




# Sinergy between drugs and devices in the fight against sudden cardiac death and heart failure

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## Abstract

The impact of sudden cardiac death (SCD) in heart failure (HF) patients is important and prevention of SCD is a reasonable and clinically justified endpoint if associated with a reduction in all-cause mortality.

According to literature, in HF with reduced ejection fraction, only three classes of agents were found effective in reducing SCD and all-cause mortality: beta-blockers, mineralcorticoid receptor antagonists and, more recently, angiotensin-receptor neprilysin-inhibitors. In the PARADIGM trial that tested sacubitril/valsartan vs. enalapril, the 20% relative risk reduction in cardiovascular deaths obtained with sacubitril/valsartan was attributable to reductions in the incidence of both SCD and death due to HF worsening and this effect can be added to the known positive effect of implantable cardioverter-defibrillators in appropriately selected patients.

In order to maximize the implementation of all the available treatments, patients with HF should be included in virtuous networks with a dialogue between all the physician involved, with commitment by all these physicians for appropriate decision-making on application of pharmacological and device treatments according to available evidence, as well as commitment for drug titration before and after device implant, taking advantage from remote monitoring, and with the safety of back up device therapy when indicated. There are potential synergistic effects of drug therapy, with all the therapies acting on neuro-hormonal and sympathetic activation, but specifically with sacubitril/valsartan, and device therapy, in particular cardiac resynchronization therapy, with added incremental benefits on positive cardiac remodelling, prevention of HF progression, and prevention of ventricular tachyarrhythmias.

## Keywords

Beta-blockers • Heart failure • Mortality • Mineralcorticoid receptor antagonists • Remote monitoring • Sacubitril/valsartan • Sudden cardiac death

## Introduction

Sudden cardiac death (SCD), defined as an unexpected death from cardiac, causes following sudden cardiac arrest occurring within 1 h of the onset of acute symptoms continues to represent an

important clinical challenge for contemporary cardiology in view of the variety of clinical conditions that may induce a risk of SCD and of the many pathophysiological factors and mechanisms that may lead to ventricular fibrillation, asystole or pulseless electrical activity.<sup>1</sup>

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In consideration of the complex interactions among the factors involved in the arrhythmogenesis of SCD, including genetic factors and the variable anatomical and functional myocardial substrates, as well as the role of potential triggers, various approaches can be considered for improving survival through a reduction of SCD (Figure 1).<sup>2,3</sup>

## Sudden cardiac death: epidemiology and impact in heart failure

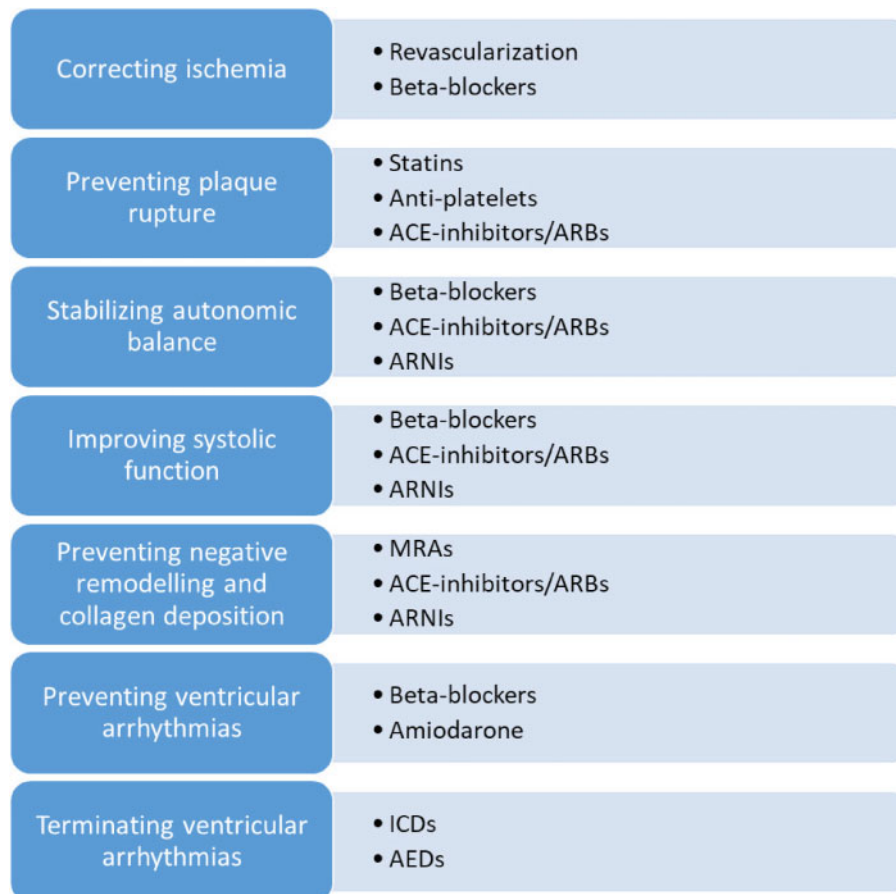
Despite the reduction in cardiovascular mortality that occurred in the last 20 years in western high-income countries as a result of improvement in prevention and care of ischaemic heart disease and heart failure (HF),<sup>4</sup> cardiovascular diseases remain the primary cause of mortality in Europe and North America, with SCD accounting for ~25% of the deaths due to cardiovascular diseases.<sup>3</sup>

The distribution of cases of SCD and the risk in absolute and relative terms have great variations moving from the general population to so-called 'high-risk groups' as shown in Figure 2 and this

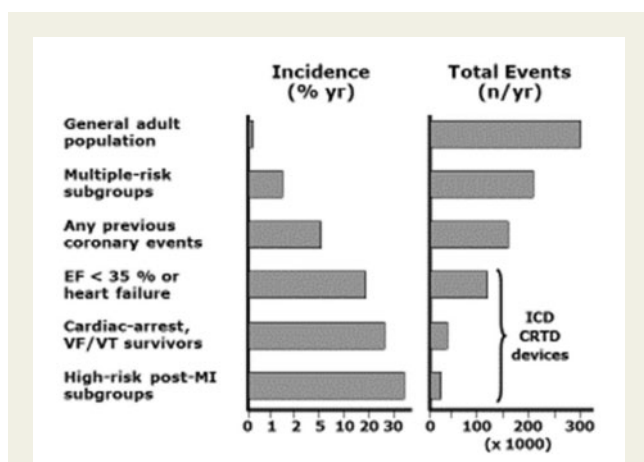
constitutes the basis for the different strategies promoted for reducing SCD.<sup>1,3</sup>

The overall incidence of SCD in an unselected adult population is 1–2 per 1000 per year,<sup>1,3</sup> but it is possible to identify, on the basis of clinical factors, some subgroups of patients at higher relative risk of SCD, for whom the incidence of SCD events at 1 year may be at least 10-fold greater than in the general population. These subgroups of patients at high risk have been evaluated in randomized clinical trials with the aim to assess the risk and cost–benefit ratio of a series of pharmacological and non-pharmacological treatments such as beta-blockers, amiodarone, or other antiarrhythmic agents, drugs for HF or implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy defibrillator (CRTD) devices. Patients with coronary artery disease and previous myocardial infarctions associated with left ventricular dysfunction as well as patients with HF with systolic dysfunction belong to subgroups at high risk of SCD, together with patients who already experienced a life-threatening ventricular tachyarrhythmia or a cardiac arrest.<sup>5</sup>

The impact of SCD in HF patients is important since up to 50% of the deaths occurring in patients with systolic HF are sudden and unexpected, with HF associated with a risk of SCD six to nine times



**Figure 1** Treatments to reduce sudden cardiac death by effecting the cardiac substrate or the ventricular arrhythmogenicity. ACE, angiotensin-converting enzyme; AED, automated external defibrillator; ARB, angiotensin-receptor blocker; ARNI, angiotensin-receptor neprilysin inhibitor; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid receptor antagonist.



**Figure 2** The epidemiology of SCD, with a variable risk of SCD according to patient subgroups in terms of incidence per year (left panel) and total number of events per year (right panel). The categories of patients who are potential candidates for device therapy are indicated (modified from Ref.<sup>1</sup>). CRTD, cardiac resynchronization therapy defibrillator; ICD, implantable cardioverter-defibrillator.

higher than the rate of SCD in the general population.<sup>3</sup> It is noteworthy that in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF), the proportion of deaths that resulted from SCD was proportionally higher in lower NYHA (New York Heart Association) functional classes. In fact, in NYHA class II, III, and IV patients, the proportion of SCD was 64%, 57%, and 33%, respectively, whereas 1-year absolute risk (cumulative incidence) of SCD was 4%, 6%, and 6%, respectively.<sup>6</sup> This observation is important since indicates that SCD may occur in patients with relatively preserved functional capacities and in whom the outcome in terms of HF-related risk of death is favourable.

The chain of events and the mechanisms leading to SCD include ventricular tachyarrhythmias, and, less frequently and usually in more compromised patients, bradyarrhythmias, asystole, or pulseless electrical activity, although the prediction in an individual patient is often uncertain. The uncertainty is also related to the concept of SCD, an entity which per se is characterized by a terminal event following a sequence of events, while it is not characterized by a single mechanism. A series of pathophysiological mechanisms (atherothrombosis leading to acute ischaemia, neuro-hormonal activation, electrolyte imbalances, etc.) may act as acute triggers, although the common result is an acute electrical or mechanical failure in remodelled and fibrotic ventricles.<sup>7</sup> However, also genetic factors may play an important role and especially in patients with preserved or mid-range left ventricular ejection fraction (LVEF) their role may become predominant for risk characterization and decision-making (Priori et al.,<sup>3</sup> Boriani et al.,<sup>8</sup> and Zegkos et al.<sup>9</sup>).

## Treatment of heart failure: goals of treatments

The fundamental objectives for HF therapy are improving symptoms, functional capacity and quality of life, slowing disease progression, decreasing the need for hospitalization, and decreasing associated

mortality.<sup>10</sup> Within the clinical scenario of HF, there are patients with preserved or reduced LVEF, but only for the latter significant results on outcomes have been demonstrated according to the rules of evidence-based medicine. Indeed, to date, no randomized trial has demonstrated a positive impact on mortality of any drug treatment in patients with HF and preserved LVEF.<sup>11</sup>

In the general approach to HF with reduced LVEF prevention of SCD is a reasonable and clinically justified endpoint if associated with a reduction in all-cause mortality, thus avoiding a simple 'conversion' in the mode of death. Therefore, in the evaluation of the impact of pharmacological and non-pharmacological treatments, the impact on SCD will always be considered in parallel with the impact on all-cause mortality. This approach should be applied to both traditional pharmacological treatments and to the many treatments that were proposed recently and whose validation requires the typical approach of evidence-based medicine.<sup>12</sup>

## Impact of traditional drugs for heart failure on sudden cardiac death

Antiarrhythmic agents, also including amiodarone, have no role in reducing SCD.<sup>2</sup> In particular, amiodarone was investigated in SCD-HeFT, a trial on the role of ICDs in primary prevention of SCD in HF and no significant improvement in survival in the amiodarone arm vs. the placebo arm of the SCD-HeFT emerged.<sup>13</sup>

A series of pharmacological treatments for HF have been tested in randomized controlled trials with regard to the impact on all-cause mortality, SCD, and other outcomes and the results are reported in detail in [Supplementary material online, Table S1](#).

Beta-blockers are a well-established component of optimized medical treatment for HF and their effects include an improvement in left ventricular structure and function (by decreasing ventricular size and increasing LVEF) as well as an important role in the prevention of arrhythmic events. Several trials have shown that beta-blockers reduce the risk of hospitalizations and death in HF patients. In a meta-analysis of all randomized controlled trials examining the use of beta-blockers vs. placebo/control for the prevention of SCD in HF patients beta-blockers result to reduce the risk of SCD by 31%, cardiovascular death by 29%, and all-cause mortality by 33%.<sup>14</sup> Despite this substantial benefit, a residual risk of SCD persists during long-term treatment with beta-blockers, thus suggesting the need for additional preventive measures.

In a meta-analysis of published literature, mineralocorticoid receptor antagonists, also called aldosterone antagonists, appeared effective with a 19% risk reduction for SCD, as well as, with the same amount, for all-cause mortality.<sup>15</sup>

A series of clinical trials have uniformly shown that angiotensin-converting enzyme (ACE) inhibitors provide survival benefits in patients with congestive HF or myocardial infarction. In a meta-analysis of 15 randomized controlled trials comparing ACE inhibitors with placebo in patients following acute myocardial infarction, ACE inhibitor therapy resulted in a 20% reduction in the risk of death and an 18% reduction in cardiovascular death and SCD (odds ratio: 0.80; 95%CI 0.70, 0.92).<sup>16</sup> However, in the setting of HF, two systematic

reviews did not find a significant effect of ACE inhibitors on the risk of SCD.<sup>17,18</sup>

There is no evidence in support of a role of angiotensin-receptor blockers (ARBs) on SCD in HF. In a meta-analysis, ARBs compared with placebo had no significant effects on all-cause mortality and compared with ACE inhibitors or in combination vs. ACE inhibitors alone, no significant differences were found in all-cause mortality or SCD.<sup>15</sup>

According to a meta-analysis targeted to assess the effectiveness of pharmacological interventions on SCD and all-cause mortality in HF with reduced LVEF only three classes of agents were found effective: beta-blockers, mineralocorticoid receptor antagonists (MRA) and more recently, as we will discuss later in this chapter, angiotensin-receptor neprilysin-inhibitors (ARNIs).<sup>15</sup>

Ivabradine was found to reduce the composite of cardiovascular death or hospital admission for worsening HF in patients who had symptomatic HF and an LVEF of 35% or lower were in sinus rhythm with heart rate 70 b.p.m. or higher.<sup>19</sup> Ivabradine had a significant effect on pump failure death, which was reduced by 26%, but no significant effect on SCD (Swedberg *et al.*<sup>19</sup>).

Recently, sodium-glucose co-transporter-2 (SGLT2) inhibitors<sup>20</sup> and vericiguat<sup>21</sup> were found effective in improving outcomes, with regard to worsening HF or cardiovascular death, but the effect on SCD need further evaluation.

## Impact of devices on sudden cardiac death in heart failure: defibrillators and cardiac resynchronization therapy

The role of ICD therapy as a rescue treatment was first conceived by Dr Michel Mirowski over 40 years ago for secondary SCD prevention in selected patients with documented ventricular tachyarrhythmias.<sup>22</sup> The first ICD was implanted in 1980 and the approval of Food and Drugs Administration was delivered in 1985 for patients who had survived two episodes of cardiac arrest. Following the first pioneering experiences, two key factors led to a progressive widespread implementation of the use of ICDs in selected patients: the technique of implant in a subcutaneous pectoral pocket, without the need for thoracotomy, and the validation, according to a series of randomized controlled trials that tested the efficacy of ICD in reducing SCD and improving overall survival, not only in the selective field of secondary prevention but also in high-risk patients with left ventricular dysfunction without previous sustained ventricular tachyarrhythmias.<sup>13,23–31</sup>

The main results of the randomized controlled trials on the efficacy of ICDs in improving survival are shown in [Table 1](#). It is noteworthy to stress that the use of all-cause mortality has the main endpoint of most of the trial was a key factor in validating ICD therapy, since the assumption that prevention of arrhythmic death or SCD translates into reduction in all-cause mortality is not always true, as demonstrated in the two trials that evaluated the ICD in the setting of a recent myocardial infarction (IRIS and DINAMIT).<sup>32,33</sup>

For all the controlled studies on ICD in SCD prevention, the main criterion for selecting patients at high risk of SCD was the presence of a depressed left ventricular function. The evidence derived from these trials, indicating that ICDs are effective in improving overall

survival at 2–5 years in appropriately selected patients with left ventricular dysfunction at high risk of SCD, was the basis for the recommendations for ICD implantation delivered by consensus guidelines.<sup>3,10</sup> The evidence of the benefit of ICD in non-ischaemic patients has always been less solid than in patients with ischaemic heart disease even if a meta-analysis including CAT, AMIOVERT, DEFINITE, and the non-ischaemic cohort of SCD-HeFT found a statistically significant benefit of ICD therapy on all-cause mortality, with a 26% relative risk reduction,<sup>34</sup> and this was the basis for the recommendations of international consensus guidelines.<sup>3,10</sup> The most recent trial is the DANISH ICD study,<sup>35</sup> a trial specifically targeted to evaluate the impact of ICD implant in the setting of systolic dysfunction due to non-ischaemic cardiomyopathy. In a follow-up of more than 5.5 years, no survival benefit occurred in the ICD group as compared with usual care in the whole population, but a significant reduction in the risk of all-cause death was found in the subgroup of patients younger than 68 years, with a 36% relative risk reduction. In interpreting this study, it is important to consider that 58% of patients received a device for cardiac resynchronization therapy (CRT). A meta-analysis of the efficacy of ICD vs. control in the setting of primary prevention in patients with HF, clearly showed that, even including the DANISH trial, the benefit of ICD on all-cause mortality is confirmed in younger patients (below 65–70 years) with a relative risk reduction of 32%, with important statistical significance.<sup>36</sup> The DANISH trial had the merit to explore with a dedicated randomized controlled trial the complex setting of non-ischaemic cardiomyopathy, and although the full picture is not completely clear, we improved our knowledge on how age may influence the effect of a prophylactic ICD on all-cause mortality. Below the age of 65–70 years old implanting an ICD appears to be clinically useful also in non-ischaemic cardiomyopathy and is therefore suggested by current guidelines,<sup>3,10</sup> even if this evidence is mostly derived from subgroup analysis. Since age is only one component of the clinical picture of an individual patient, there is need of improving outcome prediction according to more detailed patient characterization including considerations on renal function, diabetes, other comorbidities, and functional status.<sup>37,38</sup>

Device therapy for SCD prevention experienced a substantial improvement with the clinical validation of CRT, initially found effective in patients with moderate to severe HF, and more recently also in mild HF, with clinically important benefits, as shown by the trials shown in [Table 2](#).<sup>30,31,39–47</sup>

According to these trials, use of CRT in appropriately selected patients is associated with significant improvement in overall survival, as well as provides favourable effects in terms of quality of life, exercise capacity and is able to significantly reduce hospitalizations due to HF.<sup>48</sup>

Unfortunately, no one trial with an adequate statistical power compared the use of CRT with and without defibrillation capability, and therefore decision-making on individual patients with regard to the choice between CRT with only pacing (CRT-P) or with defibrillating capability (CRT-D) should be based on clinical considerations including patient age, comorbidities, and clinical status.<sup>10,48–50</sup>

According to most recent guidelines, the recommendation for implanting a CRT device in patients in sinus rhythm with moderate to severe HF (NYHA functional class III–IV) (the setting where the efficacy of CRT was initially validated) are the following: CRT is strongly

**Table 1** Main controlled trials on implantable cardioverter-defibrillators vs. amiodarone or other controls in secondary and primary prevention of sudden cardiac death out of the setting of recent myocardial infarction

Study (year)	N	Comparison	Follow-up (months)	Endpoints	P-value	RRR
Secondary prevention trials						
AVID: Antiarrhythmics Versus Implantable Defibrillators (1997) <sup>19</sup>	1016	ICD vs. AADs (amiodarone in 96%)	18	All-cause death	<0.02	31%
CIDS: Canadian Implantable Defibrillator Study (2000) <sup>21</sup>	659	ICD vs. amiodarone	36	All-cause death Arrhythmic death	0.142 0.094	20% 33%
CASH: Cardiac Arrest Study Hamburg (2000) <sup>22</sup>	288	ICD vs. amiodarone, propafenone or metoprolol	57	All-cause death	0.081	23%
Meta-analysis AVID, CASH, CIDS (2000) <sup>23</sup>	1866	ICD vs. amiodarone	28	All-cause death Arrhythmic death Non-arrhythmic death	<0.001 <0.001 NS	27% 51% 7%
Primary prevention trials						
MADIT: Multicenter Automatic Defibrillator Implantation Trial (1996) <sup>18</sup>	196	ICD vs. control	27	All-cause death	0.009	54%
MUSTT: Multicenter Unsustained Tachycardia Trial (1999) <sup>20</sup>	704	AADs or ICD (guided by EPS) vs. control ICD vs. AADs	39	Cardiac arrest or arrhythmic death All-cause death Cardiac arrest or arrhythmic death	0.04 0.06 <0.001	27% 20% 76%
MADIT II: Multicenter Automatic Defibrillator Implantation Trial II (2002) <sup>24</sup>	1232	ICD vs. control	20	All-cause death All-cause death	<0.001 0.016	60% 31%
COMPANION: Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure Trial (2004) <sup>25</sup>	1634	CRT-D vs. control	16	All-cause death or hospitalization All-cause death	0.01 0.003	20% 36%
SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial (2004) <sup>11</sup>	2521	ICD vs. amiodarone vs. placebo	45.5	All-cause death (ICD vs. placebo) All-cause death (amiodarone vs. placebo)	0.007 NS	23% -6%
MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial – Cardiac Resynchronization Therapy (2009) <sup>26</sup>	1820	ICD vs. CRT-D	54	All-cause death or HF event HF event	0.001 <0.001	36% 41%
DANISH ICD: Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischaemic Systolic Heart Failure on Mortality (2016) <sup>29</sup>	1116	ICD vs. control (CRT-D in 58%)	67.6	All-cause death	0.28	13% <sup>a</sup>

AADs, anti-arrhythmic drugs; CI, confidence interval; CRT-D, cardiac resynchronization therapy-defibrillator; EPS, electrophysiologic study; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; RRR, relative risk reduction.

<sup>a</sup>Hazard ratio 0.87 (95% CI 0.68–1.12;  $P=0.28$ ) for ICD vs control in the whole cohort, but among patients < 68 years HR 0.64 (95% CI 0.45–0.90;  $P=0.01$ ).

recommended in case of left bundle branch block (LBBB) with QRS duration >150 ms, while a lower strength of recommendations is released when QRS duration is between 130 and 150 ms, especially if not associated with LBBB.<sup>48</sup>

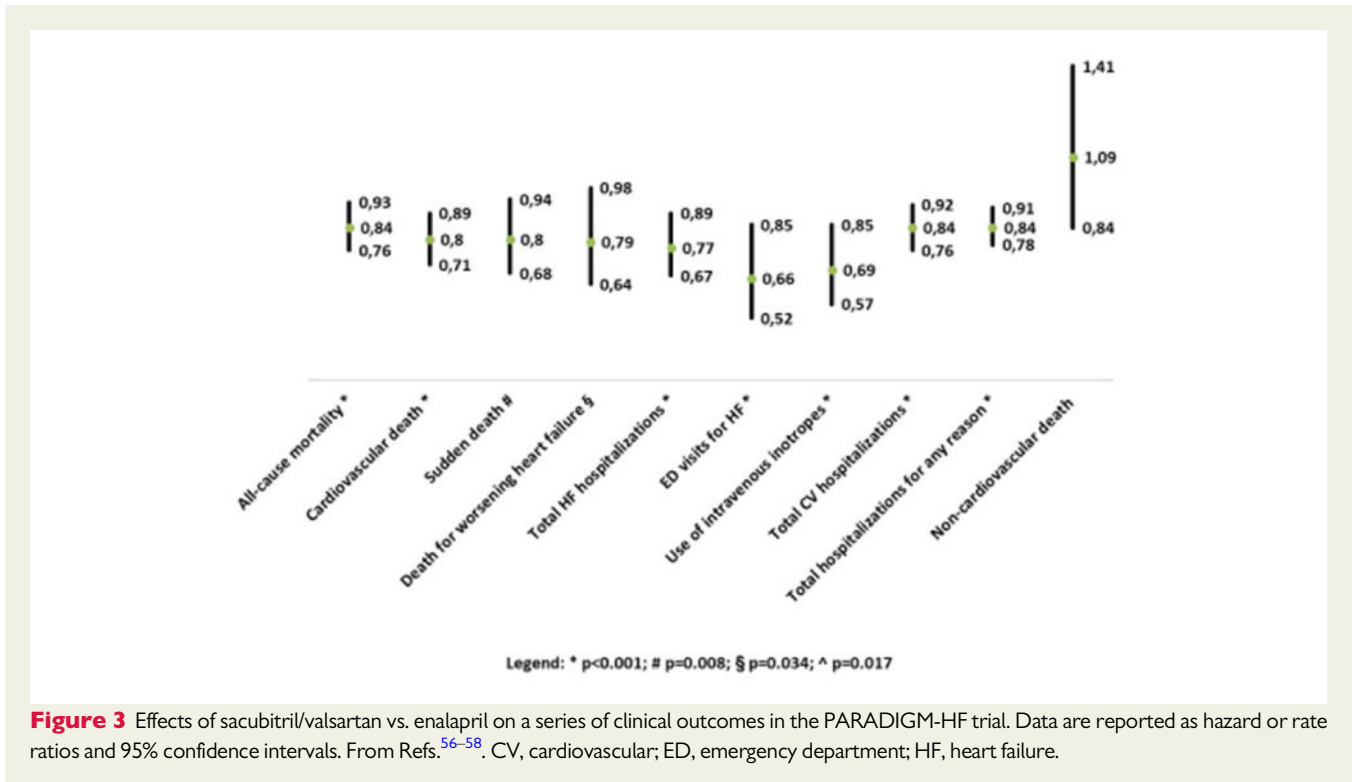
Moreover, according to guidelines, device therapy for primary prevention of SCD is indicated if LVEF remains reduced, i.e.  $\leq 35\%$ , after at least 3 months of optimal medical therapy for HF with agents acting on sympathetic and neuro-hormonal activation such as beta-blockers, ACE inhibitors, ARBs, and MRA.<sup>10,48</sup> In view of the

period of time when ICD trials were conducted, it is clear that they do not reflect the evolution of pharmacological and interventional treatments occurred in the last years, but on the other hand, it will be questionable, in ethical terms, to perform new trials enrolling patients from current daily practice, with randomization of patients at high risk of SCD to ICD vs. no-ICD treatment. Moreover, with all the limitations of non-controlled studies, at least two large-scale prospective registries that evaluated prophylactic ICD implant in HF patients using propensity score matching found a lower long-term mortality

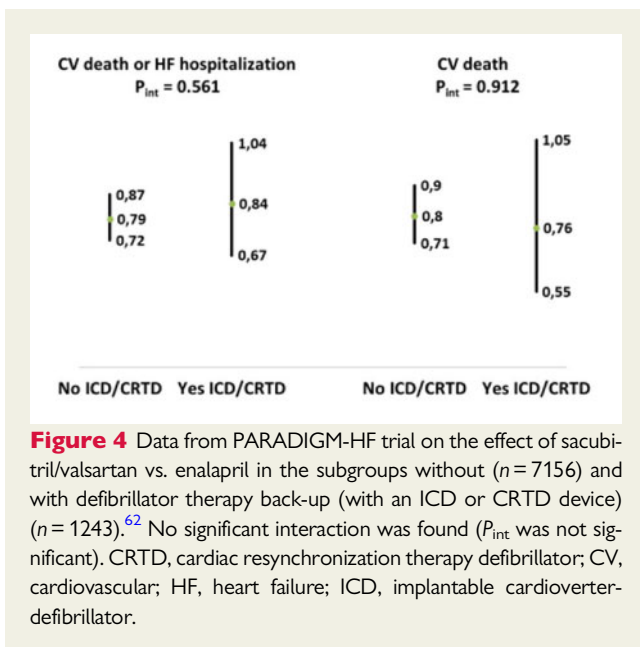
**Table 2** Controlled trials on cardiac resynchronization therapy in heart failure: study characteristics and main results

Study (year)	Trial design	N	Follow-up (months)	NYHA class	LVEF	QRS duration (ms)	Primary endpoints	Study results
MIRACLE (2002) <sup>34</sup>	Double-blind, randomized trial CRT vs. OMT	453	6	III-IV	<35%	>130	NYHA class, exercise capacity, QoL	CRT-P improved NYHA class, QoL, exercise capacity and LVEDD, and increased LVEF
MIRACLE-ICD (2003) <sup>35</sup>	Double-blind, randomized trial CRT-D vs. ICD	369	6	III-IV	<35%	>130	NYHA class, exercise capacity, QoL	CRT-D improved NYHA class, QoL, peak VO2
CONTACT-CD (2003) <sup>36</sup>	Double-blind, randomized trial CRT-D vs. ICD	490	6	II-IV	<35%	>120	NYHA class, exercise capacity, QoL	CRT-D improved exercise capacity, NYHA class, QoL, reduced LV volumes and increased LVEF
COMPANION (2004) <sup>25</sup>	Double-blind, randomized trial OMT vs. CRT-P/CRT-D	1520	15	III-IV	<35%	>120	All-cause mortality or hospitalization	CRT-P and CRT-D reduced all-cause mortality or hospitalizations
MIRACLE-ICD II (2004) <sup>37</sup>	Double-blind, randomized trial CRT-D vs. ICD	186	6	II	<35%	>130	Peak VO2	CRT-D improved NYHA, VE/CO2 and LV volumes and improved LVEF
CARE-HF (2005) <sup>38</sup>	Double-blind, randomized trial OMT vs. CRT-P	813	29	III-IV	<35%	>120	All-cause mortality or hospitalization	CRT-P reduced all-cause mortality and hospitalizations and improved NYHA class and QoL
REVERSE (2008) <sup>39</sup>	Double-blind, randomized trial CRT on vs. CRT off	610	12	I-II	<40%	>120	Worsening of clinical composite endpoint	CRT-P/CRT-D did not improve the primary endpoint and did not reduce all-cause mortality but reduced LVEF index and HF hospitalizations.
MADIT-CRT (2009) <sup>26</sup>	Single-blind, randomized trial CRT-D vs. ICD	1820	12	I-II	<30%	>130	All-cause mortality or HF hospitalizations	CRT-D reduced the endpoint of HF hospitalizations or all-cause mortality. LVEF was reduced. CRT-D did not reduce all-cause mortality
RAFT (2010) <sup>40</sup>	Double-blind, randomized trial CRT-D vs. ICD	1798	40	II-III	<30%	>120	All-cause mortality or HF hospitalizations	CRT-D reduced the endpoint all-cause mortality or HF hospitalizations. In NYHA III, CRT-D only reduced all-cause mortality
BLOCK HF (2013) <sup>41</sup>	Double-blind, randomized trial RV vs. BIV pacing	918	37	I-III	≤50%	123-125	All-cause mortality, acute HF, increase in LVEF>15%	BIV pacing was superior to RV pacing in patients with atrioventricular block, mild-to-moderate HF and abnormal LV systolic function
ECHO CRT (2013) <sup>42</sup>	Multicenter, randomized trial, CRT with echo dysynchrony	1680	19	I-IV	<35%	<130	Death from any cause or hospitalization for worsening HF	CRT did not reduce hospitalizations for HF or death from any cause. CRT increased mortality in pts with LVEF<35% and narrow QRS

CRT-D, cardiac resynchronization therapy-defibrillator; CRT-P, cardiac resynchronization therapy-pacing; HF, heart failure; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVEF, left ventricular end-systolic volume; NYHA, New York Heart Association; OMT, optimal medical therapy; QoL, quality of life.



**Figure 3** Effects of sacubitril/valsartan vs. enalapril on a series of clinical outcomes in the PARADIGM-HF trial. Data are reported as hazard or rate ratios and 95% confidence intervals. From Refs.<sup>56-58</sup>. CV, cardiovascular; ED, emergency department; HF, heart failure.



**Figure 4** Data from PARADIGM-HF trial on the effect of sacubitril/valsartan vs. enalapril in the subgroups without ( $n = 7156$ ) and with defibrillator therapy back-up (with an ICD or CRTD device) ( $n = 1243$ ).<sup>62</sup> No significant interaction was found ( $P_{int}$  was not significant). CRTD, cardiac resynchronization therapy defibrillator; CV, cardiovascular; HF, heart failure; ICD, implantable cardioverter-defibrillator.

in ICD patients vs. no-ICD patients,<sup>51,52</sup> together with an underuse of ICD therapy.<sup>51</sup>

The wearable cardioverter defibrillator is a non-invasive option that has been used in patients at risk of SCD not eligible for an ICD. Moreover, the wearable ICD has been proposed for short-term use in patients with a high risk of ventricular tachyarrhythmias that is considered to be transient with some possibility to diminish over time (i.e. severe myocarditis or severe coronary disease prior to

revascularization) or when implant of a transvenous ICD is contraindicated (i.e. infection requiring ICD system removal). Data on safety of the wearable defibrillator have been collected in a prospective registry (WERIT-II) and during a median duration period of 90 days the rate of sustained ventricular tachyarrhythmias was 3% among patients with ischaemic cardiomyopathy and 1% among non-ischaemic patients ( $P = 0.02$ ).<sup>53</sup>

Recently, the role of the wearable cardioverter defibrillator was tested in a randomized controlled trial, the VEST study that randomized 2302 patients with recent myocardial infarction and LVEF <35% to a wearable defibrillator or watchful waiting. No reduction in the primary endpoint of SCD or 90-day arrhythmic death, while the reduction in total mortality found in the group with a wearable defibrillator became insignificant after correction with various approaches of the multiplicity of tests.<sup>54</sup> In this trial, problems of adherence to wearing the defibrillator complicated the ability to demonstrate a clinical benefit and only the on-treatment and per-protocol analyses showed a benefit in patients selected for high compliance to the wearable defibrillator.<sup>55</sup>

## Sacubitril/valsartan: impact on cardiovascular mortality and on sudden cardiac death

One of the most important innovation of recent years is the evidence of benefit of ARNIs and specifically of sacubitril/valsartan, at present the only agent available for clinical practice. The use of sacubitril/valsartan has been validated by the PARADIGM trial. In this

prospective randomized trial, 8442 patients with chronic HF, NYHA functional class II–IV, with LVEF  $\leq 35\%$  ( $\leq 40\%$  for the first of the 3 years of patient enrolment), were evaluated to compare the effect of sacubitril/valsartan 97/103 mg b.i.d. compared with enalapril 10 mg b.i.d., in addition to conventional treatment, in delaying time to first occurrence of either cardiovascular death or HF hospitalization.<sup>56</sup> Sacubitril/valsartan treatment was associated to a 20% reduction of the primary endpoint, with a 21% reduction of HF hospitalizations and 20% reduction of death for cardiovascular causes.<sup>56</sup> Over 80% of deaths in PARADIGM-HF had a cardiovascular cause, of which 45% were due to SCD. Among the causes of death observed in PARADIGM-HF, SCD accounted for 35.2% of all the deaths occurred in the sacubitril/valsartan arm and for 37.2% of all the deaths occurred in the enalapril arm.<sup>57</sup>

A complete picture of the benefits highlighted by the PARADIGM-HF trial is shown in *Figure 3*, where a series of endpoint of high clinical significance resulted favourably and significantly improved by sacubitril/valsartan compared with enalapril. As expected, non-cardiovascular mortality was not affected, thus stressing the need for multidisciplinary interventions on the most important comorbidities, related to diabetes, kidney function, etc.<sup>58–61</sup>

## Sacubitril/valsartan in patients with defibrillators or cardiac resynchronization therapy: the potential for a synergistic effect

In the PARADIGM-HF trial, sacubitril/valsartan therapy was associated to a significant 20% reduction of SCD when compared with enalapril therapy and the reduction of overall mortality and SCD was observed both in patients with and without ICD or CRT-D (*Figure 4*).<sup>62</sup> Unexpectedly, considering that all patients enrolled in the PARADIGM-HF trial had an LVEF  $\leq 35\%$ , only 15% of them had an implanted ICD and 7% a CRT device. Of note, both survival curves for death for cardiovascular causes and for SCD began to diverge early in patient without ICD/CRT-D and late (after 2 years) in those with ICD/CRT-D.<sup>62</sup>

The benefits of sacubitril/valsartan in SCD reduction led to investigate in detail the interaction between ARNI e device therapy in patients with HF. De Diego et al.<sup>63</sup> investigated the effect of angiotensin-neprilysin inhibition on ventricular arrhythmias compared with angiotensin inhibition in 120 HF with reduced LVEF patients with an ICD and remote monitoring. Appropriate shocks significantly decreased in the sacubitril valsartan arm from 6.7% to 0.8%. Furthermore, sustained and non-sustained ventricular tachycardia episodes significantly decreased. No differences were observed in atrial fibrillation incidence. Similar results have been reported by Martens et al.<sup>64</sup> Possible explanation for the antiarrhythmic effects of sacubitril/valsartan include the increase of beneficial natriuretic peptides leading to diuresis, vasodilatation, decrease of sympathetic tone, and of aldosterone levels. Furthermore, cardiac fibrosis suppression and structural remodelling as well as wall stress reduction may play a role.<sup>63–66</sup>

Another potential synergistic effect of drug therapy with sacubitril/valsartan and device therapy, in particular CRT, is the incremental

benefits on positive cardiac remodelling and prevention of HF progression. However, data from registries have shown that up to 30% of CRT patients do not receive guideline-directed optimal medical therapy.<sup>67</sup> As a matter of fact, it has been clearly demonstrated that optimal medical therapy is associated with better survival in patients with implanted ICD and CRT.<sup>68,69</sup> Furthermore, continuous remote monitoring of patients with implanted devices offers a unique opportunity to early detect HF impairment and to timely optimize medical therapy.<sup>70–72</sup>

## Considerations about guideline-adherent medical and device therapy in HF

- There are good reasons to support a synergistic effect between electrical treatments and guideline-adherent pharmacological therapy, with specific focus on sacubitril/valsartan, the last agent introduced in daily practice. The clinical target should be to implement these treatments in all the patients with a guideline-adherent indication, in order to ensure the most effective treatments for improving outcomes, according to a series of considerations:
- SCD may occur unexpectedly and despite the reduction that can be obtained with sacubitril/valsartan, combined with beta-blockers and MRAs, a residual risk persists and therefore the back-up of ICD therapy for termination of malignant ventricular tachyarrhythmias may ensure the best protection at long term and maximize cardiovascular outcomes for patients who have an indication according to guidelines.<sup>3,10</sup>
- Implant of a device such as ICD, CRT-D, or CRT-P according to guidelines indications should not be postponed beyond the period indicated by guidelines (3 months of optimal medical treatment)<sup>3,10</sup> and according to national rules for prescribing sacubitril/valsartan the latter treatment can be implemented either before or after device implant.
- An extension of the period for implementation and titration of beta-blockers, MRAs, ACE inhibitors, ARBs, or sacubitril/valsartan up to 9–12 months, rather than the usual 3 months waiting period, sometimes applied in case of new-onset HF in order to maximize left ventricular remodelling and increase LVEF, implies a small but significant risk of SCD (2–4%)<sup>73,74</sup> that may be particularly dramatic in young patients. Therefore, patients at higher risk of SCD (patients with severe left ventricular dysfunction, patients with non-sustained ventricular tachycardia) and younger patients should be absolutely prioritized for not delaying ICD implant.
- It is absolutely important to titrate beta-blockers, ACE inhibitors, ARBs, or sacubitril/valsartan up to maximum tolerated doses and this process has to be applied both before and after implant of an electrical device,<sup>75,76</sup> also with the advantage of the back-up of anti-bradycardia pacing provided by electrical devices in case of excessive bradycardia following an attempt of dosage increase for a beta-blocker.<sup>77</sup>
- An improvement in LVEF during long-term follow-up is a frequent finding after implant of an ICD, even above 35%, but it is not associated with lack of appropriate device interventions for malignant ventricular tachyarrhythmias thus suggesting that the risk of ventricular tachyarrhythmias and SCD is modulated by pharmacological treatments, but a residual risk persists, along with



time, that in appropriate patients may surely benefit from the rescue role of a back-up ICD.<sup>78-81</sup>

- In patients implanted with an ICD or a CRT-D appropriate ICD shocks (especially when clustered into electrical storms) are associated with a significant increase in the subsequent risk of all-cause death<sup>82,83</sup> and therefore the occurrence of shocks, even if appropriate, should be considered a warning sign of a worsening prognosis.<sup>84</sup> Implementation of sacubitril/valsartan is in these cases absolutely appropriate in order to implement the favourable effects of this agent on ventricular tachyarrhythmias.<sup>63,64,85</sup> and maximize the ability to improve outcome as well as quality of life<sup>86</sup> and ICD electrical atrial parameters.<sup>87</sup>
- The process of reduction of left ventricular volumes, with reversal of left ventricular geometry alterations and with improvement of systolic function occurring in HF after neuro-hormonal blockade (the so-called 'left ventricular reverse remodelling') is a key factor for outcome improvement, also in terms of prevention of SCD<sup>88,89</sup> and is more pronounced with ARNI as compared with ACE inhibitors, thus supporting the rationale for instituting sacubitril/valsartan in all the patients who can be eligible for ARNI treatment.<sup>90</sup>
- CRT is a very effective non-pharmacological treatment in appropriately selected patients,<sup>91,92</sup> and structural left ventricular reverse remodelling is a key factor in determining the clinical and outcome benefits at long term.<sup>93</sup>
- CRT is primarily indicated in patients with LBBB and the haemodynamic benefit is related to correction of the electro-mechanical associated with the conduction disturbance. It is noteworthy that LBBB-associated remodelling appears to result in a limited reverse remodelling during guideline-adherent pharmacological treatment as compared with non-LBBB patients, thus indicating that in patients with LBBB implant of a CRT device, following implementation of drug treatment for a reasonable period of time, should not be deferred, waiting for an improvement of LVEF induced by pharmacological treatments that has a very limited chance to occur.<sup>94</sup> Moreover, after implant of a CRT device, there is the possibility of an increase in systolic blood pressure that may allow initiation of drugs that were not tolerated or could not be administered for hypotension before implant, such as sacubitril/valsartan, in line with the concept of additive, if not synergistic effects between CRT and ARNI.
- Remote monitoring offers the possibility to detect signals and measures data from pacemakers, ICD, and other implantable devices. The aim is to detect impending HF decompensation and to consequently take decisions on drug dosages and patients care. Unfortunately, the high expectations of benefit were not confirmed by the randomized studies performed so far.<sup>95</sup> However, some prospective non-controlled studies recently performed, indicate a positive impact on patient management with the most recent device algorithms able to collect data from multiple sensors,<sup>71,96</sup> with need to better assess the impact of these technologies through randomized controlled studies for a more detailed assessment.
- The dialogue and synergistic actions and decisions of cardiologists involved in electrophysiology and device therapy and cardiologists dedicated to HF care is important and will continue to be important for future treatments, either pharmacological or non-pharmacological.<sup>12</sup>
- The value of ICD back-up to minimize the residual risk of SCD in patients with an established indication and who are candidate to initiate sacubitril/valsartan is further supported by some data on the initial period of treatment with sacubitril/valsartan.<sup>97-99</sup> These

data are observational and related to case reports or to a collection of pharmacovigilance reports and even if they do not put into question the evidence of benefit of sacubitril/valsartan on SCD at long term, are of interest for considerations on the time course and the determinants of the effect of this agent on arrhythmogenesis and the cardiac substrate. The reverse left ventricular remodelling induced by sacubitril/valsartan may actually be the key mechanism for reducing SCD<sup>7</sup> but some months are required for this process to occur, thus with exposure to a residual risk of SCD especially in the first 3 months after treatment initiation.<sup>99</sup> These data, even if observational, strongly suggest the advantages of a combined use of sacubitril/valsartan and ICD, when indicated according to guidelines, without delaying the device implant, in order to fully achieve the benefits that these two treatments may independently exert, and with the potential for synergistic effects.

## Organizational implications for maximizing the implementation of drugs and devices in patients at risk

In view of the increasing burden of cardiovascular disease and specifically HF, there is need for improving knowledge on treatments for HF and SCD prevention of proven efficacy according to evidence-based medicine, as implemented in consensus guidelines recommendations. General practitioners, internists, physicians involved in HF care and emergency medicine, as well as electrophysiologists should dialogue and collaborate more strictly, in a perspective of patient-centred care, organizing network for appropriate patient referral both for pharmacological and device therapy. Indeed, it has been reported that in Sweden an important and substantial awareness gap was found through a survey among the medical community, thus explaining the limited referral rates and utilization of device therapy in HF patients.<sup>100</sup>

## Conclusions

In order to maximize the implementation of all the available treatments, either pharmacological or non-pharmacological, patients with HF should be included in virtuous networks with a dialogue between all the physician involved, specifically cardiologists involved in electrophysiology and device therapy and cardiologists dedicated to HF care.

A strict collaboration between specialists is absolutely needed since there are potential synergistic effects between drug therapies acting on neuro-hormonal and sympathetic activation (specifically sacubitril/valsartan) and device therapy, in particular CRT, with benefits in terms of reverse cardiac remodelling, slowing of HF progression and prevention of ventricular tachyarrhythmias.

It is absolutely important to titrate beta-blockers, ACE inhibitors, ARBs, or sacubitril/valsartan up to maximum tolerated doses and this process has to be applied both before and after implant of an electrical device.

An extension of the period for implementation and titration of beta-blockers, MRAs, ACE inhibitors, ARBs, or sacubitril/valsartan up to 9–12 months, rather than the usual 3 months waiting period, implies a small but significant risk of SCD (2–4%)<sup>73,74</sup> that may be particularly dramatic in young patients. Therefore, patients at higher risk of SCD (patients with severe left ventricular dysfunction, patients with non-sustained ventricular tachycardia) and younger patients should be prioritized for not delaying ICD implant.

## Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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