Editorial

http://dx.doi.org/10.4070/kcj.2016.46.3.307
Print ISSN 1738-5520 • On-line ISSN 1738-5555

Korean Circulation Journal

Angiotensin Receptor Blocker for Stroke Prevention in Atrial Fibrillation: beyond Blood Pressure Lowering?

Eue-Keun Choi, MD

Division of Cardiology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea

Refer to the page 335-342

The renin-angiotensin system (RAS) plays an important role in the development of various cardiovascular diseases, including atrial fibrillation (AF). The arrhythmogenic effects of angiotensin II are associated with atrial fibrosis and hypertrophy, uncoupling of gap junctions, impaired calcium regulation, alteration of various ion channels, and activation of mediators of oxidative stress and inflammation.[1] Therefore, blocking the RAS with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) inhibits angiotensin II, results not only in reduced blood pressure, but also antiarrhythmic effects, which reduce the development of AF. There is robust evidence that ACEIs or ARBs reduces the new-onset of AF in patients with significant structural heart disease, such as hypertension with left ventricular (LV) hypertrophy or heart failure with reduced ejection fraction. The Losartan Intervention For Endpoint reduction in a hypertension study, which enrolled hypertensive patients with LV hypertrophy, showed a 33% reduction in the incidence of new-onset AF in the losartan group compared with the atenolol group (6.8 vs. 10.1 per 1000 person-years). Similar results were reported in a recent meta-analysis.[2]

Angiotensin-II induces platelet activation by thromboxane A_2, and increases platelet-free calcium concentration, intracellular pH, and thrombin-induced platelet aggregation.[3] Angiotensin-II can also cause vascular inflammation, which results in a pro-thrombotic condition, especially in hypertensive patients.[4] Considering the pleiotropic effects, it is not surprising that the RAS blockade has additional protective effects on reducing pro-thrombotic events, beyond lowering blood pressure. ARBs are known to have thromboxane A2 receptor–specific antiplatelet effects, which could result in prevention of thrombotic events.[5] ARBs also decrease plasminogen activator inhibitor-1 activity, which may explain its anticoagulant and fibrinolytic properties.[6] However, there is paucity of information regarding the anti-thrombotic effects of ARBs in AF, which is a well-known, high-risk condition for thrombosis.

Choi et al.[7] measured serum levels of tissue inhibitor of matrix metalloproteinase-1, von Willebrand factor, P-selectin, and vascular cell adhesion molecule-1 using enzyme-linked immunosorbent assays at baseline and during AF in a pacing-induced canine model, and compared whether 12 weeks of ARB (candesartan cilexitil 10 mg/kg/day p.o.) treatment had an effect on these biomarkers. They also analyzed and compared the grades of atrial fibrosis between the control and ARB treatment groups. Although they did not find significant differences in the degree of fibrosis or biomarker levels associated with anti-thrombosis between the ARB and control groups, the levels of arterial adhesion molecules and endothelial fibrosis tended to decrease, suggesting the role of ARBs in reverse remodeling in the left atrium and anti-thrombosis in AF.

Choi et al.[7] noted several limitations to their study, such as the small number of animals in each group (n=4), which attenuated the statistical power. Although the reason for the choice of candesartan dosage (10 mg/kg/day) seemed to be based on the maximum tolerable dose that did not reduce the blood pressure, there is a lack of evidence that this dosage is suitable for evaluation of its anti-thrombogenecity. Considering the non-significant change in P-selectin levels following administration of candesartan, it is difficult to find consistency with previous reports on the effect of ARBs on platelet activation.

Received: April 11, 2016
Accepted: April 29, 2016
Correspondence: Eue-Keun Choi, MD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: 82-2-2072-0688, Fax: 82-2-762-9662
E-mail: choiek17@snu.ac.kr

• The author has no financial conflicts of interest.

Although this study did not provide additional information about the role of ARBs in modulating the pro-thrombotic process and endocardial remodeling, future experiments using a large number of animals and biomarkers based on this study may be informative. In addition, the clinical implications of AF would be strengthened by further elucidation of the anti-thrombotic mechanisms of ARBs in AF and finding additional effects of stroke prevention in patients with AF.

References

1. European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-429.
2. Schneider MP, Hua TA, Böhm M, Wachtell K, Kjeldsen SE, Schmieder RE. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. *J Am Coll Cardiol* 2010;55:2299-307.
3. Touyz RM, Schiffrin EL. Effects of angiotensin II and endothelin-1 on platelet aggregation and cytosolic pH and free Ca2+ concentrations in essential hypertension. *Hypertension* 1993;22:853-62.
4. Remková A, Remko M. The role of renin-angiotensin system in prothrombotic state in essential hypertension. *Physiol Res* 2010;59:13-23.
5. Murad JP, Espinosa EV, Ting HJ, Khasawneh FT. Characterization of the in vivo antiplatelet activity of the antihypertensive agent losartan. *J Cardiovasc Pharmacol Ther* 2012;17:308-14.
6. Sakamoto T, Kudoh T, Sakamoto K, Matsui K, Ogawa H. Antithrombotic effects of losartan in patients with hypertension complicated by atrial fibrillation: 4A (Angiotensin II Antagonist of platelet Aggregation in patients with Atrial fibrillation), a pilot study. *Hypertens Res* 2014;37:513-8.
7. Choi JI, Jung JS, Kim MK, et al. Effects of angiotensin-II receptor blocker on inhibition of thrombogenicity in a canine atrial fibrillation model. *Korean Circ J* 2016;46:335-42.