Drug Therapy and Heart Failure Prevention

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There are at least 5 million people in the United States living with chronic heart failure (CHF) today. Approximately 550,000 new cases of heart failure are identified in this country each year. In addition, there are tens of millions more people living with one or more risk factors for the development of heart failure, including coronary artery disease, hypertension, dyslipidemia, obesity, and diabetes, and these numbers are presently on the rise. Clinical research conducted over the last decade has focused primarily on enhancing treatment options for patients with known left ventricular (LV) dysfunction, with or without heart failure symptoms. Thanks to the treatments identified by such studies as Studies of Left Ventricular Dysfunction (SOLVD), Randomized Aldactone Evaluation Study (RALES), The Cardiac Insufficiency Bisoprolol Study II (CIBIS II), Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF), Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS), and many others, the risk of morbidity and mortality after heart failure diagnosis has been substantially lowered, provided that patients with CHF are actually treated with inhibitors of the renin-angiotensin-aldosterone system and β-blockers. In contrast, very little is known about what interventions can be utilized to improve and/or prolong the lives of the much larger and broader group of patients mentioned above, who are at risk of developing left ventricular dysfunction and CHF. Aside from appropriately treating prevailing conditions, what else, if anything, can be done to impact the future health status of these at-risk patients?

The first trial to prospectively examine this question was the Heart Outcomes Prevention Evaluation Study (HOPE). The HOPE study randomized a total of 9297 patients who were aged ≥55 years and at high risk of morbidity and mortality due to cardiovascular causes. Eligible subjects were required to have a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus one additional risk factor (hypertension, hypercholesterolemia, low HDL, smoking, or microalbuminuria). Patients were excluded from participation if they had preexisting heart failure or a known left ventricular ejection fraction of <0.40, if they were already prescribed an angiotensin converting enzyme (ACE) inhibitor, had uncontrolled hypertension or overt nephropathy, or had experienced a myocardial infarction (MI) or stroke within four weeks of study entry. Qualifying subjects were randomly assigned to 10 mg of ramipril per day or matching placebo. Mean duration of follow-up was scheduled for 5 years; however, the Data and Safety Monitoring Board halted the study early due to efficacy. The primary outcome in HOPE was a composite of MI, stroke, and death from cardiovascular causes. Secondary outcomes included death from any cause, the need for revascularization, hospitalization for unstable angina or heart failure, and diabetes complications. Other outcomes of interest were worsening angina, heart failure, and the development of diabetes.

Previously reported data from HOPE demonstrated a significant beneficial effect of ramipril on the occurrence of cardiovascular events in high-risk patients. With regard to the primary outcome, ramipril was found to reduce the combined risk of cardiovascular death, MI, and stroke by 22%. When each component was analyzed separately, the benefit remained, as evidenced by a reduction in the rate of cardiovascular death of 26%, a reduction in MI of 20%, and a reduction in the occurrence of stroke of 32%. In addition, all-cause mortality was reduced by 16%. Ramipril treatment was also associated with a reduced risk of cardiac arrest, coronary revascularization procedures, new and worsening angina, diabetic nephropathy (among diabetics), and onset of diabetes among those without a previous diagnosis.

The most recent findings from the HOPE study are described by Arnold and colleagues in this issue of Circulation. Here, the authors report that any heart failure (defined as death due to heart failure, heart failure hospitalization, the initiation of open-label ACE inhibitor for heart failure, or development of clinical signs and symptoms of heart failure) occurred in a total of 951 patients from the HOPE cohort over the term of follow-up, and the development of heart failure was associated with a 4-fold increase in mortality. The major thrust of the current publication is the discovery that treatment with ramipril significantly reduced the rate of developing heart failure in this high-risk group by 23%. Moreover, this benefit was apparent in subjects who did or did not have an MI during the study, and the treatment effects were consistent across all other relevant subgroups. Although the development of heart failure was mentioned as an end point of interest in the original HOPE protocol, it should be noted that the definition of heart failure, as given by Arnold et al., was a post-hoc construction. The first two components of this combined end point, death due to heart failure and CHF hospitalizations, were independently adjudicated by a blinded End Point Committee; however, progression to open-label ACE inhibitor, which comprised the majority of the events (~60%), was not adjudicated, and was not established as a
contributor to the heart failure end point in the original protocol. Hospitalization for heart failure, which was a predefined secondary outcome, constituted $\approx 30\%$ of the events in the combined end point, with heart failure deaths and development of signs and symptoms accounting for $10\%$. Obviously, progression to open-label ACE inhibitor is a much “softer” end point than death or hospitalization, and its occurrence could be due to factors other than development of heart failure. Therefore, the results presented by Arnold et al., although still encouraging, should be viewed with some caution.

Just as with the primary outcome data from HOPE, there is some uncertainty about the mechanism of the observed treatment effect for prevention of heart failure. The ramipril-assigned group in HOPE was previously reported to have experienced an average $3.3$ mm Hg decrease in systolic blood pressure and a $1.4$ mm Hg drop in diastolic blood pressure over the course of the study, as compared with placebo. In addition, Arnold et al discloses in this most recent analysis that a significant interaction was observed between baseline systolic pressure and treatment group with regard to the prevention of heart failure. More specifically, ramipril reduced the heart failure end point in subjects with a baseline systolic pressure $\geq$ the median ($139$ mm Hg) by $33\%$, as compared with only $9\%$ in the subjects whose baseline systolic pressure was below the median. Unarguably, there are well-substantiated cardiovascular benefits associated with the reduction of blood pressure in hypertensive and other high-risk individuals. However, on the basis of the information currently available, is it fair to conclude that the favorable action of ramipril observed in HOPE is simply a result of blood pressure reduction alone?

Given this small change in blood pressure and the large effect size of ramipril for reduction in the heart failure end point, it is likely that the treatment effects observed by Arnold et al are not explained by blood-pressure lowering alone. Activation of the renin-angiotensin system is now broadly recognized as a critical contributor to the pathogenesis and progression of a variety of cardiovascular diseases, including hypertension, coronary artery disease, and heart failure. Angiotensin II (Ang II) is a powerful vasoconstrictor of coronary and systemic vessels, as well as a potent mitogen. In addition, Ang II is believed to play a role in endothelial dysfunction and atherogenesis, and is capable of activating other hormonal and neurohormonal systems, which can, in turn, promote further damage to the cardiovascular system. By attenuating the action of Ang II, ACE inhibitors have been shown to reduce left ventricular preload and afterload, reduce LV mass, reduce systemic blood pressure, and decrease adrenergic stimulation. Moreover, as evidenced by a recently published substudy of HOPE, the direct antihypertensive effects of ACE inhibitors appear very promising. The benefits of ACE-inhibitor therapy for patients with left ventricular dysfunction and heart failure are also well-recognized. Taken together with the results of the HOPE Study, these data support the ideas that ACE inhibitors exert a measurable cardiovascular-protective effect in a broad range of patients at high-risk of cardiovascular complications, and these effects are additional to and independent of blood-pressure lowering.

Given the known role of neurohormonal activation in cardiovascular disease, the usefulness of other drug therapies to prolong the onset of heart failure in high-risk patients requires further study. $\beta$-blockers have been demonstrated to reduce heart failure in patients with uncontrolled hypertension or left ventricular dysfunction post-MI, and retard progression of heart failure in patients with a preexisting diagnosis. The effectiveness of $\beta$-blockade in preventing heart failure in high-risk subjects, such as those enrolled in HOPE, has yet to be examined. Similarly, angiotensin receptor blockers (ARBs) have only recently been evaluated in the setting of chronic heart failure. However, several trials have been planned to investigate the efficacy of ARBs in broader high-risk patient populations that more closely resemble that of HOPE. For example, the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study will compare the ARB valsartan to the calcium-channel blocker amlodipine in $>14,000$ patients to reduce cardiovascular morbidity and death in subjects with treated hypertension and one or more risk factors. Similarly, the planned Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) study will randomize $>23,000$ patients into 3 arms: telmisartan alone, ramipril alone, or telmisartan and ramipril in combination. The enrollment criteria for ONTARGET will be very similar to those described in HOPE, and the primary end point will be a composite of cardiovascular death, MI, stroke, and hospitalization for heart failure. All heart failure will be examined as a predefined secondary outcome. The results of these large, randomized studies will undoubtedly shed additional light on the HOPE data, and further delineate the impact of therapeutic interventions on the prevention of heart failure, and other cardiovascular outcomes, in high-risk patients.

Despite recent achievements in the treatment of CHF after diagnosis, mortality remains high ($\approx 50\%$ after 5 years), and direct costs incurred in the United States alone to manage heart failure patients exceed tens of billions of dollars each year. Given the progressively aging US population, the overwhelming clinical and economic burden of heart failure is only anticipated to increase in the coming decades. Therefore, the drug development challenge for the future is not only to continue to identify new therapies to combat established heart failure, but also to focus significant efforts on the discovery of novel strategies to inhibit the progression of predisposing conditions.

References


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