Statins and sudden cardiac death – mini review on available data

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Introduction

Sudden cardiac death (SCD) is defined as an unexpected natural death from a cardiovascular (CV) cause that occurs within 1 hour of symptom onset [1]. Globally SCDs account for 15–20% of all deaths. In the USA and Europe the highest annual incidence of SCD, ranging from 50 to 100 per 100 000 persons, is noted [2]. Nowadays SCD remains an important clinical and public health issue. SCD is the consequence of complex interaction between upstream determinants (such as age, sex, socioeconomic status, CV risks factors and genetic predisposition), a variety of cardiac conditions and environmental triggers [3]. 80% cases of SCD occur as a result of coronary artery disease (CAD); consequently, risk factors of CAD also predispose to SCD [4]. Other important risk factors for SCD are diabetes mellitus (DMt2)[5] and heart failure (HF)[6]. In most cases SCDs result from ventricular tachycardia (VT) and ventricular fibrillation (VF)[7]. Fatal ventricular arrhythmias in patients with CAD are mainly associated with two mechanisms: acute coronary ischemia, generally resulting from plaque rupture; and re-entry associated with areas of slow conduction and previous myocardial scarring[8]. Statins are the most effective drugs used to reduce endogenous production of cholesterol[9]. Besides their lipid-lowering effects, statins exhibit pleiotropic properties such as anti-inflammatory[10], antioxidant [11], antihypertrophic and antifibrotic effects, which might play a role in CV protection[12]. Statins can slow the progression or even induce regression of atherosclerosis [13], which may reduce myocardial ischemia, which can cause ventricular arrhythmias, and in consequence reduce the risk of SCD [14]. Large scale clinical trials indicated that statins reduce CV morbidity and mortality in high-risk populations [15]. Therefore, the purpose of the present review is to synthesize the results of recent studies on the influence of statin therapy on sudden cardiac death.

Statin therapy and SCD

Though many studies have indicated a beneficial effect of statin therapy on reducing mortality, data regarding SCD are limited. Moreover, the effects of statins on SCD have only been studied in high-risk populations. SCD was significantly reduced with statin therapy in ischemic cardiomyopathy patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) [16]. The meta-analysis of Levantesi et al.[17], which included 10 randomized controlled trials (RCTs) with 22 275 patients (4.4 years follow-up) elucidated that statin treatment was associated with a significant 19% risk reduction for SCD in patients with cardiovascular disease

(CVD). Statins' beneficial influence was independent from the changes in patient lipid levels, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high- density lipoprotein cholesterol (non-HDL- C) during the study [17]. Vrtovec et al. (2008) showed that atorvastatin might be associated with a lower incidence of SCD in patients with advanced chronic heart failure (CHF) [18]. Studies of Liao et al. (2013) [19] demonstrated that statin therapy reduced the risk of VT, VF, SCD and total mortality in HF patients. The authors suggested that both the pleiotropic and lipid-lowering properties of statins might contribute to the observed anti-arrhythmic effects of statins [19]. The reduction by statin treatment of the risk of ventricular tachyarrhythmias and SCD events was also confirmed in non-ischemic cardiomyopathy patients with HF [20]. Some studies have suggested that statins might have some direct antiarrhythmic effects [16,21]. Possible mechanisms which could explain the antiarrhythmic properties might involve the capacity of statins for NO-dependent endothelial function regulation, inflammation and oxidative stress reduction, high-risk plaque rupture and ischemia/reperfusion myocardial injury prevention, improvement in heart rate variability and decreased QT dispersion [14,22]. Recently Rahimi et al. (2012) in a meta-analysis of 29 RCTs concluded that statin therapy did not significantly reduce the risk of ventricular tachyarrhythmia and cardiac arrest, but was responsible for a significant 10% reduction in SCDs [23]. The results of that study indicated that statin therapy is highly unlikely to have a beneficial effect on the prevention of ventricular arrhythmias. The authors concluded that reduction of the risk of sudden cardiac death was associated with the reduction of LDL cholesterol by statin [23]. On the other hand, large-scale RCTs – the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [24] and the Effect of rosuvastatin in patients with chronic heart failure (GISSI-HF) [25] –showed no association between rosuvastatin therapy at a low dose and reduction in mortality from any cause. The majority of the patients in these two studies had moderate to severe HF. Among the reasons for the negative results might have been too advanced HF stage and type of statin used in these studies (the most potent – rosuvastatin) [24,25]. It has been suggested that different statins may have inconsistent benefits in CHF patients [26]. Most of the studies which showed a significant benefit used drugs other than rosuvastatin. Rosuvastatin is a hydrophilic statin, which may exert a different (according to some authors weaker) effect compared to lipophilic statins (such as atorvastatin) in preventing CV events due to their potent pleiotropic effects [26]. Xu et al. (2010) in their meta-analysis found that atorvastatin was associated with significantly decreased risks of all- cause mortality, CV mortality, and SCD in CHF patients [27]. Atorvastatin significantly reduced the rates of adverse outcomes including SCD in the highest quartile of LDL-C (≥145 mg/dl [>3.76 mmol/L]) in patients with DMt2 undergoing hemodialysis [28,29]. The most recent meta-analysis of 15 studies and 45 110 patients indicated that statins decreased all-cause mortality in CHF patients, but there was no statistically significant effect of statin therapy on reduction in the risk of sudden cardiac death in these patients [30]. Studies included in this meta-analysis evaluated simvastatin (n = 1), rosuvastatin (n = 2), atorvastatin (n = 3), multiple statins (n = 4) and non-specified statin treatment (n = 5). Based on the subanalysis the authors suggested that some statins, such as atorvastatin (hydrophilic), might provide more beneficial effects in CHF patients [30]. The kind of statin chosen for the therapy might be an important factor influencing the efficacy in patients with CHF. Moreover, statins prescribed at earlier stages of CHF might better improve clinical prognosis than in later stages [31]. Recently, Nochioka et al. [32] studied the effect of statin treatment on mortality in a large-scale cohort of patients with HF with preserved ejection fraction (HFpEF). The results of that study indicated that statin treatment improved mortality rates in HFpEF patients, which was mainly attributable to reductions in SCD and non-CV death.

Conclusions

Nowadays the role of statins in prevention of SCD and as anti-arrhythmic agents is still controversial and conflicting. Many studies focus mainly on the influence of statin therapy on mortality and do not analyze separately sudden cardiac death; therefore data regarding SCD are very limited. Effects of statins on SCD have only been studied in high-risk populations, and the results are also not consistent. The mechanism of preventing sudden cardiac death might involve pleiotropic properties of statins. However, based on published data, a direct anti-arrhythmic effect of statins against SCD is very unlikely [33,34]. Further studies are needed to confirm the benefits of statin treatment, the effects of different statins and doses, and to determine the exact mechanisms underlying the statin protection against sudden cardiac death.

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