

ACE-Inhibitors in High Vascular Risk: From Experimental Medicine to Clinical Trials

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The Renin-Angiotensin System (RAS) is a complex regulatory system with many identifiable actions. It may primarily be viewed as a powerful regulatory system for the conservation of salt, blood volume and Blood Pressure (BP) [1]. However, an increased activity of the RAS, especially in combination with other cardiovascular (CV) risk factors, may lead to a cascade of deleterious effects.

Many of these pathophysiological actions is played by Angiotensin II (Figure 1, left panel) which stimulates atherosclerosis by triggering basic reactions leading to growth, inflammation, instability and rupture of atherosclerotic plaques, facilitation of thrombosis, and ultimately increasing the risk of major vascular events [1].

Furthermore, in the presence of conditions predisposing to hypertrophy, hyperplasia, and tissue remodeling, such as hypertension, atherosclerosis, diabetes, and others, even a normal activity of the RAS may result in inadequately elevated and may thus cause a further progression of the disease [2,3].

Epidemiologic observational studies performed by measuring the levels of activity of the system support the concept that an enhanced activity of the RAS may be associated with higher risk of CV accidents. Further extensive evidence supporting this pathogenetic role of the RAS derives also from studies performed in high-risk populations [4,5]. In this context, inhibition of the RAS with angiotensin-converting enzyme inhibitors (ACE-Is) has been shown to lower BP effectively, and to attenuate the deleterious effects of Angiotensin II [1].

ACE-Is competitively block the action of ACE and thus the conversion of Angiotensin I to Angiotensin II, thereby reducing circulating and local levels of Angiotensin II [1]. This mechanism translates into beneficial actions in the processes of ventricular hypertrophy in hypertension, or vascular hypertrophy or hyperplasia in atherosclerosis and hypertension, or cardiac remodeling in Heart Failure (HF), or structural and functional abnormalities in the kidney in chronic renal failure [5-7].

In addition, the benefits of ACE-Is as standard treatment for high-risk patients with vascular disease and initially free of congestive HF have been proved beyond any reasonable doubt by some clinical trials [8]. The first of these studies, the Heart Outcomes Protection Evaluation (HOPE) trial [9], clearly demonstrated a beneficial effect of ACE-Is in patients at high risk of vascular disease because of Coronary Artery Disease (CAD), previous stroke, peripheral arterial disease or complicated diabetes. In these patients, ramipril significantly prevented CV death, stroke, Myocardial Infarction (MI), HF and diabetic microvascular complications including nephropathy. In addition, it reduced the need for angioplasty and bypass surgery [9].

Similarly, the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) [10] analyzed the prognostic impact of perindopril in over 10,000 patients with CAD. It showed that the addition of the ACE-I perindopril to standard therapy significantly reduced the composite end point of CV

death, MI, and cardiac arrest [10].

In the Survival and Ventricular Enlargement (SAVE) [11] and Studies of Left Ventricular Dysfunction (SOLVD) [12,13] trials, the long-term administration of ACE-Is therapy in MI patients with HF was associated with a significant reduction in the incidence of mortality and morbidity from CV events.

Conversely, in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial [14], the addition of trandolapril to standard therapy failed to provide any benefit in terms of death from CV causes, MI, or coronary revascularization (primary end-point). None of the examined subgroups had benefit from ACE-I therapy. This trial targeted patients with known CAD and ejection fraction equal to or greater than 40% and it was specifically conceived to extend to a lower risk population the observations emerged in the HOPE [9] study. Since a large proportion (>60%) of patients in the PEACE trial [14] were concomitantly treated with modern lipid-lowering, antiplatelet drugs and beta-blockers, it has been suggested that ACE-Is may fail to provide additional protection on top of modern CV preventive strategy.

Although conflicting results were generated exploring the impact of ACE inhibition therapy in CAD patients without HF [14,15], some recent meta-analyses suggested that ACE-Is should continue to be used in all patients with features of high vascular risk, even in a context of modern and intensive preventive strategies [4,15-17]. In this context, a pooled analysis of clinical trials from our group investigated the benefit of ACE-Is in patients at high vascular risk [4].

We used a relative (relative risk, RR) and an absolute effect measure (risk difference) for the evaluation of the benefit associated to ACE-Is. We calculated RRs and 95% confidence intervals (CIs) for all-cause death for each trial separately and for combination of studies according to random-effects model. A stratified analysis was also conducted for (a) trials which enrolled patients with vascular disease and HF and (b) trials which enrolled patients with vascular disease who did not have overt HF.

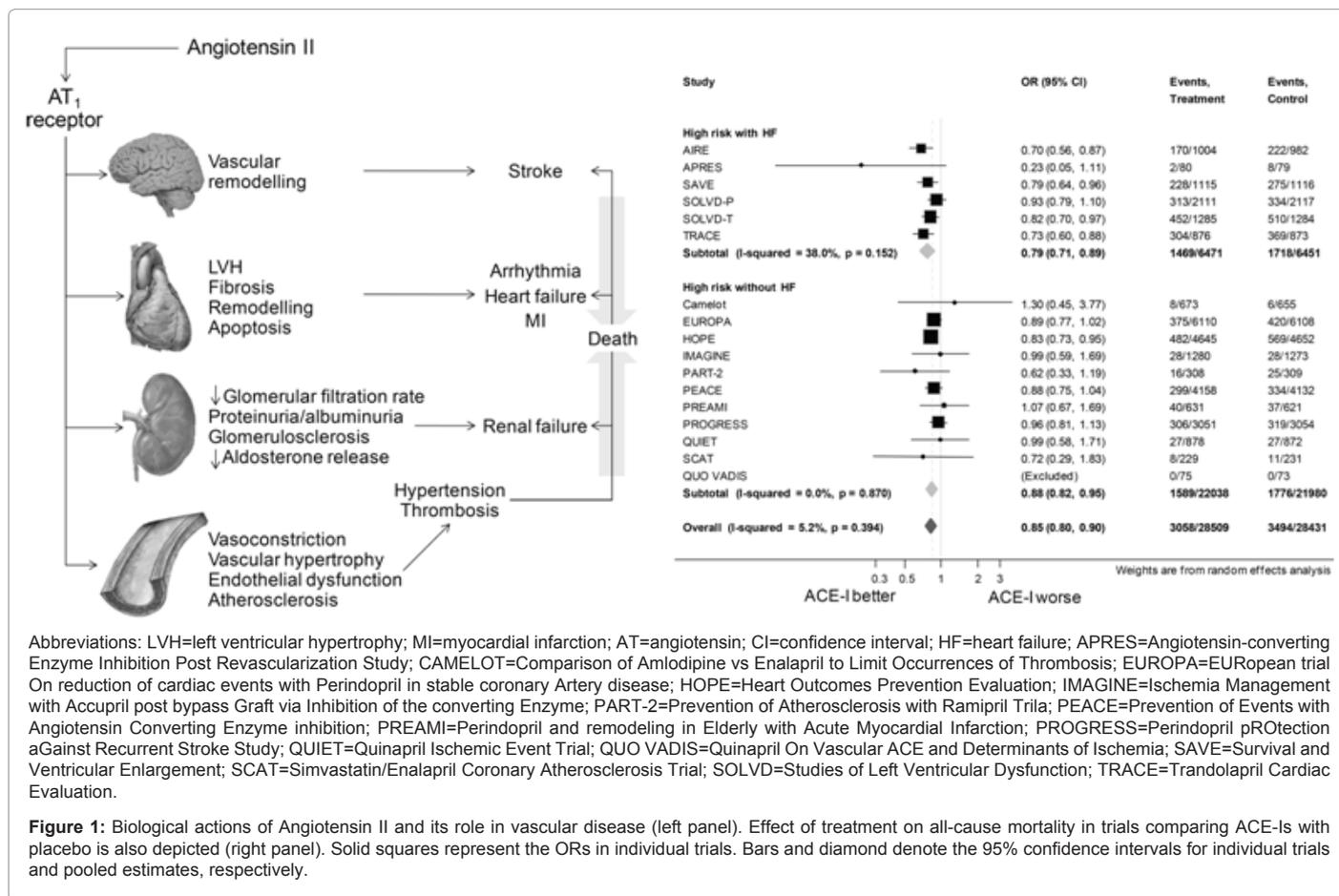
Overall, treatment with ACE-Is was associated with a significantly lower risk of all-cause mortality (RR 0.87, 95% CI: 0.83-0.91,

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Received August 29, 2013; **Accepted** August 29, 2013; **Published** September 04, 2013

Citation: Angeli F, Reboldi G, Poltronieri C, Verdecchia P (2013) ACE-Inhibitors in High Vascular Risk: From Experimental Medicine to Clinical Trials. *Cardiol Pharmacol* 2: e117. doi:[10.4172/2329-6607.1000e117](https://doi.org/10.4172/2329-6607.1000e117)

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$p < 0.0001$) compared to placebo and there was no evidence of statistical heterogeneity among the trials. Notably, ACE-Is were associated with a significant benefit in both patients with and without overt HF. In terms of absolute risk difference, ACE-Is showed a significant 4% reduction in all-cause mortality ($p < 0.0010$) and 1% ($p = 0.014$) in patients with or without HF, respectively.

Similar results are obtained using odds ratio (OR) as affect measure. Figure 1 (right panel) depicts the risk for all-cause death for each trial separately and for combination of studies. Overall, the use of ACE-Is confers a significant risk reduction of 15% (OR 0.85, 95% CI: 0.80-0.90; $p < 0.0001$). This effect was consistent in the two subgroups of clinical trials defined by the absence (OR 0.88, 95% CI: 0.82-0.95; $p = 0.001$) or presence (OR 0.79, 95% CI: 0.71-0.89; $p < 0.0001$) of overt HF at baseline. Notably, no heterogeneity was noted across trials ($I^2 = 5.2\%$, $p = 0.394$).

In conclusion, the RAS is an important contributor to the pathogenesis of CV disease and its modulation by ACE-Is improve outcomes in some conditions including hypertension, diabetes and atherosclerotic disease [5,18]. Moreover, available evidences from experimental models and clinical trials strongly suggest that ACE-Is should continue to be largely used in all patients with features of high vascular risk with or without left ventricular systolic dysfunction [4].

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