Primary Prevention of Sudden Cardiac Death in Patients with Heart Failure: How Effective is Current Pharmacologic Therapy?

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Abstract

Sudden cardiac death is the most common cause of death in the early stages of heart failure. Implantable cardioverter-defibrillator therapies substantially reduce sudden cardiac death but incur morbidity and are expensive, so are recommended only after failure of optimal medical therapy. Guidelines recommend simultaneous first-line therapy with an angiotensin converting enzyme inhibitor and a beta blocker for heart failure with reduced ejection fraction, with diuretic therapy for symptom relief. The all-cause mortality benefit of angiotensin converting enzyme inhibitors (or angiotensin receptor blockers) in this setting is largely attributable to reduced deaths related to disease progression. Addition of a beta blocker improves both all-cause survival and rates of sudden cardiac death. Where symptoms persist, introduction of a mineralocorticoid receptor antagonist is recommended and can reduce sudden cardiac death. If symptoms continue, substitution of the angiotensin converting enzyme inhibitor with the angiotensin receptor nephrilysin inhibitor sacubitril/valsartan significantly reduces all-cause mortality, with the benefit arising from fewer deaths from both sudden cardiac death and worsening heart failure. Further medical interventions should be instituted in specific situations as required. Disappointingly, despite evidence-led guidelines, approximately a quarter of patients who have heart failure with reduced ejection fraction do not receive standard therapy with an angiotensin converting enzyme inhibitor and beta blocker. It remains to be seen if recent guidelines for successive interventions in the event of non-response to standard therapy are more effectively adopted.

Keywords: ACE inhibitor; Beta blocker; Drug therapy; Heart failure; Prevention; Sacubitril/Valsartan; Sudden cardiac death

Introduction

Despite improvements in survival after diagnosis of chronic Heart Failure (HF) in recent years [1], mortality remains high. A large US study recently reported a one-year mortality rate of 30% [1] and a systematic review demonstrated that five-year mortality is higher after diagnosis of HF than for either cancer or stroke [2]. Sudden Cardiac Death (SCD) is the most common cause of death in the early course of HF when symptoms are mild, exceeding deaths due to pump failure [3-5]. In a prospective observational study of 979 patients with mild-to-moderate symptomatic HF managed under routine conditions, SCD accounted for 9% of all deaths over a median follow-up of 44 months [5]. A longitudinal study of 960 HF outpatients identified SCD as the cause of 16% of all deaths over a seven-year period, with the proportion remaining relatively constant over time [6].

The introduction of Implantable Cardioverter-Defibrillator (ICD) therapies in the 1990s represented a major step forward for improving long-term survival after HF [7]. ICD devices correct left ventricular arrhythmias, lowering the risk of SCD in patients with HF with reduced Ejection Fraction (HFrEF) due to ischemic or non-ischemic heart disease [8,9]. A recent study has reported further significant reductions in SCD when ICD therapy was combined with cardiac resynchronization therapy in patients with non-ischemic HFrEF [10]. Although ICDs remain a mainstay of SCD prevention in HF, there is an increasing emphasis on medical management to avoid ICD intervention [11]. Moreover, implantation of an ICD is expensive and incurs peri-procedural morbidity, with a risk of long-term complications, and not all patients experience a benefit. For instance, in the elderly in whom the potentially diminished lifespan and greater presence of comorbidities makes the benefit of primary prevention of SCD by ICD less certain [12]. Careful patient selection and close monitoring is essential: for example, arrhythmia may be a marker for decompensated HF with an increased risk of death after shock therapy [13]. The European Society of Cardiology (ESC) guidelines published in 2016 recommend ICDs as primary prevention only in certain categories of patients when optimal medical therapy has been prescribed for at least three months and left ventricular EF remains ≤55% [14].

The ESC guidelines recommend that patients with symptomatic HFrEF receive first-line therapy with an Angiotensin Converting Enzyme (ACE) inhibitor and a beta blocker, to reduce the risk of hospitalization for HF and death [14]. An Angiotensin Receptor Blocker (ARB) can be substituted if ACE inhibitors are not tolerated or are contraindicated. Additionally, a diuretic is recommended to reduce signs and symptoms of congestion [14]. If symptoms persist despite optimal use of these pharmacotherapies, a Mineralocorticoid Receptor Antagonist (MRA) can be added, after which replacement of the ACE inhibitor with the Angiotensin Receptor Nephrilysin Inhibitor (ARNI) sacubitril/valsartan is advised if the patient still remains symptomatic. Use of other drugs (such as the sinoatrial node inhibitor ivabradine, hydralazine and isosorbide dinitrate, or digoxin) should be instigated in specific clinical situations. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline for the management of HF also recommends combined treatment with an ACE inhibitor or ARB plus a beta blocker in

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HFrEF, with additional therapies in specific clinical presentations [15]. Antiarrhythmic drugs, which would seem a logical means of reducing SCD due to ventricular arrhythmias, have not been shown convincingly to prevent SCD in patients with ventricular arrhythmias. However, they can improve overall mortality [16] and hence are recommended as adjunctive therapy in very selected circumstances [17].

The continuing high rate of SCD in HF, however, raises questions about the effectiveness of current strategies for avoiding SCD--and, indeed, about how well treatment guidelines are implemented in routine practice.

Etiology and Diagnosis of SCD in HF

The etiology of SCD is complex [18]. It frequently arises from electrical causes, notably ventricular arrhythmias (predominantly ventricular tachycardia) and bradycardia [14,19]. Progression from ventricular tachycardia to ventricular fibrillation is the most common terminal event, but it is often uncertain if this was the primary trigger for SCD or if fibrillation occurred secondary to myocardial ischemia, Myocardial Infarction (MI) or other events rather than from HF per se. Structural remodeling of the left ventricle, characterized by hypertrophy, dilation and fibrosis secondary to excessive activation of the Renin-Angiotensin-Aldosterone (RAAS) system increases risk of an event [20], and scar formation following MI or elevated filling pressures can induce ventricular arrhythmias in a remodeled heart. Excessive sympathetic activation is also a contributory factor, triggering imbalances in electrolyte currents which predispose the ventricular myocardium to abnormal depolarizations and arrhythmias. Less frequently, SCD is caused by coronary, cerebral or aortic vascular causes [14]. This varied etiology confounds a firm definition, but generally cardiac arrest in a patient with HF known recently to be in their usual state of health is regarded as SCD.

Diagnosing the cause of SCD can thus be difficult. It is too simplistic to equate SCD with arrhythmia, although often arrhythmia is speculatively stated as the underlying event. The high prevalence of underlying ischemic heart disease and previous MI in patients with HF is a major confounder. MI as the cause of SCD in patients with HF is often detected only on autopsy, but since autopsy is not always performed MI can be substantially underreported. One review of data from the ATLAS trial found that SCD was attributed to acute MI in 28% of autopsied cases compared to only 4% of non-autopsied cases [21]. Patients with SCD often die unwitnessed at home, or before they reach hospital, making diagnosis of the cause more challenging. Conversely, a severely ill patient may have death recorded as progressive HF instead of SCD. Indeed, some early clinical trials grouped death due to progressive disease in more severe cases of HF as the same entity [22]. These difficulties contribute to the variation in reported rates of SCD in observational studies [5,6,23].

RAAS Inhibition and SCD

Upregulation of the RAAS in response to reduced cardiac output plays a key role in the development of structural and electrical remodeling in HF, and thus the development of atrial and ventricular arrhythmias [24]. Accordingly, treatment with an ACE inhibitor or ARB might be expected to reduce the rate of arrhythmia-induced SCD. Meta-analyses have confirmed that RAAS inhibition reduces the risk for atrial fibrillation across various clinical settings [25] and in HF [26,27]. One recent meta-analysis of 15 trials found that RAAS inhibition lowered the risk for atrial fibrillation by 25% across all indications, and by 42% in HF patients [26]. The V-HeFT II study has also demonstrated a reduction in pre-existing ventricular arrhythmias after initiation of enalapril, and a lower rate of new ventricular arrhythmias compared to hydralazine-isosorbide dinitrate, in patients with predominantly mild-to-moderate HF [28]. In terms of structural pathologies, ACE inhibitor or ARB therapy can also modulate the progression of ventricular dilation by reducing ventricular afterload and preload, reducing remodeling secondary to hemodynamic and neuroendocrine effects, and reducing risk for myocardial ischemia and MI [29]. ACE inhibitors reduce the risk of MI in high-risk patients without HF [30-32] and are recommended in asymptomatic patients with left ventricular systolic dysfunction [14]. Evidence for a significant reduction in MI for ACE inhibitors in HF is less convincing [33]. As discussed above, however, MI is likely to be underdiagnosed in the setting of HF, an effect that may partly account for this observation.

A number of major trials—including the CONSENSUS study of more than 6,000 patients [34]—have demonstrated a reduction in all-cause mortality in HF patients given an ACE inhibitor (Table 1) [22,34-36]. An effect on SCD is more complex to establish. In the CONSENSUS II study, performed in patients with severe HF, there was no difference in the rate of SCD for enalapril versus placebo; the effect of ACE inhibition was restricted to patients with progressive HF [38]. This is perhaps not unexpected given the preponderance of death due to progressive disease in more severe cases of HF. In the V-HeFT II trial, undertaken in 804 men in whom the NYHA class was II or III in >90% of cases, two-year mortality was significantly lower under enalapril treatment than hydralazine-isosorbide dinitrate (16% vs. 25% in controls, p=0.015) [36] and the survival benefit was largely accounted for by a decrease in SCD [28]. This observation has not been replicated in other studies, however (Table 1), and even in the cohort of enalapril-treated patients the rate of SCD exceeded 10% over a two-year period (10.8% vs. 16.2% with placebo, p=0.004) [28]. A meta-analysis of randomized, placebo-controlled trials of ACE inhibition found no significant effect on SCD or presumed arrhythmic deaths (odds ratio [OR] 0.91; 95% CI 0.73, 1.12) [33]. ACE inhibitors may reduce the risk for SCDs in non-HF patients with previous MI [39] but evidence for a reduction in SCD after MI in patients with HF or left ventricular dysfunction, is mixed [35,40,41].

Fewer studies have reported SCD as an outcome measure for ARB therapy in HF. The ELITE study, which compared losartan versus captopril in patients with NYHA class II or III HF who had not previously received an ACE inhibitor, showed a lower rate of both all-cause mortality and SCD under losartan [42]. However, the far larger ELITE II study found a non-significant trend to more SCD with losartan [43], with similar findings in the OPTIMAAL trial of 5,477 patients with acute MI and HF [44]. ARBs are thus currently considered an alternative therapy in HF patients who cannot tolerate ACE inhibitors.

Overall, the all-cause mortality benefit of ACE inhibitors or ARBs in HF appears largely due to an improvement in deaths related to disease progression, with only limited evidence for a reduction in SCD [45].

Beta Blockers and SCD

Beta blockers inhibit the effect of elevated noradrenaline levels induced by sympathetic overactivation, and restrict left ventricular remodeling [20], with reduced rates of ventricular tachycardia [46]. One recent meta-analysis of various beta blockers in 21 randomized trials of HF patients, 18 of which were versus placebo, found that the significant improvement in mortality observed under beta blocker therapy (OR 0.71 [95% 0.64, 0.80] versus controls) was matched by a reduction in SCD (OR 0.73 [95% 0.61, 0.88]) [47]. Another meta-

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analysis, which included only those trials which reported SCD rates and which excluded comparative trials of beta blockers versus ACE inhibitors, also showed that beta blocker therapy is associated with a similar reduction in both SCD (OR 0.69, 95% CI 0.62, 0.77) and all-cause mortality (0.67 [95% CI 0.59–0.76]) [48].

When given in combination with an ACE inhibitor, adding the anti-adrenergic effect of beta blockade to RAAS inhibition improves all-cause survival versus ACE inhibition alone, with a significant improvement for SCD demonstrated in most trials (Table 2) [46,49-54]. This underpins current recommendations that patients with stable, symptomatic HFrEF receive combined therapy [14]. Beta blockers are also advised in patients with asymptomatic left ventricular systolic dysfunction with a previous MI to lower the mortality risk [14].

Although earlier initiation of beta blockade could theoretically be advantageous, since the sympathetic nervous system is activated earlier than the RAAS in HF [55], there is no convincing evidence to support monotherapy with a beta blocker prior to ACE inhibitor therapy [4,56]. In the CIBIS III study, where 1,010 patients with NYHA class II or III HF were randomized to bisoprolol or enalapril for six months, followed by combined therapy for up to 24 months, there was a trend to fewer SCDs under bisoprolol, but this was partly offset by more pump failure deaths compared to enalapril [4] and overall mortality was similar [56]. In the smaller CARMEN study no difference was observed for SCD [29,30].

In the smaller CARMEN study no difference was observed for SCD (0.67 [CI 0.59–0.76]) [48]. The ARNI sacubitril/valsartan combines neprilysin inhibitor and an angiotensin receptor-neprilysin inhibitor ivabradine [33] and hydralazine with isosorbide dinitrate [34], countering the adverse effects of neurohormonal activation including vasoconstriction, sodium retention and maladaptive remodeling. The ARNI sacubitril/valsartan combines neprilysin inhibition with RAAS inhibition, and has been shown in the double-blind randomized PARADIGM trial of 8,442 patients with HFrEF to reduce all-cause mortality significantly compared to enalapril [63]. A subsequent analysis of the mode of death in PARADIGM showed that the mortality benefit was derived both from fewer deaths due to SCD and to worsening HF (Figure 1) [64].

ARNI therapy with sacubitril/valsartan is advised as a replacement for ACE inhibition where patients do not respond to addition of a MRA [14]. The neprilysin inhibitor sacubitril increases levels of vasoactive peptides such as natriuretic peptides and bradykinins [61,62], countering the adverse effects of neurohormonal activation including vasoconstriction, sodium retention and maladaptive remodeling. The ARNI sacubitril/valsartan combines neprilysin inhibition with RAAS inhibition, and has been shown in the double-blind randomized PARADIGM trial of 8,442 patients with HFrEF to reduce all-cause mortality significantly compared to enalapril [63]. A subsequent analysis of the mode of death in PARADIGM showed that the mortality benefit was derived both from fewer deaths due to SCD and to worsening HF (Figure 1) [64].

Additionally, but with weaker levels of evidence, the sinus node inhibitor ivabradine [33] and hydralazine with isosorbide dinitrate [14,15] can be considered in particular circumstances. Ivabradine, indicated for use in patients with symptomatic HFrEF in sinus rhythm with a resting heart rate of 70 bpm or higher, exerts no effect on SCD rates [65]. For hydralazine-isosorbide dinitrate, an early trial showed a reduction in SCD compared to ACE inhibition [36], but data on its effect when combined with contemporary therapy are lacking.

**Medical Intervention on SCD in the Real World**

Key recommendations for medical management of symptomatic HF are still not applied universally. Even ACE inhibitors—the cornerstone of management for more than 25 years—are not prescribed in all cases of HF. An analysis of 4,605 patients with HF in 15 European countries, published in 2015, reported that 23.8% received inappropriate drug prescriptions, defined as either no ACE inhibitor or no beta blocker, or inadequate doses of either drug [66]. In the US, one large registry analysis found that only 61.1% of patients received medical therapy as per guidelines [67], while a Spanish assessment reported that beta-blockers and ACE inhibitors were being prescribed in 75.6% and 53.4% of patients with HFrEF [68]. ESC guidelines recommend that both ACE inhibitors and beta blockers should be up-titrated to the maximum tolerated dose [14] in view of evidence for a dose-related association with mortality, particularly for beta blocker therapy [54] but also, to a lesser extent, for ACE inhibitors [69,70]. Obtaining data on whether dosing is being optimized is challenging since the dose must be individualized in each case, but the available evidence is not encouraging [66,71].

| Study         | Mean LVEF | NYHA III/IV | n | ACE inhibitor | Comparator | Protocol-specified adjunctive medical therapy | Follow-up | All-cause mortality | SCD |
|---------------|-----------|-------------|---|----------------|------------|-------------------------------------------|-----------|---------------------|-----|
| SOLVD [22]    | 25%       | 281/1457/781/43 | 2569 | Enalapril | Placebo | None specified | Mean 41 months | 35.2% vs. 39.7% (p=0.004) | No significant effect (8.2% vs. 8.8%) |
| CONSENSUS [34] | -         | -           | 253 | Enalapril | Placebo | Digitalis Diuretics | 6 months | 26% vs. 44% (p=0.001) | No significant effect (14% vs. 14%) |
| SAVE [35]     | 31% a,b   | Not reported | 2231 | Captopril | Placebo | None specified | Mean 42 months | 20% vs. 25% (p=0.019) | No significant effect (5.6% vs. 6.7%) |
| V-HeFT II [28,36] | 29%     | 46/410/345/3 | 804- | Enalapril | Hydralazine + isosorbide dinitrate | None specified | 2 years | 18% vs. 25% (p=0.016) | 10.8% vs. 16.2% (p=0.024) |
| SOLVD [37]    | 28% a,b   | 2821/1397/0/0 | 4228 | Enalapril | Placebo | No drug therapy for HF | Mean 37.4 months | 14.8% vs. 15.8% (p=0.30) | No significant effect (4.6% vs. 5.0%) |

*All patients had myocardial infarction 3–16 days prior to randomization; a All male. LVEF: Left Ventricular Ejection Fraction; NYHA: New York Heart Association

Table 1: Sudden Cardiac Death (SCD) in key randomized, double-blind trials of Angiotensin Converting Enzyme (ACE) inhibitor therapy without concomitant beta blocker therapy.
SCD remains a major source of mortality in HF, particularly in the early stages. A focus on lowering the risk for SCD must, of course, take into account the competing risks to which HF patients are exposed. Any reduction in SCD could potentially increase risk of death from pump failure, progressive heart disease if there is no effect on the underlying pathology. SCD tends to occur earlier than deaths due to pump failure [72] so a reduction in SCD could extend life expectancy. Nevertheless, lower rates of SCD are only meaningful if achieved in the context of an overall reduction in mortality. Current guidelines recommend that all symptomatic patients with HFrEF receive combination therapy with an optimally-dosed ACE inhibitor and beta blocker, with a succession of further medical therapies to be instituted in the event of non-response or intolerance. This management pathway prioritises a reduction in all-cause mortality, but would also be expected to achieve a reduction in SCD, largely due to beta blockade and, in the event of non-response to adjunctive MRA treatment, use of sacubitril/valsartan. The importance of pursuing this pathway vigorously, in contrast to simply starting an ACE inhibitor with or without a beta blocker, is evident. Even in controlled trials of combined therapy, with protocol-driven prescribing and dosing patterns, as many as 4% of patients with mild-to-moderate HF die from SCD per year [51]. Disappointingly, the available data suggest that approximately one in four HF patients does not receive both an ACE inhibitor and a beta blocker, even though it is several years since the combination was established as best practice. It remains to be seen if the recent ESC guidelines [14], including simultaneous initiation of beta blockers and ACE inhibition for symptomatic HF, and progression to a MRA or sacubitril/valsartan if symptoms persist, are more effectively adopted.

A growing advocacy now encourages the use of systematic ventricular assist devices in ambulatory HF patients, on the basis of the misconception that the clinical response to medical therapy is poor. However, annual mortality rates in HF patients with mild-to-moderate symptoms and normal renal function, especially in non-ischemic heart disease have now fallen to below 5% [73]. It is therefore important to emphasize that effective medical therapy in patients with HF in fact modifies the clinical course of the disease, including SCD, and that HF physicians must seek to optimize medical intervention in all patients [74].

**Disclosures**

Javier Diez has served as an advisor and/or as a speaker for Saint Jude Medical and Boston Scientific. Ignacio Garcia-Bolao has served as an advisor, proctor and/or as a speaker for Novartis, Bayer, Merck, Sharp and Dohme, and Sarfez Pharmaceuticals Inc. Ignacio Garcia-Bolao has served as an advisor and/or as a speaker for Saint Jude Medical and Boston Scientific.

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