Prevention of Myocardial Infarction
With ACE Inhibitors

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The “big picture” that faces the World Health Organization (WHO) is dynamic and complex, but is now punctuated by the statistics that include the following: “Cardiovascular diseases (CVDs) are the number one group of conditions causing death globally. An estimated 17.5 million people died from CVDs in 2005, representing 30% of all global deaths. Over 80% of CVD deaths occur in low- and middle-income countries.” This epidemic comes at a time when we have seen sustained major beneficial impact on cardiovascular mortality within the majority of high-income countries. The juxtaposition of these two facts is intellectually stimulating as it is easy to imagine that a creative solution exists for current global health challenges.

While it is clearly recognized that lifestyle choices, habits, and addictions can either protect or induce cardiovascular diseases, methods to induce beneficial behavioral modifications are particularly challenging and time consuming. Legislation against high salt content in foods and smoking in public places are two examples of successful population-based behavioral modifications that have been applied in high-income countries. Widespread availability of good quality healthcare has also affected both populations and individuals. Based on these experiences, the “WHO Global Action Plan for the Prevention and Control of NCDs [noncommunicable diseases] 2013-2020” has identified interventions that are considered to be feasible and will provide the greatest value for limited money. Central among these is the use of evidence-based and affordable drug therapies to prevent stroke and myocardial infarction with associated morbidity and premature mortality.

It should be noted that the WHO strategy makes no distinction between treatment of individuals having or not having known cardiovascular disease. Instead, the focus is on prevention of future stroke or myocardial infarction in those at an elevated risk of...
either a first or a repeat event. The terminology of primary vs secondary prevention is not used as it is indeed not helpful when seeking to target reversible and/or lifetime risk. This focus requires the use of drug therapies with a strong evidence base for effectiveness across a wide clinical spectrum of disease and risk. Of the main contenders for this task, four drug classes have attracted particular interest: (i) β-blockers; (ii) aspirin; (iii) angiotensin-converting enzyme (ACE) inhibitors; and (iv) statins. Aspirin and β-blocker use, prior to the development of overt cardiovascular disease, is not supported by individual trials, meta-analyses, or guidelines. To the contrary, ACE inhibitor use has an established place in the management of hypertension (particularly in the presence of diabetes and/or renal dysfunction), and statins have a place in the management of hypercholesterolemia (particularly in the presence of hypertension or diabetes). In both cases, the evidence base has been interpreted in a manner that advocates the outdated concept of a drug "class-effect." In the case of ACE inhibitors, this simplistic approach has grouped ACE inhibitors and angiotensin II type 1 receptor blockers in a single, but wider category.

Desmond Fitzgerald and Alistair S. Hall each focus our attention on the fascinating story of the discovery of ACE inhibitors from within the deadly venom of a snake. It has been suggested that the international symbol for medicine and the World Health Organization depicts a dead snake (symbolic of death) nailed to a pole as an example of “death defeated.” This is indeed the most central objective of global efforts to preserve health—namely the prevention of premature death. In this context, the ACE inhibitor story is particularly informative and inspirational.

Clinical cardiologists have a visceral understanding of the value of preventing myocardial infarction, although most of the younger colleagues will not have practiced medicine prior to the advent of routine ACE inhibitor use. Alistair S. Hall tells the story leading up to the standard use of ACE inhibition for the secondary prevention of myocardial infarction. This article provides a concise and readable overview written by an active participant in this period of discovery and development. Current guideline recommenda-
tions are summarized and highlighted with emphasis given to the practical recommendation that clinicians, healthcare providers, and policy makers seek to apply the main trials in the evidence base, as much as is possible, with regard to drug, dose, and frequency of dose.

Peter S. Sever brings insights from his own significant involvement in discovering the value of ACE inhibition in the treatment of hypertension. He highlights differential mechanisms of action and diverse effects on major cardiovascular risk factors, and the mechanisms of the different classes of antihypertensive agents, particularly when used in evidence-based combinations. Karl Swedberg reviews the ability of ACE inhibition to reduce cardiovascular death and myocardial infarction in patients with heart failure from the perspective of clinicians, researchers, and most notably pioneers. Having been the first to demonstrate, in humans, the ability of ACE inhibitors to prevent death, he concludes that treatment with an ACE inhibitor in chronic systolic heart failure has markedly changed the treatment of this condition and improved mortality and morbidity. Martin H. Strauss has had a long interest in the paradoxical effects of ACE inhibitors and angiotensin II type 1 receptor blockers with regard to prevention of death and myocardial infarction. He proposes that there is ample evidence to distinguish ACE inhibitors and ARBs into unique therapeutic classes with divergent effects on mortality and myocardial infarction.

Few stories in the history of medical research are able to interest and inspire as much as the mythical journey from “poison to panacea.” The ACE inhibitor class has multiple pharmacologically unique members with a common surname “pril.” Evidence (or, more commonly, the absence of it) further suggests that distinction also exists between this family and the tribe named “sartan.” Our hope is that this issue of Dialogues will highlight the particular value of effective ACE inhibition in addressing the WHO goal: “to save lives, improve the health and wellbeing of present and future generations and ensure that the human, social, and financial burden of NCDs does not undermine the development gains of past years (WHO 2013).”
ACE inhibition for the secondary prevention of myocardial infarction: a concise overview for clinical cardiologists

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A bite from Bothrops jararaca, a poisonous Brazilian pit viper, causes a drastic drop in blood pressure followed by circulatory collapse. One factor within the venom responsible for lowering blood pressure was isolated and identified to be an angiotensin-converting enzyme inhibitor (ACE). After discovery of drugs able to inhibit ACE, the CONSENSUS I study (COoperative North Scandinavian ENalapril SUrvival Study) was conducted and proved pivotal for the practice of cardiology. Since this study and as a result of many subsequent studies, it has been shown that ACE inhibitors have a demonstrated efficacy for the prevention of myocardial infarction in the context of primary and secondary prevention. Specifically, this has been shown for patients with coronary artery disease and additional increased risk denoted by the occurrence of ST-segment–elevation myocardial infarction (STEMI), non-STEMI, or the concomitant presence of diabetes mellitus, chronic kidney disease, hypertension, or heart failure. Furthermore, the treatment of these selected patients is supported in both US and European Guidelines, by expert opinion and multiple persuasive clinical trials. It is also considered a reasonable action to prescribe ACE inhibitors to all patients with high-risk coronary artery disease unless there is a specific contraindication.

The CONSENSUS I study (COoperative North Scandinavian ENalapril SUrvival Study) was a major “game-changer” for the practice of cardiology. Published in the *New England Journal of Medicine* in 1987, this study gave both hope and belief: hope that patients with severe heart failure (New York Heart Association [NYHA] IV with breathlessness at rest on standard therapies) could be treated with a medicine able to impact significantly the natural history of the disease (Figure 1, page 156) and belief that a new class of medicine had finally arrived. Research, until this time, had moved from patients with hypertension to those with heart failure based on the observed hemodynamic effects of these drugs. Then, a new appreciation of an alternate mode of action started to emerge, namely the ability to prevent myocardial infarction (MI).

**RENIN RENAISSANCE AND BEYOND**

The history of the angiotensin-converting enzyme (ACE) inhibitor drug class is further characterized by its dramatic origins—the poisonous venom of the Brazilian pit viper *Bothrops jararaca*. Also, ACE inhibitors had their origins in the pioneering work of a series of renaissance clinician scientists. In 1897, Robert Tigerstedt of the Karolinska Institute ground up the kidneys of rabbits and isolated an extract (renin) that caused high blood pressure to shoot up. This was followed by a “dark age” of uncertainty. In 1934, Harry Goldblatt suspected that constriction of a single kidney artery in experimental dogs (he was reluctant to constrict both as he thought it would kill the dog) triggered excess production of a humoral substance (renin), which he observed caused high blood pressure.

By 1940, Eduardo Braun-Menéndez (Buenos Aires, Argentina) and Irvine Page (Indianapolis, USA) had independently demonstrated that a large circulating protein
(angiotensinogen) was enzymatically cleaved to a much smaller peptide chain (angiotensin).\(^5\) In 1956, biochemist Leonard Skeggs Jr and his colleagues seeking to isolate this peptide found that two isolated substances raised blood pressure.\(^8\) They postulated a two-step process with renin acting at the first step. The second step was thought to result from a different enzyme, which they called the hypertension-converting enzyme and then later the angiotensin-converting enzyme.\(^9,10\) In 1960, James Davis and colleagues observed that the kidneys produced a blood-borne substance, which ultimately triggered the adrenals to release aldosterone, a salt and water-retaining hormone.\(^11\) Angiotensin II (Ang II) was subsequently shown to induce this effect,\(^12\) and the reflex renin-angiotensin-aldosterone-system (RAAS) was now complete.

Throughout the 5 million years of man’s evolution, water-borne infections have caused more deaths than any other single factor. These infections affect first the gastrointestinal system, which leads to a major loss of salt and water from the body that, in turn, results in organ hypoperfusion and death. Furthermore, ancestral location to the hot climate of Africa will have created significant physiological stress related to the hot temperature and scarcity of dietary salt far from the sea. Also in response to acute blood loss, the RAAS represents a clear life saver\(^{13}\) in certain situations, though also a potential maladaptive mechanism in modern life, particularly in some ethnic groups.\(^{14}\)

**BRAZIL TO BRITAIN**

A drastic drop in blood pressure with circulatory collapse follows the bite of the Brazilian pit viper, *Bothrops jararaca*. Seeking to understand why this was true, Silva and Ferreira took extracts of the venom and injected them into dogs and guinea pigs.\(^{2,15}\) To further advance these studies, Ferreira travelled to London to work in the lab of the pharmacologist Sir John Vane who was performing studies on the effects of Ang I, Ang II, and ACE.\(^{16}\) In 1970, this group demonstrated that extracts of the snake venom inhibited the ability of ACE to generate angiotensin II.\(^{17}\)

**POISON TO PILL**

Encouraged by Vane, the pharmaceutical company Squibb sought to advance these studies in the hope of developing a new method of blood pressure reduction. David Cushman and Miguel Ondetti sought to identify, purify, and test the ACE-inhibiting factor within the snake venom.\(^{18}\) A synthetic version of the substance was injected by Vane into human volunteers, inhibiting the conversion of angiotensin I to angiotensin II.\(^{19}\) Hypertension specialist John Laragh then injected it into two of his patients with particularly resistant high blood pressure and observed dramatic clinical effectiveness.\(^{20}\) As anticipated by the Squibb management, it proved impossible to develop an orally active agent, so the research ceased...almost. In May 1973, a paper appeared in the journal *Biochemistry* regarding the structure of carboxypeptidase A, a small molecule inhibitor
of the pancreatic digestive enzyme. This came to the attention of Cushman, who had previously observed the highly similar structure between ACE and carboxypeptidase A. The orally active drug, later known as captopril was discovered by modifying the small molecule inhibiting carboxypeptidase A.18

RATS, REMODELING, AND RANDOMIZATION

Mark Pfeffer is well known for the many randomized controlled trials he has led, but one stands out as being particularly innovative. Working together with his wife (Janice Pfeffer), the impact of the ACE inhibitor captopril on the process of left ventricular remodeling following MI was investigated22-24 This took the form of a randomized comparison, which developed into a survival study. The study group was interesting (6 rats could not be assessed fully due to postmortem cannibalization) and the findings were powerful. Risk of death was increased with the size of the MI and was reduced significantly by captopril therapy (Figure 2). This extended confidence in the potential benefits of this drug class in the context of MI and heart failure. Early clinical trials in humans had already demonstrated both the potential for intolerance and for benefit in patients with heart failure.25 Also, with the development of the nonsulfhydryl ACE inhibitor enalapril, the stage was now set for the CONSENSUS I study.

MORE ON MECHANISM

In 1986, the reported annual mortality for patients with moderate and end-stage heart failure was 50%.26 This was further emphasized in the placebo arm of the CONSENSUS I study (Figure 1). However, 10-year follow-up data confirmed that after an average of 6 months of randomized therapy (placebo or enalapril) the average survival time was extended from 521 days to 781 days, an average extension of life of 260 days (8.5 months).27 Two key challenges from these data are to determine: (i) by what therapeutic mechanism(s) is...
death being delayed, and (ii) if benefit can be gained from the much earlier use of ACE inhibitors. In response to the first challenge, a review of the mode of death implicated an attenuated progression of the clinical heart failure syndrome as the area of major impact. However, this could not distinguish between incremental MI and more gradual myocardial dysfunction with deterioration of hemodynamic performance. Clinically, it appeared that both mechanisms were important and influenced, in part, by the presence or absence of a coronary atheroma as a confounding or etiological factor in patients with heart failure.

To address both challenges regarding possible benefits from earlier use of ACE inhibitors and alternate mechanisms of benefit, additional trials were performed. The SOLVD trial (Studies Of Left Ventricular Dysfunction) on enalapril in symptomatic and asymptomatic left ventricular systolic dysfunction observed an anticipated benefit of survival and reduced heart failure admissions, but also an unexpected benefit from ACE inhibitors. The SOLVD investigators had excluded patients with unstable angina or recent MI because of the concern that an acute reduction in blood pressure due to enalapril would reduce coronary perfusion pressure and, therefore, extend or induce a MI. They gathered data on the occurrence of MI during the trial as part of the predetermined safety assessment. Consequently, observed reductions in the occurrence of MI were largely unexpected. Furthermore, posthoc analyses were performed to demonstrate this effect further, which then became a key hypothesis in need of prospective evaluation.

SAVE (1992): DELAYED ORAL ACE INHIBITION

Around the same time, a significant reduction in secondary MI was also suggested as a key mechanism for the survival benefit seen in the SAVE trial (Survival And Ventricular Enlargement) on captopril. This study recruited patients with reduced ejection fractions (<40%) following acute MI at a time when statin therapy was not yet available and when routine use of thrombolytic reperfusion therapy was in its infancy. As observed in experimental rat and dog models, the natural history for most patients with ST-segment-elevation myocardial infarction (STEMI) complicated by left ventricular impairment was the process referred to as adverse ventricular remodeling. This process was characterized by myocardial cell death and subsequent fibrotic repair with compensatory hypertrophy of adjacent healthy myocardium. ACE inhibitors were observed to beneficially attenuate ventricular aneurysm formation, pathological dilatation, and systolic dysfunction. Furthermore, they appeared to reduce the
toxic effects of high Ang II levels mediated directly to noninfarcted myocardial cells and through cardiac strain secondary to increased afterload (peripheral vascular resistance). The observed prevention of clinically detected recurrent MI was once again entirely unexpected, though having been observed, it became the focus of a large amount of interest and discussion.

HYPOTENSION AND HYPERTENSION

It is very important to note that at the time of performance of the SOLVD and SAVE trials, it was anticipated that ACE inhibitors might actually induce MI as a result of hypoperfusion across critical coronary stenoses. This effect appeared to relate specifically to an increase in MI associated with low diastolic pressure in patients with stenotic coronary artery disease (Figure 3). Subendocardial ischemia and necrosis had been observed as complicating hypotension during anesthesia and for other reasons including MI. In addition, the effect of ACE inhibitors on patients with angina demonstrated a variation in response. Potential mechanisms for this included concern about reduced perfusion beyond critical coronary stenoses as illustrated in animal models. Prevention of MI for patients with reduced systolic function of the left ventricle also challenged prior major concerns founded on the reported J-shaped relationship between excessive blood pressure reduction and major cardiac events. In many ways, this is ironic because subsequent ACE inhibitor trials prospectively designed to assess the impact of ACE inhibitors on MI prevention have been devalued by some commentators on the grounds that reduction in blood pressure is the obvious and only mechanism through which benefit resulted (see later the HOPE trial [Heart Outcomes Prevention Evaluation] and EUROPA trial [EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease] discussion.

In the SAVE study, mean blood pressure measured at 1 year for captopril-treated patients was systolic blood pressure (SBP) 119+18 mm Hg and diastolic blood pressure (DBP) 74+10 mm Hg and for placebo, SBP 125+18 mm Hg and DBP 77+10 mm Hg, a difference that was statistically significant (P<0.001). A similar difference in blood pressure (4 mm Hg) was reported by the SOLVD investigators. Due to an associated reduction in MI, the J-shaped relationship between blood pressure and adverse cardiac events was suddenly eclipsed. In its place, an alternate “lower is better” way of thinking started to emerge based not on the analysis of blood pressure–lowering trials, but on observational epidemiological studies. One meta-analysis proposed that a mean blood pressure reduction of 5 to 6 mm Hg should equate to a 14% reduction in MI. However, the magnitude of reduction in MI that was observed for SOLVD (23%) and SAVE (25%) was both: (i) in stark contrast to the increase in events prospectively predicted by the J-curve data; and (ii) far in excess of that expected to result from blood pressure reduction alone.

CONSENSUS II (1992): ASSESSING IMMEDIATE INTRAVENOUS ACE INHIBITORS

The regular use of thrombolytic therapy following acute STEMI changed the natural history of damage and repair of the heart. The CONSENSUS II study included 6090 patients of whom 3414 (56%) had received thrombolytic therapy. Patients were included if they presented within 24 hours of onset of chest pain in the presence of ST elevation, new pathological Q waves, or an elevation in cardiac enzymes. The majority of patients (66%) had already received β-blocker therapy prior to intravenous administration of either enalaprilat (1 mg over 2 hours) or matching placebo. Infusions were stopped if SBP dropped beneath 90 mm Hg or DBP fell below 60 mm Hg. If blood pressure stabilized, infusions were then restarted at the discretion of the attending physician. Oral enalapril (or placebo) was then introduced twice daily at 2.5 mg (day 2), 5 mg (day 3), 10 mg (day 4), and finally 20 mg (day 5).
This is an important study because the Safety Committee recommended stopping the study early due to a high probability of futility (ie, enalapril would not be superior to placebo) and “concern about a possible adverse effect among elderly patients with early hypotensive reactions.” Overall, there was no statistical difference in mortality (Figure 5). The mortality rate for patients with early hypotension following enalapril was 17% as compared with 9.3% for other patients treated without early hypotension. Early hypotension following placebo was associated with a mortality rate of 12%. All of the excess death occurred in patients >70 years of age at randomization (enalapril 17.3% vs placebo 14.7%) as compared with those <70 years of age (enalapril, 5.6% vs placebo, 5.0%). Reinfarction occurred in 9% of patients with either enalapril (271 of 3044) or placebo (268 of 3056). Consequently, concerns regarding the adverse effects of ACE inhibitors, subsequent to significant early hypotensives, were reinforced. Furthermore, there was significant uncertainty as to the place of ACE inhibitors following MI, particularly in the context of very early use.

**SMILE pilot (1991)**

Ambrosioni et al41 studied early administration of an ACE inhibitor after infarction, giving open-label zofenopril (a sulfhydryl containing the prodrug-ester analogue of captopril) to 103 patients from a group of 204 patients with STEMI in whom thrombolytic treatment was contraindicated. The remaining 101 patients were randomly assigned to receive conventional therapy alone. The main objective was to study the safety of administering an ACE inhibitor early in the natural history of MI, in preparation for a planned mortality investigation—the SMILE study (Survival of Myocardial Infarction Long-Term Evaluation). The authors concluded that “the clinical relevance of such treatment could not be assessed by this pilot study; however, it does offer sufficient evidence of benefit to justify a large scale investigation.”

As a follow-up to this pilot study, 1556 patients were randomized to receive either oral zofenopril (7.5 to 30 mg twice daily) or matching placebo within 24 hours of acute anterior STEMI not treated by thrombolysis because of the presence of specific contraindications.42 Six-week mortality was reduced, though not significantly (placebo group, 8.3%; zofenopril group, 6.5%—a reduction of 22%, P=0.171). However, a significant reduction was observed in the frequency of refractory congestive heart failure (heart failure not controlled by digitalis and diuretics: placebo group, 4.3%; zofenopril group, 2.2%—a reduction of 49%, P=0.018). Combination of the two end points also resulted in a statistically significant benefit (placebo group, 12.4%; zofenopril group, 8.2%—a reduction of 33%, P=0.008).

Open comparison of zofenopril and placebo is continuing to examine mortality after one year of treatment. Although the SMILE study was smaller and statistically less powerful than the CONSENSUS II investigation, the reverse trend toward an improvement in outcome is worthy of comment. Possible differences may relate to the initial oral rather than intravenous administration or the use of a sulfhydryl as opposed to a nonsulfhydryl ACE inhibitor. However, the differences in outcome more probably relate to the selection of patients. CONSENSUS II treated a largely unselected group of patients (index infarction had an anterior location in 41.5% of patients), the majority of whom had received treatment with a thrombolytic agent (53% of all patients). In contrast, no patient selected for inclusion in the SMILE study had been treated with a thrombolytic agent and all had evidence of anterior MI. Such patients would be especially prone to developing infarct expansion and subsequent left ventricular dilatation.

**CATS pilot (1991)**

In contrast with the SMILE study, the CATS (Captopril And Thrombolysis Study) pilot investigation43 opted to select only patients within six hours of the onset of a first anterior acute MI who were eligible to receive thrombolytic therapy. Fifty-seven patients were given...
either 3.0 mg or 6.25 mg captopril orally or no treat-
ment within 30 minutes of the start of a streptokinase
infusion. An earlier “dose finding” study using intra-
venous captopril had shown unacceptable, profound,
and short-lasting episodes of hypotension in all eight
patients investigated. Titrated oral administration was
considered to have an acceptable safety profile and
hence formed the basis of a larger study of 298 patients
in which echocardiography, Holter monitoring, and
neurohumoral measurements were made. Forty-six pa-

tients were randomized to receive either oral captopril
(target dose 75 mg daily) or placebo initiated within
30 minutes of starting thrombolytic therapy. The ob-
erved increases in ventricular volume over three
months were only moderate and not significantly af-
fected by captopril therapy. The CATS investigators
concluded that if captopril does produce any benefit
in the first three months after MI treated by throm-
bolysis, then it is unlikely to be due to prevention of
ventricular remodeling.

**EQUIPOISE-BALANCED UNCERTAINTY**

In the early 1990s, the introduction of routine clinical
use of aspirin and thrombolytic therapy produced a
dramatic change in the “natural history” of acute MI.
This change had not been factored into the design of
the earlier clinical trials that then recruited patients
in this new era. After coronary artery occlusion with or
without reperfusion, the subsequent course of events
involved an interplay between myocardial damage and repair, hemodynamic adaptation, and progression of
coronary atheromatous lesions, with the attendant risk
of thrombus formation and further infarction. Resultant
cardiac dysfunction, ischemia, and arrhythmias were
associated independently and in combination with sub-
sequent adverse risk. It is apparent, therefore, that there
may be many different scenarios after MI in different
patients and with diverse sequelae. The ACE inhibitor
trials of this period were conducted at a time of great
change, clinical heterogeneity, and therapeutic uncer-
tainty. Importantly, this made it entirely ethical for
placebo control to be used in the context of double-
blind, randomized trials that set out to assess impact on
the ultimate clinical end point of all-cause mortality.

**AIRE/AIREX (1993): RESOLVING THE UNCERTAINTY**

The timing of publication, study design, and positive
results of the AIRE study (Acute Infarction Ramipril
Efficacy) went a long way to resolving the considerable
uncertainty that prevailed within the scientific and
clinical community. The SAVE and CONSENSUS I trials
were both reported in 1992 and were notable for hav-

ing conflicting results. The selection of patients, the
timing of treatment initiation, and the duration of fol-

low-up all suggested possible reasons for the divergent
outcomes.

The AIRE study, strongly influenced by the CONSEN-
SUS II study design that focused on the clinical features
of heart failure, sought to identify patients with clini-
cal heart failure. Specifically, this was defined as one
or more of the following: (i) bilateral posttussive crack-
leses extending at least one-third of the way up the lung
fields in the absence of chronic pulmonary disease,
(ii) pulmonary venous congestion with interstitial or
alveolar edema on at least one chest radiograph, or
(iii) auscultatory evidence of a third heart sound with
persistent tachycardia. The SAVE and SOLVD trials
had included patients based on an ejection fraction
<40% and <35%, respectively. To the contrary, AIRE
patients were not required to have a measurement of
ejection fraction. 2006 patients were recruited from
144 centers in 14 countries. Patients were randomly
allocated to double-blind treatment with either place-
bo (992 patients) or ramipril at a target dose of 5 mg
twice daily (1014 patients) on day 3 to day 10 after
acute myocardial infarction (day 1). Patients with se-
vere heart failure resistant to conventional therapy,
where the attending physician considered the use of an
ACE inhibitor to be mandatory, were excluded. Follow-
up was continued for a minimum of 6 months and an
average of 15 months.

On intention-to-treat analysis, all-cause mortality was
significantly lower for patients randomized to receive
ramipril (170 deaths; 17%) than for those randomized
to receive placebo (222 deaths; 23%). The observed
risk reduction [ORR] was 27% with a 95% confidence
interval [CI] of 11%-40% (P=0.002). Analysis of prespec-
ified secondary outcomes revealed a risk reduction of
19% for the first validated outcome (ie, first event in
an individual patient of death, severe/resistant heart
failure, MI, or stroke. 95% CI, 5%-31%, P=0.008). Severe
resistant heart failure (necessitating open label ACE
inhibitor use) was significantly more common in the
placebo group, while stroke (ramipril, 2% vs placebo,
2%) and reinfarction (ramipril, 8% vs placebo, 9%) were
not significantly different.

One key difference between AIRE (also CONSENSUS I)
and both the SAVE and SOLVD trials was the duration
of treatment/follow-up. This would appear to have an
important impact on secondary prevention of MI (see
in this regard, the extended follow-up of AIRE patients within the UK is important. The AIREX study (AIRE EXtension) reported a mean baseline ejection fraction of 43% (measured only in a subset) and observed cause of death differences up to 5 years after randomization. Based on death certificates, secondary MI was less common in ramipril-treated patients (absolute risk reduction [ARR], 6.7%; relative risk reduction [RRR], 37%; 95% CI, 8%-57%). Deaths from causes other than known MI were also less common for patients randomized to ramipril (ARR, 4.7%; RRR, 34%; 95% CI, 1%-56%). Very importantly, the AIRE study was performed on top of standard aspirin, thrombolytic, and β-blocker therapies; and taken with the SAVE results, resolved the uncertainty regarding the value of delayed treatment of selected patients following MI.

**TRACE (1995): A HAT-TRICK OF POSITIVE TRIALS**

As the third in a series of three similar, but independent trials, the TRACE trial (TRAndolapril Cardiac Evaluation) assessed the ACE inhibitor trandolapril at a dose of just 4 mg once daily. Importantly, TRACE also achieved its primary end point of a 22% reduction in all-cause mortality (95% confidence limits [CI], 9%, 33%; P=0.001, Figure 6). The TRACE investigators also completed long-term follow-up during the period after cessation of double-blind, randomized therapy. They were able to measure median extension of life in a number of patient subsets. Among these were patients with prior angina and those with residual (active) angina. Observed absolute treatment-related extensions to life in patients with no prior angina was just 5 months as compared with 28 months for those with angina. Treatment-related extension of life for patients with no residual angina was 13 months as compared with 26 months for those with active angina. These data, together with the generalized long-term mortality benefits, do point to a significant cardioprotective effect of treatment emerging beyond three years.

The molecular structure for trandolapril is virtually identical to that of ramipril (Figure 7) due to a common initial development pathway (pharmaceutical company Hoechst developed both, but kept ramipril and sold trandolapril). However, separate marketing strategies resulted in trandolapril being trialed as a once daily therapy, while ramipril in AIRE was used twice daily.
This is an important consideration to later discussions of differing outcomes for the HOPE trial and PEACE trial (Prevention of Events with Angiotensin-Converting Enzyme inhibition), as the target dose of trandolapril studied may have been suboptimal. This may also explain why the observed reduction in reinfarction in TRACE did not achieve significance despite a median follow-up of 3 years.

**GISSI-3: LARGE, FACTORIAL, AND PRAGMATIC**

Based on the order of publication and the subsequent impact on routine clinical care, the GISSI-3 trial (Gruppo Italiano per lo Studio della Sopravvivenza nell’infarto Miocardico) was the next trial reported.\(^5\) 19 394 patients, presenting within 24 hours of symptom onset and with no clear indications for or against any of the study treatments, were randomly assigned 6 weeks of oral lisinopril (5 mg initial dose and then 10 mg once daily) or open control. The absence of placebo and blinding of this study was justified by the wish to perform a pragmatic study based on intention-to-treat and significant clinical end points (later termed the PROBE design [Prospective Randomized Blinded Endpoints]). The treatment was stopped after just 6 weeks and follow-up continued for 6 months.\(^5\) All-cause mortality was significantly lower at the end of 6 weeks (ARR, 0.8%; Figure 8), but not at 6 months. A combined end point including clinical heart failure and measured left ventricular impairment was better on lisinopril at both time points. Up to 6 months (mostly off treatment), reinfarction was 4.7% for patients randomized to lisinopril and 4.6% for those in the open control group. Once again, the duration of follow-up in this investigation was very short, assessing impact of treatment on initial MI rather than secondary prevention of MI.

**ISIS-4: ALSO LARGE, FACTORIAL, AND PRAGMATIC**

All patients presenting within 24 hours of the onset of suspected acute MI, whether of high or low risk, were considered eligible for the ISIS-4 investigation (Fourth International Study of Infarct Survival), provided that the responsible physician did not think that there was any clear indication for, or contraindication to, the trial therapies (placebo, captopril, nitrate, and magnesium).\(^5\) Patients in both placebo and captopril groups were also given oral nitrate or intravenous magnesium in a random proportion of cases. The combined hypotensive effects of streptokinase, magnesium, captopril, and nitrates (and possibly also a β-adrenoceptor antagonist) in a single individual patient were a matter of concern. The 2×2×2 factorial design of the main ISIS-4 study meant that this particular combination of
active treatments was given to more than 5000 patients. However, adverse effects occurring within this patient subset were masked by primary analyses carried out only for the main strata in the study.

There was a statistically significant 7% RRR in 5-week mortality (7.19% captopril vs 7.69% placebo; \( P = 0.02 \); Figure 9). The absolute benefits appeared to be larger in certain higher risk groups, such as those presenting patients with diabetes), which are frequently underpowered in parent studies. However, like all subgroup analysis, caution should be exercised when interpreting the findings. The “true outcome” for the treatment strategy, as a whole, should be defined with regard to the primary end point outcome for trials individually and then for trials collectively. If a subgroup fails to share an overall benefit, the default consideration should be that the analysis is still underpowered (type II error is likely, i.e., lack of benefit due to inadequate power—false negative). In the event that primary trials and combined primary analysis show no effect, it is incorrect to conclude benefit for a subgroup (type I error is likely, i.e., subgroup benefit occurred by chance—false positive). Meta-analysis cannot exceed the limits of what is reported by primary researchers and based on summary data alone cannot unravel the details of study population heterogeneity.

It is a better approach to a meta-analysis to use “patient level data” as compared with “trial level data.” That means that all the detail from every patient is used (by combining trial databases) in the analysis as compared with the summary of average observations reported in papers. Individual trial quality is also important, particularly the use of double blinding to avoid subjective systematic errors influencing results. The following three analyses for ACE inhibitors have been conducted through direct involvement of lead investigators for each trial, using patient level data. They are also based on independently persuasive/replicating studies.

**META-ANALYSIS AND MYOCARDIAL INFARCTION: PART I**

**Delayed selective use of ACE inhibitors**

A patient-level meta-analysis of the SAVE, AIRE, and TRACE trials has been performed to assess the ability of ACE inhibitor-therapy to prevent death, stroke, heart failure, and recurrent MI. The setting was secondary prevention as all patients had at least one prior MI. This was also in the context of low ejection fraction (SAVE study, <40%; TRACE study, <35%) or clinically
acute left ventricular failure (AIRE study). The rate of MI prior to study randomization for SAVE, AIRE, and TRACE was 35%, 23%, and 36%, respectively. The rate of angina prior to study randomization for SAVE, AIRE, and TRACE was 26%, 36%, and 46%, respectively. Nevertheless, patients included in this analysis were all initiated on ACE-inhibitor therapy only in the days following an index MI. Summary benefits on the occurrence of recurrent MI was a significant 20% relative risk reduction (95% CI, 6%, 31%; \( P = 0.005 \); Figure 10). In absolute terms, this was a 3% reduction (number needed to treat [NNT] to prevent one event=33; Table I) independent of baseline ejection fraction. Importantly, this was for a study duration averaging 3 years (ie, 1% absolute risk reduction for recurrent MI per year of treatment).

This meta-analysis also considered data from the SOLVD trials, which observed a 22% relative risk reduction (95% CI, 8%-35%, \( P = 0.004 \)). The combination of these two sets of studies demonstrated a significant 21% benefit (95% CI, 11%-30%, \( P = 0.0001 \)). Furthermore, sensitivity analyses that excluded individual studies and considered alternate definitions for reinfarction had no impact on these results. The consideration of reinfarction in combination with death (given the possibility of missing/underestimating fatal MI events) also had no impact on the findings. The impact of ACE inhibition in patients with different degrees of impairment of left ventricular ejection fraction also demonstrated no heterogeneity of effect inclusive of patients with a relatively preserved ejection fraction. Nevertheless, patients with the most significant degree of systolic heart failure (ejection fraction [EF] <23%) also had a large beneficial effect, which would be expected to have prevented further worsening of heart failure. However, this analysis did not address the issue of the mechanism of benefit, though it should be noted that there was no apparent impact on stroke prevention. This would point toward a blood pressure–independent effect of ACE inhibition in the prevention of MI. Readmission with worsening heart failure was significantly impacted in all studies, perhaps at least, in part, due to the reduction in secondary MI. Both of these mechanisms also affected all-cause mortality reduction as was seen in each study alone and in combination.

<table>
<thead>
<tr>
<th>Duration</th>
<th>HOPE 59 months</th>
<th>ONTARGET 56 months</th>
<th>PRoFESS 30 months</th>
<th>TRANSCEND 56 months</th>
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</thead>
<tbody>
<tr>
<td>Total mortality</td>
<td>Placebo 12.2%</td>
<td>Ramipril 10.4%</td>
<td>Telmisartan 11.6%</td>
<td>Placebo 12.3%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Placebo 12.3%</td>
<td>Ramipril 9.9%</td>
<td>Telmisartan 5.2%</td>
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</tbody>
</table>

Table 1. Summary data for HOPE and ONTARGET trials together with PRoFESS and TRANSCEND.

Abbreviations: MI, myocardial infarction; ONTARGET trial, ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; PRoFESS trial, PRevention regimen For Effectively avoiding Second Strokes; TRANSCEND trial, Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease.
META-ANALYSIS AND MYOCARDIAL INFARCTION: PART II

Early nonselective use of ACE inhibitors

Meta-analysis of four trials that assessed initiation of ACE inhibition within the first 24 hours of MI, reported primary outcomes to just 30 days. During this time, there was no evidence to support a reduction in reinfarction (Figure 11). There was evidence of frequent persistent hypotension and an excess in the rate of cardiogenic shock and renal dysfunction (Figure 12). Long-term follow-up data was published for the ISIS-4 and GISSI-3 trials, but not subject to meta-analysis. The reduction in mortality was expressed as “Benefit per 1000” rather than the more traditional absolute percent difference (effectively “Benefit per 100”). Benefits observed (per 1000) for captopril-treated patients was 4.9 (0.49%) at 35 days, 6.6 (0.66%) at 6 months, and 5.4 (0.54%) at 12 months.

ACE INHIBITORS AND STABLE CORONARY ARTERY DISEASE

In the earlier chronological account of the development of ACE inhibitors as a therapeutic option in the treatment of patients following MI, an unexpected, but highly consistent, observation was made. Stated simply, ACE inhibitors prevented recurrent MI in the years following an initial index event. It remained unclear whether such an effect would still be present outside of the context of concomitant left ventricular dysfunction. Specifically, the primary rationale for ACE inhibition had been made through demonstration of the adverse consequences of systemic activation of the renin angiotensin system, which is thought to be me-

Figure 11. Data from a meta-analysis of four trials that assessed ACE inhibitors in the context of clinical heart failure or reduced left ventricular systolic function.

Abbreviations: ACE, angiotensin-converting enzyme; 95% CL, 95% confidence limits; LVEF, left ventricular ejection fraction; NNT, number needed to treat.


Figure 12. Data from a meta-analysis of four trials that assessed initiation of ACE inhibitors within the first 24 hours of MI.

Small benefits occurred in the presence of evidence of frequent persistent hypotension and an excess in the rate of cardiogenic shock and renal dysfunction.

Abbreviations: ACE, angiotensin-converting enzyme; MI, myocardial infarction.

diated through excessive Ang II type 1 receptor (AT₁) activation. However, as basic and clinical researchers continued to study these matters in more detail, it became apparent that local/tissue-based effects of ACE/kininase II inhibition may also be important. This evidence base has been extensively reviewed and debated, but is brought into starkest relief when one considers first the persuasive clinical evidence base for ACE inhibitors and then the very unconvincing evidence base for drugs that selectively antagonize the AT₁ receptor.


Designed to investigate the effects of taking the ACE inhibitor ramipril (target dose 10 mg taken at night) for at least 4 years, on a combined cardiovascular end point of death, MI, or stroke. Patients (9541) were included if they were older than 55 years and at high risk of cardiovascular events due to history of diabetes, previous ischemic heart disease, peripheral vascular disease, or stroke. Ramipril treatment produced consistent benefits across many patient subsets and in the study as a whole ([RR, 0.78; 95% CI, 0.70-0.86; P<0.001]). Importantly, MI was significantly reduced (RR, 0.80; 95% CI, 0.70-0.90; P<0.001) representing the first prospective demonstration of this beneficial effect. At randomization, mean blood pressure was in the normal range of 139/79 mm Hg with a small additional decline occurring during the trial. A substudy evaluated changes in 24-hour blood pressure during the trial and noted that while office blood pressure did not differ between treatment groups, mean 24-hour blood pressure was significantly lower (SBP mean difference, 10 mm Hg; DBP mean difference, 4 mm Hg) as was nighttime blood pressure. Very importantly, this paper makes it clear that “according to the HOPE protocol ramipril was given once daily at bedtime.” This is in contrast to the later ONTARGET trial protocol (ONGing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), which required ramipril to be given in the morning (see later discussion).

In a long-term follow-up study involving 4528 HOPE patients, the rates of ACE inhibitor use were similar in the period after the end of the trial (72% ramipril vs 68% placebo). During this posttrial follow-up period of 2.6 years, ramipril randomization was associated with a lower relative risk of MI (19%), revascularization (16%), and new onset diabetes (34%). All benefits were independent of baseline risk and concomitant treatment. While stroke had been reduced during the blinded treatment period of the trial, no benefit was observed in the posttrial period of observation. This supports a direct impact of even modest blood pressure lowering on stroke and a separate and independent mechanism of benefit concerning prevention of coronary artery disease and occurrence of MI, which is independent of blood pressure.

**EUROPA (2003)**

The EUROPA trial demonstrated that treatment with perindopril reduced the primary end point, ie, combined risk of cardiovascular death, MI, and cardiac arrest, by 20% (P=0.003; Figure 13). As a similar result was observed in people irrespective of blood pressure at the time of entry into the study, or measured blood pressure fall during the study, blood pressure lowering alone could not explain the observed benefits of perindopril.

![Figure 13. Kaplan-Meier mortality curves for patients recruited into the EUROPA trial of oral perindopril vs placebo in patients with known stable coronary artery disease.](image-url)

**Abbreviations:** 95% CI, 95% confidence limits; ARR, absolute risk reduction; EUROPA trial, EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; NNT, number needed to treat; RRR, relative risk reduction.

To evaluate other potential mechanisms of benefit, a substudy PERTINENT (PERindopril Thrombosis, InflammatioN, Endothelial dysfunction, and Neurohormonal activation Trial) evaluated markers of endothelial dysfunction, which predispose the vascular wall to vasoconstriction, vascular inflammation, platelet activation, thrombosis, and atherosclerosis. Human umbilical vein endothelial cells (HUVECs), a type of endothelial cell, were incubated with blood taken from either normal matched controls (n=45), or from
EUROPA patients before and after 1 year of treatment with either perindopril (n=43), or placebo (n=44). Two measures of endothelial dysfunction were then assessed: (i) endothelial cell nitric oxide synthase (eNOS) expression and activity; and (ii) rate of endothelial apoptosis. Patients given perindopril had a significant increase in eNOS activity and a significant reduction in the rate of endothelial apoptosis. Blood levels of Ang II, bradykinin, tumor necrosis factor α (TNF-α), and von Willebrand factor were also assessed. All were significantly decreased by perindopril except for bradykinin, which was significantly increased. Bradykinin levels also correlated closely with eNOS activity. Many of the baseline abnormalities have been independently associated with adverse cardiovascular outcomes. Consequently, beneficial modification markers of inflammation and thrombosis, and demonstration of improved endothelial dysfunction (through mechanisms that are partially dependent on increased bradykinin) suggests antiatherosclerotic effects of perindopril that may, in part, explain the results of EUROPA.

**PEACE (2004)**

The PEACE trial primary publication\(^6\) states that “In February 2002, given the increasing evidence of the benefit of ACE inhibitors or angiotensin receptor blockers in patients with diabetes mellitus and renal disease, the steering committee, without knowledge of the outcome data and with approval from the data and safety monitoring board, advised the investigators to substitute open-label ACE inhibitors for the masked study treatment in patients with diabetes and either overt proteinuria or hypertension and microalbuminuria.” This intervention will have acted to reduce the likelihood of a difference being noted for patients treated with a target dose of trandolapril 4 mg once daily and placebo.

The publication also states “In October 1997, after 1584 patients had undergone randomization, the steering committee (without any knowledge of outcome data from the trial) concluded that recruiting 14 100 patients was not feasible and expanded the primary end point to include coronary revascularization. The sample size was reduced to 8 100 patients, and the original primary end point became a secondary end point.” This enforced intervention will have further jeopardized the trials’ ability to detect a meaningful difference in outcome due to reduced statistical power.

In this context, the following results are not a surprise. The incidence of the primary end point—death from cardiovascular causes, MI, or coronary revascularization—was 21.9% in the trandolapril group, as compared with 22.5% in the placebo group (hazard ratio [HR], 0.96; 95% CI, 0.88, 1.06; \(P=0.43\)) Based on the above considerations, there is doubt regarding the validity of the conclusion that patients with stable coronary heart disease and preserved left ventricular function obtain no benefit from trandolapril 4 mg daily. However, as a similar absence of benefit was seen with regard to MI in both the PEACE and TRACE studies, inadequate dosing with trandolapril (see earlier comments on molecular structure) cannot be excluded as an alternate reason for lack of efficacy.

**META-ANALYSIS AND MYOCARDIAL INFARCTION: PART III**

**Prevention of first and recurrent myocardial infarctions**

A study level meta-analysis of the three randomized double-blind trials of ACE inhibitor use in stable patients with established or likely coronary artery disease demonstrated efficacy in a range of patient subsets. Death was reduced significantly from all causes (HR, 0.86; 95% CI, 0.79, 0.94; \(P=0.0004\)), MI (HR, 0.82; 95% CI, 0.75, 0.91; \(P=0.0001\)), and stroke (HR, 0.77; 95% CI, 0.66, 0.89; \(P=0.0004\)). Heart failure admissions and revascularization by coronary artery bypass graft (CABG) were also significantly reduced.\(^6\) Furthermore, the analysis was extended to include earlier trials (SAVE, AIRE, TRACE, and SOLVD) demonstrating the same magnitude and significance of effect. Benefits were greater in the absence of antplatelet therapy, but also large and significant in their presence. This point addresses prior beliefs regarding a partial shared mechanism of action between ACE inhibitor and aspirin with regard to antplatelet activity. Such an overlap did appear to be present with even greater benefit from ACE inhibitors observed in the absence of aspirin. There were no interactions or shared mechanisms of action seen for concomitant treatment with statins or β-blockers.

**HOPE vs ONTARGET: RAMIPIRIL ALL-CAUSE MORTALITY RATE**

In the same patients studied in the HOPE trial, the ONTARGET trial\(^6\) sought to assess the efficacy of AT\(_1\) receptor antagonist telmisartan as compared with ramipril and in combination with ramipril. None of these three treatment options was shown to be superior to any of the others. What was noted was that patients treated with ramipril for an average of 56 months had
a mortality of 11.8% compared with a slightly lower mortality of 10.4% for the same selection of patients when treated with ramipril 8 years earlier in the HOPE study. Of note, the reverse would be expected to be true given the changes in concomitant therapy in the time between the two studies (eg, statin use in HOPE, 28.6%, in ONTARGET, 61.5%, and prior percutaneous coronary intervention (PCI) in HOPE, 18%, in ONTARGET, 30%). One notable difference between the two trials is that HOPE gave a target of 10 mg ramipril at night and ONTARGET 10 mg of ramipril in the morning. Given that cardiovascular events have their greatest incidence first thing in the morning, this may have been a critical difference in design and one that makes any claim of noninferiority for telmisartan vs ramipril, harder to substantiate.

**HOPE vs ONTARGET: RAMIPRIL MYOCARDIAL INFARCTION RATE**

In ONTARGET, patients treated with ramipril for an average of 56 months had a MI rate of 4.8% as compared with a much higher rate of 9.9% for the same selection of patients when treated with ramipril 8 years earlier in the HOPE study. This difference may result from better concomitant care (eg, statin use), but is paradoxical to the difference seen for all-cause mortality (see last paragraph). Of note, the MI rates might have been expected to increase due to changes in the definition of MI in the time between the two studies.

The GRACE registry (Global Registry of Acute Coronary Syndromes) demonstrates an increased incidence of MI >25% resulting from regular use of troponin assays.65 Further, the case fatality rate remained the same despite a broadening definition. Table I summarizes these points and includes data for two large placebo-controlled trials.66,67 The all-cause mortality for each of these was numerically higher for patients given telmisartan compared with those given placebo and no reduction in MI was observed vs placebo.

**THE GUIDELINE DILEMMA**

Randomized, double-blind, placebo-controlled trials are the most robust way to assess a treatment efficacy, particularly when assessing a clinically meaningful primary end point (eg, all-cause mortality) and time frame (eg, 5 years). As large clinical trials traditionally assess a single primary hypothesis, they are largely deterministic. By definition, this means that given a particular input (ie, patient and treatment strategy selection), they should always produce the same output. However, while this may be true of an experiment conducted in the carefully controlled environment of a laboratory, it is much harder to achieve in the context of constantly changing usual clinical care.

Clinical guidelines seek to provide a template for the best possible routine patient care with a strong analogy being the provision of a geographical map to help a user find a certain desired destination. In such an analogy, clinical trials act as single compass readings permitting correct orientation of the map. A final element is the “real world” experience, which may present challenges not anticipated by the map, eg, darkness, fog, obstacles. For this and other reasons, guidelines all include a disclaimer, which in effect states, “doctors follow these guidelines at their own risk as they cannot absolve clinicians from professional responsibility for all individual patient treatment decisions made.”

Guidelines differ over time, between nations, and within nations as has been illustrated in the controversy surrounding the latest US hypertension guidelines. Two sets were published in December 2013 being characterized in one case as “an opinion piece” and in the other case as a “scientific advisory.” This illustrates the “Guideline Dilemma.” By definition, a dilemma is a double proposition or a problem offering two possibilities, neither of which, in isolation, is practically acceptable. Both the science and the art of medicine need to be accommodated in any advice given to clinicians practicing individual Hippocratic patient care.

**ACE Inhibitor Guidelines: for acute, stable, concomitant coronary artery disease**

The ACE inhibitor class is fortunate to have arguably the strongest portfolio of placebo-controlled trials in medicine.69 Not only have many trials been performed using a wide range of drugs, doses, patients, and time, many have strongly reported beneficial findings. Despite this wealth of information, there is no randomized comparative data to compare different ACE inhibitors with regard to cardiovascular outcomes, and limited evidence regarding the efficacy of alternate doses, frequency, and timing of administration. As a resolution to this issue, clinicians are frequently exhorted to base the detailed aspects of their prescribing on successful individual trials whenever this is possible.

American and European guidelines for the use of ACE inhibitors in patients with coronary artery disease fall into three main categories: (i) STEMI; (ii) non-ST-
segment–elevation myocardial infarction (NSTEMI) and unstable angina\textsuperscript{72,73}; and (iii) stable coronary artery disease (this includes high cardiovascular risk states of diabetes, hypertension, and end-stage renal disease, and are also referred to by PCI and CABG guidelines\textsuperscript{74-77}).

These have been briefly summarized in Table II. Other guidelines recommending use of ACE inhibitors exist for patients with diabetes, hypertension, renal disease, and heart failure, many of whom will have concomitant coronary artery disease. While these are not covered here, it is appropriate to note that trial evidence for impact on death from all-causes and for new or recurrent MI is present for ACE inhibitors given alone or as part of a combination strategy.

![Figure 14. This figure depicts the summary findings of multiple trials with regard to prevention of MI based on duration of randomized treatment and follow-up.](image)

The trials with a green box indicate a statistically significant reduction in MI. Two lines relate to trials in patients with (A) heart failure and left ventricular systolic dysfunction and (B) stable coronary artery disease. The large green diamond depicts the summary of a 20% risk reduction seen in trials of at least a 6-month duration (OR, 0.80; 80% CI, 0.74, 0.87).

**Abbreviations:** MI, myocardial infarction; OR, odds ratio; 80% CI, 80% confidence limits; see main text for trial abbreviations.

### Table II. Summary of the recommendations of American and European Guidelines regarding the use of ACE inhibitors in patients with coronary artery disease.

The recommendations fall into three main categories: (a) STEMI; (b) NSTEMI/UA; (c) Stable coronary artery disease including patients with high cardiovascular risk for the disease states of diabetes, hypertension, and end-stage renal disease who were also referred by PCI and CABG guidelines.

**Abbreviations:** ACE inhibitor, angiotensin-converting enzyme inhibitor; CABG, coronary artery bypass graft; EF, ejection fraction; NSTEMI, non-ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; UA, unstable angina.

<table>
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<th>Class I Indication</th>
<th>Class II Indication</th>
<th>Refs</th>
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<tbody>
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<td>STEMI</td>
<td>ACE inhibitors should be started within 24 hours for all patients with anterior STEMI, heart failure, and EF&lt;40% unless contraindicated (Evidence Level A)</td>
<td>ACE inhibitor use is reasonable in all patients with STEMI unless contraindicated (Evidence Level A)</td>
<td>\textsuperscript{70,71}</td>
</tr>
<tr>
<td>NSTEMI/UA</td>
<td>ACE inhibitors should be given and continued indefinitely for all patients recovering from NSTEMI/UA with heart failure, hypertension, diabetes mellitus unless contraindicated (Evidence Level A)</td>
<td>ACE inhibitor use is reasonable in all patients with NSTEMI/UA unless contraindicated (Evidence Level A)</td>
<td>\textsuperscript{72,73}</td>
</tr>
<tr>
<td>Stable Coronary Artery Disease &amp; High Cardiovascular Risk PCI/CABG</td>
<td>ACE inhibitors should be given and continued indefinitely for all patients recovering from NSTEMI/UA with heart failure, hypertension, diabetes mellitus, and chronic kidney disease, unless contraindicated (Evidence Level A)</td>
<td>ACE inhibitor use is reasonable in all other patients despite absence of heart failure, hypertension, diabetes mellitus, and chronic kidney disease, unless contraindicated (Evidence Level A)</td>
<td>\textsuperscript{74-77}</td>
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### CONCLUSION

ACE inhibitors have a demonstrated efficacy for the prevention of MI in the context of secondary prevention. Specifically, this has been shown for patients with coronary artery disease and additional increased risk denoted by the occurrence of STEMI or NSTEMI or the concomitant presence of diabetes mellitus, chronic kidney disease, hypertension, or heart failure. The treatment of selected patients is supported in both US and European Guidelines, by expert opinions and multi-
ple persuasive clinical trials. Furthermore, it is considered a reasonable action to prescribe ACE inhibitors to all patients with high-risk coronary artery disease unless there is a specific contraindication. Figure 14 summarizes the benefit with regard to prevention of MI, a pattern fully mirrored in the prevention of death from all causes.

It is a practical recommendation to all clinicians, healthcare providers, and policy makers to attempt to mirror the details of the main trials in the evidence base, as much as it is possible, with regard to the drug, dose, and frequency of dose. Perindopril, with a target dose of 8 mg once daily, has the most contemporary and large evidence base (EUROPA trial60; ADVANCE trial [Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation]78; ASCOT trial [Anglo-Scandinavian Cardiac Outcomes Trial]79) followed by captopril (SAVE trial32; target of 50 mg three times a day), enalapril (SOLVD trial28,30; target of 20 mg twice a day), and ramipril (HOPE trial57; target 10 mg once at night). Trandolopril (TRACE trial and PEACE study50,62; target of 4 mg once daily) lacks evidence despite appropriate duration of follow-up, most probably as a result of dose selection. Lisinopril lacks evidence due to absence of trial data.

Guidelines recommend use of an AT1 receptor antagonist for patients intolerant to ACE inhibitors based on the VALIANT trial (Valsartan in Acute Myocardial Infarction) and the ONTARGET trial that failed to demonstrate superiority either head-to-head with ACE inhibitors or in combination with ACE inhibitors vs placebo. Therefore, second-line use of an AT1 receptor antagonist is based on a demonstration of noninferiority, which means that at least 50% of the benefits of ACE inhibitors are preserved. However, consideration of the full range of the evidence base, particularly the efficacy trials that assessed second-line use of an AT1 receptor antagonist for patients judged to be ACE inhibitor intolerant demonstrates no efficacy as compared with placebo. Therefore, ACE inhibitors remain the only proven option for prevention of the fatal and nonfatal MI events.

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Prevention of Myocardial Infarction With ACE Inhibitors

*Expert Answers to Three Key Questions*

**1.**
Angiotensin-converting enzyme inhibition: what are the effects on coronary heart disease and cardiovascular mortality in hypertensive patients?

*P. S. Sever*

**2.**
Does ACE inhibition reduce cardiovascular death and myocardial infarction in heart failure?

*K. Swedberg*

**3.**
How does ACE inhibition improve outcomes in diabetes and renal dysfunction?

*M. H. Strauss*
Angiotensin-converting enzyme inhibition: what are the effects on coronary heart disease and cardiovascular mortality in hypertensive patients?

Peter S. Sever, PhD, FRCP, FESC

International Centre for Circulatory Health - National Heart and Lung Institute - Imperial College London - UK

Angiotensin-converting enzyme inhibitors (ACE inhibitors) remain the first-choice treatment option for uncomplicated hypertension. For hypertensive patients with comorbidities and patients requiring ≥2 drugs to achieve their target blood pressure, ACE inhibitors should be incorporated into the treatment strategy. Most cardiovascular benefits of antihypertensive drugs are related to the magnitude of their effects on blood pressure lowering. However, in pooled analyses of trials involving higher risk patients, evidence shows that ACE inhibitors confer benefits beyond blood pressure lowering, particularly for coronary heart disease events and cardiovascular mortality. Blocking the renin-angiotensin-aldosterone system is associated with a significant reduction in all-cause mortality, but the benefit is limited to ACE inhibitors and is not shared by angiotensin receptor blockers.

Keywords: angiotensin-converting enzyme inhibitors; coronary heart disease; mortality

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>ABBREVIATION</th>
<th>DEFINITION</th>
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<tr>
<td>ACCOMPLISH</td>
<td>Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension [study]</td>
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<tr>
<td>ACE inhibitor</td>
<td>angiotensin-converting enzyme inhibitor</td>
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<td>ADVANCE</td>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation [trial]</td>
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<tr>
<td>ALLHAT</td>
<td>Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial</td>
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<td>ANBP-2</td>
<td>second Australian National Blood Pressure study</td>
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<td>ARB</td>
<td>angiotensin receptor blocker</td>
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<td>ASCOT-BPLA</td>
<td>Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm</td>
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<tr>
<td>AT</td>
<td>angiotensin</td>
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<tr>
<td>CCB</td>
<td>calcium channel blocker</td>
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<td>CHD</td>
<td>coronary heart disease</td>
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<td>EUROPA</td>
<td>EUROpean trial on reduction of cardiac events with Perindopril in stable coronary Artery disease [trial]</td>
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<tr>
<td>HOPE</td>
<td>Heart Outcomes Prevention Evaluation [study]</td>
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<td>HYVET</td>
<td>HYpertension in the Very Elderly Trial</td>
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<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
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<td>VALUE</td>
<td>Valsartan Antihypertensive Long-term Use Evaluation [trial]</td>
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The renin-angiotensin-aldosterone system (RAAS) plays an important role in circulatory hemodynamics through its effects on vascular tone and salt and water homeostasis. In addition, there is increasing evidence that activation of the RAAS, at a tissue level, plays a pathophysiological role in cardiac and vascular hypertrophy, glomerular sclerosis, and atherosclerosis. The RAAS activity may be inhibited by several antihypertensive drugs, which, in addition to their blood pressure–lowering properties, could confer target organ protection. This overview focuses on the trials of blood pressure–lowering with angiotensin-converting enzyme (ACE) inhibitors. In addition, it compares outcomes with placebo or other antihypertensive treatments in an attempt to establish whether it is possible to demonstrate independent blood pressure benefits with this class of...
agents with an emphasis on, but not exclusively, trials in hypertensive patients. Comparisons will be made with other drug classes, including angiotensin receptor blockers (ARBs), which also block the RAAS, but differ in several important ways in their effects on the integrity of the RAAS and its constituent hormones and receptors, several of which could lead to differential actions at a tissue level. A summary of the ways in which these agents block the RAAS is shown in Figure 1.4

The key differences between the three classes of drugs are: (i) ACE inhibitors not only block conversion of angiotensin (AT)-I to AT II, but also inhibit the breakdown of bradykinin and other peptides; (ii) ACE inhibitors prevent the action of AT II on several subtypes of angiotensin receptors by inhibiting the formation of AT I, whereas ARBs only block the AT I receptor, and (iii) direct renin inhibitors reduce plasma renin activity and circulating levels of AT II and aldosterone by blocking the rate-limiting enzyme in the biosynthetic cascade, whereas ACE inhibitors and ARBs increase renin levels and AT I and AT II using a feedback loop. The clinical importance of these distinguishing features of the three classes of drugs has been the subject of much interest over the past decade.

**EARLY PLACEBO-CONTROLLED TRIALS WITH ACE INHIBITORS**

Due to the cardiovascular benefits observed in early placebo-controlled trials on blood pressure reduction,6

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**Figure 1. Renin-angiotensin-aldosterone system.**

Black arrows show stimulation and red arrows show inhibition. Dotted lines show alternative pathways, mainly documented in experimental studies. The RAAS activity is reduced by β-blockers, direct renin inhibitors, ACE inhibitors, and angiotensin II type-1 receptor blockers. The RAAS activity is reduced by β-blockers, direct renin inhibitors, ACE inhibitors, and angiotensin II type-1 receptor blockers.

it became increasingly difficult to repeat placebo-controlled studies in hypertensive patients using newer drugs, including ACE inhibitors. Other trials comparing ACE inhibitors with placebo were carried out in very different patient populations that were not recruited on the basis of hypertension, but included those with established cardiovascular or renal disease. Therefore, unlike many of the early trials with diuretics and β-blockers, these trials did not assess reduction in coronary heart disease (CHD) or stroke risk in the primary prevention of cardiovascular disease in hypertensive subjects. The risk reductions of 30% to 40% in stroke and ≈20% in CHD observed in placebo-controlled trials with ACE inhibitors in high-risk patients were associated with a 5/2 mm Hg difference in blood pressure (Figure 2). These observations suggest that considerably greater risk reductions occur for a given difference in blood pressure than would have been predicted from the observational data (albeit in lower risk populations).

In the HOPE study (Heart Outcomes Prevention Evaluation), approximately 9000 patients, who were on average 66-years-old and had evidence of vascular disease or diabetes, were randomly assigned to ramipril 10 mg daily or placebo for a mean of 5 years. Almost half of

<table>
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<th>Trials</th>
<th>1st listed</th>
<th>2nd listed</th>
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<th>Relative risk (95% CI)</th>
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<td>473/9111</td>
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<td>0.72 (0.64-0.81)</td>
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<td>76/3794</td>
<td>119/3688</td>
<td>−8/−4</td>
<td>0.62 (0.47-0.82)</td>
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<td>140/7494</td>
<td>261/13 394</td>
<td>−4/−3</td>
<td>0.77 (0.63-0.95)</td>
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<tr>
<td>ACE inhibitor vs placebo</td>
<td>5</td>
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<tr>
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<td>274/7494</td>
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<td>219/8233</td>
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<td>More vs less</td>
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<td><strong>Total mortality</strong></td>
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<tr>
<td>ACE inhibitor vs placebo</td>
<td>5</td>
<td>839/9111</td>
<td>951/9118</td>
<td>−5/−2</td>
<td>0.88 (0.81-0.96)</td>
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<tr>
<td>CA vs placebo</td>
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<td>239/3794</td>
<td>263/3688</td>
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<td>0.99</td>
</tr>
<tr>
<td>More vs less</td>
<td>5</td>
<td>404/8034</td>
<td>549/13 948</td>
<td>−4/−3</td>
<td>0.96 (0.84-1.09)</td>
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</tr>
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Figure 2. ACE inhibitors and calcium antagonists compared with placebo, and more or less intensive blood pressure-lowering regimens. More or less refers to either a more intense or less intense, respectively, blood pressure-lowering regime. P values are derived from χ² test for homogeneity. Overall mean blood pressure was calculated by weighting the difference observed in each contributing trial by the number of individuals in the trial. *Overall mean blood pressure difference (systolic/diastolic) during follow-up in the activity-treated group compared with the control group. Negative values indicate lower mean follow-up blood pressure in the groups listed 1st (ACE, CA, and more) than in the groups listed 2nd (placebo and less).

the patients (47%) recruited into this study were hypertensive. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes. This was reduced by 22% in favor of ramipril, together with a 20% risk reduction in myocardial infarction. The reported 3/2 mm Hg reduction in blood pressure was proposed by the authors to account for no more than one quarter of the reduction in the rates of myocardial infarction. However, in HOPE, owing to administration of the short-acting ACE inhibitor ramipril at night and the measurement of blood pressure the following day, the reported differences in blood pressure between the active and placebo treatment arms may have been underestimated, particularly since a small substudy incorporating ambulatory blood pressure measurements suggested larger blood pressure differences between the two arms of the trial.

In the EUROPA trial (EUROpean trial on reduction of cardiac events with Perindopril in stable coronary Artery disease),10 more than 13 000 patients with previous coronary disease, were randomized to perindopril 8 mg daily or placebo. The average age of patients was 60 years and follow-up was 4.2 years with primary end points of cardiovascular death, nonfatal myocardial infarction, or cardiac arrest. Most patients were on concomitant β-blockers.
and lipid-lowering therapy. In those assigned perindopril, there was a highly significant 20% reduction in the primary end point and a 22% reduction in nonfatal myocardial infarction. Although blood pressure was on average 5/2 mm Hg lower in patients assigned perindopril, a similar proportional risk reduction was seen in those who were not hypertensive at baseline compared with those who were hypertensive. In a post hoc analysis, similar risk reductions were observed in patients where the ACE inhibitors had little or no effect on blood pressure, which is compatible with the hypothesis that, in this particular patient group, some of the benefits observed would be independent of blood pressure. A summary of the results of these and other placebo-controlled trials is shown in Figure 2.

HEAD-TO-HEAD COMPARISONS OF ACTIVE TREATMENTS: LIMITATIONS OF TRIAL DESIGN

After the introduction of ACE inhibitors, several head-to-head studies on hypertensive subjects were conducted comparing older treatments (diuretics or β-blockers) with ACE inhibitor-based treatment or ACE inhibitor-based treatment with calcium channel blocker (CCB)-based treatment, on several cardiovascular end points and all-cause mortality. Most of the individual studies were underpowered to detect potential differences in CHD event rates, and indeed, failed to do so. Thus, prospective meta-analyses were conducted in an attempt to determine whether ACE inhibitors conferred advantages over the older drugs (Figure 3).

The conclusion from these analyses was that there were no significant differences in total major cardiovascular events or CHD events between regimens based on ACE inhibitors, CCBs, diuretics, or β-blockers, even though ACE inhibitor-based regimens showed a lower reduction in blood pressure. There was evidence of some differences between active treatment regimens in their effects on cause-specific outcomes. For all outcomes other than heart failure, the difference between the randomized groups in achieving blood pressure reduction was directly related to the observed difference in risk.

Most national and international guidelines recommend all of the major classes of antihypertensive drugs, specifically ACE inhibitors, CCBs, diuretics, and β-blockers as first-line treatments for patients with uncomplicated hypertension, which is largely based on the meta-analyses. A subsequent meta-regression analysis used data from 26 large-scale trials comparing ACE inhibitors or ARBs with placebo or another drug class. Although there were similar blood pressure-dependent effects of ACE inhibitors and ARBs on the risk of stroke, CHD, and heart failure, ACE inhibitors, but not ARBs, showed evidence of blood pressure-independent effects on the risk of major coronary events (Figure 4).

With individual data on almost 200,000 participants, subgroup analyses have shown that for almost all cardiovascular end points, outcome benefits of ACE inhibitors compared with placebo are similar in the young (<65 years) and the old (>65 years), men and women, and those with or without diabetes.
LESSONS FROM INDIVIDUAL HYPERTENSION TRIALS INVOLVING ACE INHIBITOR-BASED TREATMENT

It is important to point out that the following trials were designed to compare treatment regimens, and not individual drugs, on various cardiovascular outcomes. Thus, where differences were observed between groups, it is difficult to assign benefits to any particular component of a treatment arm. In most trials, the vast majority of subjects ended up receiving two or more antihypertensive drugs in order to reach their blood pressure goals.

ANBP 2 trial

The ANBP 2 trial (second Australian National Blood Pressure trial) of 6083 elderly patients aged 65 to 84 was designed to compare the effects of ACE inhibitor-based regimens (usually enalapril) with those of a thiazide-based regimen (usually hydrochlorothiazide).15 The results suggested that those allocated to ACE inhibitors had an 11% reduction in the primary end point of total cardiovascular events and all-cause death, which was of borderline statistical significance. These benefits were specific to men and interpretation was further complicated by the fact that compliance was only around 60% and only a minority (38%) was on monotherapy. These results contrast with the results of the ALLHAT trial (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack) and generally appear less reliable.

ALLHAT

The ALLHAT trial randomized more than 40 000 patients in a double-blind study comparing 3 first-line agents (the CCB amlodipine, the ACE inhibitor lisinopril, and the α-blocker doxazosin) with the diuretic chlorthalidone as the reference drug.16 The α-blocker limb of the study was terminated early because of an excess of certain cardiovascular end points compared with chlorthalidone. First-line drugs were titrated monthly to achieve a target blood pressure of <140/90 mm Hg (amlodipine 2.5 to 10 mg daily, lisinopril 10 to 40 mg daily, chlorthalidone 12.5 to 25 mg daily). If goal blood pressures were not achieved, second-line medications including reserpine (0.05 to 0.2 mg daily), clonidine (0.1 to 0.3 mg twice daily [bid]), or atenolol (25 to 100 mg daily) were added. Third-line medications included hydralazine (25 to 100 mg twice daily). Hypertensive subjects recruited into ALLHAT were an average of 67 years of age, moderately high risk (≈2% CHD risk per year), 47% were female, and 32% were black. The average length of follow-up was 4.9 years. Blood pressure levels at baseline were evenly matched falling from 146/84 mm Hg in all 4 groups to 133/75 mm Hg (amlodipine), 134/74.6 mm Hg (amilodipine), 135/75.4 mm Hg (lisinopril), and 137.4/76.6 mm Hg (doxazosin). Hence, compared with the chlorthalidone group, the mean follow-up systolic blood pressure was ≈2 mm Hg higher in the lisinopril group, ≈1 mm Hg higher in the amlodipine group, and ≈3 mm Hg higher in the doxazosin group. Differences in blood pressure between the treatment limbs were greatest during the first 2 years of follow-up, after which dose titration and the addition of second-line and third-line therapy reduced these differences.

Despite these mean blood pressure differences, CHD outcomes (the primary end point) were not significantly different among those in the 4-comparator drug groups. There was a 15% excess of stroke in the lisinopril arm compared with chlorthalidone and a 26% excess of stroke when the doxazosin and chlorthalidone groups were compared. Notably, in blacks, there was a 40% excess of stroke in those assigned lisinopril compared with chlorthalidone. The ALLHAT authors concluded that these differences in stroke outcome could not be explained by differences in blood pressure. However, this depends on which reference group is chosen for the derivation of “expected outcome” to compare with the observed outcomes. The ALLHAT authors based their expected outcome on early observational studies, not the recent intervention trials involving high-risk patients in whom smaller differences in blood pressure have been associated with larger differences in outcome. Does ALLHAT provide evidence for benefits beyond blood pressure? Indirectly it does, considering that almost identical rates of coronary events occurred among the 4 blood pressure drug classes evaluated despite different degrees of blood pressure reduction, which raises the intriguing possibility that had blood pressure levels been equivalent throughout the trial in the ACE inhibitor, CCB, doxazosin, and chlorthalidone arms, perhaps the newer treatments would have conferred greater protection against CHD events.

ADVANCE trial

Earlier reports from the United Kingdom Prospective Diabetes Study (UKPDS) noted the benefits of lowering blood pressure in patients with diabetes, which was confirmed in the HOT trial (Hypertension Optimal Treatment) when better blood pressure–lowering conferred additional benefits on cardiovascular end points in the subgroup of patients with diabetes. Therefore, there was considerable interest in
the potential benefits on macrovascular and microvascular outcomes when patients with type 2 diabetes in the ADVANCE trial (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), receiving their usual treatment, were further randomized to receive a fixed combination of perindopril and indapamide on top of their current antihypertensive therapy. Of note, patients were randomized into the trial irrespective of baseline blood pressures.

A total of 11,140 patients were followed-up for an average of 4.3 years. Active treatment was associated with a 5.6/2.2 mm Hg fall in blood pressure and the primary end point of combined macrovascular and microvascular disease was significantly reduced by 9%. The reductions in macrovascular and microvascular disease, when considered separately, were of similar magnitude, but not statistically significant. Cardiovascular death and all-cause mortality were significantly reduced by 18% and 14%, respectively. Although the magnitude of benefit on the primary end point was somewhat smaller than the investigators predicted, the results of this trial provide further evidence that better blood pressure control in patients with type 2 diabetes confers additional benefits on vascular end points.

**HYVET trial**

The overall benefits of treating very elderly patients have been unclear since, in some earlier studies, any reductions in stroke outcome were offset by increases in all-cause mortality. In the HYVET trial (Hypertension in the Very Elderly Trial), 3,845 patients who were 80 years or older with sustained systolic pressures greater than 160 mm Hg were randomized to either indapamide or placebo.19 The ACE inhibitor perindopril or matching placebo were added in an attempt to achieve a target blood pressure of 150/80 mm Hg. Patients were followed-up for a median of 1.8 years, by which time active treatment had substantially lowered blood pressure (15.0/6.1 mm Hg). The trial was stopped following the second interim analysis of the data, which demonstrated a significant 41% reduction in favor of active treatment; in the primary end point of stroke events together with a reduction in all-cause mortality. In the final analysis, the revised reduction in stroke events was somewhat less (30%). All-cause mortality was significantly reduced by 21%, as was the development of heart failure (64%).

**ACCOMPLISH trial**

The ACCOMPLISH trial (Avoiding Cardiovascular events through COMbination therapy in Patients Living with Systolic Hypertension) was the first trial designed to compare two different fixed-dose combination tablets on cardiovascular outcomes.20 A total of 11,463 hypertensive patients with evident cardiovascular or renal disease were randomized to either benazepril/amlopidine or benazepril/hydrochlorothiazide, and followed-up for an average of 39 months. Additional drugs could be added to achieve target blood pressures <140/90 mm Hg. Blood pressure control was virtually identical in each of the two arms of the trial. The trial was stopped prematurely, at which time there was a highly significant 20% reduction in the primary end point of combined cardiovascular morbidity and mortality in favor of the benazepril/amlopidine combination and consistent, but nonsignificant, reductions in most components of the composite primary end point. This study provides clear evidence for advantages of CCBs over thiazide diuretics and is likely to have a major impact on the selection of optimal combinations in hypertension.

**ASCOT trial**

The blood pressure arm of the ASCOT-BPLA trial (Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm) recruited ~20,000 patients. The patients were between the ages of 40 and 79 years with either untreated or previously treated hypertension. The included patients were then randomized to receive either amlodipine (5 to 10 mg daily) or atenolol (50 to 100 mg daily).21 After dose titration, the second-line drugs, perindopril (4 to 8 mg daily) and bendroflumethiazide-K (1.25 to 2.5 mg daily), were added as required to achieve goal blood pressures of <140/90 or <130/80 mm Hg in patients with diabetes. Thereafter, the third-line drugs doxazosin-GITS (4 to 8 mg daily) and others were added to either drug regimen as required to achieve target blood pressures. Following randomization for hypertensive treatments, the patients, >10,000 patients with total cholesterol levels of ≤250 mg/dL, using a factorial design, were randomized to atorvastatin 10 mg or placebo.

The patient population recruited into ASCOT differed substantially from those recruited into several other recently reported hypertension trials in that a history of prior myocardial infarction or current CHD excluded patients from participation. Although 3 additional cardiovascular risk factors were required for entry, the overall risk of the ASCOT patient population was low (<1% per annum CHD event rate) and much less than among those recruited into ALLHAT. The average age of the patients was 63 years, 23% were female, and 95% were white.
Blood pressure levels fell from 163.9/94.5 mm Hg to 137.7/79.2 mm Hg in the atenolol-based treatment arm and from 164.1/94.8 mm Hg to 136.1/77.4 mm Hg in the amlodipine-based treatment arm. Again, better blood pressure-lowering in favor of the CCB-treatment regimen was seen early in the trial. Overall, blood pressure (integrated mean) was 2.7/1.9 mm Hg lower on the amlodipine-based regimen than the atenolol-based regimen, with maximal systolic blood pressure differences of ≈5 mm Hg in the first year, but only 1.6 mm Hg by the end of the trial.

ASCOT-BPLA was stopped prematurely because of significant all-cause mortality differences between the 2 treatment arms and concerns that those patients assigned the β-blocker/thiazide regimen would continue to be disadvantaged if the trial went to its planned completion. All-cause mortality and cardiovascular mortality were reduced significantly (11% and 24%, respectively) among those allocated to the amlodipine/perindopril regimen. The primary end point (nonfatal myocardial infarction and fatal CHD) was reduced by 10%, but this did not achieve statistical significance. However, other prespecified coronary end points, including the primary end point and excluding silent myocardial infarction, and a composite total coronary end point were significantly reduced (13% and 13%, respectively) among those allocated to the amlodipine/perindopril regimen, as were stroke events (23%).

These observations raised the question as to what extent the blood pressure differences, which predominantly occurred early in the trial, explained the differences in cardiovascular events seen in the 2 blood pressure arms of the study. The observed blood pressure difference of <3/2 mm Hg seen in ASCOT-BPLA might explain the 4% to 8% reduction in coronary outcomes and the 8% to 14% reduction in strokes based on prospective observational studies as well as explain the most recent pooled analysis of clinical trials reported by the Blood Pressure Lowering Treatment Trialists’ Collaboration.8

Correcting for blood pressure differences in randomized trials, however, is problematic, and there is no ideal way to do so. Nevertheless, further analyses using in-trial data were undertaken in an attempt to ascertain to what extent the beneficial effect of the amlodipine/perindopril regimen could have been explained by the differences in blood pressure and the other variables that occurred after randomization.

First, analyses were performed to evaluate any temporal association between blood pressure differences and coronary and stroke end points using differing censoring points throughout the trial. These analyses were then extended using a technique similar to, but more rigorous than, the serial median matching carried out in the VALUE trial (Valsartan Antihypertensive Long-term Use Evaluation) analyses.23 It was clear in the ASCOT analyses that for coronary and stroke end points, there was no apparent temporal link between the size of blood pressure differences and the difference in end points between the amlodipine/perindopril regimen and the atenolol/thiazide regimen.

In a series of analyses conducted in collaboration with Rothwell et al,24,25 trial outcomes, including both CHD and stroke end points, were closely related to measurements of in-trial blood pressure variability, and the benefits of the amlodipine/perindopril regimen (compared with the atenolol/thiazide regimen) on cardiovascular events could be explained by the differential effects on blood pressure variability rather than in-trial mean blood pressure.

**ACE inhibitors and mortality in hypertensive subjects**

Substantial benefits of ACE inhibitors on CHD events and all-cause mortality have been reported in patients with heart failure26 and these benefits seem disproportionate to the magnitude of the fall in blood pressure. Individual trials in hypertensive patients did not have sufficient power to detect differences in either cardiovascular or all-cause mortality, however, in the two trials in which ACE inhibitors formed part of the treatment strategy, namely ASCOT21 and ADVANCE,18 cardiovascular and all-cause mortality were significantly reduced compared with other treatment strategies. In HYVET,19 all-cause mortality was also reduced by perindopril-based treatment compared with placebo.

In a pooled analysis of 20 cardiovascular morbidity-mortality trials involving almost 160 000 patients of whom >two-thirds were hypertensive,27 treatment regimens including drugs that block the RAAS were again associated with significant reductions in cardiovascular (7%) and all-cause mortality (5%) compared with non-RAAS blockers (Figure 5). These analyses contain data from the IKKEI-HEART and the KYOTO HEART studies, manuscripts that have now been withdrawn from publication. Nevertheless, reanalysis of the database omitting these 2 trials would not alter the overall conclusion in relation to mortality. However, when all the trials are subdivided into those containing ACE inhibitors compared with those...
that were based on ARBs, the benefits on all-cause mortality were apparently driven exclusively by the ACE inhibitor-based regimens rather than by the ARB-based regimens. In the case of the latter, there appeared to be no benefit on all-cause mortality (Figure 6, page 188).

The interpretation of these apparent differences is complex in that comparisons between ACE inhibitors and ARBs on cardiovascular mortality show no significant differences, and in the ONTARGET trial (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), a trial of more than 17 000 patients at high risk for vascular events (70% hypertensive), comparing either ramipril 10 mg with telemesartan 80 mg, there were no differences in any cardiovascular end point, including cardiovascular death, and all-cause mortality.

CONCLUSIONS

Most cardiovascular outcomes in hypertensive patients treated with various drug regimens are related to the magnitude of the blood pressure reduction. However, there is strong evidence to support the view that some of the cardiovascular benefits of antihypertensive agents, particularly ACE inhibitors and CCBs, arise from properties beyond blood pressure-lowering, as measured conventionally in the clinic and may be differential among particular subgroups of patients. It is relevant, therefore, in some of the most recent guidelines, which they are recommended as preferred first-line therapy in uncomplicated hypertensive subjects. Additionally, ACE inhibitors, unless poorly toler-
ated, should be incorporated into combination treatment regimens, particularly in certain patient subgroups, including those with heart failure, impaired renal function, and coronary heart disease.

There is, however, a strongly held belief that the benefits of all these agents are simply related to blood pressure reduction30 and this issue will remain controversial. However, standing back from either the meta-analyses of potentially heterogeneous data, or specific findings cherry-picked from various trials, we should consider whether it is likely that all antihypertensive agents would have an equal impact on all cardiovascular outcomes for the same degree of clinical blood pressure–lowering.

Given the established multifactorial origin of cardiovascular outcomes and that different antihypertensive agents have differential impacts on many of the established cardiovascular risk factors, it would be extraordinary if all these agents were “equal” once brachial artery pressures were standardized. Different antihypertensive agents, for the same degree of blood pressure–lowering, will have significantly and clinically important differential effects on multiple variables, including lipid profiles, glucose, insulin, potassium, creatinine, angiotensin and other peptides, catecholamines, pulse rate, body weight, and central pressure, not to mention 24-hour blood pressure control. Why would all, or any, of these effects be considered trivial (compared with, say, 2 mm Hg systolic pressure) or together exert a neutral effect such that the only property of all antihypertensive agents of value is the lowering of brachial blood pressure?

On the basis of differential mechanisms of action and diverse effects on major cardiovascular risk factors, different classes of antihypertensive agents, notably those that block the RAAS, together with the CCBs, are likely to provide different cardiovascular protection and that, given sufficiently sensitive tests, these differences could be shown more clearly.

Acknowledgments: The author has received grant income from Pfizer and the Laboratoire Servier and has served as a consultant to both companies. The author is also supported by the Biomedical Research Centre Award to Imperial College Healthcare NHS Trust.

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**Figure 6. The all-cause mortality treatment effect of ACE inhibitor and ARB trials.**

**Abbreviations:** ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; HR, hazard ratio.

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Treatment of hypertension in patients 80 years of age or older.

Benazepril plus amlopidine or hydrochlorothiazide for hypertension in high-risk patients.

Prevention of cardiovascular events with an antihypertensive regimen of amlopidine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial.


Does ACE inhibition reduce cardiovascular death and myocardial infarction in heart failure?

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Treatment with an angiotensin-converting enzyme (ACE) inhibitor in chronic systolic heart failure has changed the treatment of this condition and improved mortality and morbidity. It has become a cornerstone treatment for this syndrome. In patients with heart failure and preserved ejection fraction, the effect has been promising, but not convincing for a general recommendation. In patients with acute myocardial infarction and systolic dysfunction or diabetes, ACE-inhibitors have contributed to improved outcomes in selected high-risk patients. The effects have been associated with the degree of neurohormonal activation. Initiation of therapy should be done with low doses of selected agents, increased to target doses over time in collaboration with the patient and monitoring of serum creatinine and potassium. Side effects include hypotension, dry cough, renal dysfunction, hyperkalemia, and angioedema.

Keywords: acute myocardial infarction; angiotensin-converting enzyme inhibitor; heart failure; human; treatment
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randomized study had shown improved survival by any treatment in CSHF. At that time, the CONSENSUS study (COoperative North Scandinavian ENalapril SUrvival Study), a survival study on severe CSHF, which used the new ACE inhibitor MK-421 (enalapril) was started. This study was stopped in late 1986 by the Data Safety Monitoring Board and subsequently published.  

In CONSENSUS, 253 patients diagnosed with CSHF in New York Heart Association (NYHA) class IV and a dilated heart on chest x-ray (ie, no documentation of left ventricular dysfunction) were to receive either placebo or enalapril. Patients were randomized within 14 days of screening in order to include patients who were unstable and who should have an activated RAAS system. The mean age was 70 years. After a 6-month follow-up (primary objective), the all-cause mortality in the placebo group was 44% and 26% in the enalapril group, a reduction of 40% (P=0.002). By the end of the study, there were 68 deaths in the placebo group and 50 in the enalapril group, a 27% reduction (P=0.003) (Figure 1).

It is interesting to remember how rapidly and completely the study results were accepted by the medical community. Despite the relatively small study size, another placebo-controlled study of an ACE inhibitor in patients with CSHF in NYHA class IV has not been done. In the SOLVD trial (Studies Of Left Ventricular Dysfunction), 2569 patients with symptomatic heart failure in NYHA class II to III received placebo or enalapril in addition to conventional heart failure therapy. After an average follow-up of 41.4 months, mortality was significantly reduced from 40% to 35% (P=0.0036), most notably reducing deaths attributed to progressive heart failure. Hospitalizations for heart failure were also reduced and symptoms and quality of life as assessed by a questionnaire were improved.

Patients with reduced left ventricular ejection fraction (LVEF) in the early postinfarct period were examined in the SAVE trial (Survival And Ventricular Enlargement). In this study, 2231 patients with LVEF ≤40%, but without overt heart failure or symptoms of myocardial ischemia, were randomly assigned treatment with captopril or placebo. All-cause mortality was reduced by 19% (P=0.019). In a similar evaluation with trandolapril (ie, the TRACE
study (TRAndolapril Cardiac Evaluation), 1749 patients with left ventricular dysfunction after an acute myocardial infarction (AMI) were randomly assigned to treatment with placebo or trandolapril. Treatment was initiated 3 to 7 days from the onset of the myocardial infarction. All-cause mortality was reduced by 22% ($P<0.001$). Finally, in the AIRE study (Acute Infarction Ramipril Efficacy), 2006 patients with clinical evidence of heart failure any time after the index infarction, were randomly allocated to treatment with ramipril or placebo on days 3 to 10 from the onset of infarction, and all-cause mortality was reduced by 27% ($P=0.002$) with an average follow-up of 15 months. Taken together, these studies provide strong support for the use of ACE inhibitors in post-MI patients with left ventricular dysfunction.

A meta-analysis by Flather et al further supported the beneficial effects of long-term ACE-inhibitor therapy after AMI. From a total of five trials with >1000 patients, 12 763 subjects were included. In the three postinfarction trials (SAVE, AIRE, and TRACE, $n=5966$), mortality was lower with ACE inhibitors than with placebo (23.4% vs 29.1%, odds ratio [OR], 0.74; 95% confidence interval [CI], 0.66-0.83 [Figure 2A]), as were the rates of readmission for heart failure (11.9% vs 15.5%, OR, 0.73; 95% CI, 0.63-0.85) and reinfection (10.8% vs 13.2%, OR, 0.80; 95% CI, 0.69-0.94). For all five trials, the ACE-inhibitor group had lower rates of death than the placebo group (23.0% vs 26.8%, OR, 0.80; 95% CI, 0.74-0.87 [Figure 2B]), lower rates of reinfection (571 [8.9%] vs 703 [11.0%], OR, 0.79; 95% CI, 0.70-0.89), readmission for heart failure (876 [13.7%] vs 1202 [18.9%], OR, 0.67; 95% CI, 0.61-0.74), and the composite of these events (2161 [33.8%] vs 2610 [41.0%], OR, 0.72; 95% CI, 0.67-0.78; all $P<0.0001$).

The benefits were observed early after the start of therapy and persisted over the long-term.

**Figure 2. All-cause mortality determined from several studies.**


Heart failure with preserved ejection fraction (HFPEF) is more common among the elderly and, in particular, among women. These patients are less likely to have coronary heart disease and are more likely to have hypertension and atrial fibrillation. Patients with HFPEF have a better prognosis than those with HFREF. The effect of an ACE inhibitor was assessed in the PEP-CHF trial (Perindopril in Elderly People with Chronic Heart Failure). This was a randomized, double-blind trial, comparing placebo with perindopril, 4 mg/day in patients aged >70 years with a diagnosis of heart failure, treated with diuretics, and an echocardiogram suggesting diastolic dysfunction and excluding substantial LV systolic dysfunction or valve disease. The primary end point was a composite of all-cause mortality and unplanned heart failure–related hospitalization with a minimum
follow-up of 1 year. A total of 850 patients were randomized. Their mean age was 76 (SD 5) years and 55% were women. Median follow-up was 2 1 years (interquartile range, 1 5-2 8). Overall, 107 patients assigned to placebo and 100 assigned to perindopril reached the primary end point (hazard ratio [HR], 0.919; 95% CI, 0.700-1.208, \( P=0.545 \)). After one year, reductions in the primary outcome (HR, 0.692, 95% CI, 0.474-1.010, \( P=0.055 \)) and hospitalizations for heart failure (HR, 0.628; 95% CI, 0.408-0.966, \( P=0.033 \)) were observed and both the functional class (\( P=0.03 \)) and 6-min corridor walking distance (\( P=0.011 \)) had improved in those assigned to perindopril. Many patients withdrew from perindopril (28%) and placebo (26%) after one year and started taking open-label ACE inhibitors. Uncertainty remains about the effects of an ACE inhibitor on long-term morbidity and mortality in HFPEF since PEP-CHF had insufficient power for its primary end point. However, in the first year, fewer hospitalizations for heart failure were observed on perindopril, during which most patients were on assigned therapy, suggesting that an ACE inhibitor may be of benefit in this patient population.

**ACUTE MYOCARDIAL INFARCTION**

Due to the combination of vasodilation and vascular pleiotropic effects, an effect of ACE inhibition in relation to AMI was hypothesized in addition to the effect that had been demonstrated when a left ventricular dysfunction was present as in the SAVE and AIRE trials. These trials were designed according to two strategies: early or late after the acute process, ie, treatment was started within the first week or in the postinfarction process. In the early trials, one trial in particular (CONSENSUS-II) initiated treatment within 24 hours with an iv infusion of enalaprilat in order to achieve rapid ACE inhibition,\(^{16}\) while the others used oral therapy only.

A meta-analysis of the early intervention trials (0 to 36 hours) including the four major trials\(^{16-19}\) along with 11 other trials, all including at least 1000 patients, which means that almost 100 000 patients were involved in the meta-analysis, revealed a 6.5% overall odds reduction (\( P=0.006 \)) over 30 days with an absolute benefit of about 5 fewer deaths per 1000 patients treated among those who received the ACE inhibitor (\( P=0.033 \)). The benefit may be somewhat greater (up to 10 lives saved per 1000) in certain high-risk groups, such as those with a history of a previous MI or heart failure. On the contrary, no benefit was observed in low-risk groups including patients with inferior MI without heart failure and only a trend for benefit was observed in diabetic patients. In addition, in unselected patients, the effect was small and in CONSENSUS-II, there were even indications of harm in association with early hypotensive reactions.

These results support the use of ACE inhibitors early in the treatment of acute MI, either to a wide range of patients or selectively in patients with anterior MI and in those at increased risk because of left ventricular dysfunction, previ-

<table>
<thead>
<tr>
<th>No. deaths/ No. randomized</th>
<th>Odds ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td><strong>Control</strong></td>
</tr>
<tr>
<td>CONSENSUS-II</td>
<td>220/3044 (7.23%)</td>
</tr>
<tr>
<td>GISSI-3</td>
<td>570/9682 (5.89%)</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>2035/29028 (7.01%)</td>
</tr>
<tr>
<td>CCS-1</td>
<td>676/7460 (9.06%)</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>3501/49214 (7.11%)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2=3.8 (2p=0.1) \) df=3

**Figure 3.** Meta-analysis of the effects of ACE-inhibitor therapy early after an acute myocardial infarction.

Proportional effects of ACE-inhibitor therapy on 30-day mortality in each trial are presented. Odds ratio of death among patients assigned ACE-inhibitor therapy to that among patients assigned control treatment. Odds ratios (solid squares, with areas proportional to the amount of information contributed by each trial) are plotted with their 95% CIs (horizontal lines).

**Abbreviations:** ACE inhibitor, angiotensin-converting enzyme inhibitor; CCS-1, chinese cardiac study-1; CI, confidence interval; CONSENSUS-II, COoperative North Scandinavian ENalapril Survival Study II; df, degrees of freedom; GISSI-3, Gruppo Italiano per lo Studio della Sopravvenienza nell’Infarto Miocardico-3; ISIS-4, International Study of Infarct Survival-4; O-E, observed minus expected.

ACE inhibition and heart failure - Swedberg

ACE inhibitors differ in their pharmacology, pharmacodynamic effects, metabolism, and tissue binding. Considering these differences, only agents that have been documented on outcomes should be used. In all placebo-controlled outcome trials, a forced titration design has been used, and therefore, we do not know the optimal dose.

One large study addressed the question of whether a low dose was as effective as a high dose. In the ATLAS trial (Assessment of Treatment with Lisinopril And Survival), 3164 patients with NYHA class II to IV heart failure and an ejection fraction <30% were randomly assigned to double-blind treatment with either low doses (2.5 to 5.0 mg daily, n=1596) or high doses (32.5 to 35 mg daily, n=1568) of the ACE inhibitor lisinopril, for 39 to 58 months, while background therapy for heart failure was continued. When compared with the low-dose group, patients in the high-dose group had a nonsignificant 8% lower risk of death (P=0.128), but a significant 12% lower risk of death or hospitalization for any reason (P=0.002) and 24% fewer hospitalizations for heart failure (P=0.002). These findings indicate that patients with heart failure, generally, should not be maintained on very low doses of an ACE inhibitor (unless these are the only doses that can be tolerated) and suggest that the difference in efficacy between intermediate and high doses of an ACE inhibitor (if any) is likely to be very small.

The ESC guidelines for the management of acute and chronic heart failure recommend certain ACE inhibitors and provide the respective starting dose and target dose (Table I).1

<table>
<thead>
<tr>
<th>ACE inhibitor</th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 tid</td>
<td>50 tid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 bid</td>
<td>10 to 20 bid</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 to 5.0 od</td>
<td>20 to 35 od</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 od</td>
<td>5 bid</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5 od</td>
<td>4 od</td>
</tr>
</tbody>
</table>

**Table I. Recommended ACE inhibitors, starting dose and target dose in the ESC guidelines.**

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; bid, twice daily; ESC, European Society of Cardiology; od, once daily; tid, three times daily.


When an indication for ACE-inhibitor therapy has been established, the values and potential side effects should be discussed with the patient in order to increase the understanding and adherence to the treatment, which in most cases is long-term and probably life-long. In this situation, it is particularly important to explain that the titration of the ACE inhibitor over a time period may take several months. In addition, the need for repeated control of renal function and blood potassium concentrations should be discussed. As many patients with CSHF have reduced renal function, this issue, in particular, requires careful attention because many patients will also have other neuro-hormonal blockers. Details around the monitoring are available on the ESC-guideline website (Table I).23

In patients with reduced renal function and serum creatinine >220 µmol/L, the risk of renal dysfunction is relatively high and ACE inhibitors, in general, should be avoided. Patients who have hyperkalemia >5 mmol/L should not be started until potassium levels are reduced.

**HOW TO INITIATE AND MONITOR THERAPY**

When an indication for ACE-inhibitor therapy has been established, the values and potential side effects should be discussed with the patient in order to increase the understanding and adherence to the treatment, which in most cases is long-term and probably life-long. In this situation, it is particularly important to explain that the titration of the ACE inhibitor over a time period may take several months. In addition, the need for repeated control of renal function and blood potassium concentrations should be discussed. As many patients with CSHF have reduced renal function, this issue, in particular, requires careful attention because many patients will also have other neuro-hormonal blockers. Details around the monitoring are available on the ESC-guideline website (Table I).23

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**WHO SHOULD RECEIVE AN ACE INHIBITOR**

All patients with left ventricular systolic dysfunction and a LVEF <40% in relation to an AMI or in a post-Ami ambulatory situation, should be considered for ACE-inhibitor therapy regardless of symptoms.
We recommend that dose levels are increased every second week after control of serum potassium and creatinine. In younger patients where the risk of renal dysfunction is low, the initial dose levels can be higher and increased somewhat faster. Usually, another neurohormonal blocker is concomitant, which complicates treatment and is another reason for repeated monitoring. In our experience, the initiation of neurohormonal blockade is best done in a setting with nurse-assisted outpatient monitoring in a multidisciplinary team. This approach has also been demonstrated to be associated with improved survival.24

**ADVERSE EFFECTS**

As ACE inhibitors are vasodilators, a fall in blood pressure is expected. The risk of symptomatic hypotension is low with the low starting dose. Patients who are salt and volume depleted are more prone to develop hypotension.

Thus in selected high-risk patients, a reduction in a high dose of a diuretic agent may be considered when ACE-inhibitor therapy is initiated. Of course, more attention is needed in patients with low systolic blood pressure <90 to 100 mm Hg.

Dry cough is reported among 5% to 10% of patients. It is more common among women and Asian populations. The cough is characterized by an irritation in the throat and a sensation of a nonproductive cough. It is very irritating among some patients. In these patients, an angiotensin receptor blocker (ARB) should be offered instead as the cough will then disappear.

Hyperkalemia can occur due to the withdrawal of aldosterone effects. It is rare among patients with normal renal function. As renal impairment is common among patients with CSHF, these patients are at risk. Another risk group is patients with diabetes, which also is a common comorbidity in CSHF.

Acute renal dysfunction can occur after initiation of ACE-inhibitor therapy. A mild to moderate increase in serum creatinine (15% to 20%) is not uncommon, is a sign of effective ACE inhibition, and should not indicate a withdrawal of the therapy. However, it is important to monitor that the creatinine concentration stabilizes. A marked increase in serum creatine should lead to a reduction in the dose of ACE inhibitor. Angioedema is a rare, but potentially life-threatening side effect. Symptoms range from mild gastrointestinal disturbances (eg, nausea, vomiting, diarrhea, colic) to severe dyspnea due to larynx edema, and to death. It is more frequent within the first month of therapy and among black patients. It disappears within hours after cessation of the ACE-inhibitor treatment.26 The mechanism appears to involve an accumulation of bradykinin and its metabolite desarginine-bradykinin and inhibition of the complement-1 esterase inactivator.

**CONCLUSION**

In conclusion, treatment with an ACE inhibitor in CSHF has markedly changed the treatment of this condition and improved morbidity and mortality. In AMI, these agents have contributed to improved outcomes in selected high-risk patients.

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Diabetes mellitus is an epidemic disease, with profound implications for health care worldwide. Microvascular complications include nephropathy, retinopathy, and neuropathy. Macrovascular atherosclerotic complications affect the peripheral, cerebral, and more commonly, the coronary arterial tree with angina, myocardial infarction, left ventricular dysfunction, chronic heart failure, and ultimately death. Hypertension is a common comorbidity in diabetic patients and contributes to a significant increase in cardiovascular risk. Both the target blood pressure and the preferred class of antihypertensive agents in diabetics are clinically relevant issues and are the focus of this review.

THE CARDIOVASCULAR IMPACT OF BLOOD PRESSURE REDUCTION

"The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it."

J. H. Hay, 1931

The treatment of hypertension, and reaching the target blood pressure, is predicated on reducing the risk of hard end points including cardiovascular mortality, myocardial infarction (MI), and stroke (CVA). This is regardless of the presence or absence of diabetes mellitus. A collaborative meta-analysis of prospective observational studies in 1 000 000 subjects with no known cardiovascular disease analyzed the relationship of blood pressure and mortality to assess the impact of blood pressure reduction independent of additional cardioprotective effects drugs might provide. For every 10 mm Hg reduction in systolic blood pressure, it was predicted that the risk of coronary heart disease (CHD) would decrease by 25% and CVA by 36%, with the lowest cardiovascular risk at a blood pressure of 115/75 mm Hg. Although the risk reduction in CHD is lower than CVA, death from CHD was three times more common than from CVA confirming that CHD is the primary target with the greatest benefit to the population.

This meta-analysis includes a broad range of antihypertensive agents in patients both with and without diabetes mellitus, but it is important to recognize that each drug class may or may not have provided equivalent risk reductions in the hard end points, which is an important consideration when choosing a therapeutic agent. The assumption is that a lower target blood pressure...
pressure will provide greater cardiovascular protection, but what is the evidence in patients with diabetes mellitus?

### TARGET BLOOD PRESSURE IN DIABETICS: WHAT THE GUIDELINES RECOMMEND

The prevention of vascular complications in patients with diabetes mellitus necessitates a multifactorial approach. Total mortality in the Steno diabetes-2 study was reduced by 46% (hazard ratio [HR], 0.54; 95% confidence interval [CI], 0.32-0.89; \( P = 0.02 \)) over 13.3 years when patients were randomized both to lifestyle modifications (eg, exercise, dietary changes, and smoking cessation) and to intensive vs conventional targets for HbA1C, serum cholesterol, and triglycerides. Treatment included a renin-angiotensin-aldosterone system (RAAS) inhibitor (either angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]), all patients had microalbuminuria, aspirin, and lipid-lowering agents with a target blood pressure of 130/80 mm Hg.

The target blood pressure of 130/80 mm Hg in the Steno-2 study continues to be the target in the 2014 Canadian Hypertension Education Program (CHEP); however, other guidelines are more conservative as the perception is that minimal benefit has been confirmed with more intensive blood pressure control. The 2013 European Society of Cardiology (ESC) recommends 140/85 mm Hg, the joint National Committee 8 (JNC 8) recommends 140/90 mm Hg, and the 2013 American Diabetes Association (ADA) recommends 140/80 mm Hg with the caveat being to consider 130 mm Hg in younger, lower risk diabetics. Perhaps the most influential trial for a more conservative target blood pressure is the ACCORD trial (Action to Control CardiOvascular Risk in Diabetics).

#### ACCORD TRIAL: THE BLOOD PRESSURE ARM

In the ACCORD trial (n=4733), intensive therapy with a systolic blood pressure target of <120 mm Hg (achieved 119.3 mm Hg) compared with a standard therapy targeting a systolic blood pressure <140 mm Hg (achieved 133.5 mm Hg) did not reduce the primary end point, which was a composite of cardiovascular death, nonfatal MI, and nonfatal stroke. The authors concluded that there was "no evidence (for a) strategy of intensive blood pressure control." However, the risk of stroke in the "intensive"-therapy arm of ACCORD was significantly reduced (odds ratio [OR], 0.59; 95% CI, 0.39-0.89; \( P = 0.01 \)) despite the trial being underpowered—the 4% event rate in the control arm was only half of that expected. Twenty-four strokes were prevented with intensive therapy, but there were an additional 47 serious adverse events (\( P<0.001 \)) including primarily hypotension, arrhythmia, and hyperkalemia. That being said, a small increase in non–life-threatening adverse events seems to be a small price to pay for preventing life-altering and disabling strokes.

More recently, the authors of ACCORD have reported, “a somewhat different view of the results than those published to date.” A recent preplanned secondary analysis compared single intensive interventions with combined interventions. Intensive therapy target blood pressures significantly reduced the primary combined cardiac end point in both the standard (HR, 0.74; 95% CI, 0.55-1.00; \( P = 0.049 \)) and intensive glycemia control arms (HR, 0.71; 95% CI, 0.52-0.96; \( P = 0.025 \)) compared with the combination arm of standard blood pressure and standard glycemia. In an era where a standard glycemia of HbA1c<7%
is the recommended, ACCORD suggests that a target blood pressure <120 mm Hg is a consideration, especially in those with an increased risk of stroke.

**TRIALS OF PRESPECIFIED OR ACHIEVED SYSTOLIC BLOOD PRESSURE IN DIABETES MELLITUS**

There are 2 types of trials that can address the optimal target blood pressure: (i) prespecified, where a specific target blood pressure is part of the a priori design of the trial; or (ii) achieved, where the target blood pressure is not defined, but rather it is simply what is achieved. Trials with prespecified target blood pressures are few, but may be a truer index of what the target blood pressure should be.11 Five such trials in diabetes mellitus (n=7312) compared an intensive with a standard blood pressure–lowering regimen (130/80 mm Hg vs 140-160/85-100 mm Hg). The “intensive” arm had a significantly reduced risk of stroke (OR, 0.65; 95% CI, 0.48-0.86), but there was no benefit with regard to reduction in myocardial infarction or mortality.14 In trials with achieved blood pressures <135 mm Hg vs <140 mm Hg in patients with diabetes (13 trials; n=37 736),15 all-cause mortality had a 10% risk reduction (OR, 0.9; 95% CI, 0.83-0.98) and a 17% stroke reduction (OR, 0.87; 95% CI, 0.73-0.95), but serious adverse events increased by 20% (OR, 1.2; 95% CI, 1.08-1.32). Blood pressure reduction below 130 mm Hg further reduced the risk of stroke, but no other end point with adverse events increased. The authors concluded that a target blood pressure of 130 to 135 mm Hg is optimal in diabetics, but a lower target of 120 mm Hg is a consideration if there is a higher risk of stroke.15 Others have found similar risk reductions for stroke with a lower achieved systolic pressure (OR, 0.61; 95% CI, 0.48-0.79) with a trend for risk reductions in myocardial infarction as well (29 trials; n=73 913; OR, 0.87; 95% CI, 0.74-1.02).16

The risk of stroke in diabetes mellitus is consistently reduced at intensive blood pressure targets, but the evidence for the more common end points, myocardial infarction and death, is less convincing. However, the true efficacy of a therapeutic regimen is established where the comparator is a placebo rather than another active therapy. Therefore, placebo-controlled trials where initial blood pressures are around 140 mm Hg and the end point is mortality, will provide insight into optimal target blood pressure. As there is heterogeneity among different drug classes, it is reasonable to focus on the antihypertensive agents, ACE inhibitors and ARBs, that are preferred for the treatment of diabetes mellitus, which is related, in part, to their unique nephroprotection.17 Although both are RAAS inhibitors, each has a unique mode of action, ACE inhibitors suppress angiotensin II (Ang II) and prevent the breakdown of bradykinin, whereas ARBs specifically block the Ang II type 1 receptor (AT1), but have no impact on bradykinin. As such, ACE inhibitors and ARBs may not provide identical cardiovascular protection18, therefore, they will be analyzed separately.

**PLACEBO-CONTROLLED TRIALS OF ACE INHIBITORS IN DIABETES MELLITUS**

There are 5 placebo-controlled ACE inhibitor trials in high-risk diabetics with an initial blood pressure in

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<tr>
<th>Table I. Data comparison from five placebo-controlled ACE inhibitor trials with a starting BP around 140 mm Hg and reported mortality.</th>
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<td><strong>Abbreviations:</strong> ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; BP, blood pressure; DIABYCAR, non-insulin–dependent DIABetes, HYpertension, microalbuminuria or proteinuria, CARDiovascular events, and ramipril; LEWIS, Lewis trial; MICRO-HOPE, Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation; DM, diabetes mellitus; NC, no change; ns, not significant; PERSUADE, PERindopril SUbstudy in Coronary Artery Disease and DiabEtes; RRR, relative risk reduction.</td>
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<td><strong>Follow-up Initial BP  Mortality ACE inhibitor patient profile</strong></td>
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<td>ADVANCE15</td>
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<td>DIABYCAR23</td>
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the range of 140 mm Hg, where mortality was an end point (Table I). The ADVANCE (Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation),\textsuperscript{19} and MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation)\textsuperscript{20} trials had a significant risk reduction in mortality of 14% to 24%, whereas the mortality reduction in the PERSUADE trial (PERindopril SUbstudy in Coronary Artery Disease and DiabEtes)\textsuperscript{21} and Lewis\textsuperscript{22} (15% and 44%, respectively) was not statistically significant. The DIABHYCAR trial (non-insulin–dependent DIABetes, HYpertension, microalbuminuria or proteinuria, mortality data in a meta-analysis of 11 placebo-controlled ACE inhibitor trials (n=21 997), where ACE inhibitors reduced the risk of all-cause mortality by 11% (HR, 0.89; CI, 0.89-0.99, \textit{P}=0.03)\textsuperscript{24} This is compelling evidence for a target blood pressure <140 mm Hg in diabetes mellitus, at least as it pertains to ACE inhibitors. The risk of all-cause mortality as well as for cardiovascular deaths, myocardial infarction, and heart failure was similarly reduced when the ACE inhibitor meta-analysis was broadened to include trials in diabetes mellitus with any comparator—active or placebo (23 trials, n=32 827)\textsuperscript{24}—independent of initial blood pressures (HR, 0.87; 95% CI, 0.78-0.98, \textit{P}=0.02. \textit{Table II})\textsuperscript{24}

<table>
<thead>
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<th>ACE inhibitor</th>
<th>ARBs</th>
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<tr>
<td>All-cause mortality</td>
<td>13%</td>
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<tr>
<td>CV deaths</td>
<td>17%</td>
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<tr>
<td>Major CV events</td>
<td>14%</td>
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<tr>
<td>Myocardial infarction</td>
<td>21%</td>
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<tr>
<td>Heart failure</td>
<td>19%</td>
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<tr>
<td>Stroke</td>
<td>0.95 (0.81-1.04)</td>
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</table>

\textit{Table II. Parallel meta-analyses of ACE inhibitor and ARB trials vs all comparators in patients with diabetes mellitus.} 

**Abbreviations:** ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CI, confidence interval; CV, cardiovascular; ns, not significant; RRR, relative risk reduction. Modified from reference \textsuperscript{24}: Cheng et al. JAMA Intern Med. 2014;174(5):773-785. © 2014, American Medical Association.

CARDiovascular events, and ramipril\textsuperscript{23} had no mortality reduction with ramipril 1.25 mg, but this is not unexpected considering that this small dose of ramipril had a minimal blood pressure reduction of 1.5/0.3 mm Hg. These 5 trials, with initial blood pressures around 140 mm Hg, accounted for 99% of the mortality data in a meta-analysis of 11 placebo-controlled ACE inhibitor trials (n=21 997), where ACE inhibitors reduced the risk of all-cause mortality by 11% (HR, 0.89; CI, 0.89-0.99, \textit{P}=0.03)\textsuperscript{24} Five of the ARB trials (n=8 080) in the meta-analysis, which accounted for 85% of the mortality data, had an initial blood pressure of 140 mm Hg\textsuperscript{24} with blood pressure reductions similar to that seen in the ACE inhibitors meta-analysis of placebo-controlled trials. Despite similar reductions in blood pressure, the divergent mortality effects of ACE inhibitors and ARBs vs placebo (11% vs 0%), the true measure of drug efficacy, is disconcerting. In a more inclusive meta-analysis, ARBs also did not reduce mortality risk (HR, 0.94; 95% CI, 0.82-1.08) compared with all comparators (placebo or active therapy; 13 trials; n=23 867), nor did ARBs reduce the risk of cardiovascular deaths, myocardial infarction, or heart failure (Table II)\textsuperscript{24}

**DIVERGENT CARDIOVASCULAR EFFECTS OF ACE INHIBITORS AND ARBS IN PLACEBO-CONTROLLED TRIALS**

The divergent effect of ACE inhibitors and ARBs on mortality risk extends to trials that are not limited to patients with diabetes mellitus. Two separate meta-analyses of placebo-controlled ARB trials (17 trials; n=67 374 and 13 trials; n=54 221)\textsuperscript{25,26} observed no reduction in mortality (OR, 0.99; 95% CI, 0.95-1.03; \textit{P}=0.9 and OR, 1.01; 95% CI, 0.941-1.08; \textit{P}=0.866, respectively). In contrast, ACE inhibitors, in a meta-analysis of placebo-controlled trials (13 trials; n=53 791),\textsuperscript{26} significantly reduced all-cause mortality (OR, 0.91; 95% CI, 0.84-0.97; \textit{P}=0.008) as well as myocardial infarction (OR, 0.81; 95% CI, 0.74-0.87, \textit{P}<0.001). The risk of stroke, which is thought to be entirely dependent on blood pressure reductions,\textsuperscript{2} were significantly reduced in both the ACE inhibitor and ARB meta-analyses by 10% to 20%. The BPLTTC (Blood Pressure Lower-
ing Treatment Trialists Collaboration⁴ has confirmed the relationship of blood pressure to stroke by regressing the risk of stroke against blood pressure differences within the trials; ACE inhibitors and ARBs were identical with the risk of stroke being dependent on the degree of blood pressure lowering. Therefore, blood pressure differences are unlikely to account for the divergent mortality rates in the meta-analyses.

## THE ARB MI PARADOX: THE EVIDENCE IS THERE

The data is very compelling in the placebo-controlled trials that ACE inhibitors and ARBs have divergent effects on mortality,²⁴⁻²⁶ yet this is not a new concern. A 2004 editorial in the British Medical Journal²⁷ noted that ARBs were effective antihypertensive agents and well tolerated, but they did not reduce the risk of myocardial infarction or death in high-risk patients, as was observed with ACE inhibitors. In 2006, a parallel meta-analysis of ACE inhibitor and ARB trials vs all comparators (active or placebo)¹⁸ confirmed divergent cardiovascular effects of ACE inhibitors and ARBs. ACE inhibitors (39 trials, n=154,943) reduced the relative risk of total mortality by 9% (\(P<0.0001\)) and myocardial infarction by 14% (\(P<0.0001\)), whereas ARBs (11 trials; n=55,050) did not reduce mortality (OR, 1.01; 95% CI, 0.96-1.06; \(P=0.8\)) and the risk of myocardial infarction actually increased (OR, 1.08; 95% CI, 1.01-1.16; \(P=0.03\)).

**Figure 1.** A parallel meta-analysis of ACE inhibitors and ARB trials. ACE inhibitors reduced the relative risk of total mortality by 9% (\(P<0.0001\)) and myocardial infarction by 14% (\(P<0.0001\)), whereas ARBs (11 trials; n=55,050) did not reduce mortality (OR, 1.01; 95% CI, 0.96-1.06; \(P=0.8\)) and the risk of myocardial infarction actually increased (OR, 1.08; 95% CI, 1.01-1.16; \(P=0.03\)).

**Abbreviations:** ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; OR, odds ratio.


**Figure 2.** Parallel meta-regression analyses of the risk of MI and CV death against blood pressure reductions in ACE inhibitor and ARB trials. There was a 15% risk reduction in MI and CV death (\(P=0.0001\)) between ACE inhibitor trials (blue circles) and ARB trials (green circles).

**Abbreviations:** ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction; RRR, relative risk reduction.

that, ARBs did not reduce the risk of myocardial infarction or death as did ACE inhibitors—a phenomenon called the “ARB-MI Paradox.”

**BLOOD PRESSURE–INDEPENDENT EFFECTS OF ACE INHIBITORS AND ARBS**

The divergent cardiovascular effects of ACE inhibitors and ARBs, in both diabetics and nondiabetics alike, have been confirmed and quantified in a meta-regression analysis by the BPLTTC. Blood pressure differentials within ACE inhibitor and ARB trials were regressed against the risk of CHD, MI, and death. ACE inhibitors and ARBs have identical blood pressure–dependent risk reductions in CHD. However, for any given blood pressure reduction, ACE inhibitors reduced the risk of myocardial infarction and death by an additional 9% ($P=0.002$), which is not solely dependent on the effects of lowering blood pressure with the 9% relative risk reduction occurring even in the absence of any blood pressure reductions (Figure 2). In contrast, ARBs had no blood pressure–independent effects on CHD, rather there was a small nonsignificant 7% increase in the risk of harm relative risk reduction ($\Delta RR$, −7%; 95% CI, 7% to −24%; $P=ns$) (Figure 2). More importantly, for any given blood pressure reduction, ACE inhibitors as compared with ARBs, reduces the risk of MI and death by an additional 15%, which is above and independent of blood pressure lowering ($P=0.0001$, Figure 2). The meta-regression analysis is an eloquent confirmation of the “ARB-MI Paradox.”

**CONTEMPORARY HYPERTENSION TRIALS**

The approach to the high-risk patient, especially with regard to background medications in the management of diabetes mellitus, has evolved over the decades. A contemporary parallel meta-analysis of ACE inhibitor and ARB hypertension trials published after 2000 included high-risk patients not restricted to diabetes, although some trials were limited to diabetics. ACE inhibitors reduced all-cause mortality by 10% ($P=0.004$, 7 trials; $n=76,615$), whereas ARBs produced no mortality reduction (HR, 0.99; $P=0.683$; 13 trials; $n=82,383$). Although blood pressure differences were not reported within the trials, less than 20% of the patients in the ACE inhibitor meta-analysis were in placebo-controlled trials, whereas in the ARB meta-analysis more than 50% of the patients were in placebo-controlled trials. It would be fair to assume that blood pressure reductions within placebo-controlled trials would be significantly greater than when the comparator is another active therapy, suggesting a blood pressure lowering that would bias mortality reduction in favor of ARBs and not ACE inhibitors—blood pressure differences do not explain the mortality differences in the meta-analyses. It is interesting to note, and predictable, that when the ACE inhibitor and ARB trials were included in a composite meta-analysis as a single class of RAAS inhibitors (20 trials; $n=158,998$), there was a 5% risk reduction in all-cause mortality ($P=0.05$). However, all the mortality benefits were driven by the ACE inhibitor trials, whereas ARBs showed no mortality reduction, but simply attenuated the vascular benefits of ACE inhibitors.

**ANGIOTENSIN II, BRADYKININ, AT_1, AND AT_2 RECEPTORS: HOW IT IS ALL CONNECTED**

The unique blood pressure-independent effects of ACE inhibitors, as confirmed by others, have biological plausibility. ACE inhibitors suppress Ang II, which not only plays a central role in the pathophysiology of hypertension, but also has direct toxic effects on tissues including the vasculature, heart, brain, and kidneys. Suppression of Ang II levels with ACE inhibitors may attenuate the toxic tissue effects independent of lowering blood pressure. ACE inhibitors also prevent the breakdown of bradykinin, a peptide that is important mediator in ischemic preconditioning, endothelial function, and fibrinolysis, which are all tremendously important for cardiovascular protection.

**Figure 3. ACE inhibitors suppress angiotensin II levels and upregulate bradykinin.**

ACE inhibitors prevent the breakdown of bradykinin, a peptide that is an important mediator in ischemic preconditioning, endothelial function, and fibrinolysis, which are all tremendously important for cardiovascular protection.

**Abbreviations:** ACE inhibitors, angiotensin-converting enzyme inhibitors; Ang I, angiotensin I; Ang II, angiotensin II; AT_1, angiotensin II type 1 receptor; AT_2, angiotensin II type 2 receptor; AT_4, angiotensin II type 4 receptor.

tion, and fibrinolysis (Figure 3), which are all tremendously important for cardiovascular protection. In contrast to ACE inhibitors, ARBs do not upregulate bradykinin; therefore, lack the potential cardiovascular protection of bradykinin. Secondly, ARBs do not suppress Ang II levels, rather they selectively block the AT1 receptor. Both drugs attenuate the effects of Ang II, albeit by different mechanisms, however, AT1 receptor blockade with ARBs is known to inhibit a negative feedback reflex with a resulting increase in Ang II levels by 200% to 300%, which is a worrisome phenomenon considering that Ang II has direct tissue toxicity. Although increases in Ang II concentrations have been hypothesized to play a beneficial role via stimulation of the AT2 receptor with peripheral vasodilation, AT2 stimulation in diseased coronary arteries may lead to plaque rupture, myocardial infarction, and adverse vascular remodeling.

Clearly, this could minimize or negate the potential cardiovascular benefit of blood pressure lowering via AT1 receptor blockade with ARBs (Figure 4). Therefore, this is a plausible biologic explanation for the divergent mortality effects of ACE inhibitors and ARBs.

**CHRONIC KIDNEY DISEASE**

It is well known that renal disease, either a low estimated glomerular filtration rate (eGFR) or albuminuria, is an independent predictor for end stage renal disease and cardiovascular mortality with the highest risk in those with both an eGFR <60 mL/min per 1.73 m² and macroalbuminuria. Intensive blood pressure-lowering regimens reduced the risk of end stage kidney disease in patients with chronic kidney disease as compared with standard blood pressure-lowering regimens. How-ever, the benefit may be limited to patients with proteinuria suggesting that an intensive target blood pressure of 130/80 mm Hg may only be appropriate for these patients.

In patients with diabetic nephropathy, ACE inhibitors and ARBs in a meta-analysis of 24 trials, have similar and statistically significant risk reductions in serum creatinine doubling (29% and 21%, respectively) and end stage renal disease (30% \(P=0.08\) and 22%, respectively). The risk reductions were confirmed in a more recent meta-analysis, as were microvascular complications, macroalbuminuria, and regression of albuminuria. ACE inhibitors and ARBs provided greater nephroprotective benefits when compared with other antihypertensive agents (primarily calcium channel blockers) despite similar blood pressure reductions, which provided indirect evidence for renal benefits that are not solely due to blood pressure lowering.

The unique nephroprotective benefits of ACE inhibitors and ARBs in diabetic patients makes them a preferred first-line therapy in hypertension, both for prevention and treatment of nephropathy. However, as reviewed above, only ACE inhibitors reduced mortality in the diabetic population, and not ARBs, which actually increased cardiovascular mortality in a placebo-controlled trial despite significant reductions in both blood pressure and new onset of microalbuminuria.

It is intuitive that reducing the risk of mortality takes precedent over reducing the risk of end stage renal disease, especially considering mortality is the more frequent end point. All-cause mortality is 5 to 10 times more common than the risk of end stage renal disease in high-risk patients including diabetics with the highest absolute mortality rate in patients with an eGFR <60 and macroalbuminuria.29

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**Figure 4. Plaque rupture in coronary arteries with ARBs.**

Blocking AT1 with an ARB inhibits a negative feedback loop, increasing Ang II levels 2 to 3 fold, which leads to hyperstimulation of AT2 receptors and plaque rupture in coronary arteries.

*Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; Ang I, angiotensin I; Ang II, angiotensin II; ARB, angiotensin receptor blocker; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor; AT4, angiotensin II type 4 receptor. Modified from reference 18: Strauss and Hall. Circulation. 2006;114(8):838-854. © 2006, American Heart Association, Inc.*
CONCLUSIONS: MOVING FORWARD IN DIABETES MELLITUS

The data, as discussed in this review, whether it is the individual trials, meta-analyses against placebo or all comparators, or meta-regression analyses, show that ACE inhibitors provide unique cardiovascular protection in high-risk patients, including the diabetic population and specifically for myocardial infarction and death, that is not solely dependent on blood pressure lowering. There is also compelling evidence that a reasonable target blood pressure in diabetics is 130 to 135 mm Hg, at least when treatment is with an ACE inhibitor. ARBs have no similar data for cardiovascular protection.

No review of the cardiovascular effects of ACE inhibitors and ARB would be complete without a discussion of the ONTARGET trial (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial), a large head-to-head comparison of telmisartan with ramipril in high-risk patients that included 9 000 diabetic patients. The authors’ conclusion in the abstract states that “Telmisartan was not substantially worse than the gold standard (ramipril), by a pre-determined amount (equivalence margin),” which in no way reflects statistical equivalence, rather at best, the statistically “noninferior” therapy is a second-line therapy, at least as it applies to telmisartan.

Unfortunately, the results of ONTARGET do not support a conclusion of “equivalence,” nor do they support the approval of telmisartan as a first-line therapy for cardiovascular protection that followed from the European Medicines Agency (EMA). The ONTARGET trial was not designed or powered to test for statistical equivalence, and therefore, a conclusion of equivalence is not possible, even if event rates are the same—the absence of an apparent difference does not mean that a true difference does not exist. Rather, ONTARGET included an analysis for statistical “noninferiority”, a relatively recent addition to the statistical armamentarium, a statistical concept that can prove that telmisartan is “not substantially worse than the gold standard (ramipril), by a pre-determined amount (equivalence margin),” which in no way reflects statistical equivalence, rather at best, the statistically “noninferior” therapy is a second-line therapy, at least as it applies to telmisartan.

The above description of statistical noninferiority appears to be consistent with the European Medicines Agency analysis of ONTARGET in “The Assessment Report for Micardis” (London, 2009 #EMA/CHMP/768468/2009). That report concluded: “The data do not allow to conclude that the effect of ramipril is preserved (equivalence). Even superiority of telmisartan vs placebo was not demonstrated neither when compared to a putative placebo in ONTARGET, nor when directly compared with placebo in TRANSCEND and PROFESS.”

What is indeed perplexing, and confounds the practice of evidence-based medicine, is that despite the EMA concluding that telmisartan is not even superior to a placebo, it still approved telmisartan as a first-line agent, like ramipril, and it can, therefore, be prescribed preferentially to an ACE inhibitor. At most, one would have thought that telmisartan would have been approved as second-line therapy for those who are ACE intolerant, as did the Food and Drug Administration in the United States and the Health Protection Bureau in Canada.

FINAL THOUGHTS

It would seem the time has come, after randomized trials in over 300 000 patients, that there is ample evidence to distinguish ACE inhibitors and ARBs as unique therapeutic classes with divergent effects on mortality and myocardial infarction in diabetics and nondiabetics alike. This is an urgent “public health issue” of immense proportion and one that regulatory agencies and guideline committees must address—patients’ lives depend on it.

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Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis.

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there is a lengthy tradition of seeking medicinal therapy from natural products. Given the rapid advances in molecular biology and medicinal chemistry, the debt that we owe to agents isolated from natural sources is not adequately appreciated. In the field of cardiovascular therapy, the classical natural product and its derivatives is digitalis, isolated in 1756 from Digitalis purpurea (Figure 1).

Seeking medicines from animal, as opposed to plant, sources is much less frequent, except perhaps for endogenous peptides and hormones. An unexpected source of biologically active material is the venom of snakes. While snake envenomation is rare in European countries, there is a high incidence in Asia, Africa, and South America. For example, there has been a long tradition of research on the chemistry and biology of snake venom in South America, especially in Argentina and Brazil. This paper describes how studies on the mode of action of peptides isolated from the venom of the snake Bothrops jararaca (Figure 2, page 210) led to the development of inhibitors of the angiotensin-converting enzyme (ACE). An aspect of this work was described in a previous paper that did not provide a detailed account of the scientific work on snake venoms that led to this outcome.

Two outstanding pharmacologist colleagues, Professor Sérgio Henrique Ferreira and Professor John Vane, performed the relevant studies.

**Keywords:** angiotensin I, angiotensin-converting enzyme, bradykinin; bradykinin potentiating factor; peptides; snake venom

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**Figure 1.** Digitalis purpurea (purple foxglove). From: Deutschlands Wichtigste Giftgewächse (Germany’s Most Important Poisonous Plants), Richard Schimpfky, 1893. © akg-images/bilwissedition.

**BRADYKININ**

Professor Ferreira trained in the Faculty of Medicine of Ribeirão Preto and specialized in pharmacology in the University of São Paulo, Brazil. His mentor was Professor Mauricio Rocha e Silva, who made the initial discovery of bradykinin in plasma in 1948 using snake venom. This was made possible by observing the effects of injecting venom isolated from the snake B jararaca. A major effect of snake envenomation is hypotension and shock. It is estimated that about two thousand cases of snakebite accidents occur annually in the state of São Paulo, Brazil. There has been a long tradition of scientific interest in snake venom in Brazil, made possible by the creation of the Instituto Butantan, which is based in the university campus. Thus, the discovery of bradykinin started when Dr Rosenfeld brought snake venoms to Professor Rocha e Silva’s department because the latter had a longstanding interest in the cardiovascular effects of snake venoms.

The term bradykinin was proposed by Professor Rocha e Silva in 1949 based on his observation that incubating...
plasma with either trypsin or snake venom generated a factor that reduced blood pressure in experimental animals. In addition, this factor caused a gradual contraction of isolated muscles (gut or uterus). The terminology was derived from the Greek for “slow” (that is, bradys) and “to move” (kinein). Subsequent research on bradykinin showed that it causes pain, tissue edema, vasodilatation, and a reduction in blood pressure.\(^4\) Subsequently, it was shown that bradykinin is a 9-amino-acid peptide that is generated physiologically by the actions of plasma on tissue kallikreins (bradykinin structure: Arg-Pro-Pro-Gly-Phe-Ser-Pro-Phe-Arg).

**BRADYKININ-POTENTIATING FACTOR**

Snake venom can cause hypotension, shock, and death. Previous workers had suggested that snake venom released histamine, but Professor Rocha e Silva had discovered that the venom released bradykinin rather than histamine. Ferreira, working for his doctorate in pharmacology under Professor Rocha e Silva, showed that metal-binding compounds such as dimercaptopropanol (=BAL, British Anti-Lewisite) potentiated the actions of synthetic bradykinin in vitro and in vivo.\(^5,6\)

They then examined the effect of BAL on bradykinin in snake venom and, to their surprise, found that the venom itself contained a substance or substances that strongly enhanced the actions of bradykinin. Ferreira termed the substance bradykinin-potentiating factor (BPF), which is active in vitro and in vivo, and is specific for bradykinin, having no effect on the actions of histamine or acetylcholine responses. BPF was more effective at augmenting the actions of bradykinin than the compound BAL. In 1965, therefore, BPF was the most potent potentiator of the actions of bradykinin. BPF also enhanced the action of angiotensin I.\(^7\)

When Sérgio Ferreira completed his doctorate thesis in São Paulo, he decided to seek work in a British department of pharmacology. He was accepted by Professor Paton at the University of Oxford, but Sergio’s wife wished to attend courses in a London university. As a consequence, Sergio applied for a post with Professor Vane in the Department of Pharmacology of the Royal College of Surgeons in London. He brought with him a supply of extracts of snake venom. The isolated peptides were studied for their effects on bradykinin-induced contraction of the guinea pig ileum. The most potent of these peptides was the pentapeptide V-3-b, which was subsequently synthesized by Greene and Stuart.\(^16,18\) A pivotal

In 1968, Ng and Vane\(^14\) demonstrated that angiotensin I was converted to angiotensin II by passage through the pulmonary circulation of the dog, but was minimally affected by perfusion through other tissues. In the same year, Bakhe,\(^15\) also working in Vane’s laboratory, showed that a supernatant aqueous extract of canine lung contained peptidases that converted angiotensin I to angiotensin II. BPF was shown to be an inhibitor of this converting enzyme activity. At this stage, the composition and structure of BPF were unknown, so Ferreira initiated a collaborative study on the nature of BPF with Dr Lewis Greene of Brookhaven University (New York) who was invited by Professor Rocha e Silva to visit his laboratories in Brazil. Applying ultrafiltration and gel filtration techniques it was possible to identify nine peptide structures from the snake venom. The isolated peptides were studied for their effects on bradykinin-induced contraction of the guinea pig ileum. The most potent of these peptides was the pentapeptide V-3-b, which was subsequently synthesized by Greene and Stuart.\(^16,18\) A pivotal

**Figure 2. Bothrops jararaca (Brazilian pit viper).** © Mark Moffett/Minden Pictures/Corbis.
paper was published in 1970 that involved most of Vane’s coworkers, who demonstrated, for the first time, that inhibition of pulmonary kininase by a synthetic peptide based on BPF inhibited the conversion of angiotensin I to angiotensin II, that is, the first ACE inhibitor. The pentapeptide was prepared by Greene when Ferreira was working with him in the Brookhaven National Laboratory, sponsored by the Atomic Energy Commission and the Brazilian FAPESP (Fundacao de Amparo a Pesquisa do Estado de Sao Paulo, Brazil). It was one of the 22 peptides tested for comparative effectiveness, both on the action of bradykinin and ACE. This paper is notable in that clearly Ferreira was the prime mover in attempting to identify a specific kininase inhibitor based on a combination of chemical isolation techniques followed by specific peptide synthesis.

A key translational experiment was reported in the Lancet in 1971 by Ferreira and collaborators that showed that the pentapeptide blocked the hypertensive actions of angiotensin I as a test for the role of the renin-angiotensin system in experimental hypertension in the rat. The role of serendipity in the characterization of BPF is summarized in Table I.

THE FORK IN THE ROAD

One of the classical challenges in scientific research is the decision to change or maintain a successful research strategy. In the current example of Vane and Ferreira’s collaboration, having identified a specific synthetic inhibitor of the kininase carboxypeptidase A, should efforts be made in order to find a more practical, that is, orally active inhibitor, to explore the role of angiotensin I in essential hypertension, or should BPF properties be explored further? As so often happens in scientific research, serendipity and networking play a key role. In this instance, Vane decided to contact the

Ferreira returned to the Department of Pharmacology in the Faculty of Medicine at the University of Sao Paulo, Ribeirao Preto, in the early 1970s and worked on the biological effects of his pentapeptide on experimental hypertension. Then, he began to publish papers on the role of prostaglandins in inflammatory responses. Since the coauthors included both Vane and Moncada, it would seem that Ferreira’s scientific interests moved from studying the properties of BPF to the recently discovered prostaglandin synthesis, as illustrated by the effects of aspirin (1971-1973). Ferreira’s last joint publication with Vane was in 1976, although he coauthored 3 papers with Vane’s collaborators between 1971 and 1976.

In a review on the history of the development of ACE inhibitors, Ferreira stated that “in 1970, I realized that as a basic pharmacologist, my contribution to the field was complete since I was neither an expert in hypertension nor a clinical pharmacologist nor an inspired chemist able to transform these expensive peptides into useful

Table I. Selected serendipitous events in the discovery of ACE inhibitors.

<table>
<thead>
<tr>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferreira’s observation that snake venom enhanced the action of BPF</td>
</tr>
<tr>
<td>Postgraduate studies with Vane in the Department of Pharmacology instead of Professor Paton (Oxford) for social reasons</td>
</tr>
<tr>
<td>Brought snake venom extracts to Vane’s lab and tested BPF in Vane’s superfusion apparatus</td>
</tr>
<tr>
<td>Isolation of pentapeptide from venom</td>
</tr>
</tbody>
</table>

Research Director Arnold Welch of the Squibb Company, USA, to propose a chemistry program in order to identify an orally active inhibitor of ACE. As it happens, Vane had worked with Welch when the latter was Professor of Pharmacology at Yale University prior to joining Squibb. After considerable debate within the company, a research project to find an orally active ACE inhibitor was initiated.

Perhaps it was these reflections in the early 1970s that resulted in Ferreira's change to studying the field of prostaglandin biology. In a PubMed survey (August 1, 2014), 294 papers are listed with Ferreira as a coauthor. The majority of the later papers are devoted to studies on analgesia mechanisms, interleukins, and prostaglandins. The change in research direction in the early 1970s clearly led to further exciting pharmacological mechanistic discoveries.

It is, however, appropriate that Ferreira's role in the discovery of ACE inhibitors was recognized by the CIBA Award for Hypertension Research in 1983 (Figure 3, page 211). Last year, at the 2013 SOCESP Congress (Congresso da Sociedade de Cardiologia do Estado de São Paulo), Professor Alistair Hall, Consultant in Cardiology at the Cardiology Research Unit, General Infirmary at Leeds, UK, presented Professor Sérgio H. Ferreira with a commemorative plaque (Figure 4) honoring a lifetime of research into ACE inhibitors, on the occasion of the launch of the "Professor Sérgio Prize," which will recompense outstanding clinical research on ACE inhibitors in Brazil.

**REFERENCES**


Prevention of Myocardial Infarction With ACE Inhibitors

Summaries of Ten Seminal Papers

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Leeds Teaching Hospitals NHS Trust - UK - University of Leeds - Leeds - UK (e-mail: r.khatib@leeds.ac.uk)


1. Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril
   M. A. Pfeffer and others. Circulation. 1985

2. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study

3. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions
   S. Yusuf and others. Lancet. 1992

4. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction...

5. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure
   The AIRE Study Investigators. Lancet. 1993

6. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction

7. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients

8. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients
   M. D. Flather and others. Lancet. 2000

9. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease...
   K. M. Fox and others. Lancet. 2003

10. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure...
    G. R. Dagenais and others. Lancet. 2006

Selection of seminal papers by Rani Khatib, MRPharmS, IPresc, BPharm (Hons), DPharm (PhD) - Leeds Teaching Hospitals NHS Trust - UK
University of Leeds - Leeds - UK

Highlights of the years by Sherri Smith, PhD
Publications division
Summaries of Ten Seminal Papers - Khatib

Survival after an experimental myocardial infarction: beneficial effects of long-term therapy with captopril

M. A. Pfeffer, J. M. Pfeffer, C. Steinberg, P. Finn


Pfeffer et al conducted this in vivo study that was the first to look into the impact of treatment with angiotensin-converting enzyme (ACE) inhibitors on survival in the context of myocardial infarction associated with heart failure. While it had already been shown that ACE inhibitor therapy in patients with severe heart failure led to improvement in functional capacity, it remained unclear whether such intervention might result in a prolongation of life in the presence of advanced congestive heart failure.

One of the aims of the investigation was to test the hypothesis that the ACE inhibitor captopril, known at that time to have a beneficial hemodynamic effect on ventricular performance, might prevent death after experimental myocardial infarction. Three hundred and two rats were randomly assigned to receive either captopril or placebo, starting 14 days after coronary artery ligation. The follow-up at year 1 revealed the dramatic finding of improved survival and helped to “kick-start” the further development of ACE inhibitors in man. Animals with myocardial infarctions of moderate size had the most marked improvement in survival (Figure 1), suggesting a “U”-shaped relationship between efficacy and left ventricular function. The mechanism of benefit was further suggested as being the prevention of adverse remodeling of the left ventricle with aneurysm scar formation, eccentric hypertrophy, and overall dilatation. This information also helped direct medical investigators to assess this set of changes as a surrogate for mortality benefit. In this way, it was possible to assess optimal treatment strategies in a smaller number of patients evaluated by echocardiography.

The performance of a randomized controlled trial in a cohort of rats was a unique first in the field of cardiovascular science and showed an immediate and beneficial translation into clinical practice and human benefit.

**Figure 1.** Survival of rats with moderate myocardial infarctions that had been treated with either water or captopril.


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Bíró László József, the inventor of the modern ballpoint pen, dies at age 86; Thomas Patrick Cavanaugh is sentenced to life in prison for attempting to sell stealth bomber secrets to the Soviet Union; and John Gotti becomes the leader of the powerful Gambino organized crime family in New York City, USA after the shooting of the two Mafia bosses Paul Castellano and Thomas Bilotti
Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

The CONSENSUS Trial Study Group


The CONSENSUS-I trial (COoperative North Scandinavian Enalapril Survival Study) was the first major human mortality trial of angiotensin-converting enzyme (ACE) inhibitor therapy in congestive heart failure. It was stopped prematurely by the Independent Data Review Committee due to overwhelming evidence of benefit from oral enalapril therapy. The survival benefit observed challenged the prevailing belief, at the time, that only cardiac transplantation could influence the natural history of end-stage heart failure. Drugs, such as loop diuretics and digoxin, produced symptomatic palliation, but they have not been established as providing overall prognostic benefit. This study prompted others to assess intervention at earlier stages of the disease process such as after myocardial infarction or in patients with asymptomatic left ventricular dysfunction.

Patients included in this randomized, double-blind, placebo-controlled trial were those who had a clinical diagnosis of severe congestive heart failure (symptoms at rest, New York Heart Association [NYHA] IV) irrespective of left ventricular ejection fraction. Patients treated with enalapril were more likely to improve their NYHA classification (Table I) than were placebo-treated patients (42% vs 22%) and had a favorable reduction in heart size and a reduced need for other medications for heart failure. There was a statistically and clinically significant 40% reduction in all-cause mortality in patients with severe NYHA IV symptoms. At 1 year, absolute mortality was reduced from 52% with placebo to 36% with enalapril. Furthermore, the survival benefits were maintained among patients receiving enalapril at a 2-year follow-up. While no difference was found in the incidence of sudden cardiac death, reduction in total mortality was found to be mainly due to reduction in progression of heart failure. The authors concluded that “the addition of enalapril to conventional therapy in patients with severe congestive heart failure can reduce mortality and improve symptoms.” This statement has since been substantiated by additional studies and repeated in clinical guidelines across the world.

<table>
<thead>
<tr>
<th>NYHA classification at the end of the study</th>
<th>Placebo (n=126)</th>
<th>Enalapril (n=127)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>0 (0%)</td>
<td>3 (23.6%)</td>
</tr>
<tr>
<td>NYHA II</td>
<td>2 (1.6%)</td>
<td>13 (10.2%)</td>
</tr>
<tr>
<td>NYHA III</td>
<td>25 (19.8%)</td>
<td>38 (29.9%)</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>30 (23.8%)</td>
<td>21 (16.5%)</td>
</tr>
<tr>
<td>Total mortality</td>
<td>68 (54%)</td>
<td>50 (39%)</td>
</tr>
</tbody>
</table>

Table I. Improvements in NYHA classification with enalapril. Abbreviation: NYHA, New York Heart Association.

1987

Aretha Franklin becomes the first woman inducted into the Rock and Roll Hall of Fame; Nikolaus ‘Klaus’ Barbie, also known as the “Butcher of Lyon,” goes on trial in Lyon, France for war crimes committed during World War II; and Maria Augusta von Trapp, the stepmother and matriarch of the Trapp Family Singers, dies at age 82 from heart failure.
Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions


Lancet. 1992;340(8829):1173-1178

Various studies have shown an association between high renin levels and the incidence of myocardial infarction, stroke, or death. However, in the 1980s, it remained unclear if increases in renin reflected the extent of underlying cardiac dysfunction due to advanced coronary atherosclerosis or if the stimulation of the renin-angiotensin system was directly involved in the pathogenesis of myocardial infarction. The SOLVD trials (Studies Of Left Ventricular Dysfunction) attempted to answer this uncertainty by performing a seminal, hypothesis-generating, posthoc analysis.

The SOLVD trials were large randomized, placebo-controlled studies that assessed whether the use of enalapril reduces the risk of death and heart failure progression in symptomatic or asymptomatic patients with impaired left ventricular function. The investigators then observed an unexpected finding—namely an apparent reduction in myocardial infarction or unstable angina (Table I) in patients with low ejection fraction (≤35%) already receiving treatment with diuretics, digitalis, or vasodilators other than angiotensin-converting enzyme (ACE) inhibitors. While myocardial infarction was identified as a secondary end point in the protocol, there was no objective criteria for the diagnosis of unstable angina. Therefore, results for unstable angina were interpreted cautiously. Substudies also demonstrated an attenuation of systemic neuroendocrine activation as a possible mechanism by which benefits were produced. Both trials clearly demonstrated reductions in the primary end point of death and development of overt signs of heart failure following treatment with a twice-daily oral enalapril.

The findings with regard to prevention of myocardial infarction were intriguing and raised the possibility of a wider role for ACE inhibitors in preventing major ischemic events in other populations.

### Table I. Effect of enalapril on myocardial infarction and hospitalizations for angina.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Enalapril</th>
<th>RRR (95% CL)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>362 (10.6)</td>
<td>288 (8.5)</td>
<td>23 (11, 34)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hospitalizations for angina</td>
<td>595 (17.5)</td>
<td>499 (14.7)</td>
<td>20 (9, 29)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CL, confidence levels; RRR, relative risk reduction.

1992

Two skeletons excavated in Yekaterinburg, Russia are identified as Tsar Nicholas II of Russia and Tsarina Alexandra; Dr Mae Jemison becomes the first African American woman to travel into space aboard the Space Shuttle Endeavour; and Ástor Piazzolla, an Argentine tango composer, dies at age 71.
Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial


Following-on directly from a randomized controlled survival study in rats, the SAVE trial (Survival And Ventricular Enlargement) sought to translate findings from the laboratory to the coronary care unit. Another objective was to seek to arrest the early development of adverse left ventricular remodeling and, hence, the occurrence of overt heart failure. Knowing that left ventricular dilatation and dysfunction after a myocardial infarction are both major predictors of death, and also on the premise that these are attenuated by angiotensin-converting enzyme (ACE) inhibition, the SAVE trial assessed the use of oral captopril titrated to a target dose of 50 mg three times daily. Patients were selected based on the occurrence of myocardial infarction and the measurement of a left ventricular ejection fraction ≤40%. Patients with persisting symptomatic heart failure were excluded, although those with transient acute failure were able to be included.

Based on a randomized, double-blind, placebo-controlled trial design, with an average follow-up of 42 months, it was observed that captopril-treated patients were significantly less likely to die (Figure 1). Cardiovascular death and the incidence of heart failure requiring hospitalization were also significantly reduced, as was the incidence of recurrent myocardial infarction. This last finding was unexpected, though it seemed to support similar observations from the SOLVD trials (Studies Of Left Ventricular Dysfunction). The SAVE trial affected routine practice in hospitals where the measurement of ejection fraction was routine, but some controversy remained regarding the method and timing of measurement. A position of equipoise/uncertainty was present considering that this was the first study of ACE inhibitors in this clinical setting as well as the subsequent absence of benefit that had been observed in the CONSENSUS-II study (COoperative North Scandinavian Enalapril SUrvival Study) on early intravenous ACE inhibitors.

![Figure 1. Event rate of death due to fatal or nonfatal cardiovascular events.](image)

Abbreviations: CHF, chronic heart failure; CV, cardiovascular; MI, myocardial infarction.


1992

Joe Shuster, cocreator of the DC Comics character Superman, dies at 78 of congestive heart failure and hypertension; extrasolar planets are discovered; and George HW Bush is televised vomiting into the lap of Japanese Prime Minister Kiichi Miyazawa and fainting at a state dinner in Japan
Mortality was evaluated when using angiotensin-converting enzyme (ACE) inhibitors beyond the third day after an acute myocardial infarction (day 1) during the AIRE trial (Acute Infarction Ramipril Efficacy). The trial evaluated the effect of ramipril at a target oral dose of 5 mg twice daily for postmyocardial infarction patients who exhibited clinical signs or symptoms of heart failure, either transient or ongoing. The AIRE trial excluded patients with severe heart failure. The rationale was based on evidence that showed that patients who had clinical evidence of heart failure after myocardial infarction had a poor outcome even if the manifestations of failure resolved within the first 24 hours. AIRE was an international, multicenter, multinational, double-blind, randomized, placebo-controlled study.

The average time from myocardial infarction to treatment initiation was 5 days and the average follow-up was 15 months. AIRE showed a significant reduction in the risk of the primary end point of all-cause mortality for patients randomized to receive ramipril. Also significantly reduced was the secondary combined end point of death or development of severe heart failure (Table I). Myocardial infarction was reduced nonsignificantly by just 10%, even though a later paper assessing a 5-year follow-up (AIREX) demonstrated this to be a primary mechanism by which death was prevented.

The authors of AIRE concluded that administering ramipril to patients with clinical evidence of either transient or ongoing heart failure, initiated between days 2 and 9 after a myocardial infarction, resulted in a substantial reduction in premature death from all causes. AIRE’s findings meant that clinicians were able to identify patients simply based on clinical criteria. Furthermore, following the contradictory SAVE trial (Survival And Ventricular Enlargement) and CONSENSUS-II study (COoperative North Scandinavian Enalapril Survival Study), it was possible to end any ongoing uncertainty regarding the value of this mode of therapy.

<table>
<thead>
<tr>
<th>Placebo (n=982)</th>
<th>Ramipril (n=1004)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary end point:</strong></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>222 (23%)</td>
</tr>
<tr>
<td><strong>Secondary end points:</strong></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>118 (12%)</td>
</tr>
<tr>
<td>Severe/resistant heart failure</td>
<td>133 (14%)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>71 (7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (2%)</td>
</tr>
<tr>
<td>Any event</td>
<td>337 (34%)</td>
</tr>
</tbody>
</table>

Table I. Incidences of primary and secondary end points.
A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction

L. Køber, C. Torp-Pedersen, J. E. Carlsen, H. Bagger, P. Eliasen, K. Lyngborg, J. Videbaek, D. S. Cole, L. Auclert, N. C. Pauly; Trandolapril Cardiac Evaluation (TRACE) Study Group


The TRACE study (TRAndolapril Cardiac Evaluation) was another randomized, prospective, double-blind, placebo-controlled trial that evaluated the impact of angiotensin-converting enzyme (ACE) inhibitors on mortality when used days after an acute myocardial infarction. The TRACE study enrolled patients with echocardiographic evidence of left ventricular dysfunction equivalent to a left ventricular ejection fraction of <35%. Inclusion was regardless of signs and symptoms of heart failure, and as such had a design more similar to the SAVE trial (Survival And Ventricular Enlargement) than to the AIRE trial (Acute Infarction Ramipril Efficacy). This fact was further emphasized by the substantial number (42%) of patients that had no signs or symptoms of transient or persistent heart failure.

Similar to AIRE, the average time after myocardial infarction for initiation of treatment was 4.5 days with a follow-up between 24 and 50 months. At study close, both all-cause mortality and progression to severe heart failure were reduced in patients randomized to receive treatment with oral trandolapril 4 mg (Figure 1). Recurrent myocardial infarction was also reduced, though this did not achieve statistical significance. The TRACE authors concluded that at least two-thirds of patients who have echocardiographic signs of left ventricular systolic dysfunction three to seven days after a myocardial infarction are candidates for long-term treatment with ACE inhibitors.

Alison Hargreaves becomes the first woman to climb Mt Everest alone without the aid of Sherpas or bottled oxygen; French woman Jeanne Calment reaches the confirmed age of 120 years and 238 days, making her the oldest person ever recorded; and sudden oak death, the tree disease caused by the plant pathogen *Phytophthora ramorum*, is first observed, in California, USA
Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators

S. Yusuf, P. Sleight, J. Pogue, J. Bosch, R. Davies, G. Dagenais


While previous studies examined the effect of angiotensin-converting enzyme (ACE) inhibitors in patients with symptomatic or asymptomatic heart failure, the HOPE study (Heart Outcomes Prevention Evaluation) evaluated the impact of ACE inhibitor use (ramipril 10 mg orally at night) on cardiovascular outcomes in selected high-risk patients. Specifically, selection was based on a patient being older than 55 years and having evidence of vascular disease or diabetes. It was also necessary to have at least one other risk factor as well as having no evidence of heart failure or low ejection fraction. A formal measurement of left ventricular function was not required to create an inclusive design across many countries internationally. Patients with hypertension could also be included so long as they were on stable and effective treatment prior to the study.

Compared with placebo, ramipril significantly reduced the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients (*Table I*).

These benefits appeared to be independent of peripheral mean blood pressure reduction, although this became an issue for debate and controversy. As many patients were also taking effective treatments such as aspirin, β-blockers, and lipid-lowering agents, it was suggested that ACE inhibitors offered an additional approach to the prevention of atherothrombotic complications. Specifically, these data indicated that treating 1000 high-risk patients with ramipril for 4 years would be expected to prevent a total of 150 major events in 70 patients. These data have not been rigorously applied to routine care, though they have influenced the thoughts regarding the overall benefits of ACE inhibitors as a drug class.

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Placebo (n=4645)</th>
<th>Ramipril (n=4652)</th>
<th>RRR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite: Myocardial infarction, stroke, or death from cardiovascular causes</td>
<td>826 (17.8%)</td>
<td>651 (14.0%)</td>
<td>0.78 (0.70-0.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>570 (12.3%)</td>
<td>459 (9.9%)</td>
<td>0.80 (0.70-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>226 (4.9%)</td>
<td>156 (3.4%)</td>
<td>0.68 (0.56-0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>377 (8.1%)</td>
<td>282 (6.1%)</td>
<td>0.74 (0.64-0.87)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Table I. Primary outcome incidences.*

*Abbreviations: CI, confidence interval; RRR, relative risk reduction.*

A rare century leap year date occurs, the first year divisible by 4 to have a February 29 since the year 1600, making it only the second such occasion since leap years were introduced in the late 16th century; the Øresund Bridge between Denmark and Sweden opens; and Charles M. Schulz, the American comic strip artist of the Peanuts, dies at age 77.
Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients

M. D. Flather, S. Yusuf, L. Køber, M. Pfeffer, A. Hall, G. Murray, C. Torp-Pedersen, S. Ball, J. Pogue, L. Moyé, E. Braunwald; ACE-Inhibitor Myocardial Infarction Collaborative Group

Lancet. 2000;355(9215):1575-1581

Lather et al provided this prospective systematic overview based on data from individual patients from five long-term randomized trials; SAVE (Survival And Ventricular Enlargement), AIRE (Acute Infarction Ramipril Efficacy), TRACE (TRAndolapril Cardiac Evaluation), SOLVD Treatment (Studies Of Left Ventricular Dysfunction) and SOLVD Prevention. These studies all assessed angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction or clinical heart failure. Use of data from individual patients provided more information than was available from the use of published summary data. This allowed an estimation of overall treatment effect size and the effects of treatments in subgroups of patients.

The overview was limited to randomized trials in which patients were treated with ACE inhibitors or placebo after myocardial infarction for at least 12 months. The sample size of each trial was more than 1000 patients. Their consistency was examined with the SOLVD trials, which mostly recruited patients with prior myocardial infarction at a distant time. Patients with left ventricular dysfunction after myocardial infarction who were treated with ACE inhibitors had significant overall reduction in death, myocardial infarction, and hospital admission for heart failure (Table I).

There was great consistency between trials and with the SOLVD trials. While there were greater benefits (mortality and hospital admission for heart failure) seen in patients with lower ejection fractions, there was a clinically important benefit even among patients with relatively preserved ejection fractions. The overview was also important in refuting the hypothesis of a major aspirin interaction with ACE inhibitors and indicated an additive beneficial effect of an ACE inhibitor in patients receiving β-blockers. This paper is often cited by guidelines recommending that ACE inhibitors be used routinely after acute myocardial infarction in a wide range of patients. Those with clinical heart failure or left ventricular dysfunction are seen to benefit the most from substantial reductions in mortality and morbidity.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ACE inhibitors</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVE/AIRE/TRACE</td>
<td>Death, MI, or readmission for heart failure</td>
<td>1244 (41.9%)</td>
<td>1049 (35.0%)</td>
<td>0.75 (0.67-0.83)</td>
</tr>
<tr>
<td>SOLVD</td>
<td>Death, MI, or readmission for heart failure</td>
<td>1366 (40.2%)</td>
<td>1112 (32.7%)</td>
<td>0.70 (0.64-0.83)</td>
</tr>
<tr>
<td>Total</td>
<td>Death, MI, or readmission for heart failure</td>
<td>2610 (41.0%)</td>
<td>2161 (33.8%)</td>
<td>0.72 (0.67-0.78)</td>
</tr>
</tbody>
</table>

Table I. ACE inhibitor effects on primary outcomes.

Abbreviations: ACE inhibitors, angiotensin-converting enzyme inhibitors; AIRE, Acute Infarction Ramipril Efficacy; CI, confidence interval; OR, odds ratio; SAVE, Survival And Ventricular Enlargement; SOLVD, Studies Of Left Ventricular Dysfunction; TRACE TRAndolapril Cardiac Evaluation.

2000

Carl Barks, an American cartoonist known for his Donald Duck cartoons, dies at age 99; the Tate Modern Gallery opens in London; and the Confederate submarine H. L. Hunley is raised to the surface after 136 years on the ocean floor.
Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study)

K. M. Fox; EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators

Lancet. 2003;362(9386):782-788

Beneficial effects of angiotensin-converting enzyme (ACE) inhibitors on cardiovascular outcomes in a variety of patient groups was further explored in the EUROPA trial (EUropean trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease). EUROPA evaluated a broad population of patients with stable coronary heart disease and without clinical heart failure. Similar to the HOPE study (Heart Outcomes Prevention Evaluation), patients with known left ventricular systolic dysfunction were excluded, as were patients with poorly controlled hypertension. Overall, patients had a lower level of cardiovascular risk than those in the HOPE study, possibly due to the focus on stable coronary artery disease. Most patients were fully revascularized at entry into the study.

After a mean follow-up of 4.2 years, perindopril 8 mg orally (added to standard background secondary prevention therapy) significantly reduced the relative risk of the composite primary end point of cardiovascular death, myocardial infarction, or cardiac arrest (Table I). These findings extended the benefits of ACE inhibition relative to placebo, but they were also met with debate and controversy regarding the likely mechanism of benefit. EUROPA substudies pointed to improvements in endothelial function. The authors concluded that ACE inhibitors, in addition to other secondary prevention therapies, should be considered irrespective of cardiac function or risk factors for all patients with coronary heart disease. Further estimations show that 50 patients with coronary heart disease need to be treated with an ACE inhibitor for a period of 4 years to prevent one major cardiovascular event.

<table>
<thead>
<tr>
<th>Primary outcomes</th>
<th>Placebo (n=6108)</th>
<th>Perindopril (n=6110)</th>
<th>RRR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined: Cardiovascular mortality, myocardial infarction, or cardiac arrest</td>
<td>603 (9.9%)</td>
<td>488 (8.0%)</td>
<td>20% (9 to 29)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>249 (4.1%)</td>
<td>215 (3.5%)</td>
<td>14% (–3 to 28)</td>
<td>0.107</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>378 (6.2%)</td>
<td>295 (4.8%)</td>
<td>22% (10 to 33)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>11 (0.2%)</td>
<td>6 (0.1%)</td>
<td>46% (–47 to 80)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table I. Frequency of primary outcomes.

Abbreviations: CI, confidence interval; RRR, relative risk reduction.

An American businessman is admitted to the Vietnam-France Hospital in Hanoi, Vietnam, with the first identified case of SARS; Benvenuto Cellini’s Saliera is stolen from the Kunsthistorisches Museum in Vienna; and Europe’s busiest shopping center, the Bullring in Birmingham, UK, is officially opened by Sir Albert Bore
Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials

G. R. Dagenais, J. Pogue, K. Fox, M. L. Simoons, S. Yusuf

Lancet. 2006;368(9535):581-588

Another landmark systematic review explored the use of angiotensin-converting enzyme (ACE) inhibitors in patients with stable vascular disease without known heart failure or left ventricular systolic dysfunction. The review looked at three major trials: HOPE (Heart Outcomes Prevention Evaluation), EUROPA (EUropean trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease), and PEACE (Prevention of Events with ACE inhibition) studies. The aim was to determine the consistency in reducing total mortality as well as fatal and nonfatal cardiovascular events by ACE inhibitors in this population. ACE inhibitor use resulted in a significant reduction in mortality, nonfatal myocardial infarction, all stroke, and also the need for coronary-artery bypass surgery (Table I). However, they did not reduce the need for percutaneous coronary intervention. Compared with five large trials of ACE inhibitors in patients with heart failure or left ventricular systolic dysfunction, the benefits were consistent, although they showed an additional benefit for prevention of stroke and the need for coronary revascularization. There were clear additional benefits for ACE inhibitors in patients receiving secondary prevention therapies (lipid-lowering agents, β-blockers, and antiplatelets alone or combined). Furthermore, patients across a broad range of risk for cardiovascular events benefited from ACE inhibitors, indicating no treatment threshold, at least in patients with documented vascular disease.

### Table I. Effect of ACE inhibitors on primary outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Controls events/patients (%)</th>
<th>ACE inhibitors events/patients (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>569 (12.2)</td>
<td>482 (10.4)</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td></td>
<td>Nonfatal MI</td>
<td>351 (7.5)</td>
<td>273 (5.9)</td>
<td>0.77 (0.65-0.90)</td>
</tr>
<tr>
<td>HOPE</td>
<td>All-cause stroke</td>
<td>226 (4.9)</td>
<td>156 (3.4)</td>
<td>0.68 (0.55-0.84)</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
<td>439 (9.4)</td>
<td>352 (7.6)</td>
<td>0.79 (0.68-0.91)</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>420 (6.9)</td>
<td>375 (6.1)</td>
<td>0.89 (0.77-1.02)</td>
</tr>
<tr>
<td>EUROPA</td>
<td>Nonfatal MI</td>
<td>378 (6.2)</td>
<td>295 (4.8)</td>
<td>0.77 (0.66-0.90)</td>
</tr>
<tr>
<td></td>
<td>All-cause stroke</td>
<td>102 (1.7)</td>
<td>98 (1.6)</td>
<td>0.96 (0.73-1.27)</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
<td>288 (4.7)</td>
<td>276 (4.5)</td>
<td>0.96 (0.81-1.13)</td>
</tr>
<tr>
<td></td>
<td>All-cause mortality</td>
<td>334 (8.1)</td>
<td>299 (7.2)</td>
<td>0.88 (0.75-1.04)</td>
</tr>
<tr>
<td>PEACE</td>
<td>Nonfatal MI</td>
<td>220 (5.3)</td>
<td>222 (5.3)</td>
<td>1.00 (0.83-1.21)</td>
</tr>
<tr>
<td></td>
<td>All-cause stroke</td>
<td>92 (2.2)</td>
<td>71 (1.7)</td>
<td>0.76 (0.56-1.04)</td>
</tr>
<tr>
<td></td>
<td>CABG</td>
<td>271 (6.5)</td>
<td>294 (7.1)</td>
<td>0.91 (0.77-1.08)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACE inhibitors, angiotensin-converting enzyme inhibitors; CABG, coronary artery bypass graft; CI, confidence interval; EUROPA, EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease; HOPE, Heart Outcomes Prevention Evaluation; OR, odds ratio; PEACE, Prevention of Events with Angiotensin Converting Enzyme inhibition.

2006

The Walt Disney Company buys Pixar for 7.4 billion dollars; a swan with avian flu is discovered in Cellardyke in Fife, Scotland, making it the first case in the UK; and the world’s largest mud volcano is created by the blowout of a natural gas well being drilled in the subdistrict of Porong, Sidoarjo in East Java, Indonesia.
## Prevention of Myocardial Infarction With ACE Inhibitors

### Bibliography of One Hundred Key Papers

selected by **Alistair S. Hall, MB, ChB, PhD, FRCP, FESC**

Leeds MRC Medical Bioinformatics Centre - Leeds Medical School - University of Leeds - UK

(e-mail: a.s.hall@leeds.ac.uk)

<table>
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<tr>
<th>Author(s)</th>
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<tr>
<th>Authors</th>
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</table>
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<table>
<thead>
<tr>
<th>Author(s)</th>
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<tbody>
<tr>
<td>Author(s)</td>
<td>Title</td>
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<td>-------------------------------------------------------------------------</td>
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