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

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Fundamental research into molecular mechanisms of atrial fibrillation (AF) and improved understanding of processes involved in the initiation and maintenance of AF have transformed the traditional approach to its management by targeting only the electrical aspects, usually with antiarrhythmic drugs and, recently, by ablation. The antiarrhythmic potential of upstream therapies, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ARBs), statins, and n-3 (ω-3) polyunsaturated fatty acids, extends beyond the benefit of treating underlying heart disease to modifying the atrial substrate and intervening in specific mechanisms of AF. The key target is structural remodelling of the atria, particularly inflammation and fibrosis, although there is evidence to suggest the direct involvement at the ion channel level. Positive clinical reports supported by robust experimental data have suggested that upstream therapies can be valuable strategies for primary prevention of AF in selected patients and have resulted in several class IIA recommendations in the new European guidelines on AF. However, these results have not been consistently replicated in the secondary prevention setting, and several recent randomized controlled studies failed to demonstrate any effect of upstream therapies on AF burden or on major cardiovascular outcomes. Part II of the review summarizes the evidence base for the use of upstream therapies for secondary prevention of AF.

Introduction

Continuous remodelling of the atria associated with atrial fibrillation (AF) is a multifactorial process, which occurs at various levels, including altered ion current function, changes in atrial myocyte metabolism, and local autonomic regulation. Structural transformation plays an essential role in the initiation and, particularly, perpetuation of AF. Fibrosis is a major constituent of structural (and functional) remodelling and a convergent outcome of tissue reparative and reactive responses to inflammation, stretch, repetitive oxidative stress, ageing, and apoptosis. Structural transformation of the atria involves multiple pathways, among which the angiotensin II-mediated signalling system plays a central role eliciting a range of tissue responses at electrical and structural levels. Inflammation and oxidative stress are leading pathogenic mechanisms in special forms of AF (e.g. post-operative AF), but are also applied to AF in the general population and senile AF.

A variety of animal models of AF have repeatedly demonstrated the association between AF and atrial fibrosis, inflammation, and oxidative stress, and the protective effects of treatment with inhibitors of the renin–angiotensin–aldosterone system (RAAS) and agents with anti-inflammatory and antioxidant properties, such as statins and polyunsaturated fatty acids (PUFAs). Accumulating experimental evidence and positive results of several retrospective analyses and observational studies prompted clinical research into the innovative approach to management of AF by targeting both the formation and evolution of the substrate for AF with traditionally non-antiarrhythmic drugs referred to as upstream therapy. The appeal of upstream therapies, which include angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs),

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aldosterone antagonists, statins, and n-3 (ω-3) PUFAs, is in their potential to prevent both the new-onset arrhythmia (primary prevention) and recurrent AF (secondary prevention).5

However, as the number of clinical reports has been growing and the results of properly designed randomized controlled studies (RCTs) have become available, it has emerged that the antiarrhythmic effects of upstream therapies in primary prevention and secondary prevention settings are not equivalent. While the overwhelming majority of primary prevention analyses have reported the consistent reduction in new-onset AF with RAAS inhibitors and statins, the results of the secondary prevention studies turned out to be less impressive. This may be due to fundamental differences in the AF milieu and, hence, the expectations from upstream therapies in the primary and secondary prevention settings should probably be different. Therefore, evidence of the role of upstream therapies for primary and secondary prevention of AF has been considered separately. Part II of this review considers evidence for the prevention of recurrent AF.

Inhibitors of the renin–angiotensin–aldosterone system

Angiotensin II-mediated proarrhythmic action at the atrial level, including structural and electrical transformation of the atria, and the protective effects of various RAAS inhibitors have been consistently demonstrated in experimental models and subsequently have been replicated in clinical settings. Thus, among upstream therapies for secondary prevention of AF, the antiarrhythmic potential of ACEIs and particularly ARBs is best studied (see Part I: Primary Prevention, Table 1).6

Atrial fibrillation recurrence post-cardioversion

The promising results of early retrospective analyses from the TRACE (Trandolapril Cardiovascular Evaluation)7 and SOLVD (Studies of Left Ventricular Dysfunction)8 trials reporting the lower rates of new-onset AF with ACEI-based therapy propped up by growing experimental evidence prompted several secondary prevention studies in patients with persistent AF undergoing electrical cardioversion (Figure 1). The retrospective analysis from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study has shown that, although in the general study population risk of AF recurrence in 421 patients treated with RAAS inhibitors in the initial 2-month follow-up did not differ from the risk observed in 732 patients not taking RAAS inhibitors [hazard ratio (HR), 0.91; 95% confidence interval (CI), 0.77–1.09], patients with congestive heart failure (CHF) treated with RAAS inhibitors had fewer AF recurrences (11.9 vs. 35.9%; P < 0.0001).9

The study by Madrid et al.10 was one of the first prospective randomized trials to demonstrate the association between RAAS inhibition and the recurrence of AF after electrical or pharmacological (amiodarone) cardioversion. In this study, 154 patients with the first or recurrent persistent AF episode (median duration, 6 months) and moderate underlying heart disease (hypertension, 42%; lone AF, 21.5%) were randomized to receive a combination of irbesartan 150–300 mg and amiodarone or amiodarone alone for at least 3 weeks before planned electrical cardioversion. Spontaneous conversion to sinus rhythm occurred in 42 and 38.9% patients, respectively (P = 0.693). Adjunct therapy with irbesartan was associated with a greater likelihood of sinus rhythm at 2 months (84.8 vs. 63.2%; P = 0.008) and after a median follow-up of 254 days (79.5 and 55.9%, P = 0.007) compared with amiodarone alone (HR, 0.35; 95% CI, 0.12–0.46; P = 0.018; adjusted HR, 0.19; 95% CI, 0.04–0.86; P = 0.031).

Ueng et al.11 conducted a similarly designed study in 145 patients with persistent AF (hypertension, 32.3%; coronary artery disease, 19.3%; lone AF, 20%) randomized to treatment with amiodarone in combination with enalapril 20 mg daily or with amiodarone alone 4 weeks before planned electrical cardioversion. After a median follow-up of 270 days, 74.3% of patients in the combination group remained in sinus rhythm compared with 57.3% of patients in the amiodarone group (P = 0.021). There was a trend towards fewer immediate recurrences of AF (4.3 vs. 14.7%, P = 0.067) and recurrences at 4 weeks (15.7 vs. 38.7%, P = 0.002). The combination of amiodarone and enalapril was most effective in patients with the left atrial diameter >4 cm.

However, both studies were open-label, without a placebo group, and none tested the antiarrhythmic effect of RAAS inhibitors alone. Conversely, a double-blind, placebo-controlled study CAPRAF (Candesartan in the Prevention of Relapsing Atrial Fibrillation) failed to demonstrate any benefit on promotion of sinus rhythm after cardioversion in patients who did not receive antiarrhythmic drugs.12 In the CAPRAF study, 171 patients (~50% with lone AF) received placebo or candesartan 8 mg/day for 3–6 weeks before and 16 mg/day after cardioversion. The 6-month recurrence rate was 65% in the placebo arm and 71% in the candesartan arm. Similarly, in a non-randomized series of 107 patients who did not take antiarrhythmic drugs (except for β-blockers and calcium antagonists), pre-treatment with an ACEI was associated with greater immediate success of electrical cardioversion (96 vs. 80%; P = 0.004), but had no impact on the incidence of AF recurrence at 1 month compared with no treatment (51 vs. 50%).13 In the very early, small, double-blind, randomized, placebo-controlled study in 30 patients with CHF NYHA (New York Heart Association) class II–III, lisopril 10 mg/day, added on top of background therapy with digoxin, diuretics, and nitrates, improved haemodynamic parameters, reduced plasma norepinephrine levels, and increased chances of maintaining sinus rhythm at 6 weeks (71 vs. 36%), but had no effect on the left atrial size.14

The largest study of an ARB for secondary prevention of AF, the double-blind, placebo-controlled GISSI-AF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca Atrial Fibrillation) trial, randomized 1442 patients with mixed paroxysmal and persistent AF who were in sinus rhythm at the time of enrolment to treatment with valsartan (titrated up to 320 mg) or placebo on top of optimal medical therapy including antiarrhythmic drugs.15 The majority of patients (88.3%) had cardioversion within 2 weeks prior to enrolment. Hypertension was the prevalent underlying pathology (85.4% of patients), whereas coronary artery disease and CHF were uncommon (12.4 and
patients with CHF (HR, 0.81; 95% CI, 0.48–1.35; 
rent AF between the valsartan and placebo groups in 114 
blockers (30%), or ACEIs (57%), or the presence of underlying 
by the use of antiarrhythmic drugs (74% of patients), beta-
P 0.89; 95% CI, 0.64–1.23; 
than one AF episode during 1-year follow-up (adjusted HR, 
patients in the valsartan arm and 52.1% in the placebo arm 
of patients with more than one AF recurrence. Thus, 51.4% of 
primary endpoint of time to first AF recurrence and number 
demonstrate any effect of an ARB-based regimen on the 
with a left atrial diameter of 
longer (see Part I: Primary Prevention). 6 The ACTIVE I (Atrial 
therapies for primary prevention of AF follow-up was 3 years or 
)delling, whereas in studies that reported the benefit of upstream 
prevent but not reverse atrial remodelling pre-disposing to AF 
greatest benefit has so far been seen in patients without pre-
use of upstream therapies for secondary prevention of AF. The 
greatest benefit has so far been seen in patients without pre-
existing AF, suggesting that therapy with ACEIs and ARBs might 
prevent but not reverse atrial remodelling pre-disposing to AF 
or that the duration of therapy (1 year) is too short to demonstr-
strate any benefit due to reversal or delaying of further atrial remo-
delling, whereas in studies that reported the benefit of upstream 
therapies for primary prevention of AF follow-up was 3 years or 
longer (see Part I: Primary Prevention). 5 The ACTIVE I (Atrial 
ablation Clopidogrel Trial with Irbesartan for prevention of 
Vascular Events – Irbesarten; Amio, amiodarone; CAPRAF, Candesartan in the Prevention of Relapsing Atrial Fibrillation; DCC, direct current cardiover-
Japanese Rhythm Management Trial for Atrial Fibrillation; PAF, paroxysmal atrial fibrillation; RR, relative risk. aPatients who developed persistent 
Additional treatments for AF secondary prevention include anticoagulation with or without antiplatelet therapy, which may reduce the risk of stroke. bAlthough the benefit of upstream therapies for secondary prevention of AF is well-established, the optimal strategy for secondary prevention remains controversial. cAF recurrence was detected on at least one 
follow-up electrocardiogram (ECG) in 36.8% of patients who received irbesartan and 38.1% of patients who received placebo [relative risk (RR), 0.97; 95% CI, 0.85–1.07; P = 0.41]. There was also no difference between the irbesartan and placebo arms in the number of patients who had AF at inclusion and were found to be in sinus rhythm at follow-up (10.6% vs 9.7%) as well as the need for cardioversion. A small transtelephonic ECG substudy in 185 patients who were in sinus rhythm at randomization showed a similar distribution of AF recurrence between the irbesartan and placebo groups (68.6% vs 62.6%; HR, 1.14; 95% CI, 0.80– 
1.64; P = 0.46). In the ACTIVE I study, the mean follow-up was 4.1 years, comparable to that in the primary prevention reports, suggesting that the benefit of RAAS inhibitors in the secondary prevention setting is diminished.

Recurrent of ‘lone’ atrial fibrillation post-cardioversion

Some, but not all, 17 reports in patients with AF and no structural heart disease have suggested that treatment with ACEIs/ARBs may enhance the antiarrhythmic effect of amiodarone 18 or propafenone 19 following cardioversion. They did not, however, provide information on the efficacy of ACEI/ARB monotherapy and were
limited by their open-label design and lack of a placebo group. Following their main study, Madrid et al. reported the beneficial dose-dependent effect of irbesartan added to amiodarone in 90 patients with AF and no structural heart disease: 77% of patients treated with irbesartan 300 mg/day maintained sinus rhythm compared with 65% on irbesartan 150 mg/day, and 52% on amiodarone alone. Despite the absence of formal structural heart disease (e.g., left ventricular dysfunction, left ventricular hypertrophy, etc.), patients in this study did not have strictly lone AF as many had mild hypertension that would promote atrial remodelling and would warrant therapy with RAAS inhibitors. In a small study in the Romanian patients with lone AF, combination therapy with an ACEI and propafenone was more effective in promoting sinus rhythm at 1 year after cardioversion compared with propafenone alone (37.5 vs. 20%). However, the overall recurrence rate was high, particularly for lone AF, and the mean left atrial size of 4.5 cm pointed to some degree of remodelling.

In a randomized, placebo-controlled study in 62 patients with the first episode of AF <24 h cardioverted by intravenous propafenone, subsequent treatment with ramipril 5 mg/day was associated with a greater likelihood of remaining free from a recurrent episode of AF off antiarrhythmic drug therapy at 3 years compared with placebo (90 vs. 68%; \( P < 0.03 \)). However, in the CAPRAF study, in which approximately half the patients had lone AF, there was no difference in AF recurrence between the candesartan and placebo groups, despite a slightly higher proportion of patients with lone AF (51.1 vs. 44.7%; \( P = 0.398 \)) and less hypertension (24.4 vs. 35.3%; \( P = 0.120 \)) in the candesartan group.

**Paroxysmal atrial fibrillation**

Evidence to support the use of ACEIs or ARBs in patients with paroxysmal AF remains controversial. The results of several medium-size studies with a follow-up of 1–2 years have pointed to a lower incidence of recurrent paroxysmal AF with ARB- or ACEI-based treatment, often added to antiarrhythmic drug therapy. In 369 patients with mild hypertension and mainly paroxysmal AF (although some patients had prior cardioversion), lower rates of recurrence at 1 year were observed in the valsartan- and ramipril-treated groups compared with amlodipine (16.1, 27.9, and 47.4%, respectively), despite similar reductions in blood pressure. Valsartan was more effective than atenolol in preventing recurrent paroxysmal AF (20.3 vs. 34.1%) in 296 patients with hypertension and diabetes mellitus. Previously, the same group of authors have reported that the combination of amiodarone and losartan has proven more effective than the combination of amiodarone and amlodipine prevention of recurrent paroxysmal AF in 250 patients with mild hypertension (13 vs. 39%). In an open-label study in 171 patients with paroxysmal AF, no significant structural heart disease, and no atrial remodelling, patients treated with losartan 50–100 mg/day or perindopril 2–4 mg/day in addition to amiodarone were less likely to have recurrence of AF at 2 years compared with patients who received amiodarone alone (19, 24, and 41%, respectively). This corresponded to a reduction of RR of 54% with added losartan and 41% with added perindopril.

However, other studies failed to show any benefit from ACEIs and ARBs on the occurrence of paroxysmal AF. In a retrospective analysis in 319 Japanese patients, long-term therapy with enalapril 5 mg/day in addition to antiarrhythmic drugs did not prevent progression to permanent AF during a maximum follow-up of 10 years. In the CTAF (Canadian Trial of Atrial Fibrillation) study, in patients with mixed paroxysmal and persistent AF treated with amiodarone, sotalol, or propafenone, therapy with RAAS inhibitors was not associated with additional benefit on the recurrence of AF. However, this was a retrospective analysis and only 12% of 403 patients received RAAS inhibitors at enrolment.

A recent open-label randomized J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) II study in 318 patients with moderate hypertension and paroxysmal AF showed no difference in AF burden detected by daily transtelephonic ECG monitoring during 1-year treatment with candesartan 8–12 mg/day compared with amlodipine 2.5–5 mg/day (3.8 ± 5 vs. 4.8 ± 6.3 days/month; \( P = 0.016 \)), nor did it find any difference in symptomatic AF burden (1.4 ± 3.0 vs. 1.4 ± 2.9 days/month; \( P = 0.903 \)). Patients in J-RHYTHM had normal left ventricular function and no advance atrial remodelling (the left atrial diameter at baseline was 38.9 ± 6.7 cm in the candesartan group and 39.3 ± 6.8 cm in the amlodipine group); 31% received beta-blockers and ~70% received class I antiarrhythmic drugs at the discretion of the treating physician. The frequency and duration of AF episodes were reduced in both treatment groups at 1 year compared with baseline, in parallel with reductions in blood pressure. Of note, fewer patients in the candesartan group developed persistent AF compared with the amlodipine-treated group (8.2 vs. 15%), but this trend did not reach statistical significance. The treatment modality had no effect on quality of life.

The ANTI-PAF (Angiotensin II Antagonist in Paroxysmal Atrial Fibrillation) trial presented at the European Society of Cardiology Congress in 2010 was a prospective, randomized, placebo-controlled, double-blind study designed to prove the principal concept that RAAS inhibition with olmesartan 40 mg/day may suppress paroxysmal AF in patients without significant structural heart disease who were not receiving antiarrhythmic drugs. The study enrolled 425 patients, 42.8% of whom had hypertension without left ventricular hypertrophy, 8.2% diabetes, 6.6% coronary artery disease, and 35% a left atrial diameter >4 cm. The primary endpoint of AF burden, defined as the percentage of days with documented episodes of paroxysmal AF identified on daily transtelephonic ECG recordings and additional ECG transmissions during symptoms, was not different between the olmesartan and placebo groups. Secondary outcome parameters including time to first AF recurrence, first symptomatic AF recurrence, time to persistent AF, and time to prescription of amiodarone were also identical.

**Atrial fibrillation recurrence after pulmonary vein ablation**

The occurrence of atrial tachycardia or recurrence of AF during the first 3 months after pulmonary vein ablation is common and, among other mechanisms, is thought to be secondary to inflammation and oxidative stress as well as nerve-ending damage and resulting imbalance of the cardiac autonomic nervous system following radiofrequency injury. Increased C-reactive protein (CRP) levels have been linked to a greater likelihood of early recurrence of AF, possibly making it resistant to antiarrhythmic drugs. It is plausible that local angiotensin II levels are also increased in response to injury incurred by pulmonary vein ablation. Early AF often subsides
spontaneously after several months upon the resolution of inflammation and ‘maturation’ of lesions, without the need for re-ablation. The RAAS inhibitors and statins may facilitate post-ablation atrial remodelling due to their anti-inflammatory, antioxidant, and antifibrotic action, whereas pre-treatment with these agents before ablation may halt the pre-existent angiotensin II- and inflammation-mediated pathways of maintenance of AF.

This hypothesis has been explored in several retrospective studies in patients undergoing pulmonary vein ablation for paroxysmal and persistent AF. The overall outcome from these studies was that therapy with ACEIs and ARBs had no consistent effect on the recurrence of AF after ablation (Figure 2), although not all studies differentiated between early and late recurrence of AF and between AF and other atrial rhythms (e.g. left atrial tachycardias). Patel et al. analysed the effect of RAAS inhibitors and statins on early (within 8 weeks after ablation) recurrences of atrial tachyarrhythmias, but found no difference between the RAAS inhibitor, statin, and control groups (34.6, 44, and 43%, respectively). The combined use of RAAS inhibitors had also proven ineffective in preventing recurrent AF after ablation.

Several studies attempted to identify patients and therapies that appeared to confer some benefit. Thus, in the South Korean study in 152 patients, those with persistent AF treated with RAAS inhibitors were less likely to have a recurrence of AF compared with no treatment (12.1 vs. 61.1%; \( P < 0.01 \)), whereas no effect from therapy was found in patients with paroxysmal AF (24.2 vs. 22.9%; \( P = 0.87 \)). However, these findings have not been reproduced in other studies which included patients with both forms of AF. In one of the first analyses in 177 patients with mainly paroxysmal AF, the use of ARBs was associated with a non-significant trend towards the lower recurrence rate compared with no treatment (HR, 1.29; 95% CI, 0.57–2.93; \( P = 0.54 \)). A similar effect was seen in the recent larger study in 419 patients with mixed paroxysmal and persistent AF in which there were slightly fewer recurrences of AF in the ARB-treated group compared with no treatment (61.9 vs. 77.6%; \( P = 0.021 \)), but this effect was lost after multivariate adjustments.

However, because of the retrospective nature, the studies of RAAS inhibitors after pulmonary vein ablation had significant

![Figure 2](image-url)
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Drug and dose</th>
<th>Primary or secondary prevention</th>
<th>Clinic setting</th>
<th>Primary endpoint</th>
<th>Follow-up</th>
<th>Expected completion, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTAF 2, NCT00461903</td>
<td>320</td>
<td>Perindopril 8 mg/day</td>
<td>Secondary</td>
<td>Paroxysmal or persistent AF in hypertension</td>
<td>Time to first sustained recurrence of AF</td>
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<td>Not stated</td>
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<td>200</td>
<td>Valsartan 160–320 mg/day</td>
<td>Secondary</td>
<td>Post-cardioversion</td>
<td>Time to first recurrence of AF</td>
<td>Not stated</td>
<td>Terminated because of problems with recruitment</td>
</tr>
<tr>
<td>CREATIVE-AF,</td>
<td>60</td>
<td>Irbesartan 150–300 mg/day</td>
<td>Secondary</td>
<td>Persistent AF or permanent AF</td>
<td>Changes in biomarkers of oxidative stress and adhesion molecules*</td>
<td>22 weeks</td>
<td>2010</td>
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<td>Eplerenone 50 mg/day</td>
<td>Secondary</td>
<td>Post-cardioversion</td>
<td>Recurrence of AF</td>
<td>8 weeks</td>
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<tr>
<td>RACE 3, NCT00877643</td>
<td>250</td>
<td>Aldosterone antagonist, statin (type and dose not specified)</td>
<td>Secondary</td>
<td>Recent-onset persistent AF and mild-to-moderate CHF</td>
<td>Maintenance of sinus rhythm post-cardioversion</td>
<td>1 year</td>
<td>2012</td>
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<tr>
<td>Taichung study, NCT00689598</td>
<td>30</td>
<td>Spironolactone 25–50 mg/day</td>
<td>Secondary</td>
<td>Paroxysmal AF</td>
<td>Time to first ECG-confirmed recurrence of AF</td>
<td>3 months</td>
<td>2011</td>
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<td>390</td>
<td>Ramipril 5 mg/day</td>
<td>Primary</td>
<td>Post-atrial flutter ablation</td>
<td>Clinically relevant symptomatic or asymptomatic AF</td>
<td>1 year</td>
<td>2014</td>
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<td>Taiwan study, NCT00647257</td>
<td>220</td>
<td>Losartan 100 mg/day</td>
<td>Primary</td>
<td>Sinus node dysfunction treated with pacemaker</td>
<td>Proportion of patients with any AF and permanent AF</td>
<td>1 year</td>
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<td>777</td>
<td>Ramipril, spironolactone (dose not specified)</td>
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<td>In hospital</td>
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<tr>
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<td>Losartan 50 mg/day</td>
<td>Primary</td>
<td>Surgery for lung cancer</td>
<td>Incidence of postoperative AF</td>
<td>10 days</td>
<td>2013</td>
</tr>
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</table>

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin-receptor blockers; CREATIVE-AF, Impact of Irbesartan on Oxidative Stress and C-Reactive Protein Levels in Patients with Persistent Atrial Fibrillation; CTAF-2, Canadian Trial of Atrial Fibrillation-2; DRAFT, Diovan to Reduce post-cardioversion recurrence of Atrial Fibrillation Trial; ECG, electrocardiogram; EPLERAF, EPLERenone in the prevention of Atrial Fibrillation recurrences after cardioversion; PREFACE, PREvention of atrial Fibrillation by inhibition of Angiotensin Converting Enzyme after radiofrequency ablation of atrial flutter; PRESAGE, PREvention of atrial fibrillation in patientS undergoing thorAcic surGERy; RACE 3, Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure 3.

*Cerebrovascular events, cardiovascular hospitalization, and outpatient visits are secondary endpoints; clinically relevant cardiovascular events are the secondary endpoint.

Current status of all studies except for NCT00461903, NCT00343499, NCT00613496, and NCT00689598 was updated on http://clinicaltrials.gov/ in 2010-11.
inherent limitations.\(^{41}\) Importantly, although patients enrolled in these studies had no major structural heart disease, near-normal left ventricular ejection fraction, and only mildly dilated left atria, those who received therapy with RAAS inhibitors (and/or statins) were generally sicker, with more co-morbidities such as coronary artery disease, hypertension, and diabetes, and therefore more likely to have a recurrence of AF. Thus, even with multiple adjustments for the treatment effect, differences in clinical characteristics between treated and control patients are too significant to assess the true effect of treatment. The consistency of drug use and doses could not be ensured throughout follow-up and data on the incidence of early vs. late recurrence of AF have not been reported. It is also possible that the benefit of therapy may be too small to be detected compared with significant changes in the left atrial electromorphology and structure introduced by ablation.

**Meta-analyses**

Despite conflicting results of secondary prevention trials, several meta-analyses have nevertheless found a significant reduction in the incidence of recurrent AF associated with therapy with RAAS inhibitors. Relative risk reductions of 48, 51, and 45% have been reported in post-cardioversion studies,\(^{42-44}\) and 63% in studies of paroxysmal or mixed persistent and self-terminating AF (not necessarily involving cardioversion)\(^{46}\) (see Part I: Primary Prevention, Figure 2).\(^{6}\) However, significant heterogeneity has been reported in some analyses and the assignment of studies as post-cardioversion (e.g. GISSI-AF in recent meta-analysis by Schneider et al.\(^ {46}\)) or medical therapy is debatable.

**Effects on atrial remodelling**

Most evidence of the preventative effect of ACEIs and ARBs on the occurrence of atrial remodelling came from various animal models where treatment was started before or at least simultaneously with induction of AF;\(^ {45-47}\) but there is limited experimental evidence whether this therapy can lead to reversal of remodelling. After 4 weeks of rapid atrial pacing in dogs, treatment with olmesartan for a further 4 weeks resulted in complete restoration of normal atrial size on therapy (which could be seen as a reversal of the effect of upstream therapies may be greater in remodelled atria. Analysis of atrial tissue samples from patients with lone AF undergoing surgical ablation has shown that collagen accumulation was significantly attenuated and microcapillary rarification was less pronounced in patients treated with ACEIs compared with no ACEIs.\(^ {51}\) Therapy with irbesartan was associated with reduced left atrial stunning after electrical cardioversion, but in this study irbesartan had no effect on the recurrence of AF at 4 weeks.\(^ {52}\) However, the GISSI-AF trial, which used a left atrial size \(>4.5\) cm as one of the inclusion criteria, showed no benefit from therapy with valsartan on secondary prevention of AF.\(^ {54}\)

Because of the relative paucity and controversy of both experimental and clinical data on reverse remodelling and secondary prevention of AF, no strong recommendation can be made regarding the use of ACEIs and ARBs specifically for the reduction of AF recurrences. Nevertheless, the majority of patients are likely to receive therapy with RAAS inhibition for other indications (e.g. hypertension), which may potentially reduce the incidence of recurrent AF. The new European Society of Cardiology guidelines on AF assigned a class Ib recommendation (level of evidence B) for the use of RAAS inhibitors for secondary prevention of recurrent paroxysmal AF and AF after cardioversion in selected patient categories.\(^ {53}\) Several ongoing RCTs with different RAAS inhibitors are underway (Table 1).

**Aldosterone antagonists**

The proarrhythmic mechanisms associated with increased aldosterone levels include atrial fibrosis, apoptosis, hypertrophy, inflammation, and extracellular matrix remodelling, but the direct effects of aldosterone on AF substrate have not been fully investigated.\(^ {54}\) At the atrial level, aldosterone increased the \(I_{Ca,l}\) current and reduced the binding of ryanodine receptor-inhibitory FK506-binding protein, further enhancing calcium leak from the sarcoplasmic reticulum, which is associated with delayed afterdepolarizations.\(^ {55}\) There are limited clinical data implicating aldosterone in the development and maintenance of AF. Increased plasma aldosterone levels\(^ {56,57}\) and up-regulation of aldosterone receptors in the atria\(^ {58}\) have been reported in patients with AF. A decrease in aldosterone levels was observed after cardioversion of AF, and post-cardioversion aldosterone levels correlated with the maintenance of sinus rhythm in patients with normal left ventricular function.\(^ {57,58}\) Furthermore, patients with persistently elevated aldosterone levels were almost 4.5 times likely to progress from paroxysmal AF to a permanent form (15.2% vs. 4.6%; 95% Cl, 2.26–8.81; \(P < 0.0001\)).\(^ {59}\)

The role of aldosterone antagonists has not been specifically studied for secondary prevention of AF, but preliminary data point at the potential of spironolactone to reduce the incidence of recurrent AF after electrical cardioversion in patients with hypertension and mild left ventricular systolic dysfunction.\(^ {60}\) Adding spironolactone to treatment with beta-blockers and/or ACEIs was associated with a significant reduction in the number of AF episodes during a 12-month follow-up in 158 patients with recurrent paroxysmal (51%) and persistent AF despite anti-arrhythmic drug therapy.\(^ {61}\) Several ongoing trials are set to investigate the antiarrhythmic effect of spironolactone and eplerenone in AF in patients undergoing heart surgery, patients with recent CHF, and after electrical cardioversion (Table 1).
Upstream therapies for management of atrial fibrillation

Statins

Atrial fibrillation recurrence post-cardioversion

Accumulation of experimental and clinical evidence of the role of inflammation in pathogenesis of AF, the likely association between CRP levels and risk of new-onset and recurrent AF, and established anti-inflammatory effects of statins formed a background for a series of studies, which explored the effects of statins on the recurrence of AF after electrical cardioversion, but have yielded conflicting results. While earlier, retrospective observational studies and some RCTs have reported a significant reduction in AF recurrence rates by 28–81% associated with statin use, double-blind, placebo-controlled trials showed no benefit from the use of statins on the recurrence of AF after cardioversion (RR, 1.12; 95% CI, 0.85–1.46). Consequently, meta-analysis of four RCTs in 424 patients showed no benefit from the use of statins on the recurrence of AF after cardioversion (RR, 1.12; 95% CI, 0.85–1.46).

The use of beta-blockers was relatively high in both treatment and control or placebo arms of RCTs (between 30 and 83%). In the Canadian Registry of Atrial Fibrillation (CARAF), therapy with statins has been reported to suppress the recurrence of AF after first cardioversion for recent-onset AF, but only in patients who received concomitant beta-blockers. This finding remains unexplained, but it is plausible that patients treated with beta-blockers may have clinical characteristics that make them prone to benefit from statins (e.g. more severe underlying heart disease). Consequently, adding atorvastatin to losartan in patients with hypertension and recent paroxysmal AF had no incremental benefit with respect to AF suppression, but helped by further reducing the recurrence rate of AF when added to atenolol.

Paroxysmal atrial fibrillation

Animal models, in which the effect of statins on substrate formation and inducibility of AF were tested, were models of self-terminating AF. Consequently, the efficacy of statins in clinical studies seemed to be more consistent in paroxysmal AF and repeat cardioversion at 6 months between the atorvastatin and placebo arms (38 vs. 39% and 22 vs. 23%, respectively). In the StopAF (Statin Therapy for the Prevention of Atrial Fibrillation) in 64 patients after cardioversion for persistent AF, treatment with atorvastatin 80 mg reduced inflammatory markers, such as CRP and interleukin-6 levels, but had no effect on mediators of oxidative stress and on the recurrence of AF (66.7% vs 83.9% with atorvastatin vs. placebo; HR, 0.99; 96% CI, 0.98–1.01; P = 0.3). Consequently, meta-analysis of four RCTs in 424 patients showed no benefit from the use of statins on the recurrence of AF after cardioversion (RR, 1.12; 95% CI, 0.85–1.46).

The use of beta-blockers was relatively high in both treatment and control or placebo arms of RCTs (between 30 and 83%). In the Canadian Registry of Atrial Fibrillation (CARAF), therapy with statins has been reported to suppress the recurrence of AF after first cardioversion for recent-onset AF, but only in patients who received concomitant beta-blockers. This finding remains unexplained, but it is plausible that patients treated with beta-blockers may have clinical characteristics that make them prone to benefit from statins (e.g. more severe underlying heart disease). Consequently, adding atorvastatin to losartan in patients with hypertension and recent paroxysmal AF had no incremental benefit with respect to AF suppression, but helped by further reducing the recurrence rate of AF when added to atenolol.
reversible AF associated with cardiac surgery than in AF requiring cardioversion, although evidence is very limited.\textsuperscript{75–78} Thus, in the observational cohort study in patients with sick sinus syndrome and paroxysmal AF treated with pacemakers, the use of statins reduced the number of AF episodes compared with no treatment (OR, 0.33; 95% CI, 0.14–0.74; \( P = 0.007 \)).\textsuperscript{77} In a study in 80 patients with paroxysmal AF and hypertension, 65% of patients randomized to atorvastatin 20–40 mg/day had no sustained (>48 h) episodes of AF at 6 months compared with 10% of patients randomized to placebo (OR, 13.5; 95% CI, 2.8–46.7; \( P = 0.001 \)).\textsuperscript{78} In 326 patients with recurrent paroxysmal AF and hypertension, the combined therapy with atorvastatin 20 mg and atenolol was associated with a significantly lower recurrence rate at 1 year compared with atenolol and placebo (24.3 vs. 36.2%; \( P < 0.05 \)), whereas atorvastatin had no additional benefit above placebo (15.6 vs. 17.2%) in patients treated with losartan.\textsuperscript{75}

There is no consistency in the relationship between the reduction in inflammatory markers and the beneficial effects of statins on AF.\textsuperscript{72,78,79} It is unclear whether inflammation plays the same role in the atria, which underwent significant structural remodelling, and whether remodelled atria should be exposed to longer treatment with statins than was utilized in the RCTs. There is also little evidence whether one statin may be superior to another. Higher-potency statins (e.g., atorvastatin) appeared to be superior to other agents in a large population of patients with CHF (primary AF prevention),\textsuperscript{80} with post-operative AF,\textsuperscript{81,82} and after electrical cardioversion.\textsuperscript{82} In the latter small retrospective non-randomized study of 65 patients, atorvastatin 10–20 mg was associated with a lower incidence of recurrent AF compared with simvastatin 20–40 mg (38 vs. 66.7%; OR, 0.31; 95% CI, 0.11–0.65; \( P = 0.02 \)).\textsuperscript{83} The antiarrhythmic effect of other drugs (e.g., ACEIs and ARBs) may reduce the amount of benefit derived from a statin.

### Atrial fibrillation recurrence after pulmonary vein ablation

Several retrospective studies that explored the effects of statins on the recurrence of AF after pulmonary vein ablation have been partly discussed earlier. In several studies in patients with mixed, mainly paroxysmal AF, treatment with statins was not associated with a lower incidence of AF (Figure 2)\textsuperscript{33,34,37,38} nor had it any effect on CRP and fibrinogen levels.\textsuperscript{33}

### Meta-analyses

Meta-analyses showed an overall trend towards lower AF recurrence rates in association with statin use, with a wide range of relative risk reductions (23–67%), but this did not reach statistical significance when only RCTs were considered\textsuperscript{84,85} (see Part I: Primary Prevention, Figure 4). However, significant heterogeneity of patient populations with respect to underlying heart disease, duration, and type of AF (hence the potentially different contribution of inflammation to pathogenesis of AF) is a significant limitation of these meta-analyses. The type and doses of statins and duration of treatment have also varied. More recent meta-analysis of 15 hypothesis-testing trials in 68,504 patients showed no benefit of statins for secondary prevention of AF.\textsuperscript{86}
In summary, the key mechanism or mechanisms of the anti-arrhythmic effect of statins on atrial myocardium have not been established, and the weight of the evidence on substrate formation and reverse remodelling is unknown. Hence, the target patient population and methods of predicting and monitoring the effect (e.g. CRP, biomarkers) have not been well identified. The dose and duration of treatment also remain an open question. Limited and controversial evidence and lack of data from RCTs preclude developing any definite recommendations for the use of statins for secondary prevention of AF. Several ongoing prospective RCTs have been designed to assess the antiarrhythmic value of statins in this clinical setting (Table 2).

### Polyunsaturated fatty acids

The effects of PUFAs on structural atrial remodelling and inducibility of AF have been well demonstrated in various animal models of AF, but the positive results from the animal experiments have not been consistently reproduced in both the primary and secondary clinical settings. There is limited evidence of the efficacy of PUFAs in secondary prevention in AF and the studies, mainly available as preliminary reports, are controversial (Table 3). In a randomized study in 50 patients without structural heart disease who underwent electrophysiological testing for suspected supraventricular tachycardia, therapy with PUFAs at 2 g/day for at least 1 month was associated with an 89% reduction in AF inducibility ($P = 0.009$) as well as other evidence of reduced vulnerability to AF such as longer atrial refractoriness and less conduction delay. Similar to the observations in the epidemiological study, higher serum levels of docosahexaenoic acid (DHA) but not eicosapentaenoic acid (EPA) levels were associated with decreased inducibility of AF (OR, 0.37; 95% CI, 0.14–0.99; $P = 0.049$).

### Atrial fibrillation recurrence post-cardioversion

The preliminary results of a randomized, placebo-controlled study in 199 patients with recurrent persistent AF have shown that therapy with PUFAs 1 g/day and amiodarone was associated with a lower incidence of AF recurrence after cardioversion compared with amiodarone and placebo at 1 month (6 vs. 12.1%; $P < 0.01$) and 1 year (40 vs. 72%; $P = 0.007$). However, in a double-blind, placebo-controlled study in 204 patients, which employed transtelephonic ECG transmission for rhythm monitoring, therapy with PUFAs 3 g/day before (for at least 1 week) and 2 g/day after electrical cardioversion, in addition to antiarrhythmic drug therapy, did not facilitate spontaneous conversion or immediate success of electrical cardioversion and did not reduce the recurrence rate at 6 months compared with placebo (58.9 vs. 51.1%; $P = 0.28$). The mean time to first recurrence of AF was 83 days in the PUFAs-treated group and 106 days in the placebo group. The concomitant use of antiarrhythmic drugs (approximately two-thirds of patients) did not affect the outcome. Similarly, no effect of PUFAs on AF recurrence following cardioversion was demonstrated in 108 patients who did not receive any antiarrhythmic drug therapy.

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### Table 3 Polyunsaturated fatty acids for secondary prevention of atrial fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Design</th>
<th>Clinical setting</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>AF outcome PUFAs vs. control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biscione (2005)</td>
<td>40</td>
<td>Cross-over</td>
<td>Paroxysmal AF and pacemaker</td>
<td>1 g/day</td>
<td>4 months on treatment; 67% reduction in AF burden from 3.89 to 1.06% of total time; $P = 0.0001$</td>
<td>early recurrence: 21.1 vs. 37.6%, $P = 0.007$; late recurrence: 6.0 vs. 12.1%, $P = 0.0001$</td>
</tr>
<tr>
<td>Patel (2009)</td>
<td>258</td>
<td>Nested case controlled</td>
<td>Post-ablation</td>
<td>Minimum 655 mg/day</td>
<td>28 + 7 months</td>
<td>early recurrence: 27.1 vs. 44.1%, $P &lt; 0.0001$; late recurrence: 23.2 vs. 31.7%, $P = 0.003$</td>
</tr>
<tr>
<td>Nodari (2010)</td>
<td>199</td>
<td>Randomized placebo-controlled</td>
<td>Post-cardioversion</td>
<td>1 g/day</td>
<td>1 year</td>
<td>early recurrence: 11.5 vs. 20.0%, $P = 0.0007$; late recurrence: 11.2 vs. 18.2%, $P = 0.001$</td>
</tr>
<tr>
<td>Bianconi (2010)</td>
<td>204</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Post-cardioversion</td>
<td>3 g/day before, 2 g/day after cardioversion</td>
<td>6 months</td>
<td>early recurrence: 15.5 vs. 25.8%, $P = 0.02$; late recurrence: 14.6 vs. 24.2%, $P = 0.03$</td>
</tr>
<tr>
<td>Kowey (2010)</td>
<td>542</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Persistent AF</td>
<td>8 g/day after 7 days, 4 g/day thereafter</td>
<td>6 months</td>
<td>early recurrence: 14.0 vs. 21.4%, $P = 0.03$; late recurrence: 11.2 vs. 15.2%, $P = 0.02$</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; HR, hazard ratio. In brackets, 95% confidence intervals.
and who were pre-treated with PUFAs for a longer period (minimum 4 weeks).91

Paroxysmal atrial fibrillation

In a small study in 40 patients with paroxysmal AF, treatment with PUFAs at 1 g/day for 4 months was associated with a 59% reduction in the number of AF episodes and a 67% reduction in AF burden detected by a permanent dual-chamber pacemaker compared with no treatment.92 After discontinuation of therapy for further 4 months, the number of AF episodes and AF burden reverted to baseline levels. However, a recent double-blind, placebo-controlled P-OM3 (efficacy and safety of Prescription of OMEga-3 fatty acids for prevention of recurrent symptomatic atrial fibrillation) study did not show any effect of therapy with PUFAs at 8 g/day for the first 7 days and at 4 g/day thereafter on the 6-month recurrence rates of symptomatic AF or atrial flutter (the primary endpoint) in 542 patients with paroxysmal AF compared with placebo (52 vs. 48%; HR, 1.15; 95% CI, 0.90–1.46; P = 0.26).93 There was no difference between PUFA-treated and placebo groups in the number of secondary endpoints, e.g. first symptomatic recurrence of AF in 121 patients with persistent AF (50 vs. 33%; HR, 1.64; 95% CI, 0.92–2.92; P = 0.09) as well as the total AF recurrences in patients with paroxysmal AF (59 vs. 55%; P = 0.33) and persistent AF (63 vs. 50%; P = 0.30).

Atrial fibrillation recurrence after pulmonary vein ablation

In a nested case–control analysis of 258 patients with little structural heart disease who had pulmonary vein isolation (nearly 70% for paroxysmal AF), the use of PUFA supplements was associated with a lower incidence of AF recurrence compared with non-users after a mean follow-up of 28 ± 7 months (23.2 vs. 31.7%; P < 0.03).94 However, despite matching attempts, patients in the non-PUFAs group had significantly higher levels of CRP, which were demonstrated to predict AF recurrence after ablation.90–92

There are several plausible explanations for these controversial results.95 The antifibrillatory mechanism of PUFAs is multifactorial and includes action at the substrate level (e.g. anti-inflammatory) and direct electrophysiological effects on the ion channels, the potency of which is likely to depend on the clinical situation and AF milieu. Like RAAS inhibitors and statins, PUFAs may produce a differential effect in the remodelled and unremodelled atria. Despite compelling evidence from experimental models, there has been no study demonstrating reverse remodelling with PUFAs. The doses used in clinical trials were generally lower than those applied in animal experiments, and the duration of treatment may have not been long enough for the antiarrhythmic effect to fully develop. Speculatively, the content of individual PUFAs may be more important than the total PUFA concentration because of the differences in the effects produced by DHA and EPA.87,88

The results of several larger prospective randomized clinical trials are expected (Table 4), but at present there is no robust evidence to make any recommendation for the use of PUFAs for secondary prevention of AF.53

Corticosteroids

Evidence for the use of corticosteroids as upstream therapy for secondary prevention of AF is extremely sparse. In a double-blind, randomized, placebo-controlled study, 104 patients with a very recent onset (mean, 6 h) symptomatic episode of AF were randomized after pharmacological (amiodarone) or electrical cardioversion to therapy with methylprednisolone 16 mg for 4 weeks tapered to 4 mg for 4 months or placebo.96 All patients received propafenone for maintenance of sinus rhythm following cardioversion. There were significantly fewer recurrences of AF (9.6 vs. 50%) and fewer patients developed permanent AF (1.9 vs. 28.9%) in the corticosteroid group compared with placebo after a median follow-up of 23.6 months. The reduction in AF recurrence in the corticosteroid group was paralleled by the reduction in CRP levels, whereas increased CRP levels significantly correlated with risk of recurrent AF. There were no serious adverse effects from corticosteroid therapy, despite the need for dose adjustment in several patients with hypertension or diabetes.

The preliminary results of retrospective cohort analysis in 68 patients who underwent catheter ablation for AF and were receiving short-term intravenous dexamethasone at any time during hospitalization (n = 37) indicated that administration of corticosteroids was associated with a markedly reduced risk of early AF recurrence after ablation (OR, 0.18; 95% CI, 0.04–0.78) compared with no therapy.97 This effect was dose dependent, with a 17% reduction in risk of AF for each dexamethasone milligram-equivalent. These limited observations negate evidence for lack of the effect or even the proarrhythmic effect of steroids in epidemiological surveys; further adequately designed prospective studies, which will address the dose and duration of treatment, are warranted before considering using steroids as upstream therapy for secondary prevention of general forms of AF.53

Effects on major cardiovascular outcomes in patients with atrial fibrillation

An important observation from the LIFE study was that losartan-based therapy not only prevented AF and prolonged time when patients stayed in sinus rhythm but, in addition, improved major cardiovascular outcomes in patients with a history of AF compared with atenolol. Thus, the occurrence of the primary composite endpoint of cardiovascular mortality, stroke, and myocardial infarction was reduced by 42% as were its components (42% reduction in cardiovascular death and 45% reduction in stroke), and there was a trend towards lower all-cause mortality (HR, 0.67; 95% CI, 0.42–1.06; P = 0.09) (Table 5).98 In the US cohort study, there have been fewer AF-related hospitalizations in the ACEI-treated patients (HR, 0.74; 95% CI, 0.62–0.89).99 Consistent with other reports, the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) investigators observed significantly worse outcome in patients who had a history of AF and in patients who developed new-onset AF compared with their counterparts who maintained sinus rhythm (HR, 2.546 and 2.295, respectively; P < 0.0001 for
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Drug and dose</th>
<th>Prevention</th>
<th>Clinical setting</th>
<th>Primary outcome</th>
<th>Follow-up</th>
<th>Expected completion, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPERA, NCT00970489</td>
<td>1516</td>
<td>ω-3 PUFA 8 g/day 2–4 days before cardiac surgery, 2g/day until discharge vs. olive oil</td>
<td>Primary</td>
<td>Heart surgery</td>
<td>Freedom from post-operative AF</td>
<td>10 days or until discharge</td>
<td>2011</td>
</tr>
<tr>
<td>PROFI</td>
<td>200</td>
<td>ω-3 PUFA 1 g/day 1–4 weeks before and 30 days after cardiac surgery</td>
<td>Primary</td>
<td>Heart surgery</td>
<td>Freedom from post-operative AF</td>
<td>30 days</td>
<td>Not stated</td>
</tr>
<tr>
<td>NCT01175330</td>
<td>150</td>
<td>ω-3 PUFA emulsion 1 ml/kg/day intravenously for 7 days after surgery vs. lipid emulsion</td>
<td>Primary</td>
<td>CABG</td>
<td>Freedom from post-operative AFa</td>
<td>2 years</td>
<td>2012</td>
</tr>
<tr>
<td>NCT01259284</td>
<td>252</td>
<td>ω-3 PUFA vs. atorvastatin vs. placebo (doses not specified) 5 days before and 9 days after surgery</td>
<td>Primary</td>
<td>Surgery for lung cancer</td>
<td>Incidence of sustained (&gt;15 minutes) AF or AF requiring intervention</td>
<td>9 days or until discharge</td>
<td>2014</td>
</tr>
<tr>
<td>FORwARD, NCT00597220</td>
<td>1400</td>
<td>ω-3 PUFA 1 g/day vs. corn oil</td>
<td>Secondary</td>
<td>Symptomatic paroxysmal or persistent AF (post-cardioversion); in sinus rhythm at enrolment</td>
<td>Survival free from AF</td>
<td>1 year</td>
<td>2010</td>
</tr>
<tr>
<td>NCT00552084</td>
<td>450</td>
<td>ω-3 PUFA 4 g/day</td>
<td>Secondary</td>
<td>Paroxysmal and persistent AF</td>
<td>Recurrence of any AF and symptomatic AF, inflammatory markers (C-reactive protein, interleukin-6)</td>
<td>6 months</td>
<td>2012</td>
</tr>
<tr>
<td>Post-ablation, NCT00791089</td>
<td>200</td>
<td>ω-3 PUFA 4 g/day 4 weeks before and 3 months after ablation vs. placebo (not specified)</td>
<td>Secondary</td>
<td>Paroxysmal and persistent AF undergoing ablation</td>
<td>Freedom from any atrial arrhythmias without antiarrhythmic drug therapy</td>
<td>6 months</td>
<td>2010</td>
</tr>
<tr>
<td>PUFA, NCT00841451</td>
<td>Not available</td>
<td>ω-3 PUFA vs. placebo (not specified)</td>
<td>Secondary</td>
<td>Paroxysmal and persistent AF undergoing pulmonary vein isolation</td>
<td>Early recurrence of AF post-ablation</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>AFFORD, NCT01235130</td>
<td>332</td>
<td>ω-3 PUFA 2.4 g/day 5 vs. soya bean oil</td>
<td>Secondary</td>
<td>Paroxysmal and persistent AF</td>
<td>Time to first recurrence of AF</td>
<td>67 weeks</td>
<td>2011</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; AFFORD, A Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Effect of Long-chain N-3 Polyunsaturated Fatty Acids (OMEGA-3) on Arrhythmia Recurrence in Atrial Fibrillation; CABG, coronary artery bypass grafting; FORwARD, Fish Oil Research with ω-3 for Atrial Fibrillation Recurrence Delay; OPERA, Omega-3 fatty acids for Prevention of post-operative Atrial Fibrillation; PROFI, Prevention of atrial fibrillation after CABG with Omega-3 polyunsaturated fatty acids; PUFA, Pulmonary Vein Isolation Outcomes With Fish Oils; ω-3 PUFA, polyunsaturated fatty acids.

aAll-cause mortality is a secondary endpoint.

First symptomatic recurrence of AF in all patients is a secondary endpoint.

Current status of studies, except for PROFI, NCT00552084, and NCT00791089, was updated on http://clinicaltrials.gov/ in 2010–11. The design of the FORwARD study and update were published in 2009.
Table 5  Effects of upstream therapies on major cardiovascular outcomes in patients with atrial fibrillation

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Design</th>
<th>Clinical setting</th>
<th>Treatment</th>
<th>Follow-up, years</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>US cohort (2004)</td>
<td>10 926</td>
<td>Observational</td>
<td>Hypertension</td>
<td>ACEIs vs. CCBs</td>
<td>4.5</td>
<td>AF-related hospitalization: HR, 0.74 (0.62–0.89)</td>
</tr>
<tr>
<td>LIFE (2005)</td>
<td>8851</td>
<td>Planned secondary analysis (amendment)</td>
<td>Hypertension with left ventricular hypertrophy</td>
<td>Losartan vs. atenolol</td>
<td>4.8</td>
<td>Primary endpoint (cardiovascular mortality, stroke, myocardial infarction): HR, 0.58 (0.39–0.88); ( P = 0.009 )</td>
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<td>All-Cause mortality: HR, 0.67 (0.42–1.06); ( P = 0.09 )</td>
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<td></td>
<td>Cardiovascular mortality: HR, 0.58 (0.33–0.99); ( P = 0.048 )</td>
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<td></td>
<td>Stroke: HR, 0.55 (0.31–0.97); ( P = 0.039 )</td>
</tr>
<tr>
<td>VALUE (2007)</td>
<td>13 760</td>
<td>Planned secondary analysis (amendment)</td>
<td>Hypertension</td>
<td>Valsartan vs. amlodipine</td>
<td>5</td>
<td>No difference of cardiovascular mortality and morbidity: 21 vs. 23%; ( P = 0.59 )</td>
</tr>
<tr>
<td>HOPE (2007)</td>
<td>8335</td>
<td>Post hoc</td>
<td>Cardiovascular risk factors</td>
<td>Ramipril vs. placebo</td>
<td>4.5</td>
<td>No difference in hospitalization for AF or heart failure</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>All hospitalization: 20.6 vs. 19.9%; ( P = 0.70 )</td>
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<td></td>
<td>Cardiovascular hospitalization: 15.8 vs. 16.9%; ( P = 0.59 )</td>
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<td>Death: 1.1 vs. 1%; ( P = 0.78 )</td>
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<td>Thromboembolic events: 1.4% vs. 0.3%; ( P = 0.04 )</td>
</tr>
<tr>
<td>GISSI-AF (2009)</td>
<td>1442</td>
<td>Prospective RCT</td>
<td>AF and risk factors</td>
<td>Valsartan vs. placebo</td>
<td>1</td>
<td>No difference in the primary endpoint (stroke, myocardial infarction, or vascular death)</td>
</tr>
<tr>
<td>ACTIVE I (2010)</td>
<td>9016</td>
<td>Prospective RCT</td>
<td>AF and risk factors</td>
<td>Irbesartan vs. placebo</td>
<td>4.1</td>
<td>Heart failure hospitalization: HR, 0.86 (0.76–0.98); ( P = 0.02 )</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>No difference in AF-related hospitalization</td>
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<td></td>
<td>In post hoc analysis, stroke, TIA or systemic embolism: HR, 0.87 (0.77–0.98); ( P = 0.02 )</td>
</tr>
<tr>
<td>ANTIPAF (2011)</td>
<td>425</td>
<td>Prospective RCT</td>
<td>Paroxysmal AF, mild hypertension</td>
<td>Olmesartan vs. placebo</td>
<td>1</td>
<td>No difference in secondary endpoints of cardiovascular hospitalizations, outpatient visits, and cerebrovascular events</td>
</tr>
<tr>
<td>J-RHYTHM II</td>
<td>318</td>
<td>Prospective RCT</td>
<td>AF and hypertension</td>
<td>Candesartan vs. amlodipine</td>
<td>1</td>
<td>No difference in the secondary endpoint of cardiovascular events (cardiac death, myocardial infarction, stroke, heart failure, major bleeding), although the number of events was low</td>
</tr>
<tr>
<td>EuroHeart Survey (2008)</td>
<td>5333</td>
<td>Observational</td>
<td>Any AF</td>
<td>Statins (any brand)</td>
<td>1</td>
<td>All-cause mortality: OR, 0.77 (0.50–1.20); ( P = 0.247 )</td>
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<tr>
<td></td>
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<td></td>
<td>Composite of all-cause mortality, thrombo-embolism, heart failure, bleeding: OR, 0.76 (0.58–0.98); ( P = 0.031 )</td>
</tr>
<tr>
<td>AFFIRM (2010)</td>
<td>4060</td>
<td>Post hoc</td>
<td>AF and age ( \geq 65 ) years</td>
<td>Statins (any brand)</td>
<td>3.5</td>
<td>All-cause mortality: HR, 0.77 (0.62–0.95); ( P = 0.01 )</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Cardiovascular mortality: HR, 0.71 (0.53–0.95); ( P = 0.02 )</td>
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<td>Stroke: HR, 0.56 (0.36–0.89); ( P = 0.01 )</td>
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<td>Combined: HR, 0.81 (0.69–0.96); ( P = 0.01 )</td>
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ACEIs, angiotensin-converting enzyme inhibitor; ACTIVE I, Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events—Irbesartan; AF, atrial fibrillation; AFFIRM, Atrial Fibrillation Follow-up Investigation of Rhythm Management; ANTIPAF, Angiotensin II antagonist in Paroxysmal Atrial Fibrillation; CCBs, calcium current blockers; HOPE, Heart Outcomes Prevention Evaluation; GISSI-AF, Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza Cardiaca Atrial Fibrillation; HR, hazard ratio; LIFE, Losartan Intervention For Endpoint reduction in hypertension; LVH, left ventricular hypertrophy; OR, odds ratio; RCT, randomized controlled study; TIA, transient ischaemic attack; US cohort, United States cohort; VALUE, Valsartan Antihypertensive Long-term Use Evaluation. In brackets, 95% confidence interval.
both). However, they did not find any effect on major cardiovascular outcomes in patients with new-onset AF, although the number of primary endpoint events (sudden cardiac death, fatal and non-fatal myocardial infarction, revascularization-related death, and heart failure death and hospitalization) was low: 53 (21%) events in the valsartan group and 68 (23%) events in the amlodipine group ($P = 0.59$).

In the GISSI-AF trial in 1142 patients with AF, there were no differences between valsartan and placebo in secondary endpoints including hospitalization for any reason (20.6 vs. 19.9%), cardiovascular hospitalization (15.8 vs. 16.9%), or death (1.1 vs. 1.0%). However, 10 (1.4%) patients treated with valsartan developed thrombo-embolic complications compared with 2 (0.3%) in the placebo group (HR, 5.06; 95% CI, 1.11–23.11; $P = 0.4$). There were four ischaemic strokes (0.6%) in the valsartan group and none in the placebo group. The J-RHYTHM II study attempted to analyse cardiovascular events as secondary endpoints, all of which occurred in the amlodipine-treated group, but there were too few of these (three episodes of stroke and one episode of major bleeding) to make any relevant conclusion. Similarly, in the ANTIpAF study, there was no difference in cardiovascular hospitalizations, outpatient visits, and cerebrovascular events among patients with paroxysmal AF treated with olmesartan compared with placebo.

In the ACTIVE I trial of 9016 patients with AF and risk factors, therapy with irbesartan had no effect on the co-primary composite endpoint of stroke, myocardial infarction, and vascular death, or stroke, myocardial infarction, vascular death, and hospitalization for CHF, although its hospitalization component was reduced by 14% which was statistically significant (95% CI, 0.76 to 0.98; $P = 0.020$). The post hoc analysis showed a modest, but statistically significant, reduction in the composite of stroke, transient ischaemic attacks, and systemic embolism by 13% (95% CI, 0.77–0.98; $P = 0.02$) in association with irbesartan compared with placebo (2.9% vs. 3.3%). There was also a 40% reduction in primary haemorrhagic stroke and secondary transformation of ischaemic stroke, probably as a result of a lower blood pressure in the irbesartan group, although the number of these events was small. Therapy with irbesartan did not affect the risk of hospitalization for AF. Yet, RAAS inhibitors have not yet proven to offer a significant advantage over other therapies in improving major cardiovascular outcomes in patients with a history of, or new-onset, AF.

Less evidence is available on the effects of statins on major cardiovascular outcomes, specifically in patients with AF. In the Euro Heart Survey on AF in the mixed AF patient population, although there was no difference in all-cause mortality, the use of statins was associated with a significantly lower incidence of a combined endpoint of all-cause mortality, thrombo-embolism, major bleeding, and heart failure at 1-year (OR, 0.76; 95% CI, 0.58–0.98; $P = 0.031$). There was also a non-significant trend towards reduced all-cause mortality (OR, 0.77; 95% CI, 0.50–1.20; $P = 0.247$). In post hoc analysis of the AFFIRM trial in 4060 patients, lipid-lowering therapy (mainly statins) at the time of randomization has been found to reduce all-cause mortality by 23%, cardiovascular mortality by 29%, ischaemic stroke by 44%, and the combined endpoint of these outcomes by 19%.

Conclusions

There is controversial evidence that it is possible to prevent recurrences of AF whereas the primary prevention of AF may well be feasible (Part I: Primary Prevention). This is not entirely surprising since underlying atrial remodelling may have gone too far to be successfully reversed. Indeed, although it may be possible to retard the process of atrial remodelling, its reversal has not been successfully demonstrated in animal models or in humans. Apart from some small trials of ACEIs and ARBs in combination with antiarrhythmic therapy, clinical trials have been consistently negative in suppressing AF recurrence. Further clinical trials involving conventional and newer agents that may inhibit or reverse atrial remodelling are underway and several will report soon. However, it seems highly likely that clinical success will only be achieved when AF is detected and treated before any substantial atrial remodelling has occurred.

Conflict of interest: I.S. is an advisor and speaker for sanofi aventis, BMS, Takeda, Daiichi, Boehringer Ingelheim, Servier, and Merck. A.J.C. is an advisor and speaker for Servier, Novartis, sanofi aventis, Astra Zeneca, Cardiome, Prism, Astellas, Xention, ARXy, Prism, BMS, Daiichi, Merck, Medtronic, St. Jude, Biotronic, Boehringer Ingleheim, and Boston Scientific.

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Upstream therapies for management of atrial fibrillation


