for primary prevention, the evidence includes small cohort studies of patients with these conditions treated with ICDs. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. The limited evidence for patients with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome has
reported high rates of appropriate shocks. No studies were identified on the use of ICDs for patients with short QT syndrome. Studies comparing outcomes between patients treated and untreated with ICDs are not available. However, given the relatively small patient populations with these channelopathies and the high-risk of cardiac arrhythmias, clinical trials are unlikely. Given the long-term high-risk of SCD in patients with inherited cardiac ion channelopathy, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of TV-ICDs in patients with inherited cardiac ion channelopathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had symptomatic life-threatening sustained ventricular tachycardia or ventricular fibrillation (VF) or who have been resuscitated from sudden cardiac arrest (secondary prevention) who receive TV-ICD placement, the evidence includes multiple well-designed and well-conducted RCTs as well as systematic reviews of these trials. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Systematic reviews of RCTs have demonstrated a 25% reduction in mortality for ICD compared with medical therapy. Analysis of data from a large administrative database has confirmed that this mortality benefit is generalizable to the clinical setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Subcutaneous ICDs
For individuals who need an ICD and have a contraindication to a TV-ICD but no indications for antibradycardia pacing and no antitachycardia pacing-responsive arrhythmias who receive S-ICD placement, the evidence includes nonrandomized studies and case series. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Nonrandomized controlled studies have reported success rates in terminating laboratory-induced VF that are similar to TV-ICD. Case series have reported high rates of detection and successful conversion of VF, and inappropriate shock rates in the range reported for TV-ICD. Given the need for ICD placement in this population at risk for SCD, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of S-ICDs in patients with contraindication to TV-ICD. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have need for an ICD and have no contraindication to TV-ICD but no indications for antibradycardia pacing and no antitachycardia pacing-responsive arrhythmias who receive S-ICD placement, the evidence includes nonrandomized studies and case series. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Nonrandomized controlled studies have reported success rates in terminating laboratory-induced VF that are similar to TV-ICD. However, there is scant evidence on comparative clinical outcomes of both types of ICD over longer periods. Case series have reported high rates of detection and successful conversion of ventricular tachycardia, and inappropriate shock rates in the range reported for TV-ICD. This evidence does not support conclusions on whether there are small differences in efficacy between the two types of devices, which may be clinically important due to the nature to the disorder being treated. Also, adverse event rates are uncertain, with variable rates reported. At least one RCT is currently underway comparing S-ICD with TV-ICD. The evidence is insufficient to determine the effects of the technology on health outcomes.
Clinical input was obtained in 2011 and 2015 on the use of ICDs in pediatric populations and for primary prevention in patients with cardiac ion channelopathies, and on the use of the S-ICD. For the use of ICDs in children with HCM or with a history of congenital heart disease, the evidence includes case series. These conditions have a low prevalence and heterogeneous patient populations, creating barriers to trials. There was a consensus that the use of ICDs in certain pediatric populations, consistent with specialty society guidelines, is medically necessary.

Indications for the use of ICDs to prevent SCD in HCM in pediatric patients parallel those in adults. There was also consensus that the use of an ICD should be considered medically necessary for primary prevention of ventricular arrhythmias in adults and children with a diagnosis of QTS, Brugada syndrome, short QT syndrome, or catecholaminergic polymorphic ventricular tachycardia.

Criteria for determining patients at high-risk of SCD for the cardiac ion channelopathies was derived from clinical input and specialty society guidelines. There was a consensus that the use of an S-ICD should be considered medically necessary, particularly for patients with indications for an ICD but who have difficult vascular access (e.g., children or patients undergoing chronic dialysis) or have had TV-ICD lead explantation due to complications.

II. Policy Criteria

The use of a subcutaneous ICD is covered (subject to Limitations and Administrative Guidelines) when all of the following criteria are met:

A. The patient has a contraindication to a transvenous ICD due to 1 or more of the following:
   1. Lack of adequate vascular access.
   2. Compelling reason to preserve existing vascular access (i.e., need for chronic dialysis; younger patient with anticipated long-term need for ICD therapy).
   3. History of need for explantation of a transvenous ICD due to a complication, with ongoing need for ICD therapy.

B. The patient does not have an indication for antibrady pacing.

C. The patient does not have ventricular arrhythmias known or anticipated to respond to antitachycardia pacing.

D. The patient has at least one of the following indications for an ICD:
   1. For primary prevention in an adult patient when one of the following criteria are met:
      a. Ischemic cardiomyopathy with New York Heart Association (NYHA) functional class II or III symptoms, a history of myocardial infarction at least 40 days before ICD treatment, and left ventricular ejection fraction of 35% or less.
      b. Ischemic cardiomyopathy with NYHA functional class I symptoms, a history of myocardial infarction at least 40 days before ICD treatment, and left ventricular ejection fraction of 30% or less.
      c. Nonischemic dilated cardiomyopathy and left ventricular ejection fraction of 35% or less, after reversible causes have been excluded, and the response to optimal medical therapy has been adequately determined.
      d. Hypertrophic cardiomyopathy (HCM) with 1 or more major risk factors for sudden cardiac death (history of premature HCM-related sudden death in ≥1 first-degree relatives younger than 50 years; left ventricular hypertrophy greater than 30 mm; ≥1 runs of nonsustained ventricular tachycardia at heart rates of ≥120 beats per minute on 24-hour Holter monitoring; prior unexplained syncope inconsistent with neurocardiogenic origin) and judged to be at high risk for sudden cardiac death by a physician experienced in the care of patients with HCM.
      e. Diagnosis of any one of the following cardiac ion channelopathies and considered to be at high risk for sudden cardiac death (see Policy Guidelines section):
Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

- congenital long QT syndrome; OR
- Brugada syndrome; OR
- short QT syndrome; OR
- catecholaminergic polymorphic ventricular tachycardia.

2. For secondary prevention in an adult patient with a history of a life-threatening clinical event associated with ventricular arrhythmic events such as sustained ventricular tachyarrhythmia, after reversible causes (eg, acute ischemia) have been excluded.

3. For a pediatric patient when one of the following criteria are met:
   a. Survivor of cardiac arrest, after reversible causes have been excluded.
   b. Symptomatic, sustained ventricular tachycardia in association with congenital heart disease in patients who have undergone hemodynamic and electrophysiologic evaluation.
   c. Congenital heart disease with recurrent syncope of undetermined origin in the presence of ventricular dysfunction or inducible ventricular arrhythmias.
   d. HCM with 1 or more major risk factors for sudden cardiac death (history of premature HCM-related sudden death in ≥1 first-degree relatives <50 years; massive left ventricular hypertrophy based on age-specific norms; prior unexplained syncope inconsistent with neurocardiogenic origin) and judged to be at high risk for sudden cardiac death by a physician experienced in the care of patients with HCM.
   e. Diagnosis of any one of the following cardiac ion channelopathies and considered to be at high risk for sudden cardiac death (see Policy Guidelines):
      - congenital long QT syndrome; OR
      - Brugada syndrome; OR
      - short QT syndrome; OR
      - catecholaminergic polymorphic ventricular tachycardia.

III. Policy Guidelines

This evidence review addresses the use of implantable cardioverter defibrillator (ICD) devices as stand-alone interventions, not as combination devices to treat heart failure (ie, cardiac resynchronization devices) or in combination with pacemakers. Unless specified, the policy statements and rationale refer to transvenous ICDs.

Indications for pediatric ICD use are based on American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) guidelines published in 2008 (updated in 2012), which acknowledged the lack of primary research on pediatric patients in this field (see Rationale section). These indications derive from nonrandomized studies, extrapolation from adult clinical trials, and expert consensus.

Criteria for ICD Implantation in Patients With Cardiac Ion Channelopathies

Individuals with cardiac ion channelopathies may have a history of a life-threatening clinical event associated with ventricular arrhythmic events such as sustained ventricular tachyarrhythmia, after reversible causes, in which case they should be considered for ICD implantation for secondary prevention, even if they do not meet criteria for primary prevention.

Criteria for ICD placement in patients with cardiac ion channelopathies derive from results of clinical input, a 2013 consensus statement from the HRS, European Heart Rhythm Association (EHRA), and the Asia-Pacific Heart Rhythm Society on the diagnosis and management of patients with inherited primary arrhythmia syndromes (Priori et al [2013]), 2017 guidelines from ACC, AHA,
and HRS on the management of heart failure (Al-Khatib et al [2017]), and a report from the HRS and EHRA’s Second Consensus Conference on Brugada syndrome.

Indications for consideration for ICD placement for each cardiac ion channelopathy are as follows:

- **Long QT syndrome (LQTS):**
  - Patients with a diagnosis of LQTS who are survivors of cardiac arrest
  - Patients with a diagnosis of LQTS who experience recurrent syncopal events while on β-blocker therapy.

- **Brugada syndrome (BrS):**
  - Patients with a diagnosis of BrS who are survivors of cardiac arrest
  - Patients with a diagnosis of BrS who have documented spontaneous sustained ventricular tachycardia (VT) with or without syncope
  - Patients with a spontaneous diagnostic type 1 electrocardiogram (ECG) who have a history of syncope, seizure, or nocturnal agonal respiration judged to be likely caused by ventricular arrhythmias (after noncardiac causes have been ruled out)
  - Patients with a diagnosis of BrS who develop ventricular fibrillation during programmed electrical stimulation.
  - Patients with a diagnosis of CPVT who are survivors of cardiac arrest
  - Patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or left cardiac sympathetic denervation.

- **Catecholaminergic polymorphic ventricular tachycardia (CPVT):**
  - Patients with a diagnosis of CPVT who are survivors of cardiac arrest
  - Patients with a diagnosis of CPVT who experience recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or left cardiac sympathetic denervation.

- **Short QT syndrome (SQTS):**
  - Patients with a diagnosis of SQTS who are survivors of cardiac arrest
  - Patients with a diagnosis of SQTS who are symptomatic and have documented spontaneous VT with or without syncope
  - Patients with a diagnosis of SQTS or are asymptomatic or symptomatic and have a family history of sudden cardiac death.

**NOTE:** For congenital LQTS, patients may have 1 or more clinical or historical findings other than those outlined above that could, alone or in combination, put them at higher risk for sudden cardiac death. They can include patients with a family history of sudden cardiac death due to LQTS, infants with a diagnosis of LQTS with functional 2:1 atrioventricular block, patients with a diagnosis of LQTS in conjunction with a diagnosis of Jervell and Lange-Nielsen syndrome or Timothy syndrome, and patients with a diagnosis of LQTS with profound QT prolongation (>550 ms). These factors should be evaluated on an individualized basis by a clinician with expertise in LQTS when considering the need for ICD placement.

**IV. Limitations**

A. The use of a subcutaneous ICD is not covered, as it is not known to be effective in improving health outcomes for individuals who do not meet the criteria outlined above (see II.A).

B. The use of the ICD is not indicated, as it is not known to be effective in improving health outcomes in primary prevention in adult patients who:
1. Have had an acute myocardial infarction (ie, <40 days before ICD treatment);
2. Have NYHA class IV congestive heart failure (unless patient is eligible to receive a combination cardiac resynchronization therapy ICD device);
3. Have had a cardiac revascularization procedure in past 3 months (coronary artery bypass graft or percutaneous transluminal coronary angioplasty) or are candidates for a cardiac revascularization procedure; OR
4. Have noncardiac disease that would be associated with life expectancy less than 1 year.

C. The use of the ICD for secondary prevention is not indicated as it is not known to be effective in improving health outcomes for adult patients who do not meet the criteria for secondary prevention (see II.D.2).

D. The use of the ICD is not indicated, as it is not known to be effective in improving health outcomes for pediatric patients who do not meet the above criteria (see II.D.3.a-e).

V. Administrative Guidelines

Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

Documentation supporting that the payment determination criteria were met should be maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
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<tr>
<td>33241</td>
<td>Removal of implantable defibrillator pulse generator only</td>
</tr>
<tr>
<td>33270</td>
<td>Insertion or replacement of permanent subcutaneous implantable defibrillator system, with subcutaneous electrode, including defibrillation threshold evaluation, induction of arrhythmia, evaluation of sensing for arrhythmia termination, and programming or</td>
</tr>
<tr>
<td>33271</td>
<td>Insertion of subcutaneous implantable defibrillator electrode</td>
</tr>
<tr>
<td>33272</td>
<td>Removal of subcutaneous implantable defibrillator electrode</td>
</tr>
<tr>
<td>33273</td>
<td>Repositioning of previously implanted subcutaneous implantable defibrillator electrode</td>
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<td>93282-93284</td>
<td>Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional, codes specific to the type of device</td>
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<td>93260</td>
<td>Programming device evaluation (in person) with iterative adjustment of the implantable device to test the function of the device and select optimal permanent programmed values with analysis, review and report by a physician or other qualified health care professional; implantable subcutaneous lead defibrillator system</td>
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<td>93261</td>
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<td>93289</td>
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<tr>
<td>93640-93644</td>
<td>Electrophysiologic evaluation; codes specific to the type of device</td>
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VI. Scientific Background

Ventricular Arrhythmia and Sudden Cardiac Death

The risk of ventricular arrhythmia and SCD may be significantly increased in various cardiac conditions such as ischemic cardiomyopathy, particularly when associated with reduced left ventricular ejection fraction and prior myocardial infarction; nonischemic dilated cardiomyopathy with reduced left ventricular ejection fraction; hypertrophic cardiomyopathy and additional risk factors; congenital heart disease, particularly with recurrent syncope; and cardiac ion channelopathies.

Treatment

Implantable cardioverter defibrillators (ICDs) monitor a patient's heart rate, recognize ventricular fibrillation or ventricular tachycardia (VT), and deliver an electric shock to terminate these arrhythmias to reduce the risk of SCD. Indications for ICD placement can be broadly subdivided into (1) secondary prevention, ie, use in patients who have experienced a potentially life-threatening episode of VT (near SCD); and (2) primary prevention, ie, use in patients who are considered at high-risk for SCD but who have not yet experienced life-threatening VT or ventricular fibrillation.

The standard ICD placement surgery involves placement of a generator in the subcutaneous tissue of the chest wall. Transvenous leads are attached to the generator and threaded intravenously into the endocardium. The leads sense and transmit information on cardiac rhythm to the generator, which analyzes the rhythm information and produces an electrical ventricular fibrillation shock when a malignant arrhythmia is recognized.

A subcutaneous ICD (S-ICD) has been developed. It does not use transvenous leads and thus avoids the need for venous access and complications associated with the insertion of venous leads. Rather, the S-ICD uses a subcutaneous electrode implanted adjacent to the left sternum. The electrodes sense the cardiac rhythm and deliver countershocks through the subcutaneous tissue of the chest wall.

Several automatic ICDs have been approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process. The FDA-labeled indications generally include patients who have experienced life-threatening VT associated with cardiac arrest or VT associated with hemodynamic compromise and resistance to pharmacologic treatment. Also, devices typically have approval in the secondary prevention setting for patients with previous myocardial infarction and reduced ejection fraction.

Regulatory Status

Transvenous Implantable Cardioverter Defibrillators

A large number of ICDs have been approved by the FDA through the premarket approval (PMA) process (FDA product code: LWS). A 2014 review of the FDA approvals of cardiac implantable devices reported that, between 1979 and 2012, the FDA approved 19 ICDs (7 pulse generators, 3 leads, 9 combined systems) through new PMA applications. Many originally approved ICDs have received multiple supplemental applications. A selective summary of some currently available ICDs is provided in Table 1.

Subcutaneous ICDs

In 2012, the Subcutaneous Implantable Defibrillator (S-ICD™) System was approved by the FDA through the PMA process for the treatment of life-threatening ventricular tachyarrhythmias in
patients who do not have symptomatic bradycardia, incessant VT, or spontaneous, frequently recurring VT that is reliably terminated with antitachycardia pacing (see Table 1).

In 2015, the Emblem™ S-ICD (Boston Scientific), which is smaller and longer-lasting than the original S-ICD, was approved by the FDA through the PMA supplement process.

### Table 1. Implantable Cardioverter Defibrillators With FDA Approval

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Original PMA Approval Date</th>
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<tbody>
<tr>
<td>Transvenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellipse™/Fortify Assura™ Family (originally: Cadence Tiered Therapy Defibrillation System)</td>
<td>St. Jude Medical</td>
<td>Jul 1993</td>
</tr>
<tr>
<td>Dynagen™, Inogen™, Origen™, and Teligen® Family (originally: Ventak, Vitality, Cofient family)</td>
<td>Boston Scientific</td>
<td>Jan 1998</td>
</tr>
<tr>
<td>Evera™ Family (originally: Virtuosos/Entrust/Maximo/Intrisic/Marquis family)</td>
<td>Medtronic</td>
<td>Dec 1998</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subcutaneous Implantable Defibrillator System (S-ICD™)</td>
<td>Cameron Health; acquired by Boston Scientific</td>
<td>Sep 2012</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; PMA: premarket application.

NOTE: ICDs may be combined with other pacing devices, such as pacemakers for atrial fibrillation, or biventricular pacemakers designed to treat heart failure. This evidence review addresses ICDs alone when used solely to treat patients at risk for ventricular arrhythmias.

**Rationale**

This evidence review was created in March 1996 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through March 21, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.
Transvenous Implantable Cardioverter Defibrillators

Clinical Context and Therapy Purpose

The purpose of TV-ICD placement is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a high-risk of sudden cardiac death (SCD) due to ischemic cardiomyopathy in adulthood.

The question addressed in this evidence review is: Do ICDs improve the net health outcome in individuals with ischemic cardiomyopathy in adulthood who are at high-risk of cardiac death?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with a high-risk of SCD due to ischemic cardiomyopathy in adulthood who are at high-risk of sudden cardiac arrest.

Interventions

The therapy being considered is TV-ICD placement. An ICD is a device designed to monitor a patient’s heart rate, recognize ventricular fibrillation or ventricular tachycardia, and deliver an electric shock to terminate these arrhythmias to reduce the risk of sudden death. Patients with a high-risk of SCD due to ischemic cardiomyopathy in adulthood are actively managed by cardiologists, cardiovascular surgeons, neurologists, and primary care providers in an inpatient clinical setting.

Comparators

Comparators of interest include medical management without ICD placement. Guideline based medical management for ischemic cardiovascular disease including antihypertensive therapy and antiarrhythmic medications. These are managed by cardiologists and primary care providers in an outpatient clinical setting.

Outcomes

The general outcomes of interest are overall survival (OS), morbid events, QOL, treatment-related mortality, and treatment-related morbidity.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
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<tbody>
<tr>
<td>Quality of life</td>
<td>Can be assessed patient reported data such as surveys and questionnaires</td>
<td>1 week to 5 years</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Can be assessed rates of adverse events, including inappropriate shock, lead failure, infection, and other complications</td>
<td>1 week to 5 years</td>
</tr>
</tbody>
</table>

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought. Studies with duplicative or overlapping populations were excluded.

**Primary Prevention in Adults**
TV-ICDs have been evaluated for primary prevention in a number of populations considered at high-risk of SCD, including those with ischemic cardiomyopathy, nonischemic dilated cardiomyopathy (NIDCM), and hypertrophic cardiomyopathy (HCM). There is a large body of evidence, including a number of RCTs and systematic reviews of these trials, addressing the role of ICDs for primary prevention and identifying specific populations who may benefit.

**Ischemic Cardiomyopathy and NIDCM**

Randomized Controlled Trials
At least 13 RCTs of ICDs for primary prevention have been conducted. Five were in populations with ischemic cardiomyopathy with prior myocardial infarction (MI; usually ≥3 weeks post-MI):
- Multicenter Automatic Defibrillator Implantation Trial (MADIT);
- MADIT II;
- Coronary Artery Bypass Graft (CABG) Patch trial;
- Multicenter Unsustained Tachycardia Trial (MUSTT); and
- Sudden Cardiac Death in Heart Failure (SCD HeFT) trial.

Three trials were conducted in patients implanted with ICD in the first few weeks following MI (recent MI):
- Defibrillator in Acute Myocardial Infarction Trial (DINAMIT);
- Immediate Risk Stratification Improves Survival (IRIS) trial; and
- BETA-blocker STRategy plus ICD (BEST-ICD) trial.

Six trials were conducted in populations with NIDCM:
- Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial;
- Amiodarone Versus Implantable Cardioverter-Defibrillator (AMIOVIRT) trial;
- Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial;
- SCD HeFT trial;
- Cardiomyopathy Trial (CAT); and
- Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality (DANISH).

The characteristics and mortality results for these three groups of trials are shown in Table 3. Most trials for both ischemic and nonischemic cardiomyopathy have reported results consistent with a mortality benefit for ICD in patients with left ventricular systolic dysfunction or with heart failure and reduced ejection fraction, although not all trials were powered for the mortality outcome and some findings were not statistically significant. However, the DINAMIT, IRIS, and BEST-ICD trials did not support a mortality benefit for ICD in the early weeks following MI, and CABG Patch showed no benefit in patients having recently undergone coronary revascularization. Another notable exception is the 2016 DANISH trial, which enrolled primarily outpatients with nonischemic cardiomyopathy (NICM) in stable condition who were almost all receiving b-blocker or angiotensin-converting enzyme inhibitors, with the majority also receiving mineralocorticoid-
receptor antagonists. While overall mortality did not differ significantly between the ICD and medical therapy groups in DANISH, SCD was significantly reduced in the ICD group (4% vs 8%; hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.31 to 0.82).

Table 3. Characteristics and Results of RCTs of ICDs for Primary Prevention

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Treatment Groups</th>
<th>Mean Follow-Up</th>
<th>Mortality Results</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Group</td>
<td>N</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICM with prior MI</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>
| MADIT (1996)   | • LVEF ≤35%  
• Asymptomatic non-SVT  
• MI ≥3 wk prior  
• Inducible VT  
• NYHA class I-III | • ICD  
• Standard therapy | 95  
101           | 27 mo (trial stopped early by DSMB) | 0.46  
0.26 to 0.82  |
| MADIT II (2002) | • LVEF ≤30%  
• No history of VT  
• MI ≥1 mo prior  
• NYHA class I-III | • ICD  
• Standard therapy | 742  
490           | 20 mo (trial stopped early by DSMB) | 0.69  
0.51 to 0.93  |
| CABG Patch (1997) | • Scheduled for CABG  
• LVEF ≤35%  
• No sustained VT or VF  
• Signal-averaged ECG abnormalities  
• 82% had prior MI, time since MI not reported | • ICD during CABG  
• No ICD | 446  
454           | 32 mo | 1.07  
0.81 to 1.42  |
| MUSTT (1999)   | • LVEF ≤40%  
• Asymptomatic non-SVT  
• Inducible VT  
• MI ≥4 d prior (median, ≥3 y prior)  
• No sustained VT | • EPS-guided therapy  
(AAD with or without ICD) (202 got ICD)  
• Standard therapy | 351  
353           | 39 mo | 5-y outcomes:  
EPS-guided vs standard therapy: 0.80  
ICD vs AAD alone: 0.42 | 0.64 to 1.01  
0.29 to 0.61 |
<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnoses</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCD HeFT (2005)</td>
<td>LVEF ≤35% • NYHA class II-III • No asymptomatic VT • 52% received ICM •</td>
<td>Ischemic patients: • ICD • Amiodarone • Placebo</td>
<td>45 mo</td>
<td>ICD vs placebo • Ischemic: 0.79a Overall: 0.77a</td>
</tr>
<tr>
<td></td>
<td>Treated with ACE inhibitors and b-blockers</td>
<td></td>
<td></td>
<td>0.60 to 1.04 • 0.62 to 0.96</td>
</tr>
<tr>
<td>ICM with recent MI</td>
<td>LVEF ≤35% • NYHA class I-III • MI in preceding 6-40 d (mean, 18 d) •</td>
<td>ICD • Standard therapy</td>
<td>332 342 30 mo</td>
<td>1.08 • 0.76 to 1.55</td>
</tr>
<tr>
<td></td>
<td>Reduced HR variability or elevated resting HR</td>
<td></td>
<td></td>
<td>0.76 to 1.55</td>
</tr>
<tr>
<td>DINAMIT (2004)</td>
<td>LVEF ≤35% • NYHA class I-III • MI in preceding 6-40 d (mean, 18 d) •</td>
<td>ICD • Standard therapy</td>
<td>445 453 37 mo</td>
<td>1.04 • 0.81 to 1.35</td>
</tr>
<tr>
<td></td>
<td>MI in preceding 5-31 d • At least 1 of the following: • oLVEF ≤40% and</td>
<td></td>
<td></td>
<td>0.81 to 1.35</td>
</tr>
<tr>
<td></td>
<td>MI in preceding 5-30 d • At least 1 other risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRIS (2009)</td>
<td>LVEF ≤35% • NYHA class I-III • MI in preceding 5-30 d • At least 1 other</td>
<td>ICD • Standard therapy</td>
<td>79 540 d 1-year mortality</td>
<td>14% • EPS-guided therapy: 18% 2-y mortality</td>
</tr>
<tr>
<td></td>
<td>risk factor</td>
<td></td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>BEST-ICD (2005)</td>
<td>LVEF ≤35% • NYHA class I-III • MI in preceding 5-30 d • At least 1 other</td>
<td>EPS-guided therapy (24 got ICD) • Standard therapy</td>
<td>1-year</td>
<td>14% • EPS-guided therapy: 18% 2-y mortality</td>
</tr>
<tr>
<td></td>
<td>risk factor</td>
<td></td>
<td>mortality</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Inclusion Criteria</td>
<td>Intervention</td>
<td>Follow-up</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------</td>
</tr>
<tr>
<td><strong>Nonischemic cardiomyopathy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>DEFINITE</strong> (2004)</td>
<td>• LVEF ≤35% • NYHA class II-IV</td>
<td>• ICD and medical therapy • Medical therapy alone</td>
<td>229</td>
<td>0.65 (0.40 to 1.06)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonischemic patients: • ICD • Amiodarone • Placebo</td>
<td>398</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>419</td>
<td>394</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SCD HeFT</strong> (2005)</td>
<td>• LVEF ≤35% • NYHA class II-III • No asymptomatic SVT • 48% with non-ICM • Treated with ACE inhibitor and b-blocker</td>
<td>Nonischemic patients: • ICD • Amiodarone • Placebo</td>
<td>270</td>
<td>0.73 (^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>127</td>
<td>Overall: 0.77 (^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>285</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>16 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>COMPANION</strong> (2004)</td>
<td>• LVEF ≤35% • NYHA class III-IV • DCM</td>
<td>Nonischemic patients: • CRT-D • Medical therapy • CRT</td>
<td>51</td>
<td>2 yr 1-y survival (^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>52</td>
<td>ICD: 96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amiodarone: 90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-γ survival (^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICD: 88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Amiodarone: 87%</td>
</tr>
<tr>
<td><strong>AMIOVIRT</strong> (2003)</td>
<td>• LVEF ≤35% • NYHA class I-III • DCM • Asymptomatic non-SVT</td>
<td>• ICD • Amiodarone</td>
<td>50</td>
<td>23 mo (trials stopped early due to low event rates)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>54</td>
<td>ICD: 4 deaths (8%) (^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control: 2 deaths (3.7%)</td>
</tr>
<tr>
<td><strong>CAT</strong> (2002)</td>
<td>• LVEF ≤30% • NYHA class II-III • No symptomatic VT, VF, or bradycardia • Recent-onset DCM</td>
<td>• ICD • Control</td>
<td>556</td>
<td>5.6 yr (^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>560</td>
<td>Overall: 0.68 to 1.12</td>
</tr>
<tr>
<td><strong>DANISH</strong> (2016)</td>
<td>• LVEF ≤35% • NYHA class II-IV • 58% received CRT • Almost all patients on ACE</td>
<td>• ICD and medical therapy • Medical therapy</td>
<td>556</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>560</td>
<td></td>
</tr>
</tbody>
</table>
inhibitors or b-blockers; »60% treated with mineralocorticoid-receptor antagonist

AAD: antiarrhythmic drugs; ACE: angiotensin-converting enzyme; CABG: coronary artery bypass grafting; CI: confidence interval; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy implantable cardioverter defibrillator; DCM: dilated cardiomyopathy; DSMB: Data Safety Monitoring Board; ECG: electrocardiogram; EPS: electrophysiologic study; HR: heart rate; ICD: implantable cardioverter defibrillator; ICM: ischemic cardiomyopathy; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; RCT: randomized controlled trial; SVT: sustained ventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.

a 97.5% CI.
b Relative risk.
c Median.
d Hazard ratio not given, no significant differences.

Systematic Reviews
Woods et al (2015) published an individual patient data network meta-analysis of primary prevention RCTs evaluating implantable cardiac devices, including studies of patients with heart failure and reduced ejection fraction and excluding studies of patients with recent MI or coronary revascularization. The COMPANION, DEFINITE, MADIT, MADIT II, SCD HeFT, AMIOVIRT, and CAT trials were included, representing 6134 patients for the direct ICD comparisons and 12638 patients overall.

Subsequent systematic reviews and meta-analyses of ICD trials in NICM incorporated the 2016 DANISH trial results. Two reviews published in 2017 included the CAT, AMIOVIRT, DEFINITE, SCD HeFT, COMPANION, and DANISH trials; other reviews included all but the COMPANION trial. All reviews have concluded that there was a statistically significant overall reduction in mortality for ICD vs medical therapy, ranging from 20% to 23%, even with the inclusion of the null DANISH results.

The risk for death varies by age, sex, and clinical characteristics such as LVEF and time since revascularization and comorbid conditions (eg, diabetes, kidney disease). Meta-analyses have examined whether there is a beneficial effect on mortality of ICD in these subgroups. Earley et al (2014) conducted a review of evidence for the Agency for Healthcare Research and Quality on use of ICD across important clinical subgroups. Reviewers included 10 studies that provided subgroup analyses. Subgroup data were available from at least 4 studies for sex, age (<65 years vs ≥65 years), and QRS interval (<120 ms vs ≥120 ms); they were combined to calculate a relative odds ratio using random-effects meta-analyses. Other comparisons of subgroups were not meta-analyzed because too few studies compared them; however, no consistent differences between subgroups were found across studies for diabetes. The Woods et al (2015) individual patient data network meta-analysis (described previously) also examined ICD and medical therapy in various subgroups, and similarly concluded that ICD reduced mortality in patients with heart failure and reduced ejection for QRS interval less than 120 ms, 120 to 149 ms, and 150 ms or higher, ages less than 60 and 60 and older, and for men. However, the effect on mortality in women was not statistically significant (HR=0.93; 95% CI, 0.73 to 1.18).
Table 4. Characteristics of Systematic Reviews & Meta-Analysis of ICDs for Primary Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woods (2015)</td>
<td>1990-2010</td>
<td>13</td>
<td>Patients with heart failure who received ICD</td>
<td>12,638 (17–2,521)</td>
<td>RCT</td>
<td>NR</td>
</tr>
<tr>
<td>Earley (2014)</td>
<td>1996-2010</td>
<td>14</td>
<td>Adults eligible to receive an ICD for primary prevention of SCD</td>
<td>NR</td>
<td>RCT, Nonrandomized comparative studies</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR: not reported; ICD: implantable cardioverter defibrillator; RCT: randomized controlled trial; SCD: sudden cardiac death.

Table 5. Results of Systematic Reviews & Meta-Analysis of ICDs for Primary Prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.71 (CI 0.63–0.80)</td>
</tr>
<tr>
<td>Earley (2014)</td>
<td>Mortality Benefit of Variables (ROR)</td>
</tr>
<tr>
<td>Sex</td>
<td>0.95 (CI 0.75–1.27)</td>
</tr>
<tr>
<td>Age</td>
<td>0.93 (CI 0.73–1.20)</td>
</tr>
<tr>
<td>QRS interval</td>
<td>1.13 (CI 0.82–1.54)</td>
</tr>
</tbody>
</table>

MT: medical therapy; CI: 95% confidence interval; ROR: relative odds ratio; ICD: implantable cardioverter defibrillator.

Registry Studies
Fontenla et al (2016) reported on results from the Spanish UMBRELLA Registry, a multicenter, observational, prospective nationwide registry of 1514 patients implanted with Medtronic ICDs equipped with remote monitoring (NCT01561144) who were enrolled between 2012 and 2013. Mean age was 64 years; 82% of the patients were men; and 65% received an ICD for primary prevention. Fifty-one percent of the patients had ischemic heart disease, 30% had NICM, 7% had HCM, 3% had Brugada syndrome (BrS), and 1.4% had long QT syndrome (LQTS). Mean follow-up was 26 months. The cumulative incidence of sustained ventricular arrhythmias was 15% (95% CI, 13% to 16%) at 1 year, 23% (95% CI, 21% to 25%) at 2 years, and 31% (95% CI, 28% to 34%) at 3 years. Thirteen percent of the episodes of sustained ventricular arrhythmias self-terminated and did not require shocks. One hundred seventy-five (12%) patients had 482 appropriate shocks, and 76 (5%) patients had 190 inappropriate shocks.

High-Risk HCM
Schinkel et al (2012) conducted a systematic review and meta-analysis of 27 observational studies (16 cohorts, 2190 patients) reporting outcomes after ICD therapy for HCM. Most patients (83%) received an ICD for primary prevention of SCD. Mean age was 42, 38% of patients were women, and patients had a mean of 1.8 risk factors for SCD. With a mean follow-up of 3.7 years, 14% of patients had an appropriate ICD intervention with an annualized rate of 3.3%. Twenty percent of patients had an inappropriate ICD intervention, for an annualized rate of 4.8%. The annualized cardiac mortality rate was 0.6%, the noncardiac mortality rate was 0.4%, and heart transplantation rate was 0.5%.

Magnusson et al (2015) reported on outcomes for 321 patients with HCM treated with an ICD and enrolled in a Swedish registry. Over a mean follow-up of 5.4 years, appropriate ICD discharges in response to ventricular tachycardia (VT) or ventricular fibrillation (VF) occurred in 77 (24%) patients, corresponding to an annual rate of appropriate discharges of 5.3%. At least 1 inappropriate shock occurred in 46 (14.3%) patients, corresponding to an annualized event rate of
3.0%. Ninety-two (28.7%) patients required at least 1 surgical intervention for an ICD-related complication, with a total of 150 ICD-related reinterventions. Most reinterventions (n=105 [70%]) were related to lead dysfunction.

**Inherited Cardiac Ion Channelopathy**
ICDs have been used for primary and secondary prevention in patients with a number of hereditary disorders (also called cardiac ion channelopathies) that predispose to ventricular arrhythmias and SCD, including LQTS, BrS, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia (CPVT). Some of these conditions are extremely rare. Use of ICDs has been described in small cohorts of patients with LQTS, BrS, and CPVT.

**Long QT Syndrome**
Horner et al (2010) reported on outcomes for 51 patients with genetically confirmed LQTS treated with an ICD from 2000 to 2010 who were included in a single-center retrospective analysis of 459 patients with genetically confirmed LQTS.24, Of patients treated with ICDs (84%) received the device as primary prevention. Twelve (24%) patients received appropriate VF or torsades de pointes-terminated ICD shocks. Factors associated with appropriate shocks included secondary prevention indications (p=0.008), QT corrected duration greater than 500 ms (p<0.001), non-LQT3 genotype (p=0.02), documented syncope (p=0.05), documented torsades de pointes (p=0.003), and a negative sudden family death history (p<0.001). Inappropriate shocks were delivered in 15 (29%) patients. Patients with the LQT3 genotype only received inappropriate shocks.

**Brugada Syndrome**
Hernandez-Ojeda et al (2017) reported on results from a single-center registry of 104 patients with BrS who were treated with ICDs.25, Ten (9.6%) patients received an ICD for secondary prevention and in 94 (90.4%) patients received an ICD for primary prevention. During an average 9.3-year follow-up, 21 (20.2%) patients received a total of 81 appropriate shocks. In multivariate analysis, type 1 electrocardiogram with syncope and secondary prevention indication were significant predictors of appropriate therapy. Nine (8.7%) patients received 37 inappropriate shocks. Twenty-one (20.2%) patients had other ICD-related complications. Conte et al (2015) described outcomes for a cohort of 176 patients with spontaneous or drug-induced Brugada type 1 electrocardiographic (ECG) findings who received an ICD at a single institution and were followed for at least 6 months. Before ICD implantation, 14.2% of subjects had a history of aborted SCD due to sustained spontaneous ventricular arrhythmias, 59.7% had at least 1 episode of syncope, and 25.1% were asymptomatic. Over a mean follow-up of 83.8 months, 30 (17%) patients had spontaneous sustained ventricular arrhythmias detected. Sustained ventricular arrhythmias were terminated by ICD shocks in 28 (15.9%) patients and antitachycardia pacing in 2 (1.1%) patients. However, 33 (18.7%) patients experienced inappropriate shocks. Dores et al (2015) reported on results of a Portuguese registry that included 55 patients with BrS, 36 of whom were treated with ICDs for primary or secondary prevention. Before ICD placement, 52.8% of subjects were asymptomatic, 30.6% had a history of syncope with suspected arrhythmic cause, and 16.7% had a history of aborted SCD. Over a mean follow-up of 74 months, 7 patients experienced appropriate shocks, corresponding to an incidence rate of 19.4% and an annual event rate of 2.8%. In multivariable analysis, predictors of appropriate shocks were a history of aborted SCD (HR=7.87; 95% CI, 1.27 to 49.6; p=0.027) and nonsustained VT during follow-up (HR=6.73; 95% CI, 1.27 to 35.7; p=0.025).
Catecholaminergic Polymorphic Ventricular Tachycardia
Roses-Noguer et al (2014) reported on results of a small retrospective study of 13 patients with CPVT who received an ICD. The indication for ICD therapy was syncope despite maximal β-blocker therapy in 6 (46%) patients and aborted SCD in 7 (54%) patients. Over a median follow-up of 4.0 years, 10 (77%) patients received a median of 4 shocks. For 96 shocks, 87 ECGs were available for review; of those, 63 (72%) were appropriate and 24 (28%) inappropriate. Among appropriate shocks, 20 (32%) restored sinus rhythm.

Section Summary: TV-ICD for Primary Prevention in Adults
Ischemic Cardiomyopathy and NIDCM
A large body of RCTs has addressed the effectiveness of TV-ICD implantation for primary prevention in patients at high-risk of SCD due to ischemic cardiomyopathy and NICM. Evidence from several RCTs has demonstrated improvements in outcomes with ICD treatment for patients with symptomatic heart failure due to ischemic or NICM with an LVEF of 35% or less. The notable exceptions are that data from several RCTs, including the BEST-ICD, DINAMIT and IRIS trials and subgroup analyses from earlier RCTs, have shown that outcomes with ICD therapy do not appear to improve for patients treated with an ICD within 40 days of recent MI and the CABG Patch trial did not find a benefit for patients undergoing coronary revascularization.

HCM
Less evidence is available for the use of ICDs for primary prevention in patients with HCM. In a meta-analysis of cohort studies, the annual rates of appropriate ICD discharge were 3.3%, and the mortality rate was 1%. Given the long-term high-risk of SCD in patients with HCM, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence for the use of SCDs in patients with HCM.

Inherited Cardiac Ion Channelopathy
The evidence related to the use of ICDs in patients with inherited cardiac ion channelopathy includes primarily single-center cohort studies or registries of patients with LQTS, BrS, and CPVT that have reported on appropriate shock rates. Patient populations typically include a mix of those requiring ICD placement for primary or secondary prevention. The limited available data for ICDs for LQTS and CPVT have indicated high rates of appropriate shocks. For BrS, more data are available and have suggested that rates of appropriate shocks are similarly high. Studies comparing outcomes between patients treated and untreated with ICDs are not available. However, given the relatively small patient populations and the high-risk of cardiac arrhythmias, clinical trials are unlikely. Given the long-term high-risk of SCD in patients with inherited cardiac ion channelopathy, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence for the use of SCDs in patients with inherited cardiac ion channelopathy.

Secondary Prevention in Adults
At least five trials comparing ICD plus medical therapy with medical therapy alone have been conducted in the secondary prevention setting: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial (n=1016), Cardiac Arrest Survival in Hamburg (CASH) trial (n=288), Canadian Implantable Defibrillator Study (CIDS) (n=659), Defibrillator Versus beta-Blockers for Unexplained Death in Thailand (DEBUT) trial (n=66; pilot, n=20; main study, n=46), and Wever et al (1995) (N=60). The trials are shown in Table 6. Mean length of follow-up varied from 18 to 57 months across trials. Lee et al (2003) combined the AVID, CASH, CIDS, and Wever et al (1995) trials
in a meta-analysis of secondary prevention trials. The mortality analysis included 2023 participants and 518 events. In combined estimates, the ICD group had a significant reduction in both mortality (HR=0.75; 95% CI, 0.64 to 0.87) and SCD (HR=0.50; 95% CI, 0.34 to 0.62) compared with the group receiving medical therapy alone. To support National Institute for Health and Care Excellence guidance on the use of ICDs, AVID, CASH, CIDS, and the pilot DEBUT participants were combined in a meta-analysis. The results were similar, indicating a reduction in mortality for ICDs compared with medical therapy alone (relative risk [RR], 0.75; 95% CI, 0.61 to 0.93). Two other meta-analyses that included AVID, CIDS, and CASH reached similar conclusions.

Table 6. RCTs of ICDs for Secondary Prevention

<table>
<thead>
<tr>
<th>Trials</th>
<th>Participants</th>
<th>Treatment Groups</th>
<th>Mortality Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Group</td>
<td>N</td>
</tr>
<tr>
<td>AVID (1997)</td>
<td>Patients resuscitated from near-fatal VT/VF, SVT with syncope, or SVT with LVEF ≤40% and symptoms</td>
<td>ICD</td>
<td>507</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AAD</td>
<td>509</td>
</tr>
<tr>
<td>CASH (2000)</td>
<td>Patients resuscitated from cardiac arrest due to sustained ventricular arrhythmia</td>
<td>ICD</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodarone</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metoprolol</td>
<td>97</td>
</tr>
<tr>
<td>CIDS (2000)</td>
<td>Patients with VF, out-of-hospital cardiac arrest requiring defibrillation, VT with syncope, VT with rate ≥150/min causing presyncope or angina in patient with LVEF ≤35% or syncope with inducible VT inducible</td>
<td>ICD</td>
<td>329</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amiodarone</td>
<td>331</td>
</tr>
<tr>
<td>Wever et al (1995)</td>
<td>Patients with previous MI and resuscitated cardiac arrest due to VT or VF and inducible VT</td>
<td>ICD</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AAD</td>
<td>31</td>
</tr>
<tr>
<td>DEBUT (2003)</td>
<td>Patients were either SUDS or probable SUDS survivors with ECG abnormalities showing a RBBB-like pattern with ST elevation in the right precordial leads and inducible VT/VF</td>
<td>Pilot</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICD</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-blocker therapy</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Main trial</td>
<td>29</td>
</tr>
</tbody>
</table>

AAD: antiarrhythmic drugs; CI: confidence interval; DSMB: data safety monitoring board; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; LVEF: left ventricular ejection fraction; MI: myocardial infarction; RBBB: right bundle-branch block; RCT: randomized controlled trial; RR: relative risk; SUDS: sudden unexplained death syndrome; SVT: sustained ventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.

An analysis by Chan and Hayward (2005) using the National Veterans Administration database previously confirmed that this mortality benefit is generalizable to the clinical setting. A cohort of 6996 patients in the National Veterans Administration database, from 1995 to 1999, who had new-onset ventricular arrhythmia and preexisting ischemic heart disease and congestive heart...
failure were included. Of those, 1442 patients had received an ICD. Mortality was determined through the National Death Index at three years from the hospital discharge date. The cohort was stratified by quintiles of a multivariable propensity score created using many demographic and clinical confounders. The propensity score-adjusted mortality reduction for ICD compared with no ICD was an RR of 0.72 (95% CI, 0.69 to 0.79) for all-cause mortality and an RR of 0.70 (95% CI, 0.63 to 0.78) for cardiovascular mortality.

Section Summary: Secondary Prevention in Adults
Systematic reviews of RCTs in patients who have experienced symptomatic life-threatening sustained VT or VF or have been successfully resuscitated from sudden cardiac arrest have shown a 25% reduction in mortality for ICD compared with medical therapy. Analysis of data from a large administrative database has confirmed that this mortality benefit is generalizable to the clinical setting.

TV-ICDs in Pediatric Populations
There is limited direct evidence on the efficacy of ICDs in the pediatric population. Most published studies have retrospectively analyzed small case series. Some representative series are reviewed next.

The largest published series, by Berul et al (2008), combined pediatric patients and patients with congenital heart disease from 4 clinical centers. Median age was 16 years, although some adults included were as old as 54 years. A total of 443 patients were included. The most common diagnoses were tetralogy of Fallot and HCM. ICD placement was performed for primary prevention in 52% of patients and secondary prevention in 48%. Over a 2-year follow-up, appropriate shocks occurred in 26% of patients and inappropriate shocks occurred in 21%.

Silka et al (1993) compiled a database of 125 pediatric patients treated with an ICD through a query of the manufacturers of commercially available devices. Indications for ICD placement were survivors of cardiac arrest (95 [76%] patients), drug-refractory VT (13 [10%] patients), and syncope with heart disease and inducible VT (13 [10%] patients). During a mean follow-up of 31 months, 73 (59%) patients received at least 1 appropriate shock and 25 (20%) received at least 1 inappropriate shock. Actutimes rates of SCD-free survival were 97% at 1 year, 95% at 2 years, and 90% at 5 years.

Alexander et al (2004) reported on 90 ICD procedures in 76 young patients (mean age, 16 years; range, 1-30 years). Indications for placement were 27 (36%) patients with cardiac arrest or sustained VT, 40 (53%) with syncope, 17 (22%) with palpitations, 40 (53%) with spontaneous ventricular arrhythmias, and 36 (47%) with inducible VT. Numerous patients had more than one indication for ICD in this study. Over a median follow-up of 2 years, 28% of patients received an appropriate shock and 25% received an inappropriate shock. Lewandowski et al (2010) reported on long-term follow-up for 63 patients, between the ages 6 and 21 years, who were treated with an ICD device. At 10-year follow-up, 13 (21%) patients had surgical infections. Fourteen (22%) patients experienced at least 1 appropriate shock and 17 (27%) had at least 1 inappropriate shock. Serious psychological sequelae developed in 27 (43%) patients.

Section Summary: TV-ICDs in Pediatric Populations
The available evidence for the use of ICDs in pediatric patients is limited and consists primarily of small case series that include mixed populations with mixed indications for device placement.
Overall, these studies have reported both relatively high rates of appropriate and inappropriate shocks. Pediatric patients may be eligible for ICD placement if they have inherited cardiac ion channelopathy (see Inherited Cardiac Ion Channelopathy section).

**Adverse Events Associated With TV-ICDs**

**Systematic Reviews: Mixed Adverse Events**

Persson et al (2014) conducted a systematic review of adverse events following ICD placement. In-hospital serious adverse event rates ranged from 1.2% to 1.4%, most frequently pneumothorax (0.4%-0.5%) and cardiac arrest (0.3%).

In another systematic review of adverse events following ICD placement, Ezzat et al (2015) compared event rates reported in clinical trials of ICDs with those reported in the U.S. National Cardiovascular Data Registry. Complication rates in the RCTs were higher than those in the U.S. registry, which reports only in-hospital complications (9.1% in the RCTs vs 3.08% in the U.S. registry, p<0.01). The overall complication rate was similar to that reported by Kirkfelt et al (2014), in a population-based cohort study including all Danish patients who underwent a cardiac implantable electronic device procedure from 2010 to 2011 (562 [9.5%] 5918 patients with at least 1 complication).

Van Rees et al (2011) reported on results of a systematic review of RCTs assessing implant-related complications of ICDs and CRT devices. Reviewers included 18 trials and 3 subgroup analyses. Twelve trials assessed ICDs, 4 of which used both thoracotomy and nonthoracotomy ICDs (n=951) and 8 of which used nonthoracotomy ICDs (n=3828). For nonthoracotomy ICD placement, the rates for in-hospital and 30-day mortality were 0.2% and 0.6%, respectively, and pneumothorax was reported in 0.9% of cases. For thoracotomy ICD placement, the average in-hospital mortality rate was 2.7%. For nonthoracotomy ICD placement, the overall lead dislodgement rate was 1.8%.

Olde Nordkamp et al (2016) reported on a systematic review and meta-analysis of studies reporting on ICD complications in individuals with inherited arrhythmia syndromes. Reviewers included 63 cohort studies with a total of 4916 patients (710 [10%] with arrhythmogenic right VT; 1037 [21%] with BrS; 28 [0.6%] with CPVT; 2466 [50%] with HCM; 162 [3.3%] with lamin A/C gene variants; 462 [9.4%] with LQTS; 51 [1.0%] with short QT syndrome).

<table>
<thead>
<tr>
<th>Study</th>
<th>Dates</th>
<th>Trials</th>
<th>Participants</th>
<th>N (Range)</th>
<th>Design</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persson (2014)</td>
<td>2005–12</td>
<td>53</td>
<td>Patients receiving ICD placement</td>
<td>NR</td>
<td>Cohort studies</td>
<td>NR</td>
</tr>
<tr>
<td>Olde Nordkamp (2016)</td>
<td>1997–14</td>
<td>63</td>
<td>Patients with inherited arrhythmia syndromes receiving ICD placement</td>
<td>4916 (NR)</td>
<td>Cohort</td>
<td>NR</td>
</tr>
</tbody>
</table>

ICD: implantable cardioverter defibrillator; NR: not reported; RCT: randomized controlled trials; TV-ICD: transvenous implantable cardioverter defibrillator.
Table 8. Systematic Reviews & Meta-Analysis Results for Adverse Events Associated With TV-ICDs

<table>
<thead>
<tr>
<th>Study</th>
<th>Rate of Adverse Events</th>
<th>Rates of Specific Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persson (2014)</td>
<td>1.2%–1.4%</td>
<td>Device-related: &lt;0.1%–6.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lead-related: &lt;0.1%–3.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection: 0.2%–3.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate shock: 3%–21%</td>
</tr>
<tr>
<td>Ezzat (2015)</td>
<td>9.1 (CI 6.4%–12.6%)</td>
<td>Access-related: 2.1% (CI 1.3%–3.3%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lead-related: 5.8% (CI 3.3%–9.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Generator-related: 2.7% (CI 1.3%–5.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection: 1.5% (CI 0.8%–2.6%)</td>
</tr>
<tr>
<td>Olde Nordkamp (2016)</td>
<td>22% (4.4% per year; 3.6%–5.2%; p&lt;0.001)</td>
<td>Lead malfunction: 10.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Infection: 3.0% (0.53% per year)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inappropriate shock: 20% (4.7% per year; CI 4.2%–5.3%; p&lt;0.001)</td>
</tr>
</tbody>
</table>

CI: 95% confidence interval; TV-ICD: transvenous implantable cardioverter defibrillator.

1 Only serious adverse events, which included cardiac arrest, cardiac perforation, cardiac valve injury, coronary venous dissection, hemothorax, pneumothorax, deep phlebitis, transient ischemic attack, stroke, myocardial infarction, pericardial tamponade, arteriovenous fistula, and, in one study, lead dislodgement.

Systematic Review: Specific Complications

Lead Failure

The failure of leads in specific ICD devices led the U.S. Food and Drug Administration to require St. Jude Medical to conduct three-year postmarket surveillance studies to address concerns related to premature insulation failure and important questions related to follow-up of affected patients. An evaluation by Hauser et al (2010) found that 57 deaths and 48 serious cardiovascular injuries associated with device-assisted ICD or pacemaker lead extraction were reported to the Food and Drug Administration’s Manufacturers and User Defined Experience database. Providencia et al (2015) reported on a meta-analysis of 17 observational studies evaluating the performance of 49871 leads (5538 Durata, 10605 Endotak Reliance, 16119 Sprint Quattro, 11709 Sprint Fidelis, 5900 Riata). Overall, the incidence of lead failure was 0.93 per 100 lead-years (95% CI, 0.88 to 0.98). In an analysis of studies restricted to head-to-head comparisons of leads, there were no significant differences in the lead failure rates among nonrecalled leads (Endotak Reliance, Durata, Sprint Quattro).

Birnie et al (2012) reported on clinical predictors of failure for 3169 Sprint Fidelis leads implanted from 2003 to 2007 at 11 centers participating in the Canadian Heart Rhythm Society study. A total of 251 lead failures occurred, corresponding to a 5-year lead failure rate of 16.8%. Factors associated with higher failure rates included female sex (HR=1.51; 95% CI, 1.14 to 2.04; p=0.005), axillary vein access (HR=1.94; 95% CI, 1.23 to 3.04), and subclavian vein access (HR=1.63; 95% CI, 1.08 to 2.46). In a study from 3 centers reporting on predictors of Fidelis lead failures, compared with Quattro lead failures, Hauser et al (2011) reported a failure rate for the Fidelis lead of 2.81% per year (vs 0.42% per year for Quattro leads; p<0.001). In an earlier study from 12 Canadian centers, Gould et al (2008) reported on outcomes from ICD replacements due to ICD advisories from 2004 to 2005, which included 451 replacements (of 2635 advisory ICD devices). Over 355 days of follow-up, 41 (9.1%) complications occurred, including 27 (5.9%) requiring surgical reintervention and 2 deaths.

In a large prospective multicenter study, Poole et al (2010) reported on complications rates associated with generator replacements and/or upgrade procedures of pacemaker or ICD devices,
which included 1031 patients without a planned transvenous lead replacement (cohort 1) and 713 with a planned transvenous lead replacement (cohort 2). A total of 9.8% and 21.9% of cohort 1 and 19.2% and 25.7% of cohort 2 had a single chamber ICD and a dual chamber ICD, respectively, at baseline. Overall periprocedural complication rates for those with a planned transvenous lead replacement were a cardiac perforation in 0.7%, pneumothorax or hemothorax in 0.8%, cardiac arrest in 0.3%, and, most commonly, need to reoperate because of lead dislodgement or malfunction in 7.9%. Although rates were not specifically reported for ICD replacements, complication rates were higher for ICDs and CRT devices than pacemakers.

Ricci et al (2012) evaluated the incidence of lead failure in a cohort of 414 patients given an ICD with Sprint Fidelis leads. Patients were followed for a median of 35 months. Lead failures occurred in 9.7% (40/414) of patients, for an annual rate of 3.2% per patient-year. Most lead failures (87.5%) were due to lead fracture. Median time until recognition of lead failure, or until an adverse event, was 2.2 days. A total of 22 (5.3%) patients received an inappropriate shock due to lead failure.

Cheng et al (2010) examined the rate of lead dislodgements in patients enrolled in a national cardiovascular registry. Of 226764 patients treated with an ICD between 2006 and 2008, lead dislodgement occurred in 2628 (1.2%). Factors associated with lead dislodgement were New York Heart Association class IV heart failure, AF or atrial flutter, a combined ICD and CRT device, and having the procedure performed by a non-electrophysiologist. Lead dislodgement was associated with an increased risk for other cardiac adverse events and death.

In another single-center study, Faulknier et al (2010) reported on the time-dependent hazard of failure of Sprint Fidelis leads. Over an average follow-up of 2.3 years, 38 (8.9%) of 426 leads failed. There was a 3-year lead survival rate of 90.8% (95% CI, 87.4% to 94.3%), with a hazard of fracture increasing exponentially over time by a power of 2.13 (95% CI, 1.98 to 2.27; p<0.001).

Infection Rates

Several publications have reported on infection rates in patients receiving an ICD. Smit et al (2010) published a retrospective, descriptive analysis of the types and distribution of infections associated with ICDs over a 10-year period in Denmark. Of 91 total infections identified, 39 (42.8%) were localized pocket infections, 26 (28.6%) were endocarditis, 17 (18.7%) were ICD-associated bacteremic infections, and 9 (9.9%) were acute postsurgical infections. Nery et al (2010) reported on the rate of ICD-associated infections among consecutive patients treated with an ICD at a tertiary referral center. Twenty-four of 2417 patients had infections, for a rate of 1.0%. Twenty-two (91.7%) of the 24 patients with infections required device replacement. Factors associated with infection were device replacement (vs de novo implantation) and use of a complex device (eg, combined ICD plus CRT or dual-/triple-chamber devices). Sohail et al (2011) performed a case-control study evaluating the risk factors for an ICD-related infection in 68 patients and 136 matched controls. On multivariate analysis, the presence of epicardial leads (odds ratio [OR], 9.7; p=0.03) and postoperative complications at the insertion site (OR=27.2, p<0.001) were significant risk factors for early infection. For late-onset infections, hospitalization for more than 3 days (OR=33.1, p<0.001 for 2 days vs 1 day) and chronic obstructive pulmonary disease (OR=9.8, p=0.02) were significant risk factors.

Chua et al (2000) described the diagnosis and management of infections in a retrospective case series that included 123 patients, 36 of whom were treated for ICD infections. Most (n=117 [95%]) patients required removal of the device and all lead material. Of those who had all hardware
removed, one patient experienced a relapse, while three of the six patients who did not undergo hardware removal experienced a relapse.

Borleffs et al (2010) also reported on complications after ICD replacement for pocket-related complications, including infection or hematoma, in a single-center study. Of 3161 ICDs included, 145 surgical reinterventions were required for 122 ICDs in 114 patients. Ninety-five (66%) reinterventions were due to infection, and the remaining 50 (34%) were due to other causes. Compared with first-implanted ICDs, the occurrence of surgical reintervention in replacements was 2.5 (95% CI, 1.6 to 3.7) times higher for infection and 1.7 (95% CI, 0.9 to 3.0) times higher for non-infection-related causes.

**Inappropriate Shocks**

Inappropriate shocks may occur with ICDs due to faulty sensing or sensing of atrial arrhythmias with rapid ventricular conduction; these shocks may lead to reduced QOL and risk of ventricular arrhythmias. In the MADIT II trial (described above), 1 or more inappropriate shocks occurred in 11.5% of ICD subjects and were associated with a greater likelihood of mortality (HR=2.29; 95% CI, 1.11 to 4.71; p=0.02).

Tan et al (2014) conducted a systematic review to identify outcomes and adverse events associated with ICDs with built-in therapy-reduction programming. Six randomized trials and 2 nonrandomized cohort studies (total n=7687 patients) were included (3598 with conventional ICDs, 4089 therapy-reduction programming). A total of 267 (4.9%) patients received inappropriate ICD shocks, 99 (3.4%) in the therapy-reduction group and 168 (6.9%) in the conventional programming group (RR=0.50; 95% CI, 0.37 to 0.61; p<0.001). Therapy-reduction programming was associated with a significantly lower risk of death than conventional programming (RR=0.30; 95% CI, 0.16 to 0.41; p<0.001.)

Sterns et al (2016) reported on results of an RCT comparing a strategy using a prolonged VF detection time to reduce inappropriate shocks with a standard strategy among secondary prevention patients. This trial reported on a prespecified subgroup analysis of the PainFree SST trial, which compared standard with prolonged detection in patients receiving an ICD for secondary prevention. Patients treated for secondary prevention indications were randomized to a prolonged VF detection period (n=352) or a standard detection period (n=353). At 1 year, arrhythmic syncope-free rates were 96.9% in the intervention group, and 97.7% in the control group (rate difference, -1.1%; 90% lower confidence limit, -3.5%; above the prespecified noninferiority margin of -5%; p=0.003 for noninferiority).

Auricchio et al (2015) assessed data from the PainFree SST trial, specifically newer ICD programming strategies for reducing inappropriate shocks. A total of 2790 patients with an indication for ICD placement were given a device programmed with a SmartShock Technology designed to differentiate between ventricular arrhythmias and other rhythms. The inappropriate shock incidence for dual-/triple-chamber ICDs was 1.5% at 1 year (95% CI, 1.0% to 2.1%), 2.8% at 2 years (95% CI, 2.1% to 3.8%), and 3.9% at 3 years (95% CI, 2.8% to 5.4%).

**Other Complications**

Lee et al (2010) evaluated rates of early complications among patients enrolled in a prospective, multicenter population-based registry of all newly implanted ICDs in Ontario, from 2007 through 2009. Of 3340 patients receiving an ICD, major complications (lead dislodgement requiring
intervention, myocardial perforation, tamponade, pneumothorax, infection, skin erosion, hematoma requiring intervention) within 45 days of implantation occurred in 4.1% of new implants. Major complications were more common in women, in patients who received a combined ICD-CRT device, and in patients with a left ventricular end-systolic size of larger than 45 mm. Direct implant-related complications were associated with a major increase in early death (HR=24.9; p<0.01).

Furniss et al (2015) prospectively evaluated changes in high-sensitivity troponin T levels and ECG results that occur during ICD placement alone, ICD placement with testing, and ICD testing alone. The 13 subjects undergoing ICD placement alone had a median increase in high-sensitivity troponin T level of 95% (p=0.005) while the 13 undergoing implantation and testing had a median increase of 161% (p=0.005). Those undergoing testing alone demonstrated no significant change in high-sensitivity troponin T levels.

Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

Clinical Context and Therapy Purpose

The purpose of S-ICD placement is to provide a treatment option that is an alternative to or an improvement on existing therapies such as medical management without ICD placement, in patients who have an indication for cardioversion but have a contraindication to TV-ICD.

The question addressed in this evidence review is: Do ICDs improve the net health outcome in individuals who have an indication for cardioversion but have a contraindication to TV-ICD?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals who need an ICD and with or without a contraindication to TV-ICD.

Interventions

The therapy being considered is S-ICD.

An ICD is a device designed to monitor a patient’s heart rate, recognize ventricular fibrillation or ventricular tachycardia, and deliver an electric shock to terminate these arrhythmias to reduce the risk of sudden death. A subcutaneous ICD (S-ICD, which lacks transvenous leads, is intended to reduce lead-related complications.

Patients who need an ICD and have a contraindication to TV-ICD are actively managed by cardiologists, cardiovascular surgeons, neurologists, and primary care providers in an inpatient clinical setting.

Comparators

Comparators of interest include medical management without ICD placement or TV-ICD placement.

Outcomes

The general outcomes of interest are OS, morbid events, QOL, treatment-related mortality, and treatment-related morbidity.
Table 9. Outcomes of Interest for Individuals who need an implantable cardioverter defibrillator and have a contraindication to transvenous ICD

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Details</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of life</td>
<td>Can be assessed patient reported data such as surveys and questionnaires</td>
<td>1 week to 5 years</td>
</tr>
<tr>
<td>Treatment-related morbidity</td>
<td>Can be assessed rates of adverse events, including inappropriate shock, lead failure, infection, and other complications</td>
<td>1 week to 5 years</td>
</tr>
</tbody>
</table>

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

The S-ICD is intended for patients who have standard indications for an ICD, but who do not require pacing for bradycardia or antitachycardia overdrive pacing for VT. The S-ICD has been proposed to benefit patients with limited vascular access (including patients undergoing renal dialysis or children) or those who have had complications requiring TV-ICDs explantation. No RCTs were identified comparing the performance of an S-ICD with that of TV-ICDs. The first multicenter, randomized trial (PRAETORIAN; NCT01296022) to directly compare S-ICDs with TV-ICDs is underway.

S-ICD Efficacy
Several observational studies have compared S-ICD to TV-ICD.

Observational Studies
The observational studies are briefly described in Table 10. All studies were performed in the U.S. and/or Europe.

Noncomparative Studies
The Implant and Midterm Outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry (EFFORTLESS) is a multicenter European registry reporting outcomes for patients treated with S-ICD. Several publications from EFFORTLESS, the pivotal trial submitted to the Food and Drug Administration for the investigational device exemption, and other noncomparative studies are described in Table 11.

Table 10. Summary of Observational Comparative Studies of S-ICD and TV-ICD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>N</th>
<th>Follow-Up</th>
<th>Results</th>
<th>Outcomes</th>
<th>TV-ICD</th>
<th>S-ICD</th>
<th>DC TV-ICD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mithani et al (2018)</td>
<td>Matching based on</td>
<td>182</td>
<td>180 d</td>
<td>• Inappropriate shocks</td>
<td>2.2%</td>
<td>1.1%</td>
<td>1.1%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Follow-Up</td>
<td>Outcomes</td>
<td></td>
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<tr>
<td>Honarbakhsh et al (2017)</td>
<td>Propensity matched case-control</td>
<td>138 (69 matched pairs)</td>
<td>32 mo</td>
<td>• Total device-related complications&lt;br&gt;• Infections&lt;br&gt;• Inappropriate shocks&lt;br&gt;• Failure to cardiovert VA</td>
<td>29% 5.8% 8.7% 1.4% 9% 1.4% 4.3% 1.4%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobe et al (2017)</td>
<td>Sex- and age-matched case-control</td>
<td>120 (60 pairs); 84 pairs analyzed</td>
<td>942 d vs 622 d</td>
<td>• Posttraumatic stress disorder&lt;br&gt;• Major depression&lt;br&gt;• SF-12 physical well-being score&lt;br&gt;• SF-12 mental well-being score</td>
<td>14.3% 9.5% 40 52 14.3% 4.8% 47 52</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pedersen et al (2016)</td>
<td>Retrospective analysis of propensity-matched cohort</td>
<td>334 (167 matched pairs)</td>
<td>6 mo</td>
<td>• SF-12 physical well-being score&lt;br&gt;• SF-12 mental well-being score</td>
<td>43 45 44 45</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brouwer et al (2016)</td>
<td>Retrospective analysis of propensity-matched cohort</td>
<td>280 (140 matched pairs)</td>
<td>5 y</td>
<td>• Overall complications&lt;br&gt;• Lead complications&lt;br&gt;• Non-lead complications&lt;br&gt;• Infections&lt;br&gt;• Appropriate ICD intervention (HR=2.4; 95% CI, NR; p=0.01)&lt;br&gt;• Inappropriate ICD intervention (HR=1.3; 95% CI, NR; p=0.42)&lt;br&gt;• Survival</td>
<td>18% 11.5% 2.2% 3.6% 31% 30% 95% 14% 0.8% 9.9% 4.1% 17% 21% 96%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friedman et al (2016)</td>
<td>Retrospective analysis of propensity-matched cohort from NCDR for ICD</td>
<td>5760 (1920 matched groups)</td>
<td>NR</td>
<td>• Any in-hospital complication&lt;br&gt;• Deaths&lt;br&gt;• Infections&lt;br&gt;• Lead dislodgements&lt;br&gt;• Pneumothorax</td>
<td>0.6% 0.1% 0.2% 0.2% 0.9% 0.2% 0.5% 0.1% 0% 0% 0% 0.5% 0.1% 0.6% 0.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kobe et al (2013)</td>
<td>Sex- and age-matched case-control</td>
<td>138 (69 matched pairs)</td>
<td>217 d</td>
<td>• Pericardial effusion&lt;br&gt;• Successful termination of induced VF&lt;br&gt;• Appropriate shocks&lt;br&gt;• Inappropriate shocks</td>
<td>1 91% 9 3 0 90% 3 5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; DC: dual chamber; HR: hazard ratio; ICD: implantable cardioverter defibrillator; NCDR: National Cardiovascular Data Registry; NR: not reported; SF-12: 12-Item Short-Form Health Survey; S-ICD:
subcutaneous implantable cardioverter defibrillator; TV-ICD: transvenous implantable cardioverter defibrillator; VA: ventricular arrhythmia; VF: ventricular fibrillation.

\(^{a}\) Mean.
\(^{b}\) Median.

Table 11. Summary of Observational Studies of S-ICD

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>N</th>
<th>Mean FU</th>
<th>Outcomes</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
| Lambiase et al (2014); Olde Nordkamp et al (2015); Boersma et al (2017) EFFORTLESS S-ICD Registry | 10 European countries | 985     | 3.1 y   | • Complication-rates by 360 d | 8.4%  
|             |           | 928     | 1 y     |          | 8.1%  
|             |           | 697     | 2 y     | • Inappropriate shocks by 360 d | 11.7% 
|             |           | 498     | 3 y     |          | 11.7% 
|             |           | 300     | 4 y     | • Complication rates through follow-up | 13.5% 
|             |           | 82      | 5 y     | • Inappropriate shocks through follow-up |        
|             |           |         |         | • Appropriate shocks through follow-up |        |
|             |           |         |         | • Complication-free at 180 d | 99%    
|             |           |         |         | • Inappropriate shocks | 13%    
|             |           |         |         | • Episodes of discrete spontaneous VT or VF, all successfully converted | 38     |
| Burke et al (2015); Boersma et al (2016); Lambiase et al (2016) EFFORTLESS and IDE studies | Multiple European countries, U.S., New Zealand | 882     | 651 d   | • Complications within 3 y | 11%    
|             |           |         |         | • Infections requiring device removal or revision | 1.7%   
|             |           |         |         | • Annual mortality rate | 1.6%   
|             |           |         |         | • 2-y cumulative mortality | 3.2%   
|             |           |         |         | • Incidence of therapy for VT or VF: | 5.3%   
|             |           |         |         | o1 year | 7.9%   
|             |           |         |         | o2 years | 10.5%  
|             |           |         |         | o3 years | 13.1%  
|             |           |         |         | • Incidence of inappropriate shock at 3 y |        |
| Bardy et al (2010); Theuns et al (2015) | Europe, New Zealand | 55      | 5.8 y   | • Devices replaced | 26 (47%) 
|             |           |         |         | • Devices explanted | 5 (9%) 
|             |           |         |         | • Replaced with TV-ICD | 4 (7%) 
|             |           |         |         | • Shocks recorded in 16 (29%) patients | 119    
| Olde-Nordkamp et al (2012) | Netherlands | 118     | 18 mo   | • All device-related complications | 14%    
|             |           |         |         | • Infections | 5.9%   
|             |           |         |         | • Dislodgements of device/leads | 3.3%   
|             |           |         |         | • Skin erosion | 1.7%   
|             |           |         |         | • Battery failure | 1.7%   
|             |           |         |         | • Replaced with TV-ICD | 1 (0.8%) 
|             |           |         |         | • Appropriate shocks experienced in 8 patients | 45     
|             |           |         |         |                     | 33     
|             |           |         |         |                     | 2      |
Inappropriate Shocks

Although Kobe et al (2017) reported no differences between inappropriate shock rates in patients treated TV-ICD or S-ICD, noncomparative studies have reported relatively high rates of inappropriate shocks with S-ICD. Inappropriate shocks from S-ICDs often result from T-wave oversensing. Because the sensing algorithm and the discrimination algorithm for arrhythmia detection are fixed in the S-ICD, management to reduce inappropriate shocks for an S-ICD differs from that for a TV-ICD. Kooiman et al (2014) reported on inappropriate shock rates among 69 patients treated at a single-center with an S-ICD between 2009 and 2012 who were not enrolled in 1 of 2 other concurrent trials. Over a total follow-up of 1316 months (median per patient, 21 months), the annual incidence of inappropriate shocks was 10.8%. In eight patients, inappropriate shocks were related to T-wave oversensing. After patients underwent adjustment of the sensing vector, no further inappropriate shocks occurred in 87.5% of patients with T-wave oversensing.

Section Summary: S-ICD

Contraindications to TV-ICD

Nonrandomized studies have suggested that S-ICDs are as effective as TV-ICDs at terminating laboratory-induced ventricular arrhythmias. Data from two large patient registries have suggested that S-ICDs are effective at terminating ventricular arrhythmias when they occur. Given the need for cardioverter defibrillation for SCD risk in this population, with the assumption that appropriate shocks are life-saving, these rates suggest S-ICDs, in patients with contraindication to TV-ICD, are likely improvements over medical management alone.

No Contraindications to TV-ICD

No RCTs directly comparing TV-ICDs with S-ICDs were identified, and therefore evidence is not sufficient to show that outcomes for S-ICDs are noninferior to those for TV-ICD for patients who could otherwise receive TV-ICD.

Summary of Evidence

TV-ICDs

For individuals who have a high-risk of SCD due to ischemic or to nonischemic cardiomyopathy in adulthood who receive TV-ICD placement for primary prevention, the evidence includes multiple well-designed and well-conducted RCTs as well as systematic reviews of these trials. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Multiple, well-done RCTs have shown a benefit in overall mortality for patients with ischemic cardiomyopathy and reduced ejection fraction. RCTs assessing early ICD use following recent MI did not support a benefit for immediate vs delayed implantation for at least 40 days. For nonischemic cardiomyopathy, there is less clinical trial data, but pooled estimates of available evidence from RCTs enrolling patients with nonischemic cardiomyopathy and from subgroup analyses of RCTs with mixed populations have supported a survival benefit for this group. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
For individuals who have a high-risk of SCD due to HCM in adulthood who receive TV-ICD placement for primary prevention, the evidence includes several large registry studies. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. In these studies, the annual rate of appropriate ICD discharge ranged from 3.6% to 5.3%. Given the long-term high-risk of SCD in patients with HCM, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of ICDs in patients with HCM. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have a high-risk of SCD due to an inherited cardiac ion channelopathy who receive TV-ICD placement for primary prevention, the evidence includes small cohort studies of patients with these conditions treated with ICDs. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. The limited evidence for patients with LQTS, CPVT, and BrS has reported high rates of appropriate shocks. No studies were identified on the use of ICDs for patients with short QT syndrome. Studies comparing outcomes between patients treated and untreated with ICDs are not available. However, given the relatively small patient populations with these channelopathies and the high-risk of cardiac arrhythmias, clinical trials are unlikely. Given the long-term high-risk of SCD in patients with inherited cardiac ion channelopathy, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of TV-ICDs in patients with inherited cardiac ion channelopathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have had symptomatic life-threatening sustained VT or VF or who have been resuscitated from sudden cardiac arrest (secondary prevention) who receive TV-ICD placement, the evidence includes multiple well-designed and well-conducted RCTs as well as systematic reviews of these trials. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Systematic reviews of RCTs have demonstrated a 25% reduction in mortality for ICD compared with medical therapy. Analysis of data from a large administrative database has confirmed that this mortality benefit is generalizable to the clinical setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

S-ICDs
For individuals who need an ICD and have a contraindication to a TV-ICD but no indications for antibradycardia pacing and no antitachycardia pacing-responsive arrhythmias who receive S-ICD placement, the evidence includes nonrandomized studies and case series. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Nonrandomized controlled studies have reported success rates in terminating laboratory-induced VF that are similar to TV-ICD. Case series have reported high-rates of detection and successful conversion of VF, and inappropriate shock rates in the range reported for TV-ICD. Given the need for ICD placement in this population at risk for SCD, with the assumption that appropriate shocks are life-saving, these rates are considered adequate evidence to support the use of S-ICDs in patients with contraindication to TV-ICD. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who need an ICD and have no contraindication to TV-ICD but no indications for antibradycardia pacing and no antitachycardia pacing-responsive arrhythmias who
receive S-ICD placement, the evidence includes nonrandomized studies and case series. The relevant outcomes are OS, morbid events, QOL, and treatment-related mortality and morbidity. Nonrandomized controlled studies have reported success rates in terminating laboratory-induced VF that are similar to TV-ICD. However, there is scant evidence on comparative clinical outcomes of both types of ICD over longer periods. Case series have reported high rates of detection and successful conversion of ventricular tachycardia, and inappropriate shock rates in the range reported for TV-ICD. This evidence does not support conclusions on whether there are small differences in efficacy between the two types of devices, which may be clinically important due to the nature to the disorder being treated. Also, adverse event rates are uncertain, with variable rates reported. At least one RCT is currently underway comparing S-ICD with TV-ICD. The evidence is insufficient to determine the effects of the technology on health outcomes.

VII. Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2015 Input
In response to requests, input was received from 1 physician specialty society (4 responses) and 5 academic medical centers, for a total of 9 responses, while this policy was under review in 2015. Input focused on use of implantable cardioverter defibrillators (ICDs) as primary prevention for cardiac ion channelopathies and on use of the subcutaneous implantable cardioverter defibrillator (S-ICD). Reviewers generally indicated that an ICD should be considered medically necessary for primary prevention of ventricular arrhythmias in adults and children with a diagnosis of long QT syndrome, Brugada syndrome, short QT syndrome, and catecholaminergic polymorphic ventricular tachycardia. Reviewers generally indicated that the S-ICD should be considered medically necessary particularly for patients with indications for an ICD but who have difficult vascular access or have had transvenous ICD lead explantation due to complications.

2011 Input
In response to requests, input was received from 6 academic medical centers while this policy was under review in 2011. For most policy indications, including pediatric, there was general agreement from those providing input. On the question of timing of ICD placement, input was mixed, with some commenting about the potential role of early implantation in select patients. Reviewers indicated that a waiting period of nine months for patients with nonischemic cardiomyopathy was not supported by the available evidence or consistent with the prevailing practice patterns in academic medical centers. Input emphasized the difficulty of prescribing strict timeframes given the uncertainty of establishing the onset of cardiomyopathy and the inability to risk-stratify patients based on time since onset of cardiomyopathy.

PRACTICE GUIDELINES AND POSITION STATEMENTS
American College of Cardiology, American Heart Association, et al
Heart Failure
The AHA, American College of Cardiology, and Heart Rhythm Society (HRS) (2017) published joint guidelines on the management of heart failure, which updated their 2012 guidelines. These guidelines made the following recommendations on the use of ICD devices (see Tables 12-17). The
recommendations for the use of an ICD apply only if meaningful survival is expected to be greater than one year.

### Table 12. Guidelines on Device-Based Therapy of Cardiac Rhythm Abnormalities

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients with ischemic heart disease, who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) or stable VT (LOE: B-NR) not due to reversible causes...&quot;</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;A transvenous ICD provides intermediate value in the secondary prevention of SCD particularly when the patient’s risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status.&quot;</td>
<td></td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;In patients with ischemic heart disease and unexplained syncope who have inducible sustained monomorphic VT on electrophysiological study...&quot;</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated...&quot;</td>
<td></td>
<td>Ila</td>
</tr>
<tr>
<td>&quot;In patients resuscitated from SCA due to coronary artery spasm, an ICD in addition to medical therapy may be reasonable...&quot;</td>
<td></td>
<td>Ilb</td>
</tr>
<tr>
<td>&quot;In patients with arrhythmogenic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated SCA, sustained VT, significant ventricular dysfunction with RVEF or LVEF ≤35%).&quot;</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed due to VA...&quot;</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

COR: class of recommendation; ICD: implantable cardioverter defibrillator; LOE: level of evidence; LVEF: left ventricular ejection fraction; RVEF: right ventricular ejection fraction; SCA: sudden cardiac arrest; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

### Table 13. Guidelines on Use of ICDs as a Primary Prevention of Ischemic Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT...&quot;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>&quot;In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT...&quot;</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>&quot;A transvenous ICD provides high value in the primary prevention of SCD particularly when the patient’s risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient’s burden of comorbidities and functional status...&quot;</td>
<td></td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;In patients with NSVT due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study...&quot;</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;In nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD...&quot;</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;An ICD is not indicated for NYHA class IV patients with medication-refractory HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities.&quot;</td>
<td>III*</td>
<td>C-EO</td>
</tr>
</tbody>
</table>

CRT: cardiac resynchronization therapy; COR: class of recommendation; ICD: implantable cardioverter defibrillator; GDMT: guideline-directed management and therapy; HF: heart failure; LOE: level of evidence; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSVT: nonsustained ventricular tachycardia; NYHA: New York Heart Association; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

* No benefit.
Table 14. Guidelines on Use of ICDs for Nonischemic Cardiomyopathy

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients with NICM who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) (1-4) or stable VT (LOE: B-NR) (5) not due to reversible causes...&quot;</td>
<td>I</td>
<td>B-R</td>
</tr>
<tr>
<td>&quot; In patients with NICM who experience syncope presumed to be due to VA and who do not meet indications for a primary prevention ICD, an ICD or an electrophysiological study for risk stratification for SCD can be beneficial...&quot;</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with NICM, HF with NYHA class II-III symptoms and an LVEF of 35% or less, despite GDMT...&quot;</td>
<td>Ila</td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;In patients with NICM, HF with NYHA class I symptoms and an LVEF of 35% or less, despite GDMT...&quot;</td>
<td>IIb</td>
<td>B-R</td>
</tr>
<tr>
<td>&quot;In patients with NICM, HF with NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities, an ICD should not be implanted.&quot;</td>
<td>IIIa</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

COR: class of recommendation; CRT: cardiac resynchronization therapy; GDMT: guideline-directed management and therapy; HF: heart failure; ICD: implantable cardioverter defibrillator; LOE: level of evidence; LVAD: left ventricular assist device; LVEF: left ventricular ejection fraction; NICM: nonischemic cardiomyopathy; NYHA: New York Heart Association; SCA: sudden cardiac arrest; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

a No benefit.

Table 15. Guidelines on Use of ICDs for HCM

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients with HCM who have survived an SCA due to VT or VF, or have spontaneous sustained VT causing syncope or hemodynamic compromise...&quot;</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with HCM and 1 or more of the following risk factors...&quot;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Maximum LV wall thickness ≥30 mm (LOE: B-NR).</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
<tr>
<td>b. SCD in 1 or more first-degree relatives presumably caused by HCM (LOE: C-LD).</td>
<td></td>
<td>C-LD</td>
</tr>
<tr>
<td>c. 1 or more episodes of unexplained syncope within the preceding 6 months (LOE: C-LD)&quot;</td>
<td></td>
<td>C-LD</td>
</tr>
<tr>
<td>&quot;In patients with HCM who have spontaneous NSVT (LOE: C-LD) or an abnormal blood pressure response with exercise (LOE: B-NR), who also have additional SCD risk modifiers or high risk features...&quot;</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with HCM who have NSVT (LOE: B-NR) or an abnormal blood pressure response with exercise (LOE: B-NR) but do not have any other SCD risk modifiers, an ICD may be considered, but its benefit is uncertain.&quot;</td>
<td>IIb</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with an identified HCM genotype in the absence of SCD risk factors, an ICD should not be implanted&quot;</td>
<td>IIIa</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

COR: class of recommendation; HCM: hypertrophic cardiomyopathy; ICD: implantable cardioverter defibrillator; LOE: level of evidence; LV: left ventricular; NSVT: nonsustained ventricular tachycardia; SCA: sudden cardiac arrest; SCD: sudden cardiac death; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

a No benefit.

Table 16. Guidelines on Use of ICDs for Other Conditions

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients with HFrEF who are awaiting heart transplant and who otherwise would not qualify for an ICD (e.g., NYHA class IV and/or use of inotropes) with a plan to discharge home, an ICD is reasonable&quot;</td>
<td>IIa</td>
<td>B-NR</td>
</tr>
</tbody>
</table>
"In patients with an LVAD and sustained VA, an ICD can be beneficial."

"In patients with a heart transplant and severe allograft vasculopathy with LV dysfunction..."

"In patients with neuromuscular disorders, primary and secondary prevention ICDs are recommended for the same indications as for patients with NICM..."

"In patients with a cardiac channelopathy (see Guideline Tables 7.9 and 7.9.1)"

"In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope (see Guideline Table 7.9.1.2)"

"In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA..."

"In patients with early repolarization pattern on ECG and cardiac arrest or sustained VA..."

"In patients resuscitated from SCA due to idiopathic polymorphic VT or VF..."

"For older patients and those with significant comorbidities, who meet indications for a primary prevention ICD, an ICD is reasonable."

"In patients with adult congenital heart disease with SCA due to VT or VF in the absence of reversible causes..."

"In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiological study with ICD implantation for inducible sustained VA is reasonable..."

"In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA..."

"In patients with early repolarization pattern on ECG and cardiac arrest or sustained VA..."

"In patients resuscitated from SCA due to idiopathic polymorphic VT or VF..."

"For older patients and those with significant comorbidities, who meet indications for a primary prevention ICD, an ICD is reasonable."

"In patients with adult congenital heart disease with SCA due to VT or VF in the absence of reversible causes..."

"In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiological study with ICD implantation for inducible sustained VA is reasonable...

COR: class of recommendation; ECG: electrocardiogram; HFrEF: heart failure with reduced ejection fraction; ICD: implantable cardioverter defibrillator; LOE: level of evidence; LV: left ventricle; LVAD: left ventricular assist device; NICM: nonischemic cardiomyopathy; NYHA: New York Heart Association; SCA: sudden cardiac arrest; VA: ventricular arrhythmia; VF: ventricular fibrillation; VT: ventricular tachycardia.

Table 17. Guidelines on Use of Subcutaneous ICDs

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;In patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated, a subcutaneous implantable cardioverter-defibrillator is recommended.&quot;</td>
<td>I</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients who meet indication for an ICD, implantation of a subcutaneous implantable cardioverter-defibrillator is reasonable if pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated.&quot;</td>
<td>Ila</td>
<td>B-NR</td>
</tr>
<tr>
<td>&quot;In patients with an indication for bradycardia pacing or CRT, or for whom antitachycardia pacing for VT termination is required, a subcutaneous implantable cardioverter-defibrillator should not be implanted.&quot;</td>
<td>III*</td>
<td>B-NR</td>
</tr>
</tbody>
</table>

CRT: cardiac resynchronization therapy; COR: class of recommendation; ICD: implantable cardioverter defibrillator; LOE: level of evidence; VT: ventricular tachycardia.

* Harm.

The 2013 update made the following recommendations on ICD therapy for children (see Table 18).

Table 18. Guidelines on ICD Therapy for Children

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD implantation is indicated in the survivor of cardiac arrest after evaluation to define the cause of the event and to exclude any reversible causes.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ICD implantation is indicated for patients with symptomatic sustained VT in association with congenital heart disease who have undergone hemodynamic and electrophysiological evaluation.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
Catheter ablation or surgical repair may offer possible alternatives in carefully selected patients.

ICD implantation is reasonable for patients with congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias at electrophysiological study.  

ICD implantation may be considered for patients with recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause.

All class III recommendations found in Section 3, "Indications for Implantable Cardioverter-Defibrillator Therapy," apply to pediatric patients and patients with congenital heart disease, and ICD implantation is not indicated in these patient populations.

**ICD Therapy in Patients Not Well Represented in Clinical Trials**

The HRS, the American College of Cardiology, and AHA (2014) published an expert consensus statement on the use of ICD therapy for patients not included or poorly represented in ICD clinical trials. The statement presented a number of consensus-based guidelines on the use of ICDs in select patient populations.

**American Heart Association**

AHA (2010) issued a scientific statement, endorsed by HRS, on cardiovascular implantable electronic device infections and their management. This statement made the following recommendations on the removal of device-related infections (see Table 19).

**Table 19. Guidelines on the Management of CIED Infections**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Complete device and lead removal is recommended for all patients with CIED pocket infection as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Complete device and lead removal is recommended for patients with occult staphylococcal bacteremia.</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

CIED: cardiovascular implantable electronic device; COR: class of recommendation; LOE: level of evidence.

**Heart Rhythm Society et al**

The HRS, the European Heart Rhythm Association, and the Asia-Pacific Heart Rhythm Society (2013) issued a consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, which included recommendations on ICD use in patients with long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia, and short QT syndrome (see Table 20).

**Table 20. Guidelines on the Diagnosis and Management of Inherited Primary Arrhythmia Syndromes**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long QT syndrome</td>
<td></td>
</tr>
<tr>
<td>ICD implantation is recommended for patients with a diagnosis of LQTS who are survivors of a cardiac arrest</td>
<td>I</td>
</tr>
<tr>
<td>ICD implantation can be useful in patients with a diagnosis of LQTS who experience recurrent syncopal</td>
<td>Ila</td>
</tr>
</tbody>
</table>
Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

### Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

### Events while on beta-blocker therapy

Except under special circumstances, ICD implantation is not indicated in asymptomatic LQTS patients who have not been tried on beta-blocker therapy

### Brugada Syndrome

ICD implantation is recommended in patients with a diagnosis of BrS who:
- Are survivors of a cardiac arrest and/or
- Have documented spontaneous sustained VT with or without syncope.

ICD implantation can be useful in patients with a spontaneous diagnostic type I ECG who have a history of syncope judged to be likely caused by ventricular arrhythmias.

ICD implantation may be considered in patients with a diagnosis of BrS who develop VF during programmed electrical stimulation (inducible patients).

ICD implantation is not indicated in asymptomatic BrS patients who have not been tried on beta-blocker therapy

### ICD as a standalone therapy is not indicated in asymptomatic BrS patients with a drug-induced type I ECG and on the basis of a family history of SCD alone.

### Catecholaminergic polymorphic ventricular tachycardia

ICD implantation is recommended for patients with a diagnosis of CPVT who experience cardiac arrest, recurrent syncope or polymorphic/bidirectional VT despite optimal medical management, and/or left cardiac sympathetic denervation.

ICD as a stand-alone therapy is not indicated in an asymptomatic patient with a diagnosis of CPVT

### Short QT Syndrome

ICD implantation is recommended in symptomatic patients with a diagnosis of SQTS who:
- Are survivors of cardiac arrest and/or
- Have documented spontaneous VT with or without syncope.

ICD implantation may be considered in asymptomatic patients with a diagnosis of SQTS and a family history of sudden cardiac death.

### Table 21. Guidelines on the Management of CHD

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD therapy is indicated in adults with CHD who are survivors of cardiac arrest due to ventricular fibrillation or hemodynamically unstable ventricular tachycardia after evaluation to define the cause of the event and exclude any completely reversible etiology.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ICD therapy is indicated in adults with CHD and spontaneous sustained ventricular tachycardia who have undergone hemodynamic and electrophysiologic evaluation.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ICD therapy is indicated in adults with CHD and a systemic left ventricular ejection fraction &lt;35%, biventricular physiology, and NYHA class II or III symptoms.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>ICD therapy is reasonable in selected adults with tetralogy of Fallot and multiple risk factors for sudden cardiac death, such as left ventricular systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS duration &gt;180 ms, extensive right ventricular scarring, or inducible sustained ventricular tachycardia at electrophysiologic study.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>ICD therapy may be reasonable in adults with a single or systemic right ventricular ejection fraction &lt;35%, particularly in the presence of additional risk factors such as complex ventricular arrhythmias, unexplained syncope, NYHA functional class II or III symptoms, QRS duration &gt;140 ms, or severe</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>

BrS: Brugada syndrome; COR: class of recommendation; CPVT: catecholaminergic polymorphic ventricular tachycardia; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; LQTS: long QT syndrome; SCD: sudden cardiac death; SQTS: short QT syndrome; VF: ventricular fibrillation; VT: ventricular tachycardia.

*Not recommended.

Pediatric and Congenital Electrophysiology Society and Heart Rhythm Society

The Pediatric and Congenital Electrophysiology Society and HRS (2014) issued an expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease. The statement made the following recommendations on the use of ICD therapy in adults with congenital heart disease (see Table 21).
Subcutaneous Implantable Cardioverter Defibrillator (ICD) System

<table>
<thead>
<tr>
<th>AV: arteriovenous; CHD: coronary heart disease; COR: class of recommendation; ICD: implantable cardioverter defibrillator; LOE: level of evidence; NYHA: New York Heart Association.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD therapy may be considered in adults with CHD and a systemic ventricular ejection fraction &lt;35% in the absence of overt symptoms (NYHA class I) or other known risk factors.</td>
</tr>
<tr>
<td>ICD therapy may be considered in adults with CHD and systemic AV valve regurgitation.</td>
</tr>
<tr>
<td>ICD therapy may be considered in adults with CHD and syncope of unknown origin with hemodynamically significant sustained ventricular tachycardia or fibrillation inducible at electrophysiologic study.</td>
</tr>
<tr>
<td>ICD therapy may be considered in adults with CHD and a systemic ventricular ejection fraction &lt;35% in the absence of overt symptoms (NYHA class I) or other known risk factors.</td>
</tr>
<tr>
<td>ICD therapy may be considered for nonhospitalized adults with CHD awaiting heart transplantation.</td>
</tr>
<tr>
<td>ICD therapy may be considered for adults with syncope and moderate or complex CHD in whom there is a high clinical suspicion of ventricular arrhythmia and in whom thorough invasive and noninvasive investigations have failed to define a cause.</td>
</tr>
<tr>
<td>Adults with CHD and advanced pulmonary vascular disease (Eisenmenger syndrome) are generally not considered candidates for ICD therapy.</td>
</tr>
<tr>
<td>Endocardial leads are generally avoided in adults with CHD and intracardiac shunts. Risk assessment regarding hemodynamic circumstances, concomitant anticoagulation, shunt closure prior to endocardial lead placement, or alternative approaches for lead access should be individualized.</td>
</tr>
</tbody>
</table>

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

MEDICARE NATIONAL COVERAGE
In February 2018, Medicare issued an update with minor changes to its 2005 national coverage guideline for the use of ICDs. The Centers for Medicare and Medicaid Services (CMS) determined that the evidence is adequate to conclude that an ICD is reasonable and necessary for the following:

1. “Patients with ischemic dilated cardiomyopathy (IDCM), documented prior MI, NYHA [New York Heart Association] Class II and III heart failure, and measured LVEF [left ventricular ejection fraction] of ≤ 35%;
2. Patients with non-ischemic dilated cardiomyopathy (NIDCM) >9 months, NYHA Class II and III heart failure, and measured LVEF ≤ 35%;
3. Patients who meet all current Centers for Medicare & Medicaid Services (CMS) coverage requirements for a cardiac resynchronization therapy (CRT) device and have NYHA class IV heart failure;”

For each of these groups, patients must not have:

- “Cardiogenic shock or symptomatic hypotension while in a stable baseline rhythm;
- Had a CABG [coronary artery bypass graft] or PTCA [percutaneous transluminal coronary angioplasty] within the past 3 months;
- Had an acute MI within the past 40 days;
- Clinical symptoms or findings that would make them a candidate for coronary revascularization;
- Irreversible brain damage from preexisting cerebral disease;
- Any disease, other than cardiac disease (e.g., cancer, uremia, liver failure), associated with a likelihood of survival less than 1 year;”
Also, the Centers for Medicare & Medicaid Services specified that the beneficiary receiving on ICD for primary prevention must be enrolled in an approved clinical trial or a qualifying data collection system.

**ONGOING AND UNPUBLISHED CLINICAL TRIALS**
Some currently unpublished trials that might influence this review are listed in Table 22.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02121158</td>
<td>CSP #592 - Efficacy and Safety of ICD Implantation in the Elderly</td>
<td>100</td>
<td>Aug 2020</td>
</tr>
<tr>
<td>NCT01296022</td>
<td>Randomized Trial to Study the Efficacy and Adverse Effects of the Subcutaneous and Transvenous Implantable Cardioverter Defibrillator (ICD) in Patients With a Class I or Ila Indication for ICD Without an Indication for Pacing</td>
<td>850</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT00673842</td>
<td>Risk Estimation Following Infarction Noninvasive Evaluation - ICD Efficacy</td>
<td>1000</td>
<td>Dec 2021</td>
</tr>
<tr>
<td>NCT02845531</td>
<td>Implantable Cardioverter Defibrillator Versus Optimal Medical Therapy In Patients With Variant Angina Manifesting as Aborted Sudden Cardiac Death (VARIANT ICD)</td>
<td>140</td>
<td>Jun 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

**VIII. Important Reminder**
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.
IX. References


92. Khairy P, Van Hare GF, Balaji S, et al. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). Endorsed by the governing bodies of PACES, HRS, the American College of Cardiology (ACC), the American Heart Association (AHA), the European Heart Rhythm Association (EHRA), the Canadian Heart Rhythm Society (CHRS), and the International Society for Adult Congenital Heart Disease (ISACHD). Can J Cardiol. Oct 2014;30(10):e1-e63. PMID 25262867.

X. Appendix

Table 1. New York Heart Association (NYHA) Functional Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td>
</tr>
</tbody>
</table>