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# Sudden death risk markers for patients with left ventricular ejection fractions greater than 40%☆,☆☆

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ABSTRACT

The major burden of sudden cardiac death (SCD) in patients with heart disease occurs in those with a left ventricular ejection fraction > 40%. Although the annual risk of SCD may be lower in these patients compared to those with lower LVEF, their lifetime cumulative risk of SCD may be greater due to a better overall prognosis. It is plausible that those with LVEF > 40% who are at highest risk of life-threatening arrhythmia will benefit from implantable cardioverter defibrillators. Features that identify patients with a LVEF > 40% at high risk of SCD are urgently needed. We review existing studies examining SCD markers in this sub-group and discuss gaps in the current evidence base.



Sudden cardiac death (SCD) represents a major public health problem, accounting for 50% of cardiovascular mortality and frequently affecting people of working age without preceding symptoms [1]. It is defined as unexpected death either within 1 h of the onset of cardiac symptoms in the absence of progressive cardiac deterioration; during sleep; or within 24 hours of last being seen alive [2]. SCD may be the result of ventricular fibrillation (VF), ventricular tachycardia (VT) or pulseless electrical activity (PEA). PEA may result from aneurysmal rupture or a cerebrovascular accident and therefore a proportion of cases result from vascular events. However, most research has focused on the prevention of SCD secondary to VT and VF, which will be the focus of our review.

SCD secondary to VT and VF may be reduced by pharmacological therapy and implantable cardioverter defibrillators (ICDs). Selecting patients who are most likely to benefit from these interventions is crucial to improving outcomes. The current arbiters for the guideline-directed selection of patients for primary prevention ICDs are left ventricular ejection fraction (LVEF) and New York Heart Association (NYHA) class [3,4]. This approach dichotomizes the population into low and high-risk groups, based on single measurements of subjective variables. This is recognized as sub-optimal [5]. The risk of SCD is continuous rather than binary and affected by multiple factors including structural substrate, autonomic dysfunction, electrical instability and genetic predisposition (Fig. 1). It is unsurprising that the sensitivity of the current approach is poor; only 13–20% of SCD occurs in the small group of patients with a LVEF < 40% [5,6]. A further 40% of cases occur in patients with recognized heart disease and LVEF > 40% [5]. While the absolute risk of SCD in patients with ischemic (ICM) or non-ischemic dilated cardiomyopathy (NICM) and LVEF > 40% may be lower than those with more severe impairment, there are a greater number of patients in the former group and their risk remains substantial.

An important factor to consider when selecting patients for ICD implantation is the length of time individuals are exposed to the risk of SCD. A major disadvantage of an LVEF-centered approach is that a large number of patients with a high-risk of death from other causes undergo ICD implantation. Many patients receiving ICDs die from causes other than arrhythmia and the length of time they are exposed to the risk of SCD is relatively short (Fig. 2). The DANISH trial failed to demonstrate mortality reduction with ICD implantation in a relatively sick population with NICM and a LVEF < 35% [7]. Younger patients, however, with a lower risk of death from competing causes, appeared to derive benefit in pre-specified sub-group analysis, demonstrating the importance of prognosis from non-sudden causes [7].

Patients at high-risk of SCD with a LVEF > 40% have lower competing risks and less limiting symptoms compared to those with lower LVEF. ICD therapy in this group may be more likely to prolong quality life (Fig. 2). A comparable approach is taken in hypertrophic cardiomyopathy where it is recommended that ICDs are considered in patients with a 5-year risk of SCD > 6% [8].

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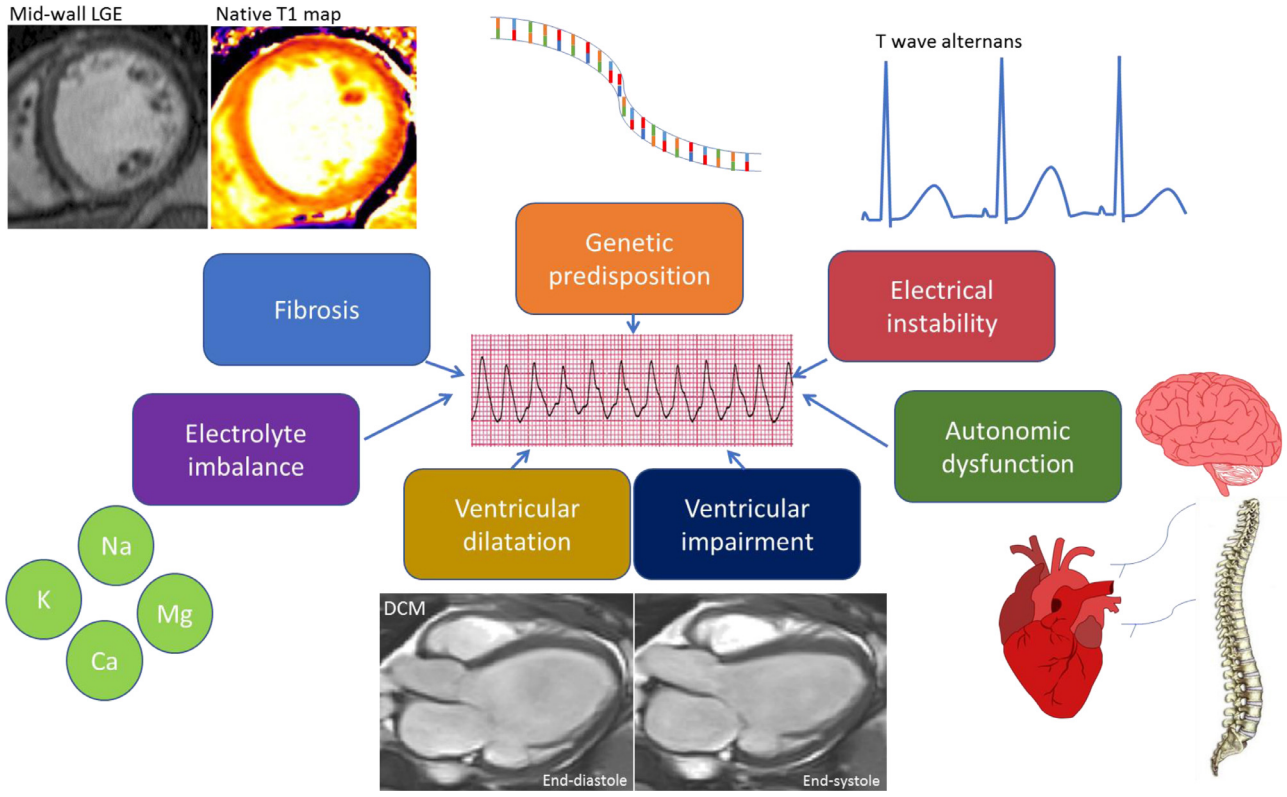


**Fig. 1.** Factors implicated in ventricular arrhythmogenesis and sudden cardiac death. The multiple interacting factors implicated in ventricular arrhythmogenesis and sudden cardiac death.

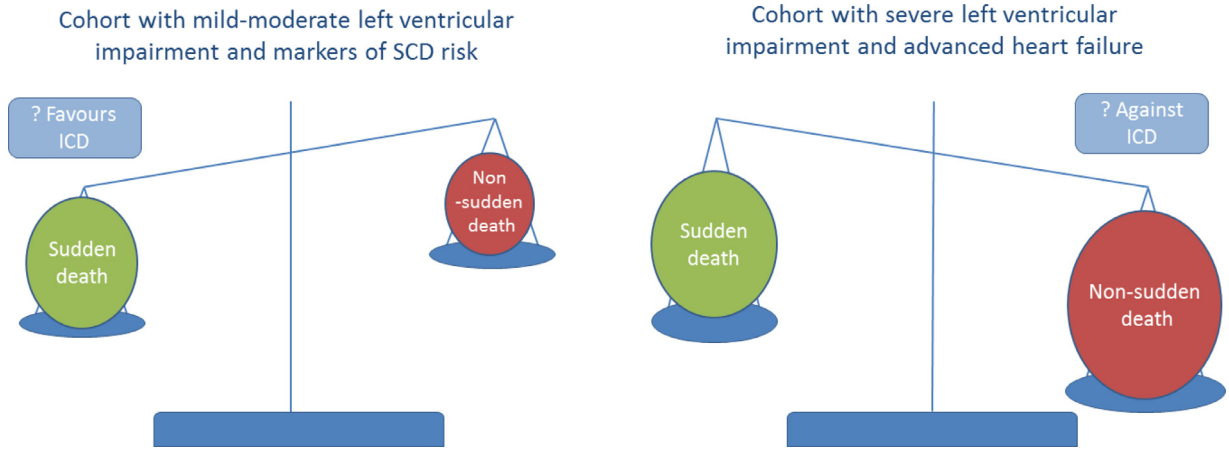


**Fig. 2.** Primary prevention implantable cardioverter defibrillators. Selecting patients who are most likely to benefit from implantable cardioverter defibrillators relies on balancing the risk of sudden cardiac death risk with the risk of death from competing causes. Those with slightly lower risks of sudden cardiac death but with much lower risks of competing causes of death may be more likely to gain longevity from this therapy.

This is much lower than the rate of SCD in the control arms of trials for ICD therapy in patients with severe LV impairment [9]. However, although patients with HCM may have a lower annual risk of SCD, their cumulative lifetime risk may be greater due to a longer exposure time, related to a lower risk of death from competing causes. Patients with HFpEF appear to be a different entity and deserve separate consideration. They tend to be older with multiple comorbidities and vulnerable to non-sudden terminal events. Their cumulative SCD risk may be relatively small.

We must also consider the effect of contemporary heart failure treatment on the incidence of SCD and the benefit of ICDs. The lack of benefit from ICD implantation in the DANISH trial may not only reflect the high risk of death from competing causes in this sick population but also the declining risk of SCD events in patients on contemporary HF therapy [10]. Evidence is accumulating on the benefit of medical therapies in patients with mid-range ejection fraction and it is therefore essential that the efficacy of additional interventions, such as ICD implantation, are evaluated in patients on optimal, contemporary heart failure therapy [11]. It is also important to acknowledge that the proportion of sudden deaths that are potentially preventable by ICDs may also be declining [12]. In a nationwide study of SCD patients who underwent autopsy, 28% were classified as sudden non-cardiac death [13]. The proportion of sudden non-cardiac deaths is, however likely to be lower in a younger, outpatient population with cardiac disease and fewer co-morbidities. Studies investigating heart rhythm at the time of death using implantable monitors, in at risk populations, will provide valuable information.

Features that identify patients with a LVEF > 40% who are at high-risk of sudden arrhythmic death are urgently needed

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