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Lipid-lowering therapy with statins, a new approach to antiarrhythmic therapy

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Abstract

Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) are the most effective and best-tolerated drugs to treat elevated levels of low-density lipoprotein cholesterol (LDL-C). In addition, they exhibit other effects unrelated to their lipid lowering effects (pleiotropic actions). In recent years, experimental and clinical evidence demonstrates that statins exert antiarrhythmic properties, reducing the recurrences of supraventricular and life-threatening ventricular arrhythmias both in patients with and without coronary artery disease (CAD). Thus, statins may constitute a novel therapeutic approach to cardiac arrhythmias. This article reviews the antiarrhythmic properties of statins as well as the possible mechanisms involved, including the lowering of LDL-C levels, the improvement of endothelial dysfunction and autonomic function, the stabilization of the atherosclerotic plaques, the antioxidant, antiinflammatory, antithrombotic and cardioprotective properties and the modulation of transmembrane ion fluxes.

Keywords: Statins; Cardiac arrhythmias; Atrial fibrillation; Ventricular tachyarrhythmias; Antiarrhythmic actions; Pleiotropic effects

Abbreviations: AF, atrial fibrillation; APD, action potential duration; $ApoE^{-/-}$, apolipoprotein E-deficient mice; ATP, adenosine triphosphate; $[Ca^{2+}]_i$, intracellular Ca^{2+} concentration; CAD, coronary artery disease; CI, confidence interval; CRP, C-reactive protein; GGPP, geranyl geranyl pyrophosphate; GTP, guanosine-triphosphate; HDL, high-density lipoproteins; HF, heart failure; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme-A; HRV, heart rate variability; hsCRP, high-sensitivity CRP; IC_{50}, concentration that produces the half-maximum blockade; $I_{Ca,L}$, inward L-type Ca^+ current; ICD, implantable cardioverter defibrillator; I_{Kur}, ultrarapid component of the delayed rectifier K^+ current; IL, interleukin; ImK, intermediate-conductance Ca^{2+}-activated K^+ channels; I_{Na}, fast inward Na^+ current; I_{NSC}, nonselective cation current; I_{to}, transient outward K^+ current; K_{ATP}, ATP-sensitive K^+ channels; Kv, voltage-gated K^+ channels; LDL-C, low-density lipoprotein cholesterol; L-NAME, L-nitro-arginine methyl ester; LPC, L-α-lysophosphatidylcholine; LV, left ventricular; LVEF, left ventricular ejection fraction; MCP, monocyte chemoattractant protein; MI, myocardial infarction; $MitoK_{ATP}$, mitochondrial K_{ATP} channels; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; NOS3, endothelial nitric oxide synthase; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; RR, risk reduction; SCD, sudden cardiac death; SMC, smooth muscle cell; TF, tissue factor; Th, T-lymphocytes helper; TNF, tumor-necrosis factor; TIMP, tissue inhibitor matrix metalloproteinase; VF, ventricular fibrillation; VSMC, vascular smooth muscle cell; VT, ventricular tachycardia.

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1. Introduction

Cardiac arrhythmias are a leading cause of morbidity and mortality (Rubart & Zipes, 2005). Sudden cardiac death (SCD), caused by ventricular tachyarrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), and less frequently by bradyarrhythmias and pulseless electrical activity, accounts for more than 300,000 deaths annually in the US alone, and it remains a major and unresolved public health problem (Rubart & Zipes, 2005). Coronary artery disease (CAD) is the underlying structural heart disease in at least 80% of victims of these life-threatening ventricular tachyarrhythmias, even when SCD is often associated with other heart diseases, such as dilated nonischemic and hypertrophic cardiomyopathies and heart failure (HF), drugs and assorted noncardiac diseases, and may also occur in healthy young individuals (Zipes & Wellens, 1998).

Although it was hoped that current antiarrhythmic drugs would protect against VT/VF, the results of clinical trials have been quite disappointing. In fact, standard antiarrhythmic drug therapy fails to reduce, or even increases, the incidence of SCD and exhibits important limitations arising from the risk of severe side effects and potentially lethal proarrhythmia (Pratt et al., 1998). The reason for these results could be that for many decades, antiarrhythmic drug development has been concentrated on manipulating membrane cardiac ionic currents, whereas the triggering events and the arrhythmogenic substrates were not taken into consideration. Moreover, diseases most frequently associated with lethal arrhythmias, including CAD and most common cardiomyopathies, do not result from primary abnormalities in ionic channels.

Because most adult patients at risk of SCD in industrialised societies suffer from atherogenic dyslipemias and CAD (Zipes & Wellens, 1998) when considering possible therapeutic approaches, it is appropriate to pay attention to the cellular and molecular mechanisms underlying sudden arrhythmic death in atherosclerotic heart disease. If CAD and occlusive coronary thrombi associated with rupture of the atherosclerotic plaque are the trigger factors of the life-threatening ventricular tachyarrhythmias, the treatment should target the pathogenic mechanisms leading to CAD instead of using standard antiarrhythmic drugs. In fact, the greatest reduction in cardiovascular mortality, including SCD, in patients with a previous myocardial infarction (MI) and HF has been observed with beta-blockers (Gottlieb et al., 1998; López-Sendón et al., 2004) and nonantiarrhythmic drugs, which are those without major direct cardiac electrophysiological effects, such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, aldosterone antagonists, thrombolytic, antithrombotic and lipid-lowering agents (Alberte & Zipes, 2003).

Therefore, it can be speculated that the treatment of hypercholesterolemia in patients with CAD would result not only in a reduction of major coronary events but ultimately also in a reduction of arrhythmic episodes and SCD. Recent evidence has indicated that inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase ("statins") can reduce the incidence of both supraventricular and ventricular arrhythmias in patients with or without CAD. However, this effect is not observed with other lipid-lowering drugs. Therefore, this article focuses on the antiarrhythmic effects of statins. We firstly analyzed the mechanisms involved in ventricular and atrial arrhythmias in patients with CAD, then the experimental and clinical evidence supporting the antiarrhythmic properties of statins and, finally, the possible mechanisms involved in these antiarrhythmic actions.

2. Ventricular arrhythmias in patients with coronary artery disease

Atherosclerosis is primarily a chronic vascular inflammatory disorder characterized by infiltration of the arterial wall by macrophages and T-lymphocytes and elevated levels of inflammation markers such cytokines (tumor-necrosis factor [TNF]-α, interleukin (IL)-1, IL-6, IL-18, CD40 ligand), chemokines (IL-8, monocyte chemoattractant protein [MCP]-1), acute phase reactants (high-sensitivity C reactive protein (CRP), serum amyloid A) and soluble cell adhesion molecules (E- and P-selectins, vascular, intercellular and their counter ligand CD11a/CD18 in the monocyte) (Bellosta et al., 1998; Bonetti et al., 2002; Davignon, 2004; Schonbeck & Libby, 2004; Jain & Ridker, 2005; Liao & Laufs, 2005; Ray & Cannon, 2005). Plaque rupture

followed by superimposed thrombus formation is a major cause of acute coronary syndromes (Conti, 2001; Libby, 2001). Plaque composition and stability, rather than the volume or the severity of stenosis, are the main determinants of atherosclerotic complications (Dupuis et al., 1999). Unstable plaques prone to fissuring or disruption are characterized by a thin fibrous cap, high-lipid content, few smooth muscle cells (SMC), and excess of activated macrophages and T-lymphocytes in the cap (Conti, 2001; Libby, 2001). Activated macrophages play a key role in destabilizing the plaque by their ability to secrete several cytokines, which in turn decreases collagen production by vascular SMC (VSMC), matrix metalloproteinase (MMP) and elastases, which degrades the extracellular matrix, leading to weakening of the fibrous cap and plaque instability (Galis et al., 1994).

We already mention that CAD is the underlying heart disease in 80% of victims of life-threatening ventricular tachyarrhythmias and recent occlusive thrombus is present in 15~64% of patients who died suddenly (Mehta et al., 1997; Zipes & Wellens, 1998; Rubart & Zipes, 2005). Postmortem examinations suggest that SCD victims can be divided into (a) patients without a prior history of heart disease in whom acute coronary thrombosis that leads to fatal VF (sometimes preceded by polymorphic VT) may be the first manifestation of coronary atherosclerosis and (b) substrate-related or nonischemic SCD, which occurs more frequently in the presence of a myocardial scar from a previous MI and impaired left ventricular (LV) function (Mehta et al., 1997). In these patients, scarred myocardium may provide the substrate for reentrant ventricular arrhythmias, most commonly monomorphic VT that may degenerate into VF. In fact, in experimental models acute ischemia superimposed on a previous MI is an arrhythmogenic mechanism, whereas the same degree of acute ischemia in the absence of myocardial scar is not arrhythmogenic (Furukawa et al., 1991). Also, ischemia superimposed at the border zone of a 1-month MI, where reentrant circuits are formed, is more arrhythmogenic than ischemia at a distance from the infarct zone in swine (Cinca et al., 1997). In many patients, however, the combination of both mechanisms, myocardial ischemia and scarring, is probably responsible for the genesis of lethal ventricular arrhythmias.

Abrupt cessation of coronary blood flow decreases cellular adenosine triphosphate (ATP) content and produces marked changes in the distribution of Na^+, Ca^{2+} and K^+ ions across the cardiac membrane (Tomaselli & Zipes, 2004; Rubart & Zipes, 2005). Net cellular K^+ efflux through ATP-dependent, inward rectifier and other voltage-gated K^+ (Kv) channels and subsequent accumulation of K^+ in the interstitial fluid leads to membrane depolarization, slows intracardiac conduction velocity and increases dispersion of ventricular repolarization and refractoriness, effects that facilitate reentrant arrhythmias. Ischemia also inhibits Na^+–K^+ ATPase activity and increases that of the Na^+/H^+ exchanger, effects leading to an increase in intracellular Na^+ concentration. These changes in Na^+ and K^+ across the cardiomyocyte membrane in turn increase the intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via the Na^+–Ca^{2+} exchanger operating in the reverse mode and activate L-type Ca^{2+} channels. This progressive Ca^{2+} overload increases the probability for triggered-induced ventricular arrhythmias associated to delayed afterdepolarizations, whereas augmented L-type Ca^{2+} current ($I_{Ca,L}$) can also lead to ventricular arrhythmias triggered by early afterdepolarizations. Increased Ca^{2+} overload, together with an increased production of oxygen free radicals, acidosis and increased catecholamine levels, would lead to increased automaticity that may facilitate the development of VT/VF.

Recurrent VT in patients with CAD is believed to result also, in part, from cardiac structural remodeling due to the formation of anatomic barriers (interstitial fibrosis), regions of slow conduction and prolonged and heterogeneous repolarization across the ventricular wall (Pfeffer & Braunwald, 1990). An MI often initiates the remodeling process, but ischemia, inflammation, neurohumoral activation, and other factors (including electrolyte and acid–base abnormalities, hypoxia, drug-induced proarrhythmic effects and superimposition of ischemia on a previous MI) continue for years. The importance of remodeling to arrhythmogenesis in CAD is suggested by the delay between MI and the first episode of VT (Anderson, 2003).

The observation that beta-blockers improve survival and reduce the incidence of SCD in patients after MI suggests that in both acute ischemia and substrate-related SCD the increased sympathetic tone plays an important role in the genesis of SCD from VT/VF. (Mehta et al., 1997; Shusterman et al., 1998). In addition to electrical and structural remodeling, neural remodeling in the form of sympathetic nerve sprouting may also result in ventricular arrhythmias in dogs with MI and complete atrioventricular block (Cao et al., 2000a) and in patients with severe HF (Cao et al., 2000b). Myocardial infarction results in sympathetic denervation of regions of necrosis/fibrosis and of myocardium in areas distal to the infarct and hyperinnervation in the periphery of injured myocardium, this latter effect being significantly higher in patients with ventricular tachyarrhythmias (Cao et al., 2000a, 2000b). These changes can create gradients of refractoriness and excitability contributing to the arrhythmogenic substrate and are correlated directly with the occurrence of spontaneous ventricular arrhythmias and SCD. In addition, local elevated noradrenaline levels may induce coronary artery vasoconstriction, increasing myocardial regional ischemia. In a rabbit model, hypercholesterolemia results in cardiac hypertrophy and sympathetic hyperinnervation, increases $I_{Ca,L}$ density and prolongs in an inhomogeneous manner the duration of the ventricular action potentials (QT interval) leading to an increased dispersion of repolarization even in the absence of coronary artery stenosis or MI (Liu et al., 2003). Interestingly, this neural and electrophysiological remodeling is significantly higher in patients with a history of tachyarrhythmias than in the patients without tachyarrhythmias (Cao et al., 2000a, 2000b). The prolongation of the ventricular action potentials and the increase in $I_{Ca,L}$ during sympathetic stimulation could lead to an increase in the $[Ca^{2+}]_i$, which appears to be the common denominator in the generation of triggered activity. Thus, increased sympathetic activity and sympathetic hyperinnervation may be, in part, responsible for the occurrence of ventricular tachyarrhythmias and SCD in post-MI patients (Cao et al., 2000a, 2000b; Rubart & Zipes, 2005).

3. Mechanisms involved in atrial fibrillation

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice and is associated with many forms of heart disease, including CAD, HF, arterial hypertension, valvular disease and cardiac surgery (Fuster et al., 2006). It is associated with significant morbidity and mortality, accounting for over one-third of all strokes over the age of 60 years (Wolf et al., 1987). AF is often a self-perpetuating disease. In many patients initial paroxysms of AF that terminate spontaneously within a few days, become more frequent and of longer duration to the point where they become persistent (i.e., AF requires cardioversion to restore sinus rhythm) and then permanent over time (AF cannot be converted to sinus rhythm). In the past decade we learned that AF results in progressive changes in the electrophysiological, structural and contractile properties of the atria in a way that promotes its maintenance and recurrence (i.e., "AF begets AF") and may alter the response to antiarrhythmic drugs (Nattel, 2002; Tamargo et al., 2004a). Electrical changes include heterogeneous shortening of atrial action potential duration (APD) and refractoriness, loss of atrial refractoriness adaptation to rate and slow intra-atrial conduction, whereas structural changes include atrial dilatation, fibrosis, hypertrophy, fatty infiltration, increase in intracellular glycogen, mitochondrial swelling, sarcoplasmic reticulum disruption, myolysis and patchy apoptosis (Nattel, 2002; Tamargo et al., 2004a; Fuster et al., 2006).

Other factors potentially involved in the induction or maintenance of AF include focal inflammation, endothelial/endocardial dysfunction, oxidative stress, ischemia and autonomic nervous system activity (Tamargo et al., 2004a; Fuster et al., 2006). Evidence for an inflammatory contribution to some forms of AF was initially suggested by the high incidence (25~40%) of AF after cardiac surgery and the association of AF with myocarditis and pericarditis (Boos et al., 2006). Fromer et al. (1990) analyze 2 cases of drug refractory ectopic atrial tachycardia and histopathologic examination of the resected right atria shows right atrial focal myocarditis without concomitant ventricular myocarditis. Thus, they conclude that focal atrial myocarditis may represent 1 cause of drug-resistant ectopic atrial tachycardia. The hypothesis that lone paroxysmal AF may be due to isolated atrial myocarditis is supported by the presence of atrial lymphocytic myocarditis in 66% of the endomyocardial biopsies of the right atrial septum of patients with drug-resistant paroxysmal lone AF (Frustaci et al., 1997) and the prevention of AF recurrences in patients treated with oral methylprednisolone (Dernellis & Panaretou, 2004) or nonsteroidal antiinflammatory medications after coronary artery bypass graft surgery (Cheruku et al., 2004). In patients undergoing cardiopulmonary bypass surgery, the activation of the complement system and the release of proinflammatory cytokines follow a biphasic behaviour. IL-6 levels reached a maximum at 6 hr postsurgery, whereas CRP levels peaked on the second and third postoperative days, coinciding with the peak incidence of atrial arrhythmias (Bruins et al., 1997). Moreover, a close correlation between the −174C/G IL-6 gene variant, the inflammatory response to surgery and the development of postoperative atrial arrhtyhmias has been recently reported (Gaudino et al., 2003). Furthermore, the presence of circulating autoantibodies against cardiac myosin heavy chain in a significant percentage of patients with idiopathic paroxysmal AF raises the possibility of an inflammatory autoimmune process (Maixent et al., 1998).

The presence of systemic inflammation determined by elevations in the levels of high-sensitivity CRP (hs-CRP), a marker of systemic inflammation, has also been associated with persistence of AF. In addition, there is a significant association between circulating hs-CRP levels and risk of future cardiovascular events, including stroke, SCD, plaque rupture, peripheral vascular disease and MI (Ridker, 2001; Szmitko et al., 2003). Levels of CRP are higher in patients with atrial arrhythmias compared with controls in sinus rhythm, those with persistent AF have higher CRP levels than those with paroxysmal AF and both have higher levels than controls (Chung et al., 2001). Moreover, levels of CRP are higher in patients with paroxysmal AF compared with controls and a low CRP level predicts successful cardioversion (Dernellis & Panaretou, 2005). In the *Cardiovascular Health Study* high CRP levels are not only associated with the presence of AF but also predict the patients at increased risk for future development of AF (Avilés et al., 2003). Moreover, CRP levels remain a significant independent predictor of AF even after adjustment for multiple risk factors of AF, including hypertension and CAD (Avilés et al., 2003; Anderson et al., 2004). Thus, and even when the cause of elevated CRP levels in AF patients remains unknown, elevated levels of hs-CRP may reflect an inflammatory state, which subsequently may promote the persistence of the arrhythmia (Chung et al., 2001).

Recent evidence indicates that endothelial dysfunction and increased oxidative stress may also play an important role in maintaining AF (Mihm et al., 2001; Cai et al., 2002; Nattel, 2002; Tamargo et al., 2004a; Fuster et al., 2006). In experimental models, AF induced by rapid atrial pacing is associated with a marked decrease (70%) in endocardial nitric oxide (NO) bioavailability and endothelial NO synthase (NOS3) expression in the left atria, whereas both values remained unaltered in the aorta and right atria (Cai et al., 2002). Rapid atrial pacing also decreases atrial tissue levels of ascorbate, an antioxidant and peroxynitrite decomposition catalyst, and increases atrial oxidative stress and peroxynitrite formation, leading to loss of NO bioactivity. Moreover, the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent superoxide production is increased in the fibrillating human atria, which suggests that reactive oxygen species may play an important role in the atrial oxidative injury and both in the electrical and structural remodeling of the atria in patients with AF (Kim et al., 2005). Supplementation with ascorbate attenuates the pacing-induced atrial effective refractory period shortening and the accumulation of peroxynitrite in chronically instrumented dogs and when given before and for 5 days following cardiac bypass surgery it reduces the incidence of postoperative AF (16.3% vs. 34.9% in control subjects; Carnes et al., 2001).

Experimental data suggest that atrial ischemia may create a substrate for AF maintenance (Sinno et al., 2003; Fuster et al.,

2006). In a canine model, atrial ischemia induced by occlusion of an atrial branch of the right coronary artery that did not provide blood flow to the ventricles promotes the persistence of AF induced by burst pacing, apparently by causing localized atrial conduction slowing within the ischemic zone, which may stabilize atrial reentry that maintains AF (Sinno et al., 2003). In addition, stenosis of the right coronary or the sinoatrial nodal arteries predisposes patients to AF after coronary artery bypass grafting (Mendes et al., 1995; Kolvekar et al., 1997).

Increased sympathetic or parasympathetic tone has been implicated in the initiation of AF. Autonomic ganglia containing parasympathetic and sympathetic fibers are present on the epicardial surface of both atria, clustered on the posterior wall near the ostia of the pulmonary veins, superior vena cava and coronary sinus. In animal models, parasympathetic stimulation shortens atrial and pulmonary vein refractory periods, potentiating initiation and maintenance of AF (Schauerte et al., 2000), whereas vagal denervation of the atria prevents induction of AF (Elvan et al., 1995). Pure autonomic initiation of clinical AF is uncommon and seen only in situations of high sympathetic or high vagal tone but recordings of heart rate variability (HRV) disclose autonomic perturbations that precede the onset of AF in some patients (Bettoni & Zimmermann, 2002; Tomita et al., 2003).

4. Inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase

Statins are the most effective and best-tolerated drugs to treat elevated levels of low-density lipoprotein cholesterol (LDL-C). They competitively inhibit HMG-CoA reductase, which is responsible for converting HMG-CoA to mevalonate, the rate-limiting step for cholesterol synthesis (Fig. 1). The K_i (inhibition constant) values for the statin-enzyme complexes range between 0.1 and 44 nM, whereas Michaelis constant (K_m) for HMG-CoA is 4 μM (Holdgate et al., 2003). Statins possess an HMG-like moiety that inhibits HMG-CoA reductase by binding to the active site of the enzyme, thus sterically inhibiting the substrate from binding. The statins differ from each other in the rigid, hydrophobic structures covalently linked to the HMG-like moiety. Lovastatin, pravastatin and simvastatin are fungal derivatives that share a common hexahydronaphtalene ring present in the structure of compactin, the first statin studied in humans. Fluvastatin, atorvastatin and rosuvastatin are fully synthetic inhibitors containing a fluorophenyl group that forms a structural analog of the HMG-CoA intermediate. Lipophilic statins (atorvastatin, lovastatin, simvastatin) can penetrate easily cell membrane in any organ, whereas hepatic uptake of hydrophilic statins (pravastatin and rosuvastatin) is dependent on the presence of a specific carrier-mediated mechanism (Yamazaki et al., 1993).

Statins inhibit cholesterogenesis in the liver and other tissues, which results in an increased expression of LDL receptors that clear cholesterol-rich LDL and LDL precursors from the circulation (Brown & Goldstein, 1998). Thus, statins reduce levels of total cholesterol (20~35%), LDL-C (25~55%) and triglycerides (10~20%) and increase high-density lipoprotein (HDL) cholesterol (5~10%) levels (Cheung et al., 2004; Cholesterol Treatment Trialists' Collaborators, 2005). Results from both secondary and primary large-scale, multicenter

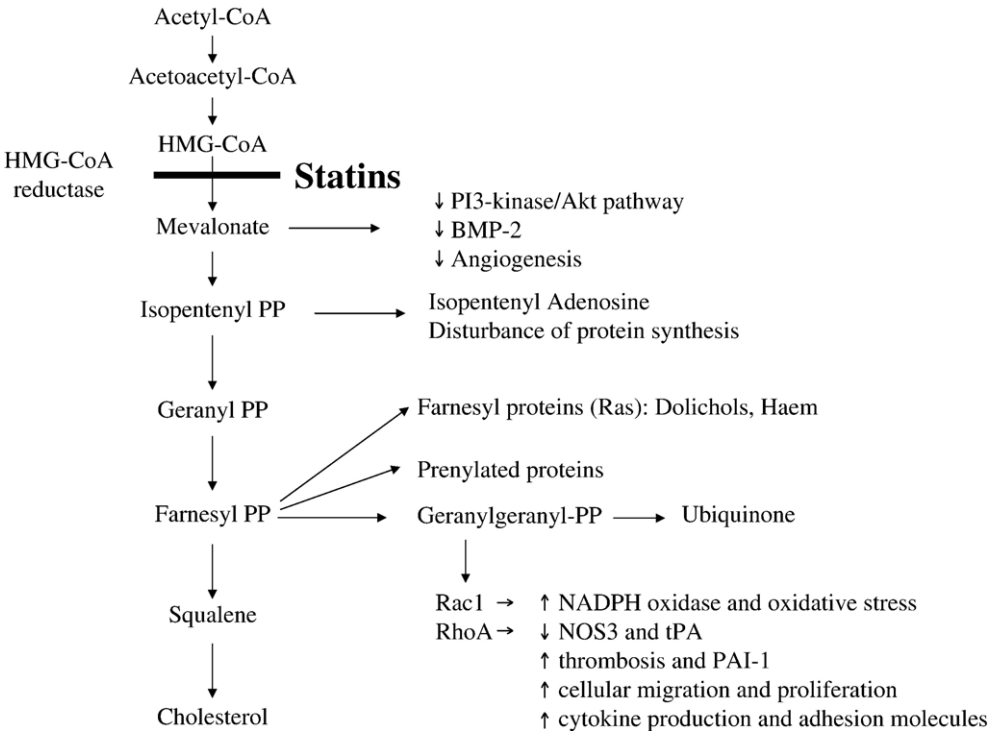

Fig. 1. Molecular pathway for cholesterol synthesis. Inhibition of HMG-CoA reductase inhibits cholesterol synthesis and isoprenoid production. BMP-2, bone morphogenetic protein; NADPH, nicotinamide adenine dinucleotide phosphate; PP, pyrophosphate; NOS3, endothelial NO synthase; PAI-1, plasminogen activator inhibitor-1; PI3, phosphatidylinositol 3-kinase/protein; t-PA, tissue-type plasminogen activator.

prevention trials have consistently demonstrated that statin therapy significantly reduce the risk of major coronary events (unstable angina pectoris, MI, coronary death and need for coronary revascularization), stroke and all-cause and cardiovascular mortality (Cheung et al., 2004; Cholesterol Treatment Trialists' Collaborators, 2005). These beneficial effects are observed in patients with and without CAD, hypercholesterolemia, hypertension, diabetes mellitus and, particularly, in smokers.

4.1. Pleiotropic effects

Although statins exert their major effects on CAD by lowering LDL-C, a multitude of potentially cardioprotective effects have being ascribed to these drugs, largely based on in vitro and ex vivo data (Bonetti et al., 2002; Davignon, 2004). The pleiotropic effects of statins that are summarized in Table 3 have been related to the inhibition of the synthesis of isoprenoid intermediates of the mevalonate pathway, such as isopentenyl adenosine, farnesylpyrophosphate and geranyl-geranyl pyrophosphate (GGPP) (Fig. 1). These intermediates serve as lipid anchors for post-translational modification of a variety of proteins involved in intracellular signal transduction pathways, including heterotrimeric G proteins and small guanosine-triphosphate (GTP)-binding proteins, such as Ras, Rho and Rac1. Indeed, isoprenoids are essential for maintaining membrane fluidity and regulation of cell growth and differentiation, gene expression, cytoskeletal assembly and cell motility, protein and lipid trafficking, nuclear transport, and host defense (Bellosta et al., 1998; Bonetti et al., 2002; Davignon, 2004; Liao & Laufs, 2005).

The pleiotropic actions of statins include improved endothelial function, modulation of autonomic function, stabilization of vulnerable plaques and antioxidant, antiinflammatory, antithrombotic and cardioprotective effects (Table 3). In addition, statins may exert direct antiarrhythmic effects by modulating the physicochemical properties of the cardiac sarcolema resulting in alterations of transmembrane cardiac ion fluxes that may directly affect the electrophysiological properties of cardiac muscle.

5. Effects of statins on cardiac arrhythmias

5.1. Ventricular arrhythmias

5.1.1. Effects in experimental models

In anesthetized rats subjected to 5-min ischemia and 10-min reperfusion, chronic oral administration of pravastatin (0.02, 0.2, or 2 mg/kg for 22 days, once daily) does not modify serum cholesterol but significantly reduces the incidence of ischemia-induced VT (70% vs. 9% at 2 mg/kg) and the incidence of reperfusion-induced lethal VF (90% vs. 20% at 0.2 mg/kg) (Chen et al., 2003). However, acute pravastatin (0.2 or 2 mg/kg, once orally) and chronically administrated fluvastatin (0.2, 2 or 4 mg/kg) have no significant effect on these arrhythmias. In these experiments, there are no significant changes in blood pressure, heart rate, QT interval, and serum cholesterol among pravastatin-, fluvastatin- and vehicle-treated groups. Thus, the antiarrhythmic effects of pravastatin are independent of its cholesterol-lowering effect.

5.1.2. Effects in clinical studies

Two large secondary prevention trials have provided evidence that statins reduced SCD. The *Scandinavian Simvastatin Survival Study* (1994) included patients with CAD and high cholesterol levels. During a follow-up of 5.4 years, the instantaneous death and death within 1 hr (most likely due to VT and/or VF) in the absence of confirmed MI accounted for 63 of 189 in the placebo group as compared to 37 of 111 coronary deaths in the simvastatin group (crude reduction in SCD of 26%) and this reduction in presumable arrhythmic death was less than the effect on all CAD deaths (42%). *The Long-term Intervention with Pravastatin in Ischemic Disease* (The LIPID Study Group, 1998) study enrolled patients with CAD and a broad range of cholesterol levels. In the placebo group, 211 deaths were classified as sudden as compared to 182 in pravastatin-treated patients, which represents a reduction of SCD of 14%. Although in these trials no separate statistical analysis of the SCD was performed, these observations suggest that statins might exert a beneficial effect on the incidence of lethal ventricular arrhythmias and reduce the relative risk of SCD (RR, 0.20; 95% CI, 0.05–0.33) in patients with CAD.

Several studies found that statins can suppress ventricular arrhythmias in patients with or without CAD (Table 1). De Sutter et al. (2000) explore the antiarrhythmic effects of lipid-lowering drugs in an observational nonrandomized study performed in 78 patients with CAD and life-threatening ventricular arrhythmias treated with an implantable cardioverter defibrillator (ICD). Patients with ventricular tachyarrhythmias in the setting of acute MI and those in whom the arrhythmia could not be induced at electrophysiological study after revascularization were excluded. After a mean follow-up of 16 months, patients receiving lipid-lowering drugs (statins, 59%; fibrates, 41%) have a lower incidence of recurrences of VT/VF (22% vs. 57%, $p=.004$) and of the combined end-point of cardiac death and hospitalization (15% vs. 45%, $p=.015$). Moreover, in this study, ICD therapy for fast VT is also significantly lower in patients receiving lipid lowering drugs (11% vs. 35%, $p=.032$). These results suggest that the use of lipid lowering drugs is associated with a reduction of recurrences of ventricular tachyarrhythmias in patients with CAD and ICD implants.

In the *Antiarrhythmics Versus Implantable Defibrillators* (AVID) study including 237 patients with CAD and ventricular arrhythmias treated with an ICD, lipid-lowering therapy (statins, 79%; fibrates, 19%; bile acid resins, 3%) is also associated with a reduction in the relative hazard for VT/VF recurrence (40%, $p=.003$), all-cause mortality (36%, $p=.03$) and cardiac mortality (39%, $p=.04$) (Mitchell et al., 2003). The benefit appears early in follow-up in this study that included patients with several comorbid conditions (congestive HF, 45%; chronic lung, 16%; renal disease, 8%) excluded from the Scandinavian Survival Study Group (1994) and LIPID trials (The LIPID Study Group, 1998). In the *Multicenter Automatic Defibrillator Implantation* (MADIT)-II study, 654 patients receiving an ICD were categorized by the percentage of days each patient received

Table 1
Studies of statins to prevent ventricular tachyarrhythmias

Study	Design/*n*	Medication/subjects	Odds ratio/RRR (95% CI)	Comments
Patients with ICD				
Lipid lowering therapy prevents recurrences of life-threatening VA (De Sutter et al., 2000)	Observational *n*=78	Lipid-lowering users vs. nonusers/patients with CAD and VA treated with an ICD	0.61 (0.34–0.77) (p=.004)	Lipid-lowering drugs is associated with a reduction of recurrences of VA in patients with CAD and ICD implants
On VA recurrence (Mitchell et al., 2003)	Prospective, multicenter, R *n*=237	Lipid-lowering users vs. nonusers/patients with CAD and near-fatal VA with an ICD	0.40 (0.15–0.58) (p=.04)	Lipid-lowering therapy decreases the risk of VA recurrence
On recurrent VA (Chiu et al., 2005)	Prospective *n*=281	Statin users vs. nonusers/patients with CAD treated with a ICD	0.60 (0.41–0.89) (p=.01)	Statin use decreases the risk of VA that would require ICD
On first recurrence VA (De Sutter et al., 2006)	Prospective, R, PC *n*=106	Atorvastatin 80 mg/day vs. no drug/patients with life-threatening VA requiring an ICD	21% vs. 38% 0.47 (0.22–0.98) (p=.04)	Atorvastatin reduces the first recurrence of VA after 1-year treatment
On patients with nonischemic dilated cardiomyopathy (Goldberger et al., 2006)	Prospective, R *n*=458	Statin users vs. nonusers/patients with nonischemic dilated cardiomyopathy at risk for VA	0.22 (0.09–0.58) (p=.001)	Statin therapy reduces the rate of total mortality and arrhythmic sudden death
On patients with an ICD (Vyas et al., 2006)	R, open, parallel-groups *n*=654	Statin users vs. nonusers/patients with a previous MI (EF=30%) receiving an ICD	0.65 (0.49–0.87) (p<.01)	Statins reduce the risk of cardiac detah or VT/VF
Patients without ICD				
On post CABG arrhythmias (Dotani et al., 2000)	Retrospective, nonrandomized *n*=323	Lipid-lowering users vs. nonusers/patients undergoing CABG	0.23 (0.08–0.65) (p=.006)	Preoperative statin use decreases the incidence of death, unstable angina and cardiac arrhythmias (sustained AF, sustained or nonsustained VT and VF)
On acute MI (Kayikcioglu et al., 2003)	Prospective *n*=72	Pravastatin 40 mg/day vs. no drug/patients with acute MI	27% vs. 63% (p=.006)	Statins reduce the incidence of in-hospital VA in acute MI
In patients with systolic HF (Horwich et al., 2004)	*n*=551	Statin users vs. nonusers	0.41 (0.18–0.94) (p=.01)	Statin use decreases mortality and the need of urgent cardiac transplantation
In the acute phase of MI (Fonarow et al., 2005)	Prospective, observational *n*=174,635	Statin users vs. nonusers/ patients with acute MI	3.7% vs. 4.7% 0.23 (0.22–0.25) (p<.001)	Statins given within the first 24 hr of hospitalization for acute MI reduce the rate of VT/VF
On NSVT after ST-elevation MI (Lorenz et al., 2005)	Prospective, multicenter, observational *n*=346	Statin users vs. nonusers/ patients with ST-elevation MI	0.39 (0.15–0.98) (p<.047)	In patients with ST-elevation MI under statin treatment NSVT is not associated with an adverse long-term prognosis
Outcomes after VF out-of-hospital cardiac arrest (Bunch et al., 2006)	*n*=208	Statin users vs. nonusers	0.68 (0.17–0.73) (p=.001)	Statin use was associated with decreased mortality

CABG, coronary artery bypass grafting; CAD, coronary artery disease; 95% CI, 95% confidence interval; EF, ejection fraction; ICD, implantable cardioverter defibrillator MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; PC, placebo-controlled; R, randomized; RRR, relative risk reduction; VA/VF/VT, ventricular arrhythmias/fibrillation/tachycardia.

statins during follow-up (Vyas et al., 2006). In this study, the cumulative rate of ICD therapy for VT/VF or SCD, whichever occurred first, was significantly reduced in those with ≥ 90% statin usage compared to those with lower statin usage (≤ 10%, p=.01). The time-dependent statin/no statin therapy hazard ratio was 0.65 for the endpoint of VT/VF or cardiac death (p<.01) and 0.72 (p=.046) for VT/VF after adjusting for relevant covariates. In another study performed on 281 patients who had CAD and underwent ICD implantation statin therapy was associated with a significant decrease in the risk of ventricular arrhythmias that required ICD therapy (30% vs. 50%, p=.0007), an effect that was attributed to a decrease in ischemia (Chiu et al., 2005). After adjusting for age, LV ejection fraction (LVEF), gender and beta-blocker therapy, hazard ratio for the first ICD therapy among patients who used statins was 0.60 (p=.01). These findings indicate that statins reduce the incidence of life-threatening ventricular arrhythmias in high-risk patients with CAD. Patients with ischemic heart disease are predisposed to worse short- and long-term outcomes after VF out-of-hospital cardiac arrest. In 87 patients who survive to hospital discharge with neurologic recovery, use of an ICD and statin therapy is associated with decreased mortality (Bunch et al., 2006).

Other studies have analyzed the effects of statins in patients undergoing coronary surgery. In a nonrandomized retrospective study performed on 323 patients, preoperative statin therapy significantly reduced the incidences of death, MI, unstable angina and arrhythmias (sustained AF, atrial flutter, sustained or nonsustained VT and VF) (p=.006) 1-year after coronary artery bypass graft surgery (Dotani et al., 2000). In addition, there was an increase in the cardiovascular adverse outcomes among patients taking other lipid-lowering drugs compared to those taking statins (27% vs. 12%, p=.01).

Ventricular late potentials correspond to fragmented activation of ventricular tissue and are thought to originate from areas of slow and inhomogeneous conduction within diseased myocardium. Pravastatin administered early after acute ST-elevated MI (<6 h) decreases the rate of ventricular late potentials and the incidence of in-hospital ventricular arrhythmias (27% vs. 63%,

$p=.021$) and cardiovascular events following thrombolytic therapy (Kayikcioglu et al., 2003). These effects were attributed to the prevention of new myocardial ischemic episodes due to early stabilization of vulnerable plaques, improvement in endothelial function, a decrease in platelet thrombus deposition and a reduction in inflammation. Data from the *National Registry of Myocardial Infarction 4*, a prospective, observational study, also found that new treatment with statins in the first 24 h of admission for acute MI was associated with a decreased risk of in-hospital mortality compared with no statin use (4% as compared with 15.4%, $p<.001$) (Fonarow et al., 2005). Continuation with statin therapy in the first 24 hr of hospitalization for acute MI decreased risk of mortality compared with no statin use (5.3% vs. 15.4%, $p<.001$). In contrast, patients who have been treated with statins before hospitalization but whose therapy was discontinued had a mortality risk that was slightly higher than the risk in patients who did not use statins (16.5% vs. 15.4%, $p>.05$). Early statin use, whether newly initiated or continued, was also associated with a lower incidence of cardiac arrest, cardiogenic shock, cardiac rupture and VT/VF (4.5% and 3.7% vs. 5.6%). Thus, the use of statins within the first 24 hr of hospitalization for acute MI is associated with a significant lower rate of early complications and in-hospital mortality.

Nonsustained VT (NSVT) occurring after acute ST-elevation MI is associated with an increased long-term mortality. In 346 patients with NSVT occurring after acute ST-elevation MI, those without statin treatment and no NSVT, 1 year mortality was 9.2% but increased to 25% (OR, 3.02; 95% CI, 1.47–6.20) if NSVT were present (Lorenz et al., 2005). In patients on statin treatment and no NSVT, 1-year mortality was only 3.2%, and in the presence of NSVT 1-year mortality was not significantly increased anymore (5.3%). Thus, under statin therapy NSVT occurring after acute ST-elevation MI is not associated with an adverse long-term prognosis, suggesting that statin therapy may be associated with a stabilization of myocardium against pro-arrhythmic events (Lorenz et al., 2005).

QT interval dispersion in the surface electrocardiogram, a marker of repolarization inhomogeneity, is a noninvasive method for the evaluation of patients with increased risk of SCD or life-threatening ventricular arrhythmias. Fluvastatin treatment for 12 months decrease the QT dispersion in hyperlipidemic patients, suggesting that statins may also decrease inhomogeneity of ventricular repolarization (Mark & Katona, 2000). In postinfartion patients with severe LV dysfunction, increased QT variability is associated with an increased risk for VT/VF (Haigney et al., 2004). In a prospective case-control study on 80 patients with depressed LV function (LVEF< 0.30%) and in New York Heart Association (NYHA) class III for at least 2 months, atorvastatin shortened the QT interval and decreased QT variability and these effects were independent from changes in LDL-C levels (Vrtovec et al., 2005).

Nevertheless, the evidence demonstrating that statins reduce the recurrence of ventricular arrhythmias in CAD patients with ICDs is based on small observational studies or retrospective analyses and data from randomized, placebo-controlled studies were lacking. Very recently, however, 2 randomized trials support that the addition of statins to ICD device therapy in patients with ischemic and nonischemic diseases reduces life-threatening arrhythmias and improves survival. The *Cholesterol Lowering and Arrhythmia Recurrences after Internal Defibrillator Implantation* (CLARIDI), presented at the Heart Rhythm Society 2006 Annual Scientific Sessions, is a prospective, randomized, placebo-controlled study performed in 106 patients with CAD and life-threatening ventricular arrhythmias requiring an ICD (De Sutter et al., 2006). Forty-five percent of the patients have congestive HF (mean LVEF 39%) and 85% a previous history of acute MI. After 1-year follow-up, atorvastatin therapy (80 mg/day) results in a significant reduction in the first recurrence (21% vs. 38%) of ventricular arrhythmias requiring an appropriate ICD treatment. Moreover, a substudy of the DEFINITE (*Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation*) trial demonstrates in ICD patients with nonischemic dilated cardiomyopathy (LVEF ≤ 35%) at risk for ventricular arrhythmias that statin users have lower rates of total mortality and arrhythmic SCD than nonstatin users, regardless of whether they were randomized to ICD or medical therapy (Goldberger et al., 2006). Compared with no statin use, statin therapy reduces the rate of total mortality/resuscitated cardiac arrest (4.5% vs. 18.4%, $p<.001$) and SCD (0.9% vs. 5.2%, $p=.043$).

5.2. Atrial fibrillation

5.2.1. Effects in experimental models

Several experimental studies have demonstrated that statins reduce the incidence of AF. In a canine model of AF induced by rapid atrial pacing simvastatin suppresses tachypacing-induced shortening of atrial refractoriness and virtually abolishes AF (Shiroshita-Takeshita et al., 2004). However, these effects are not shared by the antioxidant vitamins C and E. In a canine model of sterile pericarditis, elevated CRP levels are associated with sustained AF, suggesting that electrophysiological changes resulting from inflammation may perpetuate the arrhythmia (Kumagai et al., 2004). In this model, atrial myocytes show active perimyocarditis which consisted of patchy inflammatory infiltration and lipid degeneration and extensive interstitial fibrosis. These inflammatory changes may contribute to atrial structural remodeling and increase the propensity of the arrhythmias to persist. Atorvastatin-treated animals have lower CRP levels, longer atrial refractoriness and shorter intra-atrial conduction times and shorter AF duration than the control group (Kumagai et al., 2004). These results suggest that atorvastatin can prevent atrial electrical and structural remodeling and the maintenance of AF by inhibiting inflammation.

5.2.2. Effects in clinical studies

Clinical studies also support the efficacy of statins in maintaining sinus rhythm in patients with persistent AF (Table 2). In a retrospective study performed in 62 patients with lone persistent AF, statin therapy decreases the risk of AF recurrences (42% vs. 84%, $p=.032$) after successful direct current cardioversion without affecting the defibrillation threshold (Siu et al., 2003). The beneficial effect of statins is observed during the first few months and remains during the long-term follow up of 44 months. In

Table 2
Studies of statins to prevent AF

Study	Design/*n*	Medication/subjects	OR/RRR (95% CI)	Comments
Prevention of AF recurrence after cardioversion (Siu et al., 2003)	Retrospective *n*=62	Statin users vs. nonusers/ patients with persistent lone AF (>3 months)	0.31 (0.10–0.90) (p=.032)	Patients on statins had higher cholesterol and were older than nonusers; statins decrease recurrent AF after cardioversion
Statins in protecting against AF (Young-Xu et al., 2003)	Retrospective *n*=449	Statin users vs. nonusers/ patients with CAD in SR at high risk of AF	0.48 (0.28–0.83) (p=.01)	Effect independent of changes in LDL-C; dose–response relation between length of statin use and reduction of AF
Reduction of AF after cardiac surgery (Auer et al., 2004)	*n*=253	Statin users vs. nonusers/ patients undergone major cardiac surgery	45.9% vs. 32.8% (p<.05)	Statins decrease the rate of postoperative AF in patients undergoing cardiac surgery
Recurrences of AF after ECV (Colivicchi et al., 2004)	*n*=476	Statin users vs. nonusers	0.72 (0.54–0.97) (p=.034)	Statins user had a reduction of recurrence at 1-year follow-up
Reduction of new-onset AF (Merckx et al., 2004)	*n*=667	Statin users vs. nonusers/ patients with CAD	(7.3% vs. 11.6%)	Lower rate of new-onset AF during a mean follow-up of 6.5 years
Prevent recurrences of AF after ECV (Tveit et al., 2004)	Prospective, OL, R, multicenter *n*=114	Pravastatin, 40 mg/day, vs. no drug	35% vs. 33% (CI not available)	Pravastatin does not reduce the recurrence of AF after ECV at 6-weeks follow-up
AF after noncardiac thoracic surgery (Amar et al., 2005)	Prospective *n*=130	Statin users vs. nonusers/ patients undergone major lung or esophageal resection	0.26 (0.08–0.82) (p=.022)	Preoperative use of statins reduces postoperative AF independent of CRP levels
Statins on paroxysmal AF (Dernellis & Panaretou, 2005)	SB, PC, R, prospective, parallel design *n*=80	Atorvastatin (20-40 mg/day) users vs. nonusers/patients with paroxysmal AF	10% vs. 65% (p<.001)	Atorvastatin reduces the incidence of paroxysmal AF
Reduction of AF after CABG (Marín et al., 2006)	*n*=234	Statin users vs. nonusers/ patients undergoing CABG	0.52 (0.28–0.96) (p=.038)	Statins protect against AF after CABG
Recurrence rates of AF after ECV (Ozaydin et al., 2006)	Prospective, R *n*=99	Atorvastatin (10 mg/day) vs. no drug/persistent AF	0.23 (0.064–0.82) (p=.024)	Atorvastatin decreases the recurrence rate of AF after ECV
Patients with reduced LVEF at high risk of subsequent AF (Hanna et al., 2006)	National Registry *n*=25,268 in SR	Lipid-lowering drugs users vs. nonusers	0.69 (0.64–0.74)	In patients with reduced LVEF statin use is associated with a significant reduction in the prevalence of AF
Patients undergoing cardiac surgery with cardiopulmonary bypass (Patti et al., 2006)	Prospective, R, DB, PC *n*=200	Atorvastatin (40 mg/day) initiated 7 days before surgery vs. placebo	35% vs. 57% 0.39 (0.18–0.85) (p=.017)	Atorvastatin reduces the incidence of postoperative AF and shortens the length of stay

AF, atrial fibrillation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; 95% CI, 95% confidence interval; CRP, C-reactive protein; DB, double-blind; ECV, electrical cardioversion; LDL-C, low density lipoprotein-cholesterol; OL, open-label; OR, odds ratio; PC, placebo-controlled; R, randomized; RRR, relative risk reduction; SB, single-blind; SR, sinus rhythm.

another 449 patients with chronic CAD followed by an average of 5 years, statins significantly reduce the risk of developing AF (8% vs. 15%, p=.01) and this effect is independent of their cholesterol-lowering ability (Young-Xu et al., 2003). This association remains significant after adjustment for potential confounders, including age, hypertension, LV systolic function, HF, acute ischemic events, baseline cholesterol and changes in cholesterol levels. Interestingly, in this study the incidence of AF is not reduced in patients treated with nonstatin lipid-lowering drugs such as gemfibrozil, cholestyramine, colestipol and probucol. Moreover, there is a relation between length of statin use and reduction of AF and the incidence of AF did not differ between users of nonstatin cholesterol-lowering drugs and nonusers. In another study, paroxysmal AF recorded in ambulatory electrocardiographic monitoring during everyday life was completely resolved in 65% of the patients treated with atorvastatin but only in 10% of the patients in the placebo group (p<.019) (Dernellis & Panaretou, 2005). The treatment group has also lower median CRP. In another prospective randomized study performed in 99 patients with persistent AF lasting > 48 hr who were scheduled for electrical cardioversion, those receiving atorvastatin have a higher probability for maintaining sinus rhythm compared with those who receive no drug (p=.024) (Ozaydin et al., 2006). Finally, in a multicenter registry of 25,268 patients with reduced LVEF (≤ 40%), prevalence of AF was significantly lower in patients taking lipid-lowering drugs (25.1%) compared with patients with untreated hyperlipidemia or with those not having hyperlipidemia (32.6% and 32.8%, respectively; p<.001 for both comparisons; OR, 0.69; 95% CI, 0.64–0.74) (Hanna et al., 2006). This beneficial impact is independent of the lipid profile and other known arrhythmia risk factors.

Another 2 studies concluded that statins might help in both primary and secondary prevention of AF. The first study found a lower rate of new onset AF in 667 patients at risk taking statins (7.3% vs. 11.6%), an effect restricted to those older than 65 years (Merckx et al., 2004). The other study showed that after successful pharmacologic or direct current cardioversion, statin therapy was associated with a lower risk of recurrence of persistent AF among hypertensive patients after 1-year follow-up (50.6% vs. 58.5%, p=.034) (Colivicchi et al., 2004).

However, not all the available evidence supports the benefits of statins in preventing AF recurrence. In an open study performed in 114 patients with AF>48 h who were scheduled for electrical cardioversion, pravastatin (40 mg/day) for 3 weeks before and 6 weeks after cardioversion does not affect immediate electrical cardioversion success or the recurrence rate of AF after

cardioversion (Tveit et al., 2004). The small sample size, the short length of treatment and the duration of AF prior to treatment could play a role in not finding differences between the groups.

AF is a frequent complication after cardiothoracic surgery, occurring in up to 40% of patients. Postoperative AF increases in-hospital morbidity and mortality, length of hospital stay and costs (Fuster et al., 2006). Preoperative use of statins reduces incidence of postoperative AF following coronary artery bypass grafting (Auer et al., 2004; Marín et al., 2006) and after major noncardiac thoracic (lung and esophageal resection) surgery (Amar et al., 2005). In patients undergoing coronary artery bypass grafting, statin therapy is associated with increased levels of tissue inhibitor matrix metalloproteinase (TIMP)-1 and lower concentrations of MMP-1, which suggests that statins could also be protective against AF possibly by inhibiting extracellular matrix remodeling in the atria (Marín et al., 2006). In 253 patients from the SPPAF (*Study for Prevention of Postoperative Atrial Fibrillation*) trial, those undergoing cardiac surgery without statin therapy have a significantly higher risk of postoperative AF compared to statin users (45.9% vs. 32.8%, $p<.05$) (Auer et al., 2004). In patients who have undergone major noncardiac thoracic surgery, the preoperative use of statins is associated with a 3-fold decrease in the odds of developing AF and this benefit occurs independently of increases in the levels of 2 markers of inflammation, such as CRP or IL-6 (Amar et al., 2005).

Very recently, the *Atorvastatin for Reduction of MYocardial Dysrrhythmia After cardiac surgery* (ARMYDA-3), a randomized, prospective, placebo-controlled trial, studied the effects of atorvastatin in 200 patients undergoing elective cardiac surgery with cardiopulmonary bypass (Patti et al., 2006). Treatment with atorvastatin, starting 7 days before cardiac surgery and continued in the postoperative period, significantly decreases postoperative AF (35% vs. 57%) and shortens the postoperative hospital stay (6.3 vs. 6.9 days, $p=.001$). Subgroups analysis show that atorvastatin treatment results in a lower risk of AF in patients irrespective of age, sex, presence of diabetes mellitus, hypertension and chronic obstructive pulmonary disease. Treatment benefit was more evident in patients undergoing coronary bypass operations and in those with a normal-sized left atrium, whereas it was absent after noncoronary surgery and in patients with left atrial enlargement.

6. Mechanisms of action involved in the antiarrhythmic effects of statins

6.1. Antiischemic effects

The mechanisms by which statins exert their antiarrhythmic effects have not yet been characterized at the cellular level. It can be hypothesized that in patients with CAD the antiarrhythmic effects and the reduction in SCD observed in secondary prevention trials may simply reflect their ability to lower the LDL-C levels, thereby attenuating the progression of CAD and, in some patients, promoting the regression of coronary atherosclerotic plaques. As a result, statins would reduce the number of new ischemic episodes that could have triggered the arrhythmogenic substrate to initiate and/or maintain both atrial and ventricular tachyarrhythmias.

Statins exert cardioprotective effects in an isolated perfused rat heart model of global myocardial ischemia and reperfusion in normocholesterolemic, hypercholesterolemic and diabetic animal models (Lefer et al., 1999; Wagner et al., 2000; Lefer et al., 2001; Chen et al., 2003) and in apolipoprotein E-deficient ($apoE^{-/-}$) mice fed with a high-cholesterol diet (Scalia et al., 2001). In these models, statins improve coronary blood flow, preserve LV developed pressure and cardiac contractile function, reduce the extent of myocardial necrosis, the leukocyte-endothelial cell interaction and the polymorphonuclear leukocytes accumulation in the ischemic myocardium and increase the NO production in the vasculature. Moreover, statins reduce transient ischemia even in patients with optimal anti-anginal therapy (Van Boven et al., 1996) and in patients with acute coronary syndrome, early and aggresive, lipid-lowering therapy with atorvastatin (80 mg/day) reduces recurrent ischemic events, mostly those requiring rehospitalization (Schwartz et al., 2001; Colivicchi et al., 2002).

Infarct size is markedly limited when brief periods of ischemia precede the sustained ischemia, a phenomenon known as ischemic preconditioning. Hypercholesterolemia blunted the infarct size-limiting effect of ischemic preconditioning and pravastatin restores the infarct size-limiting effect of ischemic preconditioning possibly via restoring the activation of ecto-5′-nucleotidase activity which, in turn, increases interstitial adenosine release (Ueda et al., 1999). Moreover, pretreatment with pravastatin enhances the adaptation of ischemia during coronary angioplasty, an effect abolished by aminophylline, which suggests that its cardioprotective effect may result from activation of adenosine receptors (Lee et al., 2004).

Several lines of evidence, however, indicate that the antiarrhythmic effects of statins are independent of their LDL-C lowering effects. (1) These antiarrhythmic effects are observed both in patients with normocholesterolemia and/or hypercholesterolemia and with or without CAD. (2) Ischemia is rarely present in patients with recurrent ventricular tachyarrhythmias before the onset of recorded spontaneous sustained VT. Moreover, ventricular tachyarrhythmias can often be initiated by programmed electrical stimulation in the absence of ischemia and coronary revascularization does not prevent recurrent ventricular arrhythmias in the chronic phase of MI (Anderson, 2003). (3) The magnitude of the survival benefit associated with statin therapy in patients with propensity to life-threatening VT/VF is higher than that reported from mortality trials in patients without such a demonstrated propensity (Scandinavian Survival Study Group, 1994; The LIPID Study Group, 1998). (4) The antiarrhythmic effect occurs relatively early in the follow-up. In fact, the Kaplan-Meier curves of arrhythmia-free survival for patients with and without statin therapy started to diverge very early (within 1–2 months of follow-up), long before any angiographically measurable regression of atherosclerosis (Mitchell et al., 2003; Vyas et al., 2006). Thus, reversal of atherosclerosis and/or retardation of plaque development associated could not be the sole reason for the

atiarrhythmic actions of statins observed in patients with CAD and the benefits of statins extent to mechanisms beyond their LDL-C lowering effects, that is, the so-called pleiotropic effects (Table 3).

6.2. Role of pleiotropic effects on the antiarrhythmic effects of statins

The molecular mechanisms of the pleiotropic effects of statins have been analyzed in detail previously (Bellosta et al., 1998; Bonetti et al., 2002; Davignon, 2004; Liao & Laufs, 2005). In this article we shall focus our interest in the cardiac pleiotropic effects of statins that may be involved in their antiarrhythmic actions.

6.2.1. Antiinflammatory effects

Plasma CRP are elevated in patients at risk for future cardiovascular events (Ridker, 2001). Statins exhibit potent antiinflammatory effects reducing the levels of the hs-CRP in experimental models of AF (Kumagai et al., 2004) and in patients with combined hyperlipidemia and with CAD (Albert et al., 2001; Jialal et al., 2001; Ridker et al., 2001). In the *Cholesterol and Recurrent Events* (CARE) trial, risk reduction in patients with CAD receiving statins was greater in those with higher CRP levels for a similar degree of LDL-C lowering (Ridker et al., 1999; Ridker, 2001). These results suggest that statin therapy may improve the inflammatory arrhythmogenic substrate in patients with both supraventricular and ventricular arrhythmias. Moreover, this antiinflammatory effect could be part of the mechanism of the stabilization of atherosclerotic plaques.

Table 3
Pleiotropic actions related to the antiarrhythmic effects of statins

(1) Antiinflammatory properties
- ↓ macrophage number and activation
- ↓ expression of adhesion molecules and leukocyte-endothelial interactions
- ↓ inflammatory cytokine secretion by macrophages
- Switch Th-1 to Th-2 type phenotype in lymphocytes and ↑ anti-inflammatory cytokine production

(2) Stabilization of vulnerable plaques
- ↑ SMC and collagen
- ↓ MMPs in atheroma plaque
- ↓ LDL uptake and oxidation by macrophages

(3) Improvement of endothelial dysfunction
- ↑ NO levels by stabilizing mRNA
- ↑ NO bioavailability
- ↑ expression and activity of NOS3
- ↓ endothelin-1 expression

(4) Antioxidant effects
- ↓ oxidative stress and reactive oxygen species

(5) Cardioprotective effects
- ↓ cardiac and smooth muscle hypertrophy and cardiac fibrosis

(6) Improvement of autonomic function
- ↓ HRV and sympathetic function

(7) Antithrombotic effects
- ↓ platelet activation
- ↓ coagulation factors
- ↓ tissue factor (TF) expression
- ↑ fibrinolytic activity (tPA/PAI-1 ratio)
- ↑ thrombomodulin expression

(8) Effects on cardiac ion channels and transporters
- ↓ Na^+-pump and Na^+/Ca^{2+}exchanger
- ↓ $I_{Ca,L}$ and I_{Kr}
- ↓ hKv 1.5, Kv 4.3 and ImK channels
- ↑ K_{ATP} channels

6.2.2. Improvement of endothelial dysfunction

Clinical studies provide evidence for a close association between the degree of endothelial dysfunction and clinical cardiovascular events in patients with cardiovascular risk factors, CAD or HF (Landmesser & Drexler, 2005). Statins improve coronary endothelium dysfunction and myocardial perfusion and preserve coronary microvascular integrity in hypercholesterolemic patients with CAD (Wassmann et al., 2002; Wassmann & Nickenig, 2002; Landmesser & Drexler, 2005; Liao & Laufs, 2005). High doses of atorvastatin improve peripheral endothelial function within 24 hr, but this effect disappears 1 day after discontinuation of the drug (Laufs et al., 2001). This improvement occurred before levels of LDL-C and hs-CRP decrease after 2 days of treatment, suggesting that the beneficial effects of statins are independent of LDL-C lowering or the modulation of the inflammatory state. Improvement of coronary endothelial dysfunction and myocardial perfusion would be expected to reduce the ischemic arrhythmogenic substrate.

6.2.3. Stabilization of vulnerable plaques

Atherosclerotic plaque rupture underlies the onset of around 70% of acute coronary syndromes so that modulation of plaque instability would reduce the incidence of acute coronary events and the ischemic arrhythmogenic substrate. Statins reduce the lipid core and lipid-laden macrophages and increase the relative volume of collagen within the plaque (Bellosta et al., 1998; Williams et al., 1998; Aikawa et al., 2001; Sukhova et al., 2002). They also inhibit monocyte infiltration (Bustos et al., 1998) and the activation of the monocyte/macrophage system reducing the release of proinflammatory cytokines and MMP within the plaque (Bellosta et al., 1998; Luan et al., 2003). In patients with symptomatic carotid artery stenosis, plaques removed by endarterectomy from the statin-treated patients present significantly less lipid and oxidized LDL immunoreactivity, fewer macrophages and T cells and less MMP-2 immunoreactivity, and cell apoptosis than control plaques (Crisby et al., 2001). In addition, plaques had higher collagen content and immunoreactivity to tissue inhibitor of metalloproteinase-1 (a potent inhibitor of MMP-1 and MMP-9) in the pravastatin group. These effects, which occurred independently of LDL-C levels, indicate that statin therapy is associated with changes in atherosclerotic plaque composition that favor lesion stability and reduce the risk of rupture and of acute coronary events (Bellosta et al., 1998; Bonetti et al., 2002; Luan et al., 2003; Liao & Laufs, 2005).

6.2.4. Antioxidant effects

Formation of the oxygen-derived free radical superoxide by NADPH oxidases plays a critical role in the development of a wide range of cardiovascular diseases, including AF (Kim et al., 2005). Reactive oxygen species may alter channel kinetics, including a decrease in Na^+ channel availability (Fukuda et al., 2005) and increasing the amplitude of the ultrarapid component of the delayed rectifier K^+ current (I_{Kur}) (Caouette et al., 2003), leading to slowing of conduction velocity and shortening of the cardiac APD, respectively, effects that facilitate the initiation and/or maintenance of AF. Moreover, abnormal activation NADPH oxidases in response to neurohormones (angiotensin II, norepinephrine) has been shown to contribute to cardiac myocyte hypertrophy and fibrosis (Sorescu & Griendling, 2002).

Statins reduce the NADPH oxidase-dependent production of reactive oxygen species (superoxide and hydroxy radicals) by activated macrophages (Suzumura et al., 1999; Rikitake et al., 2001), endothelial cells (Wagner et al., 2000; Feron et al., 2001; Wassmann et al., 2002) and isolated human atrial preparations obtained during cardiac bypass surgery (Maack et al., 2003). Moreover, statins enhance the activity of antioxidant enzymes such as catalase, gluthatione peroxidase and paraoxonase (Wagner et al., 2000; Dechend et al., 2001; Feron et al., 2001; Wassmann et al., 2002). However, the antioxidant effects of most statins appear only at suprapharmacological (μM) concentrations so that its physiological relevance is uncertain. Only the active O-hydroxy metabolite of atorvastatin but not the parent compound exerts potent antioxidant effects inhibiting LDL oxidation at pharmacological (nM) concentrations, being more potent than vitamin E or probucol (Mason et al., 2004).

6.2.5. Cardioprotective effects

Epidemiological studies found that hypercholesterolemia is associated with LV hypertrophy (Sundstrom et al., 2001), a major independent risk factor for total and cardiovascular mortality and SCD (Levy et al., 1990). Myocardial infarction frequently produces alterations in the geometry and structure (dilatation, hypertrophy, interstitial fibrosis) of noninfarcted ventricular myocardium, referred to as remodeling, that contributes to the development of depressed cardiac performance and is an important component of the arrhythmogenic substrate in post-MI patients (Pfeffer & Braunwald, 1990).

Statins inhibit cardiac hypertrophy induced in normotensive rats by aortic binding (Takemoto et al., 2001; Indolfi et al., 2002) or angiotensin II infusion (Oi et al., 1999), spontaneously hypertensive rats (Lee et al., 2005b), hypercholesterolemic rabbits (Lee et al., 2005a) and transgenic rats for human renin and angiotensinogen (dTGR) (Dechend et al., 2001). In hyperlipidemic patients, pravastatin reduces LV mass, and the LV mass regression correlates with the magnitude of inhibition of free radical formation assessed by 8-iso-prostaglandin F2α formation (Lee et al., 2002). These antiproliferative effects are independent of blood pressure or LDL-C reduction but are reversed by mevalonate, suggesting that they are related to the blockade of the synthesis of isoprenoids.

Since CAD represents the most common cause of chronic HF, it may be not a surprise that statins may reduce the risk of developing HF after MI. In a normocholesterolemic murine model of congestive HF after MI, statin therapy normalizes the sympathetic outflow, reduces LV dilatation and LV end-diastolic pressure, cardiac hypertrophy and interstitial fibrosis of the noninfarcted LV without affecting the infarct size, improves LVEF and reduces death due to HF and arrhythmias (Bauersachs et al., 2001; Dechend et al., 2001; Hayashidani et al., 2002). In normolipidemic rats, pravastatin administration after MI attenuates cardiomyocyte hypertrophy and reduces the inducibility of ventricular tachyarrhythmias (Lee et al., 2003). It is important to note that although in these models HF was induced by an initial episode of ischemia and infarction, ongoing pathological ventricular remodeling is unrelated to further ischemic events on the failing ventricle. Thus, the beneficial effect of statins is unrelated to their impact on subsequent ischemia (Krum & McMurray, 2002). Neurohumoral activation plays a central role in the pathogenesis of LV hypertrophy and HF and statins inhibit the expression of endothelin-1, a potent vasoconstrictor and mitogen, and beta-adrenergic receptor-stimulated apoptosis in rat ventricular myocytes and decrease angiotensin II type 1 receptors (Laufs et al., 2006) and exert a favorable modulation of the autonomic nervous system (see Section 6.2.6).

Even when HF patients were excluded in large statin trials and LVEF was either measured or studied in only a small number of patients, *post hoc* analyses of statin trials have shown their beneficial effects in patients with ischemic HF (Sacks et al., 1996; Kjekshus et al., 1997; Krum & McMurray, 2002; Raina et al., 2006). Moreover, retrospective analyses of statin use in patients enrolled in HF clinical trials show that statin use is associated with improved survival and less development of HF after MI (Raina et al., 2006). Several studies have recently reported that in patients with normal (Fukuta et al., 2005; Folkeringa et al., 2006) or reduced LVEF (< 0.40) (Christensen et al., 1999; Huikuri et al., 1999; Horwich et al., 2004; Ray & Cannon, 2005; Sola et al., 2005, 2006), statin therapy improves exercise tolerance and LVEF, lowers NYHA class, reduces markers of inflammation (hs-CRP, IL-6 and TNFα) and decreases hospitalizations for HF and all-cause mortality. There are no difference in survival among patients treated with statins who had ischemic or nonischemic HF. A similar benefit was observed in patients with nonischemic idiopathic dilated cardiomyopathy (Node et al., 2003).

Since LV hypertrophy and remodeling play an important role in the arrhythmogenic substrate that initiates and/or maintains cardiac arrhythmias in patients with hypertension, CAD and HF, it would be expected that statin therapy would reduce the arrhythmogenic risk in these populations. The possible putative mechanisms to explain the beneficial effects of statins in HF patients include prevention of ischemic coronary events through LDL-C lowering, improvement of microvascular circulation and endothelial function, plaque stabilization, reduction of cardiac hypertrophy and fibrosis, neurohumoral activation and ventricular wall stress, and to their antioxidant, antiinflammatory and direct antiarrhythmic effects (Krum & McMurray, 2002; Laufs et al., 2006).

6.2.6. Improvement of autonomic function

We already mention that sympathetic activity and sympathetic hyperinnervation participate in the occurrence of ventricular tachyarrhythmias and SCD in post-MI patients (Cao et al., 2000a, 2000b; Rubart & Zipes, 2005). Low HRV, which probably reflects a decrease in vagal tone and/or an increase in sympathetic tone, is associated with an increased risk of coronary events, all-cause mortality and susceptibility to ventricular arrhythmias in patients with CAD and is negatively affected by hypercholesterolaemia (Quintana et al., 1997; Huikuri et al., 1999). In apoE$^{-/-}$ mice (Pelat et al., 2003) and in a rabbit model of pacing-induced congestive HF (Pliquett et al., 2003), statins normalize autonomic sympathetic outflow and baroreceptor responses, decrease plasma noradrenaline levels and renal sympathetic nerve activity and increase HRV. Hypercholesterolemia is also associated with a decreased HRV in men with and without CAD, suggesting an increased risk of SCD (Christensen et al., 1999).

In patients with hypercholesterolemia pravastatin increases parasympathetic modulation of heart rate, an effect associated with an increased expression of the α-subunit of the heterotrimeric G-protein, $G_{\alpha i2}$ (Welzig et al., 2003). Atorvastatin improves autonomic function, as reflected by an increase in HRV level in hypercholesterolemic patients, with or without CAD (Pehlivanidis et al., 2001), and long-term administration of pravastatin in patients with stable angina pectoris (Van Boven et al., 1995). Statins also increase HRV in patients with previous MI with or without HF, and this effect is independent from changes in plasma LDL-C levels (Riahi et al., 2002). Moreover, short-term treatment with atorvastatin increases HRV, decreases QT interval variability and shortens the QT interval duration in patients with advanced chronic HF (mean LVEF 24% and NYHA class III) (Vrtovec et al., 2005). Thus, statin therapy exerts a favourable modulation on the sympathetic tone and autonomic dysfunction and may, therefore, reduce the risk of life-threatening arrhythmias in patients with CAD and HF.

6.2.7. Effects on cardiac ion channels and transporters

6.2.7.1. Role of membrane cholesterol on transmembrane ion fluxes. Free (unsterified) cholesterol is a major lipid class of mammalian cell membranes where it plays an essential role in determining their physicochemical properties and directly affects transmembrane ion fluxes by modulating the normal function of constituent membrane-integral proteins, like ion channels and ion pumps (Quinn, 1981; Tulenko et al., 1990; Yeagle, 1991).

Lipids are not homogeneously distributed within the lipid bilayer but spontaneously aggregate to form specialized membrane microdomains enriched in cholesterol and sphingolipids (the so-called "lipid rafts"), where many receptors and channels involved in cell signalling preferentially accumulate. In SMC, channels associated with lipid raft microdomains included voltage-gated Na^+, L-type Ca^{2+} and several K^+ channels, including several voltage-gated (Kv1.3, Kv1.5 and Kv2.1) and the large conductance Ca^{2+}-activated K^+ channels and the inward rectifier K^+ channel subunit Kir3.1 (Martens et al., 2004).

Excess of membrane cholesterol modifies the physical properties of the membrane and significantly influences transmembrane ion fluxes. In fact, enrichment of human erythrocyte and cardiac membranes and rabbit kidney medulla basolateral membrane vesicles with cholesterol increases membrane core microviscosity and stimulates Na^+–Ca^{2+} exchange, while inhibits the activity of Na^+–K^+-ATPase, Ca^{2+}-ATPase, Mg^{2+}-ATPase and Na^+, Li^+-countertransport (Ortega & Mas-Oliva, 1984; Kutryk & Pierce, 1988; Yeagle et al., 1988; Lijnen & Petrov, 1995).

Cholesterol enrichment of VSMC membranes with human LDL increases unstimulated and noradrenaline-stimulated Ca^{2+} influx, unstimulated Ca^{2+} efflux and cytosolic Ca^{2+} levels (Bialecki & Tulenko, 1989; Gleason et al., 1991). These effects that are associated with a decrease in membrane fluidity, are inhibited by L-type Ca^{2+} channel blockers (nifedipine, verapamil and diltiazem), suggesting that excess membrane cholesterol may unmask otherwise silent L-type Ca^{2+} channels that may be involved in altered arterial wall properties in dyslipemic patients. A significant increase in $^{45}Ca^{2+}$ influx is also found in erythrocytes enriched with cholesterol (Locher et al., 1984). Moreover, vasosensitivity to noradrenaline and angiotensin II increases in hypercholesterolemic patients (Howes et al., 1997) and in isolated cholesterol-enriched arteries (Bialecki & Tulenko, 1989).

Hypercholesterolemia increases free cholesterol (and cholesterol ester) in cardiac sarcolemma and decreases Na^+ current (I_{Na}) density in isolated rabbit ventricular myocytes, an effect associated with a leftward shift in the inactivation potential and a slowing of the time course of recovery (Wu et al., 1995). However, $I_{Ca,L}$ density is increased in hypercholesterolemic rabbits, an effect that may contribute to the prolongation of the ventricular APD (QT intervals) observed in this model (Wu et al., 1995) and in canine and ovine Purkinje fibers (Karagueuzian et al., 1982). In Langendorff-perfused rabbit hearts, hyperlipidemia also prolonged the QT interval and this effect was reversed by simvastatin (Lee et al., 2005a). In contrast, cholesterol-depleted rat heart myocytes in culture manifest a faster rate of depolarization and their spontaneous activity was more resistant to [Na^+] or [Ca^{2+}] deprivation, low pH, verapamil and tetrodotoxin (Hasin et al., 1980). These findings are consistent with an increase in Na^+ and Ca^{2+} currents during depolarization.

Excess membrane cholesterol also increases basal and noradrenaline-activated ^{86}Rb efflux through K^+ channels in cultured aortic SMC (Tulenko et al., 1990). In VSMC, hypercholesterolemia regulates the gene expression levels of several K^+ channels, up-regulating Kir6.2 mRNA expression (the pore-forming α-subunit of cardiac ATP-sensitive K^+ [K_{ATP}] channels) and down-regulating Kir3.1 mRNA expression (the α-subunit of a G-protein coupled K^+ channel), whereas Kir2.1 (inward rectifier K^+ channel), Kir6.1 and SUR2B (K_{ATP} β-subunits) mRNA expression are unchanged (Ren et al., 2001). Enrichment of bovine aortic endothelial cells with cholesterol decreases the inward rectifier K^+ (Kir2) current density, whereas depleting the cells of cholesterol increases the density of the current (Romanenko et al., 2002). Since neither single channel properties nor membrane capacitance are affected, cholesterol

modulates K^+ conductance by changing the number of active channels. Moreover, increasing the cholesterol concentration reduces (70–80%) the mean open time and the open probability (80%) of the high-conductance Ca^{2+}-activated K^+ channel (BK) reconstituted into lipid bilayers from rat brain homogenates (Chang et al., 1995). These data are consistent with a model in which an increase in cholesterol concentration in the cell membrane increases intrabilayer structural stress and lateral elastic stress energy (Chang et al., 1995; Mason et al., 2004). As a result, channel opening events may be compromised, resulting in a reduced probability of finding the channel in the open state, i.e., cholesterol affects the transitions between different conformational states of the channel protein (Chang et al., 1995). Hypercholesterolemia also impairs acidosis-induced dilation of rabbit coronary arterioles, an effect mediated via the activation of K_{ATP} channels (Shioiri et al., 2003). Interestingly, cholesterol depletion produces a marked hyperpolarization shift in the steady-state inactivation properties of Kv2.1 channels and alters Kv1.5 channel function by inducing a hyperpolarizing shift in the voltage dependence of activation and inactivation (Martens et al., 2004). In addition, it produced a dramatic redistribution of Kv2.1 channels from small clusters into large patches, whereas surface distribution of Kv1.4 and Kv1.3 was not altered (O'Connell & Tamkun, 2005).

6.2.7.2. Role of statins on transmembrane ion fluxes. From the previous results, it seems clear that, by reducing cholesterol content in cardiac membranes, statins could modulate the fatty acid composition and the physicochemical properties of the sarcolemma and regulate the activity of membrane integral proteins. In addition, statins could modulate ion channels through other mechanisms independent of the inhibition of cholesterol synthesis and even interacting directly with the channel proteins similarly to conventional antiarrhythmic drugs. Independently of the mechanism involved, changes in transmembrane ion fluxes induced by statins may affect the electrophysiological properties of the cardiac muscle (Lamers et al., 1987; Pound et al., 2001).

In hypercholesterolemic patients, pravastatin reduces the erythrocyte and platelet membrane cholesterol content and this effect is accompanied by an increase in activity of the Na^+–K^+ pump and a decrease in cellular Na^+ concentration (Lijnen et al., 1994). Simvastatin and atorvastatin, but not pravastatin, inhibit the contractions induced by phenylephrine in isolated aorta from normocholesterolemic rats incubated in normal and in Ca^{2+}-free media as well as the increase in $[Ca^{2+}]_i$ induced by angiotensin II in cultured rat aortic SMC (Tesfamariam et al., 1999). These effects suggest that simvastatin and atorvastatin directly relax VSMC by inhibiting Ca^{2+} influx via voltage-gated channels and Ca^{2+} release from intracellular store sites. Very recently, Vaquero et al. (2006) have demonstrated that at the nanomolar range simvastatin but not atorvastatin, inhibits the $I_{Ca,L}$ recorded in mouse ventricular myocytes (Fig. 2). The inhibition was frequency-dependent and displayed fast onset and washout kinetics (3–6 min), suggesting that it was the consequence of the direct interaction of the drug with the channel proteins. Thus, simvastatin, at the same concentration at which it inhibits the HMG-CoA reductase, also produces a marked frequency-dependent block of the $I_{Ca,L}$ (40% at 1 Hz).

Experimental studies demonstrated that simvastatin prevented AF promotion in dogs by attenuating the APD and refractoriness abbreviation and the down-regulation of the $Ca_v1.2\alpha$-subunit expression produced after 7 days of atrial tachypacing (Shiroshita-Takeshita et al., 2004). It has been proposed that the control of intracellular Ca^{2+}, which is likely altered in the face of rapid rates, would help to prevent the Ca^{2+}-dependent gene transcription responsible for the electrical remodeling (Nattel, 2002). Therefore, it is possible that the frequency-dependent reduction in $I_{Ca,L}$ produced by simvastatin might be responsible for the attenuation in $Ca_v1.2$ down-regulation and for the prevention of the electrical remodeling observed with simvastatin in the dog model of AF (Shiroshita-Takeshita et al., 2004).

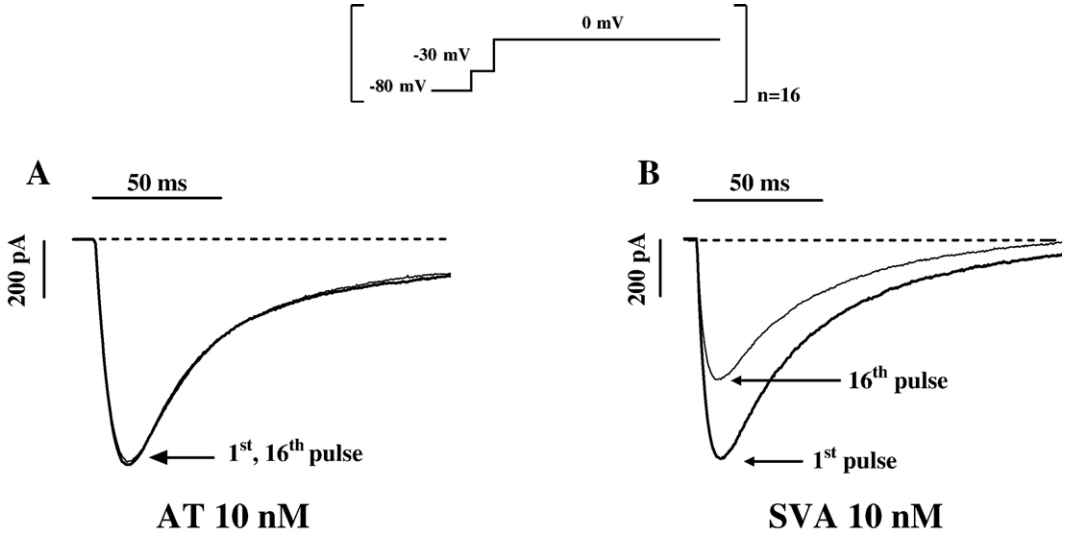

Fig. 2. Calcium currents recorded in mouse ventricular myocytes by applying trains of sixteen 150-ms pulses from −80 to 0 mV (with a prepulse of 50 ms to −30 mV to inactivate the I_{Na}) at a frequency of stimulation of 1 Hz under control conditions and in the presence of 10 nM atorvastatin (**A**) and 10 nM of the acid form of simvastatin (SVA, **B**).

Moreover, simvastatin dose-dependently delays anoxia-induced necrosis of cultured neonatal cardiomyocytes and attenuates the rise of $[Ca^{2+}]_i$ upon incubation in Na^+-free buffer (Bastiaanse et al., 1994). These protective effects are attributed to the inhibition of the sarcolemmal Na^+/Ca^{2+} exchanger and of the rise in $[Ca^{2+}]_i$ during anoxia (Bastiaanse et al., 1994). L-α-lysophosphatidylcholine (LPC) is a metabolite of phosphatidylcholine found in high concentrations in ischemic hearts (Sobel et al., 1978). In isolated cardiac myocytes LPC increases $[Ca^{2+}]_i$ and is thought to be one of the causes of Ca^{2+} overload and arrhythmias during ischemia and reperfusion (Ver Donck et al., 1992). LPC induces a nonselective cation current (I_{NSC}) in human endothelial cells and guinea pig ventricular myocytes via a G_i/G_o-coupled receptor and Rho-mediated pathway (Li et al., 2002). Fluvastatin prevents the GTP exchange of RhoA and its membrane translocation from the cytoplasm caused by LPC and inhibits the increase in $[Ca^{2+}]_i$ in human endothelial cells (Yokoyama et al., 2002) and the I_{NSC} current induced by LPC in guinea pig ventricular myocytes (Li et al., 2002). The effects of fluvastatin are reversed by GGPP or mevalonic acid.

Statins also modulate K^+ currents. In smooth muscle rabbit aortic cells, lovastatin produces a 9-fold increase in the open probability of the Ca^{2+}-activated K^+ channels presumably due to changes in plasma membrane fluidity, even when the elementary conductance of the channels does not change (Bolotina et al., 1989). In rats treated with the NOS inhibitor L-nitro-arginine methyl ester (L-NAME) for 4 weeks, pitavastatin inhibits the rise in systolic blood pressure and microvascular remodeling (medial tickening and perivascular fibrosis of coronary arterioles), these effects being independent of cholesterol lowering; in addition, pitavastatin abolishes the upregulation of intermediate-conductance Ca^{2+}-activated K^+ channels (ImK) in VSMC (Terata et al., 2003). Cerivastatin and fluvastatin enhance endothelium-dependent relaxations in the rat aorta, an effect that is abolished by the NOS inhibitor N^G-nitro-L-arginine and a PI3 kinase inhibitor (Mukai et al., 2003). At higher concentrations, both lipophilic statins, but not pravastatin, produce an endothelium-independent relaxation that is inhibited by 4-aminopyridine, a Kv channel blocker. Since K^+ channels play a role in the regulation of VSMC membrane potential, opening of Kv channels would be expected to cause membrane hyperpolarization that closes voltage-gated L-type Ca^{2+} channels, leading to smooth muscle relaxation. These results indicate that multiple mechanisms are involved in the vasodilator effects of statins, including augmentation of NO-dependent relaxations through the PI3 kinase/Akt pathway and endothelium-independent mechanisms by opening Kv channels (cerivastatin and fluvastatin) or inhibiting Ca^{2+} influx (simvastatin and atorvastatin) (Furukawa et al., 1991).

Opening of K_{ATP} channels, particularly mitochondrial K_{ATP} (mitoK_{ATP}), is a primary mechanism of cardioprotection against ischemia (Seino & Miki, 2003; Tamargo et al., 2004b). Suppression of K_{ATP} channel opening during ischemia/reperfusion may underlie the hypercholesterolemia-induced extension of no-reflow, which delays infarct healing. NO directly activates mitoK_{ATP} channels (Sasaki et al., 2000). Thus, the cardioprotective effects of statins against ischemic injury can be related to the activation of K_{ATP} channels, an effect that can be indirectly mediated by the release of NO or by increasing adenosine levels (Lee et al., 2004), an important mediator to trigger opening of K_{ATP} channels. In a model of global ischemia in rabbit hearts pravastatin exhibits a protective effect on cardiac metabolism during ischemia, inhibiting the decrease in ATP and intracellular pH and its effects are suppressed with the K_{ATP} channel blocker glibenclamide and L-NAME (Kawabata et al., 2001). These results suggest that the cardioprotection of pravastatin may be caused by the K_{ATP} channels that are mediated by the release of NO. In fact, pravastatin opens cardiac K_{ATP} channels, through the activation of the NOS3 and its cardioprotective effects were inhibited by glibenclamide, suggesting that activation of K_{ATP} channel is involved (Lee et al., 2004).

On the other hand, at nanomolar concentrations, atorvastatin but not simvastatin, inhibited the atrioselective I_{Kur} and the rapidly activating and inactivating transient outward current (I_{to}) in mouse ventricular myocytes (Gómez et al., 2005; Vaquero et al., 2005). The blockade induced was concentration-, voltage- and frequency-dependent and was not modified by the antioxidant probucol or L-NAME. These results suggest that neither the antioxidant actions nor NO are involved in the effects of both statins. As a consequence of its effects on these K^+ currents, atorvastatin prolonged the APD in mouse atria, without modifying the amplitude and maximum upstroke velocity (V_{max}) of the action potential or the resting membrane potential. These results suggest that atorvastatin does not modify the I_{Na} or the inward rectifier K^+ (I_{K1}) currents. In these experiments, atorvastatin-induced block also displays fast onset and washout kinetics and the drug does not modify the membrane capacitance, indicating that the effects are due to a direct interaction of the drug with the channel proteins without the implication of the inhibition in membrane cholesterol synthesis or putative changes in the membrane properties. It has been proposed that I_{to}/I_{Kur} block could be a promising target for the treatment of AF (Wijffels & Crijns, 2003). Indeed, in the human atria, the maintenance of the duration and the height of the plateau phase not only determines the excitation–contraction coupling, but is critical for the prevention of the occurrence of the periodic activity of sustained, high frequency, functional reentrant sources (rotors) that can be responsible for the AF (Pandit et al., 2005). Moreover, it has been demonstrated that the combined inhibition of I_{Kur} and I_{to} prolonged the atrial plateau duration and is critical for the termination of rotors. Therefore, atorvastatin could produce a cessation of fast reentrant sources by inhibiting the I_{Kur} and I_{to}.

Lovastatin also inhibits the rapid component of the delayed rectifier (I_{Kr}) in stably transfected human embryonic kidney cells in a dose-dependent manner ($IC_{50}=7.4$ μM) that showed no use dependence (Katchman et al., 2006). However, lovastatin had no appreciable effect on either APD or I_{Kr} in guinea pig ventricular myocytes.

7. Conclusions

In recent years, experimental and clinical evidence have demonstrated that statin therapy exerts antiarrhythmic effects. Clinical trials have shown that statins reduce the recurrences of

AF as well as the episodes of recurrent VT and VF in patients with CAD treated with an ICD. In addition, some results from secondary prevention trials indicated that statins might reduce SCD associated to lethal ventricular arrhythmias. Interestingly, these antiarrhythmic effects have not been observed in some studies with other lipid-lowering drugs. Although the mechanisms underlying their antiarrhythmic properties are unknown, they can be attributed to their lipid-lowering effects that reduced the ischemic burden, to their pleiotropic actions (including improvement of endothelial dysfunction and autonomic function, stabilization of the atherosclerotic plaques and antioxidant, antiinflammatory, antithrombotic and cardioprotective properties) and to direct effects on transmembrane ion fluxes. However, further investigations are needed to clarify the potentially underlying mechanisms involved in the antiarrhythmic effects of statins and more prospective studies are necessary to assess the risks and benefits of routine statin therapy in clinical practice, particularly in high-risk CAD patients.

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