Improvements in clinical outcomes with the use of angiotensin-converting enzyme inhibitors: cross-fertilization between clinical and basic investigation

Marc A. Pfeffer\textsuperscript{1} and Edward D. Frohlich\textsuperscript{2}

\textsuperscript{1}Cardiovascular Division, Brigham and Women’s Hospital, Boston, Massachusetts; and
\textsuperscript{2}Alton Ochsner Distinguished Scientist, Ochsner Clinic Foundation, New Orleans, Louisiana

Pfeffer, Marc A., and Edward D. Frohlich. Improvements in clinical outcomes with the use of angiotensin-converting enzyme inhibitors: cross-fertilization between clinical and basic investigation. \textit{Am J Physiol Heart Circ Physiol} 291: H2021–H2025, 2006. First published July 7, 2006; doi:10.1152/ajpheart.00647.2006.—The expanding clinical indications for the use of angiotensin-converting enzyme (ACE) inhibitors during the past three decades to reduce cardiovascular morbidity and mortality across a broad spectrum of cardiovascular diseases have been the consequence of impressively productive interchanges between basic science and clinical medicine. In some areas, the initial discovery from animal investigations produced the hypotheses that were confirmed and expanded in patients with specific disease processes. In the development of ACE inhibitors, there are also important examples where an unexpected discovery from clinical trials spurred a host of laboratory investigations that uncovered novel mechanisms to underpin the clinical observations. Although developed as an antihypertensive agent, these effective interchanges, termed “translational research,” have collectively produced convincing data to demonstrate that ACE inhibitors can and should be used to slow progression of renal disease, prevent and treat heart failure, attenuate adverse left ventricular remodeling after myocardial infarction and improve prognosis, reduce atherosclerotic complications in patients with coronary artery disease, and, even more recently, reduce the incidence of Type II diabetes.

ACE inhibitors, from the humble beginning in the sixties as bradykinin potentiating factors and carboxypeptidase inhibitors, certainly have grown in importance.—Erdös (17)

Pharmacological inhibition of angiotensin-converting enzyme (ACE), or known by its other action and name kininase II, has indeed come from humble beginnings as a potential means of lowering blood pressure in a select group with high renin hypertension to become one of the most widely used medications to reduce cardiovascular morbidity and mortality. The three-decade journey to its present stature provides several vivid examples of critical interplays between basic science and clinical medicine. This remarkable cross-fertilization between disciplines has continued to uncover new mechanisms of action for ACE inhibition and bradykinin augmentation that support the expanding clinical indications for the use of ACE inhibitors. In some instances, observations from clinical trials have spurred basic investigators to uncover novel pathways that may account for new clinical benefits of ACE inhibition. Conversely, there are other equally important examples whereby the initial discoveries from animal studies led directly to hypotheses testing in clinical trials that confirmed new important actions of these agents. In many respects, this international effort to better understand and to employ this major pharmacological tool can be best described as a nonvicious, productive cycle. This review will focus on the clinical achievements of ACE inhibition, highlighting the productive interplay between clinical and basic investigations. Indeed, this story, spanning these many years, provides what is eventually termed “translational research.”

Ondetti, Rubin, and Cushman (35) used what has been described as rational drug synthesis to develop specific inhibitors of ACE. The first clinically available orally active ACE inhibitor captopril was initially considered as a niche antihypertensive agent to be used only in those patients with refractory hypertension resulting from high circulating plasma renin activity. It soon became apparent that profiling angiotensin levels, although predictive of short-term response to acute ACE inhibition, was not very useful for selecting patients for long-term therapy (52). Indeed, the effectiveness of ACE inhibitors when administered chronically to lower arterial blood pressure and reduced structural alterations in the heart and vasculature of spontaneously hypertensive rats (not generally considered a model for high renin hypertension) (37), bolstered the clinical experiences demonstrating that prolonged inhibition of this enzyme could achieve clinical benefits well beyond arterial pressure control even in the absence of overt hyperactivity of the renin-angiotensin system (54). Decades ago, few would have predicted that this class of pharmacological compounds would develop into some of the best-studied hypertensive agents.

As clinical experience expanded, with over one million patients having been treated for hypertension, ACE inhibitors became accepted as one of several well-tolerated and effective...
first-line antihypertensive agents (9, 54). It is somewhat ironic that despite proven survival benefits in several cardiovascular disorders, when used as an antihypertensive agent, demonstration of distinctive differences in their ability to reduce cardiovascular complications of hypertension has been said to be no better than with other classes of blood pressure-lowering therapies (53).

RENEAL PROTECTION

Whereas clinical trials in hypertension were justified in claims that underscored the importance of blood pressure control rather than the initial class of antihypertensive therapy employed to control pressure (11, 51), experimental animal studies were generating convincing data that the unique structural and functional benefits of short- and long-term ACE inhibition therapy extended far beyond what could be anticipated from blood pressure control (22, 23). Utilizing rat models of reduced renal mass and injury, Brenner and colleagues (4) demonstrated that renal disease should be considered a progressive disorder perpetuated by hyperfiltration and glomerular capillary hypertension, producing structural alterations in the remaining functional nephrons that contributed to further impairments in renal function. Although systemic hypertension exacerbates nephrosclerosis, laboratory studies utilizing microcure techniques demonstrated that ACE inhibitors had unique renal-protective properties not exhibited by other antihypertensive agents (4, 23). When compared with other antihypertensive agents, the ACE inhibitors, by producing a more favorable balance between afferent and efferent glomerular arteriolar vasoconstriction, were far more protective of glomerular hemodynamics and conferred greater preservation of glomerular architecture. In these seminal animal studies, these hemodynamic and structural actions translated into less proteinuria and a slower decline in renal function (4, 23).

These decisive experimental observations were promptly tested in major clinical trials of patients at risk for renal deterioration. The Collaborative Study Group, led by Lewis (32), first demonstrated in adults with juvenile diabetes and overt proteinuria that randomization of therapy to captopril reduced the number of patients that either experienced a doubling of their serum creatinine concentration or required dialysis therapy. This major advance in forestalling renal failure in patients with Type I diabetes was soon followed by other randomized controlled trials such as the Ramipril Efficacy and Nephropathy (REIN), which also demonstrated the benefits of an ACE inhibitor independent of blood pressure control in reducing proteinuria and limiting the decline of glomerular filtration rate (42). In the African-American Study of Kidney disease (AASK) (2), the clinical benefits of the ACE inhibitor ramipril in reducing the deterioration of renal function and indeed progression to dialysis were found to be independent of blood pressure lowering produced by either a calcium antagonist or a β-adrenergic receptor blocker. Similar beneficial findings in patients with Type II diabetes with proteinuria, utilizing angiotensin-receptor blockers (ARBs), has made these inhibitors of the renin-angiotensin system key therapeutic components in the care of patients with diabetes or chronic kidney disease (8, 33).

Still more recently, a meta-analytic study extended the forgoing findings to non diabetic hypertensive patients (28).

HEART FAILURE

The Vasodilator Heart Failure Trial (V-HeFT), led by Cohn (12), was the first trial that demonstrated survival of patients with heart failure could be improved by medical therapy. Thus the combination of hydralazine and isordil was found to be superior to placebo or prazosin in improving survival even though arterial pressure reduction was greater with prazosin. Despite this dissociation in blood pressure lowering, the functional and survival benefits in this pioneering trial were at the time generally attributed to afterload reduction. The appreciation that ACE inhibitors could also be utilized as vasodilators, resulting in short-term improvements in hemodynamics when administered judiciously to patients with heart failure (16, 24), paved the way for subsequent clinical outcomes trials. The first direct test of whether an ACE inhibitor would prolong survival in patients with heart failure came from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) (14). This study of exceedingly high-risk patients was discontinued prematurely by its Data Safety Monitoring Committee once a definitive reduction in risk of death became apparent in patients randomized to the ACE inhibitor enalapril. Subsequently, the Studies of Left Ventricular Dysfunction (SOLVD) program demonstrated the clinical importance of inhibiting the renin-angiotensin system with an ACE inhibitor in a much larger and broader population of patients with severe heart failure (45, 46). With reductions in risk of death and hospitalizations for heart failure established across a large range of patients with heart failure by the early 1990s, ACE inhibitors became the established “cornerstone therapy” for this disorder (6). V-HeFT II (13) directly compared two previously proven agents, hydralazine-isordil (from the original V-HeFT) versus enalapril (found effective in CONSENSUS and SOLVD) in patients with symptomatic heart failure. The demonstration in V-HeFT II that enalapril was even more effective in prolonging survival than the combination of hydralazine and isordil solidified the clinical importance of ACE inhibition and conceptually moved the field from vasodilatation to neurohumoral inhibition.

MYOCARDIAL INFARCTION-REMODELING

The next major clinical advance was again pioneered in the experimental laboratory of the late Janice Pfeffer. Her studies demonstrated that ACE inhibitors attenuated the structural alterations in left ventricular cavity size and shape resulting from experimental myocardial infarction (36). This attenuation in ventricular remodeling was also associated with improved ventricular performance and prolonged survival compared with untreated animals with comparable infarct sizes (36, 40). Small mechanistic studies in patients confirmed the animal studies and demonstrated progressive ventricular enlargement while patients recovered from myocardial infarction and that ACE inhibitors reduced this time-dependent process, now termed ventricular remodeling (39, 44). These proof-of-concept clinical studies were confirmed by eight major independent randomized controlled clinical outcomes trials with ACE inhibitors in patients after acute myocardial infarction (19, 31).

The Survival and Ventricular Enlargement (SAVE) trial was the first of a series of several international, randomized, placebo-controlled trials that demonstrated significant reductions in the risk of death, development of heart failure, and subsequent myocardial infarction using an ACE inhibitor in patients
with a myocardial infarction (38). A mechanistic substudy conducted to test the hypothesis that the beneficial actions of the ACE inhibitor captopril attenuated left ventricular remodeling and a sufficient number of patients developing adverse cardiovascular events, thereby providing the important linkages between alterations in cardiac structure and risk of cardiovascular death, heart failure, and high-grade arrhythmias (48, 47). Each of the subsequent major randomized controlled clinical studies, which selected acute myocardial infarction patients at higher risk, were based on either clinical signs or symptoms [Acute Infarction Ramipril Evaluation (AIRE)], echocardiographic wall motion abnormalities [Trandolapril Cardiac Evaluation (TRACE)], or electrocardiographic location [Survival of Myocardial Infarction Long-Term Evaluation (SMILE)] and demonstrated important improvements in clinical outcomes (including survival) utilizing different ACE inhibitors (1, 3, 29).

Concurrently, other investigative groups employed an even broader approach of assessing the clinical utility of an ACE inhibitor after acute myocardial infarction and were more inclusive by not requiring symptoms or direct measures of left ventricular dysfunction. Thus the Third Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardio (GISSI-3), the Fourth International Study of Infarct Survival (ISIS-4), and the Chinese Cardiac Study Collaborative Group and the second CONSENSUS study (10, 20, 27, 49) were each major randomized, placebo-controlled trials that initiated an ACE inhibitor in a broad population of patients within the first day of an acute myocardial infarction. Except for CONSENSUS, which gave its initial dose intravenously, all trials with oral ACE inhibitors demonstrated small but statistically significant improvements in short-term survival by using an ACE inhibitor. Based on these large randomized-controlled trials, the consensus derived from international guidelines and, indeed, performance measures demonstrating that ACE inhibitors are a key component in the management acute myocardial infarction (5, 34).

MODIFICATION OF ATHEROSCLEROSIS

Although the initial thrust for testing ACE inhibitors in myocardial infarction patients was derived from animal studies, a key novel observation from these clinical trials provided the impetus for more basic and clinical investigations that probed the many interfaces between angiotensin and atherosclerosis. From both the SAVE and SOLVD trials, the risk of experiencing a myocardial infarction was reduced significantly in patients randomized to their respective ACE inhibitor (43, 47, 56). These findings indicated that ANG II had a prominent role in the pathogenesis of atherosclerosis and plaque destabilization. In animal models of atherosclerosis, the multiple mechanisms involved have incriminated angiotensin as a factor that augmented atherosclerotic burden and promotes plaque fissures (15, 18, 26, 50). Together, these clinical observations and experimental mechanistic findings provided support for the hypothesis that ACE inhibitors could be used to reduce atherosclerotic complications in patients with vascular disease beyond their already proven role in the management of those with heart failure, left ventricular dysfunction, acute myocardial infarction, or renal disease.

Three international trials were specifically designed and conducted to test the hypothesis that the inhibition of the renin-angiotensin system with an ACE inhibitor in patients with vascular disease but without overt heart failure would reduce the risk of major atherosclerotic events. In the Heart Outcomes Prevention Evaluation (HOPE) Study, randomization to the ACE inhibitor ramipril of high-risk patients with vascular disease or diabetes who were not known to have a low ejection fraction resulted in a clear reduction in risk of death attributed to cardiovascular etiologies, nonfatal myocardial infarction, and strokes (57). Similarly, in the European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA), randomization to the ACE inhibitor perindopril resulted in a reduced risk of their primary outcome of cardiovascular death, nonfatal myocardial infarction, or experiencing a cardiac arrest (21). These benefits were incremental to other proven therapies, and the magnitude was approximately a 20% reduction in adverse cardiovascular events.

The most recently completed of these trials, the Prevention of Events with Angiotensin Converting Enzyme inhibitors (PEACE) trial did not, however, demonstrate a comparable reduction in cardiovascular events in those randomized to the ACE inhibitor (6). Although there are several possible explanations, the PEACE investigators hypothesized that the overall low event rate in their population receiving intensive background therapies (blood pressure control, lipid lowering, antiplatelet and coronary revascularization procedures) reduced the potential to demonstrate incremental prognostic improvements with the addition of an ACE inhibitor. Despite the findings from PEACE, the therapeutic value of use of ACE inhibitors to reduce atherosclerotic complications remains firmly established (41).

DEVELOPMENT OF DIABETES

The HOPE trial has provided yet another key clinical observation that was confirmed in the PEACE trial: fewer patients treated with an ACE inhibitor subsequently developed diabetes mellitus (55). This important finding from clinical trials once again fueled a host of recent mechanistic studies (30), as well as an ongoing multinational randomized trial (25) designed to understand better how inhibiting the renin-angiotensin system could lower the incidence of diabetes. This nonvicious cycle whereby clinical trials uncover new data, which in turn, lead to more mechanistic studies, further expanding our understanding of pharmacology and therapeutic benefits of inhibiting ACE (kininase II), also supports the summary of the field statement by Ervin G. Erdös “…that neither ACE nor its inhibitors have yet become ‘history’ in a negative sense of the usage of this word, and undoubtedly, they will be the subjects of many studies to come” (17). This statement remains prophetic in that after four decades of investigation and extensive use, ACE inhibitors continue to provide new insight to our understanding of disease mechanisms as they are being used to extend survival and reduce disease burden.

ACKNOWLEDGMENTS

We gratefully acknowledge Dr. Ervin G. Erdős, whose pioneering contributions serve as a foundation for exploring biological, physiological, and pathophysiological roles of angiotensin-converting enzyme and the consequences of its inhibition. This paper was presented at a symposium held in his honor on October 21, 2005, at the University of Illinois at Chicago.
REFERENCES


