Angiotensin converting enzyme inhibitors and angiotensin II receptor blockers in atrial fibrillation

M. J. Levine, P. Schweitzer

Division of Cardiology, Department of Medicine, Beth Israel Medical Center, New York, N. Y., USA

Předneseno na XVII. memoriáli prof. F. Póra u příležitosti 30. výročí jeho smrti dne 12. dubna 2010 v Košicích.

Summary: Atrial fibrillation is the most prevalent clinically relevant arrhythmia; a major cause of morbidity and hospitalization. Additionally, atrial fibrillation carries a significant risk of thrombo-embolic events, specifically cerebrovascular accident. Among the most prevalent risk factors for atrial fibrillation, hypertension not only has the strongest correlation but is also the most prevalent. The renin-angiotensin-aldosterone system represents a prime target for the treatment of hypertension through the use of angiotensin-converting enzymes inhibitors and angiotensin II receptor blockers. In addition to blood pressure control, these medications have been shown to reduce the occurrence of atrial fibrillation. They have been shown to have effects at the cellular level in preventing atrial fibrosis. Additionally, these medications may prevent the development of atrial fibrillation, reduce the duration of atrial fibrillation, and facilitate electrical cardioversion in patients with the arrhythmia. Therefore, patients with, or at risk for atrial fibrillation may benefit from treatment with renin-angiotensin-aldosterone system antagonists; deriving benefits from these medications beyond simple blood pressure control.

Key words: angiotensin-converting enzymes inhibitors – angiotensin II receptor blockers – atrial fibrillation – renin-angiotensin-aldosterone system antagonists – cerebrovascular accident

Inhibitory angiotenzin konvertujícího enzymu a blokátory receptorů pro angiotenzin II v léčbě fibrilace síní

Souhrn: Fibrilace síní je nejčastější klinicky významnou arytmií a významnou příčinou morbidity a hospitalizací. Fibrilace síní je navíc spojena s významným rizikem tromboembolických příhod, obzvláště cerebrovaskulárních. Uvažujeme-li nejběžnější rizikové faktory spojené s fibrilací síní, je hypertenze faktorem, který s fibrilací síní koreluje nejsilněji, a je také rizikovým faktorem nejčastějším. Renin-angiotenzin-aldosteronový systém představuje primární cíl léčby hypertenze za použití inhibitorů angiotenzin-konvertujícího enzymu a blokátorů receptorů pro angiotenzin II. Při použití těchto léčivých přípravků bylo kromě kontroly krevního tlaku prokázáno snížení výskytu fibrilace síní. Tato léčiva jsou na buněčné úrovni účinná v prevenci fibrózy síní. Mohou navíc zabraňovat rozvoji fibrilace síní, zkracovat dobu trvání fibrilace síní a podporovat elektrickou kardioverzi u pacientů s touto arytmií. Pacienti s fibrilací síní nebo s rizikem fibrilace síní proto mohou mít prospěch z léčby antagonisty renin-angiotenzin-aldosteronového systému; tato léčiva jim přinesou terapeutické výhody přesahující prostou kontrolu krevního tlaku.

Klíčová slova: inhibitory angiotenzin-konvertujícího enzymu – blokátory receptorů pro angiotenzin II – fibrilace síní – antagonisté renin-angiotenzin-aldosteronového systému – cerebrovaskulární příhoda

Atrial Fibrillation is the most prevalent clinically relevant arrhythmia. It is estimated that over 2 million people in the United States along with over 4.5 million Europeans carry the diagnosis of atrial fibrillation [1]. Worldwide prevalence is expected to increase as developing countries experience an aging of their populations. The prevalence of atrial fibrillation has a clear relationship to age, rising from 0.1% in patients younger than 50 to almost 10% in those over 80 years old [2]. Atrial fibrillation is associated with significant morbidity and mortality along with substantial economic costs associated with both treatment and complications [1,3]. Previous studies have shown relative equivalency between rate and rhythm control, along with prevention of adverse events; most notably stroke [4]. However, with the prevalence of atrial fibrillation rapidly increasing, a third strategy may be preferable: prevention.

Multiple conditions have been identified as risk factors for the development of atrial fibrillation. First and foremost among these is hypertension [1]. While other conditions including valvular and coronary heart disease, left ventricular hypertrophy, and congestive heart failure are clearly associated with the development of atrial fibrillation, hypertension is the most prevalent risk factor and can be readily treated in most patients [5,6]. Hypertension is not only epidemiologically associated with atrial fibrillation, but has been shown, over time, to effect cardiac remodeling which ultimately leads to atrial fibrillation. Longstanding hypertension can lead to diastolic dysfunction, which in turn causes left atrial dilatation and fibrosis [1]. Left atrial fibrosis and atrial remodeling may lead to heterogeneity in atrial repolarization allowing for the development of atrial fibrillation [7].

Treatment of hypertension has been shown to reduce the incidence of atrial

fibrillation [8–10]. While the relative risk of developing atrial fibrillation related to hypertension is low (RR: 1.4–2.1) [6], the high prevalence of hypertension and the relative ease of treatment make hypertension a prime target for intervention. Control of blood pressure prevents the formation of left ventricular hypertrophy, in turn lowering the incidence of diastolic dysfunction and related left atrial dilatation. This in turn may prevent increased atrial fibrosis and electrical remodeling, an integral component in the development of atrial fibrillation [7].

The renin-angiontensin-aldosterone system (RAAS) has been shown in multiple models to influence the formation of atrial fibrosis through a number of receptors [11,12]. It is known that angiotensin II influences cardiac cell proliferation and growth, along with the formation of fibrous tissues. Alterations in the RAAS cascade as may be seen with hypertension, may lead to the proliferation of fibrous tissues, altering the pattern and timing of atrial repolarization [13,14]. Additionally, high angiotensin II states associated with hypertension may lead to left ventricular hypertrophy which in turn may lead to left atrial dilatation, further raising the risk of atrial fibrillation [15]. Given the role which angiotensin II plays in the development of atrial fibrillation, angiotensin converting enzyme inhibitors which lower serum levels of angiotensin II may reduce the frequency of atrial fibrillation, especially in hypertensive patients.

Several cohort studies have shown an association of RAAS blockade and a reduction both in incidence of atrial fibrillation as well as stroke [16–18]. Until recently, prospective studies evaluating the role of the RAAS blocking medications on the prevalence of atrial fibrillation specifically in hypertensive patients have not be available. The Captopril Prevention Project (CAPPP) enrolled over ten thousand patients comparing conventional therapy with captopril for hypertensive patients. Overall, no significant difference was observed in the primary endpoint of cardiovascular morbidity and mortality. Additionally, there was no difference seen between captopril and conventional therapy in the rate of new onset atrial fibrillation [19]. The Swedish Trial for Old Patients with Hypertension-2 (STOP-2) trial was similar in both design and outcome. In STOP-2, over six thousand patients with hypertension were randomized to one of three arms: calcium channel blockers, ACE inhibitors, or conventional therapy [20]. Patients were followed for up to six years with a primary endpoint of fatal cardiovascular events. The development of atrial fibrillation was as secondary endpoint. Similar to the CAPPP trial, STOP-2 showed no difference in either the primary endpoint, nor a reduction in new onset atrial fibrillation between conventional therapy and therapy with ACE inhibitors [20]. It should be noted that these two trials determined the incidence of atrial fibrillation through adverse event reporting followed by electrocardiogram, rather than through serial electrocardiographic evaluations.

Most recently, the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial examined the effect of an angiotensin receptor blocker on the incidence of atrial fibrillation in hypertensive patients. Prospectively enrolling over fifteen thousand patients, this trial compared valsartan with amlodipine ± additional hypertensive therapies. At a mean follow-up of 4.2 years, there was no difference in the primary endpoint of cardiovascular morbidity or mortality. However, in contrast to the CAPPP and STOP-2 trials, VALUE did show a significant reduction in atrial fibrillation. This included subgroup analysis which showed an absolute overall lower rate of atrial fibrillation with valsartan (3.67%) vs amlodipine (4.34%; $p = 0.0455$). In those patients who developed atrial fibrillation, there was a similar reduction in the absolute rate of persistent atrial fibrillation (1.35% vs 1.97%; $p = 0.0046$) in the valsartan group; however when adjusted for age, and other comorbidities these reductions were not statistically significant [21]. In contrast to CAPPP and STOP-2, VALUE specified the development of atrial fibrillation as a pre-specified endpoint and allowed for serial electrocardiograms to screen for the presence of atrial fibrillation [21].

Similar studies have used post-hoc subgroup analysis to determine the effect of RAAS altering medications on atrial fibrillation. The Losartan Intervention for End Point Reduction (LIFE) study compared losartan with atenolol in patients with both hypertension and left ventricular hypertrophy. The LIFE study showed a statistically significant reduction in the combined endpoint of death, myocardial infarction, or stroke. Additionally, subgroup analysis showed a reduction in new onset atrial fibrillation in those treated with losartan with an occurrence rate of 6.8 per 1 000 person years compared with a rate of 10.1 in atenolol treated patients ($p < 0.001$) [22]. Furthermore, there was significant prolongation of time to occurrence of atrial fibrillation in the losartan group. In contrast, subgroup analysis of the Heart Outcomes Protection Evaluation (HOPE) study compared ramipril to placebo in over nine thousand patients. While this trial did show significant reduction in mortality and cardiovascular endpoints, further analysis did not reveal any reduction in the incidence of atrial fibrillation [23]. The recently published ONTARGET trial comparing telmisartan with ramipril, alone or in combination, in over nine thousand patients also did not show a significant difference in new onset atrial fibrillation across any group [24].

Further evidence for the role of the RAAS blockade in the treatment of atrial fibrillation has come from data collected after electrical cardioversion [25–28]. Several studies have shown

that the use of RAAS modifying medications have the potential to both facilitate successful direct current electrical cardioversion, as well as, prolong the time which sinus rhythm is maintained post procedurally. A large retrospective study [26] recently showed that patients pretreated with ACEIs were more likely to be successfully cardioverted (96% vs 80%; p = 0.04), but were no less likely to remain in NSR at one month follow-up (49% vs 50%; p = NS). Other prospective studies have shown that use of the ARB Irbesartan with amiodarone facilitates the maintenance of sinus rhythm after cardioversion. Madrid et al followed 154 patients in atrial fibrillation for > 7 days through cardioversion and then for an additional 254 days (median) [25]. While there was no difference seen between groups in achievement of NSR (51.9% vs 43.9%; p = NS), those patients treated with the ARB and amiodarone were more likely to remain in sinus rhythm at the end of the 254 day follow up period (83.5% vs 52%; p = 0.0070).

Recent meta-analysis has been performed to clarify these opposing studies. The difference in results suggests that RAAS blockade may be more effective in certain populations. Healey et al [29] examined 11 trials with 56,308 patients evaluating the role of RAAS blockade in atrial fibrillation. ACEIs and ARBs were associated with an overall 28% relative risk reduction in atrial fibrillation (CI 15–40%; p = 0.0002). No significant difference was seen between patients treated with ACEI vs ARB. Those patients with a history of CHF or LVH derived the most benefit from use of RAAS blockade with 44% RR reduction and 29% respectively. Further subgroup analysis did not show a significant relative risk reduction of atrial fibrillation in patients with hypertension alone. Meta-analysis also revealed improved suppression of atrial fibrillation following cardioversion (48% RRR, 95% CI 21–65%). No other group derived significant reduction in atrial fibrillation with RAAS blockade.

Conclusion

Clearly, there is a strong relationship between the rennin-angiotensin-aldosterone system and the development of atrial fibrillation. The effects of these medications through blood pressure control, and also through effects on atrial electrical remodeling allow these medications to alter the course of the disease. These effects result in both pathophysiologic and clinical changes in the natural history of atrial fibrillation, not only through preventing recurrence of atrial fibrillation, but perhaps through prevention of the disorder itself. Multiple studies have shown that patients with high risk comorbidites: hypertension, congestive heart failure, and myocardial infarction, may benefit from these effects not only through direct hemodynamic effects of the RAAS medications, but also through the potential benefit of arrhythmia reduction. However, recent meta-analysis showed risk reduction only for those patients with heart failure and left ventricular hypertrophy. Overall, patients with or at risk for atrial fibrillation may benefit from treatment with renin-angiotensin-aldosterone system antagonists; deriving benefits from these medications beyond simple blood pressure control.

References

1. Fuster V, Rydén L, Cannom D et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation a report of the American College of Cardiology/American Heart Associate task force of practice guidelines and the European Society of Cardiology committee for practice guidelines: developed in collaboration with the European Heart Rhythm Associate then the Heart Rhythm Society. Circulation 2006; 114: 257–354.

2. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370–2375.

3. Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998; 98: 946–952.

4. Wyse DG, Waldo AL, DiMarco JP et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825–1833.

5. Krahn AD, Manfreda J, Tate RB et al. The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Med 1995; 98: 476–484.

6. Kannel WB, Wolf PA, Benjamin EJ et al. Prevalence, incidence, prognosis and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 1998; 82: 2N–9N.

7. Allessie M, Ausma J, Schotten U. Electrical, contractile, and structural remodeling during atrial fibrillation. Cardiovasc Res 2002; 54: 230–246.

8. Healey JS, Connolly SJ. Atrial fibrillation: hypertension as a causative agent, risk factor for complication and potential therapeutic target. Am J Cardiol 2003; 91: 9G–14G.

9. Miyasaka Y, Barnes M, Gersh B et al. Time trends of ischemic stroke incidence and mortality in patients diagnosed with first atrial fibrillation in 1980–2000. Stroke 2005; 36: 2362–2366.

10. Chapman N, Huxley R, Anderson C et al. Effects of a perindopril-based blood pressure-lowering regimen on the risk of recurrent stroke according to stroke subtype and medical history: the PROGRESS trial. Stroke 2004; 35: 116–121.

11. Kumagai K, Nakashima H, Urata H et al. Effects on angiotensin II type 1 receptor antagonist on electrical and structural remodeling in atrial fibrillation. J Am Coll Cardiol 2003; 41: 2197–2204.

12. McEwan PE, Gray GA, Sherry L et al. Differential effects of angiotensin II on cardiac cell proliferation and intramyocardial perivascular fibrosis in vivo. Circulation 1998; 98: 2765–2773.

13. Makkar K, Sanoski CA, Spinler S. Role of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and aldosterone antagonists in the prevention of atrial and ventricular arrhythmias. Pharmacotherapy 2009; 29: 31–48.

14. Garg S, Narula J, Marelli C et al. Role of angiotensin receptor blockers in the prevention and treatment of arrhythmias. Am J Cardiol 2006; 97: 921–925.

15. Neuberger HR, Schotten U, Verheule S et al. Development of a substrate of atrial fibrillation during chronic atrioventricular block in the goat. Circulation 2005; 111: 30–37.

16. Schaer BA, Schneider C, Jick SS et al. Risk for incident atrial fibrillation in pa-

tients who receive antihypertensive drugs: a nested case-control study. Ann Intern Med 2010; 152: 78–84.
17. Verdecchia P, Reboldi G, Gattobigio R et al. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003; 41: 218–223.
18. Heckbert SR, Wiggins KL, Glazer NL et al. Antihypertensive treatment with ACE inhibitors or beta-blockers and risk of incident atrial fibrillation in a general hypertensive population. Am J Hypertens 2009; 22: 538–544.
19. Hansson L, Lindholm L, Niskanen L et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomized trial. Lancet 1999; 353: 611–616.
20. Hansson L, Lindholm L, Ekbom T et al. Randomised trial of old and new hypertensive drugs in elderly patients: cardiovascular morbidity and mortality the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; 354: 1751–1756.
21. Schmieder RE, Kjeldsen SE, Julius S et al. Reduced incidence of new-onset atrial fibrillation with angiotensin II receptor blockade: the VALUE trial. J Hypertension 2008; 26: 403–411.
22. Watchell K, Lehto M, Gerdts E et al. Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the losartan intervention for end point reduction in hypertension (LIFE) study. J Am Coll Cardiol 2005; 45: 712–719.
23. Salehian O, Healey J, Stambler B et al. Impact of ramipril on the incidence of atrial fibrillation: results of the Heart Outcomes Protection Evaluation (HOPE) study. Am Heart J 2007; 154: 448–453.
24. Yusuf S, Teo K, Pogue J et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008; 358: 1547–1559.
25. Ueng KC, Tsai TP, Yu WC et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Eur Heart J 2003; 24: 2090–2098.
26. Madrid AH, Bueno MG, Rebollo JM et al. Use of irbesartan to maintain sinus rhythm in patients with long-lasting persistent atrial fibrillation. Circulation 2002; 106: 331–336.
27. Belluzzi F, Sernesi L, Preti P et al. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. J Am Coll Cardiol 2009; 53: 24–29.
28. Van Noord T, Crijns H, van den Berg M et al. Pretreatment with ACE inhibitors improves acute outcome of electrical cardioversion in patients with persistent atrial fibrillation. BMC Cardiovasc Disord 2005; 5: 3.
29. Healey J, Baranchuk A, Crystal E et al. Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 2005; 45: 1832–1839.

Dr. Michael Levine
www.wehealny.org
e-mail: mlevine@chpnet.org

Doručeno do redakce: 6. 6. 2010