# Prediction of sudden cardiac death: next steps in pursuit of effective methodology

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**Abbreviations**

| | |
|---|---|
| CHF | Congestive heart failure |
| ECG | Electrocardiogram |
| HFNEF | Heart failure with normal ejection fraction |
| HRV | Heart rate variability |
| ICD | Implantable cardioverter defibrillator |
| LVEF | Left ventricular ejection fraction |
| MI | Myocardial infarction |
| NYHA | New York Heart Association |
| SAECG | Signal-averaged electrocardiogram |
| SCD | Sudden cardiac death |
| VT | Ventricular tachycardia |

The recognition that severe left ventricular dysfunction is a predictor of sudden cardiac death (SCD) risk enabled widespread utilization of the implantable cardioverter defibrillator (ICD) for SCD prevention. Use of the ICD prior to any signs or symptoms of ventricular arrhythmias ("primary prevention") is particularly important for SCD because case fatality for patients with sustained ventricular tachyarrhythmias is among the highest of any disease process. At the same time, primary prevention of SCD presents a unique epidemiologic challenge for many

reasons [1, 2]: (1) high-risk subgroups constitute only a small proportion of all patients at risk for SCD, (2) the pathophysiologic etiologies of SCD are complex and infrequently recognized prior to arrest, (3) ventricular arrhythmia substrate often evolves over time and may require repeated risk stratification, (4) classification of arrhythmic death is particularly imprecise, (5) triggers for SCD may be transient, and (6) patients at high risk for SCD have many competing risks that are not ameliorated by ICDs. This review will address the limitations of risk stratification based on left ventricular ejection fraction (LVEF), summarize new developments in the field that extend beyond LVEF, and suggest new investigative approaches for refinement of SCD risk assessment.

## 1 The promise of LVEF-based prevention efforts

Two early trials, MADIT-I and Multicenter Unsustained Tachycardia Trial (MUSTT), established the role of ICDs for primary prevention of SCD based on impaired LVEF and positive electrophysiology study [3, 4]. Subsequent trials, Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT), used LVEF without additional high-risk markers for ventricular arrhythmia. MADIT-II enrolled 1,232 patients with prior myocardial infarction (MI) and New York Heart Association (NYHA) class I, II, or III, and randomized to ICD versus conventional medical therapy [5]. SCD-HEFT enrolled 2,521 patients with ischemic or non-ischemic cardiomyopathy and NYHA class II or III conges-tive heart failure (CHF) and randomized to ICD, amiodarone, or placebo [6]. MADIT-II survival curves showed a 31% reduction in risk of death (5.6% absolute risk reduction at 20-month mean follow-up), while SCD-HEFT showed a 23%

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reduction in risk of death in ICD as compared to placebo (7.2% absolute risk reduction at 5-year follow-up). There was no benefit of amiodarone as compared to placebo.

## 2 Limitations of LVEF-based prevention efforts

It quickly became evident that a significant number of patients who receive an ICD under MADIT-II or SCD-HEFT criteria do not benefit from it during intermediate-term follow-up of 2–5 years [7]. During the 20-month average follow-up of MADIT-II, the annualized rate of appropriate ICD therapies was 17% [8]. Over 5 years of follow-up in SCD-HEFT, the annualized rate of appropriate therapies was 5.1% [6]. Differences in patient populations likely were notable contributors to the disparate rates of ICD utilization. Consistent between both studies was a lack of benefit observed at the upper range of the LVEF limit for enrollment [1]. At the same time that many ICDs go unutilized, a majority of patients at risk for cardiac arrest do not qualify for an ICD despite the broadened LVEF-based indications (conceptually illustrated in Fig. 1 and in Table 1). Two population based studies in the Netherlands (Maastricht study) and Oregon, USA (The Oregon Sudden Unexpected Death Study), have demonstrated that the majority of patients who suffer SCD do not have a severely reduced LVEF. In subsets with medical history available, only 20–30% of patients who suffered SCD had LVEF low enough to have warranted primary prevention of SCD with an ICD [9–11].

Two conclusions can be drawn about current practices for primary prevention ICD use:

1. Even at the higher 17% annualized utilization rates from MADIT-II, there is considerable room for improvement in patient selection if new risk stratification methods can be developed.

2. LVEF-based prevention efforts will miss a majority of SCD patients. At the same time, the incidence of SCD among patients in the general population who have normal LVEF is so low that powerful risk stratification schemes will be necessary to define patients at high enough risk to receive an ICD (Table 1).

## 3 Limitations of existing non-LVEF risk predictors

A number of non-LVEF risk stratification tests have been evaluated individually for relevance in predicting a variety of outcomes (overall mortality, arrhythmic events/mortality, ICD shocks, and mortality benefit from ICDs). These tests include signal-averaged ECG, QRS duration, QT interval, ventricular ectopy, heart rate variability, heart rate turbulence, exercise capacity, heart failure class, heart rate recovery or ventricular ectopy after exercise, T-wave alternans, baroreceptor sensitivity, and electrophysiology study with ventricular programmed ventricular stimulation (many summarized in Table 2) [12, 13]. Clinical applicability has been limited thus far because most studies have not demonstrated sufficiently high predictive value for arrhythmic death or arrhythmic events [12]. Five were considered promising enough to be tested for their ability to predict mortality benefit from ICD use in the context of randomized trials. The first two, non-sustained ventricular tachycardia (VT) on ambulatory ECG and inducible VT during electrophysiology study, were effective in defining patients with severe ischemic cardiomyopathy who are at very high risk of SCD and benefit from an ICD [3, 4]; however, the SCD risk among patients without these markers was still uncomfortably high for patients with severely reduced LVEF, prompting subsequent trials without these predictors [5, 6]. The third non-LVEF risk stratifier, abnormal signal-averaged ECG (SAECG), was
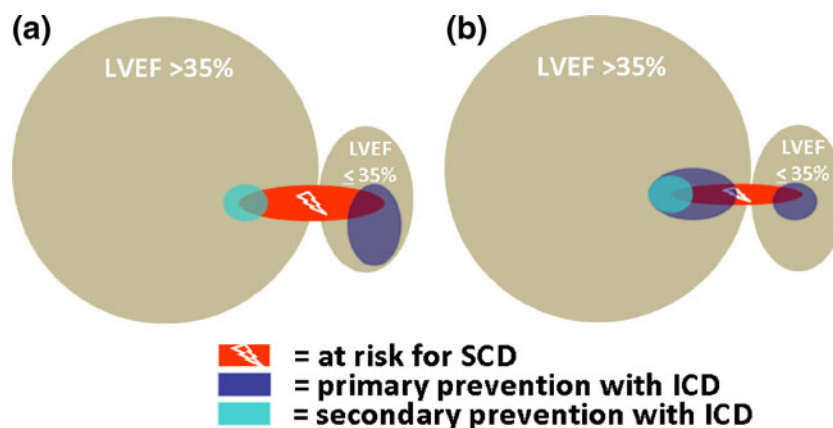


**Fig. 1** *Venn diagrams* of primary prevention and secondary prevention ICD utilization strategies, (**a**) shows the current approach, with a majority of SCD victims not previously qualifying for an ICD and many ICDs unutilized, and (**b**) shows an idealized approach with fewer cases of SCD due to fewer at-risk patients (from coronary artery disease prevention efforts) and more efficient utilization of ICDs among at-risk patients. *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac arrest, *ICD* implantable cardioverter defibrillator

**Table 1** Estimates of SCD incidence in Portland, Oregon metro area population (aged ≥45 years)

| Ejection fraction | Percent of population | Percent of SCDs | SCD incidence rate |
|---|---|---|---|
| All | 100% | 100% | 142/100,000 |
| LVEF ≤50% | 5.8% | 52% | Greater than 1,000/100,000 |
| LVEF >50% | 94.2% | 48% | Less than 100/100,000 |

The SCD incidence among patients with normal LVEF is very small, yet accounts for almost half of all SCD cases. This illustrates that in order to significantly impact the overall problem of SCD, prevention efforts must focus beyond LVEF. Estimates in this table should be used for general descriptive purposes only. We generated estimates of SCD incidence rates for normal versus abnormal LVEF by using results from the population-based Rochester Epidemiology Project [35] and applying to the same age distribution for the population-based Oregon Sudden Unexpected Death Study [10]. We assumed that the LVEF distribution for SCD patients with prior LVEF assessment applied to all patients with SCD [11]. Because of these extrapolations, we have reported ranges of SCD incidence for LVEF subcategories rather than the calculated SCD point incidence because such an incidence would have precision highly disproportionate to its level of accuracy. *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac arrest, *ICD* implantable cardioverter defibrillator

used as an entry criterion in the CABG-PATCH trial [14]. Although SAECG had shown initial promise, there was no benefit from ICD implantation in this trial. The fourth predictor, heart rate variability on 24-h Holter, was tested as an entry criterion for the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) of ICD placement within 6 to 40 days of MI in patients with LVEF ≤35% [15]. This trial also showed no benefit. The fifth predictor, microvolt T-wave alternans, has shown some promise, but when tested in the setting of primary prevention ICD use as part of SCD-HeFT, it was not predictive of arrhythmic events [16].

## 4 Identification of novel non-LVEF risk predictors

Novel risk prediction methods are acutely needed to more efficiently utilize ICDs for SCD prevention. We currently spend approximately $3.6 billion dollars annually on ICDs in the US (113,000 annual implants [17] with an assumed cost per implant of $33,000 [18]) with a large majority of devices unutilized. At the same time, current ICD guidelines do not address half of patients who will experience SCD [11]. We believe effective and efficient SCD prevention will require two simultaneous efforts:

### 4.1 Refine existing criteria for ICD-based primary prevention using clinical risk scores

Risk scores have been used to retrospectively define benefit or lack of benefit from primary prevention ICD use. Investigators from the MUSTT study identified EF-independent predictors of total and arrhythmic mortality among patients with LVEF ≤40% after MI who were assigned to the no-antiarrhythmic drug/no-ICD arm [19]. The MADIT-II investigators derived a risk score based on patient data from MADIT-II and compared the mortality rates for ICD or conventional therapy at different risk-score levels [20]. Very low and very high mortality rate cohorts

did not benefit from ICDs, while intermediate risk cohorts had a 49% risk reduction. SCD-HeFT patients were similarly evaluated using a risk score modified from the Seattle Heart Failure Model (SHFM-D) and derived in a separate population [21]. Investigators evaluated ICD benefit in each mortality quintile. Mortality risk reductions for ICD therapy ranged from 31% to 54% in first four quintiles, with no benefit in the highest risk quintile. The absolute risk reductions were 7% to 14% in the first four quintiles over nearly 4 years follow-up.

The MADIT-II and SHFM-D risk scores use non-invasive data regarding co-mordibities, functional status, and laboratory values that could be easily utilized in clinical practice. The MADIT-II score applies only to ischemic cardiomyopathy patients, while the SHFM-D score from SCD-HeFT applies to ischemic and non-ischemic cardiomyopathy patients. The SHFM-D score has 15 predictor variables (including LVEF) while the MADIT-2 score has five predictor variables and was derived separately from the SCD-HeFT validation population. Both studies show that patients with the highest overall mortality rates did not benefit from ICDs.

It may be difficult for some physicians and patients to move toward withholding ICDs based on these risk scores because they were not used as entry criteria for randomized controlled trials. The uncertainty would be clarified by a randomized trial designed to test non-inferiority of a strategy to withhold ICD treatment based on risk score for specific patients with LVEF ≤35%. While there are challenges to the conduct of such a trial, the cost of such a reseach effort would be a more fraction of the current total annual ICD expenditures in the US. Even if this research effort cost $100 million, it would represent only 3% of total annual ICD expenditures in the US.

### 4.2 Define new high-risk, ICD-eligible patients

*Develop new risk stratification tools from large unbiased community-based evaluations where all-comers with SCD are evaluated regardless of LVEF* Additional novel risk

**Table 2** Summary of existing non-LVEF risk stratification tests

| Risk stratification tests | Evidence for predicting SCD | Evidence for predicting ICD-detected VT/VF |
|---|---|---|
| Programmed ventricular stimulation | • Strong PPV in ischemic cardiomyopathy; also proven to identify patients with large mortality benefit from ICDs.<br>• Limited negative predictive value in ischemic cardiomyopathy with moderately to severely reduced LVEF.<br>• Not predictive for other cardiomyopathy etiologies. | Strong PPV for ventricular arrhythmia risk in ischemic cardiomyopathy. |
| QRS duration | Mixed findings, MUSTT found it was independently predictive while other studies did not. | Preponderance of studies shows it is not independently predictive. |
| QT interval | Population-based and cohort data showing independent prediction of SCD. | |
| T-wave alternans | Potentially promising technique, but several large cohort studies have shown limited PPV and not predictive in a large randomized trial. Generally composite outcomes measured. | |
| Signal-averaged ECG | Limited to post-MI patients. Variable PPV and no benefit for ICD implantation among positive test in CABG-PATCH. Negative predictive value has been >90%, though generally evaluated prior to widespread reperfusion of AMI. | |
| Heart rate variability and baroreflex sensitivity | Limited to post-MI patients. Aside from ATRAMI, these markers have not discriminated sudden from non-sudden death. | |
| Cardiac MRI with late gadolinium enhancement imaging | | Correlates with surrogate markers of SCD risk in patients with ischemic, non-ischemic, and hypertrophic cardiomyopathies in small studies ($n<200$ for each study). |

Several tests also predict all-cause mortality and/or cardiac events and mortality; only tests with purported or demonstrated preferential discrimination for arrhythmic events and sudden cardiac death are addressed here. See also more detailed discussions of risk stratification tests [12, 13]. *LVEF* left ventricular ejection fraction, *SCD* sudden cardiac arrest, *ICD* implantable cardioverter defibrillator, *MI* myocardial infarction, *MRI* magnetic resonance imaging, *PPV* positive predictive value

factors (clinical characteristics, biomarkers, genetic variation, etc.) could be identified from large community-based studies that collect SCD patients who have a broad range of LVEF. For example, genome-wide association studies performed in the community can yield novel genetic variations that confer protectiveness [22] as well as susceptibility [23] to SCD. Biomarkers such as C-reactive protein, B-natriuretic peptide, and fatty acid levels have been associated with SCD risk [22]. Cardiac imaging techniques have also shown promise. Nuclear imaging of cardiac sympathetic nerve activity and perfusion may identify a higher arrhythmia-risk substrate [24, 25]. Cardiac magnetic resonance imaging (MRI) showing late gadolinium enhancement (presence of scar) in patients with ischemic cardiomyopathy appears highly predictive of inducibility of sustained VT with programmed electrical stimulation [26]. Among patients with non-ischemic cardiomyopathy, the presence of late gadolinium enhancement on cardiac MRI is predictive of a composite endpoint including ICD discharges [27]. Studies of patients with hypertrophic cardiomyopathy have shown correlation between presence of LGE on cardiac MRI and markers of SCD risk or composite

endpoints including SCD [28–30]. New techniques for evaluating interstitial fibrosis by MRI are undergoing development and evaluation.

Because many genetic and clinical variables have odds ratios or relative risk ratios of 2 or less, it will be important to derive multiple independent variables from the same population. Ultimately, these factors should be combined into cost-efficient test panels.

*Utilize existing and novel risk stratification methods to identify patient populations with LVEF >35% whose annual SCD rates are at least 5%* Identifying groups with annual SCD rates greater than 5% would identify patients at higher risk than existing primary prevention ICD trials. This would increase odds of efficient of ICD utilization in subsequent trials. Risk scores using clinical factors, biomarkers, and genetic factors can be tested retrospectively in some large community-based cohorts or drug trial cohorts when modes of death are well characterized and blood/serum has been stored for subsequent analysis. Other risk stratification tests will generally require evaluation prospectively (e.g., imaging studies, novel electrocardio-

graphic methods, etc.). After identifying new patient groups with high annual SCD rates, we must evaluate the ability of ICDs to reduce all-cause mortality.

## 5 Translation of novel strategies into clinical practice

There are several pathophysiologically homogenous cohorts with LVEF >35% that may be sufficiently high risk to warrant randomized controlled trials of primary prevention ICD use:

- *Acute MI.* Within the first 30 days after MI, 1.4% of patients have SCD (annualized rate of 17% [31]). Two randomized controlled trials, DINAMIT and Immediate Risk-Stratification Improves Survival (IRIS), tested the value of ICDs in patients in the first 40 days after MI and showed no benefit [15, 32]. It is not clear whether these negative trials resulted from excessive risk of non-arrhythmic death during this time period, ventricular arrhythmia that is less amenable to ICD termination (due to recurrent acute infarction or pump failure), or risk stratification methods that did not select patients at sufficient risk for SCD. A large majority of patients in DINAMIT and IRIS were selected based on impaired LVEF combined with either impaired heart rate variability or elevated resting heart rate, both of which are poor predictors of arrhythmic events. Alternative risk stratification methods such as electrophysiology study [33] and/or MRI [34] could yield patients with higher arrhythmic event rates.
- *Ischemic CM with LVEF >35%.* Beyond the first month after MI, the SCD rate drops rapidly and is lower for patients with higher initial LVEF [31]. Nonetheless, SCD rates for those with LVEF >35% in the first year after MI remain at approximately 3% (equivalent to placebo annual arrhythmic death rate in SCD-HeFT). With appropriate risk stratification methods (for example, a combination of class 3 CHF, fragmented QRS, electrophysiology study, MRI, etc.), it is quite plausible to identify a population at higher SCD risk compared to existing primary prevention ICD patients.
- *Heart failure with normal ejection fraction (HFNEF).* Approximately 50% of patients with congestive heart failure have normal or near-normal LVEF [35]. The proportion of deaths due to ventricular arrhythmia in this group is likely significantly less than in heart failure with impaired LVEF. In fact, in the Duke database, the rate of SCD was 0.5% per year for patients with HFNEF [36]. However, several independent predictors of SCD were identified which, together with screening biomarkers or genetic studies, could identify patients at sufficient risk for ICD-based primary prevention. This

group is important to target since one half of all SCDs occur in patients with normal LVEF [9, 11].
- *Non-ischemic cardiomyopathy LVEF >35%.* Although sudden death rates are too low to warrant ICD prevention in this overall group, there may be sub-populations at sufficiently high risk to benefit from primary prevention ICD use. Risk stratification methods are not well developed, but this group will be important to target for prevention for the estimated 20% or so of patients who have SCD without significant coronary artery disease [22].

Regardless of high arrhythmic event or SCD rates in observational studies, randomized clinical trials will be necessary to prove ICD benefit in individual population subgroups. While measuring arrhythmic events increases the power of an observational study, SCD rates are substantially lower than arrhythmic event rates due to the often non-sustained nature of ventricular arrhythmias. Even high observed SCD rates do not ensure benefit from ICDs. Improvements in SCD rates can be completely offset by increases in competing causes of mortality [15, 32, 37]. To the degree that competing mortality is driven by progressive heart failure/pump failure, use of ICDs with biventricular pacing capability may further improve ICD efficacy. The economic viability of any prevention strategy using ICDs will be dependent not only on magnitude of mortality benefit, but also cost of the ICD systems used. In general, physicians and medical device manufacturers have favored the use of ICDs with maximal functionality (and higher costs). Clinical trials utilizing less expensive devices in lower risk patient populations could expand SCD prevention. However, any such strategy would be subject to physician, patient (and sometimes legal) bias toward high technology–high cost medicine.

## 6 Conclusions

Left ventricular systolic dysfunction has served for many years as an important tool for SCD risk identification and subsequent prevention efforts. While it continues to benefit a subgroup of patients at risk of SCD, the predictive ability of this test among overall patients at risk for SCD has been overestimated. A continued, aggressive search for novel predictors other than LVEF is warranted using a pathophysiologically targeted approach. Development of tests to refine SCD risk stratification and the conduct of trials to translate these to clinical practice will require more ongoing effort and expense. However, in the long run, these ongoing efforts are the answer to optimizing the utilization of an important preventive intervention such as the ICD, and preventing premature death due to SCD.

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