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Primary Prevention of Atrial Fibrillation where are we in 2012?

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Abstract

Drugs to alter or delay myocardial remodelling associated with heart failure, hypertension, or inflammation in the post-operative setting, may prevent the development of atrial fibrillation. Current experimental and clinical evidences support specific treatments for defined patient population (i.e. ACE-inhibitors and ARB for chronic heart failure and hypertension expecially with LV hypertrophy; statins, corticosteroids and possibly colchicine after cardiac surgery).

Key words: **atrial fibrillation, prevention.**

Introduction

Atrial fibrillation (AF) is an increasingly common arrhythmia because of population ageing, the improvement in the survival of patients with heart diseases, as well as progresses in medical and surgical therapies for cardiovascular diseases. On this basis, the number of patients with AF is expected to reach 6 to 16 million by 2050 in the USA, while a similar proportion is also expected in Western Europe.[1-3]

The costs of managing AF is high. In a recently published systematic review on the topic, direct cost estimates ranged from $ 2000 to 14,200 per patient-year in the USA, and from € 450 to 3000 in Europe.[4] These costs are comparable with those of other chronic conditions, such as diabetes. In the UK, direct costs of AF represented 0.9 to 2.4% of health care budget in 2000, and almost doubled over the previous 5 years. In-patient care accounted for 50-70% of annual direct costs, and in the USA AF-related hospitalizations alone had $ 6.65 billion cost in 2005. In another review, the overall estimated average annual system cost was $ 5450 (SD $ 3624) Canadian dollars in 2010 and ranged from $ 1,632 to 21,099. About one third of the costs were attributed to anticoagulation management. The largest cost was attributed to acute care, followed by outpatient and physician, and medications related costs.[5] Costs and hospitalizations attributable to AF have greatly increased over recent years and are expected to further increase in future due to population ageing. On this basis, increased awareness and attention to AF prevention is warranted, especially for primary prevention, because while data from clinical trials have shown that preventing AF recurrence after it develops does not reduce major adverse events, such as stroke and death, and there is controversial evidence that it is possible to prevent AF recurrences AF primary prevention may be feasible and efficacious for specific patients groups.[6-8] Moreover, it might have the potentiality to affect major adverse events more than secondary prevention. This seems not surprising since the underlying atrial remodelling may have gone too far to be successfully reversed after AF developing.[8]

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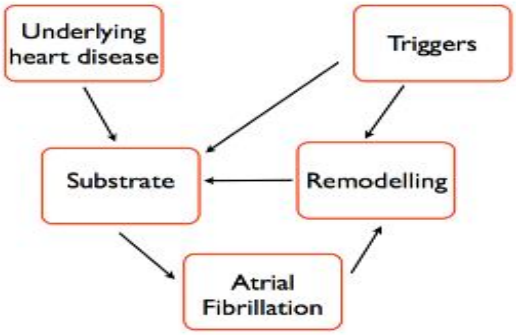
Figure 1. Upstream therapies may affect the underlying disease (i.e. ACEi, ARB, statins), the substrate, the triggers (i.e. inflammation for statins, corticosteroids, and colchicine), and the remodelling process (all agents) preventing atrial fibrillation at different levels and mechanisms.



AF is associated with hypertension, congestive heart failure, ischemic heart disease, and diabetes, that are also recognized risk factors for the arrhythmia.[9] Specific conditions, such as cardiac surgery, are also associated with an increased risk to develop AF.[10]

AF involves a continuous remodeling of the atria with electrical and structural transformations. Specific therapies may have the potentiality to affect either the formation or the evolution of the substrate for AF (upstream therapies), providing the basis for the primary prevention of AF (Figure 1).[11] Several medications not traditionally considered as anti-arrhythmic agents (angiotensin-converting enzyme inhibitors-ACEIs, angiotensin receptor blockers-ARBs, aldosterone antagonists, statins, n-3 polyunsaturated fatty acids-PUFAs, corticosteroids, and colchicine) have been evaluated for the primary prevention of AF. Aim of the present review is to summarize current experimental and clinical evidence on the primary prevention of AF.

Inhibitors of the Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system is suggested to play a key role in the development of AF through structural and electrical remodeling.

The key mechanism of antiarrhytmic action of inhibitors of the renin-angiotensin-aldosterone system (RAAS) is related to the opposition of the arrhythmogenic effects of angiotensin II, including stimulation of atrial fibrosis and hypertrophy secondary to activation of mitogen-activated protein kinases, uncoupling gap junctions, impaired calcium handling, activation of mediators of oxidative stress, and promotion of inflammation.[12,13]

Four meta-analyses have shown that ACEIs and ARBs may be effective for the primary prevention of AF in the setting of heart failure. In these studies, the risk of new-onset AF in patients with chronic heart failure was reduced by 30-50%.[14-17] These data are consistent with experimental findings of atrial fibrosis as the leading mechanism of AF in chronic heart failure models and evidence of the antifibrotic effects of RAAS inhibition. There are no data if such effects may also reduce morbidity and mortality in the setting of chronic heart failure, and if ACEIs and ARBs may reduce the incidence of AF in patients with heart failure and preserved systolic function.[18]

The effects of RAAS inhibition on primary prevention of AF is less evident in hypertensive patients. Only one of four meta-analyses[14-17] showed a statistically significant 25% reduction in relative risk of AF.[16]

The effects are less clear in patients with multiple risk factors such as hypertension, diabetes mellitus, CAD, cerebrovascular disease, peripheral artery disease, hypercholesterolemia, such as those reported in the HOPE and TRANSCEND trials.[19,20] In the setting of post-operative AF, RAAS inhibition was not efficacious for AF primary prevention.[21-24]

In a recently published meta-analysis, including 14 randomized controlled trials that reported on new onset atrial fibrillation (92,817 patients), and that compared at least one of the following drugs: angiotensin-converting enzyme inhibitors, angiotensin II-receptor blockers, and aldosterone antagonists with conventional therapy or placebo, RAAS inhibition compared with conventional therapy or placebo reduced new onset atrial fibrillation (RR=0.79; 95% CI; 0.69-0.90, p-value<0.001). ARBs showed a strong effect in the reduction of onset atrial fibrillation (RR=0.78; 95% CI: 0.66-0.92, p-value=0.009), whereas results for ACE inhibitors were not as clear but likely show no effect

(RR=0.79, 95% CI: 0.62-1:00, p-value: 0.05). Aldosterone antagonists, did not appear to play a role in the prevention of new onset atrial fibrillation (RR=0.77, 95%CI: 0.55-1.08, p-value: 0.21). Risk reduction was highest among heart failure patients.[19]

RAAS inhibition has been proven efficiacious for AF primary prevention in the setting of significant underlying heart disease (e.g. left ventricular dysfunction and hyperthrophy). Current European guidelines recognize the utility of RAAS inhibition for AF primary prevention in patients with chronic heart failure (class I, level of evidence A) or hypertension , especially with left ventricular hypertrophy "(class IIa, level of evidence IIa)".[26]

Statins

The exact mechanism by which statins may prevent AF is not fully understood. Statins may improve lipid metabolism, prevent atherosclerosis, endotelial dysfunction and neurohormonal activation, and exert anti-inflammatory and antioxidant actions.[27]

Moreover statins may antagonize the arrhythmogenic effects of angiotensin II by reducing oxidized low-density lipoproteins, regulate metalloproteinanses (MMPs), and in that way play a regulatory role in atrial structural remodelling. In animal models with sterile pericarditis and pacing, statins may attenuate atrial electrical and structural remodelling and reduce vulnerability to AF.[28-30]

Several retrospective analysis from RCTs and registries of patients with chronic heart failure have suggested a possible reduction in the incidence of new-onset AF.[31-34]

A 28-31% reduction in relative risk of developing AF has been reported in the Advancent registry[31] and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial).[32]

However in the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca Heart Failure) rosuvastatin significantly reduced the risk of AF only after adjustement for clinical variables, laboratory findings, and concomitant therapy (HR 0.820; 95% CI 0.680-0.989; p=0.038).[33] There is also limited evidence for the role of statins in the primary prevention of AF in the setting of hypertensive patients and conflicting evidence in patients with coronary artery disease and acute coronary syndromes.[18]

More convincing data have been reported for the prevention of post-operative AF.

Several retrospective studies and RCTs,[35-42] a systematic review,[43] and a meta-analysis[44] have reported a lower incidence of post-operative AF and a shorter hospital stay with statins. In the most recently published meta-analysis, 11 randomized controlled studies were analyzed and included with a total of 984 participants undergoing on or off-pump cardiac surgical procedures. Pooled analysis showed that statin pre-treatment before surgery reduced the incidence of post-operative atrial fibrillation (AF) (OR 0.40; 95%-CI: 0.29 to 0.55; p<0.01), but failed to influence short-term mortality (OR 0.98, 95%-CI: 0.14 to 7.10; p=0.98) or post-operative stroke (OR 0.70, 95%-CI: 0.14 to 3.63; p=0.67). Statin therapy was associated with a shorter length of stay of patients on the intensive care unit (ICU) (WMD: -3.39 hours; 95%-CI: -5.77 to -1.01) and in-hospital (WMD: -0.48 days; 95%-CI: -0.85 to -0.11) where significant heterogeneity was observed. No significant side effects were reported. There was no reduction in myocardial infarction (OR 0.52; 95%-CI: 0.2. to 1.30) or renal failure (OR 0.41; 95%-CI: 0.15 to 1.12).45 The role of statins for AF primary prevention has been not definitively demostrated, more evidence supports their use in the setting of post-operative AF prevention. On this basis, the 2010 ESC guidelines on atrial fibrillation management gave a class IIb recommendation for the use of statin in patients with underlying heart diseases, especially chronic heart failure (LOE B), and a class IIa recommendation for prevention of post-operative AF (LOE B).[26]

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFA) are natural constituents of cell membranes and regulate their fluidity, also modulating the activity of multiple membrane proteins. PUFA may counteract the arrhythmogenic effects of atrial stretch and have direct eletrophysiological effects on ion channels (i.e. I_{Na}, I_{Kur}, I_{Ach}, I_{to}, and I_{Ca} as well as the Na^{+}/Ca^{++} exchanger).[46-49] Additional properties include anti-inflammatory and

Table 1 Pharmacologic agents for primary prevention of atrial fibrillation.

Drug	Mechanism	Evidence
Inhibitors of the renin-angiotensin-aldosterone system (RAAS): ACEi ARB Aldosterone antagonists	Anti-angiotensin II effects	Experimental data, more convincing data in the setting of postoperative AF prevention needed.
Statins	Combined actions (lipid metabolism, atherosclerosis prevention, endotelial function, anti-inflammatory and anti-oxidant actions)	Favourable experimental data but conflicting data from epidemiological studies. Definitive proof of efficacy still lacking also in the setting of postoperative AF prevention.
n-3 PUFA	Modulation of cell membrane fluidity, multiple membrane proteins function, including ion channels (i.e. INa, IKur, IAch, Ito, and ICa as well as the Na+/Ca++ exchanger). Additional properties include anti-inflammatory and antioxidant actions.	Clinical evidence supports a 26-58% reduction in the relative risk of POAF.
Corticosteroids	Anti-inflammatory effects	Colchicine may halve several postoperative complications (PPS, postoperative effusions, POAF)
Colchicine	Anti-inflammatory effects, possible direct effect on atria	

ACEi= angiotensin-converting enzyme inhibitors, ARB= angiotensin receptor blockers; POAF= post-operative atrial fibrillation, PPS= post-pericardiotomy syndrome.

antioxidant actions and the potentiality to regulate mitogen-activated protein kinase activity.[50]

Despite these theoretical premises and experimental evidences in animal models such as those in experimental sterile pericarditis models, where PUFA reduced the inflammatory response and the AF inducibility,[51] epidemiological studies have given controversial results.[52-56]

In a recently published meta-analysis on the effects of PUFA for post-operative AF prevention, 3 RCTs were included in the analysis, enrolling a total of 431 patients. Overall incidence of post-operative AF ranged from 24 to 54%. Pooling data, n-3 PUFA did not show a significant effect on the risk of post-operative AF [risk ratio 0.89; 95% confidence interval (CI) 0.55-1.44; P=0.63]. However, meta-regression analysis showed a trend toward a benefit from n-3 PUFA supplementation when the EPA/DHA ratio was 1:2 (Q model=7.4; p model=0.02) and when preoperative β-blocker rate was lower (Q model=8.0; p model=0.01).[57]

Thus, although the theoretical background and animal experimental evidences, PUFA efficacy for the primary prevention of AF still has to be proven and ongoing clinical trials will provide further evidence for or against their use in this setting.

Corticosteroids

Inflammation is a key mechanism of AF for some forms, especially in the post-operative setting.[58] Animal studies have shown that corticosteroids may prevent electrical remodelling and inducibility of atrial tachyarrhythmias by attenuating inflammation in post-operative and atrial pacing models of AF, as well as sterile pericarditis models of atrial flutter.[59-61] In these settings, use of corticosteroids was associated with C-reactive protein levels reduction, as well as reduced activity of endothelial nitric oxide synthase and myeloperoxidase.[59-61]

These effects were not reproducible with the use of ibuprofen, probably because of the effect of NSAID limited to inhibition of cyclo-oxygenase.[62]

Three meta-analyses have shown that corticosteroids was associated with a 26-58% reduction in the relative risk of post-operative AF as well as hospital stay by one day.[63-65] Intermediate doses of corticosteroids were more efficacious compared with low or high doses.

Table 2 Primary prevention of atrial fibrillation: recommendation from 2010 ESC guidelines.[86]

Recommendation	Class of indication	Level of evidence
ACE-inhibitors, ARBs for AF prevention in patients with heart failure and reduced EF.	IIa	A
ACE-inhibitors, ARBs for AF prevention in patients with hypertension and LV hypertrophy	IIa	B
Statins for AF prevention after coronary artery bypass grafting with or without valvular surgery.	IIa	B
Statins for AF prevention in patients with underlying heart disease, especially heart failure	IIb	B
Upstream therapies with ACEi, ARB, statins for AF primary prevention in patients without heart diseases.	III	C

ACE= angiotensin converting-enzyme, ARB= angiotensin receptor blockers, AF= atrial fibrillation, EF= ejection fraction, LV=left ventricle.

However, use of corticosteroids was associated with an increased risk of hyperglycemia, post-operative pneumonia, urinary tract infections, and gastrointestinal bleeding. High dose corticosteroids may also have a proarrhythmic effect.[66,67]

Also other epidemiological reports suggest that use of corticosteroids, especially at high doses, may be associated with an increased risk of AF.[68,69]

Nevertheless, based on available evidence, current European guidelines gave a class IIb recommendation for the use of corticosteroids for the prevention of AF after cardiac surgery (LOE B). [26]

At present, two large randomised controlled trials are ongoing to further clarify the role of corticosteroids for AF prevention in the post-operative setting or after ablation (ClinicalTrials.gov Identifier: NCT01143129, ClinicalTrials.gov Identifier: NCT00807586).

Colchicine

Colchicine is a potentially poisonous natural product and secondary metabolite, originally extracted from plants of the genus Colchicum (Autumn crocus, Colchicum autumnale, also known as the 'meadow saffron'). The drug has been used for the treatment and prevention of gouty attacks for centuries. More recently, colchicine has been studied and used in several other inflammatory conditions, i.e. serositis. Following the successful use in prevention of pericarditis in the setting of Familial Mediterranean Fever, the drug has been used for the treatment and prevention of isolated and idiopathic pericarditis.[65] After non-randomized studies and initial randomised trials in acute and recurrent pericarditis, [66-69] the efficacy and safety of colchicine for pericarditis treatment and prevention has been confirmed in a recently published meta-analysis.[75]

In this meta-analysis, five controlled clinical trials were finally included (795 patients): three studies were double-blind randomised controlled trials, and two studies were open-label randomised controlled trials. Trials followed patients for a mean of 13 months. Meta-analytic pooling showed that colchicine use was associated with a reduced risk of pericarditis during follow-up (RR=0.40, 95% CI 0.30 to 0.54, p for effect <0.001, p for heterogeneity = 0.95, I(2)=0%) either for primary or secondary prevention without a significant higher risk of adverse events compared with placebo (RR=1.22, 95% CI 0.71 to 2.10, p for effect 0.48, p for heterogeneity = 0.44, I(2)=0%), but more cases of drug withdrawals (RR=1.85, 95% CI 1.04 to 3.29, p for effect 0.04, p for heterogeneity = 0.42, I(2)=0%). Gastrointestinal intolerance is the most frequent side effect (mean incidence 8%), but no severe adverse events were recorded. The exact mechanism of colchicine action is not fully understood. Most of the pharmacological effects of colchicine on cells involved in inflammation appear to be related to the capacity of colchicine to inhibit the process of microtubule self-assembly by binding tubulin with the formation of tubulin–colchicine complexes, thus interfering with several cellular functions (such as chemotaxis, degranulation, phagocytosis) in leucocytes, thereby reducing the inflammatory response. Colchicine shows a preferential concentration in leucocytes, especially neutrophils, and the peak concentration of colchicine in these cells may be more than 16 times the

peak concentration in plasma even when used at low oral doses, such as 0.5 to 1.0 mg daily.[70,76]

In the post-operative setting, colchicine used at low oral doses (0.5 to 1.0mg daily from the 3rd post-operative day for 1 month) is able to halve the incidence of several post-operative complications, including postpericardiotomy syndrome, post-operative pericardial and pleural effusions, and post-operative atrial fibrillation.[73,77,78]

In the COPPS post-operative AF study, 336 patients were included (mean age, 65.7 years; 69% males). Patients were in sinus rhythm before starting the intervention (placebo/colchicine 1.0 mg twice daily starting on post-operative day 3 followed by a maintenance dose of 0.5 mg twice daily for 1 month in patients >70 kg, halved doses for other patients or intolerant to the highest dose). Despite well-balanced baseline characteristics, patients on colchicine had a reduced incidence of post-operative AF at 1 month (12.0% versus 22.0%, respectively; P=0.021; relative risk reduction, 45%; number needed to treat, 11) with a shorter in-hospital stay (9.4±3.7 versus 10.3±4.3 days; P=0.040) and rehabilitation stay (12.1±6.1 versus 13.9±6.5 days; P=0.009). Side effects were similar in the study groups. [78]

In animal studies of experimental sterile pericarditis, profound epicardial neutrophil infiltration, which promotes gap junction remodeling, has been detected. Areas with significant neutrophil infiltration displayed necrotic changes and had a lower abundance of connexins 40 and 43.[79] Consistent with these observations, atrial myeloperoxidase levels (which reflect neutrophil/macrophage infiltration) were associated with conduction slowing and conduction heterogeneity in another canine cardiac surgery model.[80] Colchicine attenuates neutrophil activation, endothelial cell adhesion, and migration to injured tissues.[81] In addition to the potential effects of colchicine on neutrophil activation/migration/infiltration, colchicine may have relevant effects on atrial myocytes. Microtubules regulate the localization and interaction of adrenergic receptors and adenylate cyclase in caveolae (specialized lipid domains in the cell membrane).[81] As a result, microtubules modulate the phosphorylation of calcium channels and likely affect the response of the atria to autonomic stimulation.[82] Because autonomic balance is altered in the post-operative state, drugs that attenuate sympathetic activity (eg, beta-adrenergic receptor blockers or colchicine) or increase parasympathetic activity may decrease the risk of calcium overload–induced ectopy, which contributes to the initiation of post-operative AF. In that way colchicine may prevent post-operative atrial fibrillation with antiinflammatory and non-inflammatory effects.[83]

Although, at present colchicine cannot be recommended on the basis of a single positive clinical trial, there is growing evidence supporting its use for the prevention of several post-operative complications.[84,85] Further clinical trials will provide further evidence for or against this use in the perioperative setting. At present, the ongoing multicenter, double-blind, randomised COPPS-2 trial (ClinicalTrials.gov Identifier: NCT01552187) is evaluating the efficacy and safety of colchicine given 2-3 days before surgery in order to prevent several post-operative complications (atrial fibrillation, post-pericardiotomy syndrome, and post-operative effusions).

Disclosures

No disclosures relevant to this article were made by the author.

Conclusions

Interventions targeted at the substrate of AF and the modification of risk factors for AF may prevent the onset of AF in specific patient groups (chronic heart failure, hypertension with LV hyperthrophy, post-operative course after cardiac surgery). Such medical interventions include non-arrhythmic drugs that are able to modify the atrial substrate and specific mechanisms promoting the development of AF. Such treatments are also referred as upstream therapies and include ACE-inhibitors, ARBs, statins, PUFA, corticosteroids, and recently also colchicine (Table 1). These drugs may prevent or delay atrial changes, including fibrosis, hypertrophy, inflammation, oxidative stress, but may have also direct or indirect effects on atrial ion channels, gap junctions, and calcium handling. Experimental and clinical data have demonstrated that ACE-inhibitors, ARBs may prevent

AF in patients with significant underlying heart disease (left ventricular dysfunction and hypertrophy), while statins, corticosteroids, and possibly colchicine may prevent post-operative AF. At present, specific recommendations on primary prevention of AF have been issued by the 2010 ESC guidelines on the management of atrial fibrillation and are reported in details in table 2.[81]

On the contrary, 2011 AHA/ACC updated guidelines on the management of atrial fibrillation conclude that there are insufficient data at this time to permit recommendations for primary prevention of AF in populations at risk using dietary interventions, pharmacological interventions, or pacing or other devices. In the perioperative period, the American guidelines recommend betablockers to prevent post-operative AF for patients undergoing cardiac surgery, and amiodarone as appropriate prophylactic therapy for patients at high risk for post-operative AF.[82]

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