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Reassessing the need for primary prevention implantable cardioverter-defibrillators in contemporary patients with heart failure

Ilan Goldenberg, MD,[1] Justin Ezekowitz, MBBCh, MSc,[2] Christine Albert, MD, MPH, FHRS,[3] Jeffrey D. Alexis, MD,[4] Lisa Anderson, MD,[5] Elijah R. Behr, MD,[5] James Daubert, MD, FHRS,[6] Katherine E. Di Palo, PharmD, MBA, MS,[7] Kenneth A. Ellenbogen, MD, FHRS,[8] Dillon J. Dzikowicz, PhD,[1] Eileen Hsich, MD,[9] David T. Huang, MD, FHRS,[4] James L. Januzzi, MD,[10] Valentina Kutyifa, MD, PhD, FHRS,[1] Anuradha Lala, MD,[11] Anekwe Onwuanyi, MD,[12] Ileana L. Piña, MD, MPH,[13] Roopinder K. Sandhu, MD, MPH, FHRS,[14] Samuel Sears, PhD,[15] Jakub Sroubek, MD, FHRS,[9] Robert Strawderman, ScD,[16] Wojciech Zareba, MD, PhD,[1] Javed Butler, MD, MPH[17]

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ABSTRACT

The main function of the implantable cardioverter-defibrillator (ICD) is to protect against sudden cardiac death (SCD) due to ventricular tachyarrhythmia (VTA). Current guidelines provide a recommendation to implant a prophylactic ICD for the primary prevention of SCD in individuals having heart failure with reduced ejection fraction (HFrEF) who never experienced a previous sustained VTA. However, these recommendations are based on clinical trials conducted more than 20 years ago and may not be applicable to contemporary patients with HFrEF who have a lower arrhythmic risk as a result of advances in heart failure medical therapies. Thus, there is an unmet need for more appropriate selection of contemporary patients with HFrEF for a primary prevention ICD. In this article, we review data underlying the current clinical equipoise on the need for routine implantation of a primary prevention ICD in patients with HFrEF and the rationale for conducting clinical trials that aim to reassess the role of the ICD in this population.

KEYWORDS Implantable cardioverter-defibrillator; Primary prevention; Sudden cardiac death; Heart failure with reduced ejection fraction; Guideline-directed medical therapy

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From the [1]Clinical Cardiovascular Research Center, University of Rochester, Rochester, New York, [2]The Canadian VIGOUR Centre at the University of Alberta, Edmonton, Alberta, Canada, [3]Department of Cardiology Cedars-Sinai Medical Center, Los Angeles, California, [4]Division of Cardiology, Department of Medicine, University of Rochester, Rochester, New York, [5]Cardiovascular and Genomics Research Institute, St. George's, University of London, London, United Kingdom; Cardiology, St. George's University Hospitals NHS Foundation Trust, London, United Kingdom, Department of Cardiology, Mayo Clinic Healthcare, London, United Kingdom, [6]Duke University, Durham, North Carolina, [7]Department of Medicine, Montefiore Medical Center, New York, New York, [8]Department of Cardiology, Virginia Commonwealth University Health, Richmond, Virginia, [9]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, [10]Massachusetts General Hospital, Harvard Medical School, Baim Institute for Clinical Research, Boston, Massachusetts, [11]Department of Cardiology, Mount Sinai Medical Center, New York, New York, [12]Division of Cardiology, Morehouse School of Medicine, Atlanta, Georgia, [13]Department of Cardiology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, [14]Department of Cardiology, University of Calgary, Calgary, Alberta, Canada, [15]Department of Cardiology and Department of Psychology, East Carolina University, Greenville, North Carolina, [16]Department of Biostatistics, University of Rochester, Rochester, New York, and [17]Baylor Scott and White Research Institute and HealthCare, Dallas, Texas.

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Introduction

Current recommendations for prophylactic primary prevention implantable cardioverter-defibrillator (ICD) implantation in individuals with heart failure with reduced ejection fraction (HFrEF)[1–5] originate from trials that found a significant survival benefit with a primary prevention ICD with a relative mortality risk reduction of 23%–34%.[6–8] However, in those trials the majority of study participants (>70%) randomized to the ICD arm did not receive lifesaving therapy from the ICD during long-term follow-up. Subsequent data showed that the rate of appropriate ICD shocks is ∼1%–3% per year in persons with either ischemic or nonischemic HFrEF in the background of previous guideline-directed medical therapy (GDMT), comprising mainly an evidence-based beta-blocker, angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB), and mineralocorticoid receptor antagonist (MRA).[9–11] Therefore, the majority of patients may not derive benefit but are exposed to the risk of adverse events associated with the ICD (including infection and inappropriate shocks). The introduction of angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) was shown to further reduce the risk of sudden cardiac death (SCD) in patients with HFrEF.[12–14] Use of comprehensive GDMT is associated with improvement in left ventricular ejection fraction (LVEF), which may explain in part the impact on risk for SCD.[15–17]

Three trials currently are reassessing the role of primary prevention ICDs in the setting of contemporary GDMT. The PROFID EHRA (Prevention of Sudden Cardiac Death After Myocardial Infarction by Defibrillator Implantation) trial in Europe aims to evaluate the benefit or harm of routine ICD implantation for primary prevention of SCD with contemporary GDMT in 3595 postmyocardial infarction patients with reduced LVEF ≤35%. The BRITISH (Using cardiovascular magnetic resonance identified scar as the Benchmark Risk Indication Tool for Implantable cardioverter defibrillators in patients with Non-Ischemic Cardiomyopathy and Severe systolic Heart failure) trial will assess whether the use of cardiac magnetic resonance–defined scar to direct ICD implantation in 1252 patients with nonischemic HFrEF and LVEF ≤35% is associated with a reduction in mortality. The CONTEMP-ICD (Comparative Effectiveness of ICD Versus Non-ICD Therapy in Contemporary Heart Failure Patients at a Low Risk for Arrhythmic Death) trial will randomize 3290 participants with ischemic or nonischemic HFrEF on optimal GDMT with a low arrhythmic risk, from the United States and Canada, to non-ICD vs ICD treatment arms.

Herein we review data on the current clinical equipoise on the need for routine implantation of a primary prevention ICD in patients with either ischemic or nonischemic HFrEF who receive contemporary GDMT to inform why conducting trials that aim to update the standard of care regarding primary prevention ICDs for patients with HFrEF is ethically justified and important.

Abbreviations

ACEI: angiotensin-converting enzyme inhibitor

ARB: angiotensin receptor blocker

ARNI: angiotensin receptor-neprilysin inhibitor

CV: cardiovascular

GDMT: guideline-directed medical therapy

HF: heart failure

HFrEF: heart failure with reduced ejection fraction

ICD: implantable cardioverter-defibrillator

LVEF: left ventricular ejection fraction

MRA: mineralocorticoid receptor antagonist

SCD: sudden cardiac death

SGLT2i: sodium-glucose cotransporter-2 inhibitor

VTA: ventricular tachyarrhythmia

ICD for the primary prevention of sudden death

The main function of an ICD is to protect a person against SCD due to ventricular tachyarrhythmia (VTA), by delivering a cardioverting or defibrillating shock and/or antitachycardia pacing, based on device programming.[18–21] During its early implementation, the ICD was used for individuals who had survived SCD or experienced life-threatening VTA.[22–25] In 1996, the first randomized controlled trial investigating the efficacy of prophylactic primary prevention ICD in patients at high risk for VTA but without previous arrhythmic events was published.[6] Since then, 3 primary prevention trials (MADIT-II [Multicenter Automatic Defibrillator Implantation Trial II],[6] DEFINITE [Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation],[7] and SCD-HeFT [Sudden Cardiac Death in Heart Failure Trial][8]) published in 2002–2005 reported all-cause mortality relative risk reductions in the range of 23%–31% with prophylactic ICD placement in persons with HFrEF (Figure 1).[6–8] This was largely driven by a reduction in SCD and was similar between those with ischemic and nonischemic HFrEF (hazard ratio [HR] 0.79 for ischemic and 0.73 for nonischemic etiology).[8] The absolute risk reduction in the risk of all-cause mortality with primary prevention ICDs was 6%–7% over 5 years.[6–8] These studies provided the evidence for the current recommendation for a primary prevention ICD in persons with HFrEF.[1–5]

However, significant advances in HFrEF medical therapy have occurred since the conduction of these trials, which had an impact on symptoms, left ventricular function, and risk for death.[12–17] Thus, the absolute benefit of the ICD in contemporary patients with HFrEF now may be lower, resulting in uncertainty regarding the balance of risks and benefits of primary prevention ICDs in all contemporary patients with HFrEF.[25–29] The variable risk-to-benefit ratio of the ICD in contemporary patients with HFrEF, as well as the improvement in HFrEF management compared to previous landmark ICD trials, both result in a clinical equipoise on the need for routine implantation of a primary prevention ICD in contemporary patients with HFrEF (Figure 2).

Attenuated benefit in contemporary patients with HFrEF

Declining utilization rates of the ICD

In the 3 landmark primary prevention ICD trials, the overall rate of appropriate ICD therapy for VTA was 27% (MADIT-

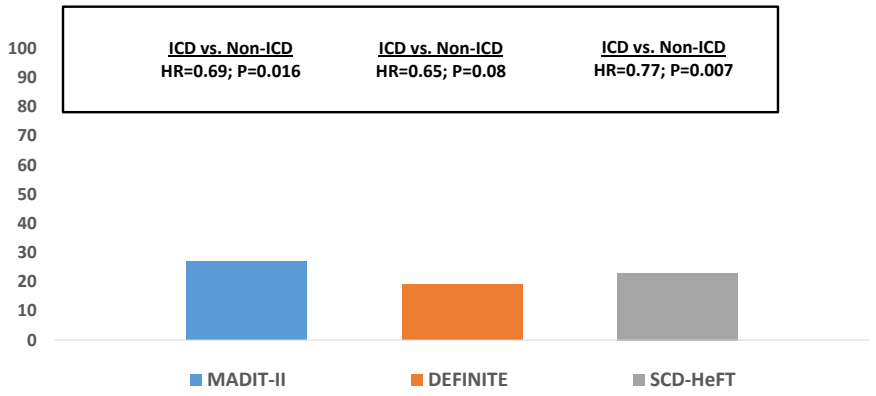

Figure 1
Outcomes and rates of appropriate implantable cardioverter-defibrillator (ICD) therapy for ventricular tachyarrhythmias in landmark primary prevention ICD trials. HR = hazard ratio. (Data are derived from references 6–8.)

II),[6] 20% (DEFINITE),[7] and 19% (SCD-HeFT)[8] at 5 years (Figure 1). Thus, most participants did not utilize the device during the trial, despite a statistically significant overall mortality reduction. Accordingly, in MADIT-II, ICD therapy was associated with only 0.167 life-year saved (2 months) during the trial[6] and 0.52 life-year saved (6.2 months) over an extended follow-up of 8 years.[30] An analysis of >4000 participants enrolled in 3 MADIT primary prevention ICD trials (MADIT-II, MADIT-CRT, MADIT-RIT) from 1997 to 2011 showed a further reduction in the 1-year rate of life-threatening fast VTA (≥200 bpm or ventricular fibrillation) in ICD recipients: from 7% in MADIT-II (conducted in the years 1997–2001); 5% in MADIT-CRT (conducted in the years 2004–2009); and to 3% in MADIT-RIT (conducted in the years 2009–2011).[10,31] In a more recent analysis of a national registry, which included individuals with a primary prevention ICD from 2010–2015, we reported an appropriate shock rate of only 1%–3% per year, which was lower than the rate of inappropriate ICD therapy.[11] Of note, contemporary data demonstrating the low rate of appropriate ICD therapy for VTA in real-world and clinical trial settings were observed in the setting of standard GDMT for HFrEF, comprising mainly beta-blocker, ACEI or ARB, and MRA in approximately one-quarter of patients, even before the advent of ARNI and SGLT2i, 2 therapies that seem to further reduce event rates.

Mechanisms that may explain the recent reduction in the rate of appropriate ICD therapy among primary prevention recipients are multiple, and include improved coronary

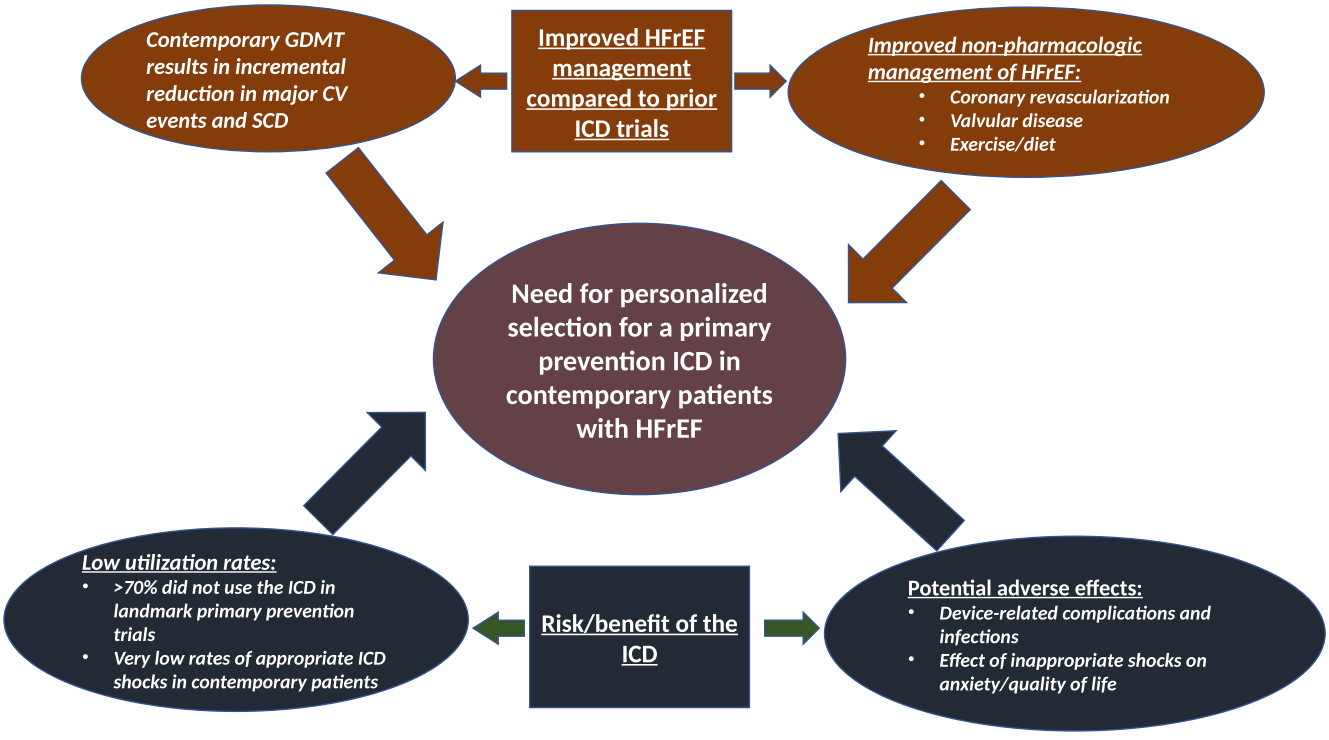

Figure 2
Clinical equipoise on the need for a primary prevention implantable cardioverter-defibrillator (ICD) in all contemporary patients with heart failure with reduced ejection fraction (HFrEF). CV = cardiovascular; GDMT = guideline-directed medical therapy; SCD = sudden cardiac death.

revascularization rates, improved HFrEF GDMT, more advanced ICD programming to a high-rate cutoff and longer delays before treatment, broader application of ICDs into lower-risk populations, and improved management of valvular disease (Figure 2).

Nevertheless, yearly rates of appropriate ICD shocks on average of 2% still are compatible with the up to 20% appropriate ICD shock rate over the current estimated ICD battery lifetime. Furthermore, these data do not take into account that a relatively high proportion of mortality cases among patients with no ICD that may be due to VTA.[32] Therefore, additional risk stratification strategies for arrhythmic risk within the HFrEF population still are warranted, despite declining appropriate ICD intervention rates (see section on Risk Stratification for a Primary Prevention ICD in Patients With HFrEF).

Declining rates of SCD

Improved GDMT has been associated with a corresponding decline in the risk of SCD in patients with HFrEF (Figure 3).[33] Declining rates of SCD in contemporary patients with HFrEF may explain the outcome of the more recent DANISH (Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure) trial (Figure 4).[34] In this study, 1116 patients with nonischemic HFrEF who received standard GDMT (beta-blocker 92%; ACEI/ARB 96%; MRA 58%) were randomized to ICD vs no ICD treatment. Both the absolute rate of SCD and the proportion of deaths due to SCD were lower in this trial compared to the earlier trials, and at 8 years, treatment with an ICD was not associated with a significant survival benefit (hazard ratio 0.82; $P = .28$).[33] However, the generalizability of the DANISH trial results to real-world patients with nonischemic HFrEF is limited by several important factors, including (1) the inclusion of elevated pro-BNP in the eligibility criteria, which may have biased the results toward a higher risk of heart failure [HF] death than SCD; (2) the fact that 58% of patients in both arms of the trial received a cardiac resynchronization therapy device; (3) the high level of target GDMT achieved at baseline that does not reflect real-world clinical practice; and (4) the lack of statistical power to assess noninferiority. It also should be noted that the prespecified subgroup analysis of DANISH showed an age-dependent association between ICD implantation and mortality, wherein an age cutoff for ICD implantation at ≤70 years yielded the highest survival for the population as a whole.[35] The limitations of DANISH and its *post hoc* findings resulted in a subsequent discrepancy between U.S. and European recommendations for a primary prevention ICD in patients with a nonischemic etiology of HFrEF.[2–5] Therefore, additional studies are needed to further reassess the role of the ICD in contemporary patients with chronic nonischemic HFrEF.

Improved medical management and coronary revascularization rates were shown to reduce arrhythmic risk and improve survival in contemporary patients with chronic ischemic HFrEF.[36] Furthermore, a survey of current practice reported that the majority of patients (>90%) who receive a primary prevention ICD, regardless of HF etiology, undergo generator replacement even though they have not experienced any ventricular tachycardia or appropriate ICD therapy.[37] Thus, there is an unmet need to reassess the yield of ICD placement for the primary prevention of SCD in contemporary patients with either ischemic or nonischemic HFrEF.

Contemporary therapy for HF

Newer pharmacologic therapies for HFrEF, including ARNI[12] and SGLT2i,[13,14] were shown to further reduce the risk of HF events, cardiovascular (CV) mortality, and SCD, when administered on top of standard GDMT. A recent cross-trial

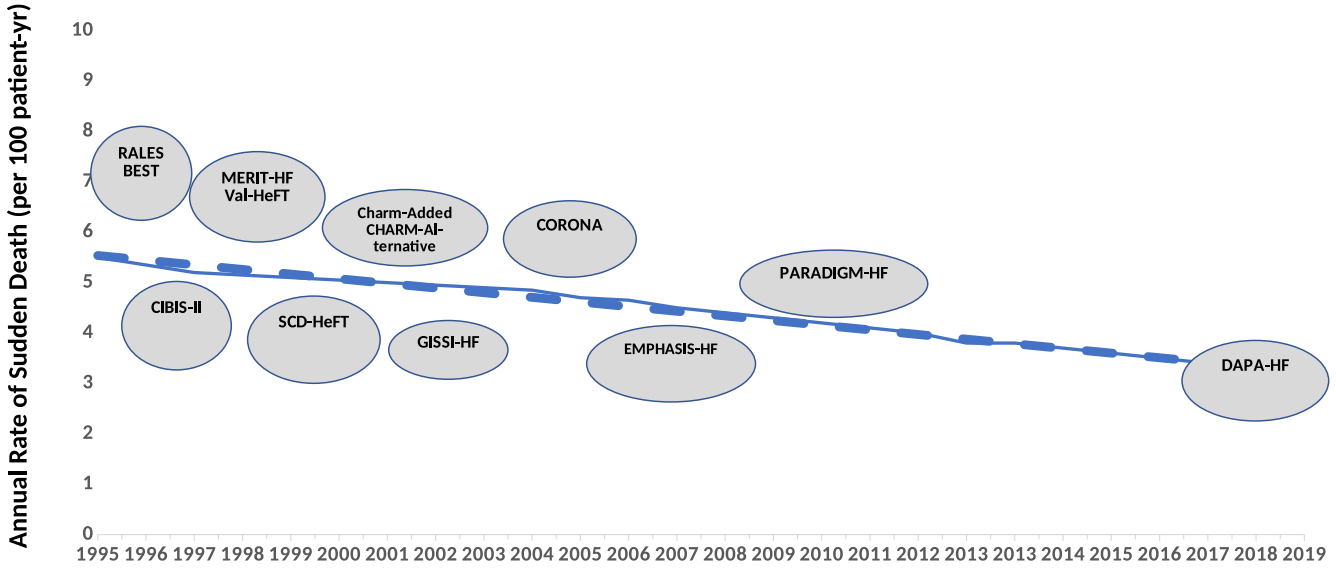

Figure 3
Decline in the rate of sudden cardiac death in clinical trials of patients with heart failure with reduced ejection fraction over the past 3 decades. (Modified from reference 33.)

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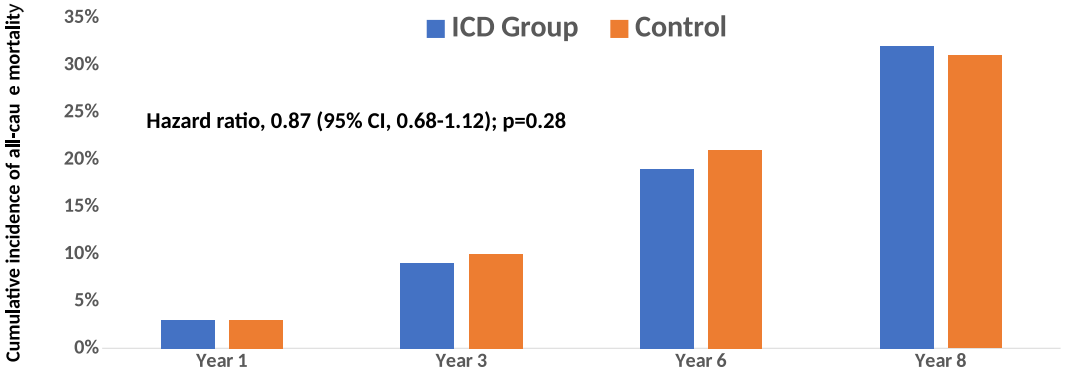

Figure 4
All-cause mortality during follow-up by treatment arm in the DANISH trial. CI = confidence interval; ICD = implantable cardioverter-defibrillator. (Modified from reference 34.)

analysis (the Lancet 2020)[38] showed that the anticipated aggregate treatment effects of comprehensive contemporary GDMT with beta-blocker, MRA, ARNI, and SGLT2i are substantially greater compared with dual therapy of ACEI/ARB and beta-blocker, resulting in an additional 62% reduction in the risk of the composite outcome of HF/CV death, a 50% reduction in the risk of CV death alone, leading to 6.3 years of life gained with early implementation of contemporary HF management.[38] A recent network meta-analysis of 75 HFrEF trials, representing 95,444 participants, further showed that a combination of ARNI, beta-blocker, MRA, and SGLT2i is most effective in reducing all-cause death (hazard ratio 0.39; 95% confidence interval 0.31–0.49) (Figure 5A).[39] Thus, comprehensive contemporary GDMT for HFrEF is likely to attenuate the survival benefit of prophylactic ICD therapy shown in previous landmark trials.

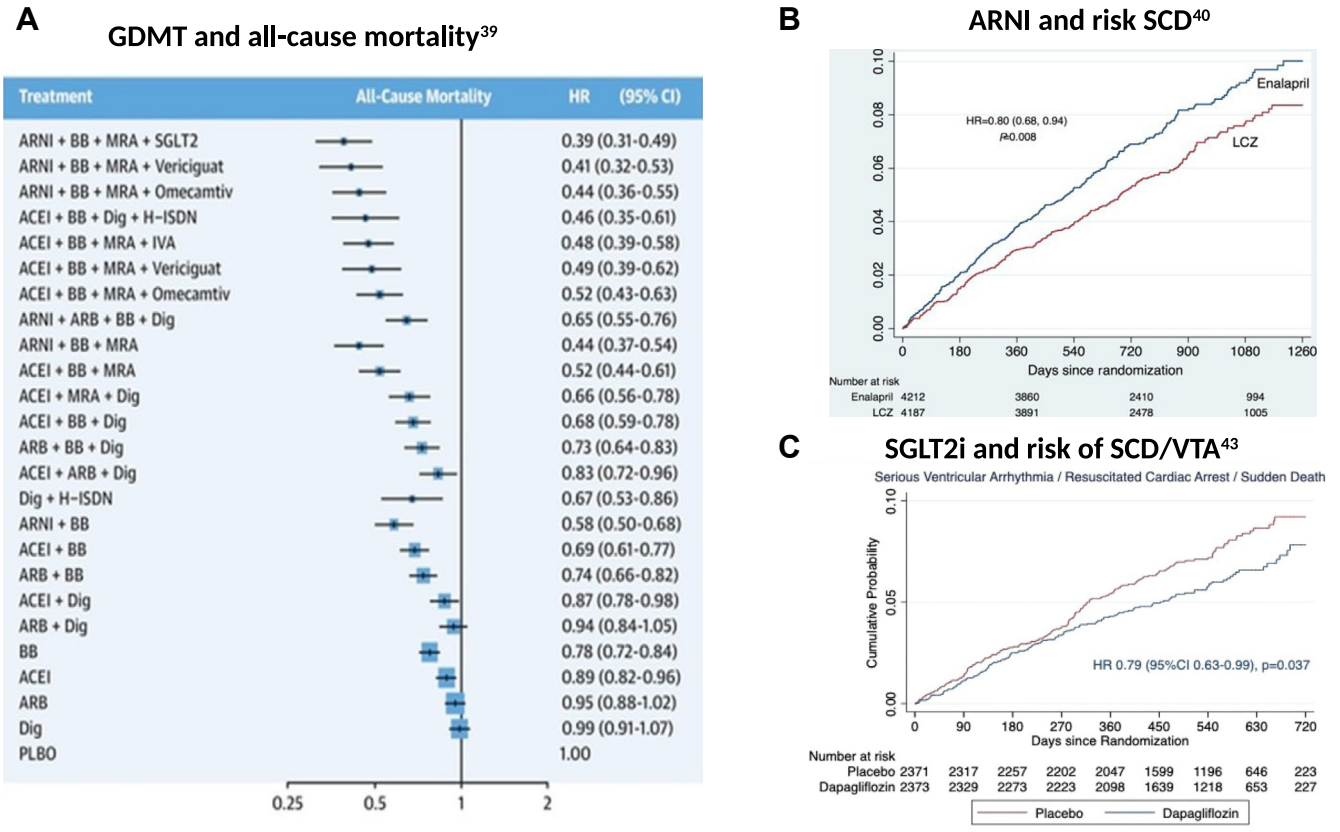

Figure 5
A: Effect of contemporary guideline directed medical therapy (GDMT) on all-cause mortality. **B:** Effect of angiotensin receptor-neprilysin inhibitor (ARNI) on the risk of sudden cardiac death (SCD). **C:** Effect of sodium-glucose cotransporter-2 inhibitor (SGLT2i) on the risk of SCD or ventricular tachyarrhythmia (VTA). BB = beta-blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; Dig = digoxin; H-ISDN = hydralazine-isosorbide mononitrate; HR = hazard ratio; IVA = ivabradine, LCZ = LCZ696 (ARNI); MRA = mineralocorticoid receptor antagonist. [Reprinted with permission from references 39 (**A**), 40 (**B**), and 43 (**C**).]

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ARNI

In the PARADIGM-HF (Prospective Comparison of ARNI with an ACE-Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[12] sacubitril/valsartan was associated with a significant 20% reduction in the composite primary outcome of CV death or hospitalization for HF and with a 16% reduction in all-cause mortality.[12] Accordingly, ARNI treatment now has a Class I recommendation for patients with HFrEF.[4,5] Importantly, in PARADIGM-HF, treatment with ARNI was also shown to be associated with a significant reduction in VTA, appropriate ICD shocks, and SCD (Figure 5B).[40,41] Nevertheless, in this trial, primary prevention ICDs were underutilized, particularly in Eastern Europe, and use of an ICD still was associated with a reduction in SCD.[42] However, ICD use was not randomized,[42] so this result remains subject to confounding by patient characteristics. In the PROVE-HF (Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/Valsartan Therapy for Heart Failure) study, use of sacubitril/valsartan was associated with 62% of study participants who were eligible for ICD implantation with LVEF $\leq$35% at study entry showing LVEF >35% after 12 months of treatment.[15]

SGLT2i

The DAPA-HF (Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure With Reduced Ejection Fraction) and EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trials have shown significant improvement in outcomes in patients with HFrEF when treated with SGLT2i.[13,14] Moreover, in DAPA-HF, use of dapagliflozin also was associated with a significant 21% relative risk reduction in SCD or serious ventricular arrhythmias (Figure 5C).[43] In a manner similar to sacubitril/valsartan, use of SGLT2i may also result in reverse cardiac remodeling, which would be expected to reduce risk for VTA and SCA.[16,17]

It should be noted that, even though guidelines strongly recommend that patients with HFrEF be treated with all 4-pillar GDMT at optimal dosages,[4] implementation of this recommendation is variable and suboptimal in real-world clinical practice,[44] possibly because of intolerability and copay issues. Thus, patients with HFrEF who are on suboptimal GDMT still may need to be protected by an ICD (see section on Optimized Medical Management).

Adverse events and health care utilization associated with primary ICD implantation

Most contemporary patients implanted with a primary prevention ICD do not utilize the device during long-term follow-up but still are exposed to the risk of device-related complications that may necessitate hospitalization and operative device revision or replacement. Thus, more appropriate selection for primary ICD therapy has important patient-centered and health care utilization implications.

Patient-related outcomes

ICDs can prevent SCD but cannot affect the underlying cardiac substrate. Thus, the potential longer lifespan enjoyed by persons with a primary prevention ICD is shifting the clinical burden to the resulting increase in CV events and to the possibility of repeated ICD shocks.[45–47] Figure 6 shows 4-year rates of CV events associated with transvenous ICD vs no ICD treatment, showing increased rates of HF admissions (10%),[48] inappropriate ICD shocks (8%),[49] and major device-related complications requiring admission and/or intervention (10%).[49,50] Multiple studies have shown that approximately one-third of persons who receive either an appropriate or inappropriate ICD shock develop some form of psychological distress in the aftermath, and

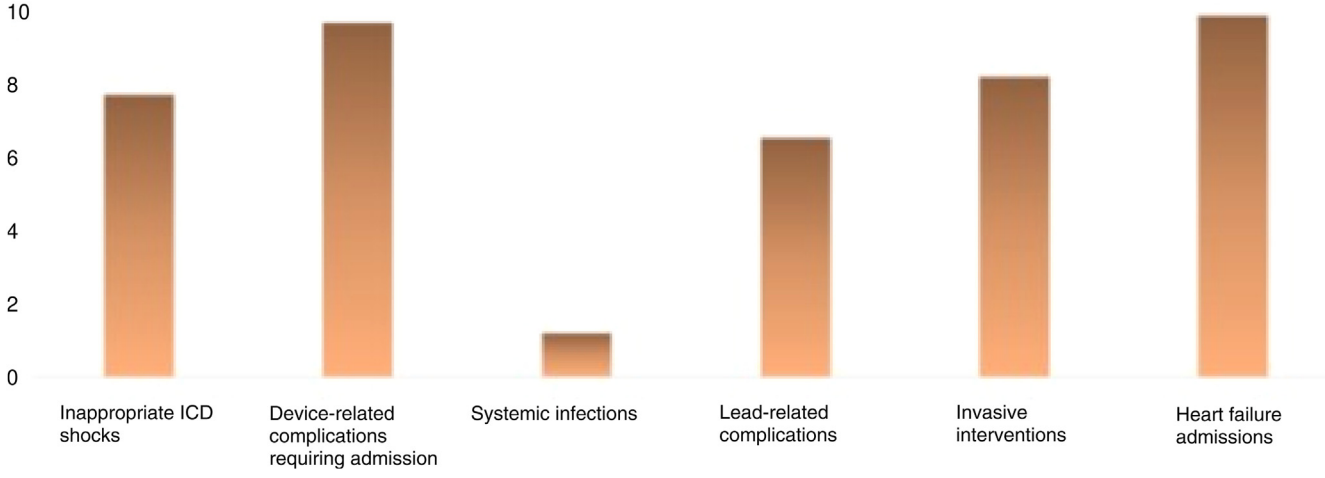

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Figure 6
Four-year rates of major cardiovascular complications associated with implantable cardioverter-defibrillator (ICD) vs no ICD therapy. (Data are derived from references 48–50.)

substantial reductions in physical activity have been noted,[45–47] whereas currently only a distinct minority of individuals with an ICD receive appropriate lifesaving therapy from the device (1%–3% annually).[11] Regardless of ICD shocks, up to 15% of persons express some difficulty in emotional adjustment following ICD implantation, with younger patients most affected.[47] Thus, the potential survival benefit of prophylactic ICD placement comes at the cost of increased risk for major CV complications, reduced quality of life, and increased potential for postshock anxiety. It should also be noted that the current risks associated with ICDs have decreased significantly (including rates of inappropriate shocks).[51] Therefore, the risks/benefits of the ICD in a contemporary setting are unclear.

Health care utilization

Despite lack of contemporary data on uniform benefit of routine ICD implant in all patients with HFrEF and the risk of device-related complications and inappropriate ICD shocks, the number of ICD implants is rising globally. According to a recent report, the global ICD market was valued at $6.6 billion in the year 2017 and is estimated to reach $8.3 billion by 2026.[52,53] Furthermore, MADIT-II data on the cost-effectiveness of prophylactic ICD per current guidelines suggest a relatively high incremental cost-effectiveness ratio of $235,000 per year-of-life saved at 3.5 years and $78,600 to $114,000 at 12 years.[54] Thus, findings from trials designed to personalize selection for primary ICD therapy may have major implications on health care utilization.

Risk stratification for a primary prevention ICD in patients with HFrEF

As noted earlier, 3 trials currently are reassessing the role of primary prevention ICDs, using different risk stratification approaches. The PROFID EHRA trial in Europe aims to evaluate the noninferiority of no ICD vs routine ICD implantation in 3595 postmyocardial infarction patients with reduced LVEF ≤35% who receive optimal GDMT.[55] This trial is conducted without further risk stratification for arrhythmic risk in this population.

Cardiac magnetic resonance–identified scar has emerged as a compelling risk factor for the prediction of SCD in nonischemic HFrEF.[56,57] However, data with regard to its utility in stratifying patients who would benefit from an ICD vs those who would not are limited.[58,59] The BRITISH trial will assess whether the use of cardiac magnetic resonance–defined scar to direct ICD implantation in 1252 patients with nonischemic HFrEF and LVEF ≤35% is associated with a reduction in mortality.[60]

In the CONTEMP-ICD trial, we will rely on clinical risk assessment by weighing the patient-specific risk of VTA (for which primary device implantation may be lifesaving) against the competing risk of nonarrhythmic mortality (for which primary ICD implantation does not provide protection). We recently developed and externally validated an ICD benefit prediction score that integrates these competing risks (Figure 7).[61] The study population comprised all 4531 patients

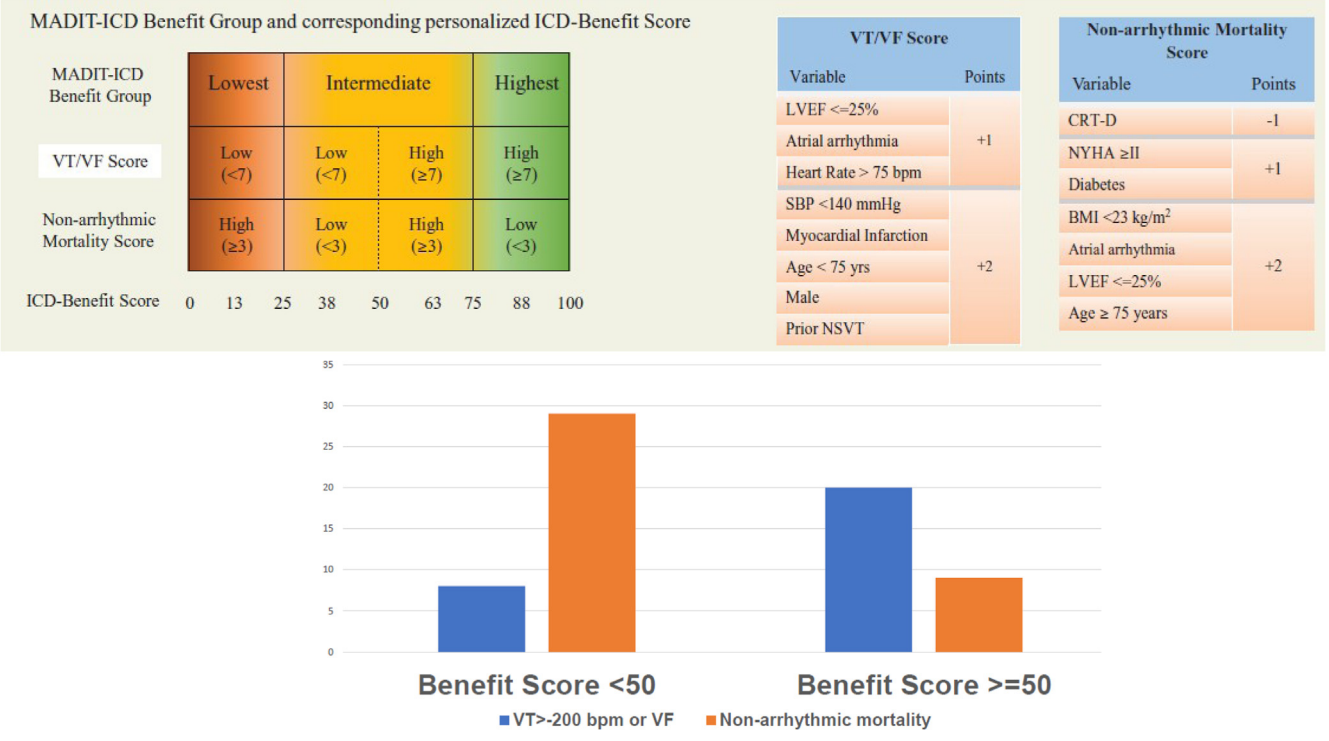

Figure 7

MADIT-ICD Benefit Score*. BMI = body mass index; CRT-D = cardiac resynchronization therapy–defibrillator; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; SBP = systolic blood pressure. VF = ventricular fibrillation; VT = ventricular tachycardia. (Reprinted with permission from reference 61.)

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enrolled in all MADIT trials (MADIT-II, MADIT-CRT, MADIT-RISK, and MADIT-RIT), including 3001 patients with ischemic cardiomyopathy (66%) and 1532 patients with nonischemic cardiomyopathy (34%). We identified 8 simple clinical predictors of life-threatening VTA (ventricular tachycardia ≥200 bpm or ventricular fibrillation) and 7 predictors of nonarrhythmic mortality (Figure 7, right). The 2 scores were combined to create a scale of ICD benefit in the total population (Figure 7, left), and a personalized ICD Benefit Score was developed based on the distribution of the 2 competing risks scores in the study population (https://is.gd/madit). The C indices for VTA and nonarrhythmic mortality scores were 0.83 and 0.81, respectively. External validation in the more contemporary primary prevention RAID (Ranolazine in High-Risk ICD Patients) trial population[61] and in additional 4 independent large external contemporary cohorts[62–65] confirmed model stability, with similar C indices for the VTA and the nonarrhythmic mortality scores. Nevertheless, additional, more comprehensive, external validations studies for the MADIT-ICD Benefit Score are warranted in contemporary patients with HFrEF. Furthermore, there is a need to continue developing and refining new risk scores for primary ICD implant in contemporary cohorts, which will include clinical, biological, and advanced imaging factors that are not included in the present score.

The MADIT-ICD Benefit Score can be used to identify persons with HFrEF with a lower predicted risk of life-threatening VTA vs nonarrhythmic mortality (Figure 7, bottom) who may not benefit from a primary prevention ICD and thus was incorporated into the inclusion criteria of the CONTEMPT-ICD trial (Table 1). We decided to rely on clinical risk stratification, despite its potential limitations compared to structural risk assessment by use of cardiac magnetic resonance–defined scar burden, to enhance the generalizability and practical dissemination of the trial results into clinical practice because the routine use of cardiac magnetic resonance in patients with either ischemic or nonischemic HFrEF still has not been uniformly implemented into real-world clinical practice. Nevertheless, it is possible that the clinical score may fail to identify patients with high structural risk for VTA. Therefore, cardiac magnetic resonance imaging data, when performed as standard of care, will also be collected during the trial to determine the incremental yield of scar burden assessment to clinical risk stratification.

CONTEMP-ICD trial

CONTEMP-ICD is a prospective, multicenter, open-label, randomized controlled trial enrolling 3290 participants with HFrEF who are treated with optimally tolerated stable GDMT and are eligible for a primary prevention ICD[4,5] but who have a lower predicted risk of life-threatening VTA than nonarrhythmic mortality. We have obtained letters of support from principal investigators of 115 U.S. and Canadian centers, each stating that they agree that there is an equipoise on the need for routine implantation of a primary prevention ICD in all patients with HFrEF. Both electrophysiology and HF specialists from each site will participate in the trial, as either site Principal Investigator or Co-Principal Investigator, to ensure comprehensive assessment of management and outcomes in both arms. Enrolled participants will be randomized to non-ICD vs ICD treatment arms. We hypothesize that in patients with HFrEF who are at a lower predicted arrhythmic risk, non-ICD is noninferior to ICD with respect to the primary

Table 1 Eligibility criteria for CONTEMP-ICD

Inclusion criteria	Exclusion criteria
Age ≥18 years	Existing ICD/CRT-D
Class I or IIa indication for a primary prevention ICD[4]	Class I or IIa indication for CRT[4]
Echocardiogram* documenting LVEF ≤35% after being stable for 1 month on optimal GDMT†	Acute MI within the past 3 months
Optimal GDMT is prespecified as either receiving all 4 pillar therapies (beta-blockers, ARNI, MRA, and SGLT2i) or GDMT Score[66] ≥6 (with documented reason for not receiving all 4 therapies)	Chronic renal failure requiring hemodialysis
MADIT-ICD Benefit Score < 50[61]: This range includes only patients in whom the predicted risk of nonarrhythmic mortality is greater than the predicted risk for the development of life-threatening ventricular tachyarrhythmias (Figure 7, bottom)	Coronary revascularization within the past 3 months
Ischemic or nonischemic‡ cardiomyopathy	History of sustained VT or VF
	Life expectancy <1 year
	Inability to consent

ARNI = angiotensin receptor-neprilysin inhibitor; CONTEMP-ICD = Comparative Effectiveness of ICD Versus Non-ICD Therapy in Contemporary Heart Failure Patients at a Low Risk for Arrhythmic Death; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; VF = ventricular fibrillation; VT = ventricular tachycardia.

*Performed as a standard of care procedure.

†Components of GDMT Score may be updated per update in heart failure guidelines.

‡Unless known genetic cause of cardiomyopathy.

endpoint of all-cause mortality and superior with respect to the secondary endpoint of survival free of major CV events requiring admission (Figure 6). Eligibility criteria are listed in Table 1. The trial is funded by the Patient Centered Outcome Research Institute (PCORI) and has engaged representatives from Heart Rhythm Society (HRS), Heart Failure Society of America (HFSA), American College of Cardiology (ACC), American Heart Association (AHA), Association of Black Cardiologist (ABC), and Women Heart. The trial is further endorsed globally by the Canadian Heart Rhythm Society (CHRS), Canadian Heart Failure Society (CHFS), European Heart Rhythm Association (EHRA), and Heart Failure Association of the ESC (HFA).

Mitigating concerns of randomization to non-ICD treatment in contemporary patients with HFrEF

Participants randomized to the non-ICD arm of the CONTEMP-ICD trial will be treated with stable optimal GDMT at enrollment based on inclusion criteria but will not receive an ICD for primary prevention. Therefore, participants allocated to this arm will not be protected from the risk of SCD upon the development of life-threatening ventricular tachycardia/ventricular fibrillation. Although the rates of SCD have declined substantially over time among ambulatory persons with HFrEF in randomized clinical trials of pharmacologic therapy,[33] there still is evidence of residual SCD and VTA rates among patients with HFrEF in several observational registries and recent clinical trials.[40–42,67] Furthermore, in contrast to the negative outcome in DANISH, recent observational data and a meta-analysis still show a survival benefit of primary ICD in patients with HFrEF.[68–72] The CONTEMP-ICD trial is designed to mitigate concerns of non-ICD treatment in persons with HFrEF, despite indication for the device, by utilizing the following measures:

1. *Personalized Risk Assessment:* Inclusion criteria will require having a lower predicted risk of life-threatening VTA vs nonarrhythmic mortality based on the MADIT-ICD Benefit Score (Figure 7, bottom).[61] Despite being new, we believe that using the novel MADIT-ICD Benefit Score in this comparative effectiveness clinical trial has important advantages: (I) using the score can reduce ethical concerns of randomizing patients who have a high predicted arrhythmic risk to no-ICD therapy; (II) it takes into account the competing risk of life-threatening ventricular tachycardia/ventricular fibrillation vs the competing risk of nonarrhythmic mortality (whereas older scores, such as the Seattle Heart Failure Model[73,74] and our previous MADIT-II score,[75] only stratified risk by all-cause mortality); (III) it is based on simple, readily available, clinical factors that can easily be implemented in real-world clinical practice following trial completion; and (IV) high performance and external validation in contemporary cohorts.[61–65] Nevertheless, the aforementioned limitations of the score, including the need for additional external real-world contemporary validation studies and the fact that it does not take into account structural risk, will be presented to patients and providers.
2. *Optimized Medical Management:* Guidelines recommend that patients with HFrEF be treated with multiple medications proven to improve outcomes, as tolerated.[4,5] Currently the "4 pillars" of GDMT for HFrEF consist of beta-blocker, ARNI (or ACEI/ARB as an alternative if ARNI not tolerated or inaccessible), MRA, and SGLT2i. However, implementation of this recommendation is variable and suboptimal in practice.[76] Furthermore, current guidelines for a primary prevention ICD state that consideration should be given to patients "on GDMT" but do not specify the type and dosages comprising optimal GDMT required prior to device implantation or documentation of reasons for lack of optimal GDMT,[1–5] resulting in wide variability in the medical management of patients who receive an ICD.[44,76] To address variability in management for HFrEF in clinical practice, the inclusion criteria of the CONTEMPT-ICD trial require that candidates for participation either are treated with all "4 pillars" of GDMT (Figure 8, left) or have GDMT Score $\geq$6 (Figure 8, right).[66] The GDMT Score was developed by the Heart Failure Collaboratory (comprising investigators, clinicians, patients, government representatives including U.S. Food and Drug Administration, and National Institutes of Health participants, payers) to ensure consistent and optimal GDMT management in clinical trials of HFrEF.[66]
3. *Implementation of GDMT Optimization:* Novel HF medications require 3–6 months to meaningfully improve reverse remodeling and LVEF as well as to impact patients' CV mortality or SCD risk.'[77] In CONTEMP-ICD, recently developed guidance will be provided to sites on protocolized 4-pillar GDMT implementation in patients with newly diagnosed HFrEF,[78] with real-world measures to address co-pay issues and consideration of providing SCD protection with a temporary wearable cardioverter-defibrillator while patients are being medically optimized.[79] Following contemporary GDMT optimization, individuals with newly diagnosed HFrEF will be screened for eligibility for the trial.
4. *Discussion With Eligible Patients:* The potential risk of not being implanted with a primary prevention ICD, despite current guideline recommendation, will be discussed in detail with eligible patients before enrollment and will be detailed and stressed in the patient consent form. Patient discussion material was carefully developed by the Steering Committee and our Patient Partners.
5. *In-Trial Risk Assessment:* Study participants who will develop sustained ventricular tachycardia or ventricular fibrillation during the trial will cross over to the ICD arm and will be implanted with an ICD for secondary prevention. In addition, the trial will utilize a group sequential design for monitoring harm of non ICD vs ICD using the log-rank statistic for time to death at an overall 1-sided significance level of 2.5%. A data safety monitoring board will closely follow unblinded data, with stringent stopping rules upon any signal of potential harm.

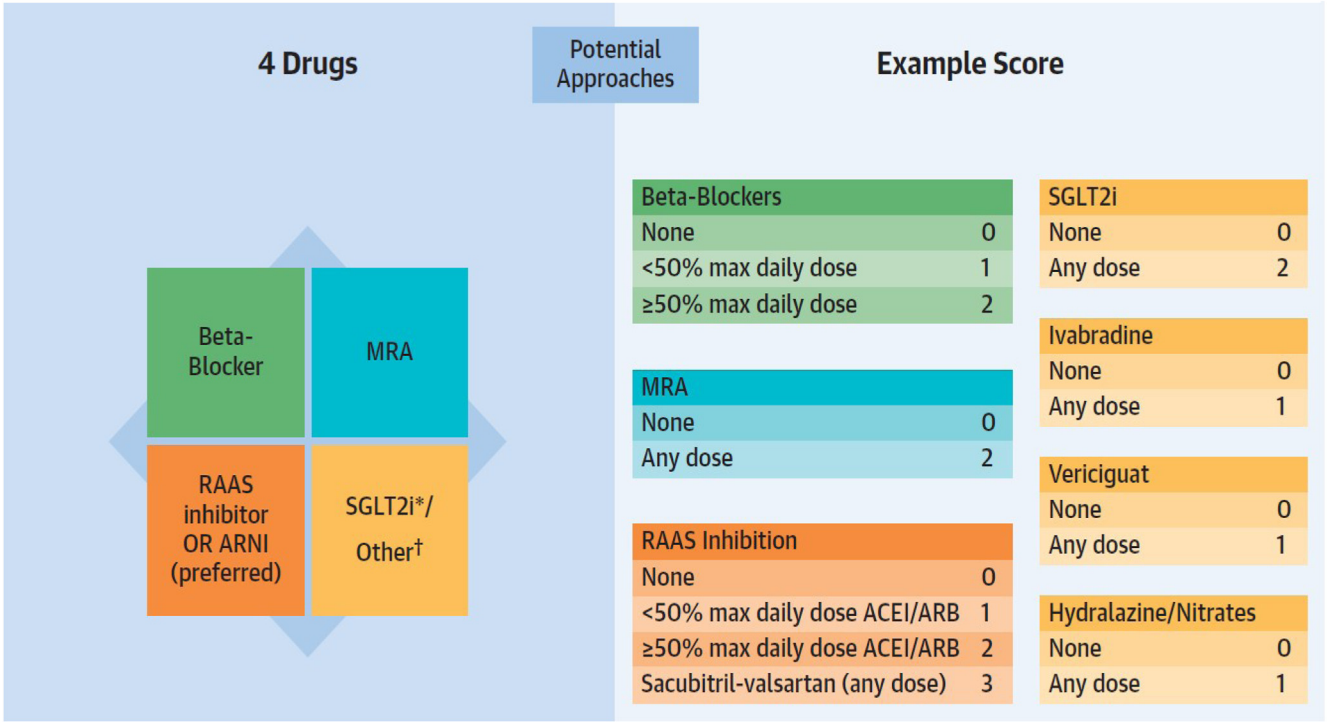

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Figure 8
Guideline-directed medical therapy (GDMT) Score. RAAS = renin-angiotensin-aldosterone system; other abbreviations as in Figure 5. (Reprinted with permission from reference 76.)

6. *Exclusion of Individuals Who Are Eligible for Cardiac Resynchronization Therapy:* Cardiac resynchronization therapy was shown to result in reverse remodeling, HF improvement, and antiarrhythmic effects.[80] This is particularly evident in those in sinus rhythm with left bundle branch block who form ~25% of patients with HFrEF.[71] This mode of therapy should not be denied to eligible HFrEF patients. Thus, CONTEMP-ICD is focused on current equipoise on the need for prophylactic ICD placement in HFrEF patients who are at lower arrhythmic risk and are not indicated for cardiac resynchronization therapy.
7. *Crossover:* The protocol allows crossover from the non-ICD to the ICD arm, based on provider (treating physician) discretion. The primary analysis of the study will be performed on an intention-to-treat basis. However, we will also carry out a secondary on-treatment analysis that takes into account crossover between arms during the trial to validate the consistency of our findings after taking into account the outcome of patients who received an ICD during the trial.

Conclusion

Landmark primary prevention ICD trials have shown a survival benefit with prophylactic ICD placement. However, rates of life-threatening VTA and the need for appropriate intervention by the ICD in primary prevention recipients have declined as a result of advancements in pharmacological and nonpharmacologic HF therapy, reaching an average of 2% per year. The recent introduction of ARNI and SGTL2i was shown to further improve CV morbidity and mortality and SCD in patients with HFrEF. Thus, patients with HFrEF and a low arrhythmic risk may not derive a benefit from a prophylactic ICD but still may be exposed to the complications of an intracardiac device. CONTEMP-ICD will compare ICD to non-ICD therapy in HFrEF patients with a predicted low arrhythmic risk, and this trial may significantly impact the management of a large and increasing population of HF patients globally. If the trial confirms the hypothesis, it is expected that approximately one-half of HFrEF patients who currently are being referred for prophylactic ICD placement will no longer be indicated for a device.

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Address reprint requests and correspondence: Dr Ilan Goldenberg, Clinical Cardiovascular Research Center, University of

Rochester Medical Center, 265 Crittenden Blvd, CU 420653, Rochester, NY14642. E-mail address: ilan.goldenberg@heart.rochester.edu; or Dr Javed Butler, Baylor Scott and White Research Institute, 3434 Live Oak St, Dallas, TX 75204. E-mail address: Javed.Butler@BSWHealth.org

References

1. Epstein AE, DiMarco JP, Ellenbogen KA, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2013;127:e283–e352.
2. Al-Khatib SM, Stevenson WG, Ackerman MJ, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm 2018;15:e190–e252.
3. Zeppenfeld K, Tfelt-Hansen J, de Riva M, et al; ESC Scientific Document Group. 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Eur Heart J 2022;43:3997–4126.
4. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e876–e894.
5. McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: DEVELOPED by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2022;24:4–131.
6. Moss AJ, Zareba W, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial II Investigators. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–883.
7. Kadish A, Dyer A, Daubert JP, et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004;350:2151–2158.
8. Bardy GH, Lee KL, Mark DB, et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–237.
9. Goldenberg I, Huang DT, Nielsen JC. The role of implantable cardioverter-defibrillators and sudden cardiac death prevention: indications, device selection, and outcome. Eur Heart J 2020;41:2003–2011.
10. Kutyifa V, Cannom DS, Daubert JP, et al. Decline in ventricular arrhythmia events and mortality in the Multicenter Defibrillator Implantation Trials. Heart Rhythm 2019;16:966–969.
11. Sabbag A, Suleiman M, Laish-Farkash A, et al; Israeli Working Group of Pacing and Electrophysiology. Contemporary rates of appropriate shock therapy in patients who receive implantable device therapy in a real-world setting: From the Israeli ICD Registry. Heart Rhythm 2015;12:2426–2433.
12. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.
13. McMurray JJV, Solomon SD, Inzucchi SE; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
14. Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383:1413–1424.
15. Felker GM, Butler J, Ibrahim NE, et al; PROVE-HF Investigators. Implantable cardioverter-defibrillator eligibility after initiation of sacubitril/valsartan in chronic heart failure: insights from PROVE-HF. Circulation 2021;144:180–182.
16. Santos-Gallego CG, Vargas-Delgado AP, Requena-Ibanez JA; EMPA-TROPISM (ATRU-4) Investigators. Randomized trial of empagliflozin in nondiabetic patients with heart failure and reduced ejection fraction. J Am Coll Cardiol 2021;77:243–255.
17. Lee MMY, Brooksbank KJM, Wetherall K. Effect of empagliflozin on left ventricular volumes in patients with type 2 diabetes, or prediabetes, and heart failure with reduced ejection fraction (SUGAR-DM-HF). Circulation 2021;143:516–525.
18. Beck CS, Pritchard WH, Feil HS. Ventricular fibrillation of long duration abolished by electric shock. J Am Med Assoc 1947;135:985.
19. Zoll PM, Linenthal AJ, Gibson W, Paul MH, Norman LR. Termination of ventricular fibrillation in man by externally applied electric countershock. N Engl J Med 1956;254:727–732.
20. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. N Engl J Med 1980;303:322–324.
21. Mirowski M. The automatic implantable cardioverter-defibrillator: an overview. J Am Coll Cardiol 1985;6:461–466.
22. Antiarrhythmics versus Implantable Defibrillators Investigator. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576–1583.
23. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297–1302.
24. Kuck KH, Cappato R, Siebels J, Ruppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000;102:748–754.
25. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg . Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071–2078.
26. Butler J, Talha KM, Aktas MK, Zareba W, Goldenberg I. Role of implantable cardioverter defibrillator in heart failure with contemporary medical therapy. Circ Heart Fail 2022;15:e009634.
27. Boriani G, Leyva F. Prophylactic cardioverter defibrillator utilization in the "real world": a conundrum. Int J Cardiol 2012;156:123–124.
28. Barra S, Providencia R, Paiva L, Heck P, Agarwal S. Implantable cardioverter-defibrillators in the elderly: rationale and specific age-related considerations. Europace 2015;17:174.
29. Fonarow GC, Albert NM, Curtis AB, et al. Associations between outpatient heart failure process-of-care measures and mortality. Circulation 2011;123:1601.
30. Goldenberg I, Gillespie J, Moss AJ, et al. Executive Committee of the Multicenter Automatic Defibrillator Implantation Trial II. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. Circulation 2010;122:1265–1271.
31. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275–2283.
32. Packer M. What causes sudden death in patients with chronic heart failure and a reduced ejection fraction? Eur Heart J 2020;41:1757–1763.
33. Shen L, Jhund PS, Petrie MC, et al. Declining risk of sudden death in heart failure. N Engl J Med 2017;377:41–51.
34. Kober L, Thune JJ, Nielsen JC, et al; DANISH Investigators. Defibrillator implantation in patients with nonischemic systolic heart failure. N Engl J Med 2016;375:1221–1230.
35. Elming MB, Nielsen JC, Haarbo J, et al. Age and outcomes of primary prevention implantable cardioverter-defibrillators in patients with nonischemic systolic heart failure. Circulation 2017;136:1772–1780.
36. Barsheshet A, Goldenberg I, Narins CR, et al. Time dependence of life-threatening ventricular tachyarrhythmias after coronary revascularization in MADIT-CRT. Heart Rhythm 2010;7:1421–1427.
37. Tilz R, Boveda S, Deharo JC, Dobreanu D, Haugaa KH, Dagres N. Replacement of implantable cardioverter defibrillators and cardiac resynchronization therapy devices: results of the European Heart Rhythm Association survey. Europace 2016;18:945–949.
38. Vaduganathan M, Claggett BL, Jhund PS, et al. Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials. Lancet 2020;396:121–128.
39. Tromp J, Ouwerkerk W, van Veldhuisen DJ, et al. A systematic review and network meta-analysis of pharmacological treatment of heart failure with reduced ejection fraction. JACC Heart Fail 2022;10:73–84.
40. Desai AS, McMurray JJ, Packer M, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J 2015;36:1990–1997.
41. Martens P, Nuyens D, Rivero-Ayerza M, et al. Sacubitril/valsartan reduces ventricular arrhythmias in parallel with left ventricular reverse remodeling in heart failure with reduced ejection fraction. Clin Res Cardiol 2019;108:1074–1082.
42. Rohde LE, Chatterjee NA, Vaduganathan M, et al. Sacubitril/valsartan and sudden cardiac death according to implantable cardioverter-defibrillator use and heart failure cause: a PARADIGM-HF analysis. JACC Heart Fail 2020;8:844–855.
43. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. Eur Heart J 2021;42:3727–3738.
44. Greene SJ, Butler J, Albert NM, et al. Medical therapy for heart failure with reduced ejection fraction: the CHAMP-HF Registry. J Am Coll Cardiol 2018;72:351–366.
45. Ahmad M, Bloomstein L, Roelke M, Bernstein AD, Parsonnet V. Patients' attitudes toward implanted defibrillator shocks. Pacing Clin Electrophysiol 2000;23:934–938.
46. Mark DB, Anstrom KJ, Sun JL, et al; Sudden Cardiac Death in Heart Failure Trial Investigators. Quality of life with defibrillator therapy or amiodarone in heart failure. N Engl J Med 2008;359:999–1008.
47. Sears SF, Conti JB. Quality of life and psychological functioning of ICD patients. Heart 2002;87:488–493.
48. Goldenberg I, Moss AJ, Hall WJ, et al; Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Investigators. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. Circulation 2006;113:2810–2817.
49. Knops RE, Olde Nordkamp LRA, Delnoy PHM, et al; PRAETORIAN Investigators. Subcutaneous or transvenous defibrillator therapy. N Engl J Med 2020;383:526–536.

50. Knops RE, Pepplinkhuizen S, Delnoy PPHM, et al. Device-related complications in subcutaneous versus transvenous ICD: a secondary analysis of the PRAETORIAN trial. Eur Heart J 2022;43:4872–4883.
51. Ruwald MH, Ruwald AC, Johansen JB, et al. Temporal incidence of appropriate and inappropriate therapy and mortality in secondary prevention ICD patients by cardiac diagnosis. JACC Clin Electrophysiol 2021;7:781–792.
52. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics—2022 update: a report from the American Heart Association. Circulation 2022; 145:e153–e639. Erratum in Circulation 2022;146:e141.
53. Defibrillator - Market Share Analysis, Industry Trends & Statistics, Growth Forecasts 2021 - 2029. https://www.researchandmarkets.com/reports/5176041/defibrillator-market-share-analysis-industry#rela0-4969038. Accessed February 17, 2024.
54. Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. J Am Coll Cardiol 2006;47:2310–2318.
55. Dagres N, Peek N, Leclercq C, Hindricks G. The PROFID project. Eur Heart J 2020;41:3781–3782.
56. Gulati A, Jabbour A, Ismail TF, et al. Association of fibrosis with mortality and sudden cardiac death in patients with nonischemic dilated cardiomyopathy. JAMA 2013;309:896–908.
57. Di Marco A, Anguera I, Schmitt M, et al. Late gadolinium enhancement and the risk for ventricular arrhythmias or sudden death in dilated cardiomyopathy: systematic review and meta-analysis. JACC Heart Fail 2017;5:28–38.
58. Gutman SJ, Costello BT, Papapostolou S, et al. Reduction in mortality from implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy patients is dependent on the presence of left ventricular scar. Eur Heart J 2019;40:542–550.
59. Elming MB, Hammer-Hansen S, Voges I, et al. Myocardial fibrosis and the effect of primary prophylactic defibrillator implantation in patients with non-ischemic systolic heart failure—DANISH-MRI. Am Heart J 2020;221:165–176.
60. Flett A, Cebula A, Nicholas Z, Adam R, et al. Rationale and study protocol for the BRITISH randomized trial (Using cardiovascular magnetic resonance identified scar as the benchmark risk indication tool for implantable cardioverter defibrillators in patients with nonischemic cardiomyopathy and severe systolic heart failure). Am Heart J 2023;266:149–158.
61. Younis A, Goldberger JJ, Kutyifa V, et al. Predicted benefit of an implantable cardioverter-defibrillator: the MADIT-ICD benefit score. Eur Heart J 2021; 42:1676–1684.
62. Goldenberg I, Younis A, Aktas MK, et al. Risk stratification for a primary prevention ICD: performance of the MADIT-ICD Benefit Score in a contemporary real world cohort. Heart Rhythm 2024;21(Suppl):S255.
63. Willy K, Köbe J, Reinke F, et al. Usefulness of the MADIT-ICD benefit score in a large mixed patient cohort of primary prevention of sudden cardiac death. Pers Med 2022;12:1240.
64. Song K, Hu Y, Chen W, Hua W, Jin Z. Prediction efficiency of MADIT-ICD benefit score for outcome in Asian patients with implantable cardioverter-defibrillator. Int J Gen Med 2022;15:4409–4416.
65. Dauw J, Martens P, Nijst P, et al. The MADIT-ICD benefit score helps to select implantable cardioverter-defibrillator candidates in cardiac resynchronization therapy. Europace 2022;24:1276–1283.
66. Fiuzat M, Hamo CE, Butler J, et al. Optimal background pharmacological therapy for heart failure patients in clinical trials. J Am Coll Cardiol 2022;79:504–510.
67. Leyva F, Israel CW, Singh J. Declining risk of sudden cardiac death in heart failure: fact or myth? Circulation 2023;147:759–767.
68. Zabel M, Willems R, Lubinski A, et al. EU-CERT-ICD SI. Clinical effectiveness of primary prevention implantable cardioverter-defibrillators: results of the EU-CERT-ICD controlled multicentre cohort study. Eur Heart J 2020; 41:3437–3447.
69. Uijl SB, Westermann BL, Stolfo SM, et al. Association between use of primary-prevention implantable cardioverter-defibrillators and mortality in patients with heart failure: a prospective propensity score-matched analysis from the Swedish Heart Failure Registry. Circulation 2019;140:1530–1539.
70. Barra S, Providência R, Narayanan K, et al. Time trends in sudden cardiac death risk in heart failure patients with cardiac resynchronization therapy: a systematic review. Eur Heart J 2020;41:1976–1986.
71. Ahmed A, Auricchio A, Mittal S, et al. Mortality benefit among primary prevention implantable cardioverter-defibrillator recipients on contemporary heart failure treatment. JACC Clin Electrophysiol 2024;10:916–926.
72. Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP. Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. Eur Heart J 2017;38:1738–1746.
73. Levy WC, Lee KL, Hellkamp AS, et al. Maximizing survival benefit with primary prevention ICD therapy in a heart failure population. Circulation 2009; 120:835–842.
74. Bilchick KC, Wang Y, Cheng A, et al. Seattle Heart Failure Model (SHFM) for overall survival and the Seattle Proportional Risk Model (SPRM) Seattle heart failure and proportional risk models predict benefit from implantable cardioverter-defibrillators. J Am Coll Cardiol 2017;69:2606–2618.
75. Goldenberg I, Vyas AK, Hall WJ, et al; MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288–296.
76. Vaduganathan M, Fonarow GC, Greene SJ, et al. Contemporary treatment patterns and clinical outcomes of comorbid diabetes mellitus and HFrEF: the CHAMP-HF Registry. JACC Heart Fail 2020;8:469–480.
77. Veltmann C, Duncker D, Doering M, et al. Therapy duration and improvement of ventricular function in de novo heart failure: the Heart Failure Optimization study. Eur Heart J 2024;45:2771–2781.
78. Maddox TM, Januzzi JL Jr, Allen LA, et al. 2024 ACC Expert consensus decision pathway for treatment of heart failure with reduced ejection fraction: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2024;8:1444–1488.
79. Kutyifa V, Moss AJ, Klein H, et al. Use of the wearable cardioverter defibrillator in high-risk cardiac patients: data from the Prospective Registry of Patients Using the Wearable Cardioverter Defibrillator (WEARIT-II Registry). Circulation 2015; 132:1613–1619.
80. Ouellet G, Huang DT, Moss AJ, et al. Effect of cardiac resynchronization therapy on the risk of first and recurrent ventricular tachyarrhythmic events in MADIT-CRT. J Am Coll Cardiol 2012;60:1809–1816.