The prevalence of coronary artery disease (CAD) has increased over several decades. With increased awareness, early diagnosis and improved non-invasive and invasive modalities, the population has significantly grown. Patients present with varying degrees of pathology, from stable angina to myocardial infarction and cardiogenic shock. As a result, some patients may develop left ventricular dysfunction and subsequent heart failure, whereas others may avoid this complication. Heart failure patients have received increased attention given their acuity, the need for repeated hospitalizations due to recurrent decompensations, increasing healthcare costs and subsequent poor quality of life. With increased data, evidence based medications have proven to reduce mortality and re-hospitalizations in patients with heart failure, with less hospital admissions and shorter stays as well as improved quality of life.

Multiple randomized trials have shown the symptomatic improvement, reduction in hospitalizations as well as improved mortality, with the use of renin-angiotensin system inhibitors (RASI) in heart failure patients (1-4). Most marked and proven benefit is in patients with reduced left ventricular function. Subsequently, RASI became part of the 2013 American College of Cardiology/American Heart Association guidelines (5), the 2010 Heart Failure Society of America guidelines (6), and the 2012 European Society of Cardiology task force guidelines (7). Yet in patients with a left ventricular ejection fraction (LVEF) of >40% or not in clinical heart failure, many studies have demonstrated no benefit with RASI.

In this context, Bangalore and colleagues describe their meta-analysis to evaluate the efficacy of RASi in patients with CAD without heart failure, compared with active controls or placebo. They included 24 trials, involving 61,961 patients, who were followed up to an average of 3.2 years. Trials comparing angiotensin converting enzyme inhibitors to angiotensin receptor blockers, were excluded. Patients included had an LVEF ≥40% or without clinical heart failure, and with at least one year of follow up. Standard primary outcomes including all-cause mortality, cardiovascular death, myocardial infarction, stroke, angina pectoris and heart failure were included. Secondary outcomes included revascularization, incident diabetes and drug withdrawal due to adverse effects. Eighteen trials compared RASi to placebo and 7 trials had an active control including calcium channel blockers, thiazide diuretic and conventional treatment. RASi reduced the risk of all-cause mortality when compared with placebo (RR: 0.84; 95% confidence interval (CI): 0.72 to 0.98) but not when compared with active controls (RR: 1.05; 95% CI: 0.94 to 1.17; P=0.006). Similarly, RASi reduced the risk of cardiovascular mortality when compared with placebo (RR: 0.74; 95% CI: 0.59 to 0.94) but not when compared with active controls (RR: 1.08; 95% CI: 0.93 to 1.25; P=0.001). The study concluded that although RASi reduced the risk of cardiovascular events (including all-cause mortality) when compared with placebo, no such benefit was seen when compared with active controls. In addition, in patients with stable CAD without heart failure, the current body of evidence from randomized trials shows a significant benefit of RASi for the reduction of cardiovascular events and all-
cause mortality only in comparison with placebo but not with active controls. This benefit seen against placebo was mainly in trials with high baseline characteristics in the control population.

Importantly, this meta-analysis evaluated trials with an LVEF of ≥40% and without chronic kidney disease. There is solid evidence supporting the benefit of RASi in a population with reduced LVEF and/or chronic kidney disease, as seen in the SAVE (8) and SOLVD (2) trials. Across the different trials included in the meta-analysis, patients were enrolled based on either an actual LVEF measurement or the presence or absence of clinical heart failure in other trials. The authors pointed towards the benefits of RASi with the “blood pressure independent effect” given the fact that mean systolic blood pressures in the trial patients upon entry was less than 140 mmHg. It is also important to note that different RASi agents have different tissue properties and activities at the level of the vasculature (9), and so efficacy may differ.

The idea of masked hypertension cannot be ignored as this has been studied, and has shown that a quarter of the normotensive-in-the-office-patients can have this entity (10). It is plausible that when comparing RASi to placebo, the benefit was seen due to undiagnosed/masked hypertension treatment with the RASi group. Likewise when comparing RASi to controls like amlodipine or hydrochlorothiazide, the failure to show such benefit was due to the antihypertensive effect of the control medications.

The authors stated the results of the meta-analysis were similar to that of other negative trials like QUIET, CAMELOT, PEACE and IMAGINE trials. However, within the trials quoted, the methods non-inclusive of timing of randomization, dosage and follow up need to be taken into context for the utilization of this data in making recommendations. In QUIET (The Quinapril Ischemic Event Trial), the investigators utilized a 20 mg dose of enalapril, which was believed to be too low of a dose to have a significant endothelial effect, especially when compared to the TREND (Trial on Reversing Endothelial Dysfunction) study with a higher dose that showed improved endothelial reactivity. In addition, a follow up 3 years may have been too short to show a greater benefit. For example, in HOPE (Heart Outcomes Prevention Evaluation) investigators utilized high doses of ramipril, showed a significant reduction in ischemic events in patients with known vascular disease and/or diabetes mellitus, in the presence of preserved LVEF but only after a longer follow up. In CAMELOT (Comparison of Amlodipine vs. Enalapril to Limit Occurrences of Thrombosis), in the subset of enalapril vs. placebo, there was a reduction in cardiovascular events. In CAMELOT’s enalapril vs. amlodipine arm, the primary endpoint was reduced in the amlodipine arm, though only hospitalization rates for angina was statistically significant. In PEACE (Prevention of Events with Angiotensin-Converting Enzyme Inhibition), the control population received intensive current standard therapy, including revascularization and lipid lowering agents, with lower rates of cardiovascular events, when compared to the placebo groups in HOPE or EUROPA (EUropean Trial on Reduction Of Cardiac Events With Perindopril in Stable CAD). Also, the IMAGINE (Ischemia Management with Accupril Post Bypass Graft via Inhibition of Angiotensin Converting Enzyme) trial had a short time between surgery and randomization to the use of ACEI (angiotensin converting enzyme inhibitors) or placebo, which have potentially led to the demonstration of a lack of benefit in the ACEI arm. In contrast, within HOPE and EUROPA, the time between CABG (coronary artery bypass grafting) and randomization to drug vs. placebo was much longer, which subsequently showed a relative risk reduction in post CABG patients treated with ACEI.

So where do we go from here? How should one management change? It appears that patients with established CAD with no clinical heart failure and/or no reduced LVEF have a signal towards benefitting from RASi. RASi use has shown benefit with increasing comorbidities in CAD patients, especially with chronic kidney disease, hypertension and diabetes mellitus. The authors’ culmination of data suggests the use of RASi has unclear utility in patients with stable CAD and preserved LVEF. However, with the present data, RASi use in high-risk population should be considered in the individualized treatment of patients with CAD.

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None.

Footnote

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