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REVIEW

Upstream therapies for management of atrial fibrillation: review of clinical evidence and implications for European Society of Cardiology guidelines. Part I: primary prevention

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Atrial fibrillation (AF) is associated with significant morbidity and mortality. It is also a progressive disease secondary to continuous structural remodelling of the atria due to AF itself, to changes associated with ageing, and to deterioration of underlying heart disease. Current management aims at preventing the recurrence of AF and its consequences (secondary prevention) and includes risk assessment and prevention of stroke, ventricular rate control, and rhythm control therapies including antiarrhythmic drugs and catheter or surgical ablation. The concept of primary prevention of AF with interventions targeting the development of substrate and modifying risk factors for AF has emerged as a result of recent experiments that suggested novel targets for mechanism-based therapies. Upstream therapy refers to the use of non-antiarrhythmic drugs that modify the atrial substrate- or target-specific mechanisms of AF to prevent the occurrence or recurrence of the arrhythmia. Such agents include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), statins, *n*-3 (*ω*-3) polyunsaturated fatty acids, and possibly corticosteroids. Animal experiments have compellingly demonstrated the protective effect of these agents against electrical and structural atrial remodelling in association with AF. The key targets of upstream therapy are structural changes in the atria, such as fibrosis, hypertrophy, inflammation, and oxidative stress, but direct and indirect effects on atrial ion channels, gap junctions, and calcium handling are also applied. Although there have been no formal randomized controlled studies (RCTs) in the primary prevention setting, retrospective analyses and reports from the studies in which AF was a pre-specified secondary endpoint have shown a sustained reduction in new-onset AF with ACEIs and ARBs in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy), and in the incidence of AF after cardiac surgery in patients treated with statins. In the secondary prevention setting, the results with upstream therapies are significantly less encouraging. Although the results of hypothesis-generating small clinical studies or retrospective analyses in selected patient categories have been positive, larger prospective RCTs have yielded controversial, mostly negative, results. Notably, the controversy exists on whether upstream therapy may impact mortality and major non-fatal cardiovascular events in patients with AF. This has been addressed in retrospective analyses and large prospective RCTs, but the results remain inconclusive pending further reports. This review provides a contemporary evidence-based insight into the role of upstream therapies in primary (Part I) and secondary (Part II) prevention of AF.

Keywords Atrial fibrillation • Remodelling • Prevention • Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Aldosterone antagonists • HMG-CoA reductase inhibitors • Statins • *n*-3 (*ω*-3) Polyunsaturated fatty acids • Corticosteroids

Introduction

Atrial fibrillation (AF) is an increasingly common arrhythmia and now stands at epidemic proportion. A rising proportion of the older population, markedly improved survival from previously fatal cardiovascular conditions, and a recently observed trend towards a continuous increase in the incidence of AF among younger ages will result in a considerable increase in the number of patients with AF over the next four decades. The number of patients with AF in the USA is expected to reach 5.6–15.9 million by 2050.[1–3] A similar increase in the proportion of population with AF is likely to be seen in Western Europe.[4]

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Furthermore, an increased awareness of the arrhythmia, improved diagnostic tools, and a wider use of implantable rhythm control or rhythm monitoring devices will lead to a more frequent recognition of silent and short transient episodes of AF.[5]

Atrial fibrillation is a result of continuous remodelling of the atria, which involves electrical and structural transformation, altered metabolism, and autonomic changes secondary to ageing, progression of underlying heart disease, and genetic and environmental factors. Atrial fibrillation is increasingly associated with hypertension, congestive heart failure (CHF), ischaemic heart disease, and diabetes, all of which are recognized risk factors for the arrhythmia.[6] It is prevalent after surgery, particularly cardiothoracic interventions.[7]

The concept of upstream therapies is appealing because these therapies target both the formation and evolution of the substrate for AF. Theoretically, they may provide primary prevention of new-onset AF and secondary prevention of recurrent AF.[8] The antiarrhythmic potential of a variety of traditionally non-antiarrhythmic drugs has been explored, including angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), aldosterone antagonists, statins, and *n*-3 (*ω*-3) polyunsaturated fatty acids (PUFAs). As clinical evidence has accumulated, it has become clear that upstream therapies may have a differential effect on primary prevention and secondary prevention. Therefore, data on primary and secondary prevention of AF in different patient subsets are reviewed separately.

Inhibitors of the renin–angiotensin–aldosterone system

Experimental evidence

The key mechanism of antiarrhythmic action of inhibitors of the renin–angiotensin–aldosterone system (RAAS) relates to opposing the arrhythmogenic effects of angiotensin II, which include stimulation of atrial fibrosis and hypertrophy secondary to activation of mitogen-activated protein kinases, uncoupling gap junctions, impaired calcium handling, alteration of ion channel dynamics, activation of mediators of oxidative stress, and promotion of inflammation.[9,10] Elevated levels of ACE and angiotensin II and upregulation of profibrotic angiotensin II type I receptors in the atrial myocardium have been reported in animal AF models and in patients with AF.[10–13] A recent meta-analysis of 18 case–control studies in 7577 subjects showed that individuals with an ACE gene mutation resulting in high ACE levels had a 1.36-fold risk of developing AF than those with genotypes associated with intermediate or low ACE levels.[14] This association was stronger in patients with hypertension, who had a 1.64–2.76-fold increased risk of AF in the presence of ACE gene polymorphism associated with high ACE levels.

Consequently, treatment with ACEIs and ARBs has been shown to counteract the proarrhythmic effects of angiotensin II by reducing interstitial fibrosis in CHF or rapid atrial pacing models of AF and preventing shortening of the atrial effective refractory period (*Figure 1*).[13,15] This effect was independent of reductions in the atrial pressure suggesting mechanisms other than unloading the atria.[13] In patch-clamp experiments, irbesartan produced a modest, but measurable, blocking effect on the hKv1.5 and Kv4.3 channels, which carry I_{Kur} and I_{to} ion currents.[16] In cultured atrial neonatal rat cardiomyocytes exposed to stretch, losartan prevented stretch-induced, angiotensin II-mediated hypertrophy of atrial myocytes and modulated expression of genes encoding for several putative channel proteins and the density of corresponding ion currents, such as I_{K1}, I_{Kur}, and I_{to}.[17] Losartan reduced an angiotensin II-induced increase in automaticity in isolated rabbit pulmonary vein tissue preparations and single cardiomyocytes.[18] Irbesartan and valsartan have been shown to counteract local angiotensin II-induced norepinephrine spillover in the rat atria,[19] thereby alleviating increased heterogeneity of local sympathetic stimulation, which is associated with increased dispersion of refractoriness and greater vulnerability to AF. Angiotensin-converting enzyme inhibitors and ARBs may prevent angiotensin II-induced gap junctional remodelling.[20] In *ex vivo* paced human atrial tissue and *in vivo* in pigs, olmesartan and irbesartan reduced expression of the vascular cell adhesion molecule-1 caused by rapid atrial pacing.[21] In addition to blockade of the angiotensin II-mediated pro-inflammatory pathway, new-generation ARBs, telmisartan and irbesartan, activate peroxisome proliferator-activated receptor (PPAR)-dependent anti-inflammatory mechanisms and can offer a broader anti-inflammatory and metabolic protection.[22] There is compelling experimental and clinical evidence of the efficacy of RAAS inhibitors in primary prevention of AF, but data on their role in secondary prevention are controversial (*Table 1*).

Congestive heart failure

Congestive heart failure is one of the most important risk factors for AF and, as evidenced by multivariate analysis from the Framingham Study, increases risk of AF by 4.5-fold in men and 5.9-fold in women.[23] Common in elderly patients, diastolic left ventricular dysfunction is associated with a 5.26-fold increased risk of AF.[24] The occurrence of CHF in middle age confers an 8% risk of developing AF over a 10-year period if the patient's age at time of CHF diagnosis was 55–64 years, which rises to >30% if CHF was diagnosed at 45–54 years.[25] Furthermore, the presence of CHF not only increases the likelihood of developing AF, but is the leading independent predictor of progression to permanent AF, with an odds ratio (OR) of 2.2 [95% confidence interval (CI), 1.54–3.22; $P < 0.01$].[26] New-onset AF in CHF is associated with clinical deterioration and poor prognosis.[27] Thus, intervening to prevent or delay the occurrence and progression of AF is vital in patients with CHF.

The adverse effect of new-onset or recurrent AF on morbidity and mortality in CHF, irrespective of the background therapy, has been reported.[28,29] Although the AF-CHF (Atrial Fibrillation in Congestive Heart Failure) trial showed no benefit from the rhythm control strategy, which employed antiarrhythmic drugs,[30] there are reports that the absence of AF is associated with fewer symptoms and better functional status and left ventricular function in patients with CHF.[31,32] The true benefit of preserving sinus rhythm in patients with CHF in the AF-CHF and other secondary prevention studies might have been offset by the relatively low efficacy and adverse effects of antiarrhythmic drugs. Thus, upstream therapies (e.g. RAAS inhibitors) that target both the

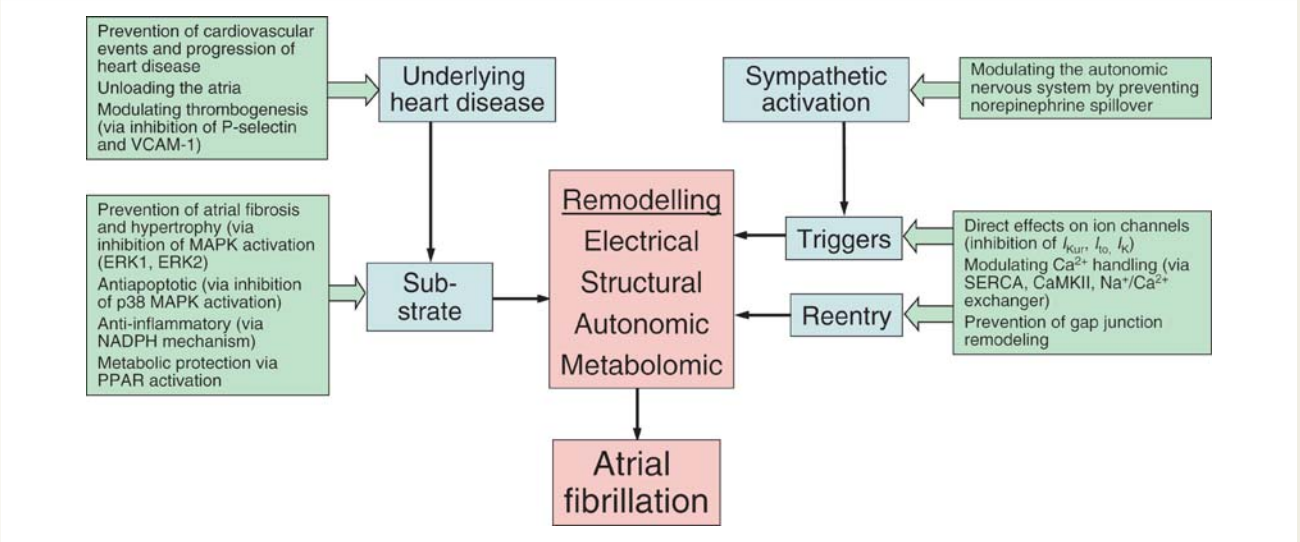

Figure 1 Pathophysiological processes associated with atrial remodelling that may be targets, potentially modifiable by angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers. CaMKII, Ca^{2+}/calmodulin-dependent protein kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinases; NADPH, nicotinamide adenine dinucleotide phosphate; PPAR, peroxisome proliferator-activated receptor; SERCA, sarcoendoplasmic reticulum Ca^{2+}-adenosine triphosphatase; VCAM, vascular cell adhesion molecule. Adapted from Savelieva and Camm.[8]

Table 1 Evidence base for inhibitors of renin–angiotensin inhibitors for prevention of atrial fibrillation

Level of evidence	Studies	Primary prevention	Secondary prevention
Experimental data	Multiple well-conducted studies	All reported the beneficial effect of treatment on electrical and structural remodelling and inducibility of AF	Isolated studies, controversial results
Retrospective studies	Multiple retrospective and observational studies	The majority of studies reported the beneficial effect of treatment on new-onset AF	Limited mixed results
Small prospective studies	Several small-size open-label and double-blind randomized placebo-controlled studies in patients with persistent AF undergoing electrical cardioversion and patients with paroxysmal or mixed paroxysmal and persistent AF	Not available	Positive open-label studies; double-blind placebo-controlled studies reported mixed results, but were mainly negative
Large prospective randomized-controlled studies with AF as a primary endpoint	GISSI-AF, J-RHYTHM II, ANTIPAF	Not available	Reported no effect on prevention of AF recurrence in patients with paroxysmal and mixed paroxysmal and persistent AF
Meta-analyses	Five meta-analyses which included different numbers and types of studies	Consistent significant risk reductions by 32–48% in patients with congestive heart failure; an overall positive trend in myocardial infarction (risk reductions by 10–28%, but not significant in some analyses); mixed results in patients with hypertension (risk reductions by 6–23%, but not significant in all but one meta-analysis)	All reported significant risk reductions by 45–63%

ACEIs, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ANTIPAF, ANgiotensin II antagonisT In Paroxysmal Atrial Fibrillation; ARBs, angiotensin receptor blockers; GISSI AF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Atrial Fibrillation; J-RHYTHM II, Japanese Rhythm Management Trial for Atrial Fibrillation.

underlying condition and the substrate formation for AF may offer a greater benefit than specific antiarrhythmic drugs.[33]

Mechanisms of the occurrence and domestication of AF in the presence of CHF include stretch-induced slowing and heterogeneity of conduction. The lines of conduction block occur around acquired anatomical obstacles such as scars, patchy fibrosis, stretch-induced longitudinal dissociation, or areas of myocardium at different stages of recovery and excitability. Increased local synthesis of angiotensin II in the presence of atrial stretch and elevated systemic levels of angiotensin II and catecholamines associated with CHF promote further electrophysiological changes, atrial fibrosis, and atrial hypertrophy.[33] Atrial fibrosis plays a significant role in promoting AF associated with CHF.[34,35] Chronic atrial volume overload and dilatation create a 'critical mass' needed for maintenance of multiple re-entrant circuits.[36] Ionic and electrical remodelling in the presence of CHF probably differs from remodelling in other forms of AF, e.g. AF induced by rapid atrial pacing.[34,35] Upstream therapies counteracting the profibrotic effects of angiotensin II may, theoretically, be more effective than specific antiarrhythmic drugs that target specific ion channels.

The first large study to report the beneficial effect of RAAS inhibition on the occurrence of new-onset AF was the TRACE (Trandolapril Cardiac Evaluation) study in patients with recent myocardial infarction and ejection fraction (EF) $\leq$35%.[37] Patients who received trandolapril were less likely to develop new-onset AF during 2–4 years of follow-up compared with the placebo group (2.8 vs. 5.3%; OR, 0.45, 95% CI, 0.26–0.76; $P = 0.01$). The report from the TRACE study was followed by similar retrospective analysis of the single-centre results from the SOLVD (Studies of Left Ventricular Dysfunction) trial, which also demonstrated less AF occurrence in patients with CHF and EF $\leq$35% with enalapril as opposed to placebo after 2.9 years of follow-up [5.4 vs. 24%; hazard ratio (HR), 0.22, 95% CI, 0.11–0.44; $P < 0.0001$].[38]

Later studies with ARBs yielded similar results. In the Valsartan Heart Failure Trial (Val-HeFT) study in 4395 patients with symptomatic CHF and EF <40%, therapy with valsartan was associated with a 37% reduction in relative risk of newly detected AF compared with placebo (5.12 vs. 7.95%; $P = 0.0002$) during 1.9 years.[39] This benefit from an ARB was present despite a high (93%) rate of concomitant use of ACEIs. This study has also demonstrated that the occurrence of AF was independently associated with adverse major outcomes such as all-cause death and combined mortality and morbidity, which increased by 40 and 38%, respectively, in the presence of AF. However, whether valsartan therapy improved outcome within the new-onset AF group compared with placebo has not been reported.

One of the limitations of these retrospective analyses was that AF was not a pre-specified endpoint and a significant proportion of asymptomatic or mildly symptomatic episodes might not have been reported. The CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) programme designated AF as one of the secondary endpoints. The AF substudy from the CHARM trials has shown that adding candesartan to conventional CHF therapy in 6379 patients with symptomatic CHF and without a history of AF at enrolment led to a lower incidence of new-onset AF compared with placebo, albeit this reduction was not as significant as in the previous reports (5.55 vs. 6.74%; OR 0.81, 95% CI, 0.662–0.998; $P = 0.048$).[40]

Of note, the magnitude of the preventative effect of RAAS inhibition varies in patients with a different degree of impairment of left ventricular function. Thus, although statistically there was no heterogeneity of the effect of candesartan on AF between the three component trials in the CHARM programme, the greatest benefit was seen in patients with impaired systolic function and without the concurrent use of ACEIs enrolled in the CHARM-alternative study and the least in patients with CHF and preserved systolic function.[39] Similarly, irbesartan did not influence the incidence of AF reported as an adverse event in the I-PRESERVE (Irbesartan in patients with heart failure and PRESERVEd ejection fraction) trial.[41]

Four meta-analyses have shown that risk of new-onset AF in patients with CHF was reduced by 30–48%, suggesting that ACEIs and ARBs may be effective in primary prevention of AF in this clinical setting (*Figure 2*).[42–45] This is consistent with experimental evidence of atrial fibrosis as the leading mechanism of AF in CHF models and evidence of antifibrotic effects of RAAS inhibition. It is unclear whether therapy with ACEIs and ARBs can prevent or delay the occurrence of AF in patients with CHF and preserved systolic function. There is no direct evidence that upstream therapies with RAAS inhibitors can reduce morbidity and mortality in patients with CHF by deterring AF.

Hypertension

Hypertension is the most prevalent condition and a risk factor associated with AF as well as increased risk of stroke in AF patients. In the epidemiological surveys, hypertension was associated with a 1.8-fold increased risk of developing new-onset AF[23] and a 1.52-fold increased risk of progression to permanent AF.[26] Likewise in CHF, patients with concomitant AF and hypertension had a significantly greater risk of all-cause death (OR, 2.32), cardiovascular mortality (OR, 3.06), and sudden cardiac death (OR, 2.93); $P < 0.001$ for all.[46] Atrial fibrillation significantly increased the risk of stroke and CHF by 2.44–2.84-fold and 2.35–3.02, respectively.[45,46] In the ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial), new-onset and pre-existing AF conferred similar risks for major cardiovascular outcomes.[47]

Inhibition of RAAS is a recognized efficacious treatment for hypertension. Patients with hypertension and left ventricular hypertrophy have particularly high circulating levels of angiotensin II.[48] In addition to prevention of atrial stretch and hypertrophy secondary to increased left atrial pressure, ACEIs and ARBs can counteract the direct arrhythmogenic effects of angiotensin II. Antihypertensive therapy *per se* has been shown to prevent left atrial dilatation and even induce reverse remodelling. Thus, in patients with hypertension and no history of AF, an increased left atrial diameter at the start of treatment increased the likelihood of developing new-onset AF by a factor of 5.16 per cm, whereas the reduction in the left atrial size on treatment was associated with a 79% lower relative risk of AF.[49]

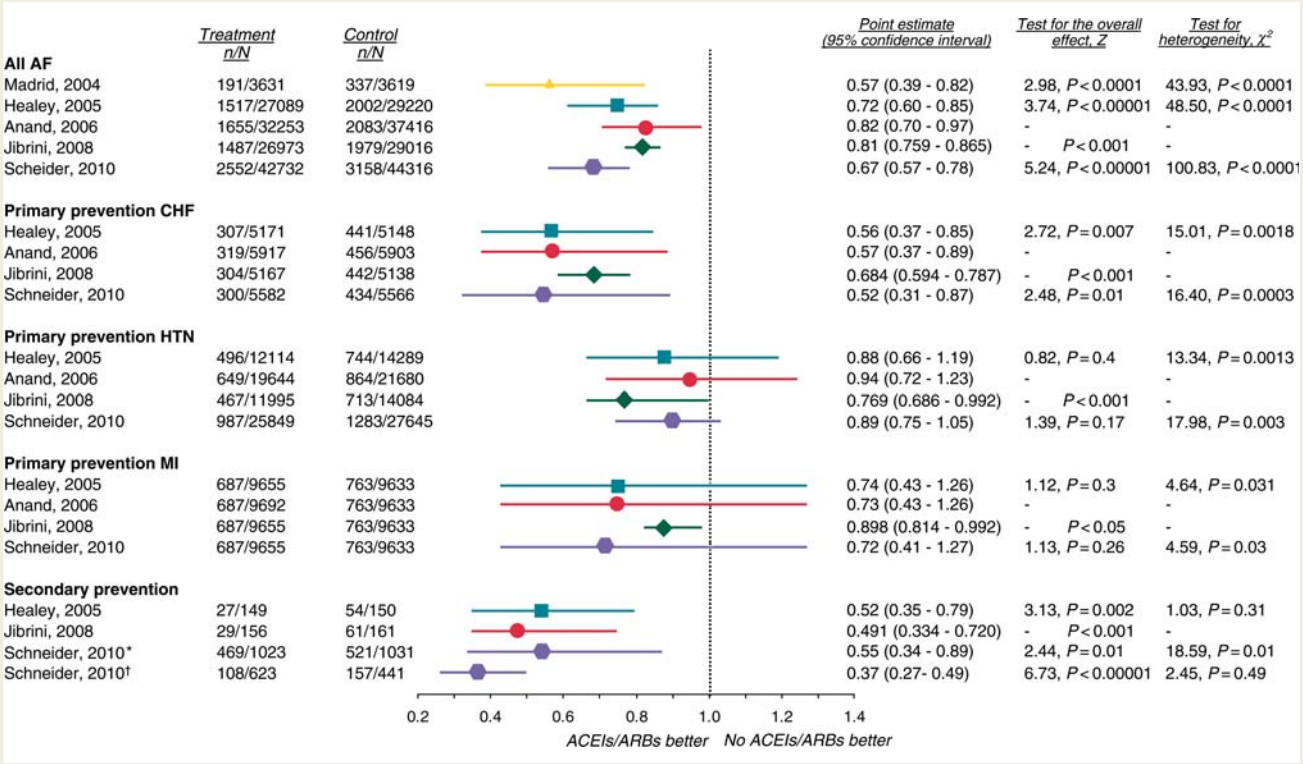

Figure 2 Efficacy of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in prevention of atrial fibrillation compared with placebo, no treatment, or alternative drug therapies in five meta-analyses (point estimate 95% confidence interval). Note that several studies have not been included in these meta-analyses. CHF, congestive heart failure; HTN, hypertension; MI, myocardial infarction. Asterisk indicates post-cardioversion studies; dagger indicates medical therapy studies. See the text for details.

Surprisingly, the effect of RAAS inhibition on primary prevention of AF in hypertension was less evident than in CHF (*Table 2*). In the CAPPP (CAPtopril Prevention Project) trial in hypertensive patients, AF, reported as an adverse event, occurred in 2.1% patients treated with captopril and in 2.5% patients who received other antihypertensive agents during a 6.1-year follow-up; the difference was not statistically significant.[50] A low incidence of AF because of the relatively young mean age of participants (52 years) and a low prevalence of risk factors, such as CHF (0.3%), coronary artery disease (CAD) (2.2%), and diabetes (5.2%), might obscure the beneficial effect of ACEI-based therapy. Nonetheless, in the STOPH-2 (Swedish Trial in Old Patients with Hypertension-2) in an older patient population (mean age 76 years) with a higher overall prevalence of AF at enrolment (4.7%) and more cardiovascular risk factors, no reduction in AF was observed with enalapril or lisinopril compared with calcium antagonists or diuretics and beta-blockers.[51]

Consequently, of four meta-analyses, which assessed the effect of ACEIs and ARBs on prevention of incident AF in patients with hypertension,[42–45] only one showed a statistically significant 25% reduction in relative risk of AF[44] (*Figure 2*). Although in meta-analyses the overall trend was in favour of RAAS inhibitors, it has mainly been driven by a marked 33% reduction in new-onset AF observed with losartan compared with atenolol in the LIFE (Losartan Intervention For Endpoint reduction in hypertension) study.[52] Unlike other trials in hypertension included in these meta-analyses, the LIFE study enrolled patients with left ventricular hypertrophy, and the reduction in AF paralleled regression of myocardial thickness, which was greater with losartan-based therapy.[53] However, the association between left ventricular hypertrophy and new-onset AF was similar in patients treated with losartan or atenolol, suggesting that the impact of left ventricular hypertrophy regression on AF may be independent of the treatment modality used to achieve this regression. Hence, a lower likelihood of AF associated with losartan therapy after adjustment for other risk factors implies an additional, possibly direct, preventative antiarrhythmic effect of an ARB. It is particularly impressive that RAAS inhibition produced a larger effect on primary prevention of AF than beta-blockade, which has been traditionally regarded as having a moderate but proven antiarrhythmic efficacy.

Two retrospective analyses from administrative databases in the USA and the UK have suggested that RAAS inhibitor-based treatment for hypertension can delay the occurrence of AF in the usual care setting. In the US longitudinal cohort study of 10 926 patients (~2.4% with a history of AF) treated with ACEIs or calcium-channel blockers and matched using propensity scoring, adjusted HR for the occurrence of AF during 4.5 years was 0.85 (95% CI, 0.74–0.97; $P = 0.0183$) in favour of ACEIs.[54] The nested case–control study of the UK General Practice Research Database included 4661 patients with AF and 18 642 matched control patients from a population of 682 993 patients treated for hypertension and found that therapy with ACEIs and ARBs was associated with a 25–29% reduction in AF compared with calcium-channel blocker-based therapy.[55]

Table 2 Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for primary prevention of atrial fibrillation in patients with hypertension and cardiovascular risk factors

Study	Design	Number of patients	Age (years)	Active drug	Comparator	Follow-up (years)	AF outcome
CAPPP (1999)	PROBE, AF based on AER	10 985	Captopril: 52.4 ± 8.3, Comparator: 52.7 ± 8.4	Captopril	Diuretics, beta-blockers	6.1	2.1% captopril vs. 2.5% beta-blockers/diuretics; $P = 0.30$
STOPH-2 (1999)	PROBE, masked endpoints, AF based on AER	6628	76.0	Enalapril, lisinopril	CCBs, beta-blockers, diuretics	4	19% enalapril/lisinopril vs. 17.1% CCBs vs. 16.4% beta-blockers/diuretics per 1000 patient-years
US cohort (2004)	Retrospective longitudinal	10 926	65.0	ACEIs	CCBs	4.5	17.9% ACEIs vs. 18.9 CCBs per 1000 patient-years; HR, 0.85 (0.74–0.97); $P = 0.0183$
LIFE (2005)	Planned secondary analysis; AF on annual ECGs	8851	Losartan: 70.3 ± 6.9, Atenolol: 70.7 ± 6.0	Losartan	Atenolol	4.8	6.8% losartan vs. 10.1% atenolol per 1000 patient-years; HR, 0.67 (0.55–0.83); $P < 0.001$
VALUE (2007)	Planned secondary analysis; AF on annual ECGs	13 760	70.5 ± 7.4	Valsartan	Amlodipine	5	3.67% valsartan vs. 4.34% amlodipine; HR, 0.843 (0.71–0.99); $P = 0.045$
ALLHAT (2009)	AF on bi-annual ECGs	39 056	55–69: 64.7%, 70–79: 28.9%, ≥90: 6.4%	Lisinopril	Amlodipine, doxazosin, chlorthalidone	4.9	20.6% lisinopril vs. 22.4% amlodipine, 16.3% doxazosin, 20.6% chlorthalidone per 1000 patients; ACEIs vs. other therapy: OR, 0.939; $P = 0.59$
UK cohort (2010)	Nested case–control analysis	23 303	60–69: 28%, ≥70: 61.8%	ACEIs, ARBs	CCBs	1	ACEIs vs. CCBs: HR, 0.79 (0.69–0.91); $P = 0.001$, ARBs vs. CCBs: HR, 0.71 (0.58–0.88); $P = 0.002$
HOPE (2007)	*Post hoc*; AF on bi-annual ECGs and hospitalization	8335, 45.7% hypertension	AF: 69.0 ± 6.2, No AF: 65.6 ± 6.6	Ramipril	Placebo	4.5	2% ramipril vs. 2.2% placebo; HR, 0.92 (0.68–1.24); $P = 0.57$
TRANSCEND (2008)	Planned secondary analysis; AF based on AER	5926, 76.4% hypertension	Telmisartan: 66.9 ± 7.3, Placebo: 66.9 ± 7.4	Telmisartan	Placebo	4.7	6.4% telmisartan vs. 6.3% placebo; HR,1.02 (0.83–1.26); $P = 0.829$
ONTARGET (2008)	Planned secondary analysis; AF based on AER	25 620, 68.5–69% hypertension	Ramipril: 66.4 ± 7.2, Telmisartan: 66.4 ± 7.1, Combination therapy: 66.5 ± 7.3	Telmisartan, Telmisartan+ ramipril	Ramipril	4.7	6.7% telmisartan vs. 6.5% combination therapy vs. 6.9% ramipril; $P =$ n.s.

ACEIs, angiotensin-converting enzyme inhibitors; AER, adverse event rates; AF, atrial fibrillation; ALLHAT, Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial; ARBs, angiotensin receptor blockers; CAPPP, CAPtopril Prevention Project; CCBs, calcium-channel blockers; ECG, electrocardiogram; HOPE, Heart Outcomes Prevention Evaluation; HR, hazard ratio; LIFE, Losartan Intervention For Endpoint reduction in hypertension; ONTARGET, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; OR, odds ratio; PROBE, prospective randomized open-label blinded Endpoint; STOPH-2, Swedish Trial in Old Patients with Hypertension-2; TRANSCEND, Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; UK cohort, United Kingdom cohort; US cohort, United States cohort; VALUE, Valsartan Antihypertensive Long-term Use Evaluation.

Further evidence of the protective effect of an ARB against AF came from the large-scale VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial in 15 245 hypertensive patients at cardiovascular risk, but not necessarily with left ventricular hypertrophy, which reported that new-onset AF was less frequent in the valsartan-treated group than in the amlodipine-treated group (3.67 vs. 4.34%; HR, 0.843; 95% CI, 0.713–0.997; $P = 0.0455$), despite slightly better blood pressure control by amlodipine.[56] There was a greater reduction in risk of persistent AF by 32% in the valsartan group. Although AF was included in a pre-specified statistical analysis, an inherent major limitation of this report was inadequate monitoring for AF occurrence. The presence or absence of AF at study entry was verified by a 12-lead ECG, and new-onset AF was identified only when the arrhythmia was present on yearly ECGs.

The most recent meta-analysis which included the VALUE trial and studies in patients at high cardiovascular risk (but not exclusively hypertension), the HOPE (Heart Outcomes Prevention Evaluation; 45.7% with hypertension),[57] and TRANSCEND (Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease; 76.4% with hypertension)[58] has shown a modest 19% reduction in the incidence of AF with RAAS inhibitors (95% CI, 0.75–1.05; $P = 0.17$), but there was a significant heterogeneity among the studies ($P = 0.003$).[45]

Cardiovascular risk factors

The effects are even less clear in patients with multiple risk factors including hypertension, diabetes mellitus, CAD, cerebrovascular disease, peripheral artery disease, hypercholesterolaemia, etc., such as those enrolled in the HOPE[57] and TRANSCEND[58] trials. In these trials, ramipril and telmisartan, respectively, had no protective effect against new-onset AF compared with placebo (*Table 2*). In the HOPE study, evidence for the presence or absence of AF was collected in 8335 patients using pre-scheduled electrocardiograms (ECG) at 2 and 4.5 years and from hospital admissions for symptomatic AF.[57] The authors found no difference in the incidence of new-onset AF between ramipril and placebo groups, but the overall incidence of AF (2.1%, or 4.7 per 1000 patient-years) was relatively low. Although patients in the HOPE study were at high cardiovascular risk, the majority (80%) presented with CAD, which is considered a less powerful specific risk factor for the development of AF than CHF and hypertension. Patients with left ventricular dysfunction or a history of CHF were excluded from the HOPE study; less than half had hypertension and only 9% had left ventricular hypertrophy. Likewise, ~75% of the TRANSCEND study patients had CAD and the mean age was 67 years, but there was a significantly greater prevalence of hypertension.[58] The median follow-up was similar to that of the HOPE study, but new-onset AF, which was a secondary endpoint, occurred more frequently. Nevertheless, the incidence of AF was not affected by treatment modality: 6.4% of patients in the telmisartan arm developed AF compared with 6.3% of patients in the placebo arm.

Post-operative atrial fibrillation

Atrial fibrillation occurs in ~25–30% of patients after isolated coronary artery bypass grafting (CABG), 40% of patients after valve surgery, and 50% of patients after combined coronary artery and valvular surgery.[59] Post-operative AF is associated with a 2-fold increase in cardiovascular morbidity and mortality, largely due to stroke and circulatory failure, and increases the subsequent risk of AF by 8.3-fold.[60] The pathophysiology of AF after cardiac surgery is multifactorial and includes oxidative stress, inflammation, impaired extracellular matrix turnover, and accelerated fibrosis. Increased production of catecholamines and angiotensin II also predisposes to AF.

Several retrospective studies have reported on the effect of RAAS inhibitors on the occurrence of AF following cardiac surgery, but the results are mainly negative.[61–64] Among 338 patients undergoing CABG and/or valvular surgery enrolled in the AFIST (Atrial Fibrillation Suppression Trial) II and III studies, there was a trend towards a lower incidence of AF with the pre-operative use of ACEIs or ARBs (adjusted OR, 0.71), but this association was not statistically significant (95% CI, 0.42–1.20; $P = 0.20$).[61] The overall incidence of post-operative AF was 32.5%: 29.1% in the RAAS inhibitors-treated group and 36.2% in the non-RAAS inhibitors group. However, in the AFIST trials, 84% of patients received concomitant therapy with beta-blockers, 38% were treated with amiodarone, and almost half the operations were off-pump, which might obscure any additional benefit from RAAS inhibitors. In a larger series of 757 patients who had isolated on-pump CABG, neither ACEIs (OR, 1.01; 95% CI, 0.75–1.61; $P = 0.63$) nor ARBs (OR, 0.78; 95% CI, 0.43–1.41; $P = 0.41$) were effective in preventing post-operative AF, which occurred in 19% of patients.[62] There are also safety concerns about the potential risk of renal dysfunction associated with RAAS inhibitors early after surgery.

Permanent pacing

An increased incidence of atrial tachyarrhythmias, including AF, is seen in patients who received a pacemaker for sinus node dysfunction or atrioventricular block, even in the absence of a history of AF. About 8–20% of pacemaker patients developed new-onset AF,[65,66] while 2% developed new persistent AF,[67] and the incidence of short asymptomatic episodes was significantly higher.[5] The likely mechanism (and the target for therapy with RAAS inhibitors) is left atrial stretch and dilatation secondary to left ventricular dyssynchrony and dysfunction caused by long-term right ventricular pacing and atrioventricular asynchrony associated with ventricular pacing. In a retrospective observational study of 160 patients with dual-chamber pacemakers, mainly (69%) for atrioventricular block, the incidence of new-onset AF at 1 year was lower in the ACEI/ARB-treated group compared with no ACEIs/ARBs (5 vs. 10%), but this difference was not statistically significant ($P = 0.21$).[68]

Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for prevention of atrial fibrillation?

Theoretically, ACEIs and ARBs may have a different potential to prevent AF because of the biology of RAAS. Angiotensin-converting enzyme inhibitors have no effect on angiotensin II production via non-ACE pathways (e.g. chymase-dependent

pathways), whereas ARBs counteract all effects of angiotensin type 1 (AT-1) receptor activation. Chymase activity in the human heart tissue extract is higher in the left atrium than in other chambers, and the role of chymase in generating angiotensin II increases in abnormal myocardium due to up-regulation of the enzyme.[69] Furthermore, ACEIs antagonize the effects of both AT-1 and AT-2 receptors, whereas ARBs selectively inhibit AT-1 receptors and stimulate AT-2 receptors, which have antiproliferative effects.

Experimental[70] and clinical studies [71,72] that compared ACEIs and ARBs failed to demonstrate the superiority of one class of RAAS inhibitors over another, although one study has found the lowest rate of recurrence in the valsartan-treated group compared with ramipril (16.1 vs. 27.9%; $P < 0.05$).[73] The effect of ACEIs and ARBs on AF was consistent in meta-analyses;[41,43] however, some reported a greater benefit from therapy with ACEIs (relative risk, 0.75; 95% CI, 0.57–0.99) than ARBs (relative risk, 0.81; 95% CI, 0.62–1.06).[43] Subsequently, the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) investigators found no difference in the incidence of new-onset AF in 25 620 patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage treated with ramipril, telmisartan, or both (6.9, 6.7, and 6.5%, respectively).[72]

In summary, there is a sustained reduction in new-onset AF in patients with significant underlying heart disease (e.g. left ventricular dysfunction and hypertrophy) treated with ACEIs or ARBs, but evidence is less robust in patients with moderate structural heart disease. The European Society of Cardiology (ESC) guidelines on management of AF recognize the potential of RAAS inhibitors for primary prevention of AF in patients with CHF [class of recommendation I, level of evidence (LOE) A] and hypertension, particularly with left ventricular hypertrophy (class IIa, LOE B).[74] Many of these patients will receive RAAS inhibitors for underlying heart disease, but in those on alternative therapies it may be prudent to opt for RAAS inhibitors in the presence of risk factors for AF. A large randomized controlled study(RCT) of a RAAS inhibitor for primary prevention of AF is unlikely in the near future. Although there are currently several ongoing studies with different RAAS inhibitors and pending further analyses from completed trials, these are secondary rather than primary prevention oriented (see Part II: Secondary Prevention).[75]

Aldosterone antagonists

A 12-fold increased risk of developing AF by patients with primary hyper-aldosteronism compared with their matched counterparts with essential hypertension with similar levels of blood pressure suggests that the association may exist between serum aldosterone levels and the occurrence of AF.[76] Aldosterone, which is mainly generated in the renal cortex, can also be produced locally in the heart. The local effects of aldosterone are likely to include inflammation, changes in matrix metalloproteinase (MMP) activity, hypertrophy, fibrosis, and probably direct electrophysiological effects. Increased expression of mineralocorticoid receptor has been reported in human AF and a cellular model of AF.[77] Pretreatment with spironolactone in a ventricular tachypacing AF model in dogs reduced the amount of atrial fibrosis and inducibility of AF.[78] In a rapid atrial pacing rabbit model of AF, eplerenone modified the $I_{Ca,L}$ current in the atria.[79] The preliminary report suggests that patients <65 years with heart failure treated with implantable cardioverter-defibrillators for primary prevention of sudden death who received spironolactone were less likely to have atrial high rate episodes of >5 min detected by the device compared with non-users (8 vs. 14%; $P = 0.04$); however, the effect was not evident in older patients.[80]

Statins

Experimental evidence

Inflammation can be a key mechanism for some forms of AF[81] because of the high incidence of AF after cardiac surgery, which is known to induce systemic inflammatory response, and the beneficial effects of drugs with anti-inflammatory properties such as steroids.[82,83] Studies in animals using a sterile pericarditis model and a post-operative AF model have demonstrated that atrial conduction properties change as a result of inflammation, which increases anisotropy, causes connexin Cx40 and Cx43 re-distribution, and extracellular matrix remodelling.[82,84–86] Evidence directly linking inflammation to AF in the setting outside cardiac surgery came from a study of atrial septal biopsies, which demonstrated isolated atrial myocarditis in patients with lone AF.[87] Increased levels of inflammatory cytokines and C-reactive protein have been reported in patients who subsequently developed AF in the general population[88,89] and in patients with CAD.[90] C-reactive protein levels correlated with the likelihood of AF recurrence after cardioversion in a meta-analysis of seven prospective observational studies.[91] Of interest, several reports identified the association between low levels of high-density lipoprotein (HDL)-cholesterol and risk of AF in the general population (HR, 2.33 for HDL-cholesterol <40 mg/dL; $P < 0.05$),[92] patients with hypertension (HR, 1.34 for HDL-cholesterol <35 mg/dL; $P = 0.005$),[46] and patients with components of metabolic syndrome (HR, 1.20 for HDL-cholesterol <40 mg/dL).[93]

The exact mechanism by which statins may prevent AF has not been established, but it is thought to be the net benefit derived from improvement of lipid metabolism and prevention of the process of atherosclerosis, anti-inflammatory, and antioxidant actions, prevention of endothelial dysfunction and neurohormonal activation, altered membrane fluidity, and ion channel conductance (*Figure 3*).[94] Statins can counteract the arrhythmogenic effects of angiotensin II by reducing oxidized low-density lipoproteins, which can up-regulate angiotensin II type 1 receptors. Statins regulate MMPs, an effect that may play a role in regulating structural remodelling associated with AF, e.g. dilatation and fibrosis. In animal experiments with sterile pericarditis, rapid atrial pacing, and ventricular tachypacing AF models, statins attenuated electrical and structural atrial remodelling and reduced vulnerability to AF.[95–97] The antiarrhythmic potential of statins has been reported in retrospective and prospective RCTs in various clinical settings (*Table 3*).

Congestive heart failure

Several retrospective analyses from RCTs and registries in patients with left ventricular dysfunction and CHF have suggested a modest

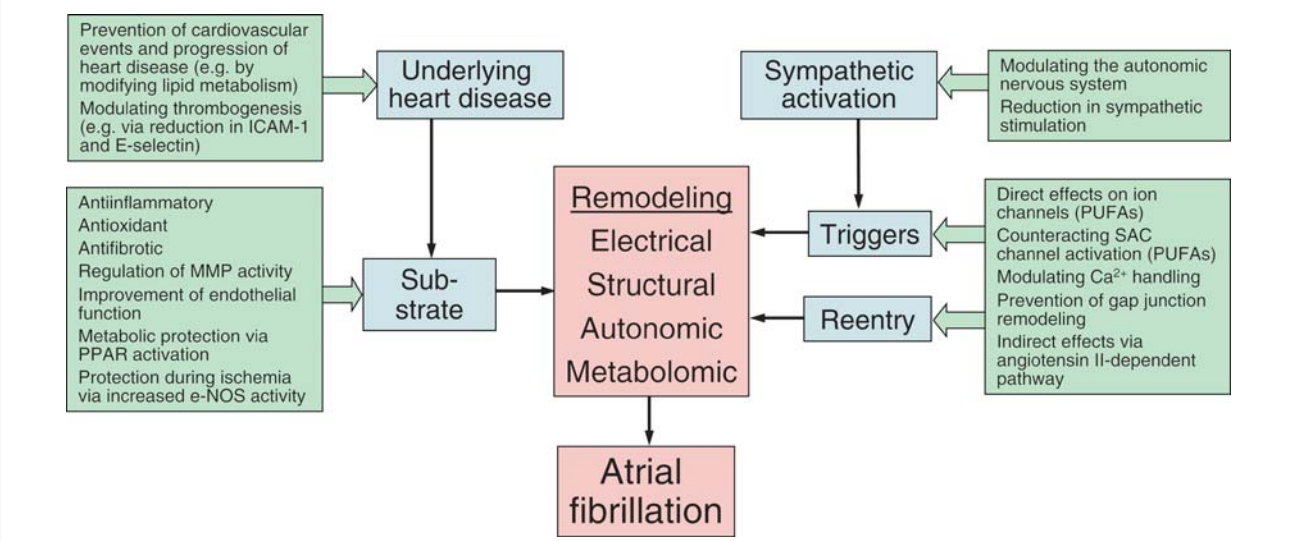

Figure 3 Pathophysiological processes associated with atrial remodelling that may be targets, potentially modifiable by statins and n-3 polyunsaturated fatty acids. e-NOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; MMP, matrix metalloproteinases; PPAR, peroxisome proliferator-activated receptor; SAC, stretch-activated channels. Reproduced from Savelieva *et al.*[94]

Table 3 Evidence base for statins for prevention of atrial fibrillation

Level of evidence	Studies	Primary prevention	Secondary prevention
Experimental data	Definitive studies in sterile pericarditis and atrial pacing models; several studies providing indirect evidence	All reported the beneficial effect of treatment on electrical and structural remodelling and inducibility of AF	Not available
Retrospective studies	Multiple retrospective and observational studies	Mixed results depending on underlying disease	Mixed results
Small prospective studies	Several small-size open-label and double-blind randomized placebo-controlled studies in patients with post-operative AF and patients with persistent AF undergoing electrical cardioversion	ARMYDA-3 reported the beneficial effect of atorvastatin on new-onset post-operative AF	Mixed results; double-blind randomized placebo-controlled studies in post-cardioversion AF were negative
Large prospective randomized-controlled studies with AF as a primary endpoint	Not available; several medium size ongoing	Not available	Not available
Meta-analyses	Four meta-analyses which included mixed and heterogenous patient populations	A non-significant trend towards lower rates of new-onset AF with statins in two meta-analyses involving heterogenous patient populations (risk reductions by 20–40%); significant reduction by 30–32% in meta-analyses of observational and small hypothesis-generating studies; a significant reduction in relative risk of post-operative AF by 34% in meta-analysis involving patients undergoing heart surgery; no effect in the largest meta-analysis of hypothesis-testing trials	A non-significant trend towards lower rates of recurrent AF with statins (risk reductions by 27–67%; significant risk reduction by 13% in meta-analysis of observational studies; no effect in the largest meta-analysis of hypothesis-testing trials

AF, atrial fibrillation; ARMYDA-3, Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery.

reduction in the incidence of AF, mainly newly detected AF, although the differentiation between truly new-onset AF and recurrent AF has not always been possible.[98–101] The magnitude of the effect varied between studies. Thus, in the Advancent^{SM} registry of 25 268 patients with an EF of ≤40% and left ventricular dysfunction of ischaemic aetiology in 72%, lipid-lowering therapy (mostly statins or combination therapy) was associated with a 31% reduction in relative risk of developing AF compared with no therapy (95% CI, 0.64–0.74; $P < 0.001$).[98] This effect was greater than that of beta-blockers and RAAS inhibitors. The SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) investigators reported a similar 28% reduction in relative risk of AF, which was comparable with that of amiodarone.[99]

However, in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure) study in 3690 patients with sinus rhythm on the baseline ECG, therapy with rosuvastatin reduced the risk of any AF during the study by only 13% (HR, 0.868; 95% CI, 0.734–1.026; $P = 0.097$). The difference with the placebo arm became statistically significant only after adjustment for clinical variables, laboratory findings, and concomitant therapy (HR, 0.820; 95% CI, 0.680–0.989; $P = 0.038$).[100] In the pre-specified subgroup of patients with no history of paroxysmal AF, the incidence of new-onset AF was 9.8% in the rosuvastatin arm and 11.6% in the placebo arm (HR, 0.848; 95% CI, 0.684–1.051; $P = 0.132$). Patients in whom AF was present on the baseline ECG (19.3%) were excluded, but whether all patients who developed AF in the course of the study had new-onset AF could not be ascertained. There was a small difference between the rosuvastatin and placebo arms in the proportion of patients with AF at study entry who were excluded from analysis (18.8 vs. 19.8%). During the study, AF occurred in 15% patients: 13.9% in the rosuvastatin group and 16% in the placebo group (absolute difference 2.1%). It is possible that more patients in the rosuvastatin arm may have had unrecognized AF at baseline and hence a greater likelihood of recurrent AF.

Because of the retrospective nature of these reports, much important information is not available, including the reliable detection of AF, AF type, and burden as discussed before, but also the brand and the dose of statins that were used. One brief report from ~10 000 patients with CHF who were prescribed statins has suggested that the intensity of treatment might play a role: thus, in this study, AF was less common in those who received high doses (atorvastatin 80 mg, simvastatin 80 mg, and lovastatin 40 mg) as opposed to lower doses of the same agent.[101]

Hypertension

There is very limited evidence for the potential of statins for primary prevention of AF in hypertension, and many studies reported a relatively low utilization of statins in this clinical setting (usually <50%). In retrospective analysis in 2304 hypertensive patients without AF at entry, therapy with statins was associated with a lower incidence of new-onset AF evidenced by the ECG at 6-month visits, self-reported, or documented during hospitalization, compared with no statins (1.2 vs. 2.5%; $P = 0.01$) reflecting a 54% reduction in relative risk over a mean follow-up of 3.5 years.[102] However, in the lipid-lowering component of the ALLHAT trial, there was no difference in the incidence of AF between the open-label pravastatin group and the usual care group (19.8 vs. 19.4 per 1000 participants; OR, 1.108; $P = 0.54$).[46] Similarly, among 5804 patients aged 70–82 years with risk factors (62% hypertension, 44% vascular disease) enrolled in the PROSPER (PROspective Study of Pravastatin in the Elderly at Risk) trial, therapy with pravastatin 40 mg/day did not reduce the likelihood of developing new-onset AF at 3.2 years compared with placebo (9.8 vs. 9.1%; HR, 1.08; 95% CI, 0.92–1.28; $P = 0.35$).[103]

Coronary artery disease and acute coronary syndrome

The role of inflammation in pathogenesis of CAD and acute coronary syndromes (ACS) as well as the efficacy of statins in primary and secondary prevention are well established.[104] Since inflammation is thought to promote AF, the anti-inflammatory and antioxidant properties of statins would be expected to produce an antiarrhythmic effect in CAD and particularly ACS. In the observational study of 449 patients with stable CAD, 9% of statin users developed new AF within a 5-year follow-up compared with 15% of those not on statins.[105] The corresponding 63% reduction in relative risk was independent of the lipid-lowering effect of statins. These observations have been further supported by a *post hoc* analysis of the HERS (Heart and Estrogen-progestin Replacement Study) in 2763 post-menopausal women with a history of CAD. According to this analysis, women who were taking statins were less likely to have AF at enrolment (OR, 0.35; 95% CI, 0.13–0.93; $P = 0.04$) and those without a history of AF were less likely to develop new-onset AF (HR, 0.45; 95% CI, 0.26–0.78; $P = 0.004$) during a mean follow-up of 4.1 years compared with women who were not taking statins.[106] In 1866 patients with mild to moderate aortic stenosis enrolled in the SAES (Simvastatin and Ezetimibe in Aortic Stenosis) study, therapy with simvastatin and ezetimibe reduced the risk of new-onset AF by 44%.[107]

In contrast, in a large cohort of 13 783 patients with CAD enrolled from five Veterans Affairs administrative databases, therapy with statins had no effect on the incidence of new-onset AF during 4.8 years of follow-up (HR, 1.0; 95% CI, 0.88–1.14; $P = 0.99$), apart from a subgroup of patients with CHF in whom statin treatment was associated with a 43% reduction in new-onset AF.[108] Subsequently, in the VA-HIT (Veterans Affairs High-density lipoprotein cholesterol Intervention Trial) in 2130 patients with CAD or cardiovascular risk factors including low levels of HDL-cholesterol, therapy with gemfibrozil had no effect on the incidence of new AF compared with placebo during 4.4 years of follow-up (5.98 vs. 5.57%; adjusted HR, 1.05; 95% CI, 0.73–1.51; $P = 0.81$).[109] There was a trend towards fewer AF events with gemfibrozil between 6 months and 3 years, which was later negated due to a sharp increase in the number of events in the gemfibrozil arm. A possible explanation can be a more frequent initiation of statins in the placebo arm after 3 years or attenuation of the protective effects of PPAR-α receptor activation on the atrial myocardium.

Evidence for the efficacy of stains in ACS is also controversial. The report from the GRACE (Global Registry of Acute Coronary Events) study, which enrolled 64 679 patients hospitalized for suspected ACS, has suggested that statin therapy prior to

hospitalization was associated with a lower incidence of in-hospital AF and atrial flutter compared with non-users (6.9 vs. 8.2%; propensity-score adjusted OR, 0.81; 95% CI, 0.73–0.89; $P < 0.0001$).[110] Another report from a single centre also indicated a lower incidence of new-onset AF in 1526 patients admitted with ACS (OR, 0.57; 95% CI, 0.39–0.83; $P < 0.01$).[111] In the French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction (FAST-MI) in 3396 patients, initiation of statin therapy within 48 h of admission led to less AF during hospitalization compared with late initiation of statins (3.9 vs. 7.0%; OR, 0.64; 95% CI, 0.45–0.92; $P = 0.017$).[112] This effect was dose-dependent, with the lowest incidence of AF (2%) in the high-dose group. In over 29 000 elderly Medicare beneficiaries hospitalized for acute myocardial infarction or coronary revascularization, lipid-lowering therapy initiated within 1 month after discharge was associated with a modest reduction in the incidence of new-onset AF during 10-year follow-up (adjusted HR, 0.90; 95% CI, 0.85–0.96).[113]

However, in a *post hoc* analysis of the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial of 2861 patients without AF at enrolment, therapy with atorvastatin 80 mg initiated within 4 days of presentation with ACS and continued for 16 weeks had no effect on the incidence of new-onset ECG-detected AF compared with placebo (1.8 vs. 1.6%; OR, 1.15; 95% CI, 0.65–2.02; $P = 0.63$).[114] Among 225 patients with AF at enrolment, 42.7% in the atorvastatin arm completed the study in sinus rhythm compared with 32.4% in the placebo arm, but this trend did not reach statistical significance (OR, 1.56; 95% CI, 0.90–2.68; $P = 0.11$). The short duration of follow-up, however, is a limitation for assessing the potential impact of statins on inflammation, myocardial remodelling, and subsequent AF.

Studies comparing high and low doses of statins also yielded conflicting results. In the FAST-MI registry, patients who received high-dose statins derived a more consistent benefit with regard to AF prevention (OR, 0.52; 95% CI, 0.28–0.95; $P = 0.034$) than patients treated with lower doses (OR, 0.40; 95% CI, 0.18–0.92; $P = 0.080$).[112] However, no benefit of high-dose statins was found in *post hoc* analysis of the PROVE IT TIMI 22 (PRavastatin or atOrVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) and A to Z (Aggrastat to Zocor) trials in 8659 patients with ACS.[115] In the PROVE IT trial, the incidence of AF at 2 years was 2.9% in the atorvastatin 80 mg arm vs. 3.3% in the pravastatin 40 mg arm (OR, 0.86; 95% CI, 0.61–1.23; $P = 0.41$). In the A to Z study, the incidence of AF was 1.6% in the simvastatin 80 mg arm compared with 0.99% in the simvastatin 20 mg arm (OR, 1.58; 95% CI, 0.92–2.70; $P = 0.096$). Consequently, pooled analysis of six RCTs, which compared high- and low-intensity statin therapy in patients with CAD or ACS, showed no difference in the occurrence of new-onset AF (4.8 vs. 4.7%; OR, 1.03; 95% CI, 0.92–1.15; $P = 0.67$).[116]

Stroke and transient ischaemic attack

In the preliminary report from the SPARCL (Stroke Prevention with Aggressive Reduction in Cholesterol Levels) study in 4731 patients with prior stroke or transient ischaemic attack, treatment with high-dose (80 mg) atorvastatin bore no antiarrhythmic benefit on the prevention of new-onset AF compared with placebo during a median follow-up of 4.8 years. Time to first occurrence of AF did not differ between groups, and the incidence of AF was 1.32 and 1.14 cases per 100 patient-years in the atorvastatin and placebo arm, respectively (HR, 1.15; 95% CI, 0.90–1.46; $P = 0.26$).[117]

Post-operative atrial fibrillation

Inflammation and oxidative stress are important contributors to the pathogenesis of AF after cardiac surgery, and post-operative AF appears to be the most feasible clinical model for studying the effects of agents with anti-inflammatory and antioxidant actions.[80] Several retrospective studies and RCTs,[118–125] a systematic review,[126] and meta-analysis of RCTs[127] have reported a lower incidence of post-operative AF and shorter hospital stay in association with statin therapy. Several studies have looked at the potential mechanism of the antifibrillatory effect of statins. Thus, in addition to the reduction in post-operative AF in 234 patients undergoing CABG, the use of statins was associated with increased tissue inhibitor of metalloproteinase (TIMP)-1 levels and TIMP-1/MMP-1 ratio.[119] Matrix metalloproteinase-1 is mainly responsible for degrading collagen type I and III, which is associated with atrial fibrosis in AF. The expression of MMP-1 correlated with the degree of fibrosis in the left and right human atrial tissue samples.[84] Unlike RAAS inhibitors, treatment with statins pre-operatively (59.6%) in 555 patients enrolled in the AFIST I–III studies prevented post-operative AF with an adjusted OR of 0.60 (95% CI, 0.37–0.99; $P = 0.048$).[120] This and other reports[121–123] suggested a possible dose-dependent effect of statins on prevention of AF. In the AFIST I–III substudy, atorvastatin 40 mg was found to be more effective than lower doses (OR, 0.45; 95% CI, 0.21–0.99).[120] In a study of 680 patients undergoing CABG and/or valve surgery, simvastatin 40 mg and atorvastatin 40 mg produced the greatest preventative effect on post-operative AF, reducing the risk by 3.89- and 2.72-fold vs. no statins, whereas at low doses (10 mg) there was no difference in AF occurrence between treated and untreated patients.[121] However, meta-analysis of RCTs found no significant association between the dose of statins and the risk of post-operative AF, but revealed the importance of duration of treatment prior to surgery (a reduction of 3% per day).[127]

The ARMYDA-3 (Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery) trial in 200 patients was the first properly designed proof-of-concept study, which demonstrated that pre-treatment with atorvastatin 40 mg starting 7 days before cardiac surgery was associated with a significant reduction in the incidence of in-hospital AF compared with placebo (35 vs. 57%; OR, 0.39; 95% CI, 0.18–0.85; $P = 0.017$).[124] C-reactive protein levels correlated with the occurrence of AF increasing risk of the arrhythmia by 2-fold, but were not influenced by treatment assignment. The study was criticized for a lower use of beta-blockers and a higher rate of combined CABG and valve surgery in the placebo group. The beneficial effect of statins on AF after off-pump CABG has also been demonstrated.[125]

Despite multiple positive reports, three retrospective analyses,[128–130] which included a significantly larger number of patients than the earlier studies, have reported no reduction in the incidence of post-operative AF (OR, 1.14; 95% CI, 0.92–1.41; $P = 0.21$[128] and OR, 1.02; 95% CI, 0.80–1.29; $P = 0.95$),[129] and even found the use of statins to be associated with more AF (OR, 1.31; 95% CI, 1.11–1.55;

$P = 0.003$).[130] Although these observations are likely to be affected by selection bias because of the retrospective nature of analyses, inherent problems with appropriate detection of AF, and the need for statistical adjustments, which are not an equivalent of randomization, these reports may reduce expectations from statin therapy to specifically AF after cardiac surgery.

Nevertheless, with all studies in the surgical setting pooled together (3 RCTs and 10 observational studies including a total of 17 643 patients), OR for any AF was 0.78 (95% CI, 0.67–0.90; $P < 0.001$) and 0.66 (95% CI, 0.51–0.84; $P < 0.001$) for new-onset AF in favour of statins.[126] This effect remained significant after multiple adjustments and has recently been reconfirmed by meta-analysis of 8 RCTs in 774 patients, which reported a 43% reduction in risk of post-operative AF with statins (95% CI, 0.45–0.72; $P < 0.0001$).[127]

Permanent pacing

Patients with permanent atrial or dual-chamber pacemakers are an increasingly used model for studying the effects of treatment on AF as it significantly improves detection and quantification of AF, including short and asymptomatic episodes. The ATAHEB (Atorvastatin Trial for Atrial Heart rate Episodes in patients with Bradycardia) trial was an open-label prospective RCT conducted in 52 patients with atrial or dual-chamber pacemakers who were randomized to atorvastatin or no treatment and followed up for 1 year.[131] The prevalent diagnosis was hypertension in >90% patients and the majority had normal left atria and normal left ventricular systolic function. There was no difference in the proportion of patients who reached the primary endpoint of time to first atrial event >1 min between the atorvastatin and control group (54.9 vs. 59.6%; $P = 0.629$), but the co-primary endpoint of atrial episodes longer than 10 min occurred significantly less frequently in the atorvastatin group than in the control group (5.8 vs. 19.2%; OR, 0.26; $P = 0.041$). In retrospective analysis of 264 patients without a history of AF, therapy with statins was not associated with a reduction in new-onset AF compared with no statins at a median follow-up of 359 days (10.5 vs. 9.8 per 100 patient-years; adjusted HR, 0.59; 95% CI, 0.31–1.12).[132]

Pooled analysis of these two studies and a study in 185 patients with a history of paroxysmal AF[133] revealed an overall 57% reduction in risk of AF (95% CI, 0.28–0.67; $P < 0.001$).[134] Although statistical heterogeneity was not detected, significant differences between these relatively small studies are too apparent to support the use of statins for prevention AF in pacemaker patients.

Meta-analyses

Other meta-analyses of the efficacy of statins for primary prevention of AF in different clinical settings have yielded controversial results (*Figure 4*).[116,135,136] The first meta-analysis by Fauchier *et al.*,[116] which included three RCTs of primary prevention (one in ACS and two in post-operative AF) in 3101 patients, has shown a non-significant trend towards fewer AF events (OR, 0.60; 95% CI, 0.27–1.37; $P = 0.23$). In meta-analysis by Liu *et al.*,[135] statin treatment was associated with a reduction in new-onset AF both after cardiac surgery (RR, 0.61; 95% CI, 0.49–0.76; $P < 0.0001$) and in the non-surgical setting (RR, 0.68; 95% CI, 0.49–0.94; $P = 0.02$), but only in the observational studies. No effect on AF was seen when the results of RCTs were analysed. The most recent meta-analysis, which has not yet been published in full, has confirmed the previous findings by showing a 30% (95% CI, 0.56–0.88; $P = 0.002$) reduction in relative risk of new-onset or recurrent AF with statins compared with control in 7 'hypothesis-generating' relatively small and short-term studies in mixed populations including patients with ACS, cardiac surgery, and after electrical cardioversion (411 events in 3609 patients).[136] However, in 15 (1514 events in 68 504 patients) 'hypothesis-testing' long-term prospective RCTs in large patient populations with and without cardiovascular pathology, the use of statins had no effect on the occurrence of (mainly) new-onset AF compared with control or placebo (risk ratio, 0.96; 95% CI, 0.87–1.07; $P = 0.49$). Further analysis revealed no difference in the effects of statins in patients with CAD vs. other underlying cardiovascular pathology.

Thus, the value of statins for primary prevention of AF has not been sufficiently demonstrated, except perhaps for patients undergoing cardiac surgery. Nevertheless, several positive reports formed the basis for a class IIb recommendation for the possible benefit of statins in patients with underlying heart disease, particularly CHF (LOE B).[74] Conversely, statins were assigned a class IIa recommendation for prevention of post-operative AF (LOE B).[74] However, even in this clinical setting, a significant amount of uncertainty exists because of limited RCTs and recent negative reports from large retrospective analyses.

Polyunsaturated fatty acids

Experimental evidence

Several mechanisms have been implicated in the antiarrhythmic action of *n*-3 PUFAs (*Figure 3*).[137] Being universal constituents of biological membranes, PUFAs—mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—regulate membrane fluidity, modulate activity of multiple membrane proteins, and counteract the arrhythmogenic effects of atrial stretch.[138] PUFAs produce direct electrophysiological effects on several ion channels, such as I_{Na}, I_{Kur}, I_{KAch}, I_{to}, and $I_{Ca,L}$ currents, and the Na^+/Ca^{2+} exchanger.[138–141] Other potential antifibrillatory mechanisms include anti-inflammatory and antioxidant actions, and regulation of mitogen-activated protein kinase activity.[137] In addition, PUFAs may reduce the adverse impact of underlying heart disease, e.g. by vasodilatation, blood pressure reduction, and improved contractile function of the myocardium.

In experimental AF, induced by rapid atrial pacing,[142] simultaneous atrioventricular pacing,[143] ventricular tachypacing,[144] vagal stimulation,[145] and cardiac surgery,[146] PUFAs alleviated shortening of atrial effective refractory periods, prevented inducibility of AF, and attenuated structural changes in the atrial myocardium. Pre-treatment with PUFAs was associated with smaller increases in activity of atrial MMPs and the content of collagen type I and III ribonucleic acid (RNA), as well as prevention of changes in expression and re-distribution of connexins Cx40 and Cx43. Polyunsaturated fatty acids decreased expression of several genes responsible for development of fibrosis and hypertrophy in the atrial myocardium.[147] In sterile pericarditis, pre-treatment with PUFA reduced the inflammatory response and

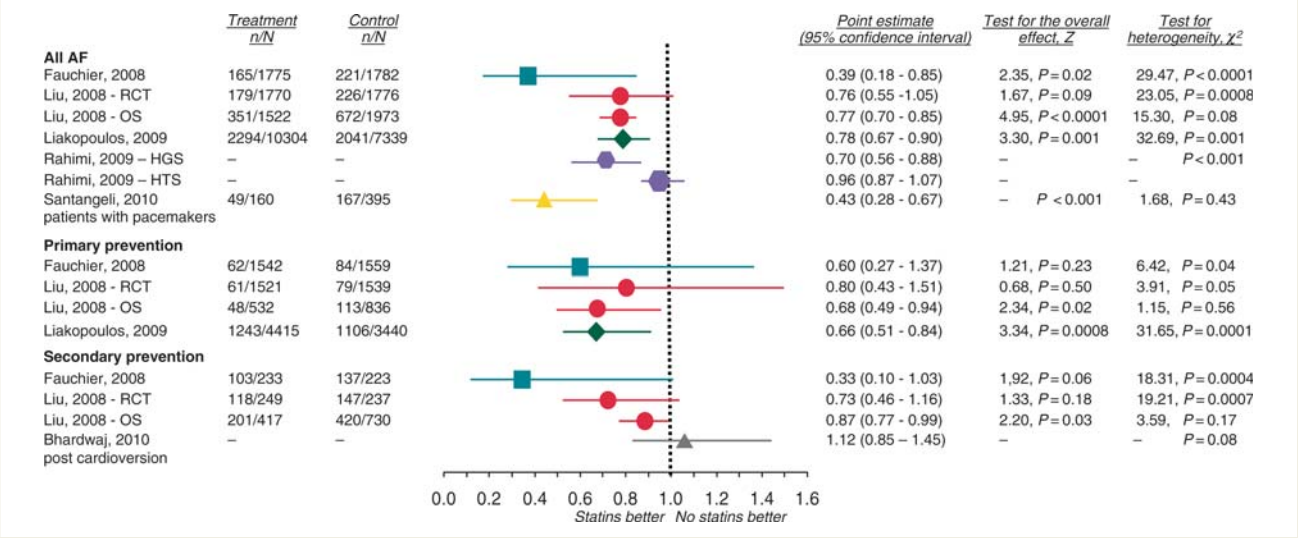

Figure 4 Efficacy of statins in prevention of atrial fibrillation compared with placebo, no treatment, or altenative drug therapies in five meta-analyses (point estimate ± 95% confidence intervals). HTG, hypothesis-testing studies; HTS, hypothesis-testing studies; OS, observational studies; RCTs, randomized controlled studies. See the text for details. Updated from Savelieva *et al.*[94]

Table 4 Evidence base for polyunsaturated fatty acids for prevention of atrial fibrillation

Level of evidence	Studies	Primary prevention	Secondary prevention
Experimental data	Several well-conducted studies in different animal models of AF	All reported the beneficial effect of treatment on electrical and structural remodelling and inducibility of AF	Not available
Retrospective studies	Several analyses from the epidemiological studies and isolated retrospective studies	Mixed results depending on patients' characteristics and type of fish consumption, but the majority of epidemiological studies showed no benefit associated with higher fish intake	Studies in patients with pacemakers and in post-ablation AF reported the reduction in AF recurrence
Small prospective studies	Several small-size open-label and double-blind randomized placebo-controlled studies in patients with post-operative AF and patients with persistent AF undergoing electrical cardioversion	Positive open-label study in post-operative AF; double-blind placebo-controlled studies reported no benefit	Mixed results in AF post-cardioversion
Large prospective randomized-controlled studies with AF as a primary endpoint	Not available	Not available	A (medium-size) POM-3 study reported no reduction in paroxysmal AF
Meta-analyses	Not available	Not available	Not available

AF, atrial fibrillation; POM-3, efficacy and safety of Prescription of OMega-3 fatty acids for prevention of recurrent symptomatic atrial fibrillation.

inducibility of AF.[148] The evidence base for the antiarrhythmic efficacy of PUFAs is summarized in *Table 4*.

General population

The reports from epidemiological studies have been controversial. The Cardiovascular Health Study of 4815 subjects has shown that consumption of broiled or baked fish one to four times per week was associated with an ~30% lower risk of incident AF at 12 years compared with fish consumption less than once a week.[149] However, similar analyses from other population-based studies reported no benefit on incident AF from higher fish intake (*Figure 5*).[150–153] Thus, in a prospective cohort of 47 949 participants in the Danish Diet, Cancer and Health Study, adjusted HRs for incident AF at 5.7 years in quintiles 2–5 were 0.86, 1.08, 1.01, and 1.34 (P for trend = 0.006) compared with the lowest quintile.[150] During a longer follow-up of 15 years of 17 679 men with no history of cardiovascular disease enrolled in the US-based Physician's Health Study, those with the highest fish

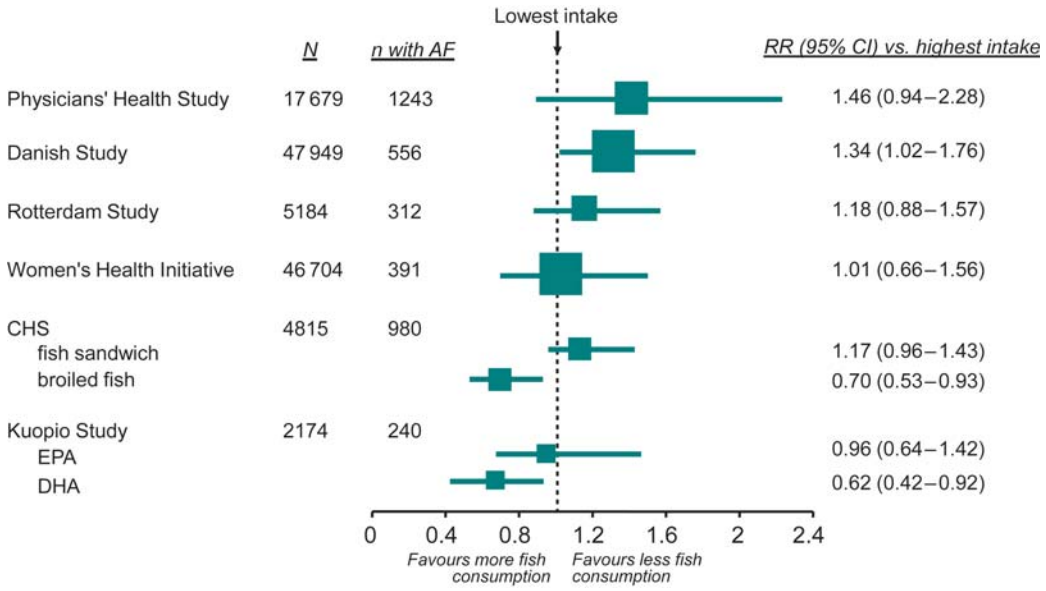

Figure 5 Risk of atrial fibrillation and fish consumption in population-based studies in the highest intake vs. the lowest intake group served as a reference (point estimate 95% confidence intervals). Adjusted for multiple variables: age, cardiovascular risk factors, and dietary and lifestyle factors. CHS, Cardiovascular Health Study; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RR, relative risk. Adapted from Savelieva *et al.*[93]

intake (≥5 meals per week) were more likely to develop AF compared with those who ate fish <1 time per month (RR, 1.46; 95% CI, 0.94–2.28; *P* for trend = 0.017).[152] Among 46 704 participants in the Women's Health Initiative study, no association was found between incident AF at 3 years and dietary ω*n*-3 fatty acid intake as well as other dietary measures (baked or broiled fish, fried fish, and total trans-fat intake).[153] Furthermore, even in the CHS study, the benefit was conferred only by broiled or baked fish, whereas consumption of fried fish or fish sandwiches was positively associated with the development of AF, possibly due to the increased levels of unfavourable *n*-6 fatty acids, trans-fat, and oxidation products due to frying.[149]

The majority of epidemiological studies relied on relatively simple dietary questionnaires to assess fish consumption and estimate the effect of PUFAs. The Rotterdam Study investigators employed a more extensive, semi-quantitative food-frequency questionnaire in order to measure intake of specific fatty acids, but found no association between dietary intake of EPA and DHA (mean, 146 ± 192 mg/day) and incident AF.[151] None of these studies provided data on serum PUFA content and risk of AF. A recent report from the Kuopio Ischemic Heart Disease Risk Factor Study in 2174 men, in which serum *n*-3 PUFA concentration was measured, has suggested that the preventative effect on AF may depend on the use of a specific acid.[154] During follow-up of 17.7 years, there was a trend towards fewer AF events documented in hospital discharge records among men in the highest PUFA content quartile compared with the reference lowest quartile (HR, 0.65; 95% CI, 0.44–0.96; *P* for trend = 0.07). When the impact of individual PUFAs was assessed, only high DHA content was associated with reduced risk of incident AF (HR, 0.62; 95% CI, 0.42–0.92; *P* = 0.02). The AF rates in the highest and the lowest quartiles of DHA serum content were 5.12 and 7.62 per 1000 person-years, respectively, whereas no association was found between serum concentrations of EPA and docosapentaenoic acid and the occurrence of AF.

Several factors, such as different mean age of the studied population, underestimation of AF, socio-economic and lifestyle differences, dietary changes during follow-up, and incidental differences in underlying heart disease, may have contributed to the variations in outcomes reported in the epidemiological surveys. Studies that showed no benefit from high PUFA intake on AF included younger and healthier individuals with a lower prevalence of hypertension and diabetes and no significant cardiovascular disease, whereas the Cardiovascular Health Study enrolled an older population of ≥65 years (mean age ~73 years) with a greater prevalence of cardiovascular disease and a greater incidence of subsequent AF (19–33 per 1000 person-years)[149] compared with a significantly lower incidence of AF in the Rotterdam Study (8.6–10 per 1000 person-years; mean age 67 years)[151] or The Danish Study (1.24–2.91 per 1000 person-years; mean age 56 years).[150] It is possible that antifibrotic and anti-inflammatory effects of PUFAs have a greater protective effect in older patients with structural heart disease, whereas the ability of PUFAs to increase parasympathetic tone may be proarrhythmic in younger individuals with normal hearts who are more likely to have vagally mediated AF.[155]

Myocardial infarction

A record-linkage analysis of databases of 3242 patients hospitalized with myocardial infarction has shown that prescription of PUFA supplements in 215 (6.6%) was associated with fewer hospitalizations for AF at 1 year (HR, 0.19; 95% CI, 0.07–0.51; *P* = 0.001).[156]

Table 5 Polyunsaturated fatty acids for prevention of atrial fibrillation after heart surgery

Study	Number of pateints	Design	Setting	Treatment	Follow-up	AF outcome PUFAs vs. control
Calò (2005)	160	Open label, no placebo	Post-CABG	Oral, 2 g/day	In-hospital	15.2 vs. 33.3%; OR; 0.32 (0.10–0.98); $P = 0.013$
Heidt (2009)	102	Placebo controlled	Post-CABG	Intravenous, 100 mg/kg/day	In-hospital	17.3 vs. 30.6%; $P < 0.05$
Cereceda (2009)	83	Placebo controlled	Post-surgery	Oral, 2 g/day (plus vitamin C, E)	In-hospital	AF incidence reduced by 73%
Saravanan (2010)	108	Double blind placebo controlled	Post-CABG	Oral, 2 g/day	In-hospital	29 vs. 22%; HR, 1.48 (0.84–2.6); $P = 0.28$
Heidarsdottir (2010)	170	Double blind placebo controlled	Post-surgery (mixed)	Oral, 2 g/day	Two weeks	54.2 vs. 54.1%; $P = 0.99$
Sandesara (2010)	243	Double blind placebo controlled	Post-surgery (mixed)	Oral, 2 g/day	Two weeks	30 vs. 33%; $P = 0.67$

AF, atrial fibrillation; CABG, coronary artery bypass grafting; HR, hazard ratio; OR, odds ratio; PUFAs, polyunsaturated fatty acids.

Post-operative atrial fibrillation

In an open-label prospective RCT in 160 patients, pre-treatment with PUFA supplements providing ~1.7–1.8 g of EPA and DHA for a minimum of 5 days before CABG and continued until discharge was associated with a lower incidence of newly diagnosed AF compared with the control group (15.2 vs. 33.3%; OR, 0.35; 95% CI, 0.16–0.76; $P = 0.013$) and, consequently, shorter hospital stay.[157] There was no difference between groups in duration of AF or the number of recurrent AF episodes during hospitalization and the prevalence of sinus rhythm at a follow-up visit at a mean of 28 days. Intravenous infusion of PUFAs at 100 mg/kg/day started on admission for CABG was associated with a significantly lower incidence of post-operative AF compared with soya oil infusion (17.3 vs. 30.6%, $P < 0.05$) as well as shorter hospitalization.[158]

These observations, however, have not been reproduced in two subsequent double-blind RCTs in which patients were randomized to therapy with PUFAs or placebo starting at a minimum of 5 days before cardiac surgery (*Table 5*).[159,160] In 108 patients undergoing isolated CABG, post-operative AF occurred in 43% of patients in the placebo (sunflower oil) group and 56% in the PUFA group, despite a significantly higher PUFA content in serum and in the right atrial appendage tissue in the treated group.[159] There was no difference in time spent in AF and length of hospital stay between groups. Similarly, in a study of 168 patients who received EPA 1.24 g and DHA 1 g 5–7 days before CABG and/or valve surgery, AF occurred in 54.1% in the placebo (sunflower oil) group and 54.2% in the PUFA group ($P = 0.99$).[160]

The results of the FISH trial (FISH oil for reduction of atrial fibrillation after cardiac surgery), which were presented at the Heart Rhythm Society Annual Sessions in 2010, also stand in contrast to the positive results of earlier studies. In this trial, 243 patients received 2 g of PUFAs at least 3 days prior to CABG with or without valve surgery or placebo (ω-6-rich corn oil). At 2 weeks, there was no significant difference in the occurrence of the primary endpoint, which was documented, clinically significant post-operative AF or flutter requiring treatment, between the PUFA-treated group and the placebo group (30 vs. 33%; $P = 0.67$).[161] Nor were there significant differences in pre-specified secondary endpoints, including length of hospital stay, subsequent hospitalization for AF, perioperative myocardial infarction, stroke, bleeding, CHF, and ventricular arrhythmias. However, the use of beta-blockers and statins was also high in this study (80 and 74%, respectively), which might obscure the protective effect of PUFAs. There are preliminary reports of the synergistic preventative effects of PUFAs and antioxidant vitamins C and E, which showed a 73% reduction in the incidence of post-operative AF, but these results are only available in the abstract form.[162]

In summary, although the theoretical background and experimental evidence suggest the antiarrhythmic effect of PUFAs in AF, proof of efficacy in large-scale trials has so far been absent. The dose of PUFAs that may produce the antiarrhythmic effect and the duration of treatment have not been established. Thus, the role of PUFAs in prophylaxis of AF after cardiac surgery remains controversial until several ongoing primary and secondary prevention trials are completed (see Part II: Secondary Prevention).[75]

Corticosteroids

Experimental evidence

Studies in animals using post-operative and atrial tachypacing models of AF[84,163] and a sterile pericarditis model of atrial flutter[164] have demonstrated that prednisolone prevented electrical remodelling and inducibility of atrial tachyarrhythmias by attenuating the inflammatory response. In these experiments, treatment with prednisolone was associated with significant reductions in C-reactive protein levels, endothelial nitric oxide synthase (e-NOS), and myeloperoxidase activity.[84,163] Of note, a non-steroidal anti-inflammatory drug, ibuprofen, had no effect on atrial remodelling or inflammatory markers, probably because its anti-inflammatory action is limited to inhibition of cyclo-oxygenase, whereas steroids target multiple inflammatory pathways.[163]

Post-operative atrial fibrillation

The use of corticosteroids for prevention of AF has been mainly explored in the context of cardiothoracic surgery.[165–168] Three independent meta-analyses have shown that therapy with corticosteroids was associated with a 26–58% reduction in relative risk of post-operative AF.[83,169,170] Hospital stay was also reduced by a mean of 0.66–1.6 days. The greatest effect was seen in patients treated with intermediate doses of steroids (e.g. 50–210 mg dexamethasone or 200–100 mg hydrocortisone equivalents) compared with lower or higher doses (OR, 0.36 [95% CI, 0.23–0.55][170] and 0.32 [95% CI, 0.21–0.50][83]), although this association has not always been present.[169] Therapy with corticosteroids had no significant effect on mortality, but there was increased risk of hyperglycaemia, post-operative pneumonia, urinary tract infections, and gastrointestinal bleeding; in addition, high-dose steroids may cause ventricular proarrhythmia and also promote AF.[171,172] These potential adverse effects deter the routine use of corticosteroids for prevention of AF after cardiac surgery, and in the ESC guidelines corticosteroid therapy was assigned a class IIb recommendation (LOE B).[74]

Epidemiological studies

In contrast to the benefit of corticosteroids seen in post-operative AF, the epidemiological reports suggest that the use of corticosteroids, particularly at high doses, may increase risk of AF.[173,174] Thus, in the Danish cohort of 20 221 patients with AF or atrial flutter and 202 130 controls without AF, ongoing therapy with corticosteroids was associated with a nearly 2-fold likelihood of AF diagnosis (adjusted OR, 1.92; 95% CI, 1.79–2.06).[173] This association was independent of underlying pulmonary or cardiovascular pathology. Similarly, in the Rotterdam Study, corticosteroid exposure increased the risk of new-onset AF by a factor of 3.75 (97% CI, 2.38–5.87).[174] This risk was dose dependent and was the greatest among subjects treated with high-dose steroids (adjusted OR, 6.07; 95% CI, 3.90–9.42). In a case–control nested analysis of 710 patients with asthma or chronic obstructive airways disease from the UK General Practice Research Database, recent therapy with oral steroids was associated with a 2-fold increased risk of AF after adjustment for the severity of pulmonary disease.[175] These reports may suffer potential bias because patients on corticosteroid therapy had higher hospitalization rates and more frequent investigations (e.g. ECG), which may have led to better diagnosis of asymptomatic AF; furthermore, some potential confounders might not have been fully accounted for, such as previously unrecognized AF or concomitant therapies (e.g. statins and RAAS inhibitors). Nevertheless, these reports pointed to the potential proarrhythmic risk of steroids, particularly at high doses.

Inflammation is likely to play a less significant role in pathogenesis of AF in the general population compared with AF after cardiac surgery, whereas underlying cardiovascular pathology may contribute more to the promotion of substrate of AF. Therapy with corticosteroids is known to be associated with a higher incidence of hypertension, diabetes, CHF, and hypokalaemia, all of which can increase risk of AF occurrence and offset any beneficial anti-inflammatory effects of steroids. Therefore, there is no evidence to support the use of corticosteroids for prevention of new-onset AF, except for post-operative AF, where their use is limited by significant side effects.

Thiazolidinediones

Diabetes mellitus is a recognized risk factor for AF as well as stroke associated with AF. In the Framingham Heart Study, the presence of diabetes conferred a 1.4 increased risk (95% CI, 1.0–2.0; $P \leq 0.05$) of AF in men and 1.6 (95% CI, 1.1–2.2; $P \leq 0.01$) in women.[23] A recent report from the Veterans Health Administration Hospitals database in 845 748 patients has shown that type II diabetes increased the risk of AF by a factor of 2.13 (95% CI, 2.10–2.16; $P < 0.0001$).[176] In the VALUE substudy, the new-onset occurrence of diabetes was associated with a 1.5-fold increased risk of developing AF and a 1.87-fold increased likelihood of progression to persistent AF.[177]

Although patients with diabetes mellitus often have other comorbidities and risk factors that may predispose to AF, such as hypertension, CHF, CAD, obesity, and sleep apnoea, there is some evidence that hyperglycaemia and diabetes may potentially affect the electrophysiological properties of the atria, causing intra-atrial conduction delay and promoting structural remodelling by activation of the AGE-RAGE (advanced glycation end product—receptor for AGE) system and up-regulation of circulating tissue growth factors.[178] AGEs derive from the non-enzymatic glycoxidation of proteins and lipids that accumulate in the plasma and tissue of patients with diabetes; binding AGEs to RAGE stimulates the production of proinflammatory cytokines and adhesion molecules, which lead to inflammation. Thus, aggressive treatment of diabetes and adequate glycaemic control may prevent or delay the occurrence of AF.

There is little direct evidence of the effects of antidiabetic drugs on AF. Peroxisome proliferator-activated receptor-γ agonists can offer protection against AF, beyond glycaemic control, due to their anti-inflammatory, antioxidant, and antifibrotic effects. In a rabbit ventricular tachypacing-induced CHF model of AF, the PPAR-γ agonist pioglitazone attenuated structural remodelling while significantly reducing transforming growth factor (TGF)-β1 and tumour necrosis factor-α and extracellular signal-regulated kinase expression.[179] These effects were similar to those observed with candesartan. In addition, PPAR-γ agonists can inhibit production of proinflammatory cytokines interleukin-1β and interleukin-6, modulate MMP activity, suppress superoxide production, induce antioxidant enzymes, and reduce angiotensin II type 1 receptor expression. In rats exposed to pressure overload after abdominal aorta constriction, treatment with pioglitazone suppressed the inflammatory and fibrotic responses measured as serum C-reactive protein levels, expression of monocyte chemoattractant protein-1, TGF-β1, collagen type I RNA, and MMP-9 activity, resulting in reduced inducibility of AF compared with untreated animals.[180] Clinical data are limited to case reports reporting a significant reduction in paroxysmal AF burden in diabetic patients treated with rosiglitazone.[181]

Conclusion

Upstream therapies with RAAS inhibitors, statins, and possibly *n*-3 PUFAs, beyond their conventional indications, may modify the arrhythmia substrate responsible for AF. The effect may be due to prevention or possibly reversal of structural changes in the

atrial myocardium and treatment of the underlying cardiovascular disease that promotes the development of AF. Compelling data from animal experiments and positive outcomes from clinical studies suggest that these therapies can be valuable for primary prevention of AF in selected patient categories. However, there is insufficient evidence to warrant a strong recommendation to expand the indications to wider patient populations at risk of AF. Nevertheless, if RAAS inhibitors or statins are warranted for proven therapy (e.g. CHF, hypertension, CAD, CABG, etc.), there is a bonus that these agents may also prevent AF. Recommendations for their use in primary prevention and LOEs have been summarized in the 2010 ESC guidelines on AF management.

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