Are Treatment Effects of ACEI and ARB in Post-MI Patients Homogeneous?

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The outcome of patients with acute myocardial infarction (MI) has been substantially improved by the introduction of reperfusion therapy and its continuous refinement. Current reperfusion methodology salvages more than 50% of the ischemic myocardium from infarction in approximately half of acute MI patients without cardiogenic shock. However, in 25% of acute MI patients, myocardial salvage by reperfusion is minimal, leaving the infarct larger than 20% of the ventricular mass. This is the subgroup of patients with large infarcts that particularly needs potent therapy for preventing subsequent heart failure.

Clinical benefits of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) in patients with MI, in terms of prognosis, have been demonstrated by a number of large randomized clinical trials. However, most of the subjects in the positive trials were Caucasian, and ethnic differences in the efficacy of ACEIs or ARBs has not yet been characterized. The pattern of polymorphism of the renin-angiotensin system (RAS) component genes differs among Caucasians, African-Americans, and Asians, and ethnic differences have been demonstrated for blood pressure response to some antihypertensive agents. Thus, the impact of ACEI or ARB therapy may differ according to race and ethnicity.

Evidence of improvement of post-MI prognosis by ACEIs and ARBs in Japanese patients is scant. A cohort study in Japan showed that the hazard ratio for all-cause mortality in patients with ischemic heart failure (n=283) was significantly reduced to 0.497 by ACEI or ARB treatment. In contrast, a larger randomized study, the JAMP study failed to show a significant reduction in cardiovascular events by ACEI. In the JAMP study, 888 patients with acute MI were randomly assigned to an ACEI treatment group or no ACEI treatment group. Survival curves of the 2 groups during a mean follow-up period of 5.8 years were not statistically different, and all-cause mortality was approximately 10% in both groups. Better clinical profiles of the patients, different medications, and different timing of the onset of treatment are possibly involved in the different results of the JAMP study and earlier positive studies (ie, the SAVE, AIRE, TRACE studies). Nevertheless, the results of the JAMP study indicate that the effect of ACEIs on prognosis after MI depends on the patient’s characteristics.

If there is an ethnic difference in the efficacy of ACEIs and ARBs for protecting post-MI patients from cardiovascular death, a similar difference would be detectable in the effects of these agents on post-MI ventricular remodeling, a surrogate marker of prognosis in heart failure patients. Unfortunately, this issue has not been examined in a large number of patients with different ethnic backgrounds. For Japanese patients, only a few small clinical studies have been carried out to assess the clinical benefit of ACEI therapy using placebo-treated controls. A phase III trial of enalapril in which 144 Japanese patients with chronic heart failure were recruited showed that this ACEI significantly reduced the left ventricular diameter and increased the left ventricular ejection fraction during a 12-week follow-up period. Two studies focusing on post-MI patients also showed that enalapril significantly suppressed dilatation of the left ventricle and improved contractile function after acute MI, compared with placebo or no treatment. These findings support the use of enalapril (and possibly other ACEIs) as a positive control in Japanese patients as well. The results of the T-VENTURE study published in this issue of the Journal, suggest that valsartan has beneficial effects, comparable to those of ACEIs, on ventricular remodeling after acute MI in Japanese. However, whether the benefit of valsartan or an ACEI is comparable with that reported for Caucasians remains unclear.

In the light of the negative results of the JAMP study, the beneficial effects of valsartan shown by the T-VENTURE study may not be directly translatable to improved mortality by valsartan treatment of Japanese patients with acute MI. However, it is notable that the effects of ACEIs and ARBs on cardiovascular events have not been consistent in large clinical trials that did not restrict the subjects to those with MI. Significant reduction of atherosclerotic cardiovascular events by an ACEI or ARB has been shown in the HOPE, EUROPA and JIKEI HEART studies, but not in the PEACE, JMIC-B and VALUE studies. A single demographic factor (including racial/ethnic difference), the entry criteria or the protocol of treatment cannot explain these discrepancies.

A simplistic approach to explain the discrepancies in the results of trials of the effects of ACEIs and ARBs on cardiovascular events is consideration of the level of RAS activation, which determines the magnitude of the response to these agents. A number of factors are known to determine the level of RAS activation: renal perfusion and activation of the sympathetic nervous system, which modulates renin...
release, and the level of expression of ACE, AT1 receptor and other RAS components, which are regulated by genetic and non-genetic mechanisms. Obviously, the severity of heart failure is a major determinant of RAS activation after MI, and ACEIs or ARBs consistently reduce the recurrence of acute MI in studies in which heart failure patients were recruited (SAVE, CHARM, JIKEI HEART), though their protective effects were not consistent in patients without overt heart failure (HOPE and EUROPA vs PEACE, JIMIC-B and VALUE). In addition, the level of low-density lipoprotein-cholesterol (LDL-C) is an important but not widely recognized determinant of the level of RAS activation.\(^5\,6\) LDL-C positively regulates expression of the AT1 receptor,\(^6\,7\) and its functional significance is indicated by the finding that the blood pressure response to angiotensin II infusion positively correlates with the plasma LDL-C level in the range of 40–160 mg/dl.\(^8\) Furthermore, suppression of carotid intimal thickening by ACEI treatment alone has been observed in hypercholesterolemic subjects (PHYLLIS Study), but not consistently in studies in which subjects were normocholesterolemic. These observations suggest that patients with more severe heart failure and/or higher LDL-C level would receive a greater benefit from ACEI or ARB therapy. Nevertheless, it is not surprising that the effects of ACEIs and ARBs on prognosis are heterogeneous, even in patients with a high atherosclerotic risk profile.

Another question that has remained unanswered is whether the protective effect of valsartan shown in the T-VENTURE study is a class effect of ARBs. In an earlier study by Onodera et al, losartan was less effective than enalapril for suppressing ventricular enlargement and dysfunction after acute MI in Japanese patients (n=203).\(^9\) In contrast, Suzuki et al earlier reported that protective effects of candesartan against ventricular remodeling were more potent than those of ACEI treatment (lisinopril, enalapril or trandolapril) in Japanese MI patients (n=157).\(^10\) The number of patients in those 2 trials and the T-VENTURE study was not large, different ACEIs were used in the ACEI arms of the 2 studies by Suzuki et al.,\(^9\) and the doses of ARBs and ACEIs were not matched for their effects on the RAS. Furthermore, "significant" inter-group differences in left ventricular dimensions and ejection fractions were actually small in terms of the absolute values. Thus, it is difficult to draw a clear conclusion regarding the superiority (or inferiority) of ARBs to ACEIs as a class of agents for prevention of post-MI remodeling in Japanese patients.

In summary, the T-VENTURE study showed that suppression of post-infarct ventricular remodeling by ACEIs can be mimicked by valsartan, an agent with better tolerability. This is certainly good news, but the impact of ARB and ACEI therapies on hard endpoints in Japanese (and other Asians) remains unclear. Post-MI patients are heterogeneous in terms of the level of RAS activation, as well as in their responses to ACEIs and ARBs. Clarification of such heterogeneity would make it possible to finely tune therapy using RAS inhibitory agents in patients with coronary artery disease.

**References**