Chapter 10

Role of Traditional Heart Failure Medications on Sudden Cardiac Death Prevention in Patients with Cardiomyopathy

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Additional information is available at the end of the chapter

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1. Introduction

Sudden cardiac death (SCD) remains a major public health issue with an estimated annual incidence of 300,000 cases per year. The ACC/AHA/ESC 2006 guidelines define SCD as "death from an unexpected circulatory arrest, usually due to a cardiac arrhythmia occurring within an hour of the onset of symptoms" [1]. Trials on traditional antiarrhythmic drugs have failed to show any mortality benefit even when compared to placebo or implantable cardiovertor defibrillators (ICDs) [2]. Most of the patients experiencing sudden cardiac arrest have left ventricular ejection fraction (LVEF) > 50%, with the majority of these patients having a history of coronary artery disease (CAD). Majority of Sudden Cardiac Arrests (85-90%) are the first arrhythmic event a patient experiences[3].Beta blocker therapy, Angiotensin enzymes inhibitors (ACE-I) as well as aldosterone antagonists have been shown to decrease the risk of sudden cardiac death especially in post myocardial infarction (MI) patients and in patients with congestive heart failure. This chapter will review the data on the effects of traditional heart failure medications, especially beta blockers, Renin Angiotensin system blockers, as well as Statin therapy on sudden cardiac death in post MI patients and in patients with cardiomyopathy.

2. β-blockers and sudden cardiac death prevention

2.1. Potential mechanisms of β-blockers on sudden cardiac death prevention

Multiple studies have suggested that the major mechanisms responsible for the cardiac arrhythmias associated with sudden cardiac death are ventricular tachycardia (VT) and

ventricular fibrillation (VF). For these arrhythmias to occur, an interaction between substrate (ventricular enlargement and/or hypertrophy, myocardial scar due to ischemic or non-ischemic injury) and triggers (electrolyte abnormalities, changes in the sympathetic and parasympathetic activity, neuro-humeral factors, and premature ventricular contractions) is necessary to initiate reentry leading to ventricular tachycardia and ventricular fibrillation (Figure 1).

Many anatomic or functional substrates such as coronary artery disease, cardiomyopathy or primary electrophysiological disease can lead to sudden cardiac death. Progression of these disease states leads to sympathetic activation. At the cellular level, sympathetic and vagal denervation caused by myocardial ischemia leads to an increase in interstitial potassium and intracellular calcium concentrations [3]. This results in slowed conduction and induces spontaneous electrical activity. All these factors contribute to reentry; which is the most common mechanism of ventricular tachycardia in patients with ischemic heart disease [4].

As myocardial ischemia progresses the neurohumoral system exerts further stimulation of the sympathetic system and the renin-angiotensin-aldosterone system (RAAS). This neurohumoral cascade leads to increasing levels of norepinephrine, angiotensin II, aldosterone, endothelin and vasopressin. Increased norepinephrine levels lead to increased preload and after-load, which in turn increases myocardial oxygen demand. Furthermore, the activation of these systems promotes fibrosis and necrosis [5-7], which over time will lead to cardiac remodeling, left ventricular dilatation, fibrosis and progression into heart failure [8].

Three types of β-receptors are known, designated β_1, β_2 and β_3 receptors. β_1 receptors are located mainly in the heart and in the kidneys and are down regulated in heart failure due to chronically elevated norepinephrine levels. β_2 receptors are located mainly in the lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle. β_3 receptors are located in fat cells. $\beta_1$and $\beta_2$receptors activate cyclic adenosine mono-phosphate (cAMP), which acts as a second messenger and leads to increased contractility (inotropy), increased heart rate (which increases myocardial oxygen demand), increased conduction velocity (which may promote reentry) and have a positive lusitropic effect, which improves active relaxation [9]. $\beta_2$receptors promote the release of renin, which in turn activates angiotensin II and aldosterone, both of which elevate the blood pressure, increase after-load, promote potassium wasting and activate fibroblasts leading to fibrosis.

β-blockers exert their protective effect on the heart via different mechanisms. β-blockers reduce ischemia by decreasing the heart rate, which is the major determinant of myocardial oxygen demand[10]. At the cellular level, β-blockers decrease electrical excitability by limiting calcium entry via catecholamine-dependent channels [9]. All this helps decrease left ventricular mass and volume, decrease LV end diastolic pressure and improve LV function [11]. β-blockers are also considered a class II antiarrhythmic medications. They decrease spontaneous depolarization, prolong the sinus node cycle length, atrioventricular conduction times and atrioventricular refractory periods. They also increase the excitable gap, which prevents reentry and increases the success of anti-tachycardia pacing [12].

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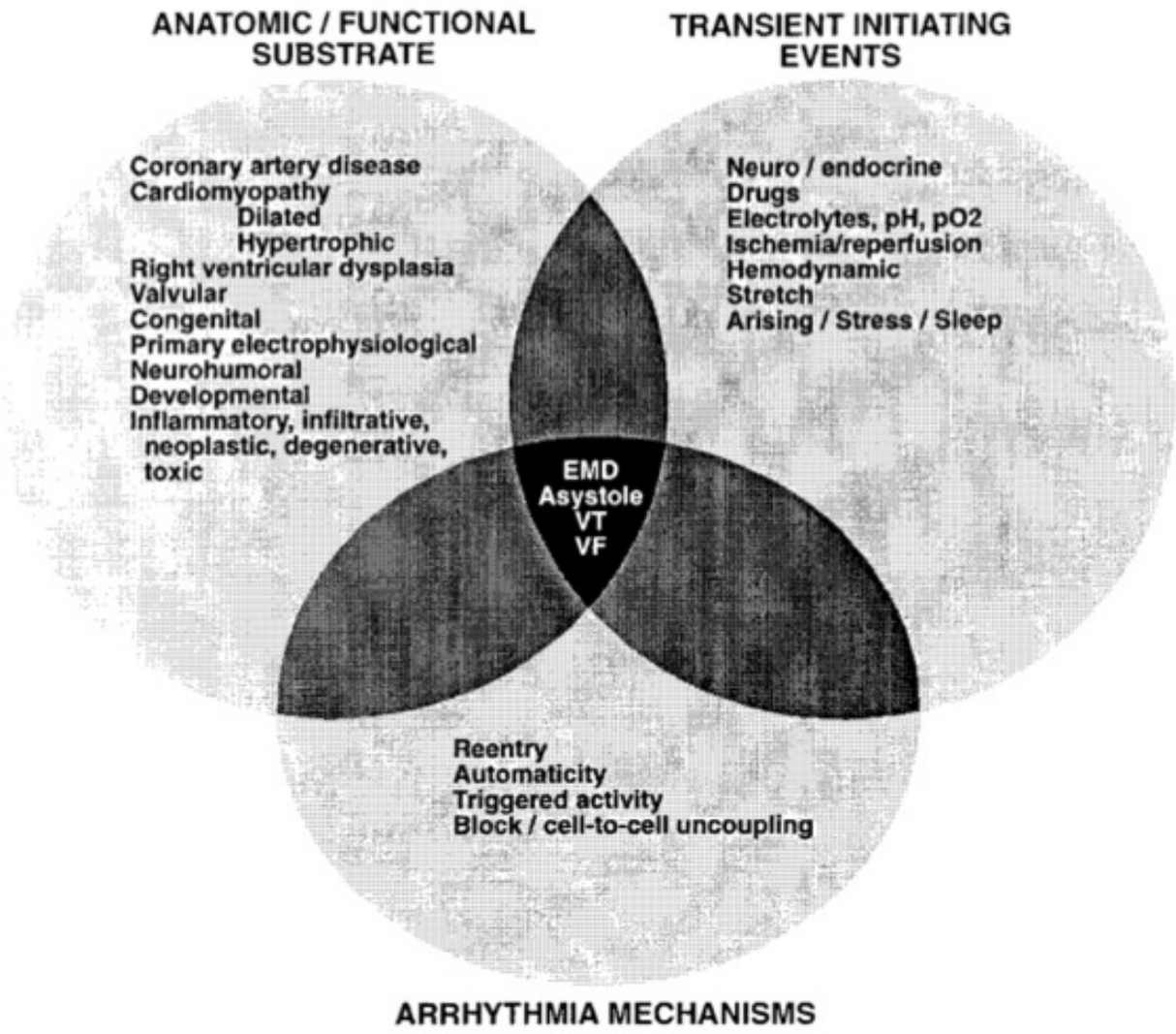

Figure 1. Venn diagram showing interaction of various anatomic/functional and transient factors that modulate potential arrhythmogenic mechanisms capable of causing sudden cardiac death (From Douglas P. Zipes and Hein J. J. Wellens "Sudden Cardiac Death" Circulation. 1998; 98:2334-2351, With Permission)

2.2. Effect of β-blockers on sudden cardiac death prevention in post myocardial infarction patients

β-blockers therapy has been studied in the post myocardial infarction (MI) patients since 1965 when propranolol was found to reduce mortality after acute MI[13]. Pivotal trials such as the *Norwegian Multicenter Study Group* (utilizing Timolol at a starting dose of 5 mgs/day with target of 20 mgs/day), *β-blocker Heart Attack Trial* (*BHAT*, utilizing propranolol at a dose of 180 to 240 mgs/day) in the 1980s showed reduction in total mortality and sudden cardiac death [14, 15]. As therapies post- MI evolved and ACE-I inhibitors were introduced several other trials, including the *Survival and Ventricular Enlargement (SAVE)* and *Acute Infarction Ramipril Efficacy (AIRE)* trials demonstrated that β-blockers provided additional reduction in cardiovascular mortality independent of the use of ACE-I inhibitors[16, 17].

A meta-analysis evaluated several randomized clinical trials looking at the benefits of β-blockers treatment post MI. This analysis revealed a significant reduction in mortality with β-blocker therapy (HR= 0.77, 95% confidence interval: 0.69 to 0.85)[18]. Secondary to lack of physician prescription of β-blocker therapy despite evidence of its benefit the Cooperative Cardiovascular Project was undertaken. This was an observational report that evaluated the care of 200,000 Medicare patients with the diagnosis of MI. Only 34% of the patients were given β-blockers. The mortality reduction for patients who were prescribed beta- blockers at the time of discharge from the hospital was 40% [19].

A sub-analysis of *BHAT* trial showed that propranolol decreased mortality and sudden cardiac death in the subset of patients with depressed LVEF [20]. But it was not until the *Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction trial (CAPRICORN)* was a focus also placed on AMI patient with left ventricular (LV) dysfunction. *CAPRICORN* was a multinational prospective, randomized trial recruiting patients with recent acute MI (3-21 days) and left ventricular (LV) dysfunction with ejection fraction (EF) ≤ 40%. A total of 984 patients were placed on placebo and 975 patients were allocated to Carvedilol therapy post MI with an average follow up of 1.3 years. The initial starting dose was 6.25 mgs orally twice daily with target dose of 25 mgs orally twice daily. All-cause mortality was lower in the carvedilol group than in the placebo group (Hazard Ratio of 0.77, 95% CI of 0.60—0.98, p=0.03) [21]. Several secondary prevention trials had demonstrated significant reductions in ventricular arrhythmias but it was not until *CAPRICORN* that patients with substantial left ventricular dysfunction also demonstrated a significant reduction in malignant ventricular arrhythmias (HR of 0.37 (95% CI 0.24 to 0.58; $p < 0.0001$)[22]. It is important to emphasise that in this trial that 98% of the patients were treated with an ACE-I inhibitor. The effect of ACE-I inhibitors on reduction of ventricular arrhythmias will be discussed in a later section.

2.3. Effect of β-blockers on sudden cardiac death prevention in patients with congestive heart failure

β-blockers were initially thought to be contra-indicated in patients with heart failure due to their negative inotropic effects in the short term. However, later studies showed they consistently improve morbidity and mortality in patients with heart failure; they also lead to a 40% reduction in hospitalization. Currently, there are 3 medications available in the United States that have shown mortality benefits in patients with heart failure. Carvedilol is a non-selective β_1, $\beta_2$and α_1 blocker that was tested in two trials and was shown to improve mortality. The first is the *US Carvedilol trial* which enrolled 1094 patients with congestive heart failure (CHF) and left ventricular ejection fraction (LVEF) of ≤ 35%. Patients were assigned to four treatment protocols based on exercise capacity. Within each protocol patients were assigned to either placebo (n=398) or Carvedilol (n=696). Although this trial was not designed as mortality trial, itdemonstrated a 65% decrease in the risk of death with Carvedilol compared to placebo ($p<0.001$). Sudden death was reduced from 3.8% in the placebo group to 1.7% in the Carvedilol group [23].

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The Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial examined the effect of Carvedilol in 2289 patients with severe CHF, defined as dyspnea at rest and LVEF ≤ 25%. This trial validated the mortality benefit of Carvedilol in patients with severe heart failure with a 50% reduction in all-cause mortality (HR 0.50, 95% CI of 0.10-0.63) [24]. Unfortunately this trial did not have data available on the impact of Carvedilol on sudden death.

The Cardiac Insufficiency Bisoprolol Study (CIBIS) II was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated the efficacy of Bisoprolol in reducing the incidence of all-cause mortality in heart failure. Bisoprolol is a $\beta_1$receptor blocker, and the target dose was 10 mgs daily. All patients enrolled received standard therapy with diuretics and ACE-I inhibitors. A total of2647 patients with New York Heart Association (NYHA) class III or IV with LVEF of ≤ 35% were randomized to either Bisoprolol (n=1327) or placebo (n=1320). This study was stopped prematurely because Bisoprolol showed a significant mortality benefit. Death from any cause in the Bisoprolol group was 11.8% versus 17.3% in the placebo group (HR, 0.66, 95% CI, 0.54-0.80). Sudden death was also reduced in the Bisoprolol group by 42% compared to the placebo group [25].

The Metoprolol CR/XL Randomized Intervention Trial in CHF (MERIT-HF) was a double-blind randomized controlled study which included 3991 patients with CHF, NYHA class II-IV with an LVEF of ≤40%. These patients were stable on optimal medical therapy. This trial evaluated whether controlled release/extended release formulation of Metoprolol taken daily would reduce mortality in this patient population. The starting dose was 12.5 mgs once daily with target dose of 200 mgs orally once daily. Patients were randomized to Metoprolol CR/XL (n=1990) up-titrated to 200 mg daily over and eight week period of time or placebo (n=2001). The trial demonstrated a 34% relative risk reduction in all-cause mortality with controlled release/extended release formulation of Metoprolol. Similar, to CIBIS II, MERIT–HF showed a 41% relative risk reduction of sudden death [26].

2.4. Effect of β-blockers on sudden cardiac death prevention in patients who survived a cardiac arrest

In patients who have implantable cardioverter defibrillators (ICDs), β-blockers have been shown to decrease the frequency of ICD shocks [27]. In an analysis of the Antiarrhythmics Versus Implantable Defibrillators Registry (*AVID registry*), β-blockers therapy was associated with lower mortality in patients with sustained ventricular tachycardia [28]. β-Blockers increase the time to first ICD shock in patients implanted for secondary prevention of sudden death[29].

Furthermore, the higher the dose of β-blockers used, the less patients experience VT and the more likely the therapies are successful. In a study of 282 patients with left ventricular dysfunction (EF < 50%) with standard indications for ICD without cardiac resynchronization therapy, the higher the dose of β-blockers

3. Renin-Angiotensin-aldosterone system and sudden cardiac death prevention

3.1. Potential mechanisms of Renin-Angiotensin-aldosterone system inhibitors/blockers on sudden cardiac death prevention

The Renin-Angiotensin-aldosterone system (RAAS) is activated during many disease states, but especially during myocardial ischemia and heart failure. Renin activates the angiotensin converting enzyme, which converts Angtiotensin I to Angiotensin II. Angiotensin II is a potent vasoconstrictor; it activates fibroblasts promoting interstitial fibrosis and scar formation. Furthermore, Angiotensin II also activates the secretion of Aldosterone and Norepinephrine. All of these factors also increase after-load, which increases myocardial oxygen demand. At the cellular level, angiotensin II decreases the effective refractory period of the cardiac myocyte and enhances conduction [30].Furthermore, Aldosterone promotes sodium retention, increases potassium secretion in the urine and activates fibroblasts leading to myocardial and vascular fibrosis. This promotes remodeling, LV dilatation and creates the substrate for reentry [31]. ACE-I inhibitors decrease preload and after-load, which decreases myocardial oxygen demand and LV end diastolic pressure. They also block Angiotensin II production and inhibit the breakdown of bradykinin [23]. Blocking angiotensin II prevents the progression of ventricular remodeling, reduces ventricular dilatation and fibrosis. ACE-I inhibitors result in a reduction in potassium depletion and have several effects on the autonomic nervous system via enhanced baroreflex sensitivity and hemodynamics which can lead to reduced sympathetic and parasympathetic tone and circulating catecholamines. Angiotensin II could persist despite treatment with ACE-I inhibitors since it can be formulated by non-ACE-I-dependent pathways. ARBs can also block the angiotensin II receptor without an increase in bradykinin levels [32].

Even with the utilization of ACE-I inhibitors or Angiotensin-Receptor blockers (ARBs) there is not full suppression of Aldosterone synthesis. Aldosterone receptor blockers prevent sudden cardiac death by controlling potassium loss, blocking aldosterone effect on the formation of collagen and by increasing the myocardial uptake of norepinephrine, which decreases sympathetic activation [32, 33]. Myocardial fibrosis may increase the risk of ventricular arrhythmias by causing variations in the ventricular conduction times. Spirinolactone decreases the level of serum markers of collagen synthesis at 6 months, which correlates with survival benefit [33].

3.2. Effect of ACE-I on sudden cardiac death prevention in post myocardial infarction patients and in patients with heart failure

Three post myocardial infarction trials; Survival and Ventricular Enlargement (SAVE), Trandolapril Cardiac Evaluation (TRACE-I) and Acute Infarction Ramipril Efficacy (AIRE) specifically investigated the impact of ACE-I inhibitors on mortality and morbidity in post MI patients who have LV dysfunction.

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Survival and Ventricular Enlargement (SAVE) was a randomized double-blind placebo controlled trial that evaluated the use of captopril (n=1115) versus placebo (n= 1116) in post MI patients with LVEF ≤ 40%. Randomization was done 3-16 days post MI. During an average of 42 months, there was an 18% RRR in all-cause mortality with captopril compared to placebo. However, there was a non-significant trend towards lower SCD in patients taking captopril (odds ratio 0.83, 95% CI 0.63-1.8)[34].

Trandolapril Cardiac Evaluation (TRACE-I) was designed to examine whether patients with a recent MI and LV dysfunction would benefit from long term ACE-I inhibitor therapy. A total of 1749 patients 3-7 days post MI with echocardiographic evidence of LV dysfunction (EF≤ 35%) were randomized to Trandolapril (n=876) or placebo (n=873). During follow up the relative risk for death from any cause in the Trandolapril group versus the placebo group was 0.78 (95 percent confidence interval, 0.67 to 0.91). The Trandolapril group also showed a significant reduction in sudden death versus the placebo group (HR 0.76, 95% CI 0.59-.98, p=0.03) [35]. TRACE-I was the first placebo-controlled trial to show a significant reduction in sudden death with the use of the ACE-I inhibitors.

The Acute Infarction Ramipril Efficacy (AIRE) Trial once again looked at the use of ACE-I inhibitors in the post MI patient who had clinical or radiological evidence of congestive heart failure (CHF) to receive Ramipril (n=1014) versus placebo (n=992). After 15 months of follow up,there was a 27% reduction in the risk of death with Ramipril compared to placebo. In this study Ramipril also reduced the risk for sudden death by approximately 30% compared to placebo (p=0.011)[36].

A further Meta-analysis looked at 15 trials including SAVE, TRACE-I and AIRE to evaluate the effect of ACE-I inhibitors on sudden death post MI. This meta-analysis revealed a significant reduction in the risk for sudden death an odds ratio of 0.80 (95% CI 0.70-0.92)[37].

Currently only three trials have reported results for sudden cardiac death in heart failure patients taking ACE-I. *The Cooperative North Scandinavian Enalapril Survival (CONSENSUS)* Study was designed to evaluate the effect of Enalapril compared to placebo on mortality in patients with severe heart failure (class IV). This study randomized 253 patients to either Enalapril (n=127) or placebo (n=126) in addition to conventional therapy. CONSENSUS showed a 40% reduction in mortality after 6 months of treatment and a 27% reduction at the end of the study. The greatest reduction in mortality was in death caused by progression of pump failure[38].

*The Studies of Left Ventricular Dysfunction (SOLVD)-Prevention trial*was designed to determine whether and ACE-I inhibitor, Enalapril, could reduce mortality, the incidence of heart failure and the rate of hospitalizations in patients with EF ≤ 35% with mild to moderate heart failure (class II or III). Following randomization, patients received double-blind treatment with either placebo (n=1284) or Enalapril (n=1285). There was noted a reduction in mortality due to progression of heart failure with a risk reduction of 16% but no clear reduction in sudden cardiac death was noted[39].

The V-HeFT-II trial was the first trial to suggest an effect of ACE-I inhibitors on sudden death in patients with heart failure. This trial compared the effects of Enalapril with hydralazine and

isosorbide dinitrate on mortality in patients with NYHA class II-III. After randomization, double blind treatment was instituted with Enalapril (n= 403) versus hydralazine/isosorbide dinitrate (n=401). Interestingly the mortality curves of the treatment arms separate early after randomization. There was a 28% relative risk reduction with Enalapril compared to hydralazine and isosorbide dinitrate (p=0.16).The overall reduction in mortality associated with Enalapril was due to a reduction in the incidence of sudden death [40].

3.3. Effect of Angiotensin-Receptor Blockers (ARBs) on sudden cardiac death prevention in patients with congestive heart failure

The Evaluation of Losartan in the Elderly Study (ELITE) is the only ARB trial to demonstrate a reduction in sudden death. This prospective, double-blind, randomized, parallel group controlled clinical trial compared the safety and efficacy in the treatment of CHF with the use of Losartan vs Captopril. Patients were randomly assigned to losartan (n=352) versus captopril (n=370). Follow up at 48 weeks showed a 45% reduction in all-cause mortality with a relative risk reduction of 36% in the incidence of sudden cardiac death [41].

ELITE II was designed to compare the effects of losartan and captopril on all-cause mortality and sudden death or resuscitated cardiac arrest. Similar to ELITE patients were randomly assigned to losartan (n=1578) or captopril (n=1574). After 1.5 years of follow there was no statistically difference in all-cause mortality, sudden death or resuscitated cardiac arrest (losartan 9% versus captopril 7.3%, p= 0.08) between the two groups[42].

3.4. Effect of Aldosterone antagonists on sudden cardiac death prevention in post MI patients and in patients with congestive heart failure

The Randomized Aldactone Evaluation Study (RALES) was a randomized double-blind placebo controlled trial. This trial hypothesized that daily treatment with Spirinolactone would reduce the risk of death from all causes among patients who had severe heart failure. Patients enrolled had class III or IV heart failure and were being treated with an ACE-I inhibitor, loop diuretic and had an EF ≤ 35%. They were randomly assigned to either Spirinolactone (n=822) or placebo (n=841). This trial was ended prematurely when analysis found that Spirinolactone demonstrated a 31% reduction in cardiac death. This reduction was due to a 36% in death related to progressive heart failure and a 29% reduction in sudden cardiac death [43].

The Eplerone Post Myocardial Heart Failure Efficacy and Survival Study (EPHESUS) was conducted to evaluate the effect of aldosterone blocker, Eplerenone on morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. In this double-blind, placebo-controlled study patients were randomly assigned to Eplerenone (n=3313) versus placebo (n=3319) in addition to optimal medical therapy. Eplerenone demonstrated a reduction in death from cardiovascular causes or hospitalization for cardiovascular events (relative risk, 0.83; 95% CI, 0.72-0.94; p=0.005). There was also a reduction in sudden death from cardiac causes (relative risk, 0.79; 95% CI 0.64-0.97; p=0.03) [44].

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4. Statins (3 hydroxy-3-methylglutaryl coenzyme-A reductase inhibitors) and sudden cardiac death prevention

4.1. Potential mechanisms of 3 hydroxy-3-methylglutaryl coenzyme A reductase inhibitors on sudden cardiac death prevention

Statins (3 Hydroxy-3-Methylglutaryl Coenzyme-A Reductase inhibitors) have been shown to decrease cardiovascular morbidity and mortality in both primary and secondary prevention trials. Statins are known to stabilize the plaque and to even promote plaque regression[45].This stabilization improves myocardial perfusion, oxidative stress and reduces the risk of plaque rupture[46]. This leads to decreased ischemic events and arrhythmic events, since even small areas of ischemia can promote reentry, induce ventricular arrhythmias and lead to sudden cardiac death. Statins improve endothelial function by increasing nitric oxide production from endothelial cells and they reduce ischemia mediated oxidative stress and intracellular calcium overload [47, 48]. They also have anti-inflammatory actions and reduce C-reactive protein, and they decrease endothelin-1 secretion [49]. All these effects will decrease myocardial ischemia, limit myocardial injury and prevent myocyte hypertrophy [50, 51].

4.2. Effect of statin therapy on shock burden and sudden cardiac death in post MI patients and in patients with congestive heart failure

Statins are widely accepted as preventing coronary heart disease death and MI; however their effect on sudden cardiac death prevention is unclear.

Randomized trial in post myocardial infarction patients showed the benefits of statins on overall mortality but failed to show benefit on sudden cardiac death prevention [52-54]. However, observational data from hospitalized patients with myocardial infarction showed that early statin administration (within 24 hours) of an acute MI led to a decrease in the incidence of VT/VF [55].

Furthermore, statins appear to decrease appropriate shocks in patients who have ICDs whether or not they received them for primary or secondary prevention of sudden cardiac death. In a subanalysis of AVID trial, a secondary prevention trial which compared anti-arrhythmic drugs to ICDs in patients who survived a cardiac arrest, patients who received statins had a lower risk of ventricular arrhythmias compared to those who are not on statins [56]. This was also demonstrated in the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II). Post hoc analysis of MADIT-II showed that patients receiving statin therapy > 90% of the time had a significantly reduced cumulative rate of ICD therapy for VT/VF or cardiac death[57].

Subsequently, an analysis of SCD-HeFT trial data was undertaken to evaluate the impact of statin use in heart failure. SCD-HeFT studied 2521 functional class II and III heart failure patients with left ventricular ejection fractions ≤ 35%. The cause of CHF was ischemic in 52% of the study patients. Statin use was reported in 965 (38%) of 2521 patients at baseline and 1187 (47%) at last follow-up with the median time to follow up of 45.5 months. This analysis revealed that mortality reduction related to statin therapy (HR= 0.70, 95% CI: 0.58-0.83] was identical in both ischemic and non-ischemic cardiomyopathy (HR 0.69 vs 0.67 respectively) [58].

5. Conclusions and future directions

Sudden cardiac death remains a challenge for health providers and policy makers. Whether more stringent guidelines for prevention and screening will be applied is balanced by the enormous costs. In order to identify the groups at risk for sudden cardiac death there must first be a standardization of the definition. The worldly variation in this definition of sudden cardiac death of 1 hour from onset of symptoms to 24 hours, not only effects epidemiological data but also alters clinical trial outcomes when evaluating the effectiveness of treatment options.

Currently, antiarrhythmic medications have failed to show any benefit of sudden cardiac death prevention, while traditional heart failure medications have been shown to decrease total mortality, sudden cardiac death and defibrillator shocks. They are only used in a small subset of patients that present in sudden cardiac death, since most of the patients who have sudden cardiac death have it as a first presentation and do not have congestive heart failure or history of coronary artery disease. This poses a diagnostic and therapeutic challenge for the clinician. Taking statins as an example, most of the primary prevention algorithms used to start lipid lowering agents usually leads to delayed intervention, especially since coronary atherosclerosis has been shown to start at a young age. The cost of starting this treatment is also enormous, especially if it is started on a global scale at a young age and it is not without side effects. Genetic studies to identify patients at risk for coronary atherosclerosis are still under development. Preventing sudden cardiac death is definitely a challenge for the 21st century clinician and might remain so for the near future.

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