ANTIOXIDANTS & REDOX SIGNALING
Volume 20, Number 8, 2014

DOI: 10.1089/ars.2013.5542

FORUM REVIEW ARTICLE

Targeting Inflammation and Oxidative Stress in Atrial Fibrillation: Role of 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase Inhibition with Statins

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Abstract

Significance: Atrial fibrillation (AF) is a burgeoning health-care problem, and the currently available therapeutic armamentarium is barely efficient. Experimental and clinical evidence implicates inflammation and myocardial oxidative stress in the pathogenesis of AF. ***Recent Advances:*** Local and systemic inflammation has been found to both precede and follow the new onset of AF, and NOX2-dependent generation of reactive oxygen species in human right atrial samples has been independently associated with the occurrence of AF in the postoperative period in patients undergoing cardiac surgery. Anti-inflammatory and antioxidant agents can prevent atrial electrical remodeling in animal models of atrial tachypacing and the new onset of AF after cardiac surgery, suggesting a causal relationship between inflammation/oxidative stress and the atrial substrate that supports AF. ***Critical Issues:*** Statin therapy, by redressing the myocardial nitroso-redox balance and reducing inflammation, has emerged as a potentially effective strategy for the prevention of AF. Evidence indicates that statins prevent AF-induced electrical remodeling in animal models of atrial tachypacing and may reduce the new onset of AF after cardiac surgery. However, whether statins have antiarrhythmic properties in humans has yet to be conclusively demonstrated, as data from randomized controlled trials specifically addressing the relevance of statin therapy for the primary and secondary prevention of AF remain scanty. ***Future Directions:*** A better understanding of the mechanisms underpinning the putative antiarrhythmic effects of statins may afford tailoring AF treatment to specific clinical settings and patient's subgroups. Large-scale randomized clinical trials are needed to support the indication of statin therapy solely on the basis of AF prevention. *Antioxid. Redox Signal*. 20, 1268–1285.

Introduction

Atrial fibrillation (AF) is a heart rhythm disturbance that is characterized by rapid, irregular electrical and mechanical activation of the atria, which causes uncoordinated contraction and favors the formation of atrial thrombi. AF is an increasing health-care burden, because of the aging population and improved survival from acute cardiovascular events, such as myocardial infarction. The lifetime risk for development of AF in all men and women older than 40 is estimated at about 25%; whereas for those without previous or concurrent cardiovascular events, the lifetime risk is 16% (60, 98). The presence of AF independently increases the risk of mortality and morbidity, mostly due to stroke and heart failure (HF), resulting in disability and high health-care cost (24, 92). AF is often associated with a number of cardiac and noncardiac risk factors, including ischemic heart disease, HF, valvular heart disease, hypertension, diabetes, alcohol abuse, thyroid disorders, and pulmonary disease (1, 50), and it is present in 3%–6% of acute medical admissions, in which the most common comorbidities are coronary artery disease and HF (24). AF is also a common postoperative complication, especially after cardiothoracic surgery (70).

Clinically, AF can be divided into paroxysmal, persistent, and permanent (24). Paroxysmal AF is defined as recurrent (two or more) episodes of AF that terminate spontaneously in <7 days, usually <24 h; whereas persistent AF describes AF episodes lasting beyond 7 days. AF is regarded as permanent

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when attempts to restore sinus rhythm have failed or have been deemed inappropriate and both patient and physician accept AF as the underlying rhythm of choice. It is important to stress that the decision to label AF as permanent reflects a (potentially reversible) management choice rather than a separate pathophysiological entity.

The mechanisms underlying the new onset of AF are hitherto only partially characterized, and the progression from paroxysmal to persistent AF as well as the factors responsible for the individual response to treatment are even further from being completely understood. In keeping with this, the pharmaceutical armamentarium currently available aims at controlling symptoms and at reducing the thromboembolic risk, the latter with agents that carry a significant risk of hemorrhagic events. The advantage of rhythm *versus* rate control remains a matter of debate (119), whereas the efficacy and safety of antiarrhythmic drugs used for the treatment of AF is an ongoing concern (74). Besides relieving symptoms, the main aim of the medical management of AF is to reduce the risk of thromboembolic stroke; however, the widely used clinically derived risk scores are not very accurate in predicting which patients with AF would benefit more from anticoagulant prophylaxis.

In view of these issues, the development of safer antiarrhythmic therapies targeted to the pathogenic mechanisms that are responsible for the initiation and perpetuation of AF would seem particularly important. In addition, a deeper insight into the pathogenesis of AF might refine the risk prediction scores for thromboembolic complications. In this context, several experimental and clinical studies have addressed the link between AF, inflammation, and oxidative stress.

Inflammation, Oxidative Stress, and AF: Cause or Effect?

A causal role of inflammation in the initiation of AF is suggested by the observation that inflammatory states, such as myocarditis, pericarditis, and cardiac surgery, are frequently associated with AF (113, 149). The first piece of evidence directly linking inflammation to AF was the histological findings of atrial myocarditis in patients with lone AF, but not in subjects with sinus rhythm (49). These findings were later confirmed in animal studies (146). However, cardiac surgery and cardiopulmonary bypass (CPB) have probably provided the strongest evidence linking a systemic inflammatory response to the new onset of AF after cardiac surgery. This is further reinforced by the observation that the postoperative peak in inflammatory markers, namely serum C-reactive protein (CRP) and interleukin 6 (IL-6), coincides with the peak incidence of AF (*i.e.*, at the 2–3 day after surgery) (21); whereas the milder systemic inflammatory response observed in patients undergoing coronary revascularisation off-pump is paralleled by a lower incidence of postoperative AF (6, 30). Moreover, preoperative levels of circulating cytokines (10) and the activity of a gp91-containing NADPH oxidase (NOX2) (76) in atrial tissue samples obtained at the time of CPB have also been independently associated with the new onset of postoperative AF and other in-hospital complications in patients undergoing cardiac surgery (9) (Fig. 1). These findings suggest that myocardial NOX2 activity preceding cardiac surgery, inflammation, and ischemia/reperfusion injury may contribute to the pathogenesis of postoperative AF and help in refining risk stratification of these patients.

Chung *et al.* were the first to report an association between AF and elevated CRP (32). In this case-control study, CRP level was more than two-fold higher in patients with AF compared with controls. The association between elevated CRP and presence of AF was further supported by large population-based cohort studies. In 5806 elderly individuals followed for a mean of 6.9 years, CRP was associated with the presence of AF; whereas in patients with sinus rhythm, elevated CRP levels were independently associated with the future development of AF (13). In another study, 1 mg/dl increase in serum CRP was associated with a seven-fold increase in the risk of recurrent AF and a 12-fold increase in the risk of permanent AF (39). A meta-analysis of seven prospective observational studies, including 420 patients (229 with and 191 without AF relapse), indicated that increased baseline CRP levels are also associated with a greater risk of AF recurrence after successful cardioversion (standardized mean difference = 0.35 units, 95% CI: 0.01–0.69) (94). Furthermore, a meta-analysis of six prospective studies, including 366 patients with AF who underwent cardioversion, found CRP levels to be higher in patients who failed to recover from sinus rhythm (Fig. 2), suggesting that CRP assessment may provide prognostic information on the success of this procedure (95, 100).

Besides CRP, other circulating inflammatory biomarkers, such as IL-6, IL-8, IL-1b, tumor necrosis factor-α (TNF-α), fibrinogen, and complement factors, have been independently associated with either incident or prevalent AF (21, 96, 127, 132, 139, 140). Indeed, in the Women's Health Study, a combined "inflammation score," including high sensitivity CRP, soluble intercellular adhesion molecules, and fibrinogen, independently predicted the new onset of AF over a median follow up of 14.4 years in 24,734 middle-aged women free of overt cardiovascular disease or cancer at baseline (34) (Fig. 3). However, patients who develop persistent AF are more likely to have undetected asymptomatic paroxysmal AF, which, in turn, might cause an increase in inflammatory markers. This raises the possibility that inflammation may be a consequence or a biomarker of AF rather than a causal mechanism (35). Indeed, restoration of sinus rhythm (either through pulmonary vein isolation or cardioversion) has been associated with reduction in CRP levels and improvement of endothelial function (71, 173). Conversely, AF induction in patients with paroxysmal AF undergoing ablation while in sinus rhythm has been associated with a rapid increase in soluble CD40 ligand (a member of the TNFα superfamily with pro-inflammatory and pro-thrombotic actions)(7) and in the endogenous nitric oxide synthase (NOS) inhibitor, asymmetric dimethylarginine (ADMA), when compared with patients who were paced at 150 beats per minute or patients with normal sinus rhythm. Both rapid pacing and AF induction increased platelet activation and thrombin generation, particularly in the left atrium, but AF also led to endothelial dysfunction and activation of the inflammatory cascade (91), suggesting that rapid atrial activation and altered blood flow are sufficient to elicit inflammation and increase pro-thrombotic risk. While the chicken or the egg causality dilemma remains, both are likely to be relevant, so that pre-existing inflammation paves the way for the initiation of AF, which, in turn, generates an

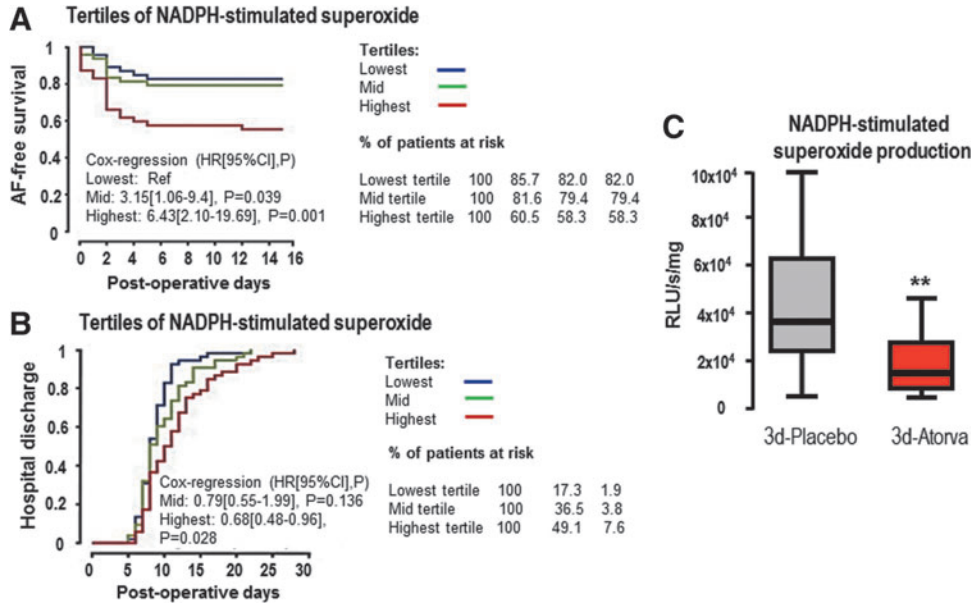

FIG. 1. Right atrial (RA) NADPH-stimulated superoxide production (an index of NOX2 activity) is independently associated with an increased risk of postoperative atrial fibrillation (AF) (A) and longer in-hospital stay (B) in patients undergoing elective cardiac surgery. Hazard ratio (HR [95% confidence interval (CI)]). *p* value derived from the Cox regression, after adjustment for age, use of beta-blockers, EuroSCORE (European System for Cardiac Operative Risk Evaluation), and postoperative AF (in **B** only). Three-day treatment with atorvastatin (atorva) 40 mg once daily decreases RA NADPH-stimulated superoxide production in statin-naïve patients undergoing cardiac surgery in a randomized, placebo-controlled comparison **(C)**. $^{**}p < 0.01$ *versus* placebo; RLU, relative light units. Modified from Antoniades *et al.* (8). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

inflammatory response that enhances atrial remodeling, thus facilitating the persistence of AF (Fig. 4).

How Do Inflammation and Oxidative Stress Induce an Arrhythmogenic Substrate?

A current understanding of the mechanisms by which inflammation (systemic or local) may lead to AF remains fairly limited. Rapid atrial activation in AF results in myocytes calcium overload (55), which, in turn, can lead to cardiomyocyte apoptosis and myolysis (4). The resulting cellular damage induces a low-grade inflammatory response, which contributes to atrial structural remodeling. Inflammation-induced structural alterations in AF are supported by evidence of neutrophil infiltrates, cardiomyocyte necrosis and apoptosis, and fibrosis in atrial biopsies (49, 171) (Fig. 4). In a canine model, acute inflammation anisotropically slowed atrial conduction in response to programmed electrical stimulation, thus setting the stage for re-entry (155). Similarly, inhomogeneous atrial conduction and increased AF susceptibility were correlated with atrial neutrophil-derived myeloperoxidase (MPO) activity ($r = 0.851$, $p < 0.001$) in a canine

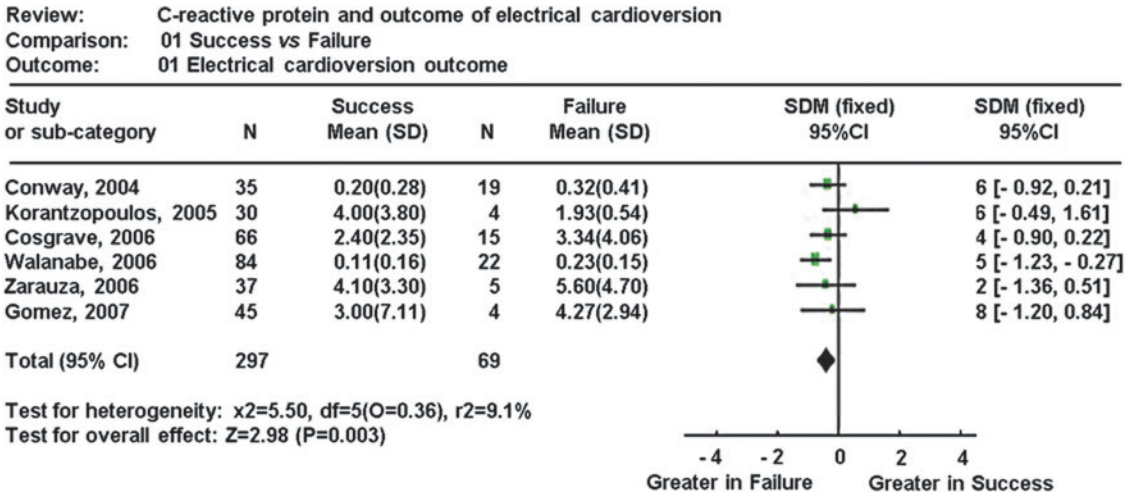

FIG. 2. C-reactive protein (CRP) levels are higher in patients with AF who fail electrical cardioversion. df = degrees of freedom; SMD = standardized mean difference. Reprinted with permission from Liu *et al.* (94). To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

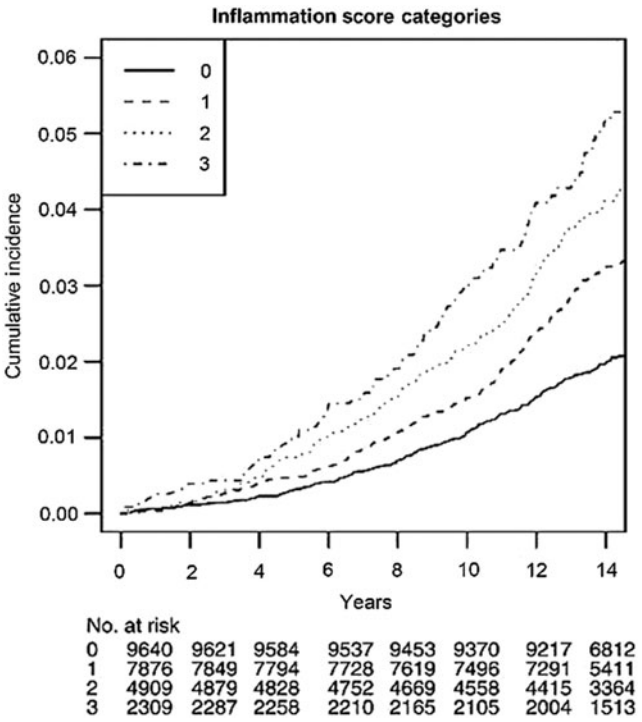

FIG. 3. Cumulative incidence of incident AF by inflammation score. The inflammation score, which included high-sensitivity CRP, soluble intercellular adhesion molecules, and fibrinogen, partitioned 24,734 middle-aged women free of overt cardiovascular disease or cancer at baseline into four groups with a proportionally higher risk of incident AF, and independently predicted the new-onset AF over a median follow up of 14.4 years. Reprinted with permission from Conen *et al.* (34).

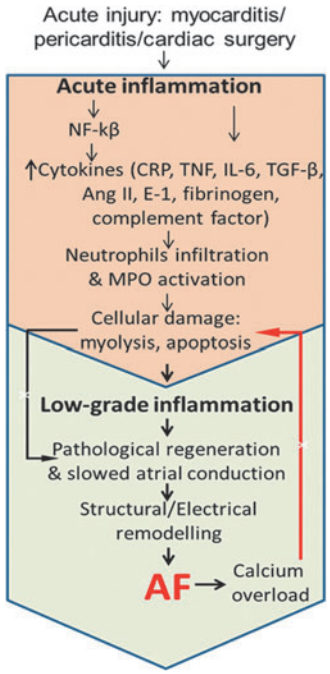

FIG. 4. Schema illustrating the role of acute and low-grade inflammation in AF. Inflammatory conditions (*e.g.*, myocarditis, pericarditis, and cardiac surgery) activate a rapid pro-inflammatory cascade involving cytokine release, leukocyte infiltration, and myeloperoxidase (MPO) activation, thus leading to atrial structural changes that provide a substrate for the maintenance of AF. Rapid atrial activation is in itself sufficient to generate local and systemic low-grade inflammation, leading to further atrial remodeling and a prothrombotic state. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

model of atriotomy or pericardiotomy (67). In the same model, anti-inflammatory therapy with methylprednisolone significantly decreased both MPO activity and the inhomogeneity of atrial conduction, thus supporting a role for neutrophil-derived inflammation in generating the atrial substrate for AF. Patients with AF have higher MPO plasma levels and a larger MPO burden in right atrial (RA) samples compared with individuals with sinus rhythm (133). Interestingly, MPO not only represents a marker of leucocyte infiltration but also appears to be causal for disease development, as MPO-deficient mice were protected from atrial fibrosis and AF susceptibility induced by angiotensin II infusion (133). Collectively, these findings indicate that inflammation-driven oxidative stress plays an important role in atrial structural remodeling.

Whether inflammation, and the resulting atrial oxidative stress, also affects atrial action potential duration (APD) and refractoriness or triggers activity from the pulmonary veins remains largely unknown. A number of sarcolemmal ionic currents have been shown to be directly or indirectly modulated by NO or reactive oxygen species (ROS) (162); however, the relevance of these mechanisms in the context of human AF remains to be conclusively demonstrated.

ROS also increase cardiac ryanodine receptor (RyR2) open probability by increasing the channel's sensitivity to cytosolic Ca and adenosine triphosphate (ATP) (43, 106), as well as by disrupting the interaction of RyR2 with triadin (93) and FKBP12.6 (179). In a murine model, mutations in RyR2 that enhance sarcoplasmic reticulum Ca leak increase susceptibility to AF by rapid atrial pacing, an effect mediated by oxidation-induced dissociation of calstabin2 from RyR2 but independent of calmodulin kinase II (CaMKII) or protein kinase A (142). On the other hand, CaMKII-dependent phosphorylation of RyR2 has been shown to increase diastolic Ca leak in RA myocytes from patients with AF (115). Overall, it is reasonable to speculate that phosphorylation and oxidation act synergistically to increase RYR2 open probability (17, 141). Indeed, oxidative stress can activate CaMKII (45) and phosphorylate RYR2 channels, which then become more prone to oxidation (141). Similarly, experimental evidence suggests that ROS-mediated disturbance of intracellular Ca and Na handling may result in electrical instability and set the stage for the development of AF (162). Importantly, ROS-induced ROS release from mitochondria can prevent ATP production and, consequently, result in activation of sarcolemmal K_{ATP} channels (11). The shorter APD and slower electrical conduction, thus, generated promote re-entry-dependent arrhythmias (5).

Finally, oxidative stress-induced atrial remodeling has been shown to modulate connexin-40 (Cx40) and connexin-43 (Cx43), thereby interfering with gap junctions among atrial cardiomyocytes (37, 156). The ensuing disruption of appropriate cell-to-cell coupling, in turn, affects electrical

conduction and refractoriness, both of which are key determinants of the re-entry circuits that sustain AF (163). The role of connexins in AF is supported by evidence that somatic mutations or polymorphisms in GJA5, the gene coding for Cx40, may predispose to AF by impairing gap-junction assembly or electrical coupling (54, 169). However, the prevalence of rare nonsynonymous sodium nitroprussides polymorphisms in the GJA5 gene in AF patients appears to be low (154), in agreement with the absence of an association between common variants in or near the GJA5 gene and AF in the most recent and largest AF genome-wide association studies (44). There is compelling evidence from both animal (18, 22, 75, 130, 138) and human (42, 72, 114, 167) studies of abnormal Cx40 and Cx43 expression and function in AF (134, 148). Overall, AF seems to be characterized not only by reduced absolute expression of Cx40 and Cx40/Cx43 ratio, but also by enhanced redistribution of both connexins from cell-end gap junctions to lateral margins (41). Heterogeneity and lateralisation either decrease or completely abrogate function of these intercellular ion channels (64, 156), hence decreasing electrical coupling amid cardiomyocytes. Moreover, Cx40 remodeling synergistically co-operates with simultaneously developing fibrosis to increase arrhythmogenicity by promoting anatomically stable re-entries during AF (64). However, the highly discrepant results obtained in different contexts and even within the same animal model obscure the relationship between connexins and AF (41, 73). For instance, higher Cx40 expression was reported in left atrial (LA) samples from patients with lone AF and mitral-valve disease-related AF; however, Cx43 expression increased only in the latter group, suggesting differential trends in connexin expression depending on the underlying pathology (167). The conflicting results provided by Cx40 knockout mice regarding AF vulnerability fuel the ongoing controversy (15, 57). Similarly, small molecules aimed at restoring adequate gap-junction conductance appear to be beneficial in some models (ischemia and mitral-valve disease-related AF) but not in other clinically relevant scenarios (*e.g.*, congestive HF) (56, 145). Noteworthy, gene transfer with either Cx40 or Cx43 has emerged as a promising novel approach to control connexin expression. Indeed, adenoviral-mediated enhanced Cx43 expression attenuates impaired electrical conduction and decreases AF inducibility (18, 66). Regarding the mechanisms underlying gap-junction remodeling in AF, TNF-α infusion in mice proved to be sufficient to induce sustained atrial fibrosis and decrease Cx40 expression, thus suggesting that down-regulation of gap junctions might contribute to the inflammation-induced increase in AF susceptibility (90).

Possible mechanisms by which oxidative stress and inflammation contribute to the formation of the electrical and structural substrate for AF are summarized in Figure 5.

What Is the Role of Myocardial Endogenous Oxidase Systems in AF?

Direct myocardial generation of ROS appears to play a crucial role in initiating and sustaining AF in animal models and humans (26, 112). Among the several potential sources of ROS present in the atrial myocardium, NADPH oxidases or NOXs, mitochondria, xanthine oxidase (XO), and "uncoupled" NOS have been associated with both the new onset of AF and the AF-induced atrial remodeling (9, 40, 76, 77, 131).

NOXs are multi-subunit transmembrane enzymes that utilize NADPH as an electron donor to reduce oxygen to superoxide anion and hydrogen peroxide. NOX2 was initially discovered in phagocytes several decades ago (83) and since then, six more family members have been identified (176). NOX-dependent ROS production depends on the expression level and the activity of the enzyme. The mode of activation differs among NOX enzymes, but NOX-dependent ROS production in cardiovascular pathology usually involves stimulation by Rac1 and protein kinase C (20). Besides playing a critical role in the microbicidal activity of neutrophils, NOX2 in the myocardium has been involved in the pathogenesis of AF. For example, induction of AF by rapid atrial pacing in pigs was associated with increased NOX-dependent ROS production in the LA (40). AF develops spontaneously in mice with cardiac-specific overexpression of a constitutively active Rac1, which activates NOX2 (3). Kim *et al.* showed that NOX2 was the main source of ROS in human RA myocytes and that

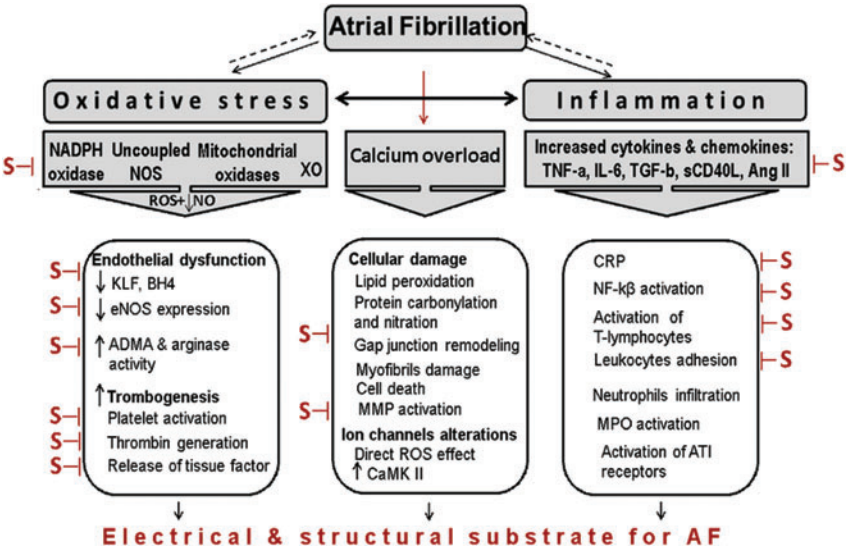

FIG. 5. A diagram depicting possible mechanisms by which oxidative stress and inflammation contribute to the formation of the electrical and structural substrate for AF. Some of the described targets of statin therapy (S) are shown in red. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

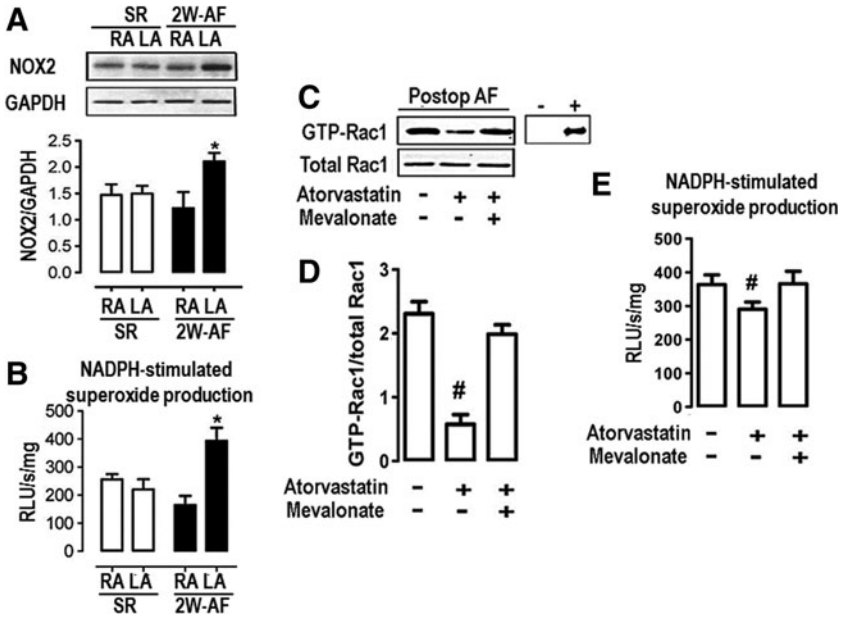

FIG. 6. After 2 weeks of AF (2W-AF), NOX2 protein expression and NADPH-stimulated superoxide production were increased in the goat left atria (LA) (A, B) compared with SR. *Ex vivo* incubation with atorvastatin caused a mevalonate-reversible inhibition of Rac1 activity **(C, D)** and of NADPH-stimulated superoxide production **(E)** in patients who went on to develop AF after cardiac surgery. RLU, Relative Light Units; postop AF, postoperative AF; RA, right atria; SR, sinus rhythm. Modified from Reilly *et al.* (131). $^{*}P<0.05$ *vs.* SR, 1-way ANOVA (n = 10 to 19); $^{\#}P<0.05$ for the mevalonate-reversible effect of atorvastatin; 1-way ANOVA (n = 8 to 19).

NOX-derived ROS production was increased in RA samples from patients with (mostly paroxysmal) AF (76). Furthermore, atrial NOX2-dependent superoxide production is independently associated with an increased risk of postoperative AF and other in-hospital complications in patients undergoing cardiac surgery (9, 77). More recently, Reilly *et al.* (131) reported an increase in atrial Rac1 and NOX2 protein level and activity 2 weeks after induction of AF in goats and in cardiac surgery patients who go on to develop postoperative AF (Fig. 6). On the other hand, "uncoupled" NOS activity and mitochondrial oxidases become the most important sources of ROS in the setting of longstanding AF and atrial structural remodeling (131). In keeping with these findings, oxidative stress assessed by NOX2 activity and urinary isoprostanes (which result from the interaction of arachidonic acid with ROS) was found to be increased in patients with paroxysmal and recent AF. By contrast, patients with longstanding AF showed similar values of urinary isoprostanes and a modest increase in NOX2 activity compared with controls (25). NOX2 expression in leucocytes is several orders of magnitude higher than that of other cells (16), rendering urinary NOX2 activity a likely marker of neutrophil activation.

Xanthine oxidoreductase has emerged as a relevant source of ROS in cardiovascular diseases and, in particular, in AF. Under physiological conditions, the enzyme functions as a dehydrogenase with NAD^+ as an electron acceptor. After oxidation of critical cysteines or partial cleavage of the enzyme, xanthine oxidoreductase switches to XO and facilitates one- as well as two-electron transfer onto oxygen (117). Thus, in situations of pre-existing oxidative stress or inflammation, XO catalyzes the conversion of hypoxanthine to xanthine and of xanthine to uric acid, and simultaneously produces superoxide anions as well as hydrogen peroxide (52). In addition to increasing oxidative stress, by producing uric acid, XO promotes inflammation through activation of pro-inflammatory cytokines and stimulation of the renin-angiotensin system (166). In keeping with the mechanism of redox-induced conversion from the dehydrogenase to the oxidase form, XO-dependent endothelial superoxide production is promoted by angiotensin II and the resulting activation of NOX2 (84). Notwithstanding the controversy concerning the role and localization of XO in the heart of nonrodent mammalian species (126), XO has been found in capillary endothelial cells, vascular smooth muscle cells, macrophages, and mast cells (61). Interestingly, the mRNA level of XO in the heart and the vascular system is low, whereas the liver expresses a high level of XO, particularly in the presence of inflammation. As XO binds to the endothelial glycocalyx after secretion into the blood, it is possible that a significant proportion of cardiac XO might originate in the liver and reside in the extracellular rather than the intracellular compartment (168). With regard to AF, XO seems to play different roles in different species. In a porcine model, atrial tachypacing caused a significant increase in XO-dependent superoxide production in the left atrium (40). However, these findings failed to be replicated in RA appendages of patients with AF (76). In a canine model of atrial tachypacing, inhibition of XO with allopurinol abrogated atrial fibrosis and the reduction in endothelial NOS (eNOS), without affecting LA diameter (135). Besides preventing atrial structural remodeling, allopurinol attenuated the electrical remodeling induced by atrial tachypacing (135). In line with these experimental findings, a small cross-sectional study showed a correlation between uric acid levels and LA diameter ($p<0.001$), a conventional but rather questionable marker of atrial structural remodeling (87). Indeed, uric acid appeared to be an independent predictor of permanent but not paroxysmal AF (adjusted odds ratio [OR] = 0.34, 95% CI: 0.137–0.949, $p=0.039$) (87), thus reinforcing its potential association with atrial structural remodeling. Moreover, an increasing body of epidemiological data has identified uric acid as a marker of AF risk (79). This association was further supported by the Atherosclerosis Risk In Communities study in which elevated serum uric acid was associated with greater AF risk (adjusted hazard ratio [HR] = 1.16, 95% CI: 1.06–1.26 per SD increase of serum uric acid differences), particularly in women and blacks (153). This gender difference was confirmed in a Japanese cohort study (152), but the mechanisms

underlying it as well as the role of ethnicity remain elusive. Finally, uric acid has also been shown to predict AF recurrence after electrical cardioversion (88). However, whether uric acid is directly involved in the pathogenesis of AF is far from being settled (166), as uric acid is influenced by diet and renal function, two factors that also impact cardiac disease development. Finally, given the dual function of xanthine oxidoreductase, whether the uric acid level is a surrogate for increase XO-mediated oxidative stress remains to be established.

NOS catalyze the generation of NO through the conversion of L-arginine into L-citrulline in the presence of oxygen and several cofactors, such as tetrahydrobiopterin (BH4), flavin cofactors (flavin mononucleotide, flavin adenine dinucleotide), and NADPH. There are three NOS isoforms: NOS1 or neuronal NOS (nNOS); NOS2 or inducible NOS (iNOS); and NOS3 or endothelial NOS (eNOS), two of which (nNOS and eNOS) are constitutively expressed in the cardiovascular system (27). Under physiological conditions, NO generated by NOSs in a tightly regulated manner participates in several cellular signaling pathways. In disease states, increased oxidative stress can lead to an increase in arginase activity, BH4 oxidation (131), and/or S-glutathionylation of the NOS reductase domain (29), all of which can "uncouple" the enzyme's activity, leading to the production of superoxide rather than NO (48). The reaction of the remaining NO with superoxide (to form highly reactive nitroso-oxidant species such as $ONOO^-$) further reduces NO availability.

Pacing-induced short-term AF has been associated with a 46% reduction in LA endocardial eNOS and a significant decrease in NO production (by 73%) (23), whereas long-standing AF in goats or humans is associated with NOS uncoupling secondary to a reduction in atrial BH4 content and an increase in arginase activity (131). It should be noted that atrial mitochondrial and NOS-mediated ROS production in goats was observed both in long-term AF and in the presence of sinus rhythm and atrial remodelling due to atrioventricular block, suggesting that structural atrial remodeling (rather than AF in itself) was responsible for these findings (131).

Others have reported induction of inducible NOS (iNOS) and increased 3-nitrotyrosine (a $OONO^-$ biomarker) in RA samples from patients with permanent AF (59) with little or no difference in eNOS expression (26, 59). In addition, the plasma level of the endogenous NOS inhibitor, ADMA, has been shown to be elevated in animals and individuals with persistent AF and to decrease after cardioversion (53). In failing canine hearts, atrial iNOS uncoupling due to BH4 depletion increased myocardial oxidative stress and was associated with shortening of the atrial effective refractory period and development of a substrate for inducible AF (116). BH4 and L-arginine supplementation restored normal iNOS activity and BH4 level and decreased AF inducibility, implying a potentially important role for NOS-generated ROS in the development of an AF substrate in HF.

Do Anti-Inflammatory and Antioxidant Agents Prevent AF?

Interventional trials of anti-inflammatory agents support a causal link between inflammation and postoperative AF. In a canine model of sterile pericarditis, topical application of the anti-inflammatory drugs ibuprofen and methylprednisolone significantly reduced the incidence of AF (155). In another canine model of atrial tachypacing, administration of prednisone was associated with attenuation of atrial electrical remodeling (resulting in lower AF inducibility), whereas ibuprofen or cyclosporin-A had no effect (144). In keeping with these findings, a double-blind randomized trial of hydrocortisone (100 mg a day for 4 days, starting on the evening before surgery) in 241 consecutive patients with sinus rhythm, undergoing on-pump cardiac surgery (coronary revascularization and/or aortic valve replacement), showed a significant reduction in the new onset AF during the first 84 h after surgery (58) (Fig. 7). This finding is in keeping with that of a meta-analysis of controlled trials (including 621 patients), which shows an average risk reduction of postoperative AF with steroid treatment (at various doses, preparation and duration) of 33% (risk ratio = 0.67, 95% CI: 0.54, 0.85, $p = 0.001$) (58). Besides preventing new-onset AF, steroids have also been shown to reduce AF recurrence early after radiofrequency ablation (80) (Fig. 7).

Ascorbate supplementation has also been shown to attenuate the pacing-induced atrial electrical remodeling in dogs and the incidence of postoperative AF or atrial flutter (16.3% *vs.* 34.9% in the ascorbate and control group, respectively) in a nonrandomized, nonplacebo-controlled comparison in 43 patients undergoing cardiac surgery; however, these preliminary findings are still awaiting confirmation in larger controlled trials. A more recent study reported no effect of ascorbate and vitamin E supplementation on AF inducibility in paced dogs, whereas simvastatin prevents both electrical remodeling and AF inducibility in the same model (146).

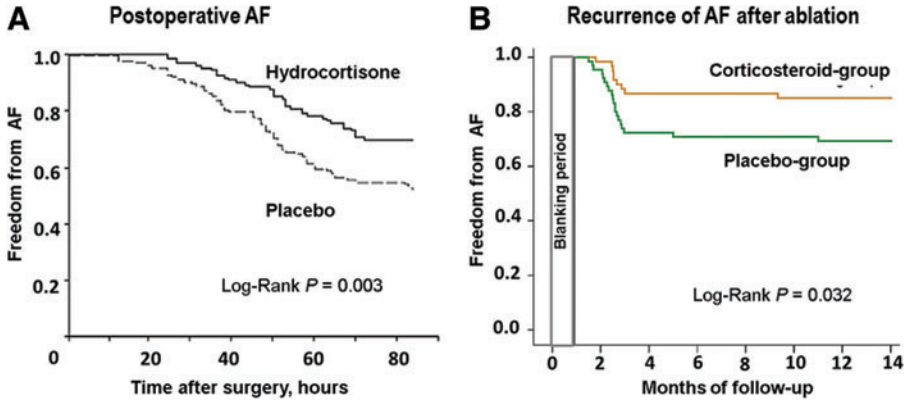

FIG. 7. Kaplan–Meier curve showing the effect of corticosteroid treatment on the incidence of AF after cardiac surgery (A) or recurrence of AF after pulmonary vein isolation (B). Reprinted with permission from Halonen *et al.* (58) **(A)** and modified from Koyama *et al.* (80) **(B)**. To see this illustration in color, the reader is referred to the web version of this article at www.liebertpub.com/ars

How do statins reduce inflammation?

Statins inhibit the 3-Hydroxy-3-methylglutaryl-coenzyme A reductase, the rate-limiting enzyme of the mevalonate pathway. Mevalonate is required for both cholesterol biosynthesis and the generation of isoprenoids that are involved in the activation of small guanosine triphosphate (GTP)ase signaling molecules. Several large clinical trials have provided evidence supporting the use of statins for the primary and secondary prevention of ischemic heart disease and stroke because of their low density lipoprotein (LDL)-cholesterol-lowering effect (14, 111). In addition, statins have anti-inflammatory and antioxidant properties that are both dependent and independent of cholesterol lowering (122, 128, 175) but which are not independently associated with the beneficial effects on patients' outcome.

The statin-mediated attenuation of isoprenylation reduces the tethering of small GTPases to the plasma membrane already at clinical relevant concentrations (33). This prevents the interaction of guanine nucleotide exchange factors with the GTPase and, thus, attenuates signaling by growth factor and cytokine receptors, as well as integrins, resulting in a global anti-inflammatory effect (177). Moreover, small GTPases of the Rho family, such as RhoA, Rac1, and CDC42, control the cytoskeleton by locally regulating actin polymerization, which impacts mRNA stability, cellular vesicle trafficking, and stress signaling. This aspect might explain why statins in endothelial cells activate a similar signaling cascade as shear stress. For example, similar to laminar flow, statins induce the transcription factor, Kruppel-like factor 2 (KLF2) in endothelial cells, which is an important mediator of cellular quiescence (12). KLF2, in turn, regulates the expression of multiple target genes, thus promoting an anti-inflammatory and anti-thrombotic endothelial phenotype (12). Several mechanisms have been proposed to mediate the up-regulation of KLF2 by statins, such as activation of the Ras homolog pathway, inhibition of mammalian target of rapamycin complex 1 (MTORC1) (147). MTORC1 activation requires Ras homolog enriched in brain (Rheb), an isoprenylated GTPase of the Ras family, and statin inhibition of Rheb was shown to prevent MTORC1 activation in vascular smooth muscle cells (161). In agreement with this, statin effects were abrogated by geranylgeranyl pyrophosphate but not farnesyl pyrophosphate, thereby implicating inhibition of geranylgeranyl pyrophosphate synthesis, and thus the Ras homolog pathway, in KLF2 induction. Inhibition of protein isoprenylation by statins has been found to influence the JAK/Signal transducer and activator of transcription signaling pathway, an intracellular signalling pathway that is activated by inflammatory cytokines in the endothelium (69). Furthermore, growth factor signaling, as activated by angiotensin II, thrombin, endothelial growth factor, platelet-derived growth factor, and the pro-fibrotic transforming growth factor β, is also attenuated by statin treatment (177). More recently, two alternative pathways have been implicated in the interaction between statins and KLF2. Lee *et al.* demonstrated that statins reverted hyperglycemia-induced overexpression of FOXO1, both *in vitro* and in a mice model of type 2 diabetes mellitus, and thus relieved the negative effect of FOXO1 on KLF2 expression (86). McLean *et al.* (108) showed that apelin/apelin receptor (APJ) signaling mediated statin-induced up-regulation of KLF2, eNOS, and thrombomodulin and the KLF2 increased expression of APJ, in a positive feedback loop. However, further studies are warranted to determine whether statins directly activate APJ or potentiate apelin-mediated activation of APJ (108).

Besides the aforementioned direct effects on the endothelium, statins can also act indirectly, for instance, by reducing T-cell cytotoxic activity against endothelial cells (136). On the other hand, statins can exert a strong anti-inflammatory and anti-thrombotic effect on blood monocyte-macrophages by decreasing the expression of many pro-inflammatory cytokines and coagulation factors. Those effects depend on modulation of several transcription factors, such as induction of peroxisome proliferator-activated factor (PPAR)-α, PPAR-γ, and KLF2 and inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells and c-ets (172).

KLF4, another member of the Kruppel-like family, has also been identified as a key regulator of endothelial homeostasis (143). Akin to KLF2, it seems to mediate the anti-inflammatory actions of statins in both endothelial cells and macrophages through the MEK5/mitogen-activated protein kinase pathway (118, 158), but its precise functions as well as the putative interaction with KLF2 remain poorly understood.

Finally, statins can activate the phospholipase A(2)-cyclooxygenase pathway, shifting the balance toward increased synthesis of the vasodilator and anti-inflammatory prostacyclin instead of other vasoconstrictor and thrombogenic prostaglandins (170).

How do statins reduce oxidative stress?

Oxidative stress can induce inflammation and senescence in endothelial cells, and statins can prevent those effects and thus improve endothelial function (120, 177). Indeed, various intracellular signaling pathways have been proposed to underlie statin-enhanced expression and activity of NOS3, sirtuin 1, and catalase. The best characterized are activation of PI3K/Akt and AMP-activated protein kinase signaling (51, 82, 151), inhibition of geranylgeranylation of the small G-protein Rho and its downstream target Rho-associated protein kinase (85), and suppression of caveolin-1 (124). In addition, statins improve eNOS function by increasing intracellular BH4 bioavailability and, possibly, by reducing ADMA levels (101) and arginase expression (63). An increase in NO bioavailability would then be expected to inhibit overexpression of adhesion molecules involved in leukocyte-endothelial cell interaction, and preserve mitochondrial membrane potential in response to oxidative stress in cardiac myocytes (68, 105). Furthermore, statins improve differentiation, survival, and functional activity of endothelial progenitor cells, which are disturbed by oxidative stress and inflammatory stimuli (97). In this way, they may contribute to angiogenesis and re-endothelialization of injured vessels (47, 164). Statins can also prevent oxidative stress by inhibiting NOX2 activity. Indeed, in addition to inhibiting transcription of NOX2 subunits, statins inhibit geranylgeranylation and thus membrane translocation of Rac1 GTPase (141, 160), which is required for activation of NOX2 (165) (Fig. 6). *Ex vivo*, atorvastatin has been shown to prevent the angiotensin-II-mediated increase in L-type Ca channels (LTCC) and Ca transient amplitude in HL-1 cells by inhibiting protein kinase C and NOX2 activity (171); however, the significance of these findings in the pathogenesis of AF (which is characterized by a reduction in

atrial LTCC and sarcolemmal Ca current) remains to be addressed.

It should be noted that the anti-inflammatory and antioxidant pleiotropic effects of statins in animal models have generally been observed with doses/concentration of statins that are higher than those employed in the clinical setting, thereby casting some doubt on their relevance to patients on statin therapy.(19) However, in keeping with previous results obtained *in vitro* and in mice models, a randomized, double-blind, placebo controlled study in patients undergoing cardiac surgery showed that 3-day treatment with atorvastatin 40 mg once daily (od) before surgery attenuated oxidative stress by inhibiting vascular and atrial Rac1-mediated activation of NOX2 (8, 9) (Fig. 1). Of note, these effects occurred before an LDL cholesterol reduction could be detected, and they were reproduced by incubation with atorvastatin *ex vivo* and reversed by mevalonate (8, 9, 131).

The putative effects of statins on oxidative stress and inflammation in AF are schematically summarized in Figure 5.

What is the Role of Statins in the Management of AF?

A number of observational studies and small clinical trials have assessed the efficacy of statins in a variety of settings and populations; however, the results are far from being consensual and there is still controversy regarding the role of statins in the primary and secondary prevention of AF.

Primary prevention of AF

Data from the nationwide French Registry of Acute ST Elevation or Non-ST Elevation Myocardial Infarction register, an observational study of patients hospitalized for acute myocardial infarction, provided the first link between statin therapy and a reduction in acute AF risk (OR = 0.64, 95% CI: 0.45–0.92, $p = 0.017$). Furthermore, results suggested a dose-response relationship, with intensive statin therapy achieving greater risk reduction than conventional therapy (36). The protective effect of statins on incident AF was further supported by a large epidemiological study (involving 27,002 subjects older than 65 years from the Taiwanese National Health Insurance research database followed up for 9 years) (65), in which the highest risk reduction associated with statin treatment was found in patients with a CHADS2 score ≥ 2 (adjusted HR = 0.69, 95% CI: 0.57–0.85, $p < 0.001$). Even though patients on statins had more cardiovascular comorbidities than controls, statin therapy remained a protective factor against new-onset AF after adjusting for potential confounders (adjusted HR = 0.81, 95% CI: 0.69–0.95, $p = 0.009$). However, a recent meta-analysis (nine randomized controlled trials with almost 60,000 patients) refuted this association and reported similar AF incidence regardless of statin treatment (OR = 1.00, 95% CI: 0.86–1.15, $p = 0.95$) (46). The protective role of statins in AF prevention in patients with coronary artery disease remains a matter of heated debate (2, 81, 125, 174). Indeed, in the Myocardial Ischemia Reduction with Acute Cholesterol Lowering (MIRACL) trial, the protection afforded by statin treatment in patients with acute coronary disease did not reach statistical significance (OR = 0.97, 95% CI: 0.72–1.31) (78). More recently, a meta-analysis suggested that statins could reduce the AF risk in patients with acute coronary syndrome. Pooled results from six studies, with more than 160,000 patients (four studies with new-onset AF and two with AF in baseline), revealed an overall risk reduction of 35% with statin therapy (95% CI: 0.55–0.77, $p < 0.0001$), with the benefit being more conspicuous for new-onset AF (RR = 0.59, 95% CI: 0.48–0.73, $p = 0.096$) than for secondary prevention of AF (RR = 0.70, 95% CI: 0.43–1.14, $p = 0.085$) (178). Finally a meta-analysis including all large-scale statin trials did not show a significant reduction in atrial fibrillation in the active treatment group (RR = 0.95, 95% CI: 0.88–1.03, $p = 0.24$), and seven longer-term trials of more intensive *versus* standard statin regimens also showed no evidence of a reduction in the risk of atrial fibrillation (RR = 1.00, 95% CI: 0.90–1.12, $p = 0.99$) (129). Taken together, these findings suggest that statin treatment is not effective in the primary prevention of AF; however, it should be noted that AF was either not recorded or not included among the outcomes of the largest statin trials and event information for these analyses was mostly based on routinely collected data on adverse events.

AF recurrence after cardioversion or radiofrequency ablation

Taking into account the relatively high rate of AF recurrence after catheter ablation and the postprocedural inflammatory state, 125 patients undergoing catheter ablation of AF were randomized in a prospective, double-blind, placebo-controlled trial to receive 80 mg atorvastatin or placebo for 3 months (150). There was no difference in symptomatic AF between groups (5% in atorvastatin *vs.* 6.5% in placebo, $p = 0.75$) or in the recurrence of atrial arrhythmia after ablation (15% in atorvastatin *vs.* 12% in placebo, $p = 0.37$). Failure to suppress arrhythmia occurred despite a significant decrease in LDL-cholesterol and mean CRP levels (mean change -0.75 ± 3, $p = 0.02$) with statins, pointing to a reduction in systemic inflammation (150).

Electrical cardioversion remains the most commonly used method for sinus rhythm restoration in patients with persistent AF, albeit with a fairly modest rate of success even in conjunction with new antiarrhythmic drugs (137). Contrary to the absence of benefit on AF recurrence after ablation, there is a trend toward a protective role of statins against arrhythmia after successful cardioversion. In a meta-analysis of six studies (515 patients with persistent AF), upstream statin therapy achieved a significant reduction in AF relapse after successful electrical cardioversion (OR = 0.662, 95% CI: 0.45–0.96, $p = 0.03$) (99). Even though the results of this meta-analysis are of potential interest, the studies included were small, of low quality, and very heterogeneous concerning type and dosage of statin. Therefore, more than changing clinical practice, these findings provide a useful background for planning future larger studies. Taken together, these findings are in line with a previous meta-analysis that compared efficacy of statins for secondary prevention of AF, either after electrical cardioversion or after ablation, which showed that statin treatment had no effect on AF recurrence after ablation (four studies, including 750 patients; RR = 1.04, 95% CI: 0.85–1.28, $p = 0.71$) but appeared to reduce the risk of AF relapse after cardioversion (12 studies, including 1790 patients; RR = 0.78, 95% CI: 0.67–0.90, $p = 0.0003$). Nonetheless, the latter result was no longer significant when the analysis was restricted to randomized controlled trials (five studies, 458 patients, RR = 0.76, 95% CI: 0.48–1.20) (38). In summary, there is no indication for statin therapy solely on the basis of prevention of AF recurrence.

AF in HF

AF is a common comorbidity in patients with HF and each adversely affects the other, as their co-existence is associated

with worse long-term prognosis (109). Despite the apparent benefit of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in reducing AF in patients with HF (102, 104, 157), the role of statins for AF prophylaxis in HF is far from being completely understood (103). The double-blind, placebo-controlled trial GISSI-HF found that rosuvastatin marginally reduced the incidence of AF in 3690 patients with HF (13.9% on rosuvastatin *vs.* 16.0% on placebo), even though the difference only reached statistical significance after adjustment for clinical variables, laboratory examinations, and background therapies (p = 0.038) (103). This study raises the possibility that statins may prevent the development of AF in patients with HF, but larger studies, considering AF as primary endpoint, are warranted to confirm this finding. The Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico on heart failure (GISSI-HF) trial confirmed that history of earlier AF enhanced susceptibility to new episodes of AF over the follow up (103), but did not show any difference in the efficacy of rosuvastatin between groups.

Postoperative AF

Postoperative AF is the most common postoperative arrhythmic complication, occurring in approximately 40% of cardiac surgery patients. Since postoperative AF is associated with adverse cardiovascular events (*e.g.*, HF, stroke), prolonged hospitalization and increased overall morbidity and mortality, prevention of its development improves prognosis of patients undergoing cardiac surgery (89).

Numerous observational studies [*e.g.*, (28, 62, 107, 121)] suggest that pre- or perioperative statin treatment reduces the occurrence of AF and improves clinical outcome in patients undergoing cardiac or major vascular surgery (by causing a 50%–70% reduction in perioperative myocardial infarction or mortality). However, in two large cohort studies, statin therapy failed to decrease (159) or even increased (110) incidence of postoperative AF. The first controlled clinical trial attesting the efficacy of perioperative statin treatment in the prevention of postoperative AF was ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery), there was a 61% reduction in AF risk (evaluated by continuous electrocardiogram (ECG) monitoring) in 200 statin naïve patients undergoing elective cardiac surgery but there was no effect on postoperative CRP or cardiac/cerebrovascular events (123). In a recent meta-analysis of 10 randomized trials (of which only four had postoperative AF as a predefined outcome) (46) evaluating the use of perioperative statin treatment in patients undergoing cardiac surgery ($n = 1001$ patients in total–study size between 40 and 200 patients), statin use was found to reduce patients' relative risk of developing postoperative AF by 63% (RR = 0.37, 95% CI: 0.28–0.51) (Fig. 8). Although these findings would be consistent with a rapid and, possibly, lipid-independent antiarrhythmic effect of statins, they have important limitations (*e.g.*, small size, nonsystematic use of continuous ECG monitoring, mostly "ancillary findings") and are less bearing on current day-to-day clinical practice, as they only randomized patients who were not on statin treatment. A large, placebo-controlled, randomized clinical trial of the effect of rosuvastatin (20 mg od) in patients undergoing cardiac surgery (www.clinicaltrials.gov/ct2/show/NCT01573143?term=STICS&rank=1) will address these pending issues. Noteworthy, the beneficial effects of statins seem to go beyond the prevention of postoperative AF. A meta-analysis of 15 randomized controlled trials (2292 patients undergoing cardiac and noncardiac surgery) showed that statins not only decrease the incidence of postoperative AF but also reduce postoperative myocardial infarction (RR = 0.53, 95% CI: 0.38–0.74), in-hospital length of stay (standardized mean difference = −0.32, 95% CI: −0.53 to −0.11), and mortality (RR = 0.62, 95% CI: 0.34–1.14), albeit not meeting the threshold for statistical significance in this case (31).

Together, these findings suggest that aggressive perioperative statin treatment may be a risk-reducing intervention in patients undergoing major surgery.

Conclusions

In conclusion, the clinical impact of the anti-inflammatory and antioxidant effects of statin therapy remains to be

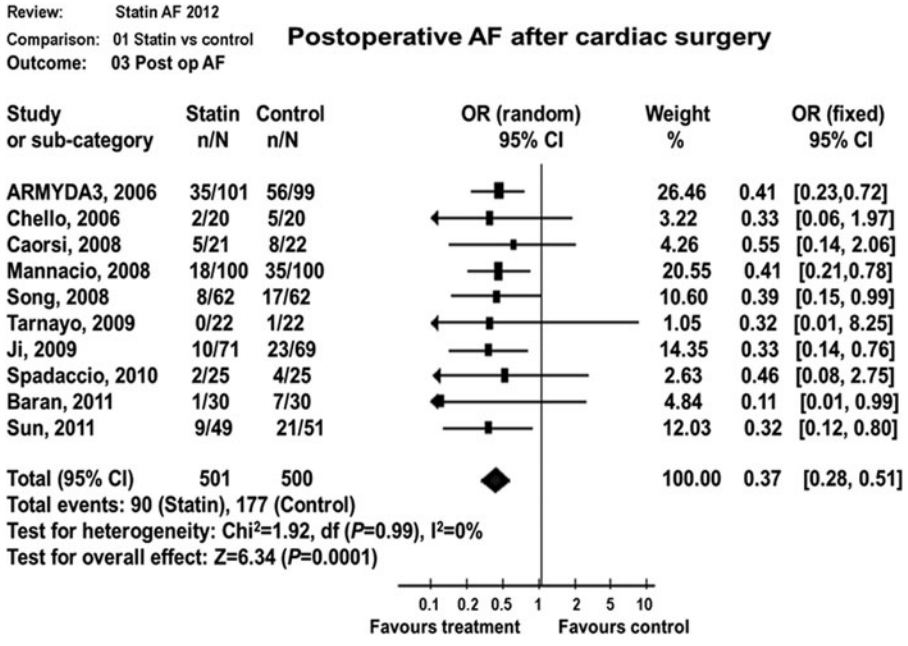

FIG. 8. A meta-analysis of 10 randomized trials (only four of which had postoperative AF as a predefined outcome) suggests that statin therapy might reduce the risk of developing postoperative AF by 63%. CI–confidence interval, OR–odds ratio. Modified from Fauchier *et al.* (46).

demonstrated. As their anti-arrhythmic effects are concerned, statins appear to attain the highest benefit in the prevention of postoperative AF, although this finding needs to be confirmed by larger clinical trials. The efficacy for secondary prevention of AF by statin therapy, albeit lower, might still be significant in some settings but not after ablation. On the other hand, statins seem to have a fairly limited benefit, if any, in the primary prevention of AF. To date, the antiarrhythmic effect of statins does not hitherto support prescribing these agents for the sole purpose of preventing incident AF or its recurrence. Large-scale randomized clinical trials are warranted to shed light on some unsolved issues, particularly regarding the benefit of statins for the management of AF in specific patients' subgroups.

Innovation

Antioxidant and anti-inflammatory effects of statins have been extensively described in animal models and humans; however, their relevance to patients' outcome remains unproven. A scattering of small clinical trials suggests that perioperative statin treatment may prevent the new onset of AF after cardiac surgery. However, the efficacy of statin therapy in AF's secondary prevention might only be significant in some settings; similarly, statins appear to be of little or no benefit in AF's primary prevention. Nevertheless, the available evidence is not robust (single-center studies of small size or "ancillary" finding" from studies designed to detect other outcomes), and larger dedicated trials are needed to conclusively test this hypothesis.

Acknowledgments

The authors are grateful for the support of the British Heart Foundation, the Fondation Leducq (Transatlantic Networks of Excellence on redox and nitrosative regulation of cardiac remodeling), and the European Union (FP7 Collaborative project EUTRAF, 261057).

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Date of first submission to ARS Central, July 19, 2013; date of acceptance, August 6, 2013.

Abbreviations Used

95% CI = 95% confidence interval
ADMA = asymmetric dimethylarginine
AF = atrial fibrillation
APD = action potential duration
APJ = apelin receptor
BH4 = tetrahydrobiopterin
CaMKII = calmodulin-kinase II
CPB = cardiopulmonary bypass
CRP = C-reactive protein
Cx40 = connexin 40
Cx43 = connexin 43
df = degrees of freedom
HF = heart failure
HMG-CoA = 3-hydroxy-3-methylglutaryl-coenzyme A
HR = hazard ratio
IL = interleukin

Abbreviations Used (Cont.)

KLF2 = kruppel-like factor 2
LA = left atrial
LTCC = L-type Ca channels
MEK = MAP kinase kinase
MPO = myeloperoxidase
MTORC1 = mammalian target of rapamycin complex 1
NO = nitric oxide
NOS = nitric oxide synthase
NOX = NADPH-oxidase
OR = odds ratio
PKA = protein kinase A
PKC = protein kinase C
PPAR = peroxisome proliferator-activated factor
RA = right atrial
Rheb = ras homolog enriched in brain
RLU = relative light units
ROS = reactive oxygen species
RR = relative risk
RyR2 = ryanodine receptor
SMD = standardized mean difference
TGF-β = transforming growth factor β
TNF-α = tumor necrosis factor α
XO = xanthine oxidase