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The Pleiotropic Effects of Statins – From Coronary Artery Disease and Stroke to Atrial Fibrillation and Ventricular Tachyarrhythmia

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Abstract

Statins, 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors, have been used for decades for the prevention of coronary artery disease and stroke. They act primarily by lowering serum cholesterol through the inhibition of cholesterol synthesis in the liver, which results in the upregulation of low-density lipoprotein receptors in the liver. This results in the removal of low-density lipoproteincholesterol. Studies have suggested that statins may demonstrate additional effects that are independent of their effects on low-density lipoprotein-cholesterol. These have been termed “pleiotropic” effects. Pleiotropic effects may be due to the inhibition of isoprenoid intermediates by statins. Isoprenoid inhibition has effects on the small guanosine triphosphate binding proteins Rac and Rho which in turn effects nicotinamide adenine dinucleotide phosphate oxidases. Therefore, there are changes in endothelial nitric oxide synthase expression, atherosclerotic plaque stability, pro-inflammatory cytokines and reactive oxygen species production, platelet reactivity, and cardiac fibrosis and hypetrophy development. Recently, statins have been compared to the ezetimibe and the recently published outcomes data on the proprotein convertase subtilisin kexin type 9 inhibitors has allowed for a reexamination of statin pleiotropy. As a result of these diverse effects, it has been suggested that statins also have anti-arrhythmic effects. This review focuses on the mechanisms of statin pleiotropy and discusses evidence from the statin clinical trials as well as examining the possible anti-arrhythmic effects atrial fibrillation and ventricular tachyarrhythmias.

Keywords

Statins; pleiotropy; coronary artery disease; stroke; atrial fibrillation; low density lipoprotein; cholesterol

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CONFLICT OF INTEREST

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1. INTRODUCTION

Cardiovascular diseases are the leading cause of death and low-density lipoprotein cholesterol (LDL-C) is responsible for atherogenesis [1, 2]. 3-hydroxy-3-methyl-glutarylcoenzyme A (HMG-CoA) reductase inhibitors, statins, decrease LDL-C levels and have been used for over 30 years for both the primary and secondary prevention of coronary artery disease (CAD) [3–7]. It has been hypothesized that statins also have effects independent of LDL-C lowering, termed pleiotropic effects [8]. Recent outcomes studies have focused on non-statin medications, such as ezetimide, the inhibitor of Niemann—Pick C1 like protein and the proprotein convertase subtilisin kexin 9 inhibitors (PCSK9i) evolocumab, bococizumab, and alirocumab [9–12]. These agents allow a re-examination of statin pleiotropy. While the contribution of the pleiotropic effects of statins to clinical outcomes remains uncertain due to the overwhelming benefits of LDL-C reduction in preventing CAD, this review focuses on both non-LDL-C lowering effects for CAD and for cardiovascular diseases where the causal link of elevated LDL-C is less certain, such as atrial fibrillation (AF), ventricular tachyarrhythmias, and stroke.

2. PHARMACOKINETIC PROPERTIES OF STATINS

Statins are reversible competitive inhibitors of HMGCoA reductase, which is the rate limiting enzyme for cholesterol biosynthesis in the liver and therefore inhibit the production of mevalonate [13]. Inhibition of cholesterol synthesis leads to decreased cholesterol production and upregulation of the LDL receptor [3]. By inhibiting mevalonate synthesis statins prevent isoprenoid intermediate sythensis, including farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP) (Fig. 1)[14]. The inhibition of FPP and GGPP production is central to statin pleiotropy.

GGPP and FPP are involved in the post-translational modification of G proteins such as Rho and Ras [15]. Ras and Rho effect cell functions, such as differentiation, proliferation, the cytoskeleton, and apoptosis [16]. Rho translocation depends on geranylgeranylation, whereas Ras translocation depends on on farnesylation [17, 18].

Statins can be divided into two groups. There are lipophilic statins (lovastatin, simvastatin, fluvastatin, atorvastatin, and pitavastatin) which cross cell membranes by passive diffusion and are relatively non-selective for hepatic tissues. The other group of statins are hydrophilic (rosuvastatin and pravastatin) and are unable to cross cell membranes and therefore require activated carrier-mediated transport. Given that the statin transporters are not present in all tissues, hydrophilic statins are more selective for hepatic tissues [19–21]. It is not clear whether statin pleiotropy is due to hepatic or non-hepatic isoprenoid inhibition effects, but it has been suggested the both lipophilic and hydrophilic statins demonstrate pleiotropy.

By affecting Rho gtpases, statins also inhibit Rho kinase's (ROCKs) activity [22]. ROCKs effect myosin light chain phosphorylation and the actin cytoskeletan. ROCK inhibition limits cardiac fibrosis and pathological remodeling [23]. Statins also inhibit Rac, a monomeric G protein which is included in the Rho GTPase subfamily [24]. Rac1 leads to left ventricular hypertrophy (LVH) by activating nicotin-amide adenine dinucleotide phosphate (NADPH)

oxidase which produces reactive oxygen species (ROS) [25]. ROS may be responsible for forming oxidized LDL, which leads to foam cell formation [26]. Additionally, statins activate peroxisome proliferator activated receptor γ (PPAR-γ), which acts to reduce ROS as well as cardiac fibrosis and may be independent of LDL-C lowering [27, 28]. The diverse statin targets have effects on different cell types (Fig. 2).

3. STATIN CELLULAR EFFECTS

3.1. Endothelial Effects of Statins

Hypercholesterolemia causes endothelial dysfunction. Impaired bioavailability of endothelial-derived nitric oxide (NO) characterizes endothelial dysfunction. Endothelial NO is involved in vascular smooth muscle cell (SMC) proliferation, leukocyte/endothelium interactions and platelet aggregation [29]. Statins upregulate endothelial NO synthase (eNOS) and therefore increase NO bioavailability [18, 30].

Statins up-regulate eNOS, increasing NO bioavailability, through multiple mechanisms. One mechanism is through ROCK inhibition. ROCK downregulates eNOS and ROCK inhibitors increase eNOS expression [31, 32]. A second mechanism that Statins increase eNOS activity is through activation of the phosphatidylinositol 3-kinase/protein kinase Akt pathway. Akt phosphorylates eNOS, and activation of the pathway therefore increases eNOS activity [33]. Caveolae are invaginations of the plasma cell mebranes. Caveolin-1 binds to eNOS in caveolae and decrease eNOS activity. Statins decrease caveolin-1 expression, and therefore increase eNOS activity [34]. Statins also induce kruppel-like factor 2 in endothelial cells (ECs), which appears to be required for eNOS expression [35]. Lastly, endothelial progenitor cells express eNOS and therefore increase NO levels. Statins increase endothelial progenitor cells; however, the increase is seen only at low statin concentrations. High statin concentrations have angiostatic effects [36, 37].

3.2. Vascular Smooth Muscle and Statins

Vascular smooth muscle cells (SMCs) are required for vascular lesion pathogenesis. Statins affect vascular SMCs, which may be one way which statins affect diseases not related to hyperlipidemia [38]. For example, cardiac transplant arteriosclerosis is not dependent on hyperlipidemia but rather is an immune mediated response against donor vascular SMCs and ECs, which nonetheless is reduced by statins [39].

Statins reduce atherosclerosis by reducing intimal thickening, cellular proliferation, and platelet activation in mice without LDL receptor [40]. Statins also increase the effects of interleukin (IL) – 18, which inhibits nuclear factor- κB activation, SMC migration, and matrix metalloproteinase-9 expression [41]. Lastly, statins inhibit the migration of pulmonary artery SMCs [42].

3.3. Statins and the Myocardium

Ras, Rac, and Rho are important for cardiac hypertrophy and are affected by statins [43]. Rac1 is necessary for myocardial hypertrophy, increased NADPH oxidase activity, and increased mineralocorticoid receptor activity and contributes to doxorubicin related

cardiotoxicity [44–46]. Statins decrease Rac1 levels, independent of lipid-lowering and atorvastatin inhibited NADPH in atrial myocardium, through a Rac1 related mechanism [47, 48].

RhoA and ROCK increase cell apoptosis and myocardial fibrosis, which may be associated with heart failure and LVH. Increased expression of RhoA results in apoptosis with increased caspase-9 activation, which is blocked by the inhibition of ROCK [49]. Mice lacking ROCK had less ischemia related fibrosis then normal nice as well as less LVH and apoptosis when exposed to stress [50, 51]. Human leukocyte ROCK activity is higher in patients with LVH then those without LVH [52, 53]. NO bioavailability is increased by statins which results in increased myocardial blood flow dur ing hypoxia [30]. Statins also reduce mitochondrial dysfunction and cardiomyocyte death [54].

Despite the above studies there is no clear evidence that statins improve outcomes in non-ischemic cardiomyopathy. Small studies have demonstrated improved ejection fraction, symptoms, lower inflammatory markers, and decreased mortality [55, 56]. Both large randomized control trials that have been conducted in heart failure, GISSI-HF and CORONA, did not show any mortality benefit [57, 58]. However, it is possible that there may be a benefit for statins if they are started earlier in the course of the disease.

3.4. Statins and Platelets

Platelet reactivity is increased in hypercholesterolemia and platelets are essential for acute coronary syndrome. Platelet reactivity and thrombin generation are decreased by statins in LDL-C dependent and independent mechanisms [59]. Statins increase eNOS while down-regulating β-thromboglobulin and platelet factor 4 in platelets [60]. Platelet factor 4 and β-thromboglobulin are both released by activated platelets and are chemoattractants for inflammatory cells. Arachidonic acid increases platelet aggregation, which is inhibited by statins compared to colestimide [61, 62]. In another study statins inhibited platelet recruitment, decreased thromboxane A2 and Rac1 while increasing NO levels [63]. In the JUPITER trial, rosuvastatin decreased thrombotic events, which appeared to be independent of LDL-C lower ing as hyperlipidemia is not a strong risk factor for thrombosis [64].

3.5. The Immune Effects of Statins

Increased LDL-C initiates the chronic inflammatory process of atherosclerosis, which is mediated by macrophages, SMCs, and T and B lymphocytes [65]. Statins decrease Rac1-mediated ROS production which reduces inflammation that is sensitive to oxidation [66]. Statins also reduce the pro-inflammatory cytokines monocyte chemotactic protein-1, IL-6, and IL-8 [67, 68]. Statins decrease matrix metalloproteinases, in both macrophages and SMCs [69]. The effect of statins on the matrix metalloproteinases may explain one mechanism through which they promote plaque stability.

Statins also effect T-cell differentiation. Statins reduce the differentiation of pro-inflammatory IL-17 helper T cells and increase forkhead box $P3^+$ $Cd4^+$ regulatory T cells [70]. Forkhead box $P3^+$ $Cd4^+$ regulatory T cells are decreased in acute coronary syndrome and their decrease is associated with worsened atherosclerotic lesions. Statins also inhibit Smad6 and Smad7, which are transforming growth factor- inhibitors. This results in

increased transforming growth factor-β expression, and induces forkhead box $P3^+$ $Cd4^+$ regulatory T cells [71]. $Cd4^+$ T lymphocytes in acute coronary syndrome induce EC apoptosis, which statins block and be a mechanism for statin related plaque stability [72].

Statins decrease the interactions between leukocytes and ECs. One mechanism is by inhibiting vascular cell adhesion molecule-1 which is mediated by increased NO production [73]. Inhibiting RhoA decreases the adhesion of ECs to monocytes and decreases the clustering of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 [74]. Statins regulate the expression of EC and platelet adhesion molecule-1, which was reversed by mevalonate and GGP [75].

4. CLINICAL EVIDENCE OF STATIN PLEIOTROPY

4.1. Coronary Artery Disease

The concept of anti-inflammatory statin pleiotropy has been examined by looking at the effects of statins on c-reactive protein (CRP). The JUPITER trial was placebo controlled, randomized, and involved primary prevention treatment with rosuvastatin that included 17, 802 patients with a LDL <130 mg/dL and a CRP ≥ 2.0 mg/L [76]. Rosuvastatin decreased the primary end point by 44%, CRP by 37%, and LDL-C by 50%. In contrast, the HOPE-3 study was also a primary prevention trial with rosuvastatin, but there was no CRP or LDL-C levels for inclusion. Rosuvastatin reduced the primary outcomes by 24% and 25% and LDL-C by 26.5%, and while rosuvastatin lowered CRP in the trial, the benefit of rosuvastatin was seen in patients with both high and normal CRP levels, which indicates the primary rosuvastatin benefit may be due to LDL-C reduction [77]. The A-Z trial included patients with acute coronary syndrome who were randomized to either 40 mg of simvastatin, titrated to 80 mg after one month versus placebo for four months followed by 20 mg of simvastatin. The higher dose simvastatin lowered LDL-C by a greater amount, but there was no change in CRP at one month and the A-Z trial failed to achieve its primary end-point [78]. However, after month four, CRP was reduced in the high intensity group, and there was a stronger trend to benefit then earlier in the trial [78]. Both groups had relatively low CRP at one month, which may be responsible for the negative result. The MIRACL trial was a placebo controlled randomized trial with atorvastatin 80 mg in patients with acute coronary syndrome and lowered its primary endpoint in both normal and elevated LDL-C and reduced CRP by 83% [79, 80].

The contribution of statin pleiotropy to clinical outcomes remains unclear, however, because of the strong association between elevated LDL-C and CAD. As already discussed, much of statin pleiotropy is due to isoprenoid inhibition, which occurs at the same time as cholesterol synthesis inhibition and makes it difficult to determine the clinical benefit of statin pleiotropy. Additionally, in the clinical trials of newer therapies, such as ezetimibe and the PCSK9i, the new medication is tested in addition to statin therapy and compared against statins therapy, which prevents quantification of any pleiotropic effects since both the intervention and control groups are receiving statin therapy.

Ezetimibe has been compared with statins, in multiple small studies with various surrogate endpoints, to help determine how much of the clinical benefit of statins is due to pleiotropy.

One problem with this approach is that ezetimibe lowers LDL-C by 15–20%, which is similar to low intensity statins, which makes it difficult to see vascular effects. Several studies have randomized patients to high intensity statins or lower intensity statins with ezetimibe and have found more improvement in vascular function and endothelial function with high intensity statins, despite similar LDL-C decrease in both groups [81–85]. But other studies have shown the opposite result [86, 87]. While these studies are interesting, they do not conclusively answer whether statins have clinical pleiotropic effects in addition to LDL-C reduction.

The PCSK9i lower LDL-C levels by approximately 60%, which is comparable to high dose statins and recent outcomes trials have been completed that allow for comparison with statin therapy [88, 89]. PCSK9i lower LDL-C by increasing the LDL receptor-mediated uptake of ApoB-containing lipoproteins, which is similar in mechanism to statins. But, since they have no effect on the mevalonate pathway they should not demonstrate pleiotropic effects that result from the inhibition of isoprenoid intermediate formation. The PCSK9i do not lower inflammatory markers, such as CRP [90]. High dose statin therapy has previously demonstrated plaque reduction, which was felt to be due to the anti-inflammatory effects of statins. The GLAGOV trial tested the PCSK9i evolocumab against placebo in addition to statin therapy and there was a reduction of LDL-C to 36.6 mg/dL compared to 93.0 mg/dL in the placebo group and there was also coronary plaque regression, indicating the plaque regression may not be due to statin pleiotropy and may be due to LDL-C reduction [10].

The large PCSK9i outcomes trials, SPIRE 1, 2 and FOURIER have been recently published [11, 12]. SPIRE 1, 2 were two randomized controlled trials that compared bococizumab in addition to background statin therapy with placebo [12]. SPIRE 1 examined high risk primary prevention or secondary prevention CAD patients with an LDL-C > 70 mg/dL and found no difference at 7 months in the primary composite endpoint of myocardial infarction (MI), stroke, revascularization, and death despite a 51.5% reduction in LDL-C. SPIRE 2 examined a similar population, but with an LDL-C > 100 mg/dL and did show a reduction in the primary composite endpoint. It should be noted that bococizumab, unlike evolocumab and alirocumab, is a humanized monoclonal antibody. The SPIRE trials were terminated early due to evidence of decreased LDL-C lowering at 1 year resulting from anti-drug antibody development in some patients, which has not been seen in the fully human monoclonal antibodies and the drug is no longer undergoing development. FOURIER compared evolocumab to placebo in those with atherosclerotic disease and LDL-C > 70 mg/dL on background statin therapy and showed a 59% reduction in LDL-C as well as a reduced risk of the primary endpoint at 48 weeks by 15% [11]. However, there was no reduction in either cardiovascular death or death from any cause during the trial [11]. The reduction seen in the primary endpoint was lower than expected based on the previous statin trials, given the significant LDL-C lowering seen with evolocumab, and raises the question if there are clinical effects of statin pleiotropy, or if there is less benefit seen at extremely low LDLC levels. Given that all of the PCSK9i outcomes trials have been done on background statin therapy, it is currently not possible to say if statin pleiotropy has clinical effects, but a study could be designed to compare PCSK9i with statin naïve patients to further investigate the hypothesis.

Trials are currently ongoing, or recently published, that either currently provide, or will provide more evidence for statin pleiotropy. The CANTOS trial is a 10, 061-patient secondary prevention randomized clinical trial that included patients who had a previous MI and elevated CRP and compared the IL-1β inhibitor, Canakinumab, to placebo. The trial was recently published and found that Canakinumab reduced CRP levels compared to placebo, but had no effect on lipid levels at 48 months [91]. Both of the higher dose regimens of Canakinumab reduced the primary composite endpoint of nonfatal MI, non-fatal stroke, and death compared to placebo. There was a higher rate of infection in the treatment group and no change in mortality. This trial provides the strongest current clinical evidence that anti-inflammatory medications reduce cardiovascular events, providing additional support to the hypothesis that inflammation plays a lipid independent role in promoting atherosclerosis. The OSYSEEY Outcomes, testing alirocumab and CIRT examining methotrexate, are both currently ongoing and will provide further information regarding statin pleiotropy, LDL-C lowering, and the clinical effects of anti-inflammatory medications on CAD.

4.2. Stroke

The link between elevated LDL-C and ischemic stroke is not as strong as it is for CAD [92]. However, statins reduce the risk of stroke by 25% in the Treating to New Targets study and the Heart Protection Study and 48% in JUPITER [93–95]. The SPARCL trial showed that atorvastatin works for the secondary prevention of stroke [96]. Recently there has also been trial evidence regarding the non-statin medications and stroke reduction. The IMPROVE-IT trial demon strated that ezetimibe added to statin therapy reduced stroke by 21% and FOURIER showed that evolocumab reduced stroke by 21% [9, 11]. Therefore is not possible to say, based on clinical trial data that stroke reduction is due to statin pleiotropy.

Statin pleiotropy in stroke may be related to the effect of statins on eNOS, given that mice that lack eNOS have increased infarct size, and ROCK inhibitors also increase eNOS and cerebral blood flow which indicates that the effect of statins in stroke may be mediated through Rho/ROCK [30, 32].

4.3. Atrial Fibrillation

AF is a multifactorial disorder that is often the result of a variety of predisposing cardiac and non-cardiac factors such as atherosclerosis, obesity, diabetes, and other pro-inflammatory diseases. AF is associated with increased atrial fibrosis and abnormal autonomic nervous system activity, and despite its association with cardiac risk factors, is not associated with elevated LDL-C [97]. Animal models show that statins may reduce AF by increasing the atrial refractory period, reducing pro-inflammatory markers such as CRP, and desensitization to beta adrenergic stimuli, and the effect was abolished by both GGPP and mevalonate [98, 99]. AF has also been associated with increased atrial oxidative stress and NADPH oxidase activity [100]. Rac1 GTPase regulates NADPH oxidase activity and is associated with AF and statin treatment reduces Rac1 and NADPH oxidase activity as well as the incidence of AF in a mouse model [101].

Based on the basic science data, statin use for the prevention of AF has been examined in statin clinical trials. A JUPITER post-hoc analysis showed a 27% reduced risk of developing

AF, and increased AF incidence was associated with increased CRP – which suggests that the anti-inflammatory effects of statins may reduce AF [102]. There was also a 13% reduced incidence of AF in an ancillary analysis of GISSI-HF [103]. There was a non-statistically significant trend to reduced AF in WOSCOPS [104]. Reduced AF incidence, however has not been seen in other statin trials [105–107]. Multiple meta-analysis have also been done, also with conflicting results regarding AF prevention [108, 109]. While the benefit of statins to prevent AF is not universally seen, it is important to note that in these studies AF was not the primary outcome and was only detected on clinic electrocardiograms or by the discretion of the treating physician and was not evaluated in a systematic way. This tends to reduce the detection of AF, as shown in recent data [110]. With more diligent monitoring, with either event monitors or implantable loop recorders it may be easier to detect an effect of statins.

The effect of statins on AF recurrence in patients with known AF has also been studied. A small randomized placebo controlled trial enrolled patients with an elevated CRP and a previous diagnosis of paroxysmal AF and found a 65% reduction of AF recurrence and a significant reduction in CRP after 6 months of treatment with atorvastatin [111]. J-RHYTHM was a randomized Japanese trial between rate control and rhythm control strategies for the treatment of paroxysmal AF [112]. A post-hoc analysis of the trial examining patients on statins did not show any reduction in AF recurrence in those on statins, but it should be noted that the statin users in the trial were significantly older, more likely to be female, more likely to have CAD, more likely to have a history of ischemic stroke, and more likely to have hypertension then statin non-users, characteristics which may make people more susceptible to AF recurrence [113]. Two small randomized controlled trials have examined the effect of statins after electrical cardioversion for AF and both found a reduced recurrence of AF at 3 months in the statin treated groups [114, 115]. However, reduction in AF recurrence was not seen in other trials of recurrence after cardioversion [116–119]. One randomized trial has been done after AF ablation and found no difference in recurrence rate at 3 months, however given the low recurrence rates in each group (95% free from AF in the atorvastatin group and 93.5% in the placebo group) and the short follow up time, the clinical results of the trial are difficult to interpret [120]. Given the small sizes of the trials and conflicting results, two meta-analysis of controlled trials have been performed and both showed that statins both reduce the recurrence of AF in general and specifically in patients undergoing electrical cardioversion [108, 121]. The heterogeneity of the patient populations, follow up time, and small trial populations make the data on AF recurrence difficult to interpret and a large randomized controlled trial would help provide clarity.

Post-operative AF (POAF) is common after cardiac surgery and is thought to be related both to myocardial injury during surgery and a pro-inflammatory post-operative state [122]. Two large randomized controlled trials have examined statin efficacy for preventing POAF. ARMYDA-3 randomized 200 statin-naive people to atorvastatin or placebo, starting 7 days before surgery and found a 35% reduction in POAF [123]. The STICS trial randomized 1922 patients to rosuvastatin or placebo and found no difference in the incidence of POAF [124]. While STICS is the larger trial, there are important differences between the two trials that may explain the results. While ARMYDA-3 included only statin naïve patients, 34% of the patients in STICS were taking statins prior to trial enrollment, which may have reduced the benefit of statin therapy. Furthermore, while patients in ARMYDA-3 all received a statin for

7 days pre-operatively, in STICS most patients received less then 7 days of therapy, with roughly 44% of the population receiving either statin or placebo for less then 3 days pre-operatively, which may not have allowed for enough time to see the effect of statin therapy on POAF prevention. Additionally, a meta-analysis of the 13 trials of statins in cardiac surgery not including STICS showed an odds ratio (OR) of 0.39 with 95% confidence intervals (CI) of 0.29–0.51 for POAF incidence [124]. Regardless of the differences between trials, there is currently not enough evidence to support that statin therapy reduces POAF after cardiac surgery. The majority of patients undergoing cardiac surgery meet other indications for statin use, and therefore many patients are taking statins prior to cardiac surgery regardless of the results of the STICS trial.

While the incidence of POAF is lower after non-cardiac surgery, statins have been studied in this setting as well. Observational data has suggested that statins may reduce POAF incidence after non-cardiac surgery [125]. Two small randomized controlled trials have been done. One examined atorvastatin given one week before and one week after pul monary resection found a 50% reduction in the incidence of POAF, but the trial was terminated early due to difficulty enrolling statin naïve patients [126]. A second study loaded patients on chronic statin therapy with atorvastatin prior to emergency non-cardiac surgery and found a POAF incidence of 6.8% in the treatment arm and 17% in the placebo arm. Although both of these trials are small, and in different populations, they suggest that there may be a benefit of statin therapy for preventing non-cardiac surgery on POAF and a larger randomized trial would help clarify the effect.

While the studies above suggest a benefit for statin treatment of AF, many of the studies are small and conflicting, which makes drawing any definitive conclusion difficult.

4.4. Ventricular Tachyarrhythmia

Sudden cardiac death (SCD) is due to coronary heart disease in 75% of cases, often due to ventricular arrhythmias (VA), and accounts for 15–20% of all death [127]. Studies of the general population with SCD have shown the majority of patients who undergo angiography after SCD have an acute occlusion [128]. It has also been shown that after MI, SCD is commonly due to repeat MI in the first month, but after 3 months, it is more commonly due to VA [129]. VA’s can be separated into monomorphic ventricular tachycardia (VT) and polymorphic VT. Monomorphic VT is most commonly due to reentry related to scar from an old MI, but can also be seen in other etiologies of cardiomyopathy and with idiopathic etiology. However, acute myocardial ischemia can modify autonomic tone and lead to increased monomorphic VT. Polymorphic VT and ventricular fibrillation can be seen in the setting of acute MI, electrolyte abnormalities, drug toxicities, and inherited channelopathies. Given the diverse mechanisms and etiologies for VA, it is unlikely that statins will reduce all VAs. Additionally, hyperlipidemia has not been identified as a consistent risk factor for SCD in epidemiologic studies of SCD and those with ventricular fibrillation may have less hyperlipidemia then those without ventricular fibrillation [130–132]. It is difficult to separate the CAD risk factors from the presence of CAD in population based studies, since CAD is the most common etiology of SCD. While much of the effects of statins on VA and SCD may be related to reductions in CAD, it has been suggested that statins have other

antiarrhythmic activity that reduce VA. Data has demonstrated that CRP is elevated in those at risk for SCD, which indicates that the anti-inflammatory properties may play a role in SCD reduction [133].

A mouse model showed that statins decrease caveolin-1 expression and promote eNOS while improving heart rate variability, a marker for autonomic function [34]. Statins have also been shown to improve low heart rate variability in humans [134]. Prolonged QTc interval predisposes to VA, primarily polymorphic VT, and statins have been shown to decrease the QTc interval in a small randomized controlled trial in patients with heart failure [135]. Ventricular late potentials represent damaged myocardium that is a substrate for VA [136]. Early statin administration after MI lead to decreased ventricular late potentials and in hospital incidence of VA, but these effects may be due primarily to reduced myocardial ischemia and may not be independent antiar-rhythmic effects [137].

Small observational studies of patients with CAD and implantable cardioverter defibrillators (ICD) found a reduced incidence of VA requiring ICD intervention in those treated with statins [138, 139]. Statin use reduced both monomorphic VT and polymorphic VT, either because statins had an effect on the re-entry circuit, or because they reduced ischemic triggers of both polymorphic and monomorphic VT. The effect was also seen in the MADIT-II trial which enrolled patients with a prior MI, and where statin users had a hazard ratio of 0.65 for VA compared to those not on statins, although the study did not separate monomorphic and polymorphic VT [140]. The same effect was seen amongst patients with non-ischemic cardiomyopathy in the MADITCRT trial, with a 77% reduction in the risk of fast VA or death [141]. In MADIT-CRT there was a decrease in VT cycle length as well a significant reduction in polymorphic VT, and although there was also a reduction in monomorphic VT, the trend did not reach statistical significance. Given that the reduction of VA is seen both in patients with CAD and patients without, this suggests a clinical effect of statins beyond coronary plaque stability and reduction of myocar-dial ischemia, possibly through autonomic modulation and reduction in inflammation.

Unfortunately, information on VA and SCD is not reliably recorded in many of the statin randomized controlled trials and the trials were not powered appropriately to detect a difference in the incidence of SCD and VA. A meta-analysis was therefore done for both the primary and secondary prevention statin trials that reported the outcome and included unpublished data from the trials [142]. The meta-analysis found no reduction of VA (OR 1.02, 95% CI 0.84–1.25, p=0.87), cardiac arrest (OR 1.05, 95% CI 0.76–1.45, p=0.84), but did show a reduction in SCD (OR .90, 95% CI 0.82–0.97, p=.01) with statin therapy [142]. The meta-analysis was unable to determine whether the VAs were polymorphic or monomorphic VT. While the meta-analysis did not show a reduction in VA with statin therapy, VA reporting was heterogeneous and there is likely to be significant under reporting of VAs in the statin trials, which may have reduced the power to detect an effect. Whether or not statins truly have benefit on VA reduction can only be assessed by a large randomized trial.

CONCLUSION

The tremendous clinical benefits of statins in reduction of CAD has been demonstrated in multiple clinical trials and led to the hypothesis that statins have pleiotropic benefits beyond LDL-C lowering. Data has shown that statins have benefits on the endothelium, vascular smooth muscle, platelets, myocardium, and immune system that cannot be explained by LDL-C reduction alone. Much of this benefit is due to inhibition of FPP and GGPP synthesis and the downstream effects on Ras, Rho, Rac, eNOS, and NADPH oxidase. While statins reduce CRP, it has been difficult to conclusively demonstrate pleiotropic statin effects in clinical trials due since cholesterol biosynthesis, FPP, and GGPP are inhibited by statins concurrently. Statins have demonstrated benefit in diseases, such as stroke, which are not clearly linked to LDL-C, but a similar benefit has been seen with the non-statin medications ezetimibe and the PCSK9i. While statins have been postulated to have anti-arrhythmic benefits on AF and VA that are not related to LDL-C reduction, those benefits have not been conclusively demonstrated in all studies. Regardless, statins will remain first line medication for cholesterol reduction and secondary prevention of MI.

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LIST OF ABBREVIATIONS

LDL-C	Low Density Lipoprotein Cholesterol
HMG-CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme
ACAD	Coronary Artery Disease
PCSK9i	Proprotein Convertase Subtilisin Kexin 9 Inhibitors
AF	Atrial Fibrillation
FPP	Farnesylpyrophosphate
GGPP	Geranylgeranylpyrophosphate
ROCK	Rho Kinase
NADPH	Nicotinamide Adenine Di-Nucleotide Phosphate
ROS	Reactive Oxygen Species
LVH	Left Ventricular Hypertrophy
PPAR-γ	Proliferator Activated Receptor γ
NO	Nitric Oxidee
NOS	Endothelial NO Synthase
ECs	Endothelial Cells

SMC	Smooth Muscle Cells
IL	interleukin
CRP	C-Reactive Protein
MI	Myocardial Infarction
POAF	Post-operative AF
OR	Odds Ratio
CI	Confidence Interval
SCD	Sudden Cardiac Death
VA	Ventricular Arrhythmias
ICD	Implantable Cardioverter Defibrillators

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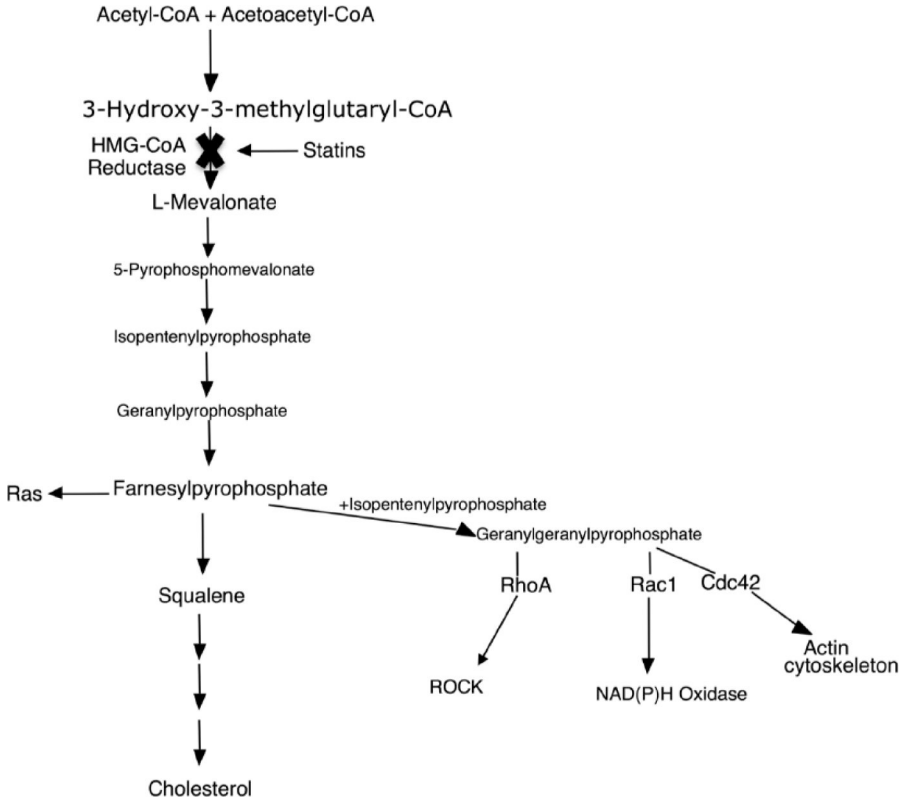

Fig. (1).

Statin Mechanism of Action. Rock – Rho Kinase; NADPH – nicotinamide adenine dinucleotide phosphate.

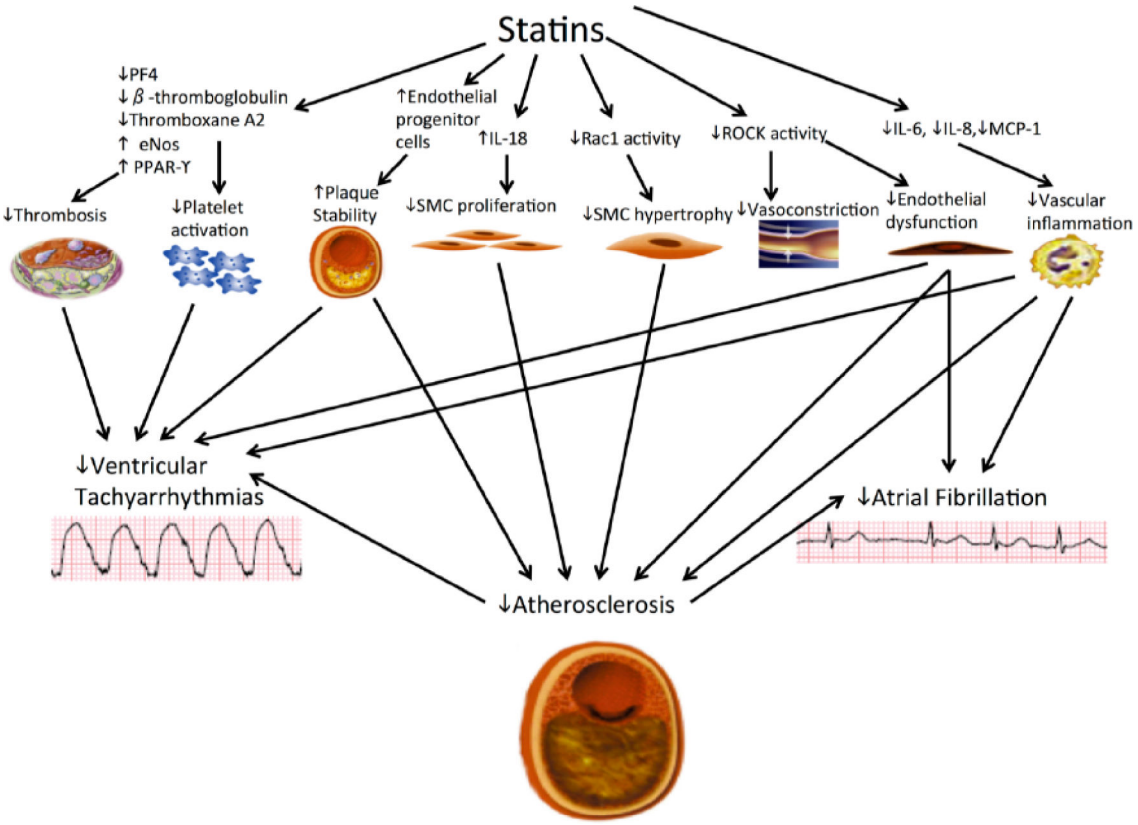

Fig. (2).

Effects of Statins by Different Tissues and Cell Types: There is interplay between the pleiotropic effects of statins and the reduction in atherosclerosis also plays a role in the possible reduction of atrial fibrillation or ventricular tachyarrhythmias that may be seen with statin use. SMC – smooth muscle cell, IL- interleukin, ROCK – rho kinase, PF – platelet factor, eNOS – endothelial nitric oxide synthase.