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Short communication

Drugs to prevent sudden cardiac death

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ABSTRACT

Sudden cardiac death (SCD) remains a major public health burden despite enormous advances in post-resuscitation care, management of structural heart diseases, and antiarrhythmic treatment modalities. Primary and secondary prevention of sudden cardiac death require understanding of the underlying substrate causing ventricular arrhythmias and its modification by pharmacological (i.e. heart failure therapy) or interventional (catheter ablation) methods. Antiarrhythmic drug therapy has experienced ups and downs during the last 30 years balancing high antiarrhythmic potential, toxic side effects and pro-arrhythmic potency. Therefore, the implantable cardioverter-defibrillator (ICD) remains irreplaceable in primary and secondary prevention of SCD. Hybrid therapy combing antiarrhythmic drugs (predominantly amiodarone) with ICD therapy represents an often-used treatment option. This short review provides an overview of current pharmacological therapy aiming to prevent SCD.

Approximately 65.000 individuals suffered from sudden cardiac death (SCD) in 2014 in Germany accounting for 30% of all cardiovascular deaths. In a study of the incidence of out-of-hospital cardiac arrest in the Maastricht area, the initial rhythm documented by emergency medical staff was either ventricular fibrillation (VF)/ventricular tachycardia (VT) in 58% of the patients and bradycardia or asystole in the remaining 42%. Despite enormous progress in resuscitation care, survival rates of victims of out of hospital cardiac arrest remain poor. The vast majority of ventricular arrhythmias - specifically VT - are associated with structural heart disease, most commonly with coronary artery disease. In approximately 10% of the at-risk patients, no arrhythmogenic substrate can be found because the ventricular arrhythmia is either of idiopathic origin or related to a primary electrical disease (i.e. Brugada syndrome, short or long QT syndrome or catecholaminergic polymorphic VT). Whereas the implantable cardioverter-defibrillator (ICD) represents the mainstay of primary and secondary prevention of SCD [1], pharmacological therapy is used to treat the underlying structural heart disease thereby impacting on cardiac remodelling and development of potential arrhythmogenic substrates [2–4,6–9]. Antiarrhythmic drug therapy may be indicated to suppress spontaneous supraventricular and ventricular arrhythmias which act as triggers for SCD [11–16,18–20].

1. Non-anti-arrhythmic agents

In structural heart disease LV remodelling and particularly myocardial interstitial fibrosis may give rise to life-threatening ventricular arrhythmias. According to a comprehensive meta-analysis, angiotensin-converting-enzyme inhibitors reduce the risk of SCD in patients with congestive heart failure and impaired LV-function by one fifth (HR = 0.80; 95% C. I. 0.70–0.92; $p < 0.001$) [2]. For instance, the HOPE trial randomized 9.297 heart failure patients to receive either placebo or ramipril. In patients receiving ramipril, there was a 21% relative risk reduction in the occurrence of cardiac arrhythmic death (RR = 0.79; 95% C. I. 0.64–0.98; $p = 0.03$) compared to placebo. Cause-specific mortality was also specifically analysed in the CHARM-Added trial examining the occurrence of SCD in 2.548 patients with depressed LVEF (≤40%) who had already been on ACE-inhibitors and had been randomized to receive additional candesartan or placebo. In the candesartan group, SCD was significantly reduced compared to control (HR = 0.85; 95% C. I. 0.73–0.99; $p = 0.04$) [3].

Neurohormonal antagonists were also demonstrated to reduce the need of ICD shock therapy as a potential surrogate marker of SCD. For instance, the COMPANION trial randomized more than 1.500 heart failure patients with NYHA III/IV symptoms to optimal heart failure medication plus cardiac resynchronization therapy or to optimal heart failure medication alone. For both, ACE-inhibitor and angiotensin receptor blocker administration, a significant reduction in appropriate ICD shocks was

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observed (HR = 0.44; 95% C. I. 0.26–0.75; $p < 0.01$; HR = 0.53; 95% C. I. 0.28–1.0; $p = 0.05$).

More recently, the PARADIGM-HF trial randomized 8.399 heart failure patients to receive either enalapril or the angiotensin-receptor/neprilysin-inhibitor LCZ696, a new renin-angiotensin-aldosterone system (RAS) modifying substance [4]. The trial showed a significant reduction in cardiovascular mortality with LCZ696 compared to enalapril. When cause-specific mortality was evaluated, it turned out that LCZ696 reduced mortality from sudden, presumably arrhythmogenic death by 20% compared to enalapril therapy (HR = 0.80; 95% C. I. 0.68–0.94; $p = 0.008$) [4]. This implies that the new RAS modifier may exert an even larger protective effect than ACE inhibitors or angiotensin-receptor-blockers.

Another important group of non-antiarrhythmic drugs, which impact on cardiovascular and specifically SCD mortality, are mineralocorticoid receptor antagonists. Aldosterone-antagonists have been associated with significant reverse remodelling and therefore are recommended for patients with symptomatic heart failure in the setting of reduced LVEF according to the current guidelines [5]. In the RALES trial, spironolactone significantly reduced the incidence of cardiac arrhythmic death by 29% compared to placebo (HR = 0.71; 95% C. I. 0.54–0.95; $p = 0.02$) [6]. This trial was stopped prematurely due to superiority. The use of eplerenone, a selective aldosterone receptor antagonist with low affinity to androgen and progesterone receptors, was investigated in the EPHESUS trial in 6.632 survivors of myocardial infarction with a LVEF ≤40% who were randomized to receive either the study drug or placebo [7]. Again, a 21% relative reduction in the incidence of SCD was demonstrated (HR = 0.79; 95% C. I. 0.64–0.97; $p = 0.03$). These findings were later reproduced in the EMPHASIS-HF trial which analysed eplerenone use in NYHA II heart failure patients with a LVEF ≤35% [8]. This trial was stopped prematurely after a median follow-up of 21 months. There was a significant reduction in all-cause mortality (HR 0.78; 95% C. I. 0.64–0.95; $p = 0.01$) along with a 24% relative risk reduction for SCD (HR = 0.76; 95% C. I. 0.54–1.07; $p = 0.12$) [8].

Statins, HMG—CoA reductase inhibitors, showed a 78% reduction in all-cause mortality and a reduction in arrhythmic sudden death (HR = 0.16; 95% C. I. 0.02–1.21; $p = 0.08$) in a subgroup analysis of the DEFINITE trial presumably mediated by their pleiotropic properties and anti-inflammatory effects. A meta-analysis of 29 trials comprising 113.568 participants on statin therapy versus control showed no significant reduction in the risk for ventricular tachyarrhythmia or cardiac arrest, whereas the risk of sudden cardiac death was significantly reduced by 10% (OR = 0.90; 95% C. I. 0.82–0.97; $p = 0.01$). Importantly, these results were not altered by elevated dosing levels [9].

2. β-receptor antagonists

The recently published European guidelines on the treatment of ventricular arrhythmias consider β-blocker therapy as the first line therapy to prevent sudden cardiac death (class I A recommendation) [10]. In fact, a relative risk reduction of SCD has been demonstrated with bisoprolol administration in patients with systolic heart failure in the CIBIS-II trial (HR = 0.56; 95% C. I. 0.39–0.80; $p = 0.001$) [11] or metoprolol succinate administration in heart failure patients with LVEF <40% and NYHA II to IV symptoms in the MERIT-HF trial (HR = 0.59; 95% C. I. 0.45–0.78; $p < 0.001$) [12]. A large comparative analysis of the 4 pivotal randomized trials in heart failure patients (CIBIS-II, MERIT-HF, COPERNICUS and SENIORS-SHF) demonstrated comparable safety and tolerability of bisoprolol, metoprolol and carvedilol regardless of NYHA class or left ventricular function [13].

3. Class I anti-arrhythmic drugs

Sodium channel blockers play no role in SCD prevention. Their use has been analysed in the Cardiac Arrhythmia Suppression Trial (CAST). Aiming to suppress premature ventricular beats, 2.309 patients after myocardial infarction were randomized to receive either encainide, flecainide, moricizine or placebo. After 10 months of follow-up, the study was discontinued early due to an increase in arrhythmic and non-arrhythmic death in the encainide and flecainide treatment arms. The authors concluded that these substances should not be used in patients after myocardial infarction presenting with symptomatic or asymptomatic ventricular arrhythmias [14]. This recommendation is reflected by the contraindication for class IC agents in post-MI patients, which has been extended to a general contraindication for all class I anti-arrhythmic agents [10].

4. Class III anti-arrhythmic drugs

The most frequently used antiarrhythmic drug, amiodarone, has multichannel blocking properties (sodium current, calcium channel and β-blocker) and inhibits triggered automaticity and re-entry. Amiodarone was shown to have a neutral effect on total mortality in several trials, for instance in the SCD-HeFT trial comparing amiodarone to placebo (HR = 1.06; 95% C. I. 0.86–1.30; $p = 0.53$) [15,1]. A meta-analysis including 8.522 patients post myocardial infarction or with systolic heart failure randomized to placebo or amiodarone demonstrated a 28% reduction in SCD, again with a neutral effect regarding overall mortality. Approximately 30% of the patients discontinued amiodarone, most often due to extracardiac toxicity [16]. Accordingly, the European guidelines recommend amiodarone for prevention of SCD [10]. In the recent published VANISH trial, 259 patients with ischemic heart disease and an ICD presenting with a history of VT despite anti-arrhythmic drug treatment were randomized to receive escalated drug therapy (i.e. newly administered amiodarone, dose escalation of amiodarone, or the combination of amiodarone and mexiletine) versus catheter ablation. The primary outcome measure was a composite of death, VT storm and appropriate ICD shock. This endpoint was observed less frequently with catheter ablation than with amiodarone (HR = 0.72; 95% C. I. 0.53–0.98; $p = 0.04$) without revealing any difference in total mortality (HR = 0.96; 95% C. I. 0.60–1.53; $p = 0.86$) [17]. In amiodarone-naïve patients, amiodarone and catheter ablation had similar efficacy in preventing recurrent VT [17].

5. Anti-arrhythmic drug therapy for hybrid therapy

Antiarrhythmic drug therapy is an important treatment strategy to suppress spontaneous ventricular arrhythmias in order to avoid painful ICD shocks. The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) study represents the largest randomized trial ($n = 412$) comparing amiodarone, sotalol, and β-blockers for ICD shock reduction including patients with a secondary prevention ICD indication. As the main result, the trial demonstrated that amiodarone reduced both the risk of appropriate and inappropriate ICD shocks compared to β-blocker therapy alone (HR = 0.27; 95% CI 0.14–0.52; $p = 0.001$). Sotalol therapy was also associated with a reduced risk of ICD shocks compared to β-blocker therapy alone (HR = 0.61; 95% C. I. 0.37–1.01; $p = 0.055$) [18]. Another trial had previously examined the use of sotalol versus placebo for ICD shock prevention. Sotalol therapy was associate with a 48% relative risk reduction for any shock or death from any cause in both patients with depressed LV function (HR = 0.52; 95% C. I. 0.37–0.74; $p < 0.001$) [19]. Furthermore, the incidence of inappropriate shocks for supraventricular arrhythmias which often trigger inappropriate ICD shocks was also significantly reduced in the sotalol cohort ($p = 0.004$) [19].

Azimilide is a potassium channel (I_{Kr} and I_{Ks}) blocker not approved for clinical use. In the SHIELD trial, 633 ICD patients were randomized to 2 doses of azimilide (75 mg and 125 mg) or placebo in a double-blind fashion. Azimilide significantly reduced the recurrence of ventricular arrhythmias appropriately terminated by ICD shocks or ATP by 57% (HR = 0.43; 95% CI 0.26–0.69; $p < 0.001$) [20].

6. Conclusion

Pharmacological therapy remains a cornerstone treatment for fighting SCD. Modern heart failure therapy comprising ACE inhibitors, angiotensin-receptor-blockers, angiotensin-receptor/neprilysin-inhibitors, mineralocorticoid receptor antagonists, and β-blockers have been demonstrated to reduce the risk for sudden, presumably arrhythmogenic death. In contrast, the role of "classical" antiarrhythmic drugs appears to be more limited. Their use, predominantly that of amiodarone, is restricted to symptomatic therapy of supraventricular arrhythmias (particularly atrial fibrillation) and to hybrid therapy of patients fitted with an ICD.

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Dr. Julia W. Erath reports receiving lecture fees and travel support from Zoll Medical and Servier and is a fellow of the Boston Scientific heart rhythm fellowship program, outside the submitted work.

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