Editorial

Atrial Fibrillation, Inflammation and Statins

Emmanuel S. Ganotakis,[1] Dimitri P. Mikhailidis,[2] Panos E. Vardas[3]

Departments of [1]Internal Medicine and [3]Cardiology, Heraklion University Hospital, Crete, Greece; [2]Department of Clinical Biochemistry (Vascular Disease Prevention Clinics), Royal Free Hospital, Royal Free and University College Medical School, London, UK

Key words: **Atrial remodelling, dyslipidaemia.**

Address:
Emmanuel S. Ganotakis

Department of Internal Medicine
University Hospital of Crete
P.O. Box 1352
71110 Heraklion
Crete, Greece
e-mail:
ganotak@med.uoc.gr

Atrial fibrillation (AF) is a common arrhythmia, especially in the elderly.[1] Approximately 4% of those older than 60 years and 9% of those older than 80 years have AF.[2] In addition, AF remains a significant complication following cardiac surgery[3] and post heart transplant.[4] The risk of stroke is increased by four- to fivefold in AF patients and AF is responsible for about 16% of all ischaemic strokes in the elderly.[5] This arrhythmia is also associated with a twofold mortality.[6] Over the next decades the number of Americans with non-valvular AF is expected to increase markedly, making AF-related stroke an important public health concern.[7]

Recently, both animal[8] and clinical studies have improved our knowledge of the pathogenesis of AF.[9] The pathophysiology of AF is complex, but in most cases it may be caused by multiple random re-entering wavelets.[10] The autonomic nervous system is a potentially potent modulator of the initiation, maintenance, termination and ventricular rate in AF.[11]

Hypertension, diabetes mellitus, male gender, age, obesity, metabolic syndrome and coronary artery disease have been identified as risk factors for non-valvular AF.[12-16] These factors are also major risk factors for vascular disease, which suggests that AF, particularly in older and hypertensive patients, might be part of the atherosclerosis spectrum. Moreover, acute or chronic haemodynamic, metabolic or inflammatory stressors may lead to structural remodelling of the atria that may promote progression and persistence of AF.[17]

The ideal therapeutic goal for AF is to achieve and maintain sinus rhythm.[18] Despite the success of aggressive procedural techniques, pharmacological therapy remains the main approach in the treatment of AF.[19] Treatment is based on rate or rhythm control to reduce symptoms, the prevention of tachycardia-mediated cardiomyopathy[20] and anticoagulation to reduce the thromboembolic risk.[21]

Statins have potent anti-inflammatory properties and it has been proposed that they may be useful in suppressing inflammation associated with AF.[19] No large prospective trials have evaluated the efficacy of statins in preventing AF: however, retrospective human data as well as animal experiments[26,27] suggest a potential benefit.

Recent findings suggested a link between inflammatory processes and the development of AF. Elevated C-reactive protein (CRP) levels are associated with the risk of developing AF[17,22] and also predict an increased risk of recurrence after successful electrical cardioversion.[23] Furthermore, treatment with glucocorticoids, statins, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) seems to reduce the recurrence of AF. Part of this anti-arrhythmic effect may be through anti-inflammatory activity.[24] Furthermore, recent data from the

Women's Health study related elevated CRP with a higher risk of developing hypertension, which is a major risk factor for AF.[25]

A retrospective analysis of patients treated with statins after coronary artery bypass surgery demonstrated a 77% reduction (p=0.006) in postoperative arrhythmias, including AF.[28] In a prospective study the preoperative use of statins was associated with a threefold decrease in the odds of developing AF in patients undergoing non-cardiac thoracic surgery.[29] This protective effect was independent of CRP levels.[29] In a cohort study of 449 patients (mean age 68 years) with coronary artery disease who were followed for a mean 5 years, statin therapy reduced the risk of developing AF by 52% (p=0.01).[30] The use of statins was also associated with a significant decrease (p=0.032) in the risk of AF recurrence after successful cardioversion.[31]

Interest has been generated in the role of renin angiotensin system (RAS) blockade in reversing electrical and structural remodelling in diseased atria.[32,33] Retrospective studies showed a preventive effect on AF development from the use of agents interfering with the RAS.[12,33] Pharmacological therapy with ACEI, ARB, statins, and perhaps aldosterone and calcium channel blockers, may have a role in the prevention of AF onset and recurrence.[33,34] The mechanism for this preventive effect in AF is probably complex. These drugs may achieve general haemodynamic changes, leading to lower intra-atrial pressure and wall-stress, or reduce atrial fibrosis, connexin43 over-expression and conduction delay.[32,33] Furthermore, several clinical studies suggest that the RAS plays a pivotal role in the pathogenesis of insulin resistance.[35] In turn, it has been proposed that insulin resistance increases the risk of AF. It is therefore of interest that obesity (a cause of insulin resistance) is associated with a greater risk of AF.[15] Both obesity and insulin resistance are associated with dyslipidaemia.[36] Whether this dyslipidaemia is a major contributor to the pathogenesis of AF in these patients remains to be established. This is an important question, since dyslipidaemia is amenable to treatment.[36]

In conclusion, the role of modifying inflammation and dyslipidaemia in the treatment of non-valvular AF remains to be clarified. Meanwhile, based on current knowledge it may be appropriate to use statins in these patients, especially since a significant proportion will have coronary artery disease or atherosclerotic changes in other arteries. In this context it is relevant that the combination of AF and peripheral arterial disease increases mortality during hospital admission and follow-up of about 17 months.[37]

References

1. Ray IB, Heist EK: Treating atrial fibrillation. What is the consensus now? Postgrad Med 2005; 118: 47-48, 51-54, 58.
2. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG: Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 1995; 155: 469-473.
3. American College of Chest Physicians guidelines for prevention and management of postoperative atrial fibrillation after cardiac surgery. www.guideline.gov.
4. Ahmari SA, Bunch TJ, Chandra A, et al: Prevalence, pathophysiology, and clinical significance of post-heart transplant atrial fibrillation and atrial flutter. J Heart Lung Transplant 2006; 25: 53-60.
5. Wolf PA, Abbott RD, Kannel WB: Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991; 22: 983-988.
6. Benjamin EJ, Levy D, Vaziri SM, et al: Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA 1994; 271: 840-844.
7. Go AS, Fang MC, Singer DE: Antithrombotic therapy for stroke prevention in atrial fibrillation. Prog Cardiovasc Dis 2005; 48: 108-124.
8. Nattel S, Shiroshita-Tkeshita A, Brundel BJ, Rivard L: Mechanisms of atrial fibrillation: lessons from animal models. Prog Cardiovasc Dis 2005; 48: 9-28.
9. Oral H: Mechanisms of atrial fibrillation: lessons from studies in patients. Prog Cardiovasc Dis. 2005; 48: 29-40.
10. Korantzopoulos P, Kolettis T, Siogas K, Goudevenos J: Atrial fibrillation and electrical remodeling: the potential role of inflammation and oxidative stress. Med Sci Monit 2003; 9: RA 225-229.
11. Olshansky B: Interrelationships between the autonomic nervous system and atrial fibrillation. Prog Cardiovasc Dis 2005; 48: 57-78.
12. Palardy M, Ducharme A: Inhibition of the renin-angiotensin system and atrial fibrillation in heart failure. Heart Drug 2005; 5: 214-219.
13. Ostgren CJ, Merlo J, Rastam L, Lindblad U: Atrial fibrillation and its association with type 2 diabetes and hypertension in a Swedish community. Diabetes Obes Metab 2004; 6: 367-374.
14. Rienstra M, Van Veldhuisen DJ, Hagens VE, et al: Gender-related differences in rhythm control treatment in persistent atrial fibrillation. Data of the rate control versus electrical cardioversion (RACE) study. J Am Coll Cardiol 2005; 46: 1298-1306.
15. Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah AS, Habib RH: Obesity and risk of new-onset atrial fibrillation after cardiac surgery. Circulation 2005; 112: 3247-3255.
16. Nicolaou VN, Papadakis JE, Karatzis EN, Dermitzaki SI, Tsakiris AK, Skoufas PD: Impact of the metabolic syndrome on atrial size in patients with new onset atrial fibrillation. Angiology 2006; (in press).
17. Aviles RJ, Martin DO, Apperson-Hancen C, et al: Inflammation as a risk factor for atrial fibrillation. Circulation 2003; 108: 3006-3010.
18. Nattel S, Khairy P, Roy D, et al: New approaches to atrial fibrillation management: a critical review of a rapidly evolving field. Drugs 2002; 62: 2377-2397.
19. Goldstein RN, Stambler BS: New antiarrhythmic drugs for prevention of atrial fibrillation. Prog Cardiovasc Dis 2005; 48: 193-208.

20. Rosenfeld LE. Atrial fibrillation: how to approach rate control: Curr Cardiol Rep 2005; 7: 391-397.
21. Singer DE, Albers GW, Dalen JE, Go AS, Halperin JL, Manning WJ: Antithrombotic therapy in atrial fibrillation: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(suppl 3): 429S-456S.
22. Chung MK, Martin DO, Sprecher D, et al: C-reactive protein elevation in patients with arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation 2001; 104: 2886-2891.
23. Malouf JF, Kanagala R, Al Atawi FO, et al: High sensitivity C-reactive protein; a novel predictor for recurrence of atrial fibrillation after successful cardioversion. J Am Coll Cardiol 2005; 46: 1284-1287.
24. Engelmann MD, Svendsen JH: Inflammation in the genesis and perpetuation of atrial fibrillation. Eur Heart J 2005; 26: 2083-2092.
25. Sesso HD, Burning JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM: C-reactive protein and the risk of developing hypertension JAMA 2003; 290: 2945-2951.
26. Shiroshita-Takeshita A, Scram G, Lavoie J, et al: Effects of simvastatin and antioxidant vitamins on atrial fibrillation promotion by atrial-tachycardia remodeling in dogs. Circulation 2004; 110: 2313-2319.
27. Kumagai K, Nakashima H, Saku K: The HMG-CoA reductase inhibitor atorvastatin prevents atrial fibrillation by inhibiting inflammation in canine sterile pericarditis model. Cardiovasc Res 2004; 62: 105-111.
28. Dotani MI, Elnicki DM, Jain AC, et al: Effect of preoperative statin therapy and cardiac outcomes after coronary bypass grafting. Am J Cardiol 2000; 86: 1128-1130.
29. Amar D, Zhang H, Heerdt PM, Park B, Fleisher M, Thaler HT: Statin use is associated with a reduction in atrial fibrillation after noncardiac thoracic surgery independent of C-reactive protein. Chest 2005; 128: 3421-3427.
30. Young-Xu Y, Jabbour S, Goldberg R, et al: Usefulness of statin drugs in protecting against atrial fibrillation in patients with coronary artery disease. Am J Cardiol 2003; 92: 1379-1383.
31. Siu CW, Lau CP, Tse HF: Prevention of atrial fibrillation recurrence by statin therapy in patients with lone atrial fibrillation after successful cardioversion. Am J Cardiol 2004; 92: 1343-1345.
32. Dilaveris P, Giannopoulos G, Synetos A, Stefanadis C: The role of renin angiotensin system blockade in the treatment of atrial fibrillation. Curr Drug Targets Cardiovasc Haematol Disord 2005; 5: 387-403.
33. Bourassa MG: Angiotensin II inhibition and prevention of atrial fibrillation and stroke. J Am Coll Cardiol 2005; 45: 720-721.
34. Lozano HF, Conde CA, Florin T, Lamas GA: Treatment and prevention of atrial fibrillation with nonantiarrhythmic pharmacologic therapy. Heart Rhythm 2005; 2: 1000-1007.
35. Yamagishi S, Takenaka K, Inoue H: Role of insulin-sensitizing property of telmisartan, a commercially available angiotensin II type receptor blocker in preventing the development of atrial fibrillation. Med Hypotheses 2006; 66: 118-120.
36. Daskalopoulou SS, Mikhailidis DP, Elisaf M: Prevention and treatment of the metabolic syndrome. Angiology 2004; 55: 589-612.
37. Conay DS, Lip GYH: Comparison of outcomes of patients with symptomatic peripheral artery disease with and without atrial fibrillation (the West Birmingham Atrial Fibrillation Project). Am J Cardiol 2004; 93: 1422-1425.