JACC: ASIA VOL. 3, NO. 3, 2023

STATE-OF-THE-ART REVIEW

Implantable Cardioverter-Defibrillator for Primary Prevention in Asia

Arwa Younis, MD, Bruce L. Wilkoff, MD

ABSTRACT

In a contemporary setting, where the risk of sudden cardiac death (SCD) is low, heart failure management is improved, and technology is advanced, identifying the patients who would benefit the most from an implantable cardioverter-defibrillator (ICD) treatment for primary prevention remains a challenge. The prevalence of SCD is lower in Asia when compared with the United States/Europe (35-45 per 100,000 person-years vs 55-100 per 100,000 person-years, respectively). Nevertheless, this should not explain the enormous gap in ICD's utilization among eligible candidates (~12% in Asia vs ~45% in the United States/Europe). The disparity between Asia and Western countries, together with significant variation among the Asian population and the previously mentioned challenges, requires an individualized approach and specific regional recommendation, especially in countries with limited resources where ICDs are being extremely underutilized This review focuses on the current knowledge of ICD therapy for SCD prevention and how to improve patient and device selection. (JACC: Asia 2023;3:321–334) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In 1988, the first automatic programmable implantable cardioverter-defibrillator (ICD) was introduced, with similar concept that current devices still use today.[1] Defibrillators were proven to be efficient in terminating ventricular tachyarrhythmia (VTA) and prevent arrhythmic death. During the first decade of ICD utilizations, the ICD was offered to patients with documented VTA for secondary prevention. Randomized trials have proven this strategy to be efficient, and ICDs were found to be superior to antiarrhythmic medications for secondary prevention and have led to a significant reduction in sudden cardiac death (SCD) and all-cause mortality.[2-4] In the late 1990s of the past century, several groups have published their results from randomized controlled trials investigating the efficacy and safety of the ICD for primary prevention.[5-8] In these trials, patients at high risk for VTA but without a prior VTA were randomized to receive an ICD vs medical therapy. In these patients, implanted for primary prevention, ICDs were associated with a significant reduction in VTA, reduction in SCD, and in all-cause mortality.

Both the American 2017 and the European Society of Cardiology (ESC) 2016 guidelines have recommended ICD implantation as Class I for primary prevention in patients with heart failure with reduced ejection fraction (HFrEF) regardless of the underlying etiology of their HFrEF.[9,10] Most of the underlying data were obtained in patients with ischemic cardiomyopathies, but in 2016, results from the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial investigating the benefit of primary prophylactic ICD therapy in patients with non-ischemic cardiomyopathy (NICM) demonstrated a low rate of SCD and VTA therapy, as well as low rate of all-cause mortality.[11] According to the DANISH trial, when compared with medical therapy, ICD was

From the Cardiac Electrophysiology and Pacing Section, Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received August 29, 2022; revised manuscript received November 16, 2022, accepted November 24, 2022.

ISSN 2772-3747 https://doi.org/10.1016/j.jacasi.2022.11.014

ABBREVIATIONS AND ACRONYMS

ARVC = arrhythmogenic right ventricular cardiomyopathy

ATP = anti-tachycardia pacing

C-MRI = cardiac magnetic resonance imaging

CRT = cardiac resynchronization therapy

CRT-D = CRT with a pacemaker and implantable cardioverter-defibrillator

ESC = European Society of Cardiology

HCM = hypertrophic cardiomyopathy

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

ICM = ischemic cardiomyopathy

IHD = ischemic heart disease

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

MI = myocardial infarction

NICM = nonischemic cardiomyopathy

NSVT = nonsustained ventricular tachycardia

PVS = programmed ventricular stimulations

SCD = sudden cardiac death

VTA = ventricular tachyarrhythmia

not associated with a significant risk reduction for all-cause mortality when implanted for primary prevention in this population.

Importantly, novel therapies, such as angiotensin receptor neprilysin inhibitor and sodium glucose co-transporter 2 inhibitors have improved patient survival, hospitalizations, and outcomes in this specific population of patients with HFrEF.[12-14] These findings, together with findings from the DANISH trial, have posed a challenge on the role of the ICDs for primary prevention in a contemporary setting, in which the incidence of SCD is much lower than in the 1990s. In response, the new 2021 ESC guidelines as well as the Australian guidelines have softened their recommendation for ICD implantation for primary prevention in NICM. Patients with ischemic cardiomyopathy (ICM) remained with a Class Ia recommendation for ICD placement, whereas in patients with symptomatic systolic NICM, the recommendation was downgraded from a Class Ib recommendation to a Class IIa recommendation.[15,16] In the authors' opinion, there is little to no evidence to support the recent downgrading of the ICD placement indication in patients with HFrEF due to NICM.

However, in a contemporary setting, and especially in Asia, where resources might be limited, comorbidities are high, and the competing risk of non-SCD is higher than in Western countries, it is mandatory to incorporate additional parameters, beyond left ventricular ejection fraction (LVEF) and the type of the cardiomyopathy, to identify patients who will derive significant benefit from primary ICD therapy. This is further supported by recent data on the declining incidence of SCD,[17] the growing pathological heterogeneity,[18] the proven benefit of cardiac resynchronization therapy (CRT) in reducing mortality,[19] and the new pharmacotherapy as well as left ventricular assist devices for the management of patients with HFrEF.[12-14,20] All together, these considerations stress the need for improved patient selection for primary ICD therapy within the HFrEF population in general, and in Asia in particular.

DEFIBRILLATORS AND SCD IN ASIA

The Asia-Pacific region is a large geographic area populated by more than two-thirds of the earth's population. This region varies significantly in ethnicity, health care systems, and economic situation. For example, implantation rates vary widely for ICDs, ranging from 1 per million in China to 160 per million population in Australia.[21] The causes of such differences are multifactorial, including differences in disease patterns, patient acceptance, cost, reimbursement, and ethnic susceptibility to arrhythmias, which was reported to be lower in some Asian populations.[22-24]

Despite these variations, a similar pattern is seen throughout the Asian region of a rapid increase in the aging population and burden of ICM in developing countries.[25] These factors, in addition to improved patient management and economic growth, have significantly led to an increase in the rate of ICD implantation for primary prevention.[26,27] Nevertheless, the overall rate of ICD use remains unacceptably low. A recent paper from the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial showed that of the 7,145 patients eligible for ICD implantation for primary prevention, only 1.7% of the Asian patients received an ICD compared with 56% of the patients in North America.[28]

Although most of the landmark trials for primary prevention ICD included mainly North American/European patients, several recent studies have demonstrated that the rapid VTA incidence and the corresponding appropriate ICD therapy in patients with an ICD in several Asian regions is similar to the landmark trials in Western countries.[29,30] This suggests, that if implanted in the appropriate Asian patient, ICDs will result in a similar benefit in reducing the overall mortality similar to Western countries. However, in Asian countries, identifying the correct patient is even more challenging than in Western countries. This may be attributed to several factors, including significantly lower risk of SCD together with higher risk of non-arrhythmic death, fewer medical resources, and lower rates of cardiac disease when compared with the Western countries.[31-33] In addition, the Asian population is heterogeneous and the differences in SCD and health care systems may vary significantly between the different regions, which poses another challenge when evaluating the role of ICDs for primary prevention in this population.

The reported incidence of SCD in China (40-45 per 100,000 person-years) was noticeably lower than that in the United States and Europe (55-100 per 100,000 person-years) but was higher than that in Japan (30-35 per 100,000 person-years) and South Korea (30 per 100,000 person-years).[31,32] These patterns and differences are also maintained among high-risk patients. For example, in patients with symptomatic heart failure, the incidence of SCD in Japan was 2.8%

TABLE 1 Randomized Controlled Trials in Patients With Ischemic Cardiomyopathy

Study Year	Inclusion Criteria	N	Age, y	EF, %	NYHA Functional Class II, %	Follow-Up, mo	Main Findings
MADIT 1996	LVEF ≤35% ≥3 wk from MI NSVT NYHA functional class I-III	196	62 ± 9	27 ± 7	63	27	ICD therapy resulted in 54% RR reduction in all-cause mortality; $P = 0.009$
CABG Patch 1997	LVEF ≤35% Abnormal SAECG Scheduled for CABG NYHA functional class I-III	900	64 ± 9	27 ± 6	71	32	ICD therapy did not reduce all-cause mortality; ICD therapy resulted in 45% RR reduction in SCD
MADIT II 2002	LVEF ≤30% ≥1 mo from MI NYHA functional class I-III	1,232	64 ± 10	23 ± 5	35	20	ICD therapy resulted in 31% RR reduction in all-cause mortality; $P = 0.016$
DINAMIT 2004	LVEF≤35% 6-40 days from MI Abnormal HRV NYHA functional class I-III	674	62 ± 11	28 ± 5	NA	33	ICD therapy did not reduce all-cause mortality; ICD therapy resulted in SCD reduction
SCD-HeFT 2005	LVEF≤35% 3 mo of GDMT NYHA functional class II-III	1,311	61 ± 9	25 ± 4	71	46	ICD therapy resulted in 23% RR reduction in all-cause mortality; $P = 0.007$

CABG-Patch = Coronary Artery Bypass Graft Patch Trial; DINAMIT = Defibrillator in Acute Myocardial Infarction Trial; GDMT = guidelines directed medical therapy HRV = heart rate variability; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NA = not available; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; RR = relative risk; SAECG = signal-averaged ECG; SCD = sudden cardiac death; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

to 3.5% and was significantly lower than the reported incidence of 5% to 9% in Western countries.[34-37] Similarly, remarkable variations are seen in patients with end-stage renal disease. In Japan, 26% of deaths were due to heart failure and only 2.5% of deaths are caused by SCD, whereas in China, 28% of deaths are caused by SCD and only 4% of deaths are due to heart failure.[38]

Although there is a trend for increase in ICD implantation for primary prevention in the Asian population, most of the eligible patients are still without a protective device. The underutilization of the ICD in patients at risk is unacceptable and should sound an alarm for improvement. The variation in SCD risk, together with the economic differences, highlights the need for region-specific recommendation. Understanding the many differences between Asia and the Western countries is critical. For example, in patients with relatively narrow QRS duration, a subanalysis of ECHO-CRT (Echocardiography Guided Cardiac Resynchronization Therapy) showed an association between heart size and CRT efficacy.[39] Another study confirmed these findings and demonstrated that in small-bodied Asian patients with a mid-range QRS, CRT was highly effective. In this study, there was a significant negative correlation between patient height and outcome. In patients with a QRS duration of 120 to 150 ms and a height <160 cm, the predicted probability of CRT response was more than 80%, compared with 40% in those with a height >180 cm.[40] Based on these findings, in the Asian population with QRS >120 ms, CRT should be recommended, especially in short patients. These recommendations are in contrast to the American and European guidelines regarding use of CRT in mid-range QRS durations. Therefore, physicians should always aim to understand the divergence between Asian populations and Western countries when it comes to applying American/European Guidelines in this population.

ISCHEMIC HEART DISEASE

Patients with HFrEF with ICM are known to be at increased risk for SCD mainly due to a high rate of scar-mediated VTAs. This understanding of the increased risk seen in these patients has led investigators early in the 1990s to conduct several randomized controlled trials evaluating the efficacy and safety of ICDs for primary prevention therapy. Trials included mainly patients with clinically stable ischemic heart disease, a documented prior myocardial infarction (MI), and a low LVEF. In the MADIT II (Multicenter Automatic Defibrillator Trial II), patients with NYHA functional class I-III with an LVEF ≤30% were included. Over a follow-up period of 20 months, ICD therapy was associated with a relative risk reduction in all-cause mortality of 31% (ICD 14% vs Control 20%; $P < 0.001$).[8] In the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial),

JACC: ASIA, VOL. 3, NO. 3, 2023
JUNE 2023:321–334

TABLE 2 Guidelines for Primary Prevention Implantation of Cardioverter-Defibrillators

	Cardiomyopathy	ACCF/AHA 2013	ESC 2016	Canadian 2017	Australian 2018	ESC 2021
LVEF ≤35% despite ≥3 mo of optimal GDMT with NYHA functional class II-III	Ischemic	Ia	Ia	Ia[a]	Ia[b]	Ia
	Nonischemic	Ia	Ib	Ia	IIa[a]	IIa[a]
LVEF ≤30% despite ≥40 days of optimal GDMT with NYHA functional class I	Ischemic	Ib	NA	NA[a]	Ia[c]	Ia

[a]At least 1 month post MI and at least 3 months post coronary revascularization procedure. [b]No mention of NYHA functional class. [c]At least 1 month post MI.

ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Cardiac Society; GDMT = guidelines directed medical therapy; LVEF = left ventricular ejection fraction; NA = not available.

patients with NYHA Class II-III and LVEF ≤35% were included. At 5 years of follow-up, the absolute reduction in risk of all-cause mortality with the ICD was 7%, with a relative risk reduction of 23% vs the non-ICD group.[6] In both trials, an ICD was implanted >40 days after the MI index and on top of optimal medical therapy. In contrast, the CABG (Coronary Artery Bypass Graft) Patch trial, which enrolled patients who were referred for coronary artery bypass graft procedure, failed to show any significant benefit with the ICD.[41] Importantly, when the device was implanted during the early post-MI phase, ICD therapy was not associated with any risk reduction.[42] Nevertheless, the results of a meta-analysis and a focused review suggests that overall, in patients with ICM with HFrEF, ICD implantation for primary prevention is a lifesaving therapy associated with a significant risk reduction in SCD and all-cause mortality.[43] **Table 1** summarizes these trials.

Overall, all 4 guidelines (American, European, Canadian, and Australian) recommend that patients with HFrEF with ICM should be implanted with an ICD for primary prevention if they are stable on maximal dose of guideline-directed medical therapy for HFrEF, are at least 40 days post MI, have an LVEF ≤35%, and are with an expected survival exceeding 1 year (**Table 2**).

NONISCHEMIC HEART DISEASE

For patients with HFrEF caused by NICM, the strength of the scientific evidence to implant an ICD for primary prevention is somewhat lower compared with patients with ICM. There are a few studies in the literature that focused only on NICM: AMIOVIRT (Amiodarone versus Implantable Defibrillator), the CAT (Cardiomyopathy Trial), and DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation).[44-46] The first trial was CAT, which was designed to randomize a total of 1,348 patients with an expected mortality rate of 30% at the end of the first year, but instead it recruited no more than 104 patients with a 5.6% 1-year mortality rate. As a result of these preliminary outcomes, the study was terminated prematurely. The next trial was the DEFINITE trial. This trial was the first completed randomized trial of primary prevention in NICM and included 458 patients with NICM, LVEF ≤35%, and premature ventricular complexes or nonsustained ventricular tachycardia (NSVT) in Holter or telemetry. After a mean follow-up of 29 months, a statistically significant risk reduction was observed in SCD rate, but not in all-cause mortality rate. During the follow-up, 68 deaths occurred: 28 patients (8.1%) in the ICD group and 40 patients (13.8%) in the standard medical care group (HR: 0.65; 95% CI: 0.40-1.06; $P = 0.08$)—close to the overall mortality target of 15% in the standard care arm and 7.5% in the ICD arm, but also not enough to reach it and show statistical significance. Although failing to achieve the primary endpoint and to show statistical significance in reducing all-cause mortality, the results of this study proved instead the true purpose of ICD therapy, that is, the reduction in arrhythmic SCD, which was outreached: 3 deaths in the ICD patients compared with 14 in the standard medical therapy patients (HR: 0.20; 95% CI: 0.06-0.71; $P = 0.006$). In the SCD-HeFT trial, nearly half the patients had NICM with a 23% relative risk reduction in all-cause mortality in the entire population with the ICD. There were also several small and underpowered trials that failed to show a significant benefit with the ICD in patients with NICM (**Table 3**).

In 2016, the results of the DANISH trial, the most recent randomized controlled trial in the field of ICD for primary prevention, were published.[11] DANISH enrolled 1,116 patients with NICM, LVEF ≤35%, and NYHA functional class ≥II. The trial did not meet the primary endpoint of reduction in all-cause mortality. During a median follow-up of 68 months, the primary outcome had occurred in 120 patients (22%) in the ICD group vs 131 patients (23%) in the control group ($P = 0.28$). Although there was not a reduction in all-cause mortality, ICD therapy was associated with a

TABLE 3 Randomized Controlled Trials in Patients With Nonischemic Cardiomyopathy

Study Year	Inclusion Criteria	N	Age, y	Design	NYHA Functional Class	Follow-Up, mo	Main Findings Regarding ICD Therapy
CAT 2002	LVEF ≤30% New onset	104	52 ± 9	ICD vs OMT	II-III	66 ± 26	Did not reduce all-cause mortality; resulted in significant RR reduction for SCD
AMIOVIRT 2003	LVEF ≤35% NSVT	103	59 ± 9	ICD vs OMT	I-III	24 ± 14	Did not reduce all-cause mortality
DEFINITE 2004	LVEF ≤35% NSVT or PVCs	458	58 ± 10	ICD vs amiodarone	I-III	29 ± 14	Resulted in 35% RR reduction in all-cause mortality; $P = 0.08$
SCD-HeFT 2005	LVEF ≤35%	792	61 ± 9	ICD vs amiodarone vs placebo	II-III	45 (median)	Resulted in 23% RR reduction in all-cause mortality; $P = 0.007$
COMPANION 2004	LVEF ≤35% QRS ≥120 ms	682	67 ± 6	OMT vs CRT-P vs CRT-D	III-IV	15 (median)	CRT-D therapy resulted in 36% RR reduction in all-cause mortality; $P = 0.001$
DANISH 2016	LVEF ≤35% High pro-BNP	1,116	61 ± 9	ICD vs OMT	II-IV	68 (median)	Did not reduce all-cause mortality; Resulted in 50% RR reduction in SCD; $P = 0.005$

AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CAT = Cardiomyopathy Trial; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial; CRT = cardiac resynchronization therapy; DANISH = Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NSVT = nonsustained ventricular tachycardia; NYHA = New York Heart Association; OMT = optimal medical therapy; PVCs = premature ventricular contractions; RR = relative risk; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

50% risk reduction in SCD (HR: 0.50; 95% CI: 0.31-0.82; $P = 0.005$), highlighting the true benefit of the ICD. Importantly, subgroup analysis demonstrated a significant reduction in the primary endpoint of all-cause mortality when analyzing the findings by age groups. Accordingly, in patients ≤70 years, ICD implantation was associated with a 58% risk reduction for death (HR: 0.42; 95% CI: 0.24-0.71; $P \leq 0.001$).[47] The findings of the DANISH trial have evoked discussion about the role of the ICD in patients with NICM and have led the ESC to soften their recommendation regarding ICD in NICM (Table 2).

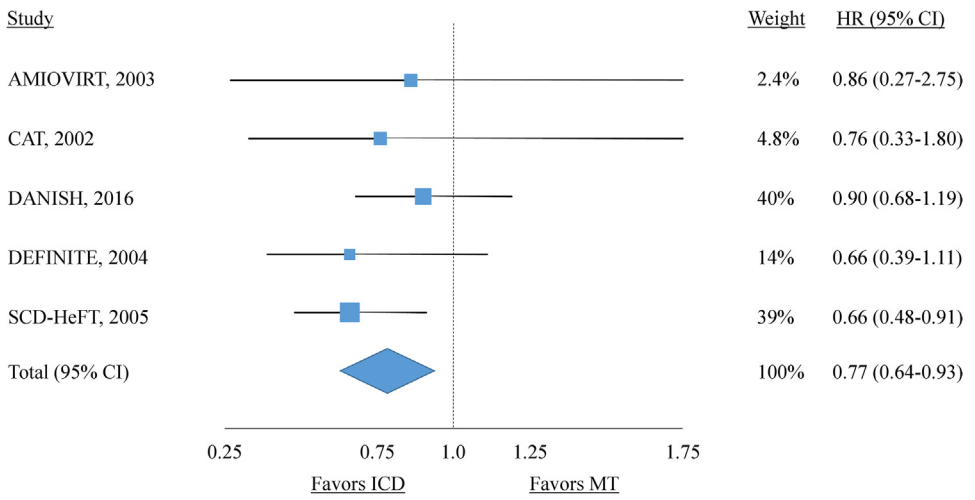
A recent meta-analysis including all available randomized trials showed a survival benefit of the ICD therapy for primary prevention in NICM (Figure 1). Treatment with ICD was associated with a 23% risk reduction for all-cause mortality, and a 57% risk reduction for SCD.[48] These findings, together with the findings from the DANISH trial (great advantage in patients <70 years or those without diabetes), highlight the need for improved patient selection when referring patients with NICM for an ICD therapy for primary prevention.

OTHER CARDIOMYOPATHIES BESIDES ICM AND NICM

Overall, all patients with NICM with LVEF ≤35%, NYHA functional class ≥II, and a life expectancy of ≥1 year, should receive an ICD for primary prevention regardless of their etiology if the etiology is irreversible. Additional specific recommendations regarding patients with NICM by etiology are found in Table 4. Both the American and the European guidelines recommend the implantation of the ICD for primary prevention therapy for patients with cardiomyopathy caused by lamin A/C mutation who have 2 or more risk factors (NSVT, LVEF <45%, non-missense mutation, and male sex).[9,10] Similarly, patients with cardiac sarcoidosis have a high risk of VTA and SCD and implantation of an ICD should be considered even in those with LVEF >35% if they have syncope, inducible sustained VTA, or an indication for permanent pacing.[49] Hypertrophic cardiomyopathy (HCM) is also known to carry an increased risk for SCD and malignant VTAs. The ESC guidelines recommend performing risk stratification for primary prevention ICD therapy using the HCM risk score, whereas in the US guidelines it is based on the presence of at least 1 risk factor from a prespecified set of clinical variables.[50] A recent large observational study suggested that the enhanced American clinical risk factor strategy is highly sensitive for predicting SCD events but is less specific for identifying patients without SCD events in HCM patients, whereas the ESC risk model is associated with a lower sensitivity but a higher specificity.[51]

Results from studies examining outcomes in arrhythmogenic right ventricular cardiomyopathy (ARVC) are diverse. Therefore, recommendations on ICD therapy for primary prophylaxis in patients with ARVC are challenging. Based on the current available data, the consensus is that patients with unexplained syncope should be considered for an ICD regardless of their ejection fraction or heart failure status. For patients without syncope, an ICD may be considered after detailed clinical assessment that takes into account family history, severity of right ventricular and left ventricular enlargement and/or dysfunction, lifelong risk of complications and impact of an ICD on lifestyle, socioeconomic status, and psychological

FIGURE 1 Individual and Summary Odds Ratios for All-Cause Mortality in Patients With NICM



Shown is meta-analysis based on risk differences and random-effects model. **Blue squares** denote study-specific risk differences (with 95% CI) and the **diamond** indicates the pooled risk difference (with 95% CI); weight is based on the sample size; on the **right** are the HRs with the corresponding 95% CI. AMIOVIRT = Amiodarone vs. Implantable Defibrillator Randomized Trial; CAT = Cardiomyopathy Trial; DANISH = Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality; DEFINITE = Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation; ICD = implantable cardioverter-defibrillator; MT = medical therapy; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

health.[9,10] In patients with congenital long QT syndrome, ICD therapy has proven itself to terminate malignant VTA and potentially save lifes.[52,53] Primary ICD therapy is recommended in patients with congenital long QT syndrome who experience syncope while receiving an adequate dose of beta-blockers, and in patients with Brugada syndrome who present with a spontaneous type 1 electrocardiogram and a history of syncope.[9,10]

PATIENT SELECTION

Not all patients with HFrEF derive consistent benefit from prophylactic implantation of the ICD. Furthermore, implantation of an ICD has a dark side that comes along with it. Despite the advancement in technologies, better discrimination algorithms, and the use of antibiotic-eluting envelopes,[54] ICD therapy remains a costly and invasive intervention that is not free of short- and long-term deadly complications.[55-58] Moreover, and as detailed previously, since the publication of most of the large ICD trials, advances in medical treatment have reduced the total mortality and SCD among patients with HFrEF. However, because both endpoints (SCD and non-SDC death) are lower, the ratio between them remained constant. The number needed to treat is now higher. A recent large observational study from Europe has confirmed these observations and has shown that the relative benefit found in the early studies (MADIT II, SCD-HeFT, and DEFINITE) is sustained 20 years later.[59] In this study, the relative risk reduction was 27%, which was similar to the risk reductions seen in the previously mentioned trials. Yet, this study showed again that ICD therapy was not beneficial in all subgroups. There appear to be patients with less survival advantage, such as older patients or diabetic patients, patients in whom the risk of non-arrhythmic mortality (non-SCD) is higher than the risk of SCD.

Improved selection for primary prevention ICD therapy in patients with HFrEF can be achieved by weighing the patient-specific risk of SCD (for whom primary device implantation may be lifesaving) against the competing risk of nonarrhythmic mortality (for whom primary ICD implantation does not provide protection).

ASSESSMENT AND EVALUATION

To date, risk stratification approaches for primary ICD therapy have focused on clinical, electrophysiological, and imaging markers. Evaluation of a candidate patient with HFrEF should always begin with gathering information regarding LVEF, NYHA functional class, cardiomyopathy type, comorbidities, life expectancy, medical therapy, cardiac

TABLE 4 Indications in Nonischemic Cardiomyopathies by Etiology

List of NICM Etiologies That Are Given Special Consideration for ICD Implantation				
Cardiomyopathy	**United States**	**If 1 of the Following:**	**Europe**	**If 1 of the Following:**
Sarcoidosis	Yes	• Scar • Syncope • Permanent pacing	Yes	• Permanent pacing
Hypertrophic	Yes	• Maximum LV wall thickness ≥30 mm • Family history of SCD • Syncope	Yes	• Estimated 5-y risk of SCD ≥6%
Long QT syndrome	Yes	• Syncope despite medication therapy	Yes	• Syncope despite medication therapy
LAMIN A/C	Yes	• ≥2 risk factors: NSVT, LVEF<45%, non-missense, male	Yes	• ≥2 risk factors: NSVT, LVEF<45%, non-missense, male
ARVC/D	Yes	• Syncope	Yes	• Syncope
Adult congenital	Yes	• Inducible VT/VF	No	

List of Other NICM Etiologies That Are Mentioned Within a Text or a Paragraph	
• Valvular • Amyloidosis • Pacing/Tachycardia induced • Post-partum • Desmin-related	• Phospholamban related • SCN5A related • Medication induced • Neuromuscular disorders • Other channelopathies

ARVC = arrhythmogenic right ventricular cardiomyopathy ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; SCD = sudden cardiac death; VF = ventricular fibrillation; VT = ventricular tachycardia.

imaging, cardiac biomarkers, electrocardiogram, and Holter findings. Physicians should weigh the risk of SCD against the risk of non-SCD and discuss together with the patient the findings of the weight scale (**Central Illustration**) to decide on ICD implantation for primary prevention.

RISK FACTORS FOR SCD AND NON-SCD

An ICD can save the patient's life if the patient suffers a malignant VTA event. Identifying risk factors for malignant VTA or SCD is crucial. Over the past several decades, numerous risk factors were reported. In this review, we try to point out the well-known and most significant risk factors. Low LVEF (<25%) is known to be one of the strongest risk factors for SCD.[60,61] Male sex also carries a high risk and was shown to double the risk when compared with female sex.[62,63] Positive family history of SCD as well as smoking history or current smoking were also reported to be independent risk factors for malignant VTA and SCD.[64,65] One important risk factor that should always be sought (including the performance of prolonged cardiac monitoring), is the presence as well as the burden of NSVT.[66-68]

ICD is less beneficial when the competing risk of death without any prior arrhythmia is higher than the risk of SCD. Among all the risk factors for non-SCD, age seems to be the strongest and the most influencer factor. In many of the older patients (age >70 years) ICDs implanted for primary prevention do not add any benefit, and can only lead to complications in these more fragile patients.[47,59,69] Similarly, high frailty index is also a strong predictor for non-SCD.[70,71] Cardiac cachexia, characterized by body wasting is a serious complication of HFrEF. The cachectic state is an independent predictor of impaired prognosis regardless of age, NYHA functional class, or LVEF. The mortality in the cachectic cohort is approximately 50% at 18 months since diagnosis.[72,73]

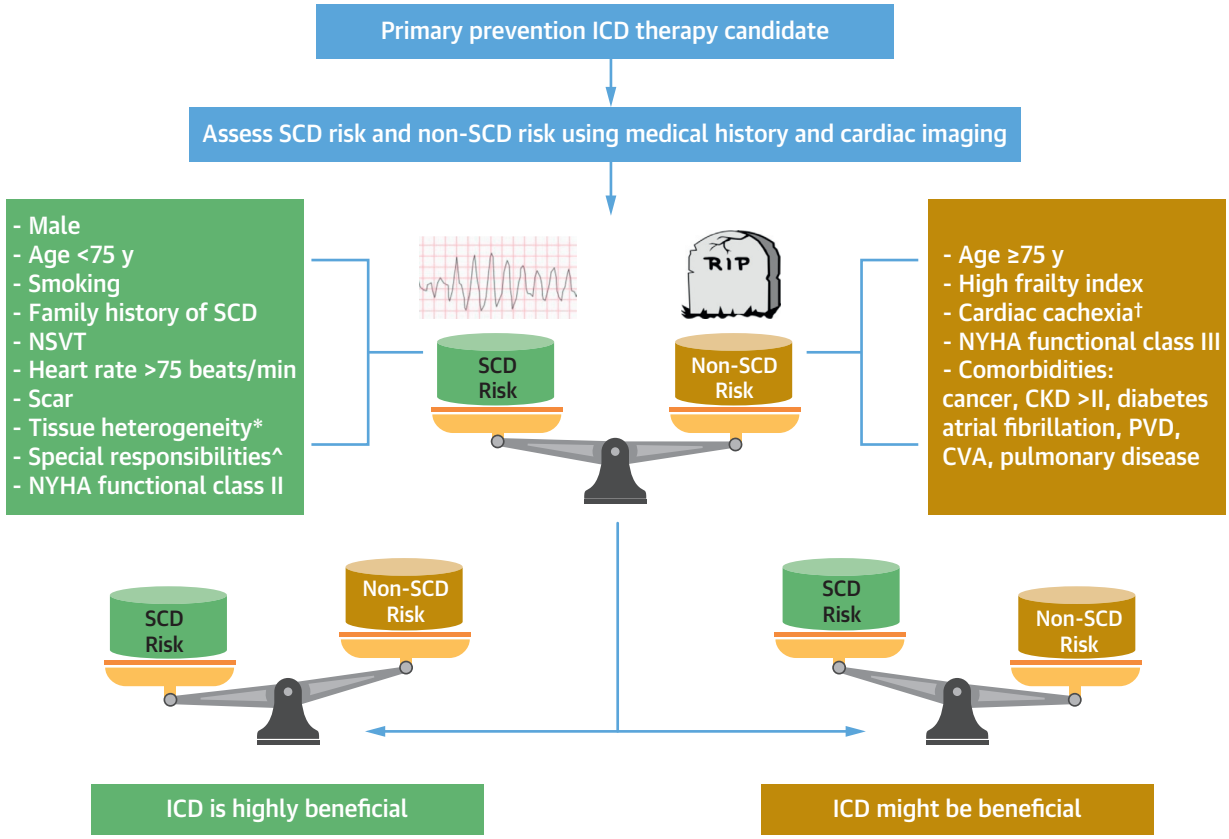
It is important to understand that there are several risk factors that show a sophisticated relationship with the benefit of the ICD, risk factors that are predictors of both SCD and non-SCD. These risk factors carry a U-shape relationship with the benefit of the ICD; for example, NYHA class, LVEF, and kidney function.[74-76] In advanced NYHA class, very low LVEF, or progressive kidney dysfunction, the risk of SCD is prominent; however, the competing risk of non-SCD is also high, and might be even higher in many of these patients. A recent study from the MADIT group showed that patients with advanced renal failure did not derive any survival benefit from primary ICD therapy.[77] Understanding this complex relationship between SCD and non-SCD is important and can assist clinicians with decision-making in implanting ICDs for primary prevention.[78,79]

PERSONALIZED RISK ASSESSMENT USING RISK SCORES

In a contemporary setting, and given all of the previously mentioned challenges, it is important to

JACC: ASIA, VOL. 3, NO. 3, 2023
JUNE 2023:321–334

CENTRAL ILLUSTRATION **Risk Stratification for Implantable Cardioverter-Defibrillator Insertion for Primary Prevention**



Younis A, et al. JACC: Asia. 2023;3(3):321–334.

This figure represents a proposed algorithm (flow chart) for risk stratification and prevention of sudden cardiac death (primary prevention) for implantable cardioverter-defibrillator (ICD) candidates. First step should include assessment of the sudden cardiac death (SCD) risk and the non-SCD risk. In candidates with increased SCD risk, ICD is highly recommended, whereas in those with increased non-SCD risk, ICD might be beneficial. CKD = chronic kidney disease; CVA = cerebrovascular disease; NSVT = nonsustained ventricular tachycardia; PVD = peripheral vascular disease. *Infarct tissue heterogeneity assessed with contrast-enhanced magnetic resonance imaging. †BMI <23 kg/m^2. ^Such as commercial pilot or bus driver.

incorporate additional parameters, beyond LVEF and cardiomyopathy type, to identify patients who will derive significant benefit from primary ICD therapy. Several risk stratification scores were developed to assist physicians in this challenging task.

The MADIT-ICD benefit score, which incorporated raw data from all the MADIT trials, and may be easily calculated using the free available website, can be used for patient-physician shared decision-making on the need for primary prevention ICD therapy.[78] The MADIT-ICD benefit score provides patient-specific estimates of the expected benefit of the ICD by providing the VTA risk, the risk for death without prior VTA (non-SCD) and the overall benefit of the ICD, in a primary prevention population based on simple clinical variables such as age, sex, LVEF, NYHA class, and comorbidities. The MADIT-ICD benefit score was validated internally, and externally in a contemporary cohort. If the reader clicks on the link, she or he will see a very intuitive tool that provides 1-, 2-, and 3-year risk estimates for VTA as well as the risk of death without VTA, and the overall predicted benefit of the ICD. In addition, the score was recently validated in a cohort of Asian patients and demonstrated consistent findings.[80]

The Seattle Heart Failure and Proportional Risk Model is another important tool that can help predict the benefit from ICD implanted for primary prevention.[79] The score integrates 2 scores into a final prediction model: the Seattle Heart Failure Model, which

predicts overall survival, and the Seattle Proportional Risk Model, which predicts proportional risk of SCD. One of the major limitations of this score is the absence of patients treated with CRT, which is known to affect both the SCD risk and the non-SCD risk.

CARDIAC IMAGING

All randomized controlled trials that have contributed to our understanding of the role of the ICD for primary prevention have relied on echocardiographic findings to determine the LVEF. However, although LVEF is an excellent predictor of overall mortality in the heart failure population, it is not sufficient in predicting the development of malignant VTA or SCD. More sophisticated imaging modalities, including strain imaging, cardiac magnetic resonance imaging (C-MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET), for the assessment of myocardial scarring, have been found to be superior predictors of the development of VTA and SCD than LVEF alone assessed in echocardiography.[81-84]

Especially, the use of C-MRI in assessing myocardial scar burden and predicting VTA among patients with HFrEF has been well explored and has been proven to be an excellent tool with great room for improvements.[85-87] The advantage of C-MRI over other modalities is multifactorial. Images from the C-MRI scan have a greater spatial resolution and are very detailed. Plus, C-MRI does not rely on vascular perfusion, which allows for its use in NICM to identify intramural scarring.[88-90] Furthermore, C-MRI not only provides essential information on the overall scar burden and distribution but also differentiates between the different types of scarring, which provides further information on the underlying electrophysiological substrate abnormality. Myocardial scar tissue facilitates the occurrence of reentry pathways that may lead to malignant VTA regardless of the underlying etiology.

In patients with ICM, tissue heterogeneity in the peri-infarct zone, as detected by contrast-enhanced C-MRI, is likely to signify a pro-arrhythmic substrate and is one of the strongest predictors of malignant VTA and appropriate ICD therapies.[91,92]

In patients with NICM, a meta-analysis incorporating data from 15 studies demonstrated that the average prevalence of myocardial scar was 41%. In these patients, the risk for adverse cardiac events was more than 3-fold higher, and the risk for VTA was 5-fold higher, as compared with patients with NICM without a scar.[93] A very recent prospective study that enrolled 1,020 consecutive patients with NICM and LVEF <50%, showed that LVEF ≤35% and scar were strongly associated with all-cause (log-rank test $P = 0.002$ and $P < 0.001$, respectively) and cardiac death ($P = 0.001$ and $P < 0.001$, respectively), whereas only scar was strongly related to SCD ($P = 0.001$), with no significant association between LVEF ≤35% and SCD risk ($P = 0.57$).[94] Based on this study, myocardial scar provided strong independent and incremental prognostic value for risk stratification for SCD and arrhythmic events, whereas LVEF had minimal to no value for arrhythmia risk stratification.

These observations suggest that C-MRI should be recommended for improved risk stratification and patient selection in ICD candidates regardless of their underlying etiology.

GENETIC TESTING AND PROGRAMMED VENTRICULAR STIMULATION

In selected patients, those with inherited channelopathies, genetic testing and programmed ventricular stimulations (PVS) may be used to improve patient risk assessment and guide clinicians on whether or not to implant an ICD. The main features of risk stratification vary among the different channelopathies (eg, long QT syndrome, Brugada syndrome), with great debate on the management of asymptomatic patients. Less clear risk stratification is available for cases of ARVC and in other uncommon familial cardiomyopathies. For most familiar cardiomyopathies, ICD therapy is the only accepted strategy in the prevention of SCD. In long QT syndrome, mutation location, as well as the number of mutations, was found to be one of the strongest independent predictors for SCD.[95,96] These findings were confirmed in patients from Japan within several different studies.[97,98] In one study that included 403 consecutive patients with Brugada syndrome, PVS inducibility presented an HR of 8.3 (95% CI: 3.6-19.4; $P < 0.001$) for arrhythmic events.[99] On the other hand, the PRELUDE (PRogrammed ELectrical stimUlation preDictive value) study, which included 308 patients with Brugada syndrome, failed to show association between VTA inducibility and arrhythmic events during follow-up.[100] So far, genetic testing and PVS have a limited role in risk evaluation and management of the individual patient without channelopathies.

DEVICE SELECTION AND PROGRAMMING

Over the past 3 decades, ICDs have evolved from a simple single-chamber shock device to more

advanced technologies, including 2- and 3-chamber devices, multiple lead options, and subcutaneous ICD, necessitating a personalized approach to device and lead selection in this population.

In patients with HFrEF who are not candidates for CRT, the first question is whether to implant a single-chamber ICD or a dual-chamber ICD. Most of the randomized controlled trials and the pooled meta-analyses failed to show any superiority of dual-chamber ICD over single-chamber ICD for primary prevention.[101-104] The rates of inappropriate shock, hospitalization, or survival were similar. Therefore, a single-chamber ICD should be generally preferred over dual-chamber ICDs unless pacing is needed. Nevertheless, in certain patients, dual-chamber ICD implantation would be beneficial and might be superior to single-chamber ICD. Dual-chamber ICDs are capable of atrial sensing and pacing and can help manage many patients with the need for pacing or those with both atrial bradycardia and tachyarrhythmias.

As devices improved, and further studies were conducted, more and more data suggested that unnecessary and inappropriate ICD shocks can lead to terrible quality of life, myocardial damage, and unnecessary health care utilizations. In response, ICD programming guidelines were modified to recommend the prolonging detection settings before delivery of any type of therapy allowing for tachycardia to spontaneously terminate. In addition, ICDs were programmed to treat the VTA with antitachycardia pacing (ATP) before delivering a shock for most of the VTAs cycle length. Three randomized trials, MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy), PROVIDE (The programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock), and ADVANCE III (Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III), prospectively investigated methods of prolonged VTA detection intervals.[105-107] All 3 trials demonstrated that prolonged detection intervals were associated with reduced inappropriate ICD therapy, appropriate ICD therapy, and reduced all-cause mortality (only in MADIT-RIT and PROVIDE). In 2019, a worldwide consensus statement from the 4 continental arrhythmia societies was published.[108] This expert consensus should guide treating physicians when programming ICDs for primary prevention. Nevertheless, these should not replace the opinion of the treating physician who has considered the patient's clinical status and desired outcome via a shared clinical decision-making process.

Despite the use of prophylactic antibiotic treatment and the advocacy of best surgical practices, ICD-related infections remained unacceptably high. An important feature that can help decrease this infectious risk is the use of an absorbable, multifilament mesh antibiotic envelope. This envelope improves the ICD stabilization within the pocket and elutes antibiotics post implantation. WRAP-IT (Worldwide Randomized Antibiotic Envelope Infection Prevention Trial) randomized a total of 6,983 patients to the envelope group vs the control group. Use of the envelope resulted in a 40% risk reduction for cardiac implantable electronic device infections over 12 months, and 37% risk reduction for major cardiac implantable electronic device-related infections over the 3-year follow-up.[54]

CRT AND SUBCUTANEOUS ICDs

Patients with HFrEF with prolonged QRS duration (reflecting electrical mechanical dyssynchrony), reduced LVEF, and symptomatic heart failure should always be considered for CRT with a pacemaker and ICD (CRT-D) instead of ICD alone. Decision on CRT is made based on several important factors, the most important ones are the QRS duration and morphology. The main indications for CRT-D are similar between the European and U.S. guidelines.[9,10] Generally, the accumulate data for significant clinical benefit from CRT is highest in patients with QRS duration ≥150 ms and left bundle branch block (LBBB), intermediate in patients with QRS duration ≥150 ms without LBBB or those with QRS duration <150 ms with LBBB, and weakest in patients with QRS duration <150 ms without LBBB.[109] Another important group of patients, is patients with reduced LVEF who have worsened their heart failure symptoms due to persistent right ventricular pacing. These patients should also be considered for CRT-D.[110]

The SICD was introduced in 2010 and was approved by the Food and Drug Administration in 2012.[111] Based on the unique feature of an entirely extracardiac and extravenous implantation, SICDs are able to reduce the common perioperative and long-term complications of the conventional transvenous implanted ICD systems. This is critical for patients with a complex anatomy and no option of an endovascular lead implantation. In these patients, the SICD offers a potential important alternative. Multiple randomized clinical studies

HIGHLIGHTS

- In the contemporary patients with heart failure who meet criteria for ICD therapy as primary prevention, treatment with ICD remains the cornerstone in SCD prevention.
- Technology and ICD devices have evolved from the simple, defibrillation-only endovascular device to more advanced technologies of multi-chamber wrapped devices and subcutaneous ICD.
- The benefit of the ICD is not uniform, and risk stratification and improved patient selection is critical, especially in countries with limited resources and increased risk of non-SCD.
- ICDs are being highly underutilized in Asia, and their use for primary prevention varies significantly between the regions.

provided evidence for the efficacy and safety of this approach.[111-113] However, SICDs are not suitable for patients requiring pacing, and those who are illegible for CRT. In addition, an SICD acts as a "shock box" and cannot treat the arrhythmia with a trial of ATP. This can have significant implications in patients with recurrent VTA. Nevertheless, limitations with respect to the not available pacing option of SICD might be overcome by a potential combination with a leadless pacemaker in the near future.

CONCLUSIONS AND SUMMARY

This review explored in detail the pros and cons of early ICD implantation for primary prevention therapy. Technology and ICD devices have evolved from the simple, defibrillation-only endovascular device to more advanced technologies of multi-chamber wrapped devices and SICD. Further advancements in ICD technologies are expected to facilitate integration of extravascular ICDs with leadless pacemakers to facilitate continuous pacing, the delivery of ATP, and the delivery of the shock. Until then, ICD implantation for primary prevention requires individualized approaches to predict the benefit of the ICD and to personalize device selection, especially in countries with limited resources and high risk of non-SCD. An ICD for primary prevention would be beneficial only if implanted in the correct patient.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Younis has reported that he has no relationships relevant to the contents of this paper to disclose. Dr Wilkoff has received research grants and/or consultancy fees from Abbott, Medtronic, and Philips.

ADDRESS FOR CORRESPONDENCE: Dr Bruce L. Wilkoff, Department of Cardiovascular Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, 9500 Euclid Avenue, Desk J2-2, Cleveland, Ohio 44195, USA. E-mail: wilkofb@ccf.org. Twitter: @arwayounis2, @BruceWilkoff.

REFERENCES

1. Kelly PA, Cannom DS, Garan H, et al. The automatic implantable cardioverter-defibrillator: efficacy, complications and survival in patients with malignant ventricular arrhythmias. *J Am Coll Cardiol*. 1988;11:1278–1286.

2. 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.

3. 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.

4. 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.

5. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med*. 1996;335:1933–1940.

6. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352:225–237.

7. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med*. 2004;350:2140–2150.

8. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346:877–883.

9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*. 2016;37:2129–2200.

10. Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Am Coll Cardiol*. 2017;70(6):776–803.

11. Køber L, Thune JJ, Nielsen JC, et al. defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med*. 2016;375:1221–1230.

12. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008.

13. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424.

14. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004.

15. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42:3599–3726.

16. Atherton JJ, Sindone A, De Pasquale CG, et al. National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: guidelines for the prevention, detection, and management of heart failure in Australia. 2018. *Heart Lung Circ*. 2018;27:1123–1208.

17. Ni H, Coady S, Rosamond W, et al. Trends from. 1987 to 2004 in sudden death due to coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J*. 2009;157:46–52.

18. Tseng ZH, Olgin JE, Vittinghoff E, et al. Prospective countywide surveillance and autopsy characterization of sudden cardiac death: POST SCD Study. *Circulation*. 2018;137:2689–2700.

19. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338.

20. Rogers JG, Pagani FD, Tatooles AJ, et al. Intrapericardial left ventricular assist device for advanced heart failure. *N Engl J Med*. 2017;376:451–460.

21. Mond HG, Proclemer A. The 11th world survey of cardiac pacing and implantable cardioverter-defibrillators: calendar year 2009–a World Society of Arrhythmia's project. *Pacing Clin Electrophysiol*. 2011;34:1013–1027.

22. Lau CP, Tse HF, Mond HG. The impact of reimbursement on the usage of pacemakers, implantable cardioverter defibrillators and radiofrequency ablation. *J Interv Card Electrophysiol*. 2006;17:177–181.

23. Siu CW, Pong V, Ho HH, et al. Are MADIT II criteria for implantable cardioverter defibrillator implantation appropriate for Chinese patients? *J Cardiovasc Electrophysiol*. 2010;21:231–235.

24. Tanno K, Miyoshi F, Watanabe N, et al. Are the MADIT II criteria for ICD implantation appropriate for Japanese patients? *Circ J*. 2005;69:19–22.

25. Kengne AP, Nakamura K, Barzi F, et al. Smoking, diabetes and cardiovascular diseases in men in the Asia Pacific region. *J Diabetes*. 2009;1:173–181.

26. Begisbayev T, Kosherbayeva L, Akhmetov V, Khvan D, Brimzhanova M. Implantation of implantable cardioverter defibrillators in Kazakhstan. *Glob Heart*. 2022;17:30.

27. Zhang S. Sudden cardiac death in China: current status and future perspectives. *EP Europace*. 2016;17:ii14–ii18.

28. 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. *J Am Coll Cardiol HF*. 2020;8:844–855.

29. Aonuma K, Ando K, Kusano K, et al. Primary results from the Japanese Heart Failure and Sudden Cardiac Death Prevention Trial (HINODE). *ESC Heart Fail*. 2022;9:1584–1596.

30. Kondo Y, Noda T, Sato Y, et al. Comparison of 2-year outcomes between primary and secondary prophylactic use of defibrillators in patients with coronary artery disease: a prospective propensity score–matched analysis from the Nippon Storm Study. *Heart Rhythm O2*. 2021;2:5–11.

31. Hayashi M, Shimizu W, Albert CM. The spectrum of epidemiology underlying sudden cardiac death. *Circ Res*. 2015;116:1887–1906.

32. Murakoshi N, Aonuma K. Epidemiology of arrhythmias and sudden cardiac death in Asia. *Circ J*. 2013;77:2419–2431.

33. Kwon S. Health care financing in Asia: key issues and challenges. *Asia Pac J Public Health*. 2011;23:651–661.

34. Fukuoka R, Kohno T, Kohsaka S, et al. Prediction of sudden cardiac death in Japanese heart failure patients: international validation of the Seattle Proportional Risk Model. *Europace*. 2020;22:588–597.

35. Hamaguchi S, Kinugawa S, Sobirin MA, et al. Mode of death in patients with heart failure and reduced vs. preserved ejection fraction: report from the registry of hospitalized heart failure patients. *Circ J*. 2012;76:1662–1669.

36. Adabag S, Smith LG, Anand IS, Berger AK, Luepker RV. Sudden cardiac death in heart failure patients with preserved ejection fraction. *J Card Fail*. 2012;18:749–754.

37. Gastelurrutia P, Pascual-Figal D, Vazquez R, et al. Obesity paradox and risk of sudden death in heart failure results from the MUerte Subita en Insuficiencia cardiaca (MUSIC) study. *Am Heart J*. 2011;161:158–164.

38. Hanafusa N, Nakai S, Iseki K, Tsubakihara Y. Japanese Society for Dialysis Therapy Renal Data Registry—a window through which we can view the details of Japanese dialysis population. *Kidney Int Suppl (2011)*. 2015;5:15–22.

39. Varma N, Sogaard P, Bax JJ, et al. Interaction of left ventricular size and sex on outcome of cardiac resynchronization therapy among patients with a narrow QRS duration in the EchoCRT Trial. *J Am Heart Assoc*. 2018;7:e009592.

40. Varma N, Wang J-A, Jaswal A, et al. CRT efficacy in "mid-range" QRS duration among Asians contrasted to non-Asians, and influence of height. *J Am Coll Cardiol EP*. 2022;8:211–221.

41. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. *N Engl J Med*. 1997;337:1569–1575.

42. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med*. 2004;351:2481–2488.

43. Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace*. 2010;12:1564–1570.

44. Bänsch D, Antz M, Boczor S, et al. Primary prevention of sudden cardiac death in idiopathic dilated cardiomyopathy. *Circulation*. 2002;105:1453–1458.

45. Strickberger SA, Hummel JD, Bartlett TG, et al. Amiodarone versus implantable cardioverter-defibrillator:randomized trial in patients with nonischemicdilated cardiomyopathy and asymptomaticnonsustained ventricular tachycardia—AMIOVIRT. *J Am Coll Cardiol*. 2003;41:1707–1712.

46. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med*. 2004;350:2151–2158.

47. Yafasova A, Butt JH, Elming MB, et al. Long-term follow-up of DANISH (The Danish Study to Assess the Efficacy of ICDs in Patients With Non-ischemic Systolic Heart Failure on Mortality). *Circulation*. 2022;145:427–436.

48. Wolff G, Lin Y, Karathanos A, et al. Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials. *Clin Res Cardiol*. 2017;106:501–513.

49. Birnie DH, Sauer WH, Bogun F, et al. HRS expert consensus statement on the diagnosis and management of arrhythmias associated with cardiac sarcoidosis. *Heart Rhythm*. 2014;11:1305–1323.

50. Elliott PM, Anastasakis A, Borger MA, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35:2733–2779.

51. Maron MS, Rowin EJ, Wessler BS, et al. Enhanced American College of Cardiology/American Heart Association strategy for prevention of sudden cardiac death in high-risk patients with hypertrophic cardiomyopathy. *JAMA Cardiol*. 2019;4:644–657.

52. Younis A, Aktas MK, Rosero S, et al. Outcome by sex in patients with long QT syndrome with an implantable cardioverter defibrillator. *J Am Heart Assoc*. 2020;9:e016398.

53. Wang M, Peterson DR, Rosero S, et al. Effectiveness of implantable cardioverter-defibrillators to reduce mortality in patients with long QT syndrome. *J Am Coll Cardiol*. 2021;78:2076–2088.

54. Tarakji KG, Mittal S, Kennergren C, et al. Antibacterial envelope to prevent cardiac implantable device infection. *N Engl J Med*. 2019;380:1895–1905.

55. Engstrom N, Dobson GP, Ng K, Letson HL. Primary prevention implantable cardiac defibrillators: a Townsville District perspective. *Front Cardiovasc Med*. 2020;7:577248.

56. Bongiorni MG, Kennergren C, Butter C, et al. The European Lead Extraction ConTRolled (ELECTRa) study: a European Heart Rhythm Association (EHRA) Registry of transvenous lead

extraction outcomes. *Eur Heart J*. 2017;38:2995–3005.

57. Younis A, Beinart R, Nehoray N, et al. Characterization of a previously unrecognized clinical phenomenon: delayed shock after cardiac implantable electronic device extraction. *Heart Rhythm*. 2017;14:1552–1558.

58. Kleemann T, Strauss M, Kouraki K, et al. Contemporary benefit-harm profile over two decades in primary prophylactic ICD-therapy. *Clin Cardiol*. 2019;42:866–872.

59. Zabel M, Willems R, Lubinski A, et al. 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.

60. Solomon SD, Zelenkofske S, McMurray JJ, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med*. 2005;352:2581–2588.

61. Buxton AE, Lee KL, Hafley GE, et al. Relation of ejection fraction and inducible ventricular tachycardia to mode of death in patients with coronary artery disease: an analysis of patients enrolled in the multicenter unsustained tachycardia trial. *Circulation*. 2002;106:2466–2472.

62. Khan HM, Leslie SJ. Risk factors for sudden cardiac death to determine high risk patients in specific patient populations that may benefit from a wearable defibrillator. *World J Cardiol*. 2019;11:103–119.

63. Skjelbred T, Rajan D, Svane J, Lynge TH, Tfelt-Hansen J. Sex differences in sudden cardiac death in a nationwide study of 54 028 deaths. *Heart*. 2022;108:1012.

64. Kaikkonen KS, Kortelainen M-L, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. *Circulation*. 2006;114:1462–1467.

65. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of sudden cardiac death: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol*. 2018;33:509–521.

66. de Sousa MR, Morillo CA, Rabelo FT, Nogueira Filho AM, Ribeiro AL. Non-sustained ventricular tachycardia as a predictor of sudden cardiac death in patients with left ventricular dysfunction: a meta-analysis. *Eur J Heart Fail*. 2008;10:1007–1014.

67. Zecchin M, Di Lenarda A, Gregori D, et al. Prognostic role of non-sustained ventricular tachycardia in a large cohort of patients with idiopathic dilated cardiomyopathy. *Ital Heart J*. 2005;6:721–727.

68. Feng YT, Feng XF. Sudden cardiac death in patients with myocardial infarction: 1.5 primary prevention. *Rev Cardiovasc Med*. 2021;22:807–816.

69. Hess PL, Matlock DD, Al-Khatib SM. Decision-making regarding primary prevention implantable cardioverter-defibrillators among older adults. *Clin Cardiol*. 2020;43:187–195.

70. Chen MY, Orkaby AR, Rosenberg MA, Driver JA. Frailty, implantable cardioverter defibrillators, and mortality: a systematic review. *J Gen Intern Med*. 2019;34:2224–2231.

71. Lee SJ, Kim CM. Individualizing prevention for older adults. *J Am Geriatr Soc*. 2018;66:229–234.

72. Anker SD, Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. *Chest*. 1999;115:836–847.

73. Anker SD, Steinborn W, Strassburg S. Cardiac cachexia. *Ann Med*. 2004;36:518–529.

74. Friedman DJ, Al-Khatib SM, Zeitler EP, et al. New York Heart Association class and the survival benefit from primary prevention implantable cardioverter defibrillators: a pooled analysis of 4 randomized controlled trials. *Am Heart J*. 2017;191:21–29.

75. Jukema JW, Timal RJ, Rotmans JI, et al. Prophylactic use of implantable cardioverter-defibrillators in the prevention of sudden cardiac death in dialysis patients. *Circulation*. 2019;139:2628–2638.

76. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol*. 2008;51:288–296.

77. Goldenberg I, Younis A, Aktas MK, McNitt S, Zareba W, Kutyifa V. Competing risk analysis of ventricular arrhythmia events in heart failure patients with moderately compromised renal dysfunction. *Europace*. 2020;22:1384–1390.

78. 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.

79. Bilchick KC, Wang Y, Cheng A, et al. Seattle heart failure and proportional risk models predict benefit from implantable cardioverter-defibrillators. *J Am Coll Cardiol*. 2017;69:2606–2618.

80. 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.

81. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. *Circulation*. 2006;114:32–39.

82. Dorbala S, Hachamovitch R, Curillova Z, et al. Incremental prognostic value of gated Rb-82 positron emission tomography myocardial perfusion imaging over clinical variables and rest LVEF. *J Am Coll Cardiol Img*. 2009;2:846–854.

83. Tsai SC, Chang YC, Chiang KF, et al. LV dyssynchrony is helpful in predicting ventricular arrhythmia in ischemic cardiomyopathy after cardiac resynchronization therapy: a preliminary study. *Medicine (Baltimore)*. 2016;95:e2840.

84. Nelson T, Garg P, Clayton RH, Lee J. The role of cardiac MRI in the management of ventricular arrhythmias in ischaemic and non-ischaemic dilated cardiomyopathy. *Arrhythm Electrophysiol Rev*. 2019;8:191–201.

85. Roes SD, Borleffs CJ, van der Geest RJ, et al. Infarct tissue heterogeneity assessed with contrast-enhanced MRI predicts spontaneous ventricular arrhythmia in patients with ischemic cardiomyopathy and implantable cardioverter-defibrillator. *Circ Cardiovasc Imaging*. 2009;2:183–190.

86. Perez-David E, Arenal A, Rubio-Guivernau JL, et al. Noninvasive identification of ventricular tachycardia-related conducting channels using contrast-enhanced magnetic resonance imaging in patients with chronic myocardial infarction: comparison of signal intensity scar mapping and endocardial voltage mapping. *J Am Coll Cardiol*. 2011;57:184–194.

87. Mavrogeni S, Petrou E, Kolovou G, Theodorakis G, Iliodromitis E. Prediction of ventricular arrhythmias using cardiovascular magnetic resonance. *Eur Heart J Cardiovasc Imaging*. 2013;14:518–525.

88. Yamashita S, Sacher F, Mahida S, et al. Role of high-resolution image integration to visualize left phrenic nerve and coronary arteries during epicardial ventricular tachycardia ablation. *Circ Arrhythm Electrophysiol*. 2015;8:371–380.

89. Bogun FM, Desjardins B, Good E, et al. Delayed-enhanced magnetic resonance imaging in nonischemic cardiomyopathy: utility for identifying the ventricular arrhythmia substrate. *J Am Coll Cardiol*. 2009;53:1138–1145.

90. Sasaki T, Miller CF, Hansford R, et al. Impact of nonischemic scar features on local ventricular electrograms and scar-related ventricular tachycardia circuits in patients with nonischemic cardiomyopathy. *Circ Arrhythm Electrophysiol*. 2013;6:1139–1147.

91. Yalin K, Golcuk E, Buyukbayrak H, et al. Infarct characteristics by CMR identifies substrate for monomorphic VT in post-MI patients with relatively preserved systolic function and ns-VT. *Pacing Clin Electrophysiol*. 2014;37:447–453.

92. Schmidt A, Azevedo CF, Cheng A, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation*. 2007;115:2006–2014.

93. Kim EK, Chattranukulchai P, Klem I. Cardiac magnetic resonance scar imaging for sudden cardiac death risk stratification in patients with nonischemic cardiomyopathy. *Korean J Radiol*. 2015;16:683–695.

94. Klem I, Klein M, Khan M, et al. Relationship of LVEF and myocardial scar to long-term mortality risk and mode of death in patients with nonischemic cardiomyopathy. *Circulation*. 2021;143:1343–1358.

95. Mathias A, Moss AJ, Lopes CM, et al. Prognostic implications of mutation-specific QTc standard deviation in congenital long QT syndrome. *Heart Rhythm*. 2013;10:720–725.

96. Goldenberg I, Bos JM, Yoruk A, et al. Risk prediction in women with congenital long QT syndrome. *J Am Heart Assoc*. 2021;10:e021088.

97. Itoh H, Shimizu W, Hayashi K, et al. Long QT syndrome with compound mutations is associated with a more severe phenotype: a Japanese multicenter study. *Heart Rhythm*. 2010;7:1411–1418.

98. Aiba T. Recent understanding of clinical sequencing and gene-based risk stratification in

inherited primary arrhythmia syndrome. *J Cardiol*. 2019;73:335–342.

99. Sieira J, Conte G, Ciconte G, et al. Prognostic value of programmed electrical stimulation in Brugada syndrome: 20 years experience. *Circ Arrhythm Electrophysiol*. 2015;8:777–784.

100. Priori SG, Gasparini M, Napolitano C, et al. Risk stratification in Brugada syndrome: results of the PRELUDE (PRogrammed ELectrical stimUlation preDictive valuE) registry. *J Am Coll Cardiol*. 2012;59:37–45.

101. Zeitler EP, Sanders GD, Singh K, et al. Single vs. dual chamber implantable cardioverter-defibrillators or programming of implantable cardioverter-defibrillators in patients without a bradycardia pacing indication: systematic review and meta-analysis. *Europace*. 2018;20:1621–1629.

102. Kolb C, Sturmer M, Babuty D, et al. Relation between detection rate and inappropriate shocks in single versus dual chamber cardioverter-defibrillator-an analysis from the OPTION trial. *Sci Rep*. 2016;6:21748.

103. Almendral J, Arribas F, Wolpert C, et al. Dual-chamber defibrillators reduce clinically significant adverse events compared with single-chamber devices: results from the DATAS (Dual chamber and Atrial Tachyarrhythmias Adverse events Study) trial. *Europace*. 2008;10:528–535.

104. Bänsch D, Steffgen F, Grönefeld G, et al. The 1+1 trial: a prospective trial of a dual- versus a single-chamber implantable defibrillator in patients with slow ventricular tachycardias. *Circulation*. 2004;110:1022–1029.

105. Saeed M, Hanna I, Robotis D, et al. Programming implantable cardioverter-defibrillators in patients with primary prevention indication to prolong time to first shock: results from the PROVIDE study. *J Cardiovasc Electrophysiol*. 2014;25:52–59.

106. Gasparini M, Proclemer A, Klersy C, et al. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. *JAMA*. 2013;309:1903–1911.

107. 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.

108. Stiles MK, Fauchier L, Morillo CA, Wilkoff BL. 2019 HRS/EHRA/APHRS/LAHRS focused update to 2015 expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing. *Europace*. 2019;21:1442–1443.

109. Woods B, Hawkins N, Mealing S, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart*. 2015;101:1800–1806.

110. Curtis AB, Worley SJ, Adamson PB, et al. Biventricular pacing for atrioventricular block and systolic dysfunction. *N Engl J Med*. 2013;368:1585–1593.

111. Weiss R, Knight BP, Gold MR, et al. Safety and efficacy of a totally subcutaneous implantable-cardioverter defibrillator. *Circulation*. 2013;128:944–953.

112. Lambiase PD, Barr C, Theuns DA, et al. Worldwide experience with a totally subcutaneous implantable defibrillator: early results from the EFFORTLESS S-ICD Registry. *Eur Heart J*. 2014;35:1657–1665.

113. Boersma L, Barr C, Knops R, et al. Implant and midterm outcomes of the Subcutaneous Implantable Cardioverter-Defibrillator Registry: the EFFORTLESS Study. *J Am Coll Cardiol*. 2017;70:830–841.

KEY WORDS Asia, ICD, implantable cardioverter-defibrillator, patient's selection, primary prevention, risk stratification