DIAL☺GUES

Different Strategies to Control the Renin-Angiotensin System

Lead Article

Expert Answers to Three Key Questions

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Preserving bradykinin or blocking angiotensin II: the cardiovascular dilemma

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The angiotensin-converting enzyme (ACE) is a largely tissue-based zinc metalloprotease that regulates the balance between the vasoconstriction and salt retention induced by angiotensin II, via the angiotensin II type 1 (AT_1) receptor, and the vasodilator and natriuretic properties of bradykinin. ACE inhibition decreases angiotensin II production and increases bradykinin availability. Since increased ACE is induced in virtually every model of cardiac injury—volume overload, atherosclerotic plaque, infarction, postinfarction remodeling, heart failure, and aging—renin-angiotensin system (RAS) blockade has become the universal first-line strategy. ACE inhibitors may be less specific in their blockade of angiotensin II than AT_1 receptor blockers, but they confer valuable cardiovascular protection by increasing the availability of bradykinin. If anything, the bradykinin effect compensates for the incomplete blockade of angiotensin II. ACE inhibitors thus remain the gold standard RAS blocker. Not only have their safety and efficacy been extensively documented, but they confer benefits that are at once biological, structural, and neuroendocrine across diseases as clinically diverse as hypertension, congestive heart failure, ischemic heart disease, myocardial infarction, and diabetic or nondiabetic nephropathy.

In the 1970s, a series of observations reported that angiotensin II (Ang II) had deleterious effects on the heart, vessels, and kidney. Then came the discovery and development of drugs blocking the renin-angiotensin system (RAS), which clarified the role of this system in several pathological conditions and led to the widespread use of angiotensin-converting enzyme (ACE) inhibitors in the treatment of cardiovascular and renal disease. Originally, these drugs were developed as therapeutic agents targeted to treat hypertension, but several clinical conditions were subsequently identified—such as congestive heart failure (CHF) and acute myocardial infarction (AMI)—in which they were also found to be effective. More recently, ACE inhibitors have been shown to be able to treat and even prevent ischemic heart disease.

SELECTED ABBREVIATIONS	
ACE	angiotensin-converting enzyme
AMI	acute myocardial infarction
Ang II	angiotensin II
$AT_{1,2,3,4}$	angiotensin II type 1; (2; 3; 4) receptor
CAD	coronary artery disease
CHF	congestive heart failure
cNOS	constitutive nitric oxide synthase
EDRF	endothelial-derived releasing factor
LVH	left ventricular hypertrophy
NO	nitric oxide
NOS	nitric oxide synthase
PAI-1	plasminogen-activator inhibitor–1
PGI_2	prostacyclin
RAS	renin-angiotensin system
t-PA	tissue-type plasminogen activator

ACE is an enzyme with multiple effects that are not all mediated by angiotensin receptors. Similarly, Ang I can be formed by nonrenin enzymes such as tonin or cathepsin and converted to Ang II by other enzymes than ACE. Clearly, the "discovery" of the ACE inhibitors did not put an end to pharmacological research in this field, and much work is currently going on to develop specific nonpeptide, orally active Ang II receptor antagonists with possibly more specific actions and fewer side effects than the ACE inhibitors. This review summarizes the pharmacology and current clinical indications of this class of drugs.

THE ANGIOTENSIN-CONVERTING ENZYME (ACE)

ACE or kinase II is a zinc metalloprotease that regulates the balance between the vasodilator and natriuretic properties of bradykinin and the vasoconstrictive and salt-retention properties of Ang II. It cleaves the C-terminal dipeptide from Ang I and bradykinin and a number of other small peptides that do not have a penultimate proline residue. Thus, ACE is strategically positioned to affect the balance between the RAS and the kallikrein-kinin system *(Figure 1)*.[1]

SELECTED TRIAL ACRONYMS	
AIRE	Acute Infarction Ramipril Efficacy
ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial
CCS–1	Chinese Captopril Study–1
CHARM	Candesartan in Heart failure Assessment in Reduction of Mortality
CONSENSUS I, II	COoperative North Scandinavian ENalapril SUrvival Study I, II
ELITE I, II	Evaluation of Losartan In The Elderly I, II
EUROPA	EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease
GISSI 3	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III
HOPE	Heart Outcomes Prevention Evaluation
ISIS-4	Fourth International Study of Infarct Survival
LIFE	Losartan Intervention For Endpoint reduction in hypertension
ONTARGET	ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
OPTIMAAL	OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan
PEACE	Prevention of Events with ACE inhibitors
PREAMI	Perindopril and Remodelling in Elderly with Acute Myocardial Infarction
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study
QUIET	QUinapril Ischemic Event Trial
RENAAL	Reduction of Endpoints in Noninsulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan
SAVE	Survival And Ventricular Enlargement
SOLVD	Studies of Left Ventricular Dysfunction
TRACE	TRAndolapril Cardiac Evaluation
TREND	Trial on Reversing ENdothelial Dysfunction
UKPDS	United Kingdom Prospective Diabetes Study
Val-HeFT	Valsartan–Heart Failure Trial
VALIANT	VALsartan In Acute myocardial iNfarcTion

Interestingly, the Michaelis-Menten constant (K_m) of ACE for the inactivation of bradykinin is more favorable than that for Ang II formation: thus, blocking of the enzyme results in increased bradykinin availability and decreased Ang II production. ACE is present in plasma and in a number of tissues, such as blood vessels, heart, kidneys, brain, and adrenal glands. Biochemical measurement of ACE activity shows that it is essential-
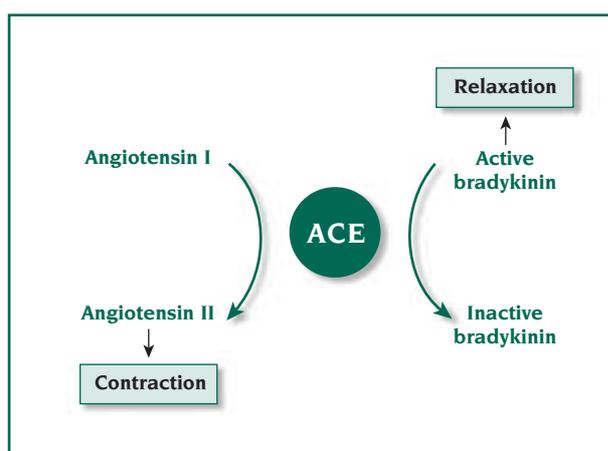
Figure 1. *Schematic representation of the function of the angiotensin-converting enzyme (ACE).*

ly a tissue-based enzyme.[2] Less than 10% of ACE is in a circulating form in the plasma.[2] The functional importance of tissue-based ACE has been demonstrated in transgenic mice without tissue ACE, but with normal plasma ACE levels: these mice are unable to activate their RAS and, consequently, develop marked hypotension and cardiovascular impairment.

Tissue ACE and the heart

Myocytes express relatively low levels of ACE or ACE mRNA, at least under physiological conditions.[3] In the normal heart, moderate levels of ACE are expressed in the right atrium, and comparatively lower levels in the left atrium and ventricles.[4] The greatest intensity of immunohistochemical ACE staining is found in the endothelium of large and small arteries and arterioles, whereas only half of the coronary capillaries are immunoreactive. This explains why ACE inhibitors cause only weak coronary dilatation. Venous vessels are almost completely devoid of the enzyme.[4] Other cardiac tissue sites expressing ACE include the endocardial layer and the cardiac valves.[4] Very little ACE, if any, is found in normal adult cardiac myocytes in situ.

Following the initial observation of ACE upregulation in pressure-overloaded, hypertrophied hearts,[3] marked

ACE induction has been reported in virtually all models of cardiac injury, including volume overload, AMI, post-AMI remodeling, and CHF.[5,6] A correlation between increased cardiac ACE levels and aging has also been found.[7]

Elevated wall stress, and the consequent stretching of the sarcolemma, is believed to be a critical factor for cardiac ACE induction because elevated enzyme levels are found exclusively in the affected ventricle. Interestingly, ACE upregulation is not restricted to the heart,[7] because fibroblasts are recruited for ACE expression in injured hearts, ie, during early remodeling after AMI.[6] Moreover, macrophages, which invade injured cardiac tissue after an acute injury, also carry high ACE activity to interstitial sites where Ang II accumulates.

Tissue ACE and the endothelium

ACE is expressed in cultured endothelial cells and levels increase exponentially after cellular confluence.[8] The endothelium plays a crucial role in maintaining normal vascular tone and structure, local homeostasis, and vascular wall proliferation processes. These processes are mediated by the reactive release of several vasoactive substances, among which nitric oxide (NO) is the most important. NO relaxes vascular smooth muscle through a cyclic guanosine monophosphate (cGMP)–mediated decrease in Ca^{2+}, resulting in vasodilatation, and inhibits platelet aggregation and expression of adhesion molecules on both monocytes and neutrophils, resulting in anticoagulation. NO also prevents structural changes by inhibiting the growth and migration of smooth muscle cells. These regulatory processes are all subject to disruption by Ang II. Ang II produced by activated endothelial ACE impairs NO bioactivity, mainly with respect to oxidative stress, via the Ang II–induced production of superoxide radicals (O_2) that scavenge NO and reduce endothelium-dependent vasodilatation.

There is evidence that ACE expression increases in the presence of atherosclerosis and may contribute to disease progression by stimulating adhesion molecule expression, increasing oxidative stress and stimulating growth. Diet et al reported that tissue ACE accumulates in regions of inflammatory cells of human atherosclerotic plaque, especially in areas of clustered macrophages and microvessel endothelial cells.[9] Thus, ACE accumulation within the plaque may favor increased production of local Ang II, thereby contributing to the pathophysiological mechanism of coronary artery disease (CAD). This hypothesis is supported by the find-

ings of an elegant experiment in which endothelial NO synthase (NOS) gene knockout mice developed atherosclerotic lesions in response to adventitial vessel wall injury[9]: wild-type mice were protected from this effect. The evidence cited above suggests that plaque ACE may be an important target for ACE-inhibitor action.

Role of the genetic variability of ACE

The chromosomal locus of the ACE gene has been linked to the variability of ACE activity and arterial hypertension, as well as to left ventricular (LV) mass (independently from blood pressure) in several rodent breeding experiments. Furthermore, a deletion/insertion (*D/I*) polymorphism of intron 16 of the human ACE gene accounts for 14% to 50% of the interindividual variation in serum ACE activity.[10] Both plasma ACE levels and the deletion allele of the polymorphism have been associated with the risk of developing AMI or LV hypertrophy (LVH).[11]

Though these results are readily reproducible, several investigators failed to duplicate them.[12] To explain this, it was suggested that, in healthy subjects, negative feedback inhibition may neutralize the genetically-enhanced expression of singular components in the Ang II synthetic cascade. In contrast, the ACE *DD* genotype may play a substantial role in the development of LVH when cardiac growth machinery is activated. This hypothesis was supported by recent data from Montgomery et al[13] in which young healthy subjects were studied before and after a rigorous exercise protocol. Only those participants who carried the ACE deletion allele showed an increase in LV mass. Thus, the ACE genotype may act only under specific conditions, suggesting an interaction between altered hemodynamics, ACE, and/or other genetic cofactors in the modulation of LV mass. In keeping with this hypothesis are the observations that pathological remodeling early after AMI occurs predominantly in those subjects with the ACE *DD* genotype.[11] Furthermore, transgenic rats with high levels of cardiac ACE expression have normal (or even smaller) hearts as long as these animals are housed under physiological conditions. However, cardiac growth and diastolic dysfunction were found to be augmented in the same ACE transgenic rats when the animals were stressed by abdominal aortic banding and subsequent cardiac pressure overload.

Similar to the above observations in the heart, genetic factors may also regulate ACE expression and production in the vasculature. As indicated above, an inser-tion (*I/D*) polymorphism in intron 16 of the ACE gene accounts for 40% of the interindividual variation in serum ACE activity. Individuals who are homozygous for the *D* allele have the highest ACE levels, while those homozygous for the *I* allele and *I/D* heterozygous have the lowest and intermediate levels, respectively. The ACE *D* allele has been associated with a number of diseases in which activation of the RAS is known to play a role, including AMI in low-risk patients, LVH, and progressive diabetic nephropathy[11]: this association has been attributed to increased formation of Ang II in individuals who carry the ACE *D* allele.

ANGIOTENSIN II RECEPTORS

Ang II acts through specific receptors, the most important being Ang II type 1 (AT$_1$) and Ang II type 2 (AT$_2$) receptors, both of which have been cloned.[14] They belong to the superfamily of G protein-coupled receptors, which contain 7 transmembrane regions. AT$_3$ and AT$_4$ Ang II receptors also exist, but their role in humans is still under debate. AT$_1$ and AT$_2$ receptors share only ≈34% homology and have distinct signal transduction pathways. The pathophysiological role of AT$_1$ receptors is clear: they mediate all the deleterious effects of Ang II, causing vasoconstriction, myocyte growth, fibrosis, arrhythmias, etc *(Figure 2)*. AT$_1$ receptor knockout mice are characterized by low blood pressure, high circulating renin levels, and decreased LV remodeling.[14] AT$_2$ receptors inhibit growth and promote cell differentiation and apoptosis.[14] Recent data suggest that they mediate the production of bradykinin, NO, and prostaglandin. Thus, AT$_2$ receptors could have an important role in counterbalancing the negative effects of AT$_1$, but this hypothesis remains to be confirmed. The distribution and function of these receptors is shown in *Figure 2*. AT$_1$ receptors are present in the kidneys, heart, vascular smooth muscle cells, brain, platelets, and placenta. AT$_2$ receptors have been localized mainly in the uterus, adrenal glands, central nervous system, heart, and kidneys. AT$_2$ receptors are abundant in the fetus and more sparsely distributed in adults; they appear to be upregulated in experimental cardiac hypertrophy, AMI, and vascular and wound healing.[14]

ACE INHIBITORS

Pharmacological effects of ACE inhibitors

ACE inhibitors differ in chemical structure, potency, bioavailability, plasma half-life, distribution, elimination, and, more importantly, in affinity for tissue-bound ACE.[1] They can be classified into 3 groups according
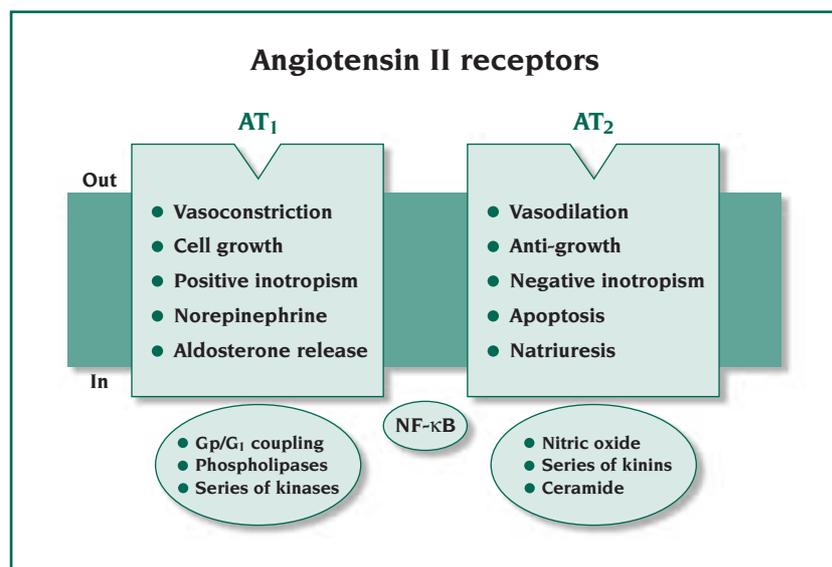
Figure 2. *Schematic representation of the function of the angiotensin II receptors.*

Abbreviations: AT$_1$, angiotensin II type 1 receptor; AT$_2$, angiotensin II type 2 receptor; NF-κB, nuclear factor–kappaB.

to their chemical structure. Some contain a sulfhydryl group, captopril being the prototype. In vitro data suggest that the presence of the sulfhydryl group may confer additional properties to ACE inhibition such as free radical scavenging and effects on prostaglandins.[1] However, the clinical relevance of these actions has never been demonstrated. Fosinopril is the prototype of ACE inhibitors that contain a phosphinyl group as their reactive moiety. Other ACE inhibitors contain a carboxyl moiety.

The majority of ACE inhibitors are administered as prodrugs, which have enhanced oral bioavailability compared with the active drugs. Relative tissue affinity differs among ACE inhibitors: quinaprilat, perindoprilat, and fosinoprilat have the highest affinity for heart homogenates *(Figure 3).* This may be important, as several investigators have shown that the antiatherosclerotic effect of ACE inhibitors is better correlated with tissue ACE levels than with circulating ACE levels.[14] The relative potency of ACE inhibitors in enhancing bradykinin levels vs reducing Ang II may also be important. Little is know in this respect. Campbell et al[15] showed that perindopril increases bradykinin levels at doses much lower than those required to reduce Ang II levels. Similarly, in dogs with

pacing-induced CHF, perindoprilat has been demonstrated to significantly reduce Ang II levels and to increase bradykinin levels.[16] ACE inhibitors block the pressor response to intravenous Ang I, but not to Ang II. Following short-term ACE-inhibitor treatment, endogenous levels of Ang II and aldosterone decrease, whereas renin activity and Ang I increase. The increase in Ang I levels may then result in degradation of Ang I to Ang 1-7 (a vasodilator) or in the formation of Ang II via non-ACE–mediated pathways. During chronic ACE inhibition, Ang II and aldosterone levels return to pretreatment levels, a phenomenon known as Ang II and aldosterone escape. This phenomenon opens up perspectives for acting on RAS by directly blocking Ang II receptors with specific Ang II receptor blockers. While the reduction of Ang II levels is pivotal in blood pressure regulation by ACE inhibitors, the contribution of bradykinin to the hemodynamic effect of ACE inhibitors is unclear.

Bradykinin has a short half-life and is thus difficult to measure: it has been reported as either increased or unchanged in patients treated with ACE inhibitors. However, the recent availability of specific bradykinin (B$_2$) receptor antagonists has shown that coadministration of ACE inhibitors with bradykinin antagonists attenuates their antihypertensive effect as well as their beneficial action on endothelial dysfunction, both in animal models and in humans.
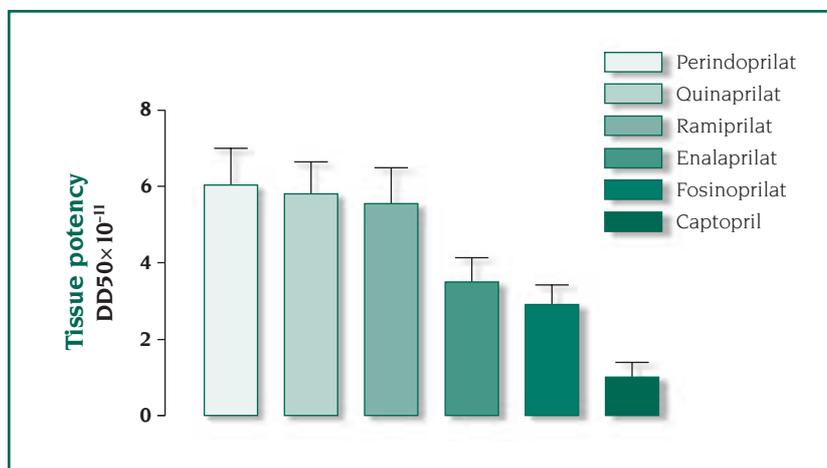
Figure 3. *Differences in relative tissue affinity of various angiotensin-converting enzyme inhibitors.*

The main pharmacological effect of ACE inhibitors is a reduction in systemic vascular resistance without or with little change in heart rate.[1] In contrast to other vasodilators, no reflex tachycardia is observed, possibly due to an effect on baroreceptor sensitivity, vagal stimulation, and reduced activation of sympathetic nerve activity. However, heart rate during exercise is not impaired. In normotensive and hypertensive subjects with normal LV function, ACE inhibitors have little effect on cardiac output and pulmonary capillary wedge pressure.[1] In the kidney, ACE inhibitors cause increased renal plasma flow and promote salt and water secretion.[1] In patients with CAD, with or without CHF, ACE inhibitors improve hemodynamics and energy supply to the myocardium via peripheral and coronary dilatation. Despite this positive hemodynamic action, the effects of ACE inhibitors on angina pectoris are not clear. A number of small-scale clinical trials on angina pectoris and/or myocardial ischemia have reported conflicting results.[1] Thus, although ACE inhibitors are able to restore the balance between oxygen supply and demand, they fail to show consistent antianginal effects.[4] This contrasts with the beneficial results obtained in long-term studies in post-AMI patients or in patients with CAD, which implies that ACE inhibitors possess other, more structural effects that underlie their anti-ischemic action, the so-called biological effects of the ACE inhibitors.

The "biological effects" of ACE inhibitors account for their antiatherosclerotic and antiremodeling actions. Interestingly, ACE inhibitors also reverse cardiac and vascular hypertrophy in hypertensive patients and reduce endothelial dysfunction in normotensive patients with CAD, hypertension, non–insulin-dependent diabetes mellitus, and CHF. ACE inhibitors improve endothelial function via attenuation of vasoconstriction and bradykinin-mediated upregulation of constitutive nitric oxide synthase (cNOS). Interestingly, in animal models and in large clinical studies, ACE inhibitors delay the development and progression of atherosclerosis. These antiatherogenic properties seem to be attributable to the inhibition of Ang II formation, bradykinin potentiation, and consequent increase in NO release, resulting in decreased migration and proliferation of vascular smooth muscle cells, decreased accumulation and activation of inflammatory cells, decreased oxidative stress, and improved endothelial function. ACE inhibitors also positively affect the fibrinolytic balance by decreasing Ang II, a potent stimulus for plasminogen-activator inhibitor–1 (PAI-1) synthesis, and by increasing bradykinin levels, thus stimulating tissue plasminogen activator (t-PA).

Clinical indications of ACE inhibitors

ACE inhibitors undoubtedly represent a milestone in cardiovascular therapy. Their pharmacological profile initially targeted them for use in the treatment of hypertension. However, after their introduction into the therapeutic armamentarium as antihypertensive agents, it became immediately apparent that these drugs could halt the progression of CAD by interrupting, at several levels, the series of events leading to end-stage CHF. Moreover, quite surprisingly, in patients with severe CHF, the ACE inhibitors were found to reduce angina pectoris and AMI recurrence rates, hospitalization for ischemic heart disease, and coronary artery bypass surgery or angioplasty. These unexpected findings led to the hypothesis that prolonged ACE inhibition reduces progression of atherosclerosis and influences mortality and hospitalization when used in CAD patients with LV dysfunction without overt CHF. The results of the Heart Outcomes Prevention Evaluation (HOPE) study[17] confirmed that this was the case in high-risk patients with CAD. Even more importantly, the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA)[18]—the largest and longest trial on ACE inhibition in patients with CAD—proved that ACE inhibition prevents mortality and AMI in patients with CAD, independently from their risk profile. Another trial, the Prevention of Events with ACE inhibitors (PEACE) study, is under way.[19]

ACE inhibitors in patients with hypertension

ACE inhibitors decrease mean systolic and diastolic pressure in hypertensive patients as well as in salt-depleted normotensive patients.[1] They are indicated in the treatment of hypertension (class I, level of evidence A). Current guidelines strongly recommend reduction of blood pressure based on patients' risk profiles.[20] The extent of blood pressure reduction achieved with the ACE inhibitors is not different from that with β-blockers or diuretics, at least in white patients, while their tolerability profile is better than that of other medications.

The acute changes in blood pressure (but not the long-term chronic ones) induced by ACE inhibitors are correlated with pretreatment renin and angiotensin levels, ie, the greatest reduction in blood pressure is seen in patients with the highest RAS activation. Thus it is likely that the chronic effects of the ACE inhibitors mainly involve the kallikrein-kinin system and the production of prostaglandins, while the acute effects main-

ly involve the reduction in Ang II. Similar to the β-blockers, ACE inhibitors seem to be less effective in black hypertensive patients,[1] probably because black subjects tend to have lower renin levels than whites. However, more recent data in African-Americans show that, contrary to former notions, ACE inhibitors have an important place in the management of hypertension and related disorders in this particular population, by offering a major benefit in terms of target-organ protection and prevention of disease progression.[21] Likewise, perindopril monotherapy (4 to 8 mg/d) has been shown to significantly reduce blood pressure in African-Americans, including in subgroups of diabetic and elderly patients aged 65 or above.[22]

One of the hallmarks of the ACE inhibitors is that they decrease blood pressure without causing compensatory tachycardia. This is in contrast to other vasodilators such as Ca^{2+} channel blockers and direct-acting vasodilators, and it is probably due to the effect of ACE inhibitors on baroreceptor sensitivity as well as to the inhibition of the sympathetic nervous system. A meta-analysis[23] of placebo-controlled trials on ACE inhibitors carried out by the Blood Pressure Treatment Trialists' Collaboration showed reductions in stroke (30%), CAD (20%), and major cardiovascular events (21%). Comparison of ACE-inhibitor–based regimens and diuretic-based or β-blocker-based regimens disclosed no detectable differences in risks between the study groups in the randomized trials. Two trials in which a head-to-head comparison of ACE inhibitors and Ca^{2+}-antagonist-based regimens was carried out, found a reduced risk of coronary artery disease events with ACE inhibition. There was no clear evidence of differences in stroke risk or total mortality. There was a trend toward a reduced risk of CHF in patients on ACE-inhibitor treatment.

In another meta-analysis in 62 605 hypertensive patients, no differences were found in outcome between ACE inhibitors and β-blockers and Ca^{2+} channel blockers.[24] The UK Prospective Diabetes Study (UKPDS)[25] compared captopril and atenolol in patients with hypertension and type 2 diabetes. This study showed no difference between the two drugs in terms of either specific beneficial or deleterious effect other than blood pressure reduction, suggesting that blood pressure reduction itself might be more important than the treatment used.

The Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) was designed to determine the effects of a blood pressure–lowering regimen in hyper-

tensive and nonhypertensive patients with a history of stroke or transient ischemic attack. Active treatment comprised a flexible regimen based on perindopril with the addition of indapamide (diuretic compound) at the physician's discretion. This combination decreased blood pressure on average by 12.5 mm Hg and stroke risk by 43%. The risk reduction in stroke was observed among both the hypertensive and nonhypertensive subjects.[26]

In summary, it seems that, in hypertension, the level of blood pressure reduction is more important that the specific treatment, although the evidence from trials in other cardiovascular conditions points to the superiority of ACE inhibitors in patients with CHF, diabetes, and high-risk cardiovascular profile. However, conflicting results were obtained in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT),[27] in which a total of 33 357 hypertensive patients with at least one other cardiovascular risk factor received either chlorthalidone, amlodipine, or lisinopril. Results disclosed no difference between treatments in the primary outcome (cardiovascular death or AMI), but lisinopril was associated with higher 6-year rates of combined cardiovascular disease, stroke, and CHF, questioning its use as first-line therapy in hypertensive patients without a high-risk cardiovascular profile or CHF.

ACE inhibitors in patients with CHF

ACE inhibitors are indicated as first-line therapy in patients with reduced LV function with or without symptoms (class I, indication, level of evidence A).

ACE inhibitors favorably alter hemodynamics in patients with CHF. They reduce afterload, preload, and systolic wall stress such that cardiac output increases without an increase in heart rate. The COoperative North Scandinavian ENalapril SUrvival Study I (CONSENSUS I) with enalapril[28] not only yielded clear efficacy data in CHF, but also resulted in better understanding of the pathophysiology of the CHF syndrome itself, showing that the positive effects of enalapril were not only due to its pharmacological action, but also to the biological improvement, resulting in a reduction of the deleterious effects of the neuroendocrine response. Accordingly, most of the beneficial effects of ACE inhibitors in CHF are now ascribed to their counteraction of neuroendocrine effects, leading to:
• Increased salt excretion, resulting from increased renal blood flow consequent upon the reduction in aldosterone and antidiuretic hormone production.

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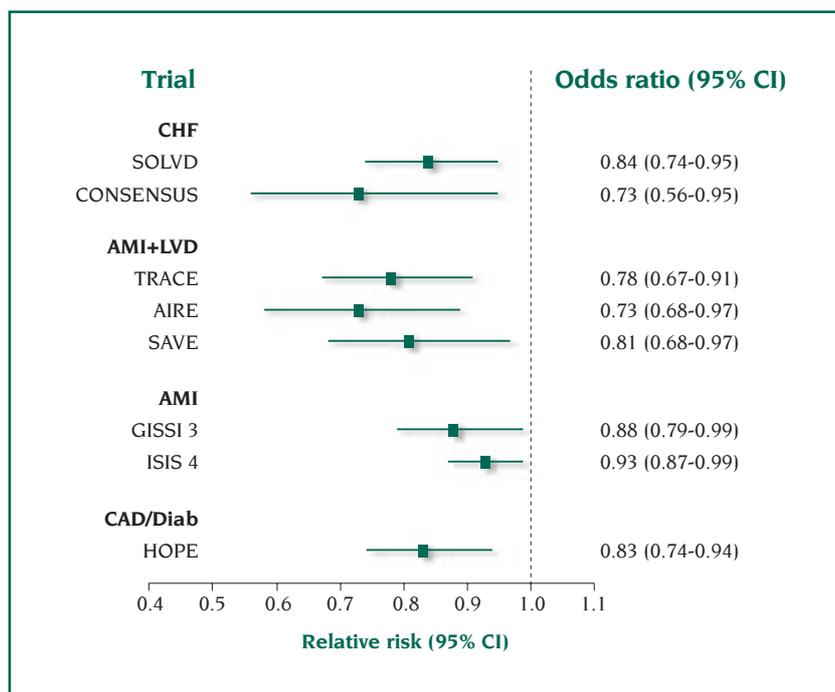
Figure 4. *Results of the main studies with angiotensin-converting enzyme inhibitors in CHF (congestive heart failure); AMI+LVD (acute myocardial infarction + left ventricular dysfunction); AMI (acute myocardial infarction); and CAD/Diab (coronary artery disease + diabetes).*

Key to trials: *see Trial Acronyms box on page 72.*

several antihypertensive drugs suggests that ACE inhibitors are the most effective agents in reducing LVH, one of the causes of diastolic dysfunction.[30] The Perindopril and Remodeling in Elderly with Acute Myocardial Infarction (PREAMI) trial is exploring the effects of perindopril in elderly patients with moderate LV dysfunction.[31] Accordingly, ACE inhibitors are recommended for the treatment of patients with symptoms of CHF and preserved LV function (class II D, level of evidence C).

• Promotion of coronary, renal, and peripheral dilatation through counteraction of the vasoconstrictive effect of Ang II and of the sympathetic system.
• Antiremodeling effect, by altering the balance between the pro-proliferative and proapoptotic effects of Ang II.
• CONSENSUS I has also provided a benchmark for designing subsequent trials in patients with CHF; since 1987, several large, prospective, randomized placebo-controlled trials have demonstrated that treatment with ACE inhibitors results in overall mortality reduction in patients with CHF due to systolic dysfunction.
• The meta-analysis shown in *Figure 4* reports the cumulative results of these trials. The reduction in mortality is present even in asymptomatic patients, although to a lesser extent.[29]

The improvement in prognosis results primarily from a reduction in the progression of CHF (mainly via an antiremodeling effect) although a decrease in incidence of sudden death and AMI may also contribute.

It is not clear to what extent bradykinin contributes to these positive effects. The study with specific Ang II receptor blockers failed to show superiority over ACE inhibitors despite a more profound and complete effect on Ang II. This unexpected finding indirectly suggests that bradykinin has a pathophysiological role. Little is known about the effect of ACE inhibitors in elderly patients with CHF or in patients with CHF due to diastolic dysfunction. A meta-analysis of trials with

All the trials with ACE inhibitors in CHF had target dosage regimens higher than those used in clinical practice. Two studies addressed the dosage issue: in one,[32] the combined end point of all-cause death and hospitalization was significantly reduced in patients receiving high-dose treatment. In the Network Trial,[33] no relationship was found between the dosage of enalapril and clinical outcome.

In summary, there is clear evidence that ACE inhibitors reduce the rate of hospitalization and mortality in patients with CHF. Dosing of ACE inhibitors should aim at the target dosage used in the clinical trials, but only when this dosage is well tolerated.

ACE inhibitors in patients after AMI

Over the past decade, in the wake of the demonstration of the striking beneficial results of prolonged ACE inhibition in patients with LV dysfunction due to ischemic heart disease, a series of trials were conducted to evaluate the role of ACE inhibition after AMI. Some studies enrolled selected, high-risk, patients with left ventricular dysfunction. Long-term treatment with ACE inhibitors was started late after the event, usually at discharge. The most important among these studies were SAVE (Survival And Ventricular Enlargement); AIRE (Acute Infarction Ramipril Efficacy); and TRACE (TRAndolapril Cardiac Evaluation), which showed consistent, significant reductions in mortality and hospi-

talization. Other randomized studies were performed in unselected patients receiving short-term treatment very early (24 h) after AMI: CONSENSUS II; GISSI 3 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III); ISIS 4 (Fourth International Study of Infarct Survival); and CCS-1(Chinese Captopril Study–1).

Overall, these trials point to a small, but definite, benefit of around 5 lives saved for every 1000 patients treated. The benefit is larger in higher-risk groups such as those with a history of AMI (18 deaths less over 1000) or with established CHF (14 deaths less over 1000). Thus, there is a clear decrease in the relative size of the beneficial effects, which is associated with a broadening of the population treated. Despite this, there is a consensus that ACE inhibitors should be used early after AMI in all patients, particularly high-risk ones.[29,30] The main questions are: (i) for how long?; and (ii) what should be the criteria for withdrawal or maintenance of treatment? As of now, these questions are no longer

a cause for debate since the results of HOPE and, particularly, of EUROPA, have shown that ACE inhibition is indicated for secondary prevention of CAD, and that the longer the treatment, the better the results.[17,18]

From the pathophysiological point of view, the results appear to be in keeping with the remodeling hypothesis based on experimental studies. The data of the Echo Subgroup of GISSI 3 confirmed this hypothesis in a large, unselected population treated very early after AMI. Although the changes observed in LV volumes were small, they were clinically and statistically relevant.[34] In addition, the activation of the RAS in the first few days after AMI is known to increase the heart rate and systemic vascular resistance and decrease coronary perfusion, leading to infarct expansion.

Thus, in summary, oral ACE inhibitors are beneficial in all patients without contraindications within 36 h after AMI (class IIa, level of evidence A), especially in the presence of impaired ejection fraction or mild-to-moderate CHF (class I, level of evidence A). Later after AMI, all patients with clinically documented CHF or asymptomatic LV dysfunction should be chronically treated with ACE inhibitors (class I, level of evidence A). Findings from the HOPE study indicate that treatment should be maintained in patients at high-risk of, or with, diabetes, while those from EUROPA indicate that all patients should be treated, independently of their risk factors.
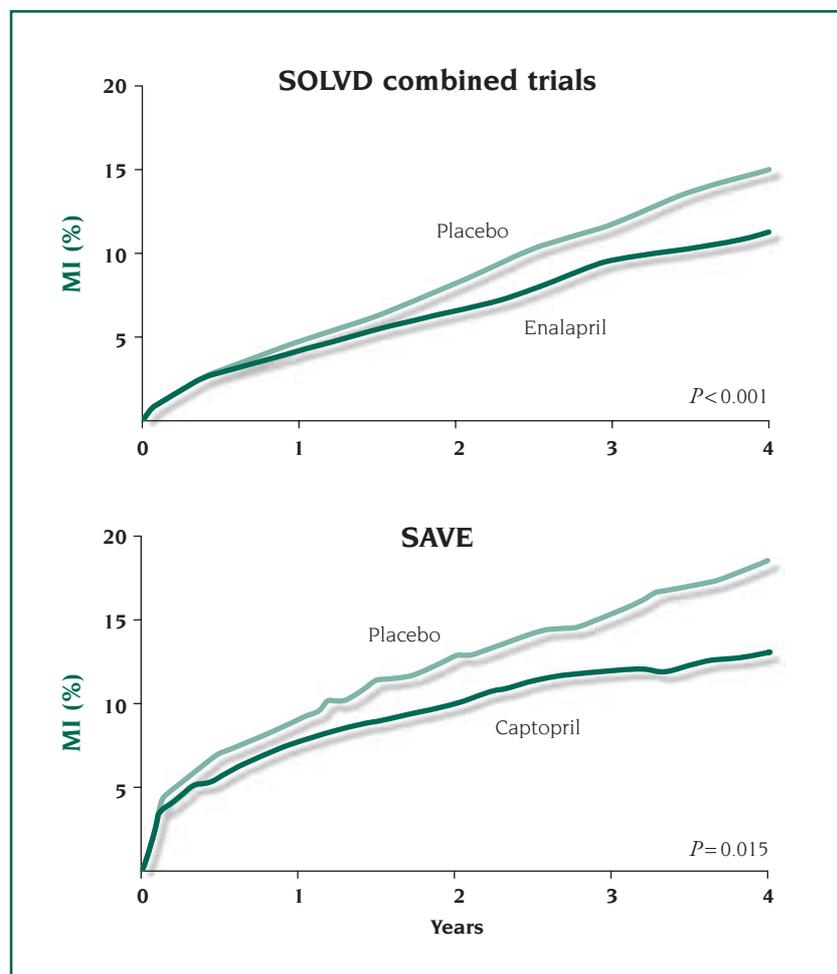
Anti-ischemic effect of ACE inhibitors

Unexpectedly, several trials on CHF showed that ACE inhibition also reduces ischemic events such as recurrence of angina pectoris, AMI, hospitalization for ischemic heart disease, and rate of coronary artery bypass surgery or angioplasty *(Figure 5)*.[35,36] The recently published PROGRESS findings showed a 38% reduction in the occurrence of nonfatal AMI, a 26% reduction in con-

Figure 5. *Reduction in occurrence of myocardial ischemia in the SOLVD and SAVE Trials.*

Key to trials: see Trial Acronyms box on page 72.

gestive heart failure, and a 26% reduction in major coronary events in the group receiving the perindopril-based treatment regimen.[26] Risk reduction in these trials is manifest as early as after 1 year of treatment. This interval in the reduction of ischemic events suggests that the mechanism of the anti-ischemic action of ACE inhibition is not only related to hemodynamic consequences or blood pressure reduction, but also to prevention of the progression of coronary atherosclerosis and/or stabilization of the atherosclerotic plaque. This finding has led researchers to propose that alteration in ACE activity, particularly in vascular tissues, may be an important factor in the development and progression of CAD. Epidemiological, genetic, and experimental studies support this point of view. Increased ACE activity is associated with damage and remodeling not only of the ventricle, but also of the vasculature. Therefore, the beneficial effects of ACE inhibitors can be distinguished as cardioprotective and vasculoprotective. Accordingly, during the past decade, use of ACE inhibitors has been studied both with respect to the treatment of acute events, and also—especially nowadays—as a preventative treatment *(Figure 6).*

This preventative role was tested, but not proved, in the QUinapril Ischemic Event Trial (QUIET), which unfortunately was not powered enough for the end point and in which quinapril was underdosed. In the HOPE study, ramipril treatment in high-risk patients was associated with a 20% reduction in AMI,[17] and a mean reduction in blood pressure of 3 and 1 mm Hg for systolic and diastolic pressure, respectively. The investigators suggest that the 20% reduction was much higher than what could be expected based on the observed blood pressure reduction.

This observation was confirmed and extended by the results of the EUROPA trial *(Figure 7),*[18] which enrolled patients with CAD, who were at lower risk than in HOPE. The major annual event rates in HOPE were 40% to 80% higher than those in EUROPA, and yet perindopril reduced the primary combined end point by 20% and the rate of AMI by 27%. Only 27% of a total of 12 218 patients randomized were hypertensive, and in these patients, there was the possibility that the long-term blood-pressure reduction induced by perindopril could have reduced the subsequent cardiovascular events. However, there was no relationship between basal values of blood pressure or degree of blood pressure reduction and the reduction in cardiovascular events, which was greater than that expected for the observed reduction in blood pressure (mean 5/2 mm Hg) achieved with perindopril. This finding implies that a specific antiatherosclerotic effect of ACE inhibition
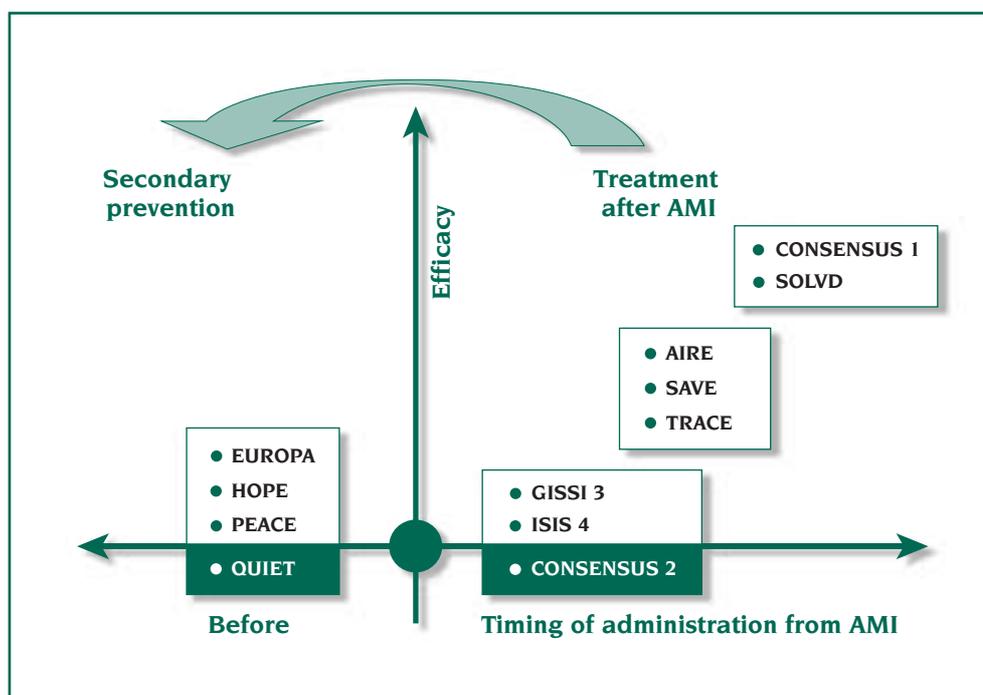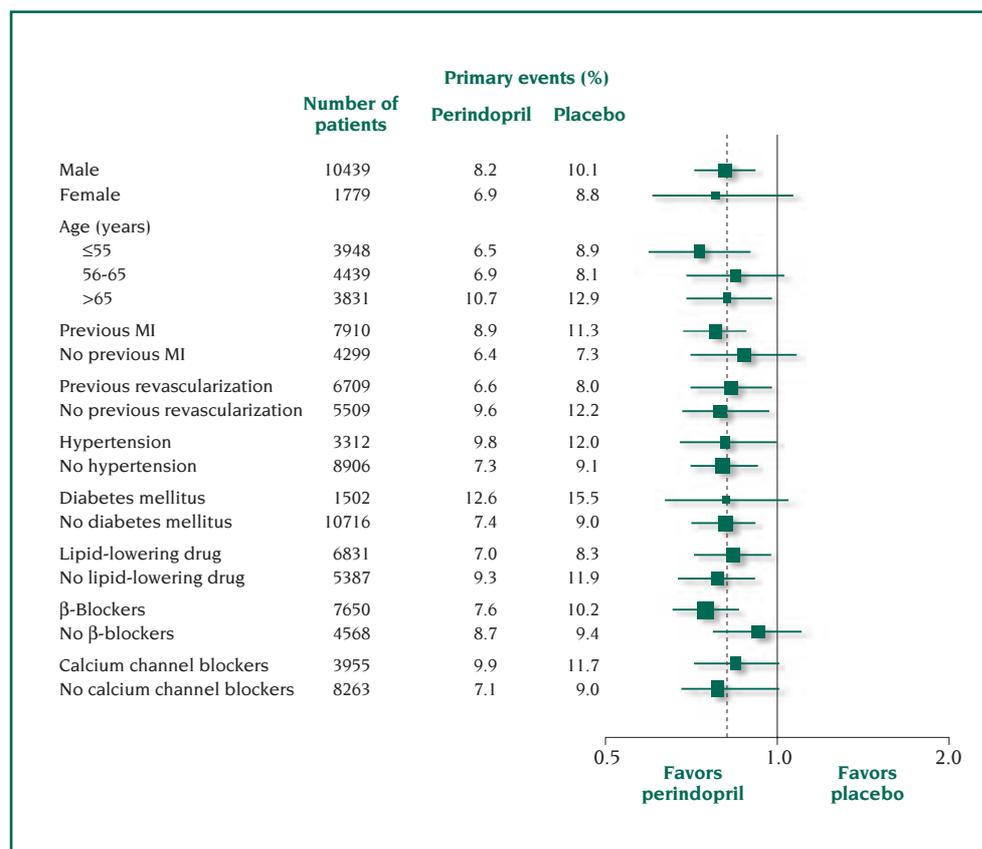

Figure 6. *Trends of angiotensin-converting enzyme inhibitor trials with regard to severity of disease and timing of administration from acute myocardial infarction (AMI) causing heart failure, for example, acute myocardial infarction.*

Key to trials: see Trial Acronyms box on page 72.

	Number of patients	Primary events (%)		
		Perindopril	Placebo	
Male	10439	8.2	10.1	
Female	1779	6.9	8.8	
Age (years)				
≤55	3948	6.5	8.9	
56-65	4439	6.9	8.1	
>65	3831	10.7	12.9	
Previous MI	7910	8.9	11.3	
No previous MI	4299	6.4	7.3	
Previous revascularization	6709	6.6	8.0	
No previous revascularization	5509	9.6	12.2	
Hypertension	3312	9.8	12.0	
No hypertension	8906	7.3	9.1	
Diabetes mellitus	1502	12.6	15.5	
No diabetes mellitus	10716	7.4	9.0	
Lipid-lowering drug	6831	7.0	8.3	
No lipid-lowering drug	5387	9.3	11.9	
β-Blockers	7650	7.6	10.2	
No β-blockers	4568	8.7	9.4	
Calcium channel blockers	3955	9.9	11.7	
No calcium channel blockers	8263	7.1	9.0	

0.5   1.0   2.0

Favors perindopril   **Favors placebo**

Figure 7. *Results from EUROPA (EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease): beneficial effect of treatment with perindopril on primary end point in predefined subgroups.*
MI, myocardial infarction. Size of squares proportional to number of patients in that group. Dashed line indicates overall relative risk.

Reproduced from reference 17: *The EURopean trial on reduction of cardiac events with Perindopril in stable coronary Artery disease Investigators. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial (the EUROPA study). Lancet. 2003;362:782-788. Copyright © 2003, Elsevier Ltd.*

should be taken into account. As for the intimate mechanism of action, several possibilities exist, which are detailed below.

ACE inhibition improves endothelial function
Alterations of endothelial function, such as impaired release of NO or other endothelium-derived relaxing factors (EDRFs), develop in many pathological conditions, including CAD. Experimental studies have shown that ACE inhibition stimulates endothelial release of NO and prostacyclin by a bradykinin-mediated mechanism, thereby enhancing endothelial-dependent vasodilatation. These and other studies have raised the question of whether or not ACE inhibition can improve coronary endothelial function in humans and whether this potentially beneficial effect of ACE inhibition is bradykinin-mediated. The results of the Trial on Reversing ENdothelial Dysfunction (TREND) support this theory.[37] This study tested the effect of ACE inhibition with quinapril on coronary artery endothelial function in patients with established CAD. In the treated group, the initial vasoconstrictor response to intracoronary infusion of acetylcholine was significantly reduced and partly normalized toward a vasodilator response, whereas no changes were observed in the placebo group.

Perindopril, an ACE inhibitor with high tissue-binding affinity, is also able to normalize coronary endothelial function in hypertensive patients to a greater extent than other classes of drugs.[38] These beneficial effects of ACE inhibition could be due to a reduction in Ang II and/or an increase in bradykinin. Inhibition of the generation of Ang II may attenuate smooth muscle contraction and the production of superoxide anions resulting from stimulation of NADH/NADPH oxidase systems of smooth muscle cells. This would inactivate endothelial-derived NO, thereby restoring endothelial function. In addition, bradykinin-induced augmentation of NO release by endothelial cells is promoted by ACE inhibition. Using the selective bradykinin B_2 receptor antagonist icatibant, Horning et al were able to demonstrate that the endothelial-dependent vasodilatation mediated by quinapril was indeed related to increased bradykinin levels.[39]

Interestingly, Zhuo et al recently showed that perindopril improved constitutive nitric oxide synthetase (cNOS) expression in the mammary artery of CAD patients subjected to coronary artery bypass grafting, while reducing the activation of tissue endothelial ACE.[40]

Thus, taken together, there is evidence that ACE inhibition has the potential to restore abnormal peripheral and coronary artery endothelial function in patients with CAD. Furthermore, experimental and clinical data support the concept that ACE inhibition improves vascular function by increasing the levels of bradykinin.

ACE inhibition exerts an antiatherogenic action

Several animal models of atherosclerosis have provided experimental evidence of an antiatherogenic effect of ACE inhibitors.[41] This effect is complex and includes protection of the endothelium, an antimitogenic action, an antithrombotic and plaque-stabilizing action, and possible antioxidant properties. Increases in mRNA for ACE and angiotensinogen have been shown in the proliferating tissue of balloon-injured vessels in rat and in humans.[4]

ACE inhibitors exert an indirect antiatherogenic action by reducing vascular smooth muscle growth and proliferation, restoring endothelial function, and reducing the propensity for plaque rupture, a crucial mechanism in the genesis and progression of atherosclerotic lesions. Ang II acts by inducing the protooncogenes s-*fos*, c-*mgc*, and c-*jun*, as well as the expression of several growth factor genes, ultimately resulting in vascular smooth muscle cell growth. In addition, Ang II favors the release by the endothelium of a neutrophil chemoattractant, leading to neutrophil accumulation.[37]

ACE inhibitors reduce the breakdown of bradykinin (which has a vasodilator effect), and induce the release of NO and prostacyclin (PGI_2) from endothelial cells. Besides being a potent vasodilator, NO has other beneficial effects on endothelial function and integrity by inhibiting platelet adhesion and aggregation and smooth muscle cell mitogenesis. By enhancing kinin accumulation, ACE inhibitors may prevent the development of proliferative atherosclerotic lesions.

ACE inhibitors exert an antithrombotic action

Experimental studies have shown that, in endothelial cells, Ang II selectivity induces the production and secretion of plasminogen activator inhibitor-1 (PAI-1), which inhibits tissue-type plasminogen activator (t-PA) in plasma. Elevated levels of t-PA play a major role in thromboembolic disease. This indicates that Ang II may have prothrombotic properties by increasing PAI-1 and consequently reducing the activity of the fibrinolytic system. Preliminary observations indicate that ACE inhibitors improve endogenous fibrinolytic function in CAD patients, suggesting a potential link between the RAS and the risk of thrombosis. In a comparative study,

the ACE inhibitor perindopril, but not the AT_1 receptor blocker losartan, was found to potentiate bradykinin-induced t-PA release in the coronary circulation, suggesting it may have a potential to reduce thrombotic cardiovascular events.[42]

ACE inhibitors exert a modulation of the sympathetic action

Ang II is an important regulator of norepinephrine release from the sympathetic nerve terminals and modulates local cardiac and vascular sympathetic activities. Inhibition of this effect may potentially account for cardiac protection and reduction in cardiovascular events. The importance of this mechanism in humans is still controversial. It is not clear whether ACE-inhibitor therapy significantly decreases plasma norepinephrine or systemic venous norepinephrine spillover.

The major problem is that all studies have been conducted in patients with CHF treated with diuretics, digitalis, and vasodilators, and that these treatments exert a significant stimulating action on the sympathetic system, which might therefore mask the beneficial effect of ACE-inhibitor therapy. When given as monotherapy to patients with CHF, ACE inhibitors do not seem to influence the neuroendocrine response, but data are scarce. The relevance of the antiadrenergic properties of ACE inhibition in humans in the absence of CHF is even less clear. In contrast, a very recently published study evaluating the effect of monotherapy with the ACEI perindopril on the 24-hour blood pressure profile and the circadian vasosympathetic balance in hypertensive diabetics with nephropathy showed that perindopril reduced the blood pressure over 24 hours. Spectral analysis of the ambulatory blood pressure monitoring (ABPM) findings suggested that this action was partially related to inhibition of sympathetic nervous activity.[43]

Acute and short-term anti-ischemic effects of ACE inhibitors

As previously stated, most of the anti-ischemic properties of ACE inhibitors have been documented during long-term trials, so that the effects in the acute ischemic setting are less clear. Bartels et al[44] have investigated the effects of perindopril on pacing-induced myocardial ischemia in a double-blind trial in CAD patients with and without LV dysfunction. After perindopril administration, the pacing-induced increase in systemic vascular resistance and LV end-diastolic pressure was significantly blunted. ST-segment depression was significantly reduced and the ischemia-induced release of atrial natriuretic peptide and norepinephrine

was inhibited. There was also less lactate release. All these effects were more pronounced in patients with LV dysfunction than in patients with normal LV function. It follows that the anti-ischemic effect of perindopril may be the consequence of a reduction in either myocardial oxygen demand or neurohumoral activation with particular reference to the sympathetic nervous system, which, in turn, can cause coronary vasoconstriction and increase in heart rate, worsening the ischemic damage.

The potential of ACE inhibitors to reduce short-term stress-induced myocardial ischemia as a result of their neurohormonal modulating, and subsequently vasodilating, effects is further proven by data from Monishita et al.[45] These authors sought to determine whether treatment with perindopril improved dobutamine-induced myocardial ischemia in CAD patients. They found that treatment significantly improved the time to onset of symptoms and reduced the magnitude of ECG ST-segment changes and the LV wall motion score.

Interestingly, the reduction in LV wall motion score elicited by perindopril closely correlates with the inhibition of serum ACE activity and the increase in plasma bradykinin concentration, suggesting once again that these biological effects of ACE inhibition may be just as central to the anti-ischemic action of the ACE inhibitors as their hemodynamic effects.

AT$_1$ RECEPTOR BLOCKERS

Pharmacological effects of AT$_1$ receptor blockers

Several orally active, selective AT$_1$ receptor antagonists have been synthesized. To date, six have been approved for clinical use (losartan, valsartan, candesartan, irbesartan, telmisartan, and eprosartan). Although they share the same mechanism of action, they have different pharmacokinetic profiles that may account for potential differences in efficacy. In addition, the starting dose in the various trials may have been chosen based on different criteria, resulting in noncomparable degrees of RAS blockade.[14]

All these compounds have a high affinity for AT$_1$ receptors in the nanomolar range and practically no affinity for AT$_2$ receptors. All have very high protein-binding activity. In addition, they exert a nonparallel displacement of the Ang II response curves in vitro. This implies that all AT$_1$ receptor antagonists are competitive, with a very slow dissociation from the receptor. Because of

this similar behavior, differences among antagonists are likely related to the dose and the duration of action of each drug rather than to differences in mechanism of action.[14]

AT$_1$ receptor blockers in patients with hypertension

AT$_1$ receptor blockers are indicated in hypertension (class I, level of evidence A). Several studies have evaluated the antihypertensive efficacy of this class of drugs in patients with mild, moderate, or severe hypertension.[46] Overall, the results of these studies show that AT$_1$ receptor blockers are as effective as the ACE inhibitors, Ca^{2+} antagonists, β-blockers, and diuretics. In monotherapy, AT$_1$ receptor blockers result in a similar degree of blood pressure reduction in young and elderly patients and men and women. They are less effective in black patients, but this is not the case when combined with diuretics. They have a good tolerability profile: in contrast to some ACE inhibitors, they do not produce first-dose hypotension or rebound phenomena after withdrawal. They do not induce cough and only rare cases of angioedema have been reported.[14]

AT$_1$ receptor blockers may be particularly indicated in some categories of hypertensive patients. One such category is type 2 diabetic patients with microproteinuria, the occurrence of which is an important parameter of cardiovascular risk and calls for very strict blood pressure control. Interestingly, although three small studies comparing the renal effects of AT$_1$ receptor blockers and ACE inhibitors found no differences, AT$_1$ receptor blockers instead of ACE inhibitors were used in a series of well-controlled and carefully monitored studies in patients with disorders ranging from overt hypertensive type 2 diabetic nephropathy to diabetic microalbuminuria with or without hypertension, which showed a renoprotective effect. Several studies suggest that ACE inhibitors provide similar renoprotection.[43,47-49] Patients with hypertension complicated by LVH are another subgroup of patients that could benefit from AT$_1$ receptor–blocker therapy. Thus, losartan, in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE),[50] was clearly more effective than atenolol in preventing cardiovascular morbidity and death. As the blood pressure reduction was nearly identical in both groups (30/17 mm Hg), losartan thus seems to confer benefits beyond those resulting from reduction in blood pressure alone. Furthermore, 1195 of the 9193 subjects enrolled in the LIFE study were diabetics. Of these, 586 were randomly assessed to losartan and 609 to atenolol. Patients were followed for

4 years. Even in this group of high-risk patients losartan was more effective than atenolol. Although AT_1 receptor blockers share the same mechanism of action, they have different pharmacokinetic profiles, which may account for the potential differences in efficacy. Several double-blind, head-to-head comparative studies have evaluated the relative antihypertensive efficacy among the various AT_1 receptor blockers. The results suggest that longer-acting compounds such as irbesartan, candesartan, and telmisartan may be more effective than losartan, particularly at trough, and provide better 24-hour control of blood pressure. However, it should be recalled that the antihypertensive efficacy seems to be mainly related to the dose and duration of action of the respective drugs. Additional studies are needed to assess whether these differences are truly clinically relevant with respect to major end points such a morbidity and mortality.

AT_1 receptor blockers in heart failure

Following the important results obtained with ACE inhibitors, several studies have investigated the effects of AT_1 receptor blockers in CHF. Several small case studies suggested that AT_1 receptors antagonists are at least as efficacious as ACE inhibitors, but with a more favorable tolerability profile. In the Evaluation of Losartan in the Elderly (ELITE I) trial, one of the secondary end points (combined mortality and hospitalization for CHF) was surprisingly lower in the losartan vs the captopril group.[51] Interestingly, in ELITE I, no difference was found in the incidence of renal dysfunction among elderly patients receiving losartan and those treated with captopril. This was the primary end point for which the sample size of the study was determined.

Despite this negative outcome, the attention of the scientific community focused on the positive data obtained in the secondary end point and an adequately sized study was started—ELITE II. Unfortunately, the preliminary positive results were not confirmed. Indeed, ELITE II showed that losartan was not superior to captopril in reducing mortality and morbidity.[52] Losartan had fewer side effects than captopril. Similar results were found in the Valsartan–Heart Failure Trial (Val-HeFT), showing that addition of valsartan to the standard treatment for CHF, with or without ACE inhibition, did not improve mortality.[53] A benefit was found when combining the primary end point (mortality) and hospitalization and in a subgroup of patients not receiving ACE inhibitors. However, the combination of β-blockers, ACE inhibitors, diuretics, and valsartan resulted in a trend toward worsening.

This finding resulted in another trial being carried out, the CHARM-Overall Program (Candesartan in Heart failure Assessment in Reduction of Mortality), to evaluate the effects of candesartan on mortality and morbidity in patients with chronic heart failure.[54] Candesartan was compared with placebo in three different patient populations: (i) patients with left ventricular ejection fraction 40% or less who were not receiving ACE inhibitors because of intolerance (CHARM Alternative); (ii) patients who were currently receiving ACE inhibitors (CHARM Added); and (iii) patients with left ventricular ejection fraction higher than 40% (CHARM Preserved). A total of 7061 patients were followed for 2 years. The primary end point of the Overall Program was all-cause mortality, while for all the component trials the end points were cardiovascular death or CHF hospitalization. Candesartan was generally well tolerated and reduced cardiovascular death and hospitalization for heart failure. There was no general heterogeneity of candesartan results across the component trials, although some differences could be detected. Some concerns were expressed about renal function, hypotension, and candesartan-induced hyperkalemia.

Therefore, in summary, available data do not show superiority of AT_1 receptor blockers over ACE inhibitors in the treatment of CHF. The ACE inhibitors thus remain the first choice for efficacy, as unequivocally supported by the considerable amount of available data. AT_1 receptor blockers should be used to reduce the deleterious effect of RAS upregulation in case of intolerance or contraindications to the ACE inhibitors.

From the pathophysiological point of view, these data indirectly suggest that, even in CHF, the increase in blood levels of bradykinin secondary to ACE inhibition is important for the final outcome.

AT_1 receptor blockers in CAD patients

Two studies on AT_1 receptor blockers vs captopril have been conducted in post-AMI patients (VALsartan In Acute myocardial iNfarcTion [VALIANT][55] and the OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan [OPTIMAAL]),[56] and one study is currently comparing an ACE inhibitor alone and in combination with an AT_1 receptor blocker (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET]).[57] OPTIMAAL failed to show a benefit of losartan over captopril in reducing all-cause mortality in high-risk patients after acute myocardial infarction. In contrast, there was a nonsignificant trend toward decrease in all-cause mor-

tality with captopril vs losartan, suggesting that ACE inhibitors should be given as first-line treatment for patients with myocardial infarction. In OPTIMAAL, the dosage of losartan was 50 mg once daily: whether a higher dose (100 mg daily), similar to that used in LIFE, would have resulted in better outcomes compared with captopril remains to be determined in future studies. VALIANT, however, tested a full dose of valsartan (20 mg) in patients after myocardial infarction vs captopril, with three therapeutic arms: valsartan alone, plus captopril, or captopril alone. Valsartan was found to be as effective as captopril. Combination of valsartan plus captopril increased the rate of adverse events without improving survival.

Thus, in conclusion, available data support the ACE inhibitors also as first choice treatment in post-MI and secondary prevention in patients with coronary artery disease. EUROPA data further suggest that ACE inhibitors should be used in all patients, independently of their risk profile.

AT$_1$ receptor blockers in renal failure

Preliminary experimental and clinical studies with AT$_1$ receptor blockers on limited numbers of patients suggest that these agents decrease the filtration fraction and reduce urinary albumin excretion. This suggests a favorable influence on renal function in patients with chronic renal failure. In the Reduction of Endpoints in Noninsulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan (RENAAL) trial,[58] losartan was compared with the usual treatment in patients with diabetic nephropathy. A significant renal benefit was reported with losartan, and the drug was generally well tolerated. The benefit was beyond that attributable to blood-pressure control in patients with hypertension, diabetes, and nephropathy.

CONCLUSIONS

AT$_1$ receptor blockers appear to provide a more specific blockade of the effects of Ang II and have better tolerability when compared with ACE inhibitors. Conversely, ACE inhibitors—by inhibiting ACE activity—not only reduce Ang II, but also increase bradykinin availability, thereby exerting marked cardioprotective and vasculoprotective effects. The ACE inhibitors have been in clinical use far longer than the AT$_1$ receptor blockers, and thus benefit from very solid data regarding their safety and efficacy profiles. Also, the majority of studies with AT$_1$ receptor blockers were performed

on top of ACE inhibition, as it would have been unethical to deprive patients of this class of drug. The evidence so far indicates that AT$_1$ receptor blockers share the same efficacy as ACE inhibitors in hypertension. AT$_1$ receptor blockers will conceivably take a growing place in the management of hypertensive patients. However, no clear advantage of AT$_1$ receptor blockers over ACE inhibitors has yet been demonstrated.

In patients with CHF, there is no evidence that AT$_1$ receptor blockers are superior to ACE inhibitors. CHF is a very well established indication for ACE inhibitors, and there is, and probably always will be, a gap between evidence-based medicine findings favoring the use of ACE inhibitors and those favoring the use of AT$_1$ receptor blockers over ACE inhibitors. The same applies to the prevention or treatment of ischemic heart disease and the treatment of patients with diabetic or nondiabetic nephropathy.

Therefore, ACE inhibitors should currently be considered as the first-line choice in all these indications, with AT$_1$ receptor blockers as an appropriate substitute in cases of intolerance to ACE inhibitors. The value of ACE inhibitor/AT$_1$ receptor blocker combination therapy has been assessed in several trials. However, whether results were clear or conflicting, the main limitation was that full-dosing ranges of both classes of drugs were not explored. Thus, one cannot ascertain whether the same effect observed in combination would have been obtained with a higher dosage of one drug alone.

Whatever the case, the one "lucky strike" for both cardiologists and above all their patients is the fact that blocking the RAS appears to be a very important strategy in almost all cardiological conditions. This can be achieved by using two different classes of drugs: the ACE inhibitors, which have been much more intensively studied than the other, the AT$_1$ receptor blockers, probably because the ACE inhibitors were the first to be available.

ACE inhibitors are very effective and well tolerated. Their effect on bradykinin probably compensates for the incomplete blockade of of angiotensin II. This and the other reasons reported above strongly argue in favor of the continued use of the ACE inhibitors as first-line therapy in patients with hypertension, CHF, and CAD.

THREE KEY QUESTIONS

Preserving bradykinin or blocking angiotensin II? In other words, ACE inhibitors or ARBs? The two legendary horns of the dilemma (in this case, the cardiovascular dilemma) could hardly be stated in fewer words, begging, it would seem, for a straight answer—yes or no, this one or that one. But we are dealing with medicine here, and, as is often the case, the answer(s) just will not be that simple/simplistic, black or white. The answer inevitably depends on context (both of the disease and of the patient), as well as on the state of our knowledge, which is evolving at an increasingly breathtaking pace. That is why the implicit question in the title of the Lead Article inevitably gives rise to further, more specific questions, voiced in the subsequent section of *Dialogues* by this issue's three Experts. The logical first step is to look at prevention, and Muzahir H. Tayebjee and Gregory Y. H. Lip ask: **"Which strategies should be used for the primary and secondary prevention of cardiovascular disease?"** Luigi Tavazzi wonders how the ACE inhibitor/ARB dilemma applies to the specific situation of the postinfarct patient: **"Which strategy should be used for postinfarct treatment?"** Finally, Willem J. Remme surveys the topic of heart failure, asking: **"Which strategy should be used for heart failure?"** The answers all point in the same direction, confirming the central role of the ACE inhibitors, backed up by a wealth of studies, with ARBs being the best choice when ACE inhibitors are not effective enough or contraindicated. Does this mean the ARBs merely play second fiddle to the ACE inhibitors? The answer to this question is still open and awaits the findings from several ongoing studies.

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Which strategies should be used for the primary and secondary prevention of cardiovascular disease?

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Cardiovascular disease (CVD) places a large burden on society globally, and effective strategies for primary and secondary prevention are vital to help cope with this. A large number of pharmacological interventions exist for combating CVD, with potential for limiting death and disability from CVD. In the last decade, there have been major advances in both treating and managing the risk factors that cause CVD, in the form of large randomized controlled clinical trials. These advances have had a huge impact on how clinicians should use particular treatments for specific conditions. In this review, we discuss relevant primary and secondary prevention approaches to managing CVD in light of recent evidence.

Cardiovascular disease (CVD) continues to be a major cause for morbidity and mortality worldwide. Thus, effective ways of preventing the development of new vascular events in patients at high risk of developing CVD (that is, primary prevention) or preventing recurrent vascular events in patients who have already sustained an event (that is, secondary prevention) will help to reduce the massive burden of CVD and improve health in the community.

SELECTED ABBREVIATIONS AND ACRONYMS	
4S	Scandinavian Simvastatin Survival Study
ARB	angiotensin-receptor blocker
ATC	Antithrombotic Trialists' Collaboration
CALM	Candesartan And Lisinopril Microalbuminuria
CAPRIE	Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events
CARE	Cholesterol And Recurrent Events
CHD	coronary heart disease
CVD	cardiovascular disease
ELITE II	Evaluation of Losartan In The Elderly–II
EUROPA	EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease
HOPE	Heart Outcomes Prevention Evaluation
LIFE	Losartan Intervention For Endpoint reduction in hypertension
LVH	left ventricular hypertrophy
MICRO-HOPE	MIcroalbuminuria, Cardiovascular and Renal Outcomes–Heart Outcomes Prevention Evaluation
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study
RAAS	renin-angiotensin-aldosterone system
UKPDS	United Kingdom Prospective Diabetes Study
WOSCOPS	West Of Scotland COronary Prevention Study

It is important to have a holistic approach to the patient, with the need to initially address nonpharmacological modifiable risk factors, such as stopping smoking and weight loss, but very often, this is not enough and drugs are frequently needed. In patients with coronary artery disease, drugs often used for primary and secondary prevention include antithrombotic agents (aspirin, clopidogrel, warfarin), β-blockers, angiotensin-converting enzyme (ACE) inhibitors [or angiotensin-receptor blockers (ARBs)], statins and (in patients with postmyocardial infarction) ω-3 polyunsaturated fatty acids.

Certainly, the renin-angiotensin-aldosterone system (RAAS) appears to be pathophysiologically involved in CVD and stroke, with activation most evident in patients with heart failure; and, importantly, increasing data suggest that inhibition of the RAAS with ACE inhibitors and ARBs is beneficial in both primary and secondary prevention of CVD and stroke.

The aim of this review is to discuss an approach to assessing cardiovascular risk, as well as highlight the strategies for primary and secondary prevention, emphasizing the expanding role of RAAS blockade.

ASSESSING CARDIOVASCULAR RISK

The approach to primary and secondary prevention has changed in that individual risk factors should no longer be treated as individual diseases, but in the context of a patient's total CVD risk. For primary prevention, risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking, and family history of CVD need to be taken into account.

Instructions on how to use the charts *(Figure 1)*

- The low risk chart should be used in Belgium, France, Greece, Italy, Luxembourg, Spain, Switzerland, and Portugal; the high risk chart should be used in all other countries of Europe.
- To estimate a person's total 10-year risk of cardiovascular disease (CVD) death, find the table for their gender, smoking status, and age. Within the table find the cell nearest to the person's systolic blood pressure (mm Hg) and total cholesterol (mmol/L or mg/dL).
- The effect of lifetime exposure to risk factors can be seen by following the table upwards. This can be used when advising younger people.
- Low-risk individuals should be offered advice to maintain their low-risk status. Those who are at 5% risk or higher or will reach this level in middle age should be given maximal attention.
- To define a person's relative risk, compare their risk category with that of a nonsmoking person of the same age and gender, blood pressure < 140/90 mm Hg and total cholesterol < 5 mmol/L (190 mg/dL).
- The chart can be used to give some indications of the effect of changes from one risk category to another, for example when the subject stops smoking or reduces other risk factors.

Qualifiers

Note that the total cardiovascular risk may be higher than indicated in the chart:

- As the person approaches the next age category.
- In asymptomatic subjects with preclinical evidence of atherosclerosis (eg, CT scan, ultrasonography).
- In subjects with a strong family history of premature CVD.
- In subjects with low HDL cholesterol levels, with raised triglyceride levels, with impaired glucose tolerance, and with raised levels of C-reactive protein, fibrinogen, homocysteine, apolipoprotein B, or Lp(a).
- In obese and sedentary subjects.

Benefits of SCORE

- Based on a large data set tested thoroughly on European data.
- Operates with hard, reproducible end points (CVD death).
- Risk of coronary heart disease (CHD) and stroke death can be derived separately.
- Enables the development of an electronic interactive version of the risk chart.
- The SCORE risk function can be calibrated to each country's national mortality statistics.

Table I. *Use of the SCORE Risk Charts (European Society of Cardiology).*

Reproduced courtesy of: *European Society of Cardiology © 2003 ESC.*

Using the new European Risk Chart based on SCORE data[1] from 12 European cohort studies, with data collected from 250 000 patients, corresponding to 3 million person-years of observation, and a total of 7000 fatal cardiovascular events, it is clear that there is a strong "additive" effect of the various risk factors to the overall risk profile. The information needed to assess scores is shown in *Table I* and *Figure 1.*
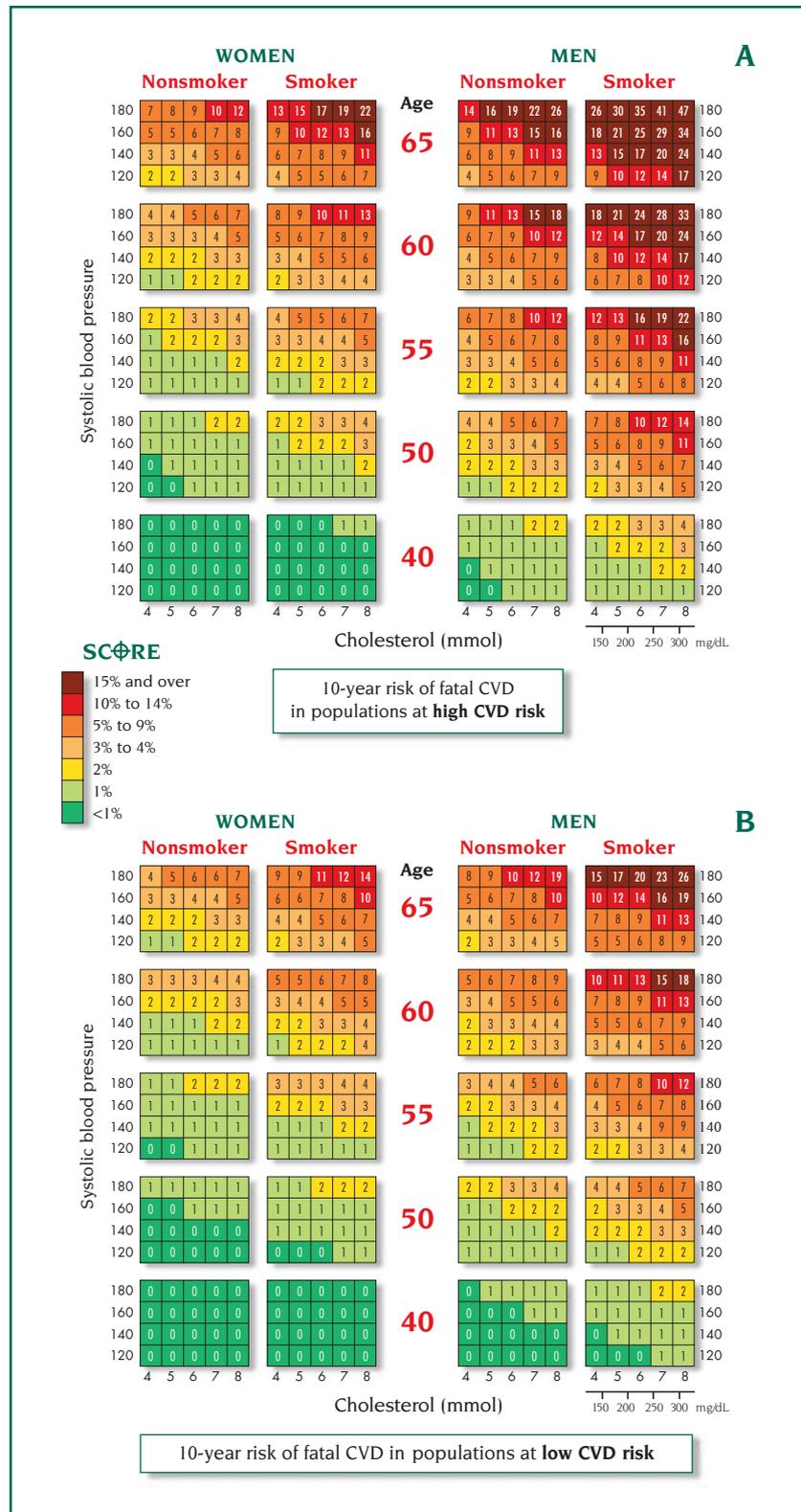
Figure 1. *10-Year risk of fatal cardiovascular disease (CVD) in high-risk* **(A)** *and low-risk* **(B)** *regions of Europe by gender, age, systolic blood pressure, total cholesterol, and smoking status.*

Reproduced courtesy of: *European Society of Cardiology © 2003 ESC.*

Thus, current treatment recommendations, such as that of the British Hypertension Society (BHS-IV, 2004) advise antihypertensive treatment according to the presence or absence of target organ damage, cardiovascular disease (CVD), or a 10-year coronary heart disease (CHD) risk of ≥15%, based on the Joint British Societies coronary risk assessment program/risk chart.[2] Similar approaches have been used by the American Joint National Committee (JNC 7) guidelines for treatment of hypertension and risk factors[3] and the European Society of Cardiology (ESC) guidelines for cardiovascular prevention.[1,4]

STRATEGY FOR PRIMARY PREVENTION

Patients in whom primary prevention is mandatory are those with risk factors, such as hypertension, diabetes, and existing vascular disease. Indeed, there almost appears to be a dose–response relationship between hypertension and the risk of stroke or CHD; conversely, the reduction in blood pressure by antihypertensive treatment reduces the risk of stroke and heart attacks.

Hypertension

The need to treat systemic hypertension is now well established: it is no longer a question of "do we treat?" but more "who and how should we treat?" Indeed, blood pressure reduction of about 10 to 12 mm Hg systolic and 5 to 6 mm Hg diastolic confers a relative reduction in stroke risk of 38% and in risk of coronary heart disease of 16% within just a few years of beginning treatment *Figure 2 (page 96)*[5] shows the algorithm devised by the British Hypertension Society for the treatment of hypertension. They suggest that in nondiabetics target blood pressure on treatment
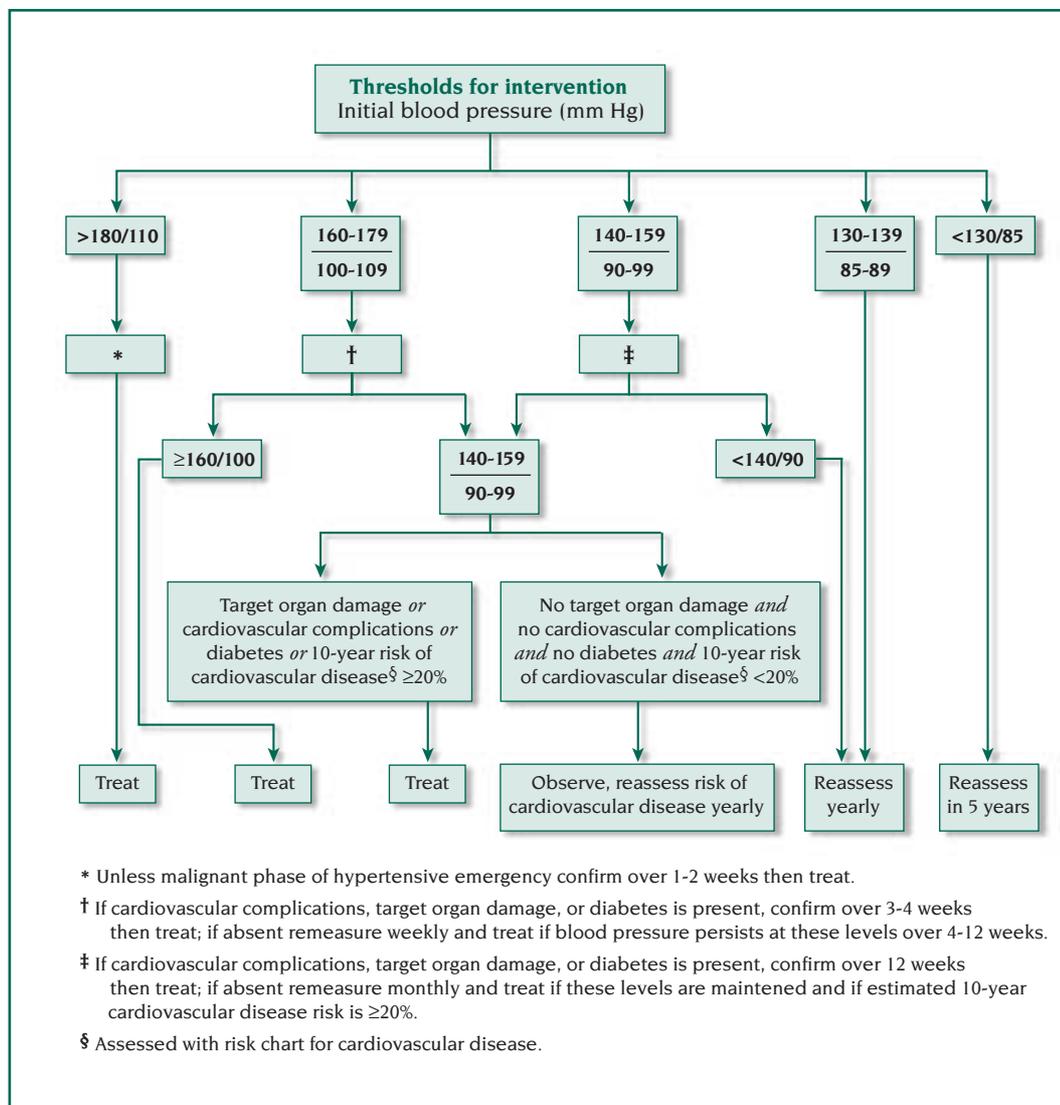
Figure 2. *Blood pressure thresholds and drug treatment in hypertension.*

Reproduced from reference 2: Williams B, Poulter NR, Brown MJ, et al, BHS guidelines working party, for the British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. BMJ. *2004;328:593-594.. Copyright © 2004, BMJ Publishing Group Ltd.*

should be <140/85 mm Hg, and in diabetics, renal impairment, or established cardiovascular disease, <135/80 mm Hg.[2]

The beneficial effects of the RAAS blockade are evident from many trials consistently showing a benefit of ACE inhibitors in reducing mortality and morbidity, even in previously normotensive patients.[6] In a Heart Outcomes Prevention Evaluation (HOPE) substudy, ramipril was shown to result in significant regression of left ventricular hypertrophy (LVH), even in normotensive patients.[7] Recently, the results of the

EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) comparing the effects of perindopril versus placebo in stable coronary heart disease with normal left ventricular function showed that perindopril was able to significantly reduce cardiovascular morbidity and mortality in both hypertensive and nonhypertensive patients.[8]

In patients who develop a cough associated with ACE inhibitors, the ARBs appear to be a suitable alternative, with increasing data on their

beneficial effects. However, trials directly comparing the ACE inhibitors and ARBs are limited. In the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial, losartan was superior to atenolol in reducing events among "high-risk" hypertensive patients with ECG-LVH, despite similar reductions in blood pressure.[9]

Diabetes

Diabetes is another major risk factor for cardiovascular disease, and its incidence is increasing. Type 2 diabetes is potentially preventable,

and is usually preceded by insulin resistance and hyperinsulinemia. One of its worrying features is that it is asymptomatic and is frequently detected too late when one of its complications has developed, and, importantly, the incidence of complications increases with the duration of the disease. The benefits of RAAS blockade in diabetes are evident as shown by studies such as the HOPE and LIFE trials, which have shown that treatment with ACE inhibitors and ARBs, respectively, reduced the incidence of new-onset diabetes.[6,9] Furthermore, risk reduction in diabetic patients is striking with the use of ACE inhibitors: the MICRO-HOPE (MIcroalbuminuria, Cardiovascular and Renal Outcomes—Heart Outcomes Prevention Evaluation study was stopped 6 months early because of the significant reduction in combined cardiovascular end points, myocardial infarction, stroke, and cardiovascular death by 25%, 22%, 33%, and 37%, respectively.[10]

It should be emphasized that hypertensive diabetic patients are a particularly high-risk group of patients. The United Kingdom Prospective Diabetes Study (UKPDS) concluded that in type 2 diabetes, tight control of blood pressure was more important than glycemic control in preventing cardiovascular disease. Furthermore, compared with nondiabetic patients, the threshold for treating hypertension is lower (<135/85 mm Hg compared with 140/90 mm Hg).[11]

What are the mechanisms of the beneficial effects of RAAS blockade? ACE inhibitors appear to be the best drug class for regressing LVH.[7] ACE inhibitors also appear to have beneficial effects on endothelial dysfunction[12] and the prothrombotic state associated with hypertension.[13,14] Some evidence also sug-

gests that ACE inhibitors have antiarrhythmic effects.[15] RAAS blockade can also delay progression of carotid artery atherosclerosis,[16] and thus can potentially prevent strokes.

Hyperlipidemia, smoking, and obesity

There is no evidence to suggest that treating the above conditions in isolation with ACE inhibitors or ARBs provides any benefit. Certainly, there is significant evidence for the treatment of hyperlipidemia with statins in patients with risk factors (Scandinavian Simvastatin Survival Study [4S]),[17] and even primary prevention (West Of Scotland COronary Prevention Study [WOSCOPS]).[18] Stopping smoking is a very effective primary preventative measure, and weight loss further reduces morbidity and mortality.

Atrial fibrillation

Atrial fibrillation is associated with an increased risk of stroke and thromboembolism. Patients with atrial fibrillation and cardiovascular risk factors such as diabetes and hypertension, as well as older subjects (>60 years) are at particularly high risk.[19] In such patients, warfarin (with international normalized ratio [INR] of 2 to 3) is recommended as primary prevention, provided there are no contraindications, while aspirin 75 to 300 mg is considered adequate for low-risk patients with lone atrial fibrillation less than 75 years.[20]

Primary prevention: practical considerations

In assessing the need for intervention, it is important to clearly document a patient's risk factors, and calculate the CVD risk using the charts based on European data *(Figure 1)*. Concomitant disorders; such

as hypertension, diabetes, atrial fibrillation, etc, should be addressed. Nonpharmacological measures should be initiated prior to starting drug treatment. For example, smoking is a significant risk factor, and needs to be dealt with aggressively since the effect of medication can be attenuated by this habit. Exercise, weight reduction, healthy diets should be encouraged.

For those who fall in the "high-risk" category, pharmacological treatment is appropriate for primary prevention. Agents such as ACE inhibition or ARBs should be considered early in diabetic patients, especially if there is coexistent hypertension or nephropathy. Furthermore, in hypertensives with LVH, these agents should be first choice. It is important to remember that many patients will require more than one drug and that certain drug combinations are synergistic and enhance the antihypertensive effect. The Birmingham Hypertension Square is an eloquent yet simple tool to help with the choice(s) of "add-on" antihypertensive therapy.[21]

To date, the most convincing evidence for the use of antiplatelet agents comes from the Antithrombotic Trialists' Collaboration (ATC).[22] This large meta-analysis included 287 studies and over 200 000 patients. In high-risk patients, there was a 25%, 33%, 25%, and 17% reduction in serious vascular events, nonfatal myocardial infarction, nonfatal stroke, and vascular mortality, respectively, with the use of aspirin 75 to 300 mg. In patients intolerant of aspirin, clopidogrel is an alternative; this drug is a thienopyridine derivative, chemically related to ticlopidine. In the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, which included 19 185 patients followed up for approximately 2 years, it

was shown that clopidogrel reduced the risk of significant vascular events by 8.7% more than aspirin.[23] Its safety profile is similar, but the drug is more expensive.

STRATEGY FOR SECONDARY PREVENTION

Patients in whom secondary prevention is mandatory are those with established cardiovascular or cerebrovascular disease, in whom treatment is aimed at reducing further events. In heart failure, ACE inhibitors are well-established therapy, reducing mortality as well as the progression of heart failure. Comparisons between ACE inhibitors and ARBs are more limited. However, the Evaluation of Losartan In The Elderly–II (ELITE II) study did not demonstrate any significant difference in survival between losartan and captopril in patients with heart failure, but found that losartan was better tolerated.[24]

Nephropathy is a predictor of cardiovascular events in diabetics, and ACE inhibitors have been shown to slow down the progression of renal disease. Indeed, ACE inhibitors are also superior to calcium antagonists in reducing nephropathy in African-Americans.[25] The Candesartan And Lisinopril Microalbuminuria (CALM) study compared the effects of lisinopril, candesartan and lisinopril plus candesartan in type 2 diabetics with hypertension and microalbuminuria and found that at 12 weeks both candesartan and lisinopril were equally effective in lowering blood pressure and reducing microalbuminuria; however, combination therapy with lisinopril and candesartan was superior to monotherapy.[26]

Recent findings suggest that RAAS blockade may even be beneficial as secondary prevention for cerebrovascular disease. The Perindopril pRO-tection aGainst REcurrent Stroke Study (PROGRESS)[27] recently demonstrated a significant 28% reduction in recurrence of stroke with perindopril-indapamide combination therapy. In a substudy of HOPE, the risk reduction of stroke in high-risk patients treated with ramipril was also statistically significant.[28]

Antithrombotic agents

As discussed above, antiplatelet agents have been shown to have a definite place in the prevention of further cardiovascular events in patients with established ischemic heart, peripheral vascular, and cerebrovascular disease. In the absence of contraindications they should be used as secondary prevention for cardiovascular disease. In secondary prevention of stroke, a combination of aspirin and dipyridamole has also been shown to reduce the risk of stroke or death by 24% compared to 13% with aspirin and 15% with dipyridamole.[29] In patients with atrial fibrillation and previous stroke or transient ischemic attack, warfarin reduces the risk of recurrent stroke by two thirds.[18]

Statins

Evidence for the use of statins in the secondary prevention of CVD continues to grow. Clear data are already available from studies such as the Candesartan And Recurrent Events (CARE) study.[30] It is thought that the action of these drugs extends beyond lipid lowering, and their anti-inflammatory effects are just as important. Recent results of the Heart Protection Study have shown a 13% reduction in total mortality, mainly because of a significant 18% reduction in CHD death and a 24% reduction in major vascular events in patients at risk for CVD treated with 40 mg simvastatin with low/normal cholesterol.[31]

Secondary prevention: practical considerations

As stated above, nonpharmacological measures should be initiated first. Aspirin or clopidogrel should be considered for all patients with CVD. Statins are appropriate for all patients with cholesterol >5 mmol/L. Aggressive lipid lowering with statins is very important, and measures should be undertaken to ensure that adequate dose adjustment are made if control has not been achieved. In the presence of atrial fibrillation warfarin is important.[19]

ACE inhibitors and ARBs are indicated in the presence of conditions such as heart failure, diabetes (especially if hypertension and nephropathy are present), and hypertension with LVH in the presence of established CVD.

CONCLUSION

A strategy for primary or secondary prevention necessitates a holistic approach to the patient. No matter what the evidence is, treatment will only be effective if it is taken. Treatment should be simplified for example, using preparations with combined drugs (eg, co-tenidone, a combination of atenolol and hydrochlorothiazide) and once-daily regimens, which would help to improve compliance. Moreover, patients should be told what their medication is for and why it is important to take it. Side effects should be explained, and other compounds should be instituted if there are problems (eg, ARB instead of ACE inhibitor for cough). In conclusion therefore, large epidemiological studies provide valuable information on how to treat populations. However, the challenge facing clinicians is the practical application of this information to the *individual* patient facing them on the ward or in clinic.

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Which strategy should be used for postinfarct treatment?

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The renin-angiotensin-aldosterone system (RAAS) is both a trophic factor and an apoptotic trigger in postinfarct ventricular remodeling. Its cardiac paracrine impact on endothelium, small vessel tone, and fluid-electrolyte balance hastens the heart failure syndrome. Although the current consensus, based largely on first year follow-up data, favors modulating the RAAS with a combination of angiotensin-converting enzyme (ACE) inhibitors and β-blockers, studies to date may have overestimated the degree of longer-term benefit. Meta-analysis of postinfarct trials shows that survival curves in patients with and without ACE-inhibitor therapy become roughly parallel after the initial 1 to 2 years. Thus, the RAAS may eventually become refractory to ACE inhibitor blockade. Ongoing trials aim to determine whether angiotensin II receptor blockade will prove more effective, in isolation or in combination with ACEI.

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EFFECT OF ACE INHIBITION EARLY AFTER MYOCARDIAL INFARCTION

An acute myocardial infarct can induce a dynamic process of changes in the architecture, shape, and size of the left ventricle, which can lead to severely compromised left ventricular function. This process—whether at the acute or chronic stage—involves both the infarcted area and more distant areas of the heart, modifying the ventricular structure, causing the ventricle to dilate and become more spherical and compromising diastolic and systolic function. This process is not homogeneous, and is, to some extent, unpredictable even in apparently similar patients. An echocardiographic substudy of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III (GISSI 3) trial[1] enrolled 614 subjects in whom a series of 4 echocardiograms were carried out: one within 48 hours of the onset of the symptoms, one at discharge from hospital, one after 6 weeks, and the last after 6 months of follow-up. Profoundly different sequences of ventricular remodeling were observed. In short, about one fifth of the subjects had pronounced left ventricular dilatation while they were in hospital, but, unexpectedly, subsequently remained stable without further geometric changes in the ventricular chamber. In contrast, about one fifth of the subjects developed no left ventricular size changes during their stay in hospital, but subsequently developed marked ventricular remodeling with progressive dilatation of the left ventricle. Of note, 92% of the patients with severe (>20%) early left ventricular dilata-

SELECTED ABBREVIATIONS AND ACRONYMS	
CAPTIN	CAptopril Plus Tissue plasminogen activator following acute myocardial INfarction
CATS	Captopril And Thrombolysis Study
CONSENSUS II	COoperative North Scandinavian ENalapril SUrvival Study II
FAMIS	Fosinopril in Acute Myocardial Infarction Study
GISSI 3	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico III
RAAS	renin-angiotensin-aldosterone system
SAVE	Survival And Ventricular Enlargement
SOLVD	Studies Of Left Ventricular Dysfunction

tion did not show any further dilatation at 6 months, and 91% of patients with severe late dilatation did not have in-hospital dilatation. While the initial left ventricular dilatation developed in parallel with a recovery of ejection fraction, the delayed dilatation was associated with a reduction in ejection fraction and thus compromised systolic ventricular function. All patients were randomized to treatment with lisinopril, which was maintained for 6 weeks and then stopped in patients with preserved left ventricular systolic function. Multivariate analysis showed that this treatment was not an independent factor correlated with the evolution of ventricular remodeling.

Large randomized placebo-controlled studies have examined the effects of angiotensin-converting enzyme (ACE) inhibition on left ventricular remodeling following an acute myocardial infarction: the most relevant are the Survival And Ventricular Enlargement (SAVE), COoperative North Scandinavian ENalapril SUrvival Study II (CONSENSUS II), and GISSI 3 trials.

An echocardiographic substudy of the SAVE trial[2] was carried out in 512 patients with acute myocardial infarction. The patients were randomized to treatment with captopril or placebo. The 420 patients having survived for more than 1 year underwent echocardiographic follow-up, which disclosed that the left ventricular end-systolic and end-diastolic areas in the patients treated with captopril for 1 year were about 3 cm[2] smaller than in the patients who had received the placebo.

An echocardiographic substudy was also carried out in the CONSENSUS II trial.[3] This trial was prematurely halted because of the lack of clinical benefits in the group of pa-

tients treated with enalapril. Nevertheless, in the echocardiographic substudy, at 6 months, the patients treated with ACE inhibitors had a smaller left ventricular end diastolic volume than those given a placebo. The absolute difference was about 3 mL/m^{2}.

By far the largest study on the effects of ACE inhibition on left ventricular remodeling following a myocardial infarction is GISSI 3.[4] In the GISSI 3 trial, the effects of lisinopril, transdermal nitrate, combined therapy with both, and no treatment were tested with a 2×2 factorial design. The treatments were assigned randomly to 19 394 eligible patients who were admitted to hospital with a diagnosis of myocardial infarct within 24 hours of the onset of their symptoms. The aim was to establish whether, and if so by how much, short-term treatment (6 weeks) was effective in modifying the patients' subsequent outcome. In the absence of specific indications for continuing the treatment, this was stopped after 6 weeks and the patients were followed up for 6 months. The GISSI 3 protocol included an echocardiographic examination in all patients 6 weeks and 6 months after the acute myocardial infarct in order to measure the combined end point of mortality and severe ventricular dysfunction. A two-dimensional echocardiogram was also performed at discharge from hospital. Overall, the echocardiographic database consisted of 8619 echocardiograms carried out at discharge, 12 125 echocardiograms at the 6-week follow-up, and 10 726 echocardiograms at the 6 month follow-up, in 50.8%, 72.6%, and 73.3%, respectively, of all the patients with a confirmed infarct and a legible echocardiogram.

Interestingly, use of an algorithm to predict left ventricular dilatation at 6 months in 7842 patients with a

predischarge echocardiogram enabled left ventricular systolic and diastolic volumes to be predicted with $r=0.72$ and $r=0.65$, respectively.[5] Patients predicted to be at risk for long-term left ventricular dilatation had an increased risk of mortality (relative risk [RR] 1.87, 95% confidence interval [CI] 1.48 to 2.36) and an increased risk of heart failure at 6 months (RR 2.59, 95% CI 2.04 to 3.28), but no increased risk of reinfarction. The variables included in the algorithm were gender, peak creatine phosphokinase (CPK) release (as a marker of infarct size and its evolution), and echocardiographic left ventricular volumes. If the accuracy of this prediction model of postinfarct left ventricular dilatation is confirmed, it should contribute to more efficient risk stratification early after myocardial infarction and facilitate decision-making on the therapeutic strategies in postinfarct patients.

The subpopulation of 6405 GISSI 3 patients with the full series of 3 legible echocardiograms was used to evaluate changes in left ventricular remodeling over time and the effect of lisinopril on this process. The left ventricular end diastolic and end systolic volumes and the ejection fraction measured at discharge were independent predictors of mortality and incidence of nonfatal heart failure at 6 months *(Figure 1).*[6] The patients in whom left ventricular asynergy exceeded 27% of the whole ventricular wall developed left ventricular enlargement over time. Treatment with lisinopril reduced the ventricular dilatation *(Figure 2).*[6] The difference in end-diastolic ventricular volumes between patients treated with lisinopril and those not treated was statistically significant in patients with the most extensive infarcts (asynergy ≥27%) while ventricular remodeling was not evident during follow-up in pa-
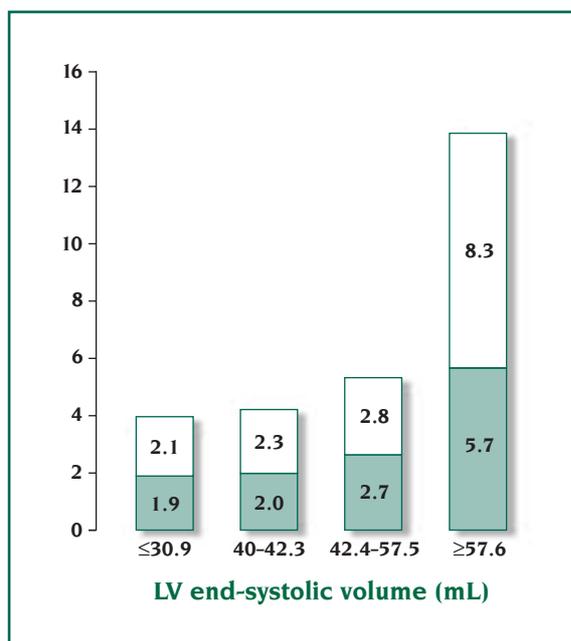
Figure 1. *Predischarge echocardiographic variables in quartiles vs 6-month mortality (■) plus nonfatal late congestive heart failure (CHF) (□). Data refer to 8606 myocardial infarction patients discharged alive.*

Reproduced from reference 6: *Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.* **Eur Heart J.** *1996;17:1646-1656. Copyright © 1996, The European Society of Cardiology.*
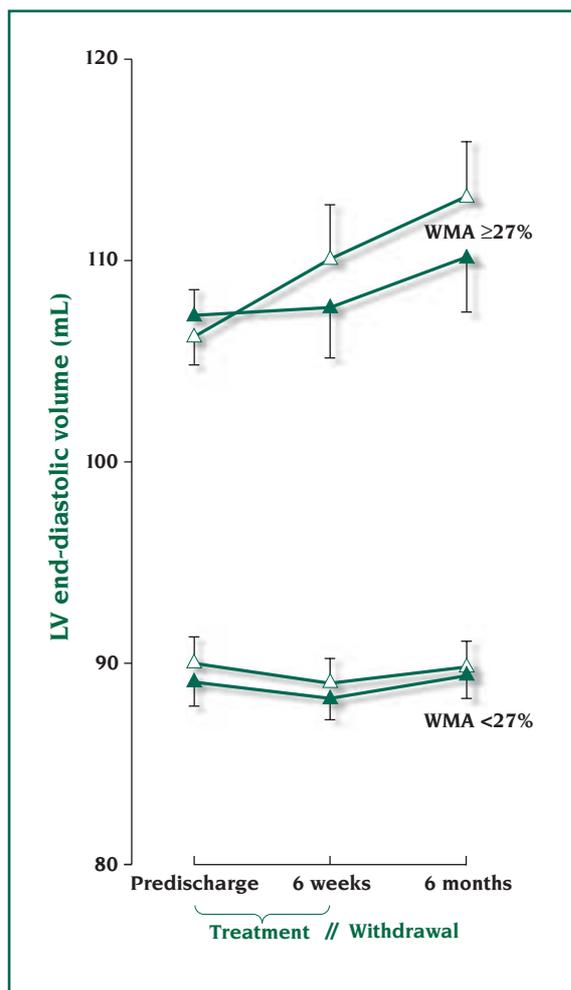
Figure 2. *Left ventricular (LV) end-diastolic volume in lisinopril (▲) and no lisinopril (△) patients with wall motion asynergy (WMA) <27% and with wall motion asynergy ≥27% (n=6405). Sample sizes were as follows: Wall motion asynergy ≥27%; lisinopril=909, no lisinopril=903. Wall motion asynergy <27%; lisinopril=2277, no lisinopril=2316.*

Reproduced from reference 6: *Nicolosi GL, Latini R, Marino P, et al. The prognostic value of predischarge quantitative two-dimensional echocardiographic measurements and the effects of early lisinopril treatment on left ventricular structure and function after acute myocardial infarction in the GISSI-3 Trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.* **Eur Heart J.** *1996;17:1646-1656. Copyright © 1996, The European Society of Cardiology.*

tients with smaller infarcts (asynergy <27%), in both study groups. This finding is in accordance with previous studies in which ventricular remodeling was observed only in patients with moderately sized or large infarcts. A similar trend over time was observed for the end-systolic volume, although the difference in this parameter between patients treated or not treated with lisinopril did not reach a statistically significant level. Given the large number of centers participating in this study and the lack of strict selection criteria for enrolling the patients, the GISSI 3 population can be considered a representative sample of the general population of patients with acute myocardial infarction in the thrombolytic era.

A meta-analysis of the effects of ACE inhibition during the acute phase of a myocardial infarct on ventricular remodeling has recently been published.[7] Data from 845 subjects, collected in three randomized studies, were analyzed. The three studies were the Captopril And Thrombolysis Study (CATS), CAptopril Plus Tissue plasminogen activator following acute myocardial INfarction (CAPTIN), and Fosinopril in Acute Myocardial Infarction Study (FAMIS) in which the patients received thrombolytic therapy and were randomized to captopril (CATS, CAPTIN) or to fosinopril (FAMIS vs placebo within 6 to 9 hours of the onset of symptoms), and underwent echocardiographic follow-up for 3 months. Left ventricular dilatation was the primary measurement outcome of the study. Eighty-five percent of the patients had had an anterior acute myocardial infarct. The analysis did not demonstrate any significant effect of ACE inhibition on left ventricular dilatation. End-diastolic and end-systolic ventricular volume both decreased by 0.5 mL/m^2 (P=0.05 and 0.061, respectively). Left ven-
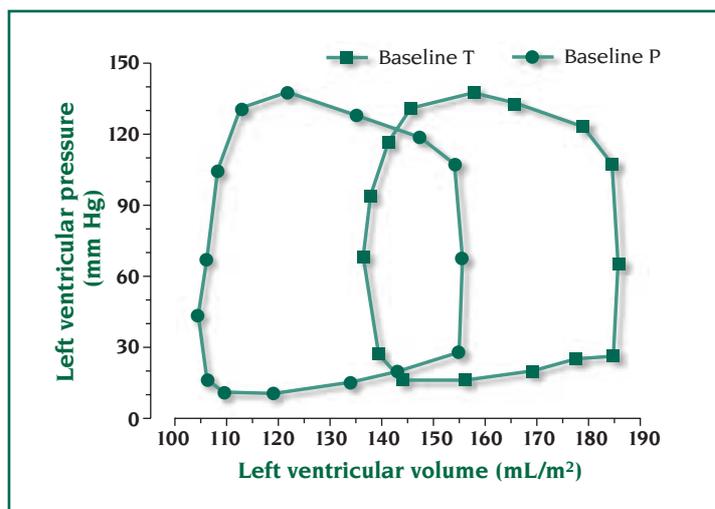
tricular dilatation was significantly reduced only in a small subgroup, which included the 26% of patients in whom, on the basis of indirect criteria, thrombolysis was considered not to have been successful and in whom reperfusion of the infarcted area had not, therefore, been achieved.

Figure 3. *Averaged left ventricular pressure-volume loops of 16 congestive heart failure patients (treatment, T) and 49 asymptomatic patients (prevention, P) before their randomization in the Studies Of Left Ventricular Dysfunction.*

Reproduced from reference 11: *Pouleur H, Rousseau MF, van Eyll C, Melin J, Youngblood M, Yusuf S, for the SOLVD Investigators. Cardiac mechanics during development of heart failure.* Circulation. *1993;87(5 suppl IV):IV114-IV20. Copyright © 1993, American Heart Association.*

Taken together, these studies demonstrate that treatment with ACE inhibitors, when started early after an acute myocardial infarct, is able to mitigate left ventricular dilatation, but not prevent it. Overall, the extent of the effect of ACE inhibition on left ventricular remodeling is limited, and certainly less substantial than that expected after the very encouraging results obtained in the small group of patients studied invasively in the Studies Of Left Ventricular Dysfunction (SOLVD) (see below).

Moreover, the available data have not shown a correlation between the effectiveness of ACE inhibition in ventricular remodeling and the

promptness of administration of these drugs during acute myocardial infarction.

It is interesting to note that a spontaneous reduction in left ventricular asynergy was observed throughout the follow-up of GISSI-3 patients, independently of the treatment given.[4] These results suggest that a spontaneous, late recovery of the myocardium damaged during an infarct not only can occur, but indeed normally does so, and that this process can last months. This implies that considerable caution should be used in interpreting the extent of a myocardial infarct and the effect of drugs on ventricular remodeling in the early postinfarct period.

EFFECT OF ACE INHIBITION LATE AFTER MYOCARDIAL INFARCTION

The effects of ACE-inhibitor therapy on left ventricular structure and function in patients with chronic

ventricular dysfunction were carefully studied in the SOLVD trials. About 70% of the patients enrolled had a history of previous myocardial infarction. Two small longitudinal substudies, one echocardiographic, the other angiographic, were carried out in subgroups of patients in both the Treatment arm (left ventricular ejection fraction <35% and clinical signs of heart failure) and the Prevention arm (ejection fraction <35 % without clinical signs of heart failure).[8-10] The patients underwent double-blind treatment with enalapril or placebo and were followed-up for 3 years. Invasive left ventricular function studies were performed at baseline and after 1 year of treatment in a small subgroup of patients. Overall, both end-diastolic and end-systolic left ventricular volumes increased in the group treated with placebo, but not in the group treated with enalapril; the difference in response to the two treatments was statistically significant. Similarly, left ventricular mass increased in patients given placebo while it tended to decrease in those treated with enalapril. It is important to note that this occurred in patients who had long-standing left ventricular hypertrophy and dilatation, which demonstrates both the chronic progressive nature of ventricular remodeling and the efficacy of treatment even when considerable structural changes in the left ventricle have already occurred. *Figure 3*[11] illustrates the mean left ventricular pressure/volume curves of the symptomatic patients enrolled in the Treatment arm and the asymptomatic ones enrolled in the Prevention arm. The fundamental difference in the functional characteristics of the left ventricle between both groups of patients, symptomatic and asymptomatic, was not the pressure in the ventricle during diastole, in particular the end-diastolic pressure (a parameter used to evaluate the

overall function of the left ventricle), nor the capacity of the ventricle to generate tension during systole (measured by the peak pressure reached during systole or, better, the peak wall stress reached during systole), nor yet the stroke volume (ie, the difference between end-diastolic volume and end-systolic volume), which were similar in the two groups of patients, but rather the ventricular volumes, which were much larger in the symptomatic patients. In brief, the finding that characterized these patients was the left ventricle's exaggerated ability to distend during diastole, in other words an excess of ventricular compliance (rather than a reduction, as diastolic dysfunction is classically interpreted). It should be noted that in the SOLVD study, as in the other studies, ventricular dilatation did not appear to be dependent on changes in ventricular filling pressure: quite the contrary, the ventricle appeared to be able to distend more at every pressure. In other words, the entirre pressure-volume curve was shifted to the right. These observations support the concept that the changes in volume, shape, and architecture that characterize ventricular remod-

Figure 4. *Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.*

Reproduced from reference 9: Konstam MA, Kronenberg MW, Rousseau MF, et al. Effects of the angiotensin-converting enzyme inhibitor enalapril on the long-term progression of left ventricular dilatation in patients with asymptomatic systolic dysfunction. SOLVD (Studies of Left Ventricular Dysfunction) Investigators. Circulation. 1993;88(5 pt 1):2277-2283. Copyright © 1993, American Heart Association.

eling are a cause rather than a consequence of the failing pump function seen during the process that leads from ventricular dysfunction to heart failure. The involvement of the renin-angiotensin-aldosterone

system (RAAS) in this process was convincingly demonstrated precisely by the SOLVD study. *Figure 4*[9] shows the pressure/volume curves of the group of patients enrolled in the Prevention arm while *Figure 5*[8]
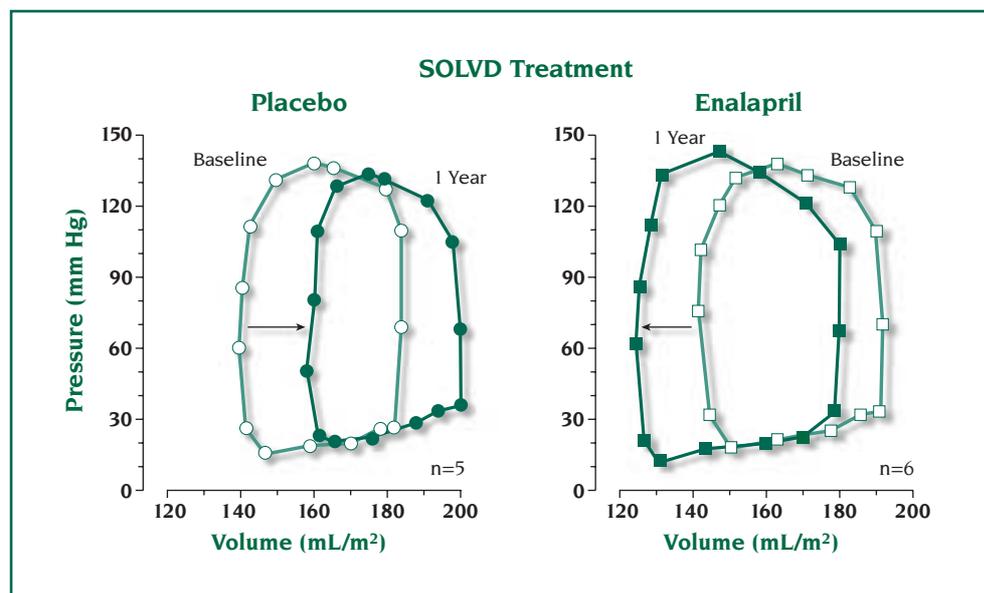
Figure 5. *Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.*

Reproduced from reference 8: Konstam MA, Rousseau MF, Kronenberg MW, et al. Effects of the angiotensin converting-enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. SOLVD Investigators. Circulation. 1992; 86:431-438. Copyright © 1992, American Heart Association.

shows the same curves for the group of patients enrolled in the Treatment arm, recorded at the time of enrollment and again 1 year later both in the patients given placebo and in those treated with enalapril. The process of ventricular dilatation continued in the patients who received placebo. In both symptomatic and asymptomatic patients, the evolution of the disease led to progressive ventricular dilatation without substantial changes in ventricular systolic function (once again suggesting that the latter is not the cause of the former). The process was inverted in the patients treated with enalapril: ventricular dilatation was halted and the size of the left ventricle tended to decrease. There was a process of inverse remodeling, a reduction in the structural changes of the ventricle. These beneficial effects of ACE inhibitors on ventricular remodeling, invasively recorded in this small substudy, were confirmed in a further substudy of the SOLVD trial, carried out with echocardiography.[10] Thirty-one patients were enrolled and followed-up with echo-Doppler evaluations performed at the time of enrollment and after 4 and 12 months of therapy. Results showed an increase in end-diastolic and end-systolic volumes, as well as left ventricular mass, in the placebo group, but not in the group treated with enalapril. The difference in the response between the two groups was statistically significant.

CONCLUSION

The message from these studies is the proof of the pathophysiologic relevance of the RAAS in the process of postinfarct ventricular remodeling and the potential benefit that can be achieved trough modulation of RAAS hyperactivity. The size of benefit cannot be evaluated in these small studies and may have been overestimated. In fact, the long-term data of the SAVE trial show a progression of ventricular remodeling, which is roughly similar after the first year postinfarct both in the patients given captopril and in the untreated patients.[12] Similarly, a meta-analysis of postinfarct trials showed a definitely lower mortality rate in patients treated with ACE inhibitors than in the control groups during the first 1 to 2 years postinfarct, then the survival curves almost became parallel.[13] In the long run, the RAAS may well escape, at least partially, the ACE blockade.

In conclusion, the RAAS is now firmly established as playing a key role both as a trophic factor and an apoptotic trigger in the ventricular remodeling process after a myocardial infarction, mainly through its cardiac paracrine activity. Subsequently, this results in unfavorable effects on the endothelium, small vessel tone, and fluid-electrolyte balance, and becomes a determinant of the heart failure syndrome. Many studies have demonstrated that modulation of the RAAS can modify the process of ventricular remodeling, thereby preventing or delaying the onset of heart failure. Current guidelines unanimously recommend the prescription of ACE inhibitors, in combination with β-blocker drugs, after a myocardial infarction with left ventricular dysfunction. Whether or not it may be possible to achieve more with the blockade of angiotensin II receptors in isolation or in combination with ACE inhibitors is a question that is now being tested in several ongoing trials.

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Which strategy should be used for heart failure?

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Angiotensin-converting enzyme (ACE) inhibitors have long been the cornerstone of heart failure (HF) therapy thanks to their unique dual mechanism of action resulting in a reduction in angiotensin II and an increase in bradykinin. Brady-kinin most likely contributes to a major extent to the well-established efficacy of the ACE inhibitors in the HF syndrome, since their beneficial effects, including attenuated cardiac remodeling and vasodilation, are fully reversed by brady-kinin B_2 receptor blockade. Whether other antagonists of the renin-angiotensin system will prove as effective as ACE inhibitors in chronic HF is as yet unknown. Although the combination of an angiotensin type I receptor antagonist and an ACE inhibitor would appear to provide more benefit than ACE inhibition alone, available studies comparing the two classes of agents show conflicting results. Consequently, guidelines on treatment of HF firmly confirm the central role of ACE inhibition in all phases of HF.

In heart failure, angiotensin-converting enzyme (ACE) inhibition is the cornerstone of treatment, and, indeed, ACE inhibitors are the first class of drug to prescribe to the patient, irrespective of the severity of heart failure. ACE inhibitors are further advocated in asymptomatic left ventricular dysfunction in order to prevent or delay worsening to symptomatic failure. Moreover, there is reason to believe that ACE inhibitors also have a place in the treatment of heart failure due to diastolic dysfunction. Consequently, treatment guidelines invariably indicate the necessity to introduce ACE inhibitors before further therapy whenever the diagnosis of heart failure has been made, and to titrate the dose until levels shown to be effective in large controlled trials are reached. This advice is based on a large number of studies clearly indicating that, in symptomatic heart failure, ACE inhibitors lead to a significant reduction in mortality, particularly in severe heart failure, and that, in addition, hospitalizations, whether all-cause, cardiovascular, or heart failure-related, decrease.

Several lines of evidence indicate that, in patients with heart failure, ACE inhibitors may prevent further cardiac remodeling—the pivotal mechanism underlying both the origin and the progression of heart failure. Furthermore, ACE inhibitors have been shown to decrease ischemic events, such as (re)infarction and unstable angina in patients with heart failure. What makes the

ACE inhibitors such useful agents in the treatment of this syndrome? In heart failure, most studies have focused on the fact that ACE inhibitors inhibit the synthesis of angiotensin II. Angiotensin II is a potent vasoconstrictor, and, as a consequence, ACE inhibitors were introduced in heart failure therapy as vasodilators in view of improving hemodynamics and thereby alleviating heart failure symptoms. Subsequently, with the important role of angiotensin II in cardiovascular remodeling becoming gradually better understood, the focus changed to prevention of cardiac remodeling, leading to beneficial effects on both morbidity and mortality. At present, it is further understood that angiotensin II may be central to several mechanisms leading to endothelial dysfunction and atherosclerosis. ACE inhibitors therefore may be of potential use in secondary prevention of myocardial ischemia. Is inhibition of angiotensin II production sufficient to explain the beneficial effect of ACE inhibitors?

ACE INHIBITION AND BRADYKININ

ACE not only converts angiotensin I to angiotensin II, it is also the major degradation enzyme for kinins, as such referred to as kininase II. As a consequence, ACE inhibitors prevent the breakdown of bradykinin. Kallikrein, the enzyme responsible for the formation of bradykinin from its precursor kininogen, is present throughout the body, so that it may be anticipated that bradykinin

is also ubiquitously present. ACE, mainly present at the cell membrane of endothelial cells, stimulates the breakdown of bradykinin to its inactive degradation products. Bradykinin normally has a very short half-life. Predominantly through coupling with the bradykinin B_2 receptor, bradykinin leads to the production of nitric oxide (NO) and endothelial-derived hyperpolarizing factor (EDHF), both leading to relaxation of smooth vascular muscle cells. In addition, bradykinin promotes the release of prostacyclin. As a consequence, bradykinin is, among others, a potent vasodilator.

A major mechanism in the activation of the kallikrein-kinin system is shear stress. An increase in blood flow will augment bradykinin production and, subsequently, lead to vascular relaxation. This process, linked to endogenous bradykinin production, can be significantly enhanced by concomitant ACE inhibition and reversed by the administration of a selective bradykinin B_2 antagonist. For the effect of the ACE inhibitors to occur, an intact endothelium is required. In a de-endothelialized vessel or a vessel with a damaged endothelium, the effect of ACE inhibition is limited or even absent. Although the measurement of bradykinin is difficult, there is some evidence that the increase in flow-derived, endothelium-dependent vasodilation following ACE inhibitors is due to an increase in endogenous bradykinin and, possibly less so, to reduced angiotensin II production. Still, the situation is not as simple that it can be explained just by the inhibition of bradykinin breakdown by ACE. ACE inhibitors may amplify the effect of bradykinin

SELECTED ABBREVIATIONS AND ACRONYMS	
ARB	angiotensin receptor blocker
CAD	coronary artery disease
CHARM	Candesartan in Heart failure Assessment in Reduction of Mortality
EDHF	endothelial-derived hyperpolarizing factor
ELITE I, II	Evaluation of Losartan in the Elderly I, II
EUROPA	EUropean trial of Reduction of cardiac events with Perindopril in stable coronary Artery disease
LVH	left ventricular hypertrophy
MCP-I	monocyte chemotactic protein–1
NEP	neural endopeptidase
NO	nitric oxide
OPTIMAAL	OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan
PAI-1	plasminogen-activator inhibitor–1
t-PA	tissue plasminogen activator
Val-HeFT	Valsartan—Heart Failure Trial
VALIANT	VALsartan In Acute myocardial iNfarcTion
VCAM-1	vascular cell adhesion molecule–1

without a clear increase in bradykinin levels, an effect that is related to the bradykinin receptor. Furthermore, recent studies have evidenced a similar effect with a bradykinin analog, which is not affected by ACE. This suggests that ACE inhibitors, or at least some of them, may actually prime the receptor for the effect of bradykinin by preventing desensitization and internalization of the receptor.

There is also some evidence that ACE may not be the most important pathway for the breakdown of bradykinin, at least not in cardiac membranes. Instead, neutral endopeptidases (NEP) may be involved, which would support the develop-

ment of NEP inhibitors in cardiovascular disorders such as coronary artery disease (CAD) and heart failure.[1] Moreover, this may be an important argument to continue work on the combination of ACE inhibitors and NEP inhibitors in a single drug, commonly referred to as a vasopeptidase inhibitor.

ROLE OF BRADYKININ IN CARDIOVASCULAR REMODELING

Activation of the kallikrein-kinin system in pathophysiologic states, such as heart failure, may be beneficial. Bradykinin has strong vasodilating effects and reduces coronary and systemic resistance. Through NO production, it inhibits vascular smooth muscle cell growth and migration, improves endothelial function, prevents platelet aggregation, and inhibits the expression of various proinflammatory proteins, such as vascular cell adhesion molecule-1 (VCAM-1), monocyte chemotactic protein–1 (MCP-1), and leukocyte adhesion molecules. The latter are stimulated by oxidative stress, induced among others by angiotensin II. ACE inhibitors oppose a dual response to these processes, reducing angiotensin II on the one hand and increasing bradykinin, and subsequently NO, on the other. In addition, bradykinin stimulates the synthesis of tissue plasminogen activator (t-PA), whereas angiotensin II activates plasminogen activator inhibitor–1 (PAI-1). ACE inhibitors may improve fibrinolytic balance through a reduction in angiotensin II and an increase in bradykinin, adding to the vasculoprotective activity of the ACE inhibitor. As such, ACE inhibitors are considered important antiatherosclerotic agents.
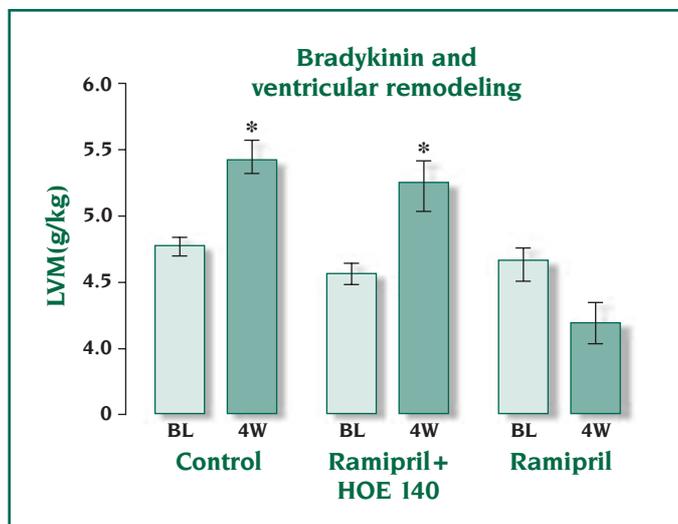
In large controlled studies, such as the EUropean trial of Reduction of cardiac events with Perindopril in stable coronary Artery disease (EU-ROPA), a secondary preventive role of the ACE inhibitor perindopril in CAD was tested in patients with proven ischemic heart disease.[2,3] Previous studies in selected patient groups, ie, with LV dysfunction and heart failure[4,5] and in patients with a high-risk profile for cardiovascular disease,[6] have established a preventive activity of this kind. The importance of the EUROPA study was that in that trial long-term secondary prevention of ischemic events was tested in all patients with CAD, irrespective of cardiac dysfunction or a high-risk profile; in short, in the all-comer CAD patient. At 4.2 years of follow-up, perindopril reduced the risk of developing the composite primary end point, ie, cardiovascular death, myocardial infarction (MI), and resuscitated cardiac arrest, in a highly significant way by 20%, but also the risk of hospital admission for heart failure by 39%, one of the secondary end points. As such, the EUROPA study is of major clinical importance.[3] The rationale behind this study lies in the important antiatherosclerotic and anti-ischemic profile of ACE inhibitors such as perindopril, effects which are predominantly bradykinin-dependent. A more detailed description of these effects is provided elsewhere in this volume.

Further to these vascular actions, bradykinin is also involved in the antiremodeling effects of ACE inhibitors in the heart. In a dog model of cardiac remodeling and hypertrophy resulting from electrically induced myocardial necrosis, McDonald and coworkers observed that ACE inhibitors could attenuate the occurrence of cardiac hypertrophy.[7] Of importance, these preventive effects of the ACE inhibitor were annihi-

Figure 1. *ACE inhibition prevents the increase in left ventricular mass (LVM) following electrically induced myocardial necrosis. Coadministration with the bradykinin B_2 receptor antagonist HOE-140 (icatibant) prevents this effect on remodeling. The bar graph shows the mean values for LVM expressed as grams per kilogram at baseline (BL) and 4 weeks (4W) in all 3 groups (control; ramipril+ HOE 140; ramipril). *Change from baseline significantly different from that observed in the ramipril group (*P<0.05).*

Reproduced from reference 7: *McDonald KM, Mock J, D'Aloia A, et al. Bradykinin antagonism inhibits the antigrowth effect of converting enzyme inhibition in the dog myocardium after discrete transmural myocardial necrosis.* Circulation. *1995;91:2043-2048. Copyright © 1995, American Heart Association.*

lated when a specific bradykinin B_2 receptor antagonist, icatibant, was coadministered *(Figure 1).* Of interest, and supporting the role of bradykinin in this action of the ACE inhibitor, an angiotensin II receptor antagonist did not have a similar antiremodeling effect in the same model. In a different model of cardiac remodeling, following myocardial infarction in different mouse strains—ie, bradykinin B_2 receptor knockout mice vs wild-type—the cardioprotective response to ACE inhibitors was significantly diminished in the bradykinin B_2 receptor knockout strain as compared with wild-type.[8] However, the lack of bradykinin B_2 receptors did not affect the remodeling process in untreated animals. Similarly, in kininogen-deficient rats due to a mutation in the kininogen gene, the induction of myocardial infarction leads to comparable infarct sizes and a similar increase in cardiomyocyte

cross-sectional area or interstitial collagen fraction in untreated kininogen-deficient or wild-type strains,[9] and functional changes are comparable. ACE inhibitors improve cardiac remodeling in the wild-type strain, but not in the kininogen-deficient rats.

In contrast to these studies carried out after an intervention, in this case for myocardial infarction, the absence of functional bradykinin B_2 receptors per se, in B_2 receptor knockout mice, may eventually result in hypertension, left ventricular hypertrophy (LVH), fibrosis, chamber dilatation, and LV dysfunction, as compared with the wild-type strain without any further intervention *(Figure 2 A and B).*[10] There is some controversy, however, as other studies have reported that, in the conditions just mentioned, a hypertensive response may only occur following high salt intake.[9]

Taken together, these studies imply that lack of kinins or their B_2 receptors does not influence cardiac remodeling and the development of LV dysfunction after myocardial infarction, but does play an important role in the cardioprotective action of the ACE inhibitor. In addition, the lack of a functional bradykinin B_2 receptor may impact on blood pressure, possibly a salt-sensitive response, and lead to dilated cardiomyopathy in the long run.

BRADYKININ AND HEART FAILURE

There are contrasting reports on the effect of heart failure on bradykinin. Multani et al reported a 50% decrease in interstitial bradykinin, measured by microdialysis, which normalized after ACE inhibition.[11] In contrast, Cheng and coworkers reported a 4-fold increase in plasma bradykinin using a similar model of heart failure, albeit of longer duration.[12] This difference in observations may depend on the sampling technique and the type of assessment. Bradykinin may be rapidly destroyed and measurements are consequently difficult to carry out. Alternatively, the duration of heart failure could be a factor. Bradykinin production may be triggered by cytokines and aldosterone, both likely to increase over time.

Bradykinin is a strong vasodilator, reducing coronary and systemic resistance. Increased bradykinin levels in heart failure would therefore be expected to improve cardiac dysfunction, if only by reducing resistance to cardiac outflow. In addition, coronary vasodilatation and reduction in myocardial ischemia in heart failure, a condition most often a consequence of ischemic heart disease, may well add to the potential beneficial effect of bradykinin in heart failure. ACE inhibition, increasing or normalizing bradykinin levels in heart failure, is likely to act through these bradykinin-related effects. Indeed, several studies have indicated that ACE inhibitors improve abnormal, endothelium-dependent vasodilatation in heart failure, an effect that appears to be related to bradykinin. In experimental models of heart failure, the bradykinin B_2 receptor antagonist icatibant was shown to attenuate ACE-inhibition–induced increases in coronary blood flow.[13]

Hornig et al[13] found a significant increase in radial artery diameter with ACE inhibitors in heart failure patients, an effect that was lost with comedication of the bradykinin B_2 receptor antagonist icatibant. Of interest, icatibant already reduced the arterial diameter at baseline before introduction of ACE inhibitors *(Figure 3, page 112).*
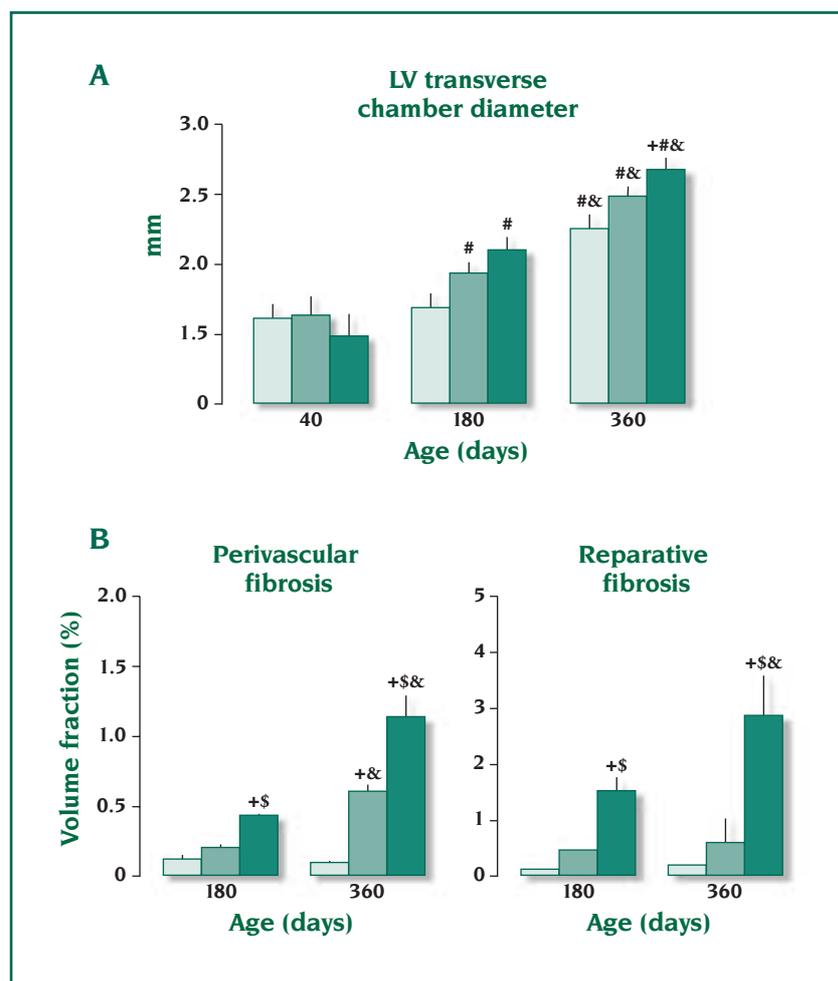
Figure 2. Panel A: Progressive increase in left ventricular (LV) chamber diameter in bradykinin B_2 receptor knockout mice (dark green columns) as compared with wild-type (pale green columns) and heterozygous (medium green columns) mouse strains. Panel B: Significant increase in perivascular and reparative fibrosis in bradykinin B_2 receptor knockout mice (dark green columns). No changes occur in wild-type and heterozygous mouse strains (pale and medium green columns, respectively). Values are means±SEM. +P<0.05 vs knockout mice at same time point; $P<0.05 vs heterozygous mice at same time point; #P<0.05 vs corresponding group at 40 days; &P<0.05 vs corresponding group at 180 days.

Reproduced from reference 10: Emanueli C, Maestri R, Corradi D, et al. Dilated and failing cardiomyopathy in bradykinin B_2 receptor knockout mice. Circulation. *1999;100:2359-2365. Copyright © 1999, American Heart Association.*
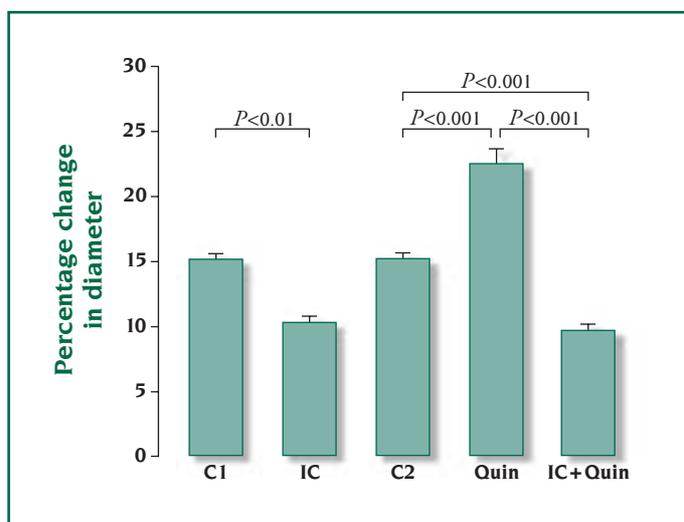
Figure 3. *The acute peripheral artery vasodilatation with angiotensin-converting enzyme (ACE) inhibition in heart failure patients (Quin = quinapril) compared with baseline (C2) is prevented by coadministration with icatibant (IC + Quin). Of importance, icatibant (IC) already contstricts the artery before ACE inhibition compared with control conditions (C1), suggesting underlying vasodilating effects of endogenous bradykinin.*

Reproduced from reference 13: Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation. *1997;95:1115-1118. Copyright © 1997, American Heart Association.*

In contrast, several studies in peripheral systemic arteries in heart failure patients led to different outcomes when exogenous bradykinin was used.[14-17] Maguire et al[15] did not observe any potentiating effect of captopril on flow-mediated dilatation induced with bradykinin infusion, whereas Davie and coworkers[16] found a significant increase in forearm blood flow following bradykinin infusion in the presence of ACE inhibitors. Of interest, in the latter study, bradykinin B_2 receptor blockade did not reduce the effect of ACE inhibitors alone, but it did so, significantly, following exogenous bradykinin administration, suggesting less or no influence of endogenous bradykinin in this model of peripheral vascular tone in heart failure. Also, Witherow et al[17] failed to observe a vasoconstricting effect of icatibant during bradykinin infusion in patients with heart failure on chronic ACE-inhibitor therapy. In contrast, a significant vasoconstrict-

ing effect was found with the B_1/B_2 receptor antagonist B9340, which is more selective for the B_1 receptor, suggesting a role of this receptor in bradykinin-induced vasodilatation in this model.

Finally, the variable effect of ACE inhibitors on peripheral artery vascular tone in heart failure could be ACE inhibitor–specific, as differential effects on conduit arteries between ACE inhibitors have been reported.[18]

Besides strong vasodilating properties, bradykinin also induces positive inotropic effects,[19] at least when administered exogenously. The underlying mechanisms of this positive inotropic effect are not clear, but could incorporate B_2 receptor–mediated effects on the inositol pathway and subsequent enhanced mobilization and reuptake of cytosolic calcium.[20] In addition, bradykinin may potentiate the release of catecholamines.

Whether bradykinin induces positive inotropic effects under normal conditions is questionable. Cheng et al observed no effect of bradykinin B_2 receptor blockade before a heart failure state was induced.[21] In contrast, after heart failure induction, when endogenous bradykinin levels became elevated, receptor blockade further depressed cardiac systolic and diastolic function, suggesting that elevated bradykinin levels may counteract the negative inotropic and lusitropic conditions resulting from the heart failure process.

Thus, ACE inhibitors may improve cardiac function not only by their antiremodeling properties, as discussed above, or by their vasodilating effects in heart failure, but also by direct inotropic and lusitropic actions. This is an interesting profile and, as it may be driven predominantly by bradykinin-related effects, it is one that may not be shared by other antagonists of the renin-angiotensin system, ie, angiotensin II receptor blockers (ARBs), at least not to the same extent.

ACE INHIBITORS AND ARBS IN HEART FAILURE—HOW DO THEY COMPARE?

There is much evidence for a beneficial effect of ACE inhibitors in heart failure. There is less and indeed inconsistent evidence for a similar effect of the ARBs. Obviously, this is in part due to the fact that ACE inhibitors have been around and studied for a much longer time than ARBs. But this may not be the only explanation.

In a head-to-head comparison between captopril and losartan of their effect on mortality in a large, controlled, double-blind trial (Evaluation of Losartan In The Elderly–II [ELITE II]), no significant difference

was observed between the two treatment arms, although there was a clear trend to a better effect of the ACE inhibitor,[21] which was more marked when sudden death was considered. At the time, this came as a surprise, as a previous study with the same agents, but in a much smaller patient sample, had indicated a benefit of losartan (ELITE I, which aimed at comparing the effect of both drug regimens on renal function in elderly heart failure patients, and found it to be comparable).[22] However, mortality was not the primary end point and the study was not powered to consider this. Consequently, when the expected beneficial effect of losartan was reevaluated in ELITE II, it did not hold anymore.

Why would one expect that an ARB could have a better effect than an ACE inhibitor?

Several animal studies have indicated that different enzymes—serine proteases—could exist in target organs such as the heart or vascular system, and would be able to degrade angiotensin I to angiotensin II, leading to a non-ACE–dependent generation of the octapeptide. The most important of these enzymes is chymase, as its effect in terms of angiotensin II production can be blocked to a large degree by chymase inhibitors. Although there has been some confusion as to the functional importance of chymases in this respect, recent studies have reported functionally important chymases in arteries and veins under normal conditions.[23,24] This, however, may be different in heart failure. Petrie et al demonstrated that in heart failure patients chymase blockade alone did not prevent resistance artery constriction induced by angiotensin I, but that ACE inhibition did *(Figure 4)*.[25] Whether or not functionally important in heart failure,

the existence of alternative pathways for angiotensin II production led to the belief that ACE inhibitors alone would not suffice to counteract angiotensin II effects in cardiovascular disease, but that an approach combining angiotensin II blockade and diminished angiotensin II production following ACE inhibitors should provide for better results.

Initially, however, clinical reality was different. The Valsartan–Heart Failure Trial (VaL-HeFT), which compared the combination ARB+ACE inhibitor vs ACE inhibitor alone, showed no difference in the first primary end point—mortality.[26]

However, a small, but significant, improvement in hospitalizations for heart failure was observed in the combined group. More recently, the results of the Candesartan in Heart failure Assessment in Reduction of Mortality (CHARM) program have become available. The CHARM program consisted of three parallel-design trials. The first, CHARM-Alternative, compared the effect of the ARB candesartan with placebo in patients with chronic heart failure due to systolic dysfunction and who were intolerant to ACE inhibitors.[27] Not surprisingly the ARB did better than the placebo. The second study, CHARM-Added, compared the combination of candesartan and ACE
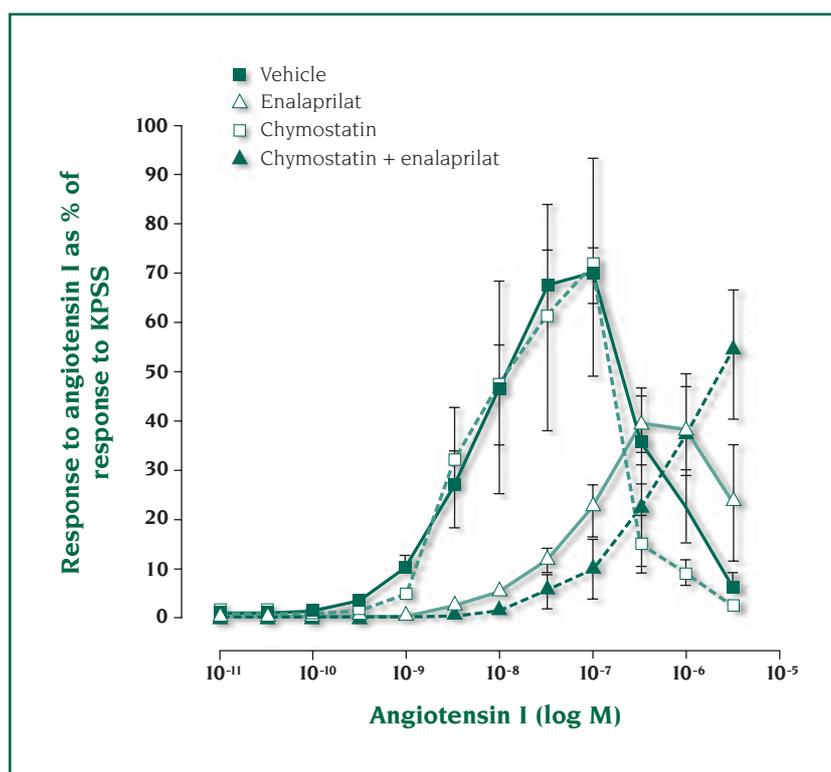
Figure 4. *The vasoconstrictive response to angiotensin I (A I) in resistance arteries from heart failure patients is significantly inhibited by enalaprilat, but not by the chymase inhibitor chymostatin, indicating greater functionality of angiotensin-converting enzyme (ACE)-dependent angiotensin II production than chymase-dependent angiotensin II production. The combination produces a greater effect than enalaprilat alone. KPSS, Krebs solution with KCl substituted for NaCl on an equimolar basis).*

inhibition with ACE inhibition alone in patients with left ventricular systolic dysfunction and chronic heart failure.[28] In this study, the combination proved superior to ACE inhibition alone. The third arm, CHARM-Preserved, studied the effect of candesartan in patients with chronic heart failure and preserved systolic cardiac function.[29] Here, no significant effect was observed.

If we now look at a different setting, that of acute heart failure, comparison of the outcome of ARBs and ACE inhibitors also yields controversial results. In the OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), the ARB losartan was compared with the ACE inhibitor captopril in patients with acute myocardial infarction at high risk.[30] In that study, captopril appeared more effective with respect to the predefined end point of cardiovascular death reduction. In contrast, in the VALsartan In Acute myocardial iNfarcTion (VALIANT) study in patients with an acute myocardial infarction and cardiac dysfunction with or without heart failure, valsartan was shown not to be inferior to ACE inhibition.[31] The reason for this discrepancy is not clear, but may relate to differences in the doses of ARBs used. However, in none of the above studies were ARBs found to be better than the ACE inhibitors.

WHICH STRATEGY SHOULD BE USED FOR HEART FAILURE?

In heart failure therapy, as in other cardiovascular syndromes, bradykinin is likely to play a pivotal role in all its phases. Consequently, ACE inhibitors will remain one of the cornerstones of heart failure treatment, not only for historical reasons, but because of their important stimulation of endogenous brady-

kinin production. A parallel reduction in angiotensin II production is a bonus in this respect.

ARBs have less well-defined effects on bradykinin, although bradykinin may increase to some extent secondary to stimulation of the (unprotected) angiotensin II type 2 (AT_2) receptor by elevated angiotensin II levels as a result of angiotensin II type 1 (AT_1) receptor blockade. As a consequence, they do not possess the unique profile of the ACE inhibitor and it is questionable whether they will replace the ACE inhibitor. Certainly, in cases where ACE inhibitors are not tolerated do current guidelines suggest the use of an ARB. It is possible that future treatment guidelines will also advocate the combined use of an ACE inhibitor and an ARB.

However, as things stand, there is little doubt that the ACE inhibitors will remain an integral part of heart failure therapy, as a result of their unique dual mechanism of action, reducing angiotensin II on the one hand, and, possibly more importantly, increasing bradykinin on the other hand.

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Icons of Cardiology

Paul Hamilton Wood: Clinician—Scientist
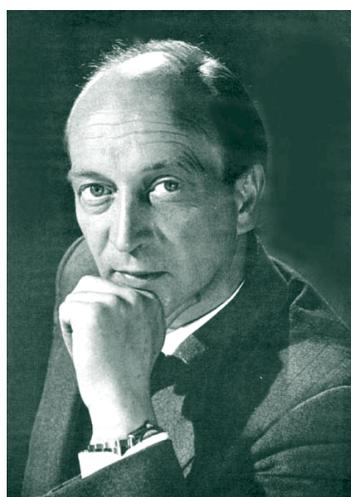
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My articles on "Icons of Cardiology" have, up to this point, described scientists whose work centered on laboratory experimentation. By elucidating both normal physiology and the abnormalities that cause human disease, these investigators contributed to the foundations of modern cardiology that made possible the remarkable clinical achievements of the past century. The present article departs from this practice by recognizing one of the great practicing cardiologists of the 20th century. Moreover, this brief biography documents my view that the approach of the skilled physician is fundamentally similar to that used in basic research. In my own experience, the epitome of both clinical medicine and scientific inquiry is personified by Paul Wood, who showed me how the "scientific method" can be used at the bedside.

Rather than attempt a scholarly definition of the scientific method, about which individuals more qualified than I have written, this article uses a few examples of Wood's approach to the patient to show how the method he used at the bedside resembles a basic scientist's effort at discovery. Wood, when he encountered a new patient, immedi-

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Paul Wood,
from a photograph published in Br Heart J. *1962;24:661-665. © BMJ Publishing Group Ltd & British Cardiac Society.*

ately formulated a plausible hypothesis to explain the patient's complaint. Following a rigorous methodology he then took the history and carried out a physical examination to test the hypothesis. Using this approach he would reach a tentative diagnosis that often confirmed the working hypothesis; however, if the data denied his hypothesis, he would formulate a new one that he tested by collecting additional clinical data. This iterative process, in which data were collected to test hypotheses and hypotheses modified to fit the data, often proceeded through several cycles in which hypotheses would be advanced and then discarded before Wood reached a working diagnosis. The latter was then tested by cardiac catheterization, which provided the "gold standard" for evaluating the

majority of Wood's cases, most of whom suffered from rheumatic and congenital heart disease. This approach is exemplified by a young woman in whom Wood diagnosed transposition of the great vessels (the anterior aorta was evidenced by a soft ejection murmur and booming single second sound) that was "corrected" by ventricular inversion (she was acyanotic and entirely asymptomatic) and atrial inversion (retrograde P waves). Wood's diagnosis was confirmed by a selective angiogram.

BIOGRAPHY

Wood was born in India in 1907, the son of an Oxford-educated English civil servant.[1-4] Between ages 3½ and 13 he attended an English preparatory school, after which he joined his family in Australia where his father had moved to become a farmer. Although small in stature Wood was tough and wiry; he excelled as a distance runner, skier, and tennis player, and at University was on the first team in football and a Rugby Blue. His size allowed him to impersonate the Duchess of Kent (later the Queen Mother) in whose guise he rode through the streets of Melbourne in an open landau to the acclaim of cheering crowds. His record as a medical student at the University of Melbourne was spotty—he passed obstetrics and surgery with honors, but failed medicine on his first exam. After receiving his MB, BS in 1931, he moved to New Zealand where he was house

physician at Christchurch General Hospital. In 1933, he went to Britain hoping to obtain a position in neurology at Queen Square, where he felt he could best use his analytical skills. However, he was turned down for this post and so instead became a house physician at the Brompton Hospital, then noted mainly for the care of patients with tuberculosis. His accomplishments at the Brompton included introducing a group of mice to a formal dinner for senior nurses[1]; according to one account, "As the sisters sat down to dine, the lids of all of the cheese dishes (previously wired) rose mysteriously and scores of mice escaped over the tables."[5] The next year he became outpatient medical officer to the National Heart Hospital where, in cardiology, he found an intellectual milieu that suited both his talents and his tastes. He flourished in this specialty and, in 1937, was appointed physician to outpatients at the National Heart Hospital and consultant at Hammersmith Hospital. Following the outbreak of World War II, he spent two years in the Emergency Medical Service and subsequently served as officer in charge of Military Hospitals in the North African and Italian campaigns, reaching the rank of brigadier and earning an OBE. One of his commanding officers said of Wood the soldier: "there was no one more demanding of discipline from below and more intolerant of it from above."[1]

After the war ended, Wood began a private practice, but soon rejoined the staff in cardiology at Hammersmith where, in 1947, he performed his first cardiac catheterization. This delighted him because, by correlating hemodynamic data with the clinical findings, he found that he was able to "measure everything."[1] While at Hammersmith, he engaged in regular battles with a colleague who "scorned Wood's ignorance of physiological principle" and whom Wood upbraided for lacking experience in cardiological practice.[1] In

1949, he returned to the Brompton where Russell Brock was pioneering the new field of cardiac surgery. Here Wood developed a new Cardiology Department and opened his own catheterization laboratory. At the same time, he rejoined the staff at the National Heart Hospital and later became Dean of Institute of Cardiology of the University of London. In these positions he thrived, becoming a leader in cardiology until his untimely death in 1962 of an arrhythmia complicating myocardial infarction.

PAUL WOOD AS A CLINICAL SCIENTIST

Wood's approach to evaluating his patients is detailed in several articles,[1,2] an obituary,[3] and a supplement to the *American Journal of Cardiology.*[4] Unlike today's academic cardiologists, most of whose work appears in peer-reviewed journals, Wood's major publication was his textbook, *The Heart and Circulation,* which was first published in 1950.[6] The 2nd edition[7] appeared 6 years later, and at the time of his death he was working on a 3rd edition. This text, while citing earlier work, centered on Wood's personal experience, which he recorded on note cards. In later years, when asked a question like: "How often do patients with aortic stenosis experience angina pectoris?" Wood would either produce the answer from memory or, if the point was obscure, consult his card file and return with an answer the following day.

Wood's ability to organize clinical data was enhanced by his quantitative mind. Both signs and symptoms were assigned numerical values and then related to physiological data such as pressures, cardiac output (measured by the Fick method), shunt flow, and pulmonary resistance. A simple grading system was used to quantify nonnumerical data: grade i (mild), grade ii (moderate), grade iii (severe) and

grade iv (gross). In the case of dyspnea, he divided grade ii (symptoms on normal activity) into iia (symptoms provoked by heavy work, like mopping) and iib (symptoms brought on by light work, like sweeping with a broom). To describe murmurs he used a relative scale; for example, the grade ii early diastolic murmur in aortic insufficiency is much softer than the grade ii ejection murmur in aortic stenosis because the amplitude of the loudest diastolic "blow" is considerably less than that of the loudest ejection murmur. When asked about grade v and grade vi murmurs, Wood just laughed and said that this nuance told him nothing of physiological or clinical value. These grading systems allowed Wood to quantify his entire clinical examination; one of his cards on tetralogy of Fallot, published by Jane Somerville,[1] shows the grades that he assigned to each patient's exercise tolerance, cyanosis, clubbing, and the intensity of the murmur and thrill caused by the pulmonic stenosis.

Wood pointed out that timing is often more important than intensity in evaluating heart sounds and murmurs. This is clear in mitral stenosis, where he estimated mitral valve area by noting the duration of the diastolic murmur (which correlates closely with the time required for dissipation of the abnormal pressure gradient across the mitral valve) and the interval between the second sound and the opening snap (which provides an indirect measurement of left atrial pressure because a short "2 - OS interval" means that the mitral valve opens earlier, at a higher pressure, as left ventricular pressure falls during isovolumic relaxation). Wood graded the duration of murmurs along with their intensity (for example, a mitral diastolic murmur could be "grade ii in intensity and grade iv in length"), which he then diagrammed in sketches that included other clinical data, such as the timing of the heart sounds. As Wood's registrar, I occasion-

ally ordered a phonocardiogram, then a "high-tech" test, to confirm my timings; this was done for my own benefit as I do not recall Wood ever having been significantly off the mark.

Once the history and physical examination were completed, a working diagnosis was formulated. This was then checked using the ECG and chest x-ray, the only technology Wood used routinely prior to catheterization. For example, if he thought a patient with mitral stenosis had pulmonary hypertension, he would say: "If I am correct, the ECG will show right ventricular hypertrophy." Wood then used the clinical data to predict the hemodynamic findings; in patients with mitral stenosis, for example, the pressure gradient across the mitral valve would be estimated and the numbers written in the chart. These written estimates made catheterization of Wood's patients a challenge to registrars who, like myself, were assigned to do these studies. If, at the end of the study, the data fit Wood's prediction, then all was well. But a major discrepancy between his clinical assessment and the catheter data led to a blood bath in which Wood challenged each element of the hemodynamic study. Being on the receiving end of his fierce comments was daunting, so that to avoid embarrassment we studied his patients *very* carefully. If, when there was a discrepancy, we had collected data of sufficient quality to convince Wood that our catheterization findings, rather than his analysis, were correct, his demeanor would change dramatically and he would say: "OK, you are correct; now where did I go wrong?" He would then go backward through his entire evaluation in an effort, generally successful, to identify what had misled him. As a result, he would not make the same mistake again.

On some issues Wood could be on shaky ground; for example, he had a favorable view of the role of anticoagulation in preventing myocardial infarc-

tion that was not shared by most cardiologists at that time. Because data from well-designed clinical trials were not then available, Wood's opinions were based largely on his own experience. These opinions, however, were not cast in concrete. Shortly before I arrived in London, Wood had changed his views regarding the use of anticoagulants in patients with pulmonary hypertension associated with large intracardiac shunts. He had initially interpreted the pulmonary artery clots found when these patients died as evidence that coagulation should be inhibited; however, after several of his patients suffered disastrous pulmonary hemorrhages, he changed his view— and stated this quite openly. Even on matters of less importance he was open-minded—with some glee he once pointed out a giant "a" wave in a patient with constrictive pericarditis, saying: "I wrote that this could not occur, but as you can see for yourself it does."

It is possible today to follow Wood's analytical approach by reading his landmark review of mitral valve disease,[8] which I view as among the finest clinical papers written in the 20th century. In this article, Wood "walks" the reader through the elements of his analysis, taking stock at every step by analyzing the pathophysiological meaning of each symptom and sign, then of the ECG and chest x-ray, and finally how these fit with the hemodynamic findings obtained at catheterization.[9] The logic of clinical science that he set out in this review reflects the precision of thought that was the hallmark of this great scientist.

To my knowledge, Wood never touched a test tube or experimental animal while I studied with him in London, but he did read the basic science literature to help in understanding clinical findings. And, as was typical of him, he used clinical findings to evaluate basic research. One day, in his office, he

opened an issue of the *American Journal of Physiology* and pointed to a paper that I believe used an animal model to explain some features of pulmonary hypertension. Wood read the conclusion with derision, saying that anyone who had cared for patients with this disease would know that the central hypothesis of the research was foolish.

Many years after Wood's death, I came to understand not only his greatness as a clinician, but also how closely the scientific method that he practiced at the bedside resembled that of basic science. This occurred at the Max Planck Institute in Heidelberg, where I was studying calcium fluxes into and out of sarcoplasmic reticulum vesicles. Each day I carried out a complex experiment designed to explain the previous day's data, which I then used to design another large experiment. I set up and carried out my experiments in the afternoons, so that by dinner time dozens of samples had been collected and placed in a scintillation counter. The next morning I retrieved the tapes with the counts, calculated the calcium fluxes, and made a series of plots that revealed a fascinating set of phenomena that served as the basis for that day's experiment. However, as I delved more deeply into the complex findings, which I later learned reflected the fact that the calcium pump was cycling between the forward and reverse directions, I began to lose my way. My data, while falling into highly reproducible patterns, were telling me nothing about the biology of the sarcoplasmic reticulum. After several weeks working at this hectic pace, I became more and more confused. One morning, while walking down the hall carrying yet another armful of scintillation counter tapes, I heard Paul Wood's voice in my mind, saying: "When you get lost, stop and retrace your steps until you reach familiar territory." The feeling was eerie! But I did just that; I stopped collecting data and spent

several days working backward through my data until I came to understand the system—the result was a paper that, while dealing with a rather arcane topic, is one of my favorites.[10]

CONCLUSION

The experiences with Paul Wood that I describe in this article are typical of those recorded by others who worked with this remarkable man.[1-4] All tell of a fiercely honest physician who quantified everything and then wove the data into a pattern that guided him in doing all that was then possible to help his patients. Errors, for Wood, were never concealed; instead, he viewed these as challenges to be identified clearly, their causes understood, and then never to be repeated.

Paul Wood, in addition to epitomizing the best in clinical medicine, stands out as the finest scientist with whom I have worked, and this includes three Nobel Prize winners. The most important lesson that he taught me is that the clinician, while using data that are often less precise than those available to the laboratory investigator, follows the same intellectual approach. Both at the bedside and in the laboratory, it is essential to begin by formulating a hypothesis and then, as data are collected to evaluate, revise, and retest the hypothesis until all possible information has been extracted, quantified, organized, and interpreted. Wood also recognized that a "final" conclusion is not, in fact, final—it is often tentative, losing its validity when new concepts and technologies uncover new information. Wood's mastery of this method, which is best suited for the research laboratory where flawed experiments can be discarded and key findings confirmed by repeating the experiment, was spectacular. His ability to apply this logical approach in a clinical setting, where error can be lethal, was the most remarkable achievement of this great scientist.

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Angiotensin-converting enzyme inhibitors

N. J. Brown, D. E. Vaughan

Circulation. 1998;97:1411-1420

Despite its relatively recent publication date of 1998, this review has since been surpassed by many exciting advances in the science and therapeutics of drugs relating to the renin-angiotensin system (RAS). This is perhaps best illustrated by a statement in the *Future Directions* section of this review that says there is "ongoing controversy over the use of selective versus nonselective angiotensin-converting enzyme (ACE) inhibitors after myocardial infarction. While this was certainly true at that time, the more recent completion of the Heart Outcomes Prevention Evaluation (HOPE) trial and of the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) has laid that particular debate to rest. This review article nevertheless covers all areas of basic pharmacology pertaining to a class of drugs that have an established major relevance to the routine care of clinical patients.

Vaughan and Brown reemphasize the importance of ACE as straddling the RAS and kallikrein-kinin system and highlight the relevance of inhibiting angiotensin II production with regard to the target receptors. It is stated that the angiotensin II type 1 (AT_1) receptor is thought to mediate most of the harmful effects, but mention is also made of the AT_2 and AT_4 receptor subtypes. The relevance of AT_2 receptor–mediated events has become much more clear over the last 6 years (vasodilation, antiproliferative, and apoptosis effects). The AT_4 receptor is thought to play a role in blood flow and natriuresis. The authors also point out that ACE inhibitors raise angiotensin I levels, which can be degraded via neutral endopeptidase (NEP) to form angiotensin 1-7. This activates the AT_{1-7} receptor, thereby promoting similar effects to those mediated by the AT_2 receptor. Also important in the overall mechanism of blood pressure–lowering properties are the effects of nitric oxide and prostacyclin mediated via tissue, as opposed to circulating, ACE. This is further emphasized by animal studies using selective bradykinin (B_2) receptor antagonists. Nevertheless, this paper does not adequately explore the effects of the different ACE inhibitor molecules on tissue versus circulating ACE inhibition. In one study, quinaprilat (known to be very

lipophilic) was the most potent at the tissue level, while lisinoprilat (hydrophilic molecule) was one of the least effective. The review also highlights the differential effect of plasma renin activity (PRA). Blacks in particular have low renin and respond less obviously to ACE-inhibitor therapy. Often higher doses are required. However, once diuretics are used, the RAS is stimulated and concomitant use of ACE inhibition is seen to be effective. This has an important message for consideration of angiotensin receptor blockers, which are also relatively ineffective when used alone, but have clear additional effects when used on top of diuretics. In contrast, ACE inhibitors are able to lower blood pressure independently of the RAS as demonstrated during long-term treatment when hormonal levels of components of the RAS return toward normal. These longer-term effects are almost certainly mediated via inhibition of tissue ACE and direct endothelial effects.

Important clinical trials are reviewed, particularly in the area of heart failure and following myocardial infarction. These sections are now somewhat superseded by newer trials that have been of vital importance in establishing ACE inhibitors in their current dominant position. Anti-atherosclerotic effects, which at that stage remained hypothetical, have subsequently been demonstrated. This is at least in part due to the work of Douglas Vaughan who has been involved in this area of research from the very beginning and has been a major advocate of these additional properties.

1998

James Cameron's film "Titanic" wins 11 Oscars, tying the record held by the 1959 epic Ben Hur; hurricane Mitch devastates Nicaragua and Honduras, killing thousands of people; and the Truth and Reconciliation Commission report, investigating human rights abuses during the apartheid years in South Africa, is published

Interaction of genetic deficiency of endothelial nitric oxide, gender, and pregnancy in vascular response to injury in mice

M. Moroi, L. Zhang, T. Yasuda, R. Virmani, H. K. Gold, M. C. Fishman, P. L. Huang

After having long been overlooked due to its ubiquitousness, the endothelium is now recognized as a massive cardiovascular organ. Were the endothelium all to be placed within a single container, it would have a combined weight greater than most solid organs. The endothelium has previously been seen as a "nonstick" lining to blood vessels; it is now recognized to have other important effects, not least the production of nitric oxide (NO, previously known as endothelial-derived relaxing factor, EDRF). The presence of constitutively active endothelial NO synthetase (eNOS) provides vasodilator tone to all vessels. This study was able to investigate mice both with intact eNOS systems and also those with genetically disrupted eNOS genes. The paper further evaluates the effect of gender and pregnancy on endothelial responses to injury. The presumption of this model, is that it provides insight into human pathologies in which endothelial cells are involved, eg, restenosis following angioplasty an the formation of atheroma. The specific hypothesis tested here is that endothelial NO is a key component in the propensity for atherosclerosis.

The study used the SV129 and the C57B0/6 strains of mice. The wild type males, females and pregnant females of these two strains were compared with eNOS mutant males, females and pregnant females. Femoral artery cuffs were placed over both femoral in mice that had been anesthetized. One was inflated to induce damage and the second used as a sham-operated vessel. Tissues were harvested from sacrificed animals at 2 weeks and fixed in paraffin and stained using immunohistochemical and other morphological techniques.

The key finding was that there was greater intimal proliferation in male compared with female mice, being most exaggerated in eNOS-deficient strains. The authors also observed that vascular intima formation was impressively inhibited by pregnancy in all the mouse strains and that this effect was independent of eNOS expression. This is in keeping with other studies where estrogen receptor–deficient mice have been shown to have less neointimal formation. This suggests that the estrogen–mediated effect is not only via the receptor, but also by some other mechanism. Of interest, the eNOS-deficient mice were hypertensive, lending weight to the belief that hypertension may in part result from endothelial deficiency. Inversely, hypertension is known to produce further endothelial dysfunction, making cause and effect more difficult to determine in man. Nevertheless, this model would indicate that a primary defect in eNOS might produce hypertension. Also of interest is the fact that inducible NO synthetase, or iNOS (produced by nonendothelial cell types) does not seem to be able to compensate for the lack of eNOS expression in the eNOS mutant mice. One explanation may be that iNOS is only increased following cellular proliferation. Furthermore, iNOS that may be produced in the vascular wall may not be generated in the appropriate location to suppress smooth muscle proliferation. A final explanation is that the iNOS protein that is induced by cuffing of the artery remains as a monomer or otherwise inactive form. Alternately the amount of L-arginine substrate may become a rate-limiting factor.

In conclusion, this model is of interest as it indicates the potential of eNOS deficiency to increase vascular changes present in hypertension, in coronary restenosis and also as part of the atherosclerotic process. This implicates the NO system in the genesis of these diseases and suggests as a useful target for drugs seeking to counter the vascular changes occurring in these disease states.

1998

Helmut Kohl is defeated by Gerhardt Schröder in the German elections, ending 16 years as chancellor; as the world economy falters, George Soros claims capitalism is starting to "come apart at the seams"; and Japanese film director Akira Kurosawa, responsible for masterpieces such as "Rashomon," "The Seven Samurai," "Ran," and "Kagemusha," dies, aged 88

Acute anti-ischemic effects of perindoprilat in men with coronary artery disease and their relation with left ventricular function

G. L. Bartels, F. M. van den Heuvel, D. J. van Veldhuisen, M. van der Ent, W. J. Remme

Am J Cardiol. 1999;83:332-336

Twenty-five patients with a history of exercise-induced ischemia were subjected to pacing-induced myocardial ischemia and various investigations either in the presence or absence of the angiotensin-converting enzyme (ACE) inhibitor perindopril, delivered as the active form, perindoprilat. All patients underwent angiography and had to have a minimum of 70% stenosis of the left coronary artery. All concomitant medication including aspirin was stopped prior to the study. Patients were permitted ongoing use of GTN spray if required. The patients were randomized into two groups, one given IV perindoprilat, the other matching placebo. Hemodynamic observations were made following treatment, and, in addition, blood samples were taken both before and also at the maximum of the first pacing and once again at the maximum pacing following delivery of the experimental treatment.

The groups were not entirely evenly matched nor of equal size, with 14 patients in the perindoprilat group and 11 patients in the control group. The mean ages were 56 years and 61 years, respectively; 79% of the perindoprilat-treated patients had had prior myocardial infarction vs 55% of the placebo group. Left ventricular (LV) ejection fraction was also significantly lower in perindopril-treated patients (40% vs 49% patients in the placebo group). All patients in the placebo group had preserved ventricular function (>40%) while those in the perindoprilat group were more heterogeneous with LV dysfunction deemed to be present in 7 of the 14 patients. These were evaluated in a subinvestigation with the low ejection fraction patients having a mean ejection fraction of 32% and the preserved ejection fraction patients having a mean ejection fraction of 48%.

Perhaps the only significance of this study comes from the fact that it may give some insight into the mechanism of the benefits seen in the later very-large-scale EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA). The key findings were that there was moderately reduced ST-segment depression induced by pacing in patients given perindoprilat, particularly when this was in the presence of asymptomatic LV dysfunction. Perhaps of interest is the fact that ischemia induced an increase in LV end-diastolic pressures (previously shown in other studies) as well as acute neurohumoral activation. This suggests a possible mechanism by which long-term ACE inhibition may be beneficial. The authors highlight the acute effects on the hemodynamic and neuroendocrine system with IV administration of perindoprilat. In their discussion, they make reference to the fact that other investigations have not seen anti-ischemic effects of ACE inhibitors until 3 to 6 months, suggesting that these are independent of neurohumoral or hemodynamic effects and probably relate to structural/tissue effects. Once again, induction of nitric oxide, bradykinin, and prostacyclin is cited as potentially important in the anti-ischemic properties of this class of drug.

The authors suggest that there is no effect of ACE inhibition in the study for patients with stable angina. This is contrary to the later findings of the EUROPA investigation. The observation that myocardial ischemia was attenuated in subjects with LV dysfunction is in keeping with earlier large-scale trials in patients with heart failure, which have almost uniformly shown a reduction in the occurrence of myocardial infarction and sudden death. The reduction of ischemia due to inhibition of the RAS either due to heart failure, diuretics, or indeed ischemia represents a potential mechanism to explain the effects observed.

— 1999 —

"Médecins sans Frontières," the French-based emergency medical assistance organization, is awarded the Nobel Peace Prize; a magnitude 7.4 earthquake strikes Turkey, killing more than 15 600 people and leaving 600 000 homeless; and US film "The Blair Witch Project" emerges as a cult classic, grossing more than $125 million for an outlay of only $30 000

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

HOPE (Heart Outcomes Prevention Evaluation) was a landmark study designed to test the hypothesis that two intervention strategies, namely, angiotensin-converting enzyme (ACE) inhibition (with ramipril) or vitamin E, would improve morbidity and mortality in patients at high risk of cardiovascular events, compared with placebo. The study involved 267 centers from 19 countries worldwide. The patients included were considered to be at high risk of future fatal or nonfatal cardiovascular events, by virtue of their age (>55 years, mean 65.9 years), existing or previous cardiovascular disease (around 80% of study participants), or diabetes. Diabetic patients had at least one other risk factor, including known vascular disease, cigarette smoking, high cholesterol, or hypertension. The primary end point was a composite of myocardial infarction (MI), stroke, or death from cardiovascular causes.

Following a run-in phase, patients were randomly assigned to receive either ramipril 10 mg or placebo in addition to usual medication, which included antihypertensive drugs (excluding ACE inhibitors), lipid-lowering agents, or aspirin. Despite a history of hypertension in nearly 47% of patients, mean blood pressure (BP) at baseline was in the normal range and the reduction in BP attributable to ramipril relatively modest (a fall of 3 to 4 mm Hg systolic BP and 1 to 2 mm Hg diastolic BP). The groups were well matched in terms of risk factors other than an excess in the placebo group for the number of individuals who have peripheral vascular disease and previous MI. While it is a possibility that this might associate with a worse outcome in the placebo group, when the trend is reversed with vitamin E treatment no adverse outcome is observed.

The trial was stopped 6 months early on the advice of the Data Monitoring Committee because of consistent evidence of the benefit of ramipril treatment on the combined primary end point. At the time of stopping, 13.9% of patients given ramipril had reached the primary end point, compared with 17.5% given placebo (relative risk [RR] 0.78%; 95% confidence interval [CI] 0.70%-0.86%, *P*<0.000002). This comprised a risk reduction of 32% for stroke, 20% for

MI, 26% for cardiovascular death, and 16% for all-cause mortality, as well as a reduction in the risk of several other end points including heart failure and revascularization procedures. The results were even more noteworthy in the 3577 diabetic subjects with a reduction of 25% in the combined primary end point in addition to lowering the risk of diabetes-related complications. The effects of antioxidant therapy with vitamin E were also evaluated, but no statistical benefits were shown.

The reduction in the combined end point, in particular the reduction in MI, exceeds the size of effect that would be expected from the modest fall in BP alone, suggesting non-BP–mediated effects. Possible explanations include reduction in angiotensin II–induced intimal and vascular smooth muscle proliferation, anti-inflammatory effects, and also atheromatous plaque stabilization. This last mechanism seems to be the most likely common pathway for benefits that were seen in both coronary and cerebral circulations.

The HOPE study was important as its results show that it is both safe and beneficial to give ramipril to patients at high vascular risk. This has extended the use of ACE inhibitors to a wider group of patients, including all patients after MI, and also other vascular patients who are currently given complementary prophylactic treatment with aspirin and statins.

2000

Charles Schulz, the cartoonist who created the "Peanuts" comic strip, dies in his sleep after a battle with colon cancer; Czar Nicolas II and his family, imprisoned and executed by Bolsheviks in 1908, are canonized y the Russian Orthodox Church; and two rival groups of scientists, led by J. Craig Venter and Francis S. Collins, announce that the human genome has been deciphered

Randomised trial of perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack

PROGRESS Collaborative Group

Lancet. 2001;358:1033-1041

In view of the fact that the risk of ischemic and hemorrhagic stroke is strongly related to the level of systolic blood pressure (SBP), the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) investigators wished to determine the benefits of BP lowering in patients with a history of cerebrovascular disease by performing a randomized, double-blind, placebo-controlled trial with perindopril either alone or in combination with indapamide, against matched placebo. Eligible patients had to have a previous stroke or transient ischemic attack (TIA) within the preceding 5 years, have no indication nor contraindication to angiotensin-converting enzyme (ACE) inhibitors, and be compliant with treatment during a 4-week run-in period. Of the 7121 patients entered into the run-in phase 1016 (14%) were either ineligible or withdrew. The trial design was relatively complex as a result of the inclusion of both hypertensive and nonhypertensive patients. Prior to randomization patients with hypertension could already be receiving antihypertensive treatment. An indication or a contraindication for use of diuretics required patients to be randomized to perindopril/placebo as monotherapy. Patients without an indication or contraindication were randomized to combination therapy with 4 mg perindopril daily plus 2.5 mg indapamide or combination therapy with identical placebo tablets. Of the 3051 patients receiving active treatment, 58% (1770) individuals received combination therapy and the remainder monotherapy with perindopril alone. Existing antihypertensive medication was continued unchanged for 51% of the perindopril-only group, and for 51% of the perindopril/indapamide combination group.

After 4 years of follow-up, active treatment reduced overall BP and risk of stroke. Active treatment (monotherapy and combination therapy, considered together) reduced systolic BP (SBP) by 9 mm Hg and diastolic BP (DBP) by 4 mm Hg vs placebo. Ten percent of patients on active treatment suffered a stroke vs 14% on placebo (relative-risk reduction of 28%; *P*<0.0001). The risk of total major vascular events in the active treatment group was 15% vs 20% in the placebo group. Active treatment also reduced the risk of stroke in hypertensive and nonhypertensive subgroups (*P*<0.01).

However, the results differed markedly according to the type of treatment. Combination therapy, perindopril plus indapamide, reduced SBP by 12 mm Hg and DBP by 5 mm Hg, and the risk of stroke by 43% (95% CI 30% to 54%). Perindopril alone reduced SBP by 5 mm Hg and DBP by 3 mm Hg, with only a 5% reduction in the occurrence of stroke (95% CI –19% to 23%). In short, the administration of perindopril alone was associated with a small relative reduction in risk with confidence intervals that cross zero, while combination therapy was associated with major reductions in risk of stroke and the secondary end points of vascular events. PROGRESS leaves the unanswered question of the effect of indapamide alone in the prevention of recurrent events. What proportion of events is due to the effects of an ACE inhibitor or a diuretic? Also, is it only the blood pressure reduction that counts or the choice of drugs?

The findings of PROGRESS are at odds with those from HOPE, which showed a 32% reduction in risk of stroke with a small reduction in BP of 3/2mm Hg (both perindopril and ramipril are lipophilic carboxyl ACE inhibitors). This may in part be explained by the differences between the two study populations and the prevalence of coronary artery disease (16% vs 80%). As ramipril significantly lowered the risk of cardiovascular events and heart failure, both of which are recognized to increase the risk of stroke, this may explain the reduction in observed strokes without a large reduction in blood pressure.

2001

V. S. Naipaul, author of "In a Free State" and "A Bend in the River," and numerous short stories, wins the Nobel Prize in Literature; US and British forces launch a bombing campaign on the Taliban government and al-Qaeda terrorist camps in Afghanistan; and 178 nations, excluding the USA, reach agreement on pollution reduction, rescuing the 1997 Kyoto Protocol

Perindopril alters vascular angiotensin-converting enzyme, AT$_1$ receptor, and nitric oxide synthase expression in patients with coronary heart disease

J. L. Zhuo, F. A. Mendelsohn, M. Ohishi

This is a particularly intriguing paper as it demonstrates the ability of the lipophilic carboxyl angiotensin-converting enzyme (ACE) inhibitor perindopril to inhibit both circulating and tissue ACE in the endothelium as well as in the adventitia of blood vessels. Furthermore, it demonstrates that vascular endothelial (eNOS) and inducible (iNOS) nitric oxide synthase can be increased in patients with ischemic heart disease treated with perindopril. Consequently, this paper brings together evidence in support of the hypothesis that endothelial dysfunction predisposes to atheroma and that ACE inhibitors are able to counter these effects. This is the hypothesis that was tested in both the Heart Outcomes Prevention Evaluation (HOPE) study (ramipril) and the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) (perindopril). Of note, both ACE inhibitors were lipophilic and differed only by a benzene ring. At the time this paper was published the results of the HOPE study were already known, though the EUROPA study was yet to be completed and published. As such this paper was able to explore the hypothesis that perindopril would produce similar effects to those already seen with ramipril, in a range of patients with vascular disease at risk of important cardiovascular events. This investigation tested the hypothesis that chronic ACE-inhibitor treatment would be able to block endothelial and adventitial ACE, resulting in a greater amount of eNOS and iNOS.

Zhuo et al investigated 14 patients with documented ischemic heart disease scheduled for coronary artery bypass surgery. Half of these patients were treated with perindopril 4 mg a day for 35 days and the other half served as controls without any treatment or drugs interfering with the renin-angiotensin system. Plasma renin activity, ACE, angiotensin I and II were all measured preoperatively. During surgery, a segment of internal mammary artery was removed for further investigation. Location of ACE was mapped using 125-iodine 35 1A (a derivative of lisinopril). AT$_1$ receptors were investigated using radiolabeling and the presence or absence of AT$_2$ receptor antagonist PD123318 of AT$_1$ receptor antagonist losartan. Vascular ACE was identified using aminocytochemistry with a polyclonal antibody generated against the 25 amino acid peptide located against the COOH terminus. AT$_1$ receptors were further localized using a similar antibody approach, as also were the two nitric oxide synthase isoforms (eNOS, iNOS).

Perindopril was shown to reduce plasma ACE activity by 70% as well as the ratio of angiotensin II to I (57%). ACE was localized to both the adventitia and endothelium in both treated and untreated patients though staining was brighter than expected for untreated patients. Those treated with perindopril had greater expression of AT$_1$ receptor binding, with AT$_2$ receptor binding unaltered. Expression of eNOS was increased pre-treatment.

This elegant study illustrates a number of key elements of the pharmacological effects of perindopril. Particularly, it shows its ability to effectively inhibit tissue ACE and to penetrate into vessels, an action that is almost certainly improved by the lipophilic character of the drug. In addition, previous studies have shown that the two active sites of ACE can be preferentially inhibited by lipophilic drugs. The fact that this work was conducted in patients with known atherosclerosis is an added benefit. The findings of this study are particularly interesting in the context of later PROGRESS and EUROPA trials both of which showed effective reduction of cardiovascular end points through treatment with perindopril. This is also in keeping with the observations of the HOPE investigation *(see review of Yusuf et al paper, page 125).*

2002

The Tamil Tigers and Sri Lankan government sign a cease-fire agreement, ending 19 years of civil war; Chechen rebels take 763 hostages in a Moscow theater; and Jiang Zemin officially retires as China's General Secretary of the Communist Party and Hu Jintao is named as his successor

Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint Reduction in hypertension study (LIFE): a randomized trial against atenolol

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LIFE (Losartan Intervention For Endpoint reduction in hypertension) was a double-blind, randomised, parallel-group trial designed to compare the effects of losartan and atenolol on cardiovascular (CV) morbidity and mortality in 9193 high-risk hypertensive patients (systolic blood pressure [SBP] 160-200 mm Hg or diastolic blood pressure [DBP] 95-115 mm Hg). All patients were 55 to 80 years old (mean age 67.4 years) and had left ventricular hypertrophy (LVH) as determined by electrocardiography (ECG). This particular paper analyses a subgroup of 1195 individuals who met the above criteria and in addition had diabetes.

The primary end point was a composite of cardiovascular morbidity and mortality. After a 2-week single-blind placebo run-in period, patients entered a minimum 4-year active treatment period. Antihypertensive therapy was titrated to achieve a target SBP <140 mm Hg (<40% of patients achieved a BP below 140 mm Hg). Patients initially received losartan 50 mg or atenolol 50 mg. After 2 months, hydrochlorothiazide (HCTZ) 12.5 mg was added if BP was not at, or below, goal BP. After 4 months, the dose of losartan or atenolol was doubled to 100 mg plus HCTZ 12.5 mg if BP was still inadequately controlled. At month 6, additional open-label antihypertensive medication, including upward titration of HCTZ, was added in order to reach goal BP. The majority of patients received combination therapy (30% of the losartan and 27% of the atenolol group were taking 100 mg of the study drug in addition to HCTZ and other drugs). Nine percent of the losartan group and 6% of the atenolol group remained on the study drug alone. During a mean follow-up time of 4.7 years, 27% and 32% of patients in the losartan and atenolol groups, respectively, discontinued therapy. As with all intention-to-treat analyses, the loss of patients on treatment may have attenuated the size of differences in the observed effects.

The primary composite end point was reduced by 24% in the losartan group vs the atenolol group (*P*=0.031; 95% CI 0.58-0.98). End point component analysis reveals that only cardiovascular mortality was reduced significantly (RR 37%; 95% CI 0.42-0.95; *P*=0.028) and was the main driver behind the reduction in the primary end point. The mean sitting BP levels at the last visit were 146/79 mm Hg in the losartan group and 148/79 mm Hg in the atenolol group. A trend toward reduced admissions for heart failure was observed among the losartan group, although this did not reach significance.

This study shows that losartan decreases the chance of cardiovascular events, death, and total mortality more than atenolol in patients with hypertension. This conclusion could, however, be misleading because, as mentioned, only a small number received the study drug alone. When choosing an antihypertensive agent, the ideal drug is tailored to the patient. Studies in the past that have been favorable to β-blockers have involved younger patients with a mean age in the 50s with a more compliant vascular system, namely, a different population to the LIFE Study. Furthermore, while this substudy of LIFE shows that losartan does reduce cardiovascular complications, any benefit is exaggerated by the higher baseline morbidity in the atenolol group. As the authors themselves state, this result should be considered in context. Consequently, the results and conclusions are directly relevant only to a population with hypertension, diabetes, a mean age of 70, and who have ECG evidence of LVH.

— 2002 —

The US National Academy of Sciences issues a report supporting the creation of embryonic stem cells to treat such illnesses as Parkinson's disease and diabetes; Stephen Jay Gould, the revered paleontologist and science writer, dies; and the trial of former Yugoslav leader Slobodan Milosevic opens at The Hague, on charges of crimes against humanity

Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomized trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan

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Lancet. 2002;360:752-760

In the OPtimal Trial In Myocardial infarction with Angiotensin II Antagonist Losartan (OPTIMAAL), 5477 patients with left ventricular (LV) dysfunction were randomized after myocardial infarction (MI) to either losartan or captopril. The hypothesis was that losartan 50 mg once daily was superior to captopril 50 mg tid in reducing mortality in a high-risk population. The population included patients with a documented MI and heart failure or an anterior Q-wave MI or reinfarction in a patient with a previous Q-wave anterior MI. Patients were aged 50 years or older. Follow-up was for a mean of 2.7 years after randomization. The dose of captopril was based on the Survival and Ventricular Enlargement (SAVE) study and that of losartan on the Evaluation of Losartan in the Elderly (ELITE-I) study, which demonstrated superiority of losartan 50 mg vs captopril 50 mg tid on survival in 722 patients of 65 years of age with heart failure.

In OPTIMAAL, the primary end point (total/all-cause mortality) and the secondary end point (incidence of sudden cardiac death or resuscitated cardiac arrest) favored captopril over losartan. Patients receiving losartan had a tendency to greater mortality (odds ratio [OR] 1.13; 95% CI 0.99 to 1.28; P=0.069), a significant increase in cardiovascular death (OR 1.17; 95% CI 1.10 to 1.34; P=0.032), and a trend toward higher rates of hospital admissions for heart failure (OR 1.16; 95% CI 0.98 to 1.37; P=0.072) compared with patients on captopril. The incidence of reinfarction and revascularization were similar in both groups.

The obvious possibility is that the ACE inhibitor captopril is superior to the angiotensin receptor blocker (ARB) losartan in patients with LV dysfunction or heart failure after MI. However, the results of OPTIMAAL contrast with those of the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study and of the Reduction of Endpoints in Noninsulin-dependent diabetes mellitus with Angiotensin II Antagonist Losartan (RENAAL) study, both of which showed beneficial effects with losartan 100 mg vs atenolol and standard antihypertensive therapy, respectively. Taken together, the results of OPTIMAAL, LIFE, and RENAAL suggest that 50 mg may be an inadequate dose of losartan and that larger doses are required to get the full beneficial effects. Nevertheless, the lack of improvement in survival with AT_1 receptor antagonists in these studies raises the possibility that the trend toward better survival (with ACE inhibitors vs AT_1 receptor antagonists) is real. Furthermore, the use of the first-generation ACE inhibitor captopril as comparator suggests the possibility that relative benefits from second/third-generation ACE inhibitors, such as ramipril and perindopril, might have achieved statistical significance. Therefore, losartan should not be considered a suitable alternative to an ACE inhibitor in patients with impaired LV function. However, the benefits seen in the Candesartan in Heart failure Assessment in Reduction of Mortality (CHARM)-Alternative trial of ACE-inhibitor–intolerant patients with heart failure does support use of candesartan in that particular setting.

─── 2002 ───

US President George W. Bush collapses when a pretzel becomes trapped in his windpipe; Zimbabwe is suspended from the Commonwealth following President Mugabe's controversial return to power; and Brazil wins the world soccer cup in Japan and South Korea, the first time the finals are held in Asia

Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM Investigators and Committees

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Angiotensin-converting enzyme (ACE) inhibitors have an established role in the prevention of death from cardiovascular disease CVD, but despite their use at target dosages, angiotensin II (AT II) can still be produced through non-ACE pathways. Further blockade of the renin-angiotensin system (RAS) with use of angiotensin receptor blockers (ARBs) may yield additional benefit over and above ACE-inhibitor use by preventing activation of the AT_1 receptor.

The Candesartan in Heart failure Assessment in Reduction of Mortality (CHARM) program addressed three different ways of using the ARB candesartan in CHF and assessing its overall effects on mortality. The study was conducted for a mean follow-up of 37 months in three distinct patient populations with symptomatic CHF. CHARM-Alternative (n=2028) examined the effects of candesartan in patients with a left ventricular ejection fraction (LVEF) <40% who were intolerant to ACE inhibitors; CHARM-Added (n=2548) included patients with a LVEF <40% who were already being treated with ACE inhibitors; and CHARM-Preserved (n=3025) assessed candesartan in those with a preserved LVEF, many of whom were not being treated with ACE inhibitors. This final group (LVEF >40%) accounts for a considerable number of all CHF patients and although they have better outcomes than those with lower LVEFs, they still have higher rates of mortality and hospital admissions due to CHF. CHARM is one of the few studies to test the effect of ACE inhibitors and ARBs in this group. The data from all three studies were analyzed together in CHARM-Overall.

In each trial, patients were randomly assigned to receive candesartan (mean dose 24 mg/d) or placebo. All studies were powered to detect an effect on the primary end point of combined CV death or CHF hospitalization. Results were as follows: (i) CHARM-Alternative: ARB 33% vs placebo 40%; hazard ratio 0.77; 95% CI (0.67-0.89); *P*=0.0004; (ii) CHARM-Added: ARB 38% vs placebo 42%; hazard ratio 0.85; 95% CI (0.75-0.96); *P*=0.011; and (iii) CHARM-Preserve: ARB 22% vs placebo 24%; hazard ratio 0.89; 95% CI (0.77-1.03); *P*=0.118. Only CHARM-Alternative and CHARM-Added

reached statistical significance in terms of the primary outcome. In CHARM-Alternative, the absolute risk reduction was 7%, vs 4% in CHARM-Added. Again, each component of the combined primary end point was reduced, and benefits were sustained whether or not patients were taking a β-blocker in addition to an ACE inhibitor. Results from CHARM-Preserved were the least convincing, showing only a trend toward benefit for the primary outcome. No difference in CV death between the two treatment arms was observed, but patients receiving candesartan had fewer admissions to hospital for CHF.

The primary end point used in the three CHARM studies has been criticized, since the use of cause-specific mortality and cause-specific hospitalization increases the likelihood of positive results. All-cause mortality of the CHARM-Overall population showed that 23% of patients on candesartan and 25% of those on placebo died, a difference of borderline statistical significance. However, total mortality was significantly reduced by 12% (*P*=0.018) in the CHARM-Added and CHARM-Alternative studies when analyzed separately. Consequently, these investigators provide the first convincing evidence for a morbidity benefit from ARBs in patients with CHF. Nevertheless, we would advise against the assumption that this is a property shared by all other members of this class irrespective of dose, frequency, and pharmacokinetic profile.

2003

Millions gather in New York and other US cities, in London, Melbourne, Paris, Seoul, and many other locations in protest over war in Iraq; the fifth Harry Potter book, "Harry Potter and the Order of the Phoenix," is released, achieving record sales; and a summer heat spell with several weeks of record temperatures above 100°F causes more than 15 000 deaths in France

Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomized, double-blind, placebo-controlled, multicenter trial (the EUROPA study)

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

Lancet. 2003;362:782-788

EUROPA (EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease) is the largest trial of stable, relatively low-risk coronary artery disease (CAD) patients. EUROPA recruited 13 655 (1437 not randomized) patients with CAD defined as previous myocardial infarction (64%), angiographic evidence of CAD (61%), coronary revascularization (55%), or a positive stress test only (5%). After a run-in period of 4 weeks (during which patients were tried on perindopril 4 mg then 8 mg), 6110 patients were randomized to perindopril 8 mg and 6108 to matching placebo. After a mean follow-up of 4.2 years, 10% of the placebo group and 8% of the perindopril group had progressed to the primary end point (a composite of cardiovascular death, myocardial infarction (MI) or cardiac arrest with successful resuscitation), which equates to a 20% relative risk reduction (95% CI 9-29, P=0.0003) with perindopril. These benefits were consistent in all predefined subgroups and also seen with the various secondary end points.

Patients with overt clinical heart failure were excluded from the trial. An assumption was made that, in the absence of clinical symptoms, left ventricular dysfunction did not exist. After follow up was completed, a reduction in admissions for heart failure, with a relative risk reduction of 39%, was observed. However overall heart failure admissions occurred uncommonly in only 1% to 2% of patients.

EUROPA was also one of the first trials to use the new ACC/ESC (American College of Cardiology/European Society of Cardiology) definition of MI in its primary end point, which defines MI as any rise in cardiac markers, including troponins. However, the proportion of MIs attributable to raised troponin concentrations (vs raised CK-MB concentrations) was not reported. This has implications in terms of the overall benefit seen. The majority of the reduction in the primary end point was due to a reduction in cardiovascular death and MI as there were only 17 cardiac arrests in the whole study (primary end point composite of cardiovascular death, MI, or cardiac arrest).

As in the Heart Outcomes Prevention Evaluation (HOPE) trial, reduction in cardiovascular events was associated with small changes in systolic (5 mm Hg) and diastolic (2 mm Hg) blood pressure. Taken together, these observations suggest that the benefit of ACE inhibition is not solely attributable to the lowering of blood pressure. Importantly, many patients were on secondary prevention measures, including 92% on antiplatelet therapy, 62% on β-blockers, and 58% on lipid-lowering therapy, and the benefits were still seen. Adding the ACE inhibitor perindopril to such therapy in patients with documented CAD is able to further reduce the risk of cardiovascular events.

A primary conclusion that can be taken from this paper is that all patients who have experienced an MI should now be considered for long-term ACE-inhibitor therapy. Furthermore, it is clear that individuals with stable asymptomatic CAD can also expect a useful benefit.

2003

Space studies reveal that the universe is
13.7 billion years old, and composed of 4% atoms,
23% dark matter, and 73% dark energy;
a colossal squid, "Mesonychoteuthis hamiltoni,"
is caught in the Antartic waters off New Zealand,
weighing 330 pounds and measuring 16 feet,
the second such squid to be caught; and
the 6 to 8 billion years old fossil of a rodent
resembling a guinea-pig the size of a buffalo
is discovered in South America

Different Strategies to Control the Renin-Angiotensin System

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selected by **Roberto Ferrari, MD, PhD**

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