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Prediction of sudden death in elderly patients with heart failure

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Abstract

Most heart failure (HF) related mortality is due to sudden cardiac death (SCD) and worsening HF, particularly in the case of reduced ejection fraction. Predicting and preventing SCD is an important goal but most works include no or few patients with advanced age, and the prevention of SCD in elderly patients with HF is still controversial. A recent reduction in the annual rate of SCD has been recently described but it is not clear if this is also true in advanced age patients. Age is associated with SCD, although physicians frequently have the perception that elderly patients with HF die mainly of pump failure, underestimating the importance of SCD. Other clinical variables that have been associated to SCD are symptoms, New York Heart Association functional class, ischemic cause, and comorbidities (chronic obstructive pulmonary disease, renal dysfunction and diabetes). Some test results that should also be considered are left ventricular ejection fraction and diameters, natriuretic peptides, non-sustained ventricular tachycardias and autonomic abnormalities. The combination of all these markers is probably the best option to predict SCD. Different risk scores have been described and, although there are no specific ones for elderly populations, most include age as a risk predictor and some were developed in populations with mean age > 65 years. Finally, it is important to stress that these scores should be able to predict any type of SCD as, although most are due to tachyarrhythmias, bradyarrhythmias also play a role, particularly in the case of the elderly.

1   Introduction

Chronic heart failure (HF) represents a major health problem. Its prevalence is ≥ 10% among people older than 70 years,[1] implies a high rate of hospitalizations, a poor prognosis, and a great impact on quality of life, health-care costs, and families. The phenotype of patients with HF has changed, mainly due to the increase in age, and the consequent increase in the number of comorbidities and medications.[2] In any case, most deaths continue to be due to sudden cardiac death (SCD) and worsening HF, particularly in the case of patients with heart failure and reduced ejection fraction (HFREF). Data from the Framingham Heart Study showed that the causes of death were different in patients with HFREF and in those with preserved ejection fraction (HFPEF) where cancer, infection, and renal disease had a predominant role.[3] Predicting and preventing SCD is an important goal in patients with HF and, therefore, has been broadly studied.[4] However, most works include no or few elderly patients and the prevention of SCD in elderly patients with HF is still controversial. In this paper we review the evidence regarding this topic.

2   Definitions (ESC 2015)

Sudden death refers to a non-traumatic, unexpected fatal event occurring within one hour of the onset of symptoms in an apparently healthy subject. If death is not witnessed, the definition applies when the victim was in good health 24 h before the event.

SCD refers to sudden death in patients where a congenital, or acquired, potentially fatal cardiac condition was known to be present during life, or autopsy has identified a cardiac or vascular anomaly, or when an arrhythmic event is a likely cause of death.

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3 Epidemiology

Cardiovascular diseases are the number one cause of death and about 25% of them are due to SCD. In the elderly, degenerative heart conditions that lead to HF are the main cause of SCD.[1] The risk of SCD is higher in men and its relation with age has been controversial, probably due to different etiologies that are age-related. However, a recent analysis of 40,195 patients with HFREF included in 12 clinical trials has clearly shown that older age is associated with SCD.[5] This association is of great importance for the clinical practice, as physicians may have the perception that advanced age patients with HF die mainly of pump failure, underestimating the importance of SCD in this group, and this may lead to suboptimal treatment.

4 Predictors of SCD in elderly patients with HF

SCD occurs in different population groups: (1) patients without a prior diagnosis of heart disease; (2) patients with a history of heart disease with no or mild cardiac dysfunction; (3) patients with a history of heart disease and severe cardiac dysfunction; and (4) those diagnosed with a defined genetically-based cause for a life-threatening cardiac arrhythmia.[6] SCD in elderly patients is mainly related to HF. The evidence to predict SCD in this age group is scarce and complex. The variables that may be used to predict SCD in elderly patients with heart failure are depicted in Table 1 and are described below.

4.1 Characteristics of heart failure

Left ventricular ejection fraction (LVEF), symptoms, and New York Heart Association (NYHA) class are related with SCD.[6] In patients with HFREF, a higher rate of SCD is observed in those with lower LVEF. Also, age, worse HF symptoms, and ischemic cause are associated with SCD.[7–17] A 50% reduction of the annual rate of SCD in these patients was been recently shown [from 6.5 % in the Randomized Aldactone Evaluation Study (RALES) trial to 3.3% in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure

Table 1. Variables that may be used to predict sudden cardiac death in elderly patients with heart failure.

Clinical characteristics of heart failure
Etiology
Systolic and diastolic function
Functional capacity
Biochemical parameters
Autonomic abnormalities and electrical instability
Risk models

(PARADIGM-HF) trial], probably due to the effects of medical treatment.[5] However, the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA),[14] that only included patients ≥ 60 years (mean age 73 years), was an outliner regarding this reduction in the annual rate of SCD, with 5.3%.

In fact, LVEF and NYHA class have been use as primary criteria in most clinical trials and have a central position in the guidelines regarding the use of implanted cardioverter defibrillators (ICD).[1,18] Different trials investigated the utility of the ICD as primary prevention in ischemic HFREF [Multicenter Automatic Defibrillator Implantation Trial (MADIT), Multicenter Unsustained Tachycardia Trial Investigators (MUSTT), MADIT II, Defibrillation in Acute Myocardial Infarction Trial (DINAMIT) and Coronary Artery Bypass Graft (CABG) Patch Trial], and found a mortality reduction in the ICD arm.[19-23] Although these studies included some elderly patients, the MUSTT study was the only one with a mean age ≥ 65 years and reported a benefit in the electrophysiological-guided therapy group with ICD. In a post-hoc analysis of MADIT-II trial (patients ≥ 75 years), a tendency to an improved survival in the ICD group was found, although the benefit did not reach statistical significance.[24] The Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality (DANISH) has recently investigated the benefits of ICD in a non-ischemic population. Although the trial did not show a mortality benefit, ICD was associated with a reduction on SCD and subgroup analysis showed that patients younger than 59 years-old had a survival benefit, while patients ≥ 68 years-old did not, suggesting that the benefit of primary prevention in the elderly is questionable in non-ischemic patients.[25]

Fewer trials have investigated the efficacy of ICD to prevent SCD in secondary prevention. The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial randomized patients to ICD or treatment with amiodarone/sotalol. This study had a mean age of 65 years and found a clear mortality benefit in the ICD group.[26] However, a combined analysis of AVID, Cardiac Arrest Study Hamburg (CASH), and Canadian Implantable Defibrillator Study (CIDS) trials found no benefit of ICDs in patients ≥ 75 years.[27]

Overall, these studies suggest that LVEF is a predictor of SCD in elderly patients. However, the fact that HFREF accounts only for < 20% of all SCD, the lack of evidence of causal relation LVEF-arrhythmia mechanisms, the variability of LVEF, and the lack of precision of its measure makes the use of LVEF to predict SCD controversial.[6,28,29] In the Oregon Sudden Unexpected Death Study,[28] the authors studied a cohort of patients who died of SCD in Oregon and

retrospectively assessed LVEF. In this elderly population, with 38% > 75 years, only a third had a reduced LVEF. In the Candesartan in Heart failure—Assessment of moRtality and Morbidity (CHARM) program, that included HFPEF,[29] and had a mean age of 66 years, 35% of deaths were due to SCD.

As we will see in the end of this review, the inclusion of LVEF in prediction models is probably a better option to determine the risk of SCD. Comorbidities should be included in these models, including chronic obstructive pulmonary disease, renal dysfunction, and diabetes.[30,31] Also HF-related factors as left ventricular diameters, natriuretic peptides, and non-sustained ventricular tachycardias may improve the prediction capability.[31]

As previously said, SCD is also an important cause of death in patients with HFPEF, which affects mainly elderly patients.[32,33] Mortality rates have varied substantially across studies, probably due to the heterogeneity in the diagnosis of this condition, particularly when the studies did not include natriuretic peptides.[34] Population-based cohort studies related mortality in this group mainly with non-cardiac causes, while clinical trials reported higher rates of cardiovascular deaths, probably due to selection bias.[34] In the Irbesartan in Heart Failure With Preserved Ejection Fraction (I-PRESERVE) trial, with a mean age > 70 years, cardiovascular diseases were responsible for 60% of deaths, and 26% of all deaths were due to SCD.[35] In this trial, performed in patients with HFPEF, age, gender, diabetes mellitus, previous myocardial infarct, left bundle branch block, and the N-terminal pro B-type natriuretic peptide (NT-pro-BNP) were identified as risk factors of SCD over five years.[36]

Biochemical markers are used for the diagnosis of HF and are related to the prognosis and to SCD. BNP and Nt-proBNP have been broadly studied. In patients with LVEF < 35%, a BNP cut-off point 130 pg/mL had a 99% negative predictive value for SCD.[37] Although BNP is lower in a population with HFPEF, a study of 615 elderly patients (mean age 70 years) showed that when similar levels of BNP were compared across the whole spectrum of LVEF, and for different cut-off levels of LVEF, the associated risk of adverse outcomes was similar in HFPEF and HFREF.[38] As we have said, an association between Nt-proBNP and SCD in patients with HFPEF has also been found.[36] Moreover, significant associations between BNP/Nt-proBNP levels and ventricular arrhythmias have been reported.[39,40] A meta-analysis of 14 studies confirmed the relation between BNP/Nt-proBNP and SCD/ventricular arrhythmias.[39] Five of the studies used in this meta-analysis had a mean age ≥ 65 years.[31,41–44] The association of natri-

uretic peptides with SCD is not merely due to a more advance HF situation.[40] However, the severity of the HF syndrome and the presence of comorbidities should be considered to predict SCD in elderly populations. BNP increases with ageing itself, probably due to age-related myocardial fibrosis and renal impairment, and with some comorbidities such as renal dysfunction, chronic obstructive pulmonary disease, low body mass index, and pulmonary hypertension.[45–48]

All the previous seen predictors of SCD are useful in elderly patients with HF but they also have important limitations that are depicted in Table 2.

4.2 Autonomic abnormalities and electrical instability

Autonomic nervous system abnormalities may be caused by the response to disturbed homoeostasis caused by HF. Arrhythmic risk is enhanced when vagal activity decreases or sympathetic activity increases,[6,49] and may increase the risk of ventricular fibrillation. The value of autonomic abnormalities to predict SCD is independent of electrical instability. There are different autonomic tests that study the variability of heart rate, arterial pressure behavior and QT interval variability that have been associated with a poor prognosis in HF patients (Table 3). Heart rate (HR) variability (R-R interval on the ECG/24 hours Holter) and baroreflex sensitivity (BRS) (provoked or spontaneous) are predictors of SCD.[50,51] HR variability represents the neurohormonal interaction with the sinus node, and decreases with sympathetic activity and with age. Low HR variability has been related with poor outcomes in patients with chronic HF.[52-56] Depressed BRS is also an independent predictor of cardiovascular mortality in elderly patients with preserved ejection fraction.[57]

Heart rate turbulence (HRT) describes short-term fluctuations in sinus cycle length that follow spontaneous ventricular premature complexes (VPCs). Usually, sinus rate initially briefly accelerates and subsequently decelerates compared with the pre-VPC rate, before returning to base-

Table 2. Main limitations of predictors of sudden cardiac death in elderly populations.

Predictors	Elderly population
Heart failure signs and symptoms	Comorbidities may mimic (anemia, obesity, chronic obstructive pulmonary disease)
Left ventricular ejection fraction	Usually preserved
Diastolic function	May be difficult to assess in elderly population
Functional class	Bad correlation
Natriuretic peptides	Increases with age and comorbidities (consider specific cut-offs)

Table 3. Autonomic abnormalities and electrical instability as risk predictors in elderly populations with heart failure.

Predictors	Associated with	Studies in elderly populations
HR variability	Poor outcomes and SCD	
HR deceleration capacity	SCD and mortality	
HR recovery after exercise	Mortality	Yes
BRS	Cardiovascular mortality and SCD	Yes
HRT	HF severity and SCD	Yes
QT variability	Cardiovascular mortality	Yes
TWA	SCD	Yes
TWR	SCD	

BRS: baroreflex sensitivity; HF: heart failure; HR: heart rate; HRT: heart rate turbulence; SCD: sudden cardiac death; TWA: T-wave alternans; TWR: T-wave morphology restitution.

line.[58,59] HRT is a vagally mediated phenomenon, reflecting baroreflex sensitivity. Increasing age is associated with a decrease in HRT.[60] In patients with HF, HRT is a predictor of HF severity and poor outcomes.[61] In the Sudden Death in Heart Failure [MUerte Subita en Insuficiencia Cardiaca (MUSIC)] registry, with a mean age of 63 years, HRT was strongly associated with SCD, also in patients > 65 years.[62] Adequate HR recovery after exercise depends on the vagal system. Impaired HR recovery after 1 min (≤ 12 beats) is a predictor of death, even in elderly population (≥ 65 years).[63] In patients with HF, it was associated independently with mortality.[64]

QT variability index is the ratio of normalized QT variability to normalized HR variation and is a non-invasive measure of repolarization lability due to autonomic abnormalities. Initially, it was related to SCD in a small-sample group of patients with HF,[65] but subsequent studies disagreed showing a positive association with cardiovascular death but not with SCD.[66,67]

T wave-derived indices have been proposed as better markers of repolarization dispersion. T wave alternans (TWA), T peak-to-end restitution, and T wave morphology restitution are markers of ventricular instability and dispersion of repolarization that could predict SCD. TWA is a beat-to-beat alternation in the morphology of the ST segment and the T wave, which reflects the temporal and spatial heterogeneity of repolarization. TWA might be associated with arrhythmic risk[68] and SCD.[69-72] However, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) trial failed to show a positive association between TWA and SCD.[73] However, in the Cardiovascular Health study TWA was independently associated with SCD in an elderly population.[74] T-wave morphology restitution (TWR) quantifies

the morphological differences between T-wave, it measures T-wave morphological change per RR increment. In a recent analysis of the MUSIC registry study, TWR was the most significance variable associated with SCD in patients with HF and independent from other clinical and ECG variables.[75,76] It was shown to be a better marker than other electrical and autonomic variables as TWA, HRT, QT variability index, T peak-to end or QRS duration. An integrated risk model with clinical (NYHA class and LVEF) and ECG derived parameters (TWA, TWR and T peak-to-end) to predict SCD has been proposed.[76,77]

Other electrical parameters as QRS duration (specially left bundle branch block), QTc, microvolt electrical potentials in the terminal QRS complex and induced/spontaneous ventricular arrhythmias have been related with SCD in patients with HF.[78] However, it is the combination of them with other predictors in risk models what may predict accurately SCD. Moreover, abnormal electrocardiographic patterns in elderly population is very high. Increased QRS amplitude, QT prolongation and non-sustained monomorphic ventricular tachycardia may be present even in patients without structural heart disease,[79] so we must be careful when interpreting them as risk predictors for SCH in elderly patients with HF.

4.3 Risk models

The combination of markers reflecting the impairment of different mechanisms based on clinical variables, biomarkers, and autonomic and electrical impairment is probably the best option to predict SCD prediction. Different risk scores have been described,[30,31,36,76,79] but there are no specific ones for elderly population, and some predictors may have important limitations in elderly populations. However, most of them include age as a risk predictor and some were developed in populations with mean age > 65 years. Interestingly several of them include comorbidities as predictors of SCD. Table 4 shows the variables most frequently included in these predictor scores. It is important to stress that these scores should be able to predict any type of SCD as, although most are due to tachyarrhythmias, bradyarrhythmias also play a role, particularly in the case of the elderly (Figure 1).[80,81]

5 Conclusions

SCD is an important cause of death in elderly patients with HF. Predictors of SCD in this group are not well-defined and specific studies are needed. We cannot define the best risk marker to predict SCD, but rather a combination of clinical, biochemical, echocardiographic and electrical

Table 4.   Variables most frequently included in SCD predictor scores.

Studies	Age, yrs	Male	NYHA	Echocardiography	Natriuretic peptides	Comorbidities	ECG	Etiology
Bilchick, *et al*.[30]	75		II	LVEF < 20%		COPD, kidney disease, diabetes		
Watanabe, *et al*.[31]	66			LVEF, LVEDD	BNP	Diabetes	NSVT	
Adabag, *et al*.[36]		Male			Nt-proBNP	Diabetes	LBBB	Myocardial infarction
Ramírez, *et al*.[76]		Male	II	LVEF			TWA, TWR, T peak to end.	
Vázquez, *et al*.[79]				LA size > 26 mm/m²	Nt-proBNP		LBBB, NSVT, Frequent VPBs	Atherosclerotic vascular events

BRS: baroreflex sensitivity; BNP: B-type natriuretic peptide; COPD: chronic obstructive pulmonary disease; HR: heart rate; HRT: heart rate turbulence; LA: left atria; LBBB: left bundle branch block; LVEDD: left ventricular end diastolic diameter; LVEF: left ventricular ejection fraction; NSVT: non-sustained ventricular tachycardia; NT-pro-BNP: N-terminal pro B-type natriuretic peptide; NYHA: New York Heart Association functional class; SCD: sudden cardiac death; VPBs: ventricular premature beats; TWA: T-wave alternans; TWR: T-wave morphology restitution.
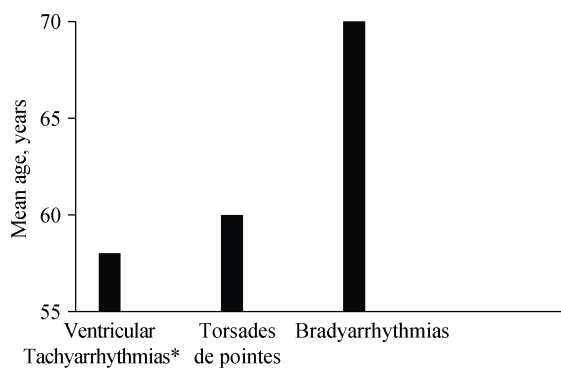

Figure 1.   Mean age of patients who died suddenly wearing a 24 hour ECG Holter recorder. Data from Bayés de Luna, *et al*.[81] *Except *torsade des pointes*.

parameters. Specific characteristics and comorbidities of elderly population should be considered in prediction and prevention of SCD.

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