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Editorial

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Renin-Angiotensin System Blockade in Acute Myocardial Infarction: Is There a Winner?

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Inhibition of the renin-angiotensin system (RAS) is known to reduce the overall risk of death and adverse cardiac events in patients with acute myocardial infarction (AMI), with abundant evidence derived from numerous clinical trials.[1] Accordingly, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are considered as a Class I recommendations in current guidelines for the treatment of patients with AMI.[2] The beneficial effect of RAS blockade can be well-explained in the molecular level. RAS blockade may play an important role in inhibiting the development of atherosclerotic plaques by restoring endothelial function, along with antioxidative, antiproliferation, and antihypertensive effects.[3] However, not all RAS blockades, specifically ACE inhibitors and ARBs, have identical effects. ACE inhibitors inhibit the activity of ACE, an essential component of the RAS which converts angiotensin I to angiotensin II and inactivates bradykinin. On the other hand, ARBs directly block the angiotensin II type 1 receptors. Consequently, circulating angiotensin II increases by a negative-feedback, and angiotensin II type 2 receptors are hyper-stimulated, which has been suggested to mediate vasodilation and nitric oxide release.[4] This unique characteristics addressed the biological plausibility of a distinct effect on clinical outcomes, between the two drugs.

The first head-to-head comparison was presented in the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) trial, in which losartan was compared with captopril in high-risk patients with AMI.[5] In more than 5,000 randomized patients, there was no significant difference between the two drugs for death from any cause (p=0.07). In another large randomized trial (VALsartan In Acute myocardial iNfarTion, VALIANT trial), investigators examined the effect of valsartan compared to captopril in patients within 10 days of myocardial infarction (MI).[6] After randomizing over 14,000 patients to ACE inhibitor, ARB, or combination therapy, valsartan was non-inferior to captopril at reducing mortality (hazard ratio [HR], 1.0; p=0.98) These 2 large trials helped RAS blockade to serve as a cornerstone in the medical treatment of AMI, but the following questions still remain;

- Are ACE inhibitors and ARBs really equivalent in patients with AMI? How can we apply the beneficial action mechanism of each drug to clinical outcomes?
- Could there be any sub-populations in which a certain drug would be superior or preferred to the other?

• In the current guideline, ARB is proposed as an alternative to ACE inhibitors particularly those who are intolerant of ACE inhibitors. Should ARB be used only in patients who are intolerable to ACE inhibitor in clinical practice?

Considering these issues, the interest in recent years has focused on meta-analyses or claim-based large observational studies.[7] Without a clear answer, the choice of these alternative treatments will still depend on individual clinical experience, the patient's tolerability, and the potency and cost of the agents.

In this issue of the *Korean Circulation Journal*, Kim et al.[8] investigated the effect of ACE inhibitor and ARB on clinical outcomes after PCI in patients with AMI, from the Korean National Health Insurance Service database between 2005 and 2014. Based on a total population of more than 50,000 patients, the ARB group contained more females, and had more co-morbidities such as old age, hypertension, diabetes, and congestive heart failure, compared to the ACE inhibitor group. Despite the more frequent co-morbidities, ARB usage was associated with a 23% lower risk of major adverse cardiac events (defined as all-cause death, MI, or stroke; HR, 0.774; 95% confidence interval, 0.715–0.838; $p<0.001$) after propensity score-matching. This all-comer based, large scale analysis suggests the possibility that ARB could be superior to ACE inhibitor as long as the drug is consistently taken with the medication possession ratio (MPR) of 80% or higher. Of course, the main findings of this study may be disputable, especially concerning the selection bias, accuracy of the operational definition, and lack of essential laboratory or angiographic findings, as recognized by the authors. Also, it should be noted that even a clear association in real-world data cannot be translated into a direct causal relationship. Still, the authors should give credit that they evaluated this issue in a large scale, real world population with AMI who underwent PCI in Korea.

This paper provides grounds for further investigation into the optimal RAS blockade method for patients with AMI based on unselected, continuous, and long-term follow-up nationwide cohorts. Several critical issues in this field should be certainly elucidated. Concerning the specific RAS blockade agent, there is still concern of the "ARB MI paradox."[9] Another issue is whether the intolerance or discontinuation of RAS blockade due to acute kidney injury, electrolyte imbalance, hypotension with end-organ compromise is an indicator of advanced disease or poor clinical outcome. This is a clinically relevant issue that has been underestimated in most clinical studies. Finally, the focus should now be on the impact of angiotensin receptor neprilysin inhibitor (ARNI) in patients with AMI. Adding neprilysin inhibition to the RAS blockade may have a favorable effect on the coronary system by the hemodynamic effect of circulating natriuretic peptides and the local vasomotor and anti-atherosclerotic actions.[10] The result of PARADISE-AMI (ClinicalTrials.gov Identifier: NCT02924727) will help address this question. This trial will compare sacubitril/valsartan and ramipril in reducing the incidence of the primary composite outcome as cardiovascular death, heart failure hospitalization, and outpatient heart failure in post-AMI patients without prior chronic heart failure.

Current guidelines do not recommend a specific RAS blockade agent that should be preferred in patients with AMI. However, as shown in this study, various studies suggest the possibility the un-equivalence between ARBs and ACE inhibitors. What we can definitely say, is that we still do not have an exact answer whether there is a winner between these 2 agents, despite the deep interest in the clinical field. We look forward to further clinical evidence which will clarify the impact of different RAS blockade agents in patients with AMI.

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