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REVIEW

Sudden Death Risk-Stratification in 2018–2019: The Old and the New

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Sudden Cardiac Death (SCD) is a major public health issue, accounting for half of all cardiovascular deaths world-wide. The implantable cardioverter-defibrillator (ICD) has been solidified as the cornerstone therapy in primary prevention of SCD in ischaemic and non-ischaemic cardiomyopathy. However, what has become increasingly clear is that the left ventricular ejection fraction (LVEF) is an inadequate tool to select patients for a prophylactic ICD, despite its widespread use for this purpose. Use of LVEF alone has poor specificity for arrhythmic versus non-arrhythmic death. In addition, the vast majority of sudden deaths occur in patients with more preserved cardiac function. Alternate predictors of sudden death include electrophysiology study, non-invasive markers of electrical instability, myocardial fibrosis, genetic and bio-markers. The challenge for the future is finding a risk stratification test, or combination of tests, that adequately select patients at high risk of SCD with low competing risk of non-sudden death.

Keywords Sudden cardiac death • Cardiomyopathy • Implantable cardioverter-defibrillator • Primary prevention

Introduction and 'Appropriate Use' ICD Guidelines

Sudden cardiac death (SCD) accounts for approximately 350,000 deaths in the United States and 20,000 deaths in Australia, every year. An implantable-cardioverter defibrillator (ICD) has proven efficacy in the primary prevention of SCD in select high-risk patients. Appropriate ICD use guidelines state that patients with left ventricular ejection fraction (LVEF) ≤30% or ≤35% with New York Heart Association (NYHA) Class II or III heart failure who are >40 days post myocardial infarction (MI) or >90 days post revascularisation are eligible for a primary prevention ICD. However, these guidelines are invariably based on the positive or negative findings of relatively few randomised trials, with little account made for the mechanistic or pathophysiological basis for SCD. Hence, many patients at risk for SCD that could potentially benefit from an ICD are missed, and patients that may never receive an appropriate ICD therapy are exposed to its risks. SCD risk stratification is concerned with optimal selection of patients for a prophylactic ICD. This review will focus on what we know and where we are heading — *the 'old and the new'* — in risk stratification for primary prevention of SCD.

Primary Prevention ICDs in Ischaemic Cardiomyopathy

In ischaemic cardiomyopathy (CM) secondary to MI it is well accepted that myocardial scar creates the substrate for ventricular tachyarrhythmia and sudden death. Current recommendations for prophylactic ICDs in ischaemic CM patients are based on the MADIT II (Multicenter Automatic Defibrillator Implantation Trial) and SDC-HeFT (Sudden Cardiac Death in Heart Failure) trials [1,2]. Patients with LVEF ≤30%, or ≤35% with NYHA Class II–III heart failure, were randomised to an ICD with a reduction in mortality compared to medical therapy. The result was a single LVEF cut-off to guide ICD implantation in ischaemic CM patients. However, use of LVEF ≤30% to guide ICD implantation in the MADIT-II trial resulted in a small absolute mortality reduction with

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low therapeutic efficiency (~17 ICDs per life saved). In the SCD-HeFT trial, use of LVEF ≤35% inclusive of heart failure resulted in even lower therapeutic efficacy with ~25 ICDs implanted to save one life. Prior to this, earlier trials had incorporated electrophysiology study (EPS) into their risk stratification models with four to five ICDs implanted per life saved [3,4]. While there is a trade-off between limiting the number of ICDs implanted per life saved and including a greater proportion of the at-risk population, there is certainly a role for better risk stratification to optimise this trade-off.

A major concern is that the risk of SCD and cardiac arrest is four- to six-fold higher in the first 0–3 months post-MI or coronary artery bypass graft (CABG) than thereafter [5,6] (Figure 1). Yet, based on both the design and results of randomised trials, guidelines exclude patients from receiving a primary prevention ICD within 40 days of MI or 90 days of revascularisation. Whilst recurrent MI or cardiac rupture account for a proportion of these early deaths, ~51% are likely due to ventricular tachyarrhythmia [7]. Three randomised trials specifically enrolled patients shortly after MI or revascularisation. The DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) recruited patients 6–40 days post-MI with LVEF ≤ 35% and autonomic dysfunction. Prophylactic ICD implantation, compared to medical therapy, failed to reduce all-cause mortality [8]. The IRIS (Immediate Risk stratification Improves Survival) trial recruited patients 5–31 days post-MI with LVEF ≤40% and elevated resting heart rate or non-sustained ventricular tachycardia (VT)

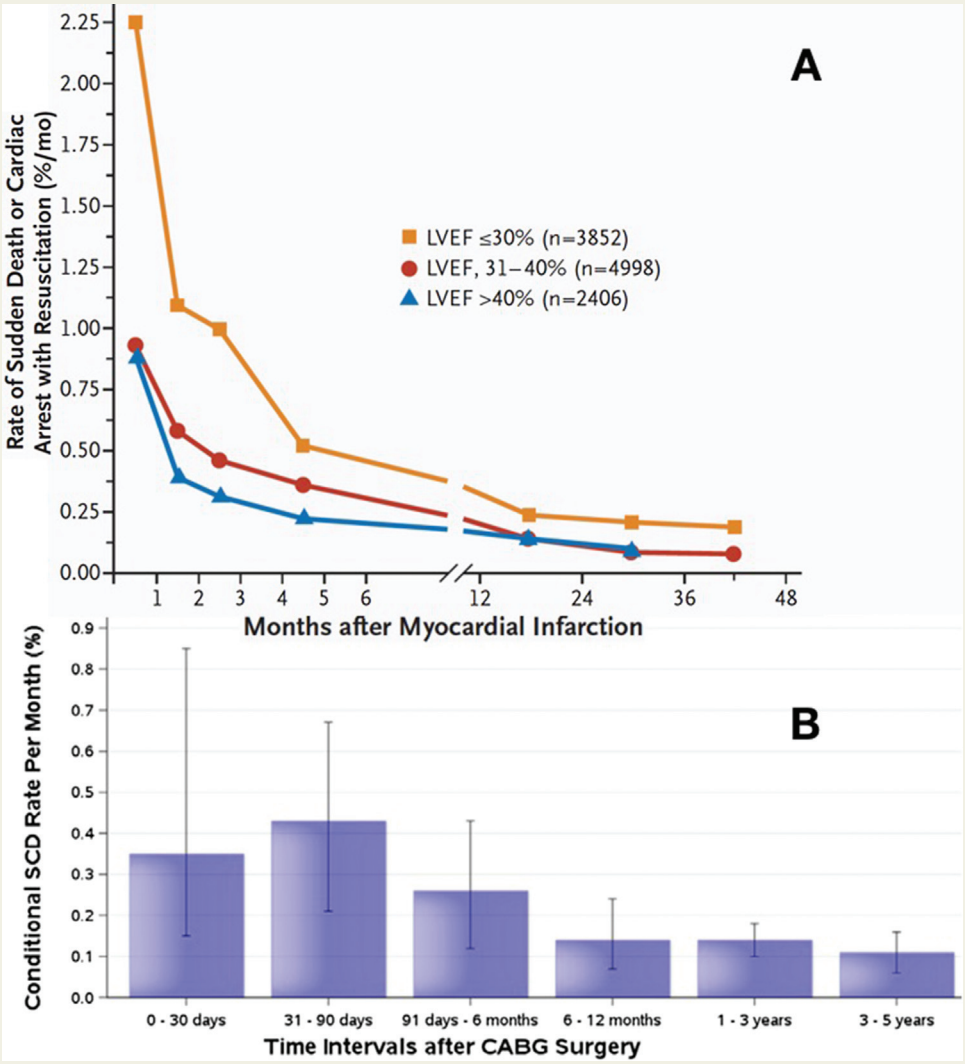

Figure 1 Risk of sudden death and cardiac arrest per month for different time periods post-MI or CABG. The monthly rate of SCD and cardiac arrest is highest in the first 0–3 months post-MI in all categories of left ventricular ejection fraction (LVEF) (Panel A). The monthly rate of SCD is highest in the 31–90 days post-CABG (Panel B). The rate of SCD declines exponentially and plateaus after 6 months following MI or revascularisation. Reproduced from Solomon et al. [5] and Rao et al. [6] with permission of the publisher. Copyright © 2005 Massachusetts Medical Society and © 2017 American Heart Association, Inc. Abbreviations: MI, myocardial infarction; CABG, coronary artery bypass graft; SCD, sudden cardiac death

and also found no benefit in all-cause mortality with an ICD [9]. The CABG Patch trial randomised patients with LVEF ≤35% and an abnormal signal averaged electrocardiograph (ECG) to either control or ICD implantation at the time of bypass surgery and showed no mortality benefit [10]. In all three trials, significant reduction in SCD was offset by an equal and opposite increase in non-sudden death.

There are multiple explanations for the negative results of these trials despite enrolment of patients with depressed LVEF, a criterion that in other settings has been associated with an ICD survival benefit. One potential explanation is based upon the type of risk stratification tests chosen. Markers of autonomic dysfunction and resting tachycardia early after MI may select patients at risk of heart failure death, rather than sudden death. An early post-MI LVEF would not have accounted for myocardial stunning and potential for LV recovery or for right ventricular/septal involvement [11]. Risk stratification tools that specifically target arrhythmic risk and measure ventricular infarction rather than function could be more helpful in this early post-MI period.

Primary Prevention ICDs in Non-Ischaemic Cardiomyopathy

Evidence supporting primary prevention ICDs in non-ischaemic cardiomyopathy (CM) comes from meta-analyses incorporating three smaller trials [12–14] with the non-ischaemic cohort (~50% of the overall participants) from the SCD-HeFT trial [2]. Whilst an overall survival benefit was seen with an ICD, each individual trial did not meet statistical significance. The more recent DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality) study reassessed the use of prophylactic ICDs in non-ischaemic CM [15]. This trial enrolled 1116 non-ischaemic CM patients with NYHA class II–III heart failure (NYHA class IV if cardiac resynchronisation therapy [CRT] was planned) with LVEF ≤35% and increased levels of B-type natriuretic peptide (BNP). Participants were required to be on guideline-directed optimal medical therapy and 58% were treated with cardiac resynchronisation therapy. The DANISH trial showed a reduction in SCD but not overall mortality, in patients assigned an ICD. Although consequent meta-analyses still demonstrate a net survival benefit from ICD therapy in non-ischaemic CM [16–18], this effect has been substantially diluted by the DANISH trial.

The lack of ICD benefit in the DANISH trial may reflect advances in medical and resynchronisation therapy. In the DANISH trial, almost every patient received beta blockers and inhibitors of the renin-angiotensin system, 60% received mineralocorticoid-receptor antagonists and 58% had CRT therapy (93% with left bundle-branch-block and QRS >150 milliseconds). In older ICD trials the majority of patients would have been sub-optimally treated by contemporary standards. A meta-analysis evaluating this specific hypothesis found no mortality benefit with an ICD in non-ischaemic CM patients receiving contemporary medical therapy [19]. However, within the DANISH trial, there were subgroups who benefited from an ICD, such as patients <59 years old. This highlights the need for risk stratification tests outside of LVEF to identify subgroups within ischaemic CM on optimal medical therapy who benefit from an ICD.

Primary Prevention ICDs in Specific Sub-Groups

There are patients who meet current appropriate use criteria for an ICD who may not benefit due to older age or competing co-morbidities. For example, there is evolving evidence to suggest primary prevention ICDs do not improve survival in patients with chronic renal failure [20,21].

Age

The median age of participants in the SCD-HeFT trial and MADIT II trial were 60 years and 64 years of age, respectively. Sub-group analysis of the DANISH trial demonstrated a survival benefit of ICDs in patients <59 years of age but not in older patients [15]. Further investigation by the DANISH investigators suggested a mortality benefit of an ICD with an age cut-off <70 years with a relative risk reduction of 30% [22]. Younger patients derived greater benefit from a prophylactic ICD as SCD comprised a greater proportion of total deaths. However, this must be interpreted with caution given elderly patients in the DANISH trial had longer duration heart failure, higher BNP levels and more co-morbidities, possibly leading to higher rates of non-sudden deaths. As a result, CRT use was appropriately higher in the older DANISH population with a possible resultant dilution of an ICD benefit.

Gender

Women are severely under-represented in cardiovascular trials, with ICD studies no exception. In the MADIT-II and SCD-HeFT ischaemic CM trials specific gender analysis demonstrated a smaller but still significant survival benefit with an ICD in women [23,24]. However, both in the female subgroup of the DANISH trial, and in meta-analysis of older ICD studies, women with non-ischaemic CM have not benefited from a prophylactic ICD [15,25].

SCD With Preserved LVEF

Individuals with impaired LVEF have the highest proportion of SCD however, absolute numbers of SCDs are higher in the general population [26–29]—the risk is lower but the size of the population is much larger. Prevention of SCD at the general population level is extremely limited due to the low incidence (60–90 SCDs per 100,000 people) and the large range of underlying causes. Another often overlooked population at risk of SCD is the large group of patients with

coronary artery disease or dilated cardiomyopathy, but relatively preserved cardiac function. Once again, the absolute numbers of SCD are far higher in these patients than in those with LVEF≤35% (Figure 1 Panel A) [5,26,28].

Risk Stratification Tests

A large number of risk stratification tests have undergone evaluation in randomised and observational studies. Whilst LVEF has been incorporated into the majority of these models, LV function alone is a poor predictor of arrhythmia. Alternate tests, selecting patients specifically at risk of arrhythmic death, are urgently required.

Electrophysiology Study (EPS)

Programmed ventricular stimulation (PVS) at EPS demonstrates the presence of an electrical substrate for re-entrant VT. It is a risk stratification test that has consistently predicted arrhythmic risk in both prospective and randomised trials [30–33]. EPS in combination with impaired LVEF has been shown in the MADIT-I and MUSTT (Multicenter UnSustained Tachycardia Trial) to result in a 23–31% absolute mortality reduction [3,4], more than four-fold the mortality reduction seen in the MADIT II trial with the use of LVEF alone. EPS performed in early post-MI patients identified those with a high rate of spontaneous ventricular tachyarrhythmia, with 17% occurring within the first 40 days [32,34,35]. Patients with LVEF≤40% but no inducible VT at EPS who were discharged without a defibrillator had an extremely low occurrence of arrhythmic mortality [36]. The use of EPS to guide prophylactic ICD implantation in patients with LVEF≤40% 3–40 days post-MI is the focus of the international multi-centre PROTECT-ICD trial, with results expected in 2021 [37].

A concern with EPS as a risk stratification tool for prophylactic ICDs is its negative predictive value. Electrophysiology study identifies re-entrant circuits in the post-infarct patient predisposing to monomorphic VT. However, EPS may not reliably predict SCD due to ventricular fibrillation or other triggering mechanisms, such as acute ischaemia or heart failure. The negative predictability of EPS appears to be critically dependent on the PVS protocol used to induce VT (Figure 2). Studies with lower negative predictive value often used PVS protocols with three extrastimuli and included inducible ventricular fibrillation (VF) as a positive result [30,31]. In EPS performed for post-MI risk stratification, 30% of patients found to be at high risk of arrhythmia would be missed if three instead of four extrastimuli were used to induce VT [35]. In contrast, inducible ventricular fibrillation (VF) or rapid ventricular flutter (<200 milliseconds cycle length) has been shown to have no prognostic significance and can be induced in patients with normal hearts [38]. Although EPS is an invasive test with the potential risk of infection, bleeding, and, rarely, pericardial tamponade, it has been shown to be safe even in the acute post-MI period.

ECG Markers

Electrocardiogram markers of electrical instability, presumed to predict SCD, include microvolt T-wave alternans (MTWA), QRS fragmentation, QRS duration and signal averaged ECG (or ventricular late potentials). The largest number of studies centred on MTWA, defined as the beat-to-beat fluctuation on the ECG related to the dispersion of repolarisation, presumed to be a marker of electrophysiological vulnerability. A large meta-analysis of non-ischaemic CM patients combined 45 studies of electrophysiological parameters; MTWA was found to be the strongest predictor of arrhythmic events (OR 4.66; 95% CI 2.55–8.53; $p < 0.001$) [39]. This predictive ability increased in patients taking beta blockers [40]. In ischaemic CM, the utility of MTWA for SCD risk assessment remains unclear. The MASTER (Microvolt T Wave Alternans Testing for Risk Stratification of Post Myocardial Infarction Patients) trial found that in post-MI patients with LVEF≤30% undergoing ICD implantation, MTWA was positive in 51% with a low predictive value for arrhythmia [41]. The ABCD trial in patients with coronary artery disease (CAD), LVEF≤40%, and nonsustained ventricular tachycardia found that MTWA by itself had limited predictive value but, when combined with EPS, both provided incremental predictive value [30]. The REFINE (Risk Estimation Following Infarction, Noninvasive Evaluation) study performed several noninvasive risk stratification tests, including MTWA, in both the early (2–4 weeks) and subacute (10–14 weeks) periods after acute MI [42]. Abnormal MTWA, in addition to impaired heart rate turbulence and LVEF<50% beyond 8 weeks after MI identified patients at risk of arrhythmia. The use of MTWA and impaired heart rate turbulence in patients with LVEF 36–50% >2 months post-MI is being evaluated in the REFINE-ICD trial (NCT 00673842) with results expected in 2021.

Autonomic Indices

Markers of autonomic tone, including heart rate variability, resting elevated heart rate and heart rate turbulence, have, so far, been disappointing in prediction of SCD. Measures of autonomic dysfunction appear to identify patients at increased mortality, but not specifically arrhythmic risk [39,43]. Incorporation of autonomic dysfunction with LVEF did not result in an ICD survival benefit early post-MI in the randomised DINAMIT and IRIS trials [8,9].

Cardiac Magnetic Resonance (cMRI)

A noninvasive imaging modality without radiation exposure, cMRI has exciting possibilities in risk stratification for SCD. Delayed gadolinium enhancement (DGE) enables

Figure 2 Programmed Ventricular Stimulation (PVS) Program at Electrophysiology Study (EPS). Pacing is performed from the right ventricular (RV) catheter with a drive train of 8 beats at 400 millisecond cycle length (CL) [1–6]. Up to 4 extrastimuli are delivered, each introduced at a coupling interval of 300 milliseconds and then decreased in 10 milliseconds steps to ventricular refractoriness. If no ventricular tachycardia (VT) is induced the initial extrastimulus is delivered 10 milliseconds outside the ventricular effective refractory period and the next extrastimulus is added (S2 = first extrastimulus, S3 = second extrastimulus, S4 = third extrastimulus, S5 = fourth extrastimulus). In this example, after introduction of the fourth extrastimulus, monomorphic ventricular tachycardia (VT) is induced and the study is positive.

visualisation of the infarct and peri-infarct zone in the post-MI setting, and the presence of mid-wall fibrosis in the non-ischaemic cardiomyopathy setting (Figure 3). Both have been postulated to provide the substrate for re-entrant tachyarrhythmia and sudden death.

In patients with ischaemic CM a relationship between the peri-infarct (or 'gray') zone on DGE-cMRI with induced and spontaneous ventricular arrhythmia has been identified [44–46]. In addition, there is emerging evidence that infarct size measured at cMRI is superior to LVEF both for identifying patients with inducible VT at EPS (98) and for predicting total mortality, SCD and arrhythmia [99,61]. Compared to echocardiographic-derived LVEF, cMRI early post-MI is also attractive as infarction on DGE is unlikely to recover. The DETERMINE (Defibrillators to Reduce Risk by MRI Evaluation) trial evaluated the efficacy of an ICD in post-MI patients with cMRI infarct mass >10% who were not ICD candidates by current LVEF criteria [47]. The trial was stopped prematurely due to slow enrolment. The PROTECT-ICD trial incorporates a pre-defined sub-study of cMRI in 400 patients early post-MI with results expected in 2021 [37].

In non-ischaemic CM, the presence of mid-wall LGE on cMRI has been validated in histological studies to represent replacement fibrosis [48]. Mid-wall fibrosis has been shown to identify non-ischaemic CM patients with impaired LVEF at increased risk of arrhythmia and SCD [48–51]. In addition, mid-wall LGE in non-ischaemic CM patients with preserved LVEF (>40%) identified patients at high risk of SCD [52]. Randomised trials are urgently needed to solidify the role of cMRI for risk stratification in the non-ischaemic CM cohort.

Biomarkers

Several biomarkers have been associated with myocardial stress and fibrosis, including B-type natriuretic peptide (BNP), troponin, galectin-3 and soluble ST2. These biomarkers are generally released in response to myocardial stretch

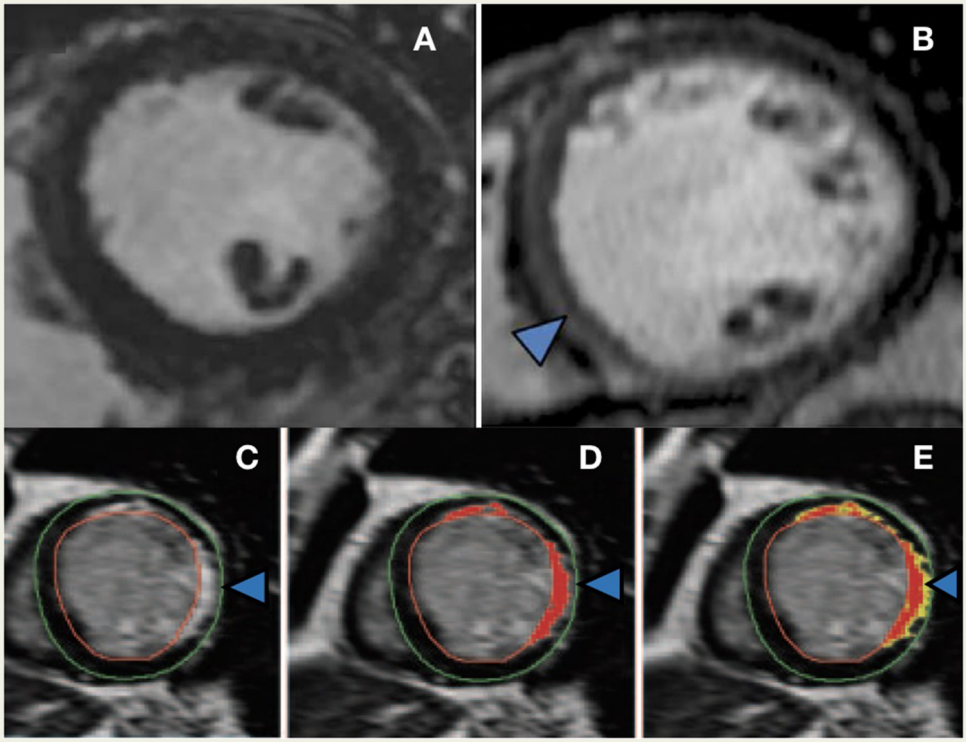

Figure 3 Delayed gadolinium enhancement on cardiac magnetic imaging. A short axis view of the mid left ventricle of a healthy control (A) can be compared with mid-wall fibrosis seen in dilated non-ischaemic CM (B, arrow). Myocardial infarction (arrows) in a post-MI patient with the endocardial (red) and epicardial (green) borders outlined demonstrating the infarct core in red and gray zone in yellow (C–E). Mid-wall fibrosis in non-ischaemic CM and the infarct core/gray zone in ischaemic CM are hypothesised to form the substrate that predisposes to sudden cardiac death. Reproduced from Halliday et al. [52] and Roes et al. [45] with permission of the publisher. Copyright © 2009 and 2017 American Heart Association, Inc. Abbreviations: CM, cardiomyopathy; MI, myocardial infarction.

or strain and increased pre-load seen in heart failure. It would seem logical therefore, that elevated biomarkers would be associated with death due to cardiac failure rather than arrhythmic death specifically. This was observed in the DANISH trial where high levels of pro-BNP were associated with less benefit from an ICD [15]. However, retrospective studies have shown a link between biomarker levels and ventricular tachyarrhythmia, out of proportion to the association with non-sudden mortality [53,54]. This requires validation in further studies.

Genetic Predictors

Familial clustering of sudden cardiac arrest and SCD as the first manifestation of coronary artery disease has been well documented [55,56]. In dilated CM, genetic mutations in the lamin A/C (LMNA) gene have been associated with more aggressive CM and higher rates of ventricular arrhythmia [57]. Despite the suggestion of a genetic predisposition to SCD, identification of specific genomic markers remains difficult. Much of the work in this area is in younger patients (1–35 years) with a link to other rarer, heritable arrhythmias or heart disease [58]. Due to the rapidly evolving area of whole-genome sequencing, further identification of high-risk mutations, and genetically individualised SCD risk remains a goal for the future.

The Wearable Cardioverter-Defibrillator (WCD)

The WCD consists of a chest garment that holds in place defibrillation and ECG monitoring electrodes (LifeVest, ZOLL Medical Corp., Pittsburgh, PA, USA). It offers a non-invasive alternative to an ICD, particularly relevant in patients with transient arrhythmic risk, such as the early post-MI period, or with newly diagnosed non-ischaemic CM in whom LV function may recover. The benefit of a WCD is the avoidance of long-term cost involved with an ICD as well as complications of bleeding, lead dislodgement, pneumothorax, cardiac perforation, infection, inappropriate activations and death. There are, however, important limitations with the WCD including lack of pacing, therapy limited to shock, reduced efficacy with obesity and compliance with wearing the vest [59]. The WCD has had widespread uptake in the United States. However, the VEST (Vest Prevention of Early Sudden Death trial) presented at the

American College of Cardiology's scientific session, failed to show a reduction in its primary endpoint of SCD, despite a 36% reduction in total mortality at 90 days [60].

Conclusions

In ischaemic CM, LVEF is neither sensitive nor specific in selecting patients to receive a prophylactic ICD. In addition, the early-post MI period remains a high risk period not covered by current ICD guidelines. In patients with non-ischaemic CM, advances in heart failure medications and cardiac resynchronisation therapy have lowered mortality and arrhythmia-attributable mortality. This has resulted in a need to move beyond the LVEF cut-off method to select patients for an ICD. Risk stratification tests that focus on the presence of underlying substrate for arrhythmia are urgently needed. Cardiac MRI, with its ability to assess the extent of myocardial scar and presence of myocardial fibrosis holds promise as a risk-stratifier. Electrophysiological study remains a key test to select for risk of arrhythmic death, and holds promise in the early post-MI period. Cost-effective selection of patients for an ICD to prevent SCD continues to be a major public health issue.

Declarations of Interest

None.

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