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Risk factors for sudden cardiac death to determine high risk patients in specific patient populations that may benefit from a wearable defibrillator

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Abstract

BACKGROUND

There is a high risk for sudden cardiac death (SCD) in certain patient groups that would not meet criteria for implantable cardioverter defibrillator (ICD) therapy. In conditions such as hypertrophic cardiomyopathy (HCM) there are clear risk scores that help define patients who are high risk for SCD and would benefit from ICD therapy. There are however many areas of uncertainty such as certain patients post myocardial infarction (MI). These patients are high risk for SCD but there is no clear tool for risk stratifying such patients.

AIM

To assess risk factors for sudden cardiac death in major cardiac disorders and to help select patients who might benefit from Wearable cardiac defibrillators (WCD).

METHODS

A literature search was performed looking for risk factors for SCD in patients post-MI, patients with left ventricular systolic dysfunction (LVSD), HCM, long QT syndrome (LQTS). There were 41 studies included and risk factors and the relative risks for SCD were compiled in table form.

RESULTS

We extracted data on relative risk for SCD of specific variables such as age, gender, ejection fraction. The greatest risk factors for SCD in post MI patients was the presence of diabetes [Hazard ratio (HR) 1.90-3.80], in patient with LVSD was ventricular tachycardia (Relative risk 3.50), in LQTS was a prolonged QTc (HR 36.53) and in patients with HCM was LVH greater than 20 mm (HR 3.10). A proportion of patients currently not suitable for ICD might benefit from a WCD

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CONCLUSION

There is a very high risk of SCD post MI, in patients with LVSD, HCM and LQTS even in those who do not meet criteria for ICD implantation. These patients may be candidates for a WCD. The development of more sensitive risk calculators to predict SCD is necessary in these patients to help guide treatment.

Key words: Sudden cardiac death; Wearable cardiac defibrillators; Myocardial infarction; Hypertrophic cardiomyopathy; Left ventricular systolic dysfunction

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Core tip: This article looks at the risk factors for sudden cardiac death (SCD) in patients post myocardial infarction, patients with left ventricular systolic dysfunction, patients with hypertrophic cardiomyopathy, patients with long QT syndrome and the relative risk for sudden cardiac death of these risk factors. This is compared to the absolute risk of SCD for these conditions. We reviewed the recommendations from current guidelines and we outline where patients are at high risk for SCD but are not eligible for implantable cardioverter defibrillator implantation. The risk factors identified in this study can be used to select patients who may benefit from Wearable cardiac defibrillators therapy.

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INTRODUCTION

Sudden cardiac death (SCD) is a major global health problem estimated to account for 15%-20% of death^[1]. The mechanism of SCD has changed substantially over the last decade with ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) accounting for between 23%-36% of out-of-hospital cardiac arrests^[2,3]. This compares to 75% of cases of SCD in the 1980's and early 1990's^[4,5]. The decline in SCD due to VT/VF is partly due to improved medical care such as the use of beta blockers and implantable cardioverter defibrillators (ICD)^[6,7]. Thus VF and pulseless VT are potentially treatable heart rhythms particularly if patients are given an early DC shock with return of an organised rhythm in up to 70% of cases after a single biphasic shock^[8]. This has led to the development of multiple measures such as automated external defibrillators in public places, ICD therapy and wearable cardioverter defibrillators (WCD) to reduce the rate of preventable death from VF/VT.

History of defibrillation

The first successful closed chest direct current cardioversion of ventricular fibrillation was performed by Paul Zoll in the 1950's^[9]. This was initially a monophasic shock but more recently biphasic shocks are used. Biphasic waveforms have superior efficacy to monophasic pulses^[8] and the European resuscitation council recommend a first shock at 150-200 J with subsequent shocks at a higher energy level if the device allows and the arrhythmia remains uncorrected^[10]. Return of sinus rhythm and spontaneous circulation after administration of biphasic shocks occurs in up to 70% in patients with VF or VT^[8]. This highlights the high efficacy of this relatively simple treatment.

The first ICD was implanted in a patient in 1980 by Mirowski *et al*^[11]. There have since been multiple studies proving the benefit of ICDs in preventing SCD and reducing all-cause mortality. These include primary prevention studies which show a reduction in mortality from SCD of between 23%-54%^[12-16] (Table 1) and secondary prevention studies which show a reduction in mortality from SCD of between 20%-28%^[17-19] (Table 2). Current guidelines based on the results of these and other studies recommend the insertion of ICD in patients more than 40 d post myocardial infarction (MI) with severe LVSD (ejection fraction less than 35%), patients with severe LVSD and in several other situations such as high risk hypertrophic cardiomyopathy (HCM) patients, patients with long QT syndrome (LQTS) with a history of cardiac arrest.

These guidelines advise against inserting an ICD for patients who survive sustained VT or VF within the first 48 h of an MI unless they have pre-existing LV impairment and are on optimal medical therapy already or they have incomplete revascularisation, as it is felt that tachyarrhythmia within this period is most likely due to the acute coronary obstruction and cardiac injury^[20].

In other patients an ICD may not be possible due to infection or lack of vascular access or patient preference. Thus, some high risk patients who would warrant an ICD do not have one. In order to address this, the WCD was developed. The WCD has been in development since 1986 and had been tested for 17 years prior to it receiving the Food and Drug Administration approval in 2002^[21]. The WCD is a device contained within a vest worn under a patient's clothes which records a patient's rhythm and delivers a shock if a shockable rhythm occurs^[22]. This has provided a much lower risk solution to ICD implantation in selected patients. Current guidelines recommend considering a WCD or ICD post MI within 40 d of their MI in patients with incomplete revascularisation, VT or VF > 48 h post MI or pre-existing LVSD^[23]. Additional groups of patients that could benefit from a WCD include patients with channelopathies such as LQTS who have not suffered a VT or VF event but have high risk features, patients with HCM who have intermediate risk features but not yet achieving criteria for ICD implantation, and also patients with infected ICDs could be offered a WCD once their ICD has been removed and they are awaiting ICD re-implantation. WCD do however come with a risk of inappropriate shocks and their efficacy can be reduced due to a lack of patient compliance.

The aim of this review is to use existing literature to identify risk factors for SCD that may help identify patients who may benefit from a WCD and to discuss the potential role that WCDs could play in reducing the risk of SCD in selected patient groups who do not currently meet guidelines for ICD implantation.

MATERIALS AND METHODS

Study design

This review included available data on risk factors for SCD in predefined patient groups. All odds ratio (OR), relative risk (RR), Exp(b) and hazard ratio (HR) were rounded to 2 decimal places for consistency. OR is a statistic defined as the ratio of the odds of variable A in the presence of variable B and the odds of variable A without the presence of variable B. RR is the ratio of the probability of an outcome in an exposed group to the probability of an outcome in an unexposed group. The HR is an expression of the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm

Inclusion and exclusion criteria

All studies that reported risk factors for SCD in patients with LVSD, LQTS, HCM or post MI. There was no restriction on age, gender, geographical area or date of publication. Studies reported in English. Any studies where the risk of SCD was not quantified by either a HR, OR or RR were excluded.

Search strategy

A literature search was performed in 4 main groups of patients: Search terms included: (risk of SCD* or risk factors for SCD* or SCD* or female gender and outcome* or mortality in patients* or mortality in women* or risk stratification for SCD* or risk of cardiac arrest* or atrial fibrillation and mortality* or echocardiographic predictors of outcome* or risk of death* or COPD and mortality* or prognosis of heart failure* or risk of death in patients*) and (post myocardial infarction* or after myocardial infarction* or after acute st elevation myocardial infarction* or after ST elevation myocardial infarction* or with inferior myocardial infarction* or following myocardial infarction* or after myocardial infarction* or myocardial scarring* or electrocardiographic abnormalities* or patients with hypertrophic cardiomyopathy* or heart failure* or patients with heart failure* or left ventricular dysfunction* or after hospitalization for heart failure* or in the community* or new diagnosis of heart failure* or LQTS*).

The risk factor in each group that was associated with SCD, was then tabulated along with the relevant studies that supported this finding.

RESULTS

Results of literature search

Table 1 Primary prevention implantable cardioverter defibrillator studies

Study	Intervention/control group	Inclusion criteria	Risk reduction of SCD with ICD
Multicenter Automatic Defibrillator Implantation Trial ^[12]	ICD <i>vs</i> antiarrhythmic drug	Previous MI; EF≤35%; nsVT; positive findings on EPS	54% (<i>P</i> = 0.001)
Multicenter Unsustained Tachycardia Trial ^[13]	EP-guided therapy <i>vs</i> placebo	Coronary disease; EF≤40%; Non-sustained VT; inducible VT at EPS	51% (<i>P</i> = 0.001)
Multicenter Automatic Defibrillator Implantation Trial 2 ^[14]	ICD <i>vs</i> optimal pharmacological treatment	Prior MI EF≤30%	31% (<i>P</i> = 0.02)
Sudden Cardiac Death in Heart Failure Trial ^[15]	ICD <i>vs</i> optimal pharmacological therapy <i>vs</i> optimal pharmacological therapy + amiodarone	Ischaemic and non-ischaemic cardiomyopathy; EF≤35%	23% (<i>P</i> = 0.007)
Defibrillator implantation in patients with nonischemic systolic heart failure ^[16]	ICD <i>vs</i> optimal pharmacological therapy	Non-ischaemic cardiomyopathy; EF≤35%	50% (<i>P</i> = 0.005)

SCD: Sudden cardiac death; ICD: Implantable cardioverter defibrillator; EF: Ejection fraction; EP: Electrophysiology; MI: Myocardial infarction; EPS: Electrophysiology studies; VT: Ventricular tachycardia.

The initial search strategy produced 21620 articles. Removal of duplicates and screening of the papers reduced the number to 480 articles. A further 435 papers were removed after reading of the full text. During data extraction an additional 4 papers were removed as a result of not having the prerequisite data available in the correct form. Forty one papers were included in the final data analysis (Figure 1)

Risk of sudden cardiac death post myocardial infarction

In patients post MI, 16 studies were identified involving a total of 250766 patients^[24-39](Table 3). The absolute risk of SCD in these studies varied from around 4.9%-8%^[24,26,30,33]. The absolute risk of SCD was 4.9% in the first month post-MI and decreased thereafter^[24]. Another study showed a cumulative risk of SCD at 1 year to be 5.3%^[26]. One study showed a risk of SCD of 7% at 30 d and 11% at 2 years^[30]. Another study showed a risk of SCD at 4% in those with EF > 35% and 8% in those with EF < 35% at one year^[33].

Several risk factors for SCD were identified post MI in order of decreasing magnitude: diabetes (HR 1.90-3.80), LVSD (HR 1.21 to 3.64), NSVT (HR 3.30), right ventricular involvement (OR 3.20), premature ventricular complexes occurring at a frequency of 10 or more per hour (HR 2.40), female gender (OR 1.09-1.76), older age (OR 1.03-1.56), LBBB (HR 1.49), non-specific intraventricular conduction delay (HR 1.44) and LVH (OR 1.40)^[24-39].

Risk factors for sudden cardiac death in heart failure

In patients with heart failure, 15 studies were identified involving a total of 65182 patients^[40-54](Table 4). The absolute risk of SCD in these studies varied from 8.8%-23.7%^[49,50]. Doval *et al*^[49] showed that in patients with NSVT the risk of SCD at 2 year was 23.7% compared to 8.8% in those who do not have NSVT at 2 years. Teerlink *et al*^[50] showed that the risk of SCD was 13% at 2 years.

Several features increasing the risk of SCD were identified in order of decreasing magnitude: VT (RR 3.50), NSVT (RR 2.77-3.89), couplets (RR 3.37), cirrhosis (OR 3.22), 1-SD difference in LV Mass (RR 2.75), a 1-SD difference in LV end systolic dimension (RR 2.73), deranged kidney function (HR 2.02-2.64), dementia (OR 2.54), cancer (OR 1.86), the degree of left ventricular impairment(less than 40%) (HR 1.29-1.80), older age (OR 1.70), COPD (OR 1.66), atrial fibrillation (HR 0.89-1.55), male gender (HR 1.21-1.50) and cerebrovascular disease (OR 1.43)^[40-54].

Risk of sudden cardiac death in the long QT syndrome

In patients with LQTS, 5 studies were identified with a total of 9758 patients^[55-59](Table 5). The absolute risk of SCD in these studies varied from 4.9%-13%^[55,57]. Sauer *et al*^[55] showed that the risk of SCD from the age of 18 until follow-up at the age of 40 was 4.9% in LQTS1, 8.0% in LQTS2 and 4.9% in LQTS3. Priori *et al*^[57] showed that the risk of SCD was 13% over 28 years of follow-up before the age of 40.

Several risk factors for SCD were identified in order of decreasing magnitude including: LQTS with a prolonged QTc interval (HR 36.53), LQTS with a normal range QTc interval (HR 10.25), LQTS 1 (HR 9.88), length of QTc interval (RR 5.34-8.36), consistent QTc interval prolongation (HR 2.23-6.67), previous history of cardiac events (syncope or aborted SCA) (HR 3.10-5.10), LQTS 3 (RR 1.80-2.76), female gender (HR 2.68), LQTS 2 (RR 1.61) and bradycardia (HR 1.02)^[55-59].

Table 2 Secondary prevention implantable cardioverter defibrillator studies

Study	Intervention/control group	Inclusion criteria	Risk reduction with ICD
Antiarrhythmics Versus Implantable Defibrillators study ^[17]	ICD <i>vs</i> antiarrhythmic drugs	Resuscitated from near-fatal VF or post-cardioversion from sustained VT	28% ($P = 0.02$)
Canadian Implantable Defibrillator Study ^[18]	ICD <i>vs</i> amiodarone	Resuscitated VF or VT or with unmonitored syncope	20% ($P = 0.14$)
Cardiac Arrest Study Hamburg ^[19]	ICD <i>vs</i> amiodarone <i>vs</i> metoprolol	Survivors of cardiac arrest secondary to documented ventricular arrhythmias	23% ($P = 0.08$)

ICD: Implantable cardioverter defibrillator; VF: Ventricular fibrillation; VT: Ventricular tachycardia.

Risk of sudden cardiac death in patients with HCM

In HCM there were 5 studies involving a total of 25823 patients^[60-64](Table 6). The risk of SCD in HCM was about 5% over 5 years^[60].

The following risk factors for SCD in order of decreasing magnitude were identified including: LVH (highest risk when greater than 20 mm) (HR 1.05-3.17), NSVT (HR 2.53-2.92), syncope (HR 2.31-2.68), left ventricular outflow tract obstruction (HR 1.01-2.41), family history of SCD (HR 1.27-2.34), abnormal blood pressure response during exercise (HR 1.30-1.38) and an enlarged left atrial diameter (HR 1.04)^[60-64].

Wearable cardioverter defibrillator studies

There are currently only a few published outcome studies of WCDs. The WCD use in patients perceived to be at high risk, early post-MI study showed that 1.6% of patients received an appropriate shock for VT/VF and up to 67% of patients with VT/VF survived because of an appropriate shock^[65]. Inappropriate shocks occurred in 1.1% of patients; none of the inappropriate shocks induced an arrhythmia.

“The aggregate national experience with the WCD vest: event rates, compliance and survival study” showed that 1.7% of patients received an appropriate shock for VT/VF. It also showed that 90% of patients survived because of an appropriate shock for VT/VF^[66]. Inappropriate shocks occurred in 1.9% of patients^[66].

The Vest Prevention of Early Sudden Death Trial compared WCD therapy to optimal medical therapy that was the control group. This trial showed that 0.6% of patients received an inappropriate shock. 1.4% of patients received an appropriate shock. The number of hours per day, the WCD was worn was 14.1 h. The risk of SCD was 1.6% in the WCD group compared to 2.4% in the control group ($P = 0.18$). All-cause mortality in the WCD group was 3.1% compared to 4.9% in the control group ($P = 0.04$)^[67](Table 7).

DISCUSSION

The risk of SCD in various groups of patients has been well studied. This has led to the development of clear criteria for ICD implantation^[23]. There is data on various subgroups of patients that quantifies the magnitude of known risk factors for SCD (post MI, LQTS, HCM and LVSD). There are clear guidelines on the use of ICD in these groups of patients but a lack of clear guidelines for WCD therapy. This study has identified risk factors for several groups of patients who may not qualify for an ICD (due to the risk associated with implantation) but could benefit from WCD. These risk factors may help select patient for WCD therapy.

In patients who have recently had an MI with severe LVSD, guidelines recommend primary prevention with an ICD should be delayed for 40 d as the degree of myocardial recovery is uncertain in the acute period. This leaves certain patients without the best possible treatment if they were to have a further episode of VT/VF or patients who develop VT/VF later as a result of left ventricular dysfunction resulting from an MI. Patients post-MI are at increased risk of SCD. Several factors are associated with this increased risk of SCD. These risk factors could be used to select patient who may benefit from WCD post MI and if their risk remains high, they could be offered an ICD at 40 d. In addition, the DINAMIT study looked at early ICD implantation within 6-40 d *vs* optimal medical therapy. The DINAMIT study showed a reduction in arrhythmic death with early ICD implantation but no effect on overall mortality^[68]. These results do raise the question of whether there are device related

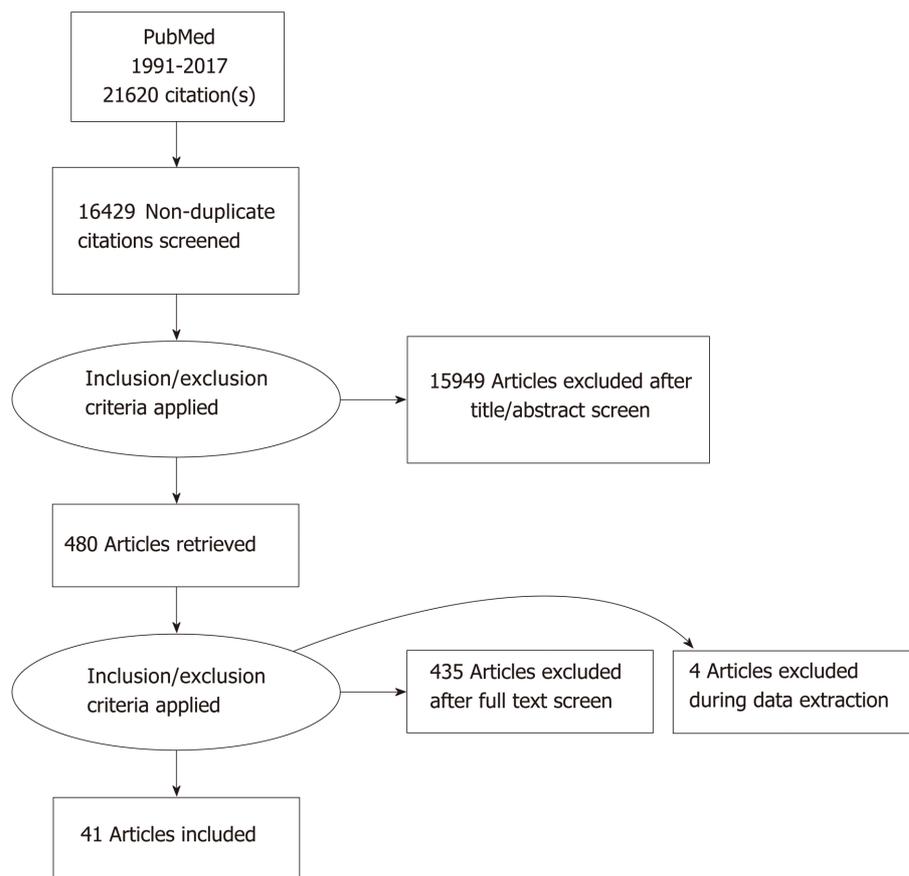


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

deaths that may reduce the overall mortality benefit such as device infections, procedural complications *etc.* These risks would not be present with WCD as there are no procedural risks associated with these devices. Some studies have advocated differentiating ICD implantation in the setting of acute MI based on whether the VT/VF occurred within 48 h in which case it could be attributed to acute MI and the treatment was revascularisation or if it occurred after 48 h in the absence of recurrent ischemia then these patients needed ICD implantation on the basis of secondary prevention and the 40 d rule in guidelines shouldn't apply^[69]. These patients could also potentially be covered by using a WCD until the 40 d window has elapsed. In addition, the highest risk of SCD is within the first 30 d of an MI and so high-risk patients who have not yet suffered VT/VF may benefit from a WCD during this period^[30]. The risk factors identified in this study could be used to help select such patients.

In patients with LVSD, guidelines only recommend an ICD if EF is less than 35 percent. This is the group of patients who are at the highest risk of SCD from LVSD. Studies of heart failure patients with an EF between 30% and 35% have shown that these patients also benefit from ICD therapy and have a lower mortality than the same group of patients without an ICD^[70]. This would also lead one to believe that patients at higher EF with more high risk features may also benefit from having a defibrillator such patients could be offered a WCD as a lower risk option than ICD implantation. Similarly patients post-MI who develop severe LVSD are not offered a ICD and are sent home for a clinic review in 40 d to assess the degree of myocardial recovery during this period. This is potentially dangerous as the absolute risk of SCD during this period is about 4.9% which is similar to the risk of SCD in patients with HCM at which an ICD would be implanted these patients should probably all be offered a WCD during this time period^[24,60]. It is important to note, however, the results of the recent VEST trial looking at the risk of SCD in WCD patient *vs* controls in the first 90 d post MI. It did not show a statistically significant reduction in SCD (1.6% *vs* 2.4%, $P = 0.18$) but there was a trend to lower risk of SCD in the WCD group. It did show a reduction in overall mortality (3.1% *vs* 4.9%, $P = 0.04$). These results are the opposite

Table 3 Risk factors for sudden cardiac death post myocardial infarction

Risk factor studied	Relative risk of SCD	P value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
Rao <i>et al</i> ^[24]	OR 1.03 (1.00-1.05) (Increasing age)	0.0163	4.9% in the 1 st month post MI	929	2012	India
Mehta <i>et al</i> ^[25]	OR 0.12; Standard error = 0.02 (Age per 1 year increase)	0.0001		2948	2001	North America
Abildstrom <i>et al</i> ^[26]	OR 1.56 (1.43-1.70) (Age per 10 years)	< 0.0001	5.3% at 1 year	5983	2002	Denmark
Female gender						
Rao <i>et al</i> ^[24]	OR 1.78 (1.02-2.85)	0.0042	4.9% in the 1st month post MI	929	2012	India
Greenland <i>et al</i> ^[27]	OR 1.72 (1.45-2.04)	< 0.0005		5839	1991	Israel
Greenland <i>et al</i> ^[27]	OR 1.32 (1.05-1.66) (Death at 1 year)	< 0.03		5839	1991	Israel
Ghaffari <i>et al</i> ^[28]	OR 1.76 (1.22-2.54) (univariate analysis)	0.002		1017	2017	Iran
Ghaffari <i>et al</i> ^[28]	OR 1.19 (0.77-1.8) (multivariate analysis)	0.407		1017	2017	Iran
Macintyre <i>et al</i> ^[29]	OR 1.09 (1.06 to 1.13) (Death at 1 year)	< 0.00001		201114	2001	UK
Male gender						
Abildstrom <i>et al</i> ^[26]	OR 1.34 (1.11-1.63)	< 0.005	5.3% at 1 year	5983	2002	Denmark
LV dysfunction						
Rao <i>et al</i> ^[24]	OR 2.35 (1.09-5.03) (Severe LV dysfunction ≤ 30%)	0.0292	4.9% in the 1st month post MI	929	2012	India
Solomon <i>et al</i> ^[30]	HR 1.21 (1.10 to 1.30) (LV depression by each 5 percentage points)		7% at 1 month post MI; 11% at 2 years post MI	14609	2005	North America, Europe and New Zealand
Klem <i>et al</i> ^[31]	HR 6.30 (1.40-28.00) (LVEF > 30% and significant scarring > 5% on CMRI compared to no scarring)	0.02		137	2012	USA
Klem <i>et al</i> ^[31]	HR 3.90 (1.20-13.10) (LVEF ≤ 30% and those with scar > 5% on CMRI compared to those with scarring)	0.03		137	2012	USA
Yeung <i>et al</i> ^[32]	HR 3.60 (1.46-8.75) (LVEF ≤ 30%)	< 0.01		610	2012	China
Chitnis <i>et al</i> ^[33]	OR 4.51 (2.20-9.24) (LVEF ≤ 35%)	< 0.0001	4% in those with EF > 35% at 1 year post MI; 8% in those with EF ≤ 35% at 1 year post MI	929	2014	India
Adabag <i>et al</i> ^[34]	HR 3.64 (1.71-7.75) (presence of heart failure based on the framingham criteria)	< 0.001		693	2008	USA
Right ventricular involvement						
Mehta <i>et al</i> ^[25]	OR 3.20 (2.40-4.10)	< 0.00001		2948	2001	Canada
Diabetes						
Yeung <i>et al</i> ^[32]	HR 1.90 (1.04-3.40)	0.04		610	2012	China
Junttila <i>et al</i> ^[35]	HR 3.80 (2.40-5.80)	< 0.001		3276	2010	Finland
Ventricular arrhythmia						

Maggioni <i>et al</i> ^[36]	RR 2.24 (1.22-4.08) (more than 10 premature ventricular beats per hour)	0.002	8676	1993	Italy
Maggioni <i>et al</i> ^[36]	RR 1.20 (0.80-1.79) (NSVT)		8676	1993	Italy
Mäkikallio <i>et al</i> ^[37]	HR 2.40 (1.30-4.40) (Ventricular premature complexes 10/h)	0.0049	2130	2005	Finland
Mäkikallio <i>et al</i> ^[37]	HR 3.30 (1.70-6.50) (NSVT)	< 0.0005	2130	2005	Finland
ECG features					
Mäkikallio <i>et al</i> ^[37]	HR 3.30 (1.70-6.50) (QRS ≥ 120 ms)	0.0004	2130	2005	Finland
Zimetbaum <i>et al</i> ^[38]	HR 1.44 (1.11-1.88) (Non-specific intraventricular conduction delay)	0.0069	1638	2004	USA
Zimetbaum <i>et al</i> ^[38]	HR 1.49 (1.02-2.17) (LBBB)	0.0400	1638	2004	USA
Zimetbaum <i>et al</i> ^[38]	HR 1.35 (1.08-1.69) (LVH)	0.0082	1638	2004	USA
Siscovick <i>et al</i> ^[39]	OR 1.40 (1.00-2.00) (LVH)	0.02	688	1996	USA

SCD: Sudden cardiac death; MI: Myocardial infarction; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

of the DINAMIT study this may be due to poor patient compliance with compliance decreasing with time during the study, which may have contributed to the lack of a significant reduction in SCD. It is important to note that at the time of SCD only 8 of 25 patients in the treatment group were wearing their WCD^[67]. Another group of patient who may benefit from a WCD are those who are awaiting heart transplantation. These patients should be offered an ICD based on current guidelines pre-transplantation; however, a WCD could be used as an alternative in these patients while they await their heart transplant.

In patients with non-ischaemic cardiomyopathy, the risk for SCD appears to be lower than those with ischaemic cardiomyopathy. They also do not appear to benefit from ICD therapy in the same way as patients with ischaemic cardiomyopathy as was shown by the recent defibrillator implantation in patients with nonischemic systolic heart failure (DANISH) study. The DANISH study showed no significant reduction in all-cause mortality between the ICD therapy and standard care group (21.6% vs 23.4%, $P = 0.28$). It did show a reduction in sudden cardiac death in the ICD group when compared to the standard care group ((4.3% vs 8.2%, $P = 0.005$)^[66]. This reinforces the need for a risk stratification tool to help determine individual risk factors that would make patients at higher risk for SCD. This study does help provide data that could be used to select not only patients for WCD but also patients who might benefit from an ICD in this patient group.

In patients with LQTS guidelines only recommend an ICD in these patients if they have survived an episode of VT/VF. This may be an unacceptable risk for some patients and a WCD could afford these patients with some protection until they meet criteria for a permanent ICD. One large study used 4 variables which included age, length of QTc, symptoms and the presence of cardiac arrest to determine the decision on whether patients were likely to benefit from therapy with an ICD in LQTS^[71]. Such a risk score could also be used to offer patients a choice between an ICD or a WCD.

Patients with HCM who have 5 year risk of death of less than 6% could be offered a WCD if they find the risk of SCD unacceptable. The ESC HCM risk-SCD calculator has a cut off of > 6% at which an ICD should be implanted. There may be patients who do not want an ICD and these patients could also be offered a WCD as an alternative.

A large WCD registry showed that WCD usage in patients with HCM and LQTS was safe, effective and associated with a high rate of compliance^[72]. A further large meta-analysis of WCD showed that WCD have a 95% success rate at terminating arrhythmias^[73]. The HCM risk-SCD calculator provides a very helpful measure of assessing a patient's risk of SCD and making treatment decisions in patients with HCM. It would be useful to develop risk calculators for SCD in other conditions,

Table 4 Risk factors for sudden cardiac death in heart failure

Risk factor studies	Relative risk of SCD	P value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
Lee <i>et al</i> ^[40]	OR 1.70 (1.45-1.99) (Age per 10 unit increase)	< 0.001		4031	2003	Canada
Cowie <i>et al</i> ^[41]	HR 1.26 (1.01 to 1.57) (Age per 10 year increase)	0.04		220	2000	UK
Taylor <i>et al</i> ^[42]	HR 1.10 CI 1.09-1.10 (Increasing age)			6162	2012	UK
Male gender						
Taylor <i>et al</i> ^[42]	HR 1.50 (1.36-1.66)			6162	2012	UK
Vaartjes <i>et al</i> ^[43]	HR 1.21 (1.14-1.28) at 28 d; HR 1.26 (1.21-1.31) at 1 year; HR 1.28 (1.24-1.31) at year 5			29053	2010	Netherlands
Comorbidities						
Lee <i>et al</i> ^[40]	OR 1.43 (1.03-1.98) 30-day mortality (Cerebrovascular disease)	0.03		4031	2003	Canada
Lee <i>et al</i> ^[40]	OR 1.66 (1.22-2.27) (COPD)	0.002		4031	2003	Canada
Lee <i>et al</i> ^[40]	OR, 3.22 (1.08-9.65) (Cirrhosis)	0.04		4031	2003	Canada
Lee <i>et al</i> ^[40]	OR 2.54 (1.77-3.65) (Dementia)	< 0.001		4031	2003	Canada
Lee <i>et al</i> ^[40]	OR 1.86 (1.28-2.70) (Cancer)	0.001		4031	2003	Canada
Yoshihisa <i>et al</i> ^[44]	HR 3.01 (1.11-8.63) (COPD)	0.038		378	2014	Japan
Fisher <i>et al</i> ^[45]	RR 1.10 (1.06-1.14) Death at 1 year; RR 1.40 (1.28-1.52) death at 5 years (COPD)			9748	2015	USA
Atrial fibrillation						
Taylor <i>et al</i> ^[44]	HR 1.55 (1.26-1.92)			6162	2012	UK
Ahmed <i>et al</i> ^[46]	HR 1.41 (1.08-1.83)			944	2005	USA
Corell <i>et al</i> ^[47]	HR 1.38 (1.07-1.78)	0.01		1019	2007	Denmark
Middlekauff <i>et al</i> ^[48]	HR 0.89 (0.55-1.23)	0.013		390	1991	USA
Ventricular arrhythmia						
Doval <i>et al</i> ^[49]	RR 2.77 (1.78-4.44) (NSVT)	< 0.001	23.7% at 2 years in those with NSVT; 8.8% at 2 years in those without NSVT	516	1996	Argentina
Doval <i>et al</i> ^[49]	RR 3.37 (1.57-7.25) (Couplets)	< 0.0005	23.7% at 2 years in those with NSVT; 8.8% at 2 years in those without NSVT	516	1996	Argentina
Teerlink <i>et al</i> ^[50]	RR 1.16 (1.09-1.24) (NSVT)	0.001	13% at 2 years	1080	2000	USA
Szabó <i>et al</i> ^[51]	RR 3.50 (1.54-7.98) (VT)	0.003		211	1994	Netherlands
Szabó <i>et al</i> ^[51]	RR 2.68 (1.11-6.48) (Freq. VT > 144 beats/min)	0.029		211	1994	Netherlands
Szabó <i>et al</i> ^[51]	RR 3.89 (1.61-9.43) (Length VT > 2s)	0.003		211	1994	Netherlands
Echocardiographic variables						
Taylor <i>et al</i> ^[42]	HR 1.80 (1.55-2.10) (EF < 40% vs > 50%)			6162	2012	UK

Taylor <i>et al</i> ^[42]	HR 1.29 (1.11–1.50) (EF 40%–50% vs > 50%)		6162	2012	UK
Shadman <i>et al</i> ^[52]	OR 1.15 (EF per 10% decrease)	0.005	9885	2015	USA
Quiñones <i>et al</i> ^[53]	RR 2.75 (1.62–4.66) (1-SD difference in LV Mass)	0.0002	1209	2000	USA
Quiñones <i>et al</i> ^[53]	RR 1.84 (1.08–3.15) (1-SD difference in LA Diameter)	0.03	1209	2000	USA
Quiñones <i>et al</i> ^[53]	RR 2.73 (1.43–5.20) (1-SD difference in lv end systolic dimension)	0.003	1209	2000	USA
Grayburn <i>et al</i> ^[54]	HR 1.01 (1.00–1.01) (LV end-diastolic volume index)	0.0012	336	2005	USA
Deranged kidney function					
Grayburn <i>et al</i> ^[54]	HR 2.023 (1.24–3.32)	0.0052	336	2005	USA
Cowie <i>et al</i> ^[41]	HR 2.64 (1.87–3.74)	< 0.001	220	2000	UK

SCD: Sudden cardiac death; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

which are more common and have a much larger impact on global mortality. This would provide patients and doctors with more information to make the best decision regarding their care.

The following groups of patients could also benefit from WCD therapy; patients who have an explanted ICD for infective endocarditis and must wait a certain time period before reinsertion, patients who have a risk of SCD but have a lower absolute risk such that the cost and risk of ICD insertion can't be justified, patients in remote areas where there is no expertise for ICD insertion, patients with myocarditis, patients with takotsubo cardiomyopathy, patients with peripartum cardiomyopathy, patients with advanced stage chronic kidney disease and children and young adults with channelopathies. The risk factors compiled in this review article could be used to help risk stratify many of these patients. The risk factors for patients post MI could be extrapolated to patients with takotsubo cardiomyopathy and myocarditis as all these processes involve an acute myocardial injury and so could be expected to have similar risk factors for SCD. In addition, the risk factors for LVSD could be extrapolated to patients with peripartum cardiomyopathy and those awaiting heart transplantation to determine high risk patients who may benefit from a WCD. There is potentially large scope for the use of WCD in carefully selected patient populations. One of the key disadvantages to WCD is the dependence on patient compliance for successful therapy as patients may decide to not wear the WCD, which can be a key limiting factor in its success.

In conclusion, we have identified multiple risk factors for sudden cardiac death in various conditions that could be used to help select patients for WCD therapy. The WCD is a landmark development that provides patients and physicians an additional therapy for the treatment of SCD; however, it is underutilized due to a lack of clear guidelines governing its usage^[74]. SCD remains a common cause of death and continued effort must be made to try and develop more targeted approaches to treatment for SCD.

Table 5 Risk factors for sudden cardiac death in the long QT syndrome

Risk factor studied	Relative risk of SCD	P value	Absolute SCD risk in cohort	Study size	Year	Country
Female gender						
Sauer <i>et al</i> ^[55]	HR 2.68 (1.10–6.50)	< 0.05	Risk between ages of 18–40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
QTc interval						
Sauer <i>et al</i> ^[55]	HR 3.34 (1.49–7.49) (QTc 500–549 ms <i>vs</i> ≤ 499 ms)	< 0.01	Risk between ages of 18–40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Sauer <i>et al</i> ^[55]	HR 6.35 (2.82–14.32) (QTc ≥ 550 ms <i>vs</i> ≤ 499 ms)	< 0.01	Risk between ages of 18–40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Moss <i>et al</i> ^[56]	HR 1.05 (1.02–1.09) (QTc per 0.01 units)	< 0.01		1496	1991	USA
Priori <i>et al</i> ^[57]	RR 5.34 (2.82–10.13) [QTc in the third quartile (469 to 498 ms)]		Risk between ages 12–40 was 13% over 28 years	580	2003	Italy
Priori <i>et al</i> ^[57]	RR 8.36 (2.53–27.21) [QTc in the highest quartile (more than 498 ms)]		Risk between ages 12–40 was 13% over 28 years	580	2003	Italy
Goldenberg <i>et al</i> ^[58]	HR 36.53 (13.35–99.95) (LQTS with prolonged QTc interval <i>vs</i> unaffected family members)	< 0.001		3386	2012	USA, Europe, Japan and Israel
Goldenberg <i>et al</i> ^[58]	HR 10.25 (3.34–31.46) (LQTS with normal-range QTc interval <i>vs</i> unaffected family members)	< 0.001		3386	2012	USA, Europe, Japan and Israel
Previous history of cardiac events						
Sauer <i>et al</i> ^[55]	HR 5.10 (2.50–10.39) (Interim time dependant syncope <i>vs</i> no interim syncope)	< 0.01	Risk between ages of 18–40: LQTS1 4.9%; LQTS2 8.0%; LQTS3 4.9%	812	2007	USA
Moss <i>et al</i> ^[56]	HR 3.10 (1.30–7.20) (History of cardiac event)	< 0.01		1496	1991	USA
Genotype						
LQTS 3						
Priori <i>et al</i> ^[57]	RR 2.76 (1.01–7.51) (Male sex)		Risk between ages 12–40 was 13% over 28 years	580	2003	Italy
Priori <i>et al</i> ^[57]	RR of 1.80 (1.07–3.04) (mutation at the LQT3 locus)		Risk between ages 12–40 was 13% over 28 years	580	2003	Italy
LQTS 2						
Priori <i>et al</i> ^[57]	RR 1.61 (1.16–2.25) (LQT2 locus)		Risk between ages 12–40 was 13% over 28 years	580	2003	Italy
LQTS 1						
Goldenberg <i>et al</i> ^[58]	HR 9.88 (1.26–37.63) (LQTS 1 mutation and normal QTc)	0.03		3386	2012	USA, Europe, Japan and Israel
Heart rate						

Moss <i>et al</i> ^[56]	HR 1.02 (1.00-1.03) (Resting heart rate less than 60 beats/min)	0.01	1496	1991	USA
Niemeijer <i>et al</i> ^[59]	Bazett: HR 2.23 (1.17-4.24) Fridericia: HR 6.67 (2.96-15.06) (Consistent Qtc interval prolongation)		3484	2015	Netherlands

SCD: Sudden cardiac death; LQTS: Long QT syndrome; QTc: QT corrected interval; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

Table 6 Risk factors for sudden cardiac death in patients with hypertrophic cardiomyopathy

Risk factor studied	Relative risk of SCD	P value	Absolute SCD risk in cohort	Study size	Year	Country
Age						
O'Mahony <i>et al</i> ^[60]	HR 0.99 (0.98-1.00) (Age 42 ± 15)	0.007	5% at 5 years	3675	2014	Europe
Syncope						
Liu <i>et al</i> ^[61]	HR 2.31 (1.22-4.38)			12146	2017	USA, China
O'Mahony <i>et al</i> ^[60]	HR 2.33 (1.69-3.19)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans <i>et al</i> ^[62]	HR 2.68 (0.97-4.38)			9357	2010	Netherlands, UK
Family history of SCD						
Christiaans <i>et al</i> ^[62]	HR 1.27 (1.16-1.38)			9357	2010	Netherlands, UK
O'Mahony <i>et al</i> ^[60]	HR 1.76 (1.32-2.24)	<0.001	5% at 5 years	3675	2014	Europe
Liu <i>et al</i> ^[61]	HR 2.34 (1.46- 3.75)			12146	2017	USA, China
Abnormal blood pressure response during exercise						
Liu <i>et al</i> ^[61]	HR 1.38 (0.65-2.89) (BP dropping on exercise)			12146	2017	USA, China
Christiaans <i>et al</i> ^[62]	HR 1.30 (0.64-1.96) (BP dropping on exercise)			9357	2010	Netherlands, UK
Non sustained ventricular tachycardia						
Liu <i>et al</i> ^[61]	HR 2.92 (1.97-4.33)			12146	2017	USA, China
Sugrue <i>et al</i> ^[63]	HR 3.36 (1.00-11.35)	0.05		52	2017	USA
O'Mahony <i>et al</i> ^[60]	HR 2.53 (1.85-3.47)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans <i>et al</i> ^[62]	HR 2.89 (2.21-3.58)			9357	2010	Netherlands, UK
Left ventricular wall thickness/hypertrophy						
Liu <i>et al</i> ^[61]	HR 3.17 (1.64-6.12) (Maximum LV wall thickness ≥ 30 mm)			12146	2017	USA, China
Maeda <i>et al</i> ^[64]	HR 1.21 (1.04-1.39) (Maximum left ventricular wall thickness per 1-mm increase)	0.011		593	2016	Japan
O'Mahony <i>et al</i> ^[60]	HR 1.05 (1.03-1.07) (Maximal LV wall thickness in mm 21.5 ± 6)	< 0.001	5% at 5 years	3675	2014	Europe
Christiaans <i>et al</i> ^[62]	HR 3.10 (1.81-4.40) (LVH ≥ 20 mm)			9357	2010	Netherlands, UK
Left ventricular outflow tract obstruction						
Liu <i>et al</i> ^[61]	HR 2.41 (1.55-3.73)			12146	2017	USA, China
O'Mahony <i>et al</i> ^[60]	HR 1.01 (1.00-1.01) [LVOT Gradient mmHG 18 (6-58)]	0.005	5% at 5 years	3675	2014	Europe
Left atrial diameter						

O'Mahony <i>et al.</i> ^[60]	HR 1.04 (1.02-1.05) (LA diameter in mm 46.2 ± 9)	< 0.001	5% at 5 years	3675	2014	Europe
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SCD: Sudden cardiac death; LVOT: Left ventricular outflow tract; HR: Hazard ratio; OR: Odds ratio; LV: Left ventricular; EF: Ejection fraction.

Table 7 Summary of wearable cardioverter defibrillator studies

Study	General findings	Survival post shock
Wearable cardioverter-defibrillator use in patients perceived to be at high risk early post-myocardial infarction ^[65]	99 out of 8453 patients received 114 inappropriate shocks. None of the inappropriate shocks induced arrhythmias. The inappropriate shock rate was 0.006 shocks per patient month of use.	67% for those with VT/VF; 62% for those treated for PMVT/VF
Aggregate national experience with the wearable cardioverter defibrillator vest: event rates, compliance and survival ^[66]	Inappropriate shocks occurred in 67/3569 (1.9%) patients	90% for VT/VF events; 73.6% for all events
Vest Prevention of Early Sudden Death Trial ^[67]	Inappropriate shocks: 0.6%; Appropriate shocks: 1.4%; Hours/day WCD worn: 14.1	Risk of SCD (WCD vs Control): 1.6% vs 2.4%, $P = 0.18$. All-cause mortality (WCD vs Control): 3.1% vs 4.9%, $P = 0.04$

VT: Ventricular tachycardia; VF: Ventricular fibrillation; WCD: Wearable cardioverter defibrillator; SCD: Sudden cardiac death.

ARTICLE HIGHLIGHTS

Research background

There are many groups of patients including those post myocardial infarction (MI), patients with hypertrophic cardiomyopathy (HCM), patients with left ventricular systolic dysfunction (LVSD) and patients with long QT syndrome (LQTS) who are at high risk of sudden cardiac death (SCD) that do not meet criteria for implantable cardioverter defibrillator (ICD) implantation. This study looked at risk factors for SCD in these patient groups, which could be used as a method for identifying patients at high risk for SCD. Patients at high risk for SCD but not meeting conventional indications for ICD therapy could be offered a WCD until an ICD was indicated.

Research motivation

There is a need for more refined risk calculators to determine the risk of SCD in various conditions as is already present for patients with HCM. There is a requisite for more refined risk calculators to determine the risk of SCD in various conditions such as patients post MI, patients with LVSD, patients with LQTS and other channelopathies, patients with post-partum cardiomyopathy, patients with takotsubo cardiomyopathy, patients with myocarditis and patients with advanced chronic renal failure. This would allow better selection of patients at high risk of SCD and allow physicians to offer their patients the best treatment for each specific patient based on their individual risk.

Research objectives

The main objectives of our study were to collate the risk factors for SCD in specific patient groups as mentioned previously. These risk factors were to be used as a guide to help in determining high-risk patients that may benefit from WCD therapy. This to the best of our knowledge is the first attempt made at collating risk factors for SCD for various conditions in one place. This should help future studies to build on this data and hopefully give rise to risk calculators for SCD in these and many more conditions.

Research methods

We performed a literature search on PubMed. The studies were then selected according to whether they met the inclusion criteria for our review article. The inclusion criteria were any study that reported risk factors for SCD in patients with LVSD, LQTS, HCM or post MI. There was no restriction on age, gender, geographical area or date of publication. Studies had to be reported in English. Any studies where the risk of SCD was not quantified by either a hazard ratio, odds ratio or relative risk were excluded. The relevant risk factors for SCD in the 4 main conditions were then collected and tabulated in table format.

Research results

We collected a large number of risk factors for SCD in all 4 patients groups. These risk factors provide a robust method of assessing a patients risk for SCD. The study also looked at several WCD studies which showed that WCD were effective at terminating VT/VF but were limited in their effectiveness by patient compliance.

Research conclusions

This review shows that there are many risk factors for SCD that to the best of our knowledge

have never been compiled together in one place such as this study has done. We also show that WCD are effective therapies for ventricular tachycardia/ventricular fibrillation, but are limited by patient compliance.

This should help in the development of more precise risk calculators for sudden cardiac death such as the existing risk calculator for HCM. This should also help select patients who may benefit from WCD.

Research perspectives

This study demonstrates the wealth of data present that could be used to create precise risk calculators for SCD. These risk calculators could be used to determine patients at high risk for SCD. It could be used to select which patients need an ICD and which could benefit from a WCD. Further study should be in the form of a meta-analysis to allow this area of research to move forward.

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