

ACE in Ischemic Heart Disease

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Ischemic heart disease: the next target for the angiotensin-converting enzyme inhibitors

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Angiotensin-converting enzyme (ACE) inhibitors have been shown to reduce the risk of death, worsening heart failure, and recurrent myocardial infarction in patients with left ventricular systolic dysfunction and heart failure. They have also been shown to reduce mortality in acute myocardial infarction and to reduce the risk of major vascular events and progression of renal disease in patients with diabetes and hypertension, compared with placebo and with calcium channel blockers. Ongoing experimental and clinical research is evaluating the potential use of ACE inhibitors in a wider range of patients, with emphasis on their possible role in the prevention of myocardial infarction, stroke, and cardiovascular death in patients with coronary artery disease without clinical manifestations of heart failure and with preserved left ventricular systolic function, and in high-risk individuals with hypertension, renal disease, and diabetes, in the absence of established ischemic heart disease.

Angiotensin-converting enzyme (ACE) inhibitors exhibit important cardioprotective and vasculoprotective properties. It is believed that these are mediated by their inhibition of both angiotensin-II generation and bradykinin degradation. Animal and human experimental studies demonstrate that ACE inhibitors are effective blood pressure-lowering agents, reduce cardiac hypertrophy, favorably influence ventricular remodeling following myocardial infarction, can lead to coronary vasodilatation, and decrease sympathetic tone. Additionally, ACE inhibitors can restore or improve endothelial function, antagonize angiotensin II-mediated vascular smooth muscle cell growth and proliferation, decrease macrophage migration and function, have antioxidant properties, and decrease thrombotic activity, by both inhibition of platelet aggregation and enhancement of endogenous fibrinolysis.^{1,2} These multiple mechanisms of action contribute to the benefits associated with the use of ACE inhibitors in hypertension, myocardial infarction, and heart failure, and suggest that they may be effective agents in a wider range of ischemic syndromes.

The main purpose of this article is to review the clinical data that support the role of ACE inhibitors in the prevention of ischemic events in a wider range of patients with established cardiovascular disease and to briefly summarize the major ongoing trials addressing this issue.

Keywords: ACE-inhibitor; myocardial infarction; clinical trial; coronary heart disease

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SELECTED ABBREVIATIONS

ACE	angiotensin-converting enzyme
LVEF	left ventricular ejection fraction
PAI-1	plasminogen activator inhibitor-1
PTCA	percutaneous transluminal coronary angioplasty
RRR	relative risk reduction

ESTABLISHED ROLES OF ACE INHIBITORS

ACE inhibitors are first-line therapy in patients with heart failure, asymptomatic left ventricular dysfunction, and in patients with recent myocardial infarction and low ejection fraction

ACE inhibitors have been clearly demonstrated to decrease mortality and hospitalizations for heart failure and acute ischemic events in patients with symptomatic heart failure. Mortality benefits have been demonstrated in studies such as the first COoperative North Scandinavian Enalapril SURvival Study (CONSENSUS) trial,³ which enrolled patients with advanced heart failure symptoms (New York Heart Association [NYHA] functional class IV) and the Studies Of Left Ventricular Dysfunction (SOLVD) Treatment trial, conducted in patients with ejection fraction $\leq 0.35\%$ and NYHA functional class II and III.⁴ These findings are further supported by the results of a systematic overview of randomized trials of ACE inhibitors in patients with heart failure.⁵ This meta-analysis of 32 trials including 3870 patients with symptomatic heart failure randomized to ACE-inhibitor therapy and 3235 controls reveals a 23% reduction in total mortality and a 35% reduction in the combined end point of mortality or hospitalization for congestive heart failure in the ACE-inhibitor group. Furthermore, similar benefits were observed with several different ACE inhibitors, suggesting a class effect, and across various subgroups defined by age, gender, etiology of heart failure, and NYHA class.

Patients with asymptomatic left ventricular dysfunction were studied in the SOLVD Prevention trial, which shows a trend towards a lower mortality among patients treated with enalapril and a significant reduction in hospital admissions for congestive heart failure.⁶

Trials in patients with recent myocardial infarction and moderate reductions in left ventricular ejection fraction (LVEF) with or without clinical manifestations of heart failure, including the Survival And Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), and (TRAndolapril Cardiac Evaluation (TRACE) trials, also demonstrate significant mortality benefits for patients treated with ACE inhibitors.⁷⁻⁹

In the SAVE trial, 2231 patients with LVEF of 40% or less, but without overt heart failure symptoms or myocardial ischemia, were randomly allocated to treat-

ment with captopril or placebo within 3 to 16 days after an acute myocardial infarction, and follow-up extended for an average of 42 months. All-cause mortality was significantly lower in the captopril group compared with the placebo group (relative risk reduction [RRR] = 19%, 95% confidence interval [CI], 3%-32%; $P=0.019$). In addition, captopril reduced the incidence of death from cardiovascular causes, development of severe heart failure, recurrent myocardial infarction, and revascularization procedures. The AIRE study evaluated 2006 patients with clinical evidence of heart failure after an acute myocardial infarction. Patients were randomized to ramipril or placebo within 3 to 10 days after the index infarction, and follow-up extended for an average of 15 months. In this higher-risk population, there was a marked 27% RRR (95% CI, 11%-40%; $P=0.002$) in all-cause mortality. Mortality benefits were apparent early, by 30 days of treatment, and extended across various subgroups. In this trial, there was a trend toward a lower risk for recurrent myocardial infarction for patients receiving ramipril, although this did not reach statistical significance. Given the much shorter duration of the AIRE study, this finding does not contradict the results of the SAVE trial with regard to potential benefits of ACE-inhibitor therapy on myocardial infarction risk, and may be a reflection of the limited number of recurrent infarctions and the lesser impact of the ACE-inhibitor therapy on vascular remodeling in this shorter treatment period. In the TRACE study, 2606 consecutive patients with echocardiographic evidence of left ventricular systolic dysfunction (LVEF $\leq 35\%$) were randomized to treatment with trandolapril or placebo for an average of 26 months. There was a 22% RRR (95% CI, 9%-35%; $P=0.001$) in all-cause mortality. Trandolapril also significantly reduced the risk of death from cardiovascular causes, sudden death, and progression to severe heart failure. There was a 14% reduction in the risk for recurrent myocardial infarction, which did not reach statistical significance, possibly again due to the relatively short duration of this trial.

A recent meta-analysis based on individual patient data from SOLVD, SAVE, TRACE, and AIRE on a total of 12 500 patients indicates that over a follow-up of about 4 to 5 years there is a 26% RRR in total mortality ($P<0.0001$) and a 20% RRR for myocardial infarction ($P<0.01$).¹⁰ There was no impact on stroke, but few patients had an elevated blood pressure. Subgroup analysis confirmed that the benefits in preventing cardiovascular death, hospitalizations for congestive heart failure, and myocardial infarction were similar in men and women, those with or without concomi-



tant use of diuretics, aspirin, or β -blockers, and those with a variety of patient characteristics. However, benefits were greatest among patients with greatest impairment of left ventricular systolic function.

Therefore, the available data from the trials of ACE inhibitors clearly demonstrate that these agents reduce mortality and morbidity in patients with compromised left ventricular function with or without recent myocardial infarction and with or without clinical manifestations of heart failure.

Early ACE-inhibitor use in patients with acute myocardial infarction

A number of large-scale trials, including the 4th International Study of Infarct Survival (ISIS-4) and the 3rd Gruppo Italiano per lo Studio della Sopravvivenza nell' Infarto miocardico (GISSI-3) trials have demonstrated improved survival with ACE-inhibitor therapy initiated in the early phase of acute myocardial infarction.^{11,12} A recent systematic overview, including almost

TRIAL ACRONYMS

ABCD	Appropriate Blood pressure Control in Diabetes
AIRE	Acute Infarction Ramipril Efficacy
ALLHAT	Antihypertensive therapy and Lipid-Lowering Heart Attack prevention Trial
CAPP	CAPtopril Prevention Project
CCS-I	Chinese Captopril Study-I
CONSENSUS	COoperative North Scandinavian ENalapril SURvival Study
CONSENSUS II	COoperative New Scandinavian ENalapril SURvival Study II
EUCLID	EURODIAB Controlled trial of Lisinopril in Insulin-Dependent diabetes mellitus
EUROPA	EUropean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease
FACET	Fosinopril Amlodipine Cardiovascular Events Trial
GISSI-3	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-III
GLANT	Group on Long-term ANtihypertensive Therapy
HEART	Healing and Early Afterload Reduction Therapy
HOPE	Heart Outcomes Prevention Evaluation
ISIS-4	4th International Study of Infarct Survival
MARCATOR	Multicenter American Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis
MERCATOR	Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis
MICRO-HOPE	Mlcroalbuminuria, Cardiovascular, and Renal Outcomes in the Heart Outcomes Prevention Evaluation
MORE-HOPE	Mechanisms Of Reduced Endpoints in the Heart Outcomes Prevention Evaluation
PART-2	Prevention of Atherosclerosis with Ramipril Therapy-2
PEACE	Prevention of Events with ACE inhibitors
PHYLLIS	Plaque HYPertension Lipid-Lowering Italian Study
PROGRESS	Perindopril pROtection aGainst REcurrent Stroke Study
QUIET	QUinapril Ischemia Event Trial
QUO VADIS	effects of QUinapril On Vascular ACE and Determinants of ISchemia
SAVE	Survival And Ventricular Enlargement
SCAT	Simvastatin Coronary Atherosclerosis Trial
SECURE	Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E
SMILE	Survival of Myocardial Infarction Long-term Evaluation
SOLVD	Studies Of Left Ventricular Dysfunction
TRACE	TRAndolapril Cardiac Evaluation
TREND	Trial on Reversing ENdothelial Dysfunction
UKPDS	UK Prospective Diabetes Study

100 000 individual patients' data from randomized trials of ACE-inhibitor treatment started in the acute phase of myocardial infarction and continued for a short time, revealed a modest, but statistically significant, 7% proportional reduction in 30-day mortality among ACE-inhibitor-allocated patients, representing avoidance of about 5 deaths per 1000 patients treated and supporting overall the use of ACE inhibitors early in acute myocardial infarction.¹³ The absolute benefits appear to be larger in patients with anterior infarction, tachycardia, previous myocardial infarction, diabetes, and Killip class II and III. Some controversy still persists as to whether all patients with acute myocardial infarction should receive ACE-inhibitor therapy or whether this treatment should be reserved for those at highest risk for adverse outcomes, such as patients with large infarcts and early evidence of heart failure. A reasonable approach would be to initiate ACE inhibitors early in the acute phase of myocardial infarction in all patients without contraindications for these agents and to withdraw treatment in lower-risk subsets at about 6 weeks. In the high-risk subgroups of patients, treatment with an ACE inhibitor should be continued indefinitely.

ACE inhibitors in hypertension, diabetes, and renal disease

The use of ACE inhibitors in the treatment of hypertension is also clearly established as single-drug therapy or in combination with other agents, in particular with diuretics. In general, the blood pressure reduction with ACE inhibitors is similar to that achieved with other antihypertensive drugs. The recent Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) lists ACE inhibitors as the preferred initial drug therapy in patients with hypertension in the presence of heart failure, myocardial infarction with systolic dysfunction, type 1 diabetes mellitus with proteinuria, and renal insufficiency of other causes in the absence of significant bilateral renal artery stenosis.¹⁴ These recommendations are supported by the trials reviewed above and a number of recent trials in diabetic nephropathy and other forms of renal disease. Lewis et al studied 409 patients with insulin-dependent diabetes mellitus and proteinuria (urinary protein excretion of ≥ 500 $\mu\text{g}/\text{day}$), but no advanced renal failure (serum creatinine ≤ 221 $\mu\text{mol}/\text{L}$) who were randomly allocated to treatment with captopril or placebo.¹⁵ Captopril treatment significantly delayed the rate of loss of renal function and was associated with a 50% reduction in the risk of the

combined end points of death, dialysis, and transplantation. This marked benefit appeared to be independent of the overall small differences in blood pressure between the treatment groups. ACE-inhibitor therapy was found to be protective against progression of renal insufficiency also in patients with renal disease of diverse etiologies, but in the absence of diabetes, and is recommended as preferred therapy in hypertensive patients with renal disease.¹⁶ Further insights into the effects of ACE inhibitors on renal disease in type 2 diabetic patients with and without hypertension and with or without microalbuminuria will be provided by the Microalbuminuria, Cardiovascular, and Renal Outcomes in the Heart Outcomes Prevention Evaluation (MICRO-HOPE) study and several other ongoing clinical trials.¹⁷ For type 2 diabetic and hypertensive patients with proteinuria, current recommendations suggest the use of ACE inhibitors or calcium channel blockers as first-line therapy. However, more recent evidence demonstrates improved cardiovascular outcomes in these patients when treated with ACE inhibitors rather than with calcium channel antagonists. Thus, the Fosinopril Amlodipine Cardiovascular Events (FACET) study conducted in 380 hypertensives with non-insulin-dependent diabetes followed up to 3.5 years reported a significantly lower risk of major cardiovascular events in those treated with fosinopril as compared with those receiving amlodipine (RRR=51%, 95% CI, 5%-74%; $P=0.03$).¹⁸ Similarly, a recently reported subgroup analysis in 470 patients in the Appropriate Blood Pressure Control in Diabetes (ABCD) trial indicated that the rates of fatal and nonfatal myocardial infarction among those assigned nisoldipine (a calcium channel blocker) was significantly higher than those assigned enalapril (adjusted risk ratio=7.0, 95% CI of 2.3%-21.4%).¹⁹ The Group on Long-term ANtihypertensive Therapy (GLANT) study conducted in 1936 patients with mild-to-moderate essential hypertension (diabetes was not an inclusion criterion) showed similar trends towards fewer cardiovascular events in individuals treated with an ACE inhibitor as compared with those receiving a calcium antagonist.²⁰ It is not clear at present whether these differences observed are real or due to selective reporting of trials that observed a difference. Nevertheless, it would be prudent to use ACE inhibitors in preference to calcium channel blockers, particularly in diabetic hypertensive patients, until the results of ongoing large, comparative trials such as the Antihypertensive therapy and Lipid-Lowering Heart Attack prevention Trial (ALLHAT) are available. The role of ACE inhibitors versus β -blockers and diuretics as first-line therapy in hypertension is less clearly defined. In



the recently published CAPtopril Prevention Project (CAPP) study, which compared conventional therapy with a diuretic/ β -blocker versus an ACE inhibitor in 10 985 hypertensives, there was no overall difference in the primary study outcome, the cluster of fatal and nonfatal myocardial infarction, and stroke and other cardiovascular deaths.²¹ Conventional therapy was superior in reducing the risk of stroke, while ACE inhibitors appeared more effective in reducing the development of diabetes and macrovascular complications in diabetic patients. There was also a trend toward lower cardiovascular mortality in patients treated with captopril, although it did not reach statistical significance (RRR=23%, 95% CI, -4%-43%; $P=0.092$). The overall lack of clear superiority for ACE inhibitors versus β -blockers is supported by the United Kingdom Prospective Diabetes Study group (UKPDS) trial in 1148 hypertensive patients with type 2 diabetes,²² which recently demonstrated a clear reduction in fatal and nonfatal macrovascular and microvascular complications in patients with diabetes allocated to a regimen of tight blood pressure control, as compared with those allocated to less tight blood pressure control, and which was similar to the two antihypertensive drug regimens used (β -blockers and ACE inhibitors).

ACE inhibitors have been shown recently to also have a role in the prevention of microvascular complications, namely, retinopathy in diabetic patients. In the EURO-DIAB Controlled trial of Lisinopril in Insulin-Dependent diabetes mellitus (EUCLID), 324 insulin-dependent diabetic patients were randomized to receive lisinopril or placebo.²³ There was a 50% reduction in the progression of retinopathy in the lisinopril group and an even larger effect was noted on retarding the progression of proliferative retinopathy. A similar benefit was observed among type 2 diabetics in the UKPDS trial.

THE EMERGING ROLE OF ACE INHIBITORS IN THE MANAGEMENT OF ISCHEMIC HEART DISEASE IN PATIENTS WITH PRESERVED LEFT VENTRICULAR FUNCTION

Epidemiologic and genetic studies: links between the renin-angiotensin system and the risk for myocardial infarction

Several epidemiologic studies have examined the relationship between plasma renin levels in hypertensive patients and the risk for ischemic events. Early studies reported conflicting results, and conclusions from

these investigations are limited by methodological shortcomings.^{24,25} The strongest epidemiological evidence for an association between plasma renin levels and the risk for subsequent myocardial infarction is provided by the prospective cohort study by Alderman et al,²⁶ who followed 1717 subjects with mild-to-moderate hypertension for a mean of 8.3 years, and reported that the risk for myocardial infarction was 5.3-fold increased among subjects with high vs low renin profiles and that this effect was independent of other established cardiovascular risk factors. It remains uncertain, however, whether these observations can be generalized to normotensive individuals. A well-conducted prospective cohort study by Meade et al²⁷ failed to demonstrate an independent association between plasma renin levels and the risk for myocardial infarction in the absence of hypertension.

A number of investigations have evaluated associations between the *ACE-DD* genotype, which identifies individuals with higher circulating and tissue levels of ACE, and the risk for different manifestations of cardiovascular disease, particularly myocardial infarction. Some studies found a clear link between the *ACE-DD* genotype and risk for myocardial infarction, which was particularly relevant in individuals otherwise felt to be at low risk for acute ischemic events based on classic cardiovascular risk factors, while other investigations failed to confirm such associations.²⁸⁻³¹ Further studies evaluating the significance of the ACE gene polymorphism and other genetic variants in the renin-angiotensin system are under way and will help resolve this important question as well as potential therapeutic implications.³²

ACE inhibitors in stable angina pectoris

Several small trials, generally of short duration, assessing the effect of ACE inhibitors on severity of angina pectoris and/or objective measures of myocardial ischemia, have reported conflicting results. These studies indicate that ACE inhibitors do not have consistent antianginal effects in short-term studies.³³⁻³⁹ The short duration of such trials precludes conclusions regarding potential long-term benefits of ACE inhibitors in chronic, stable anginal syndromes, as such potential benefits may be related to changes in the vascular wall associated with long-term ACE-inhibitor therapy. The ongoing Heart Outcomes Prevention Evaluation (HOPE) trial includes a substantial number of patients with chronic stable angina and will evaluate the impact of treatment with the ACE inhibitor ramipril on major cardiovascular outcomes.

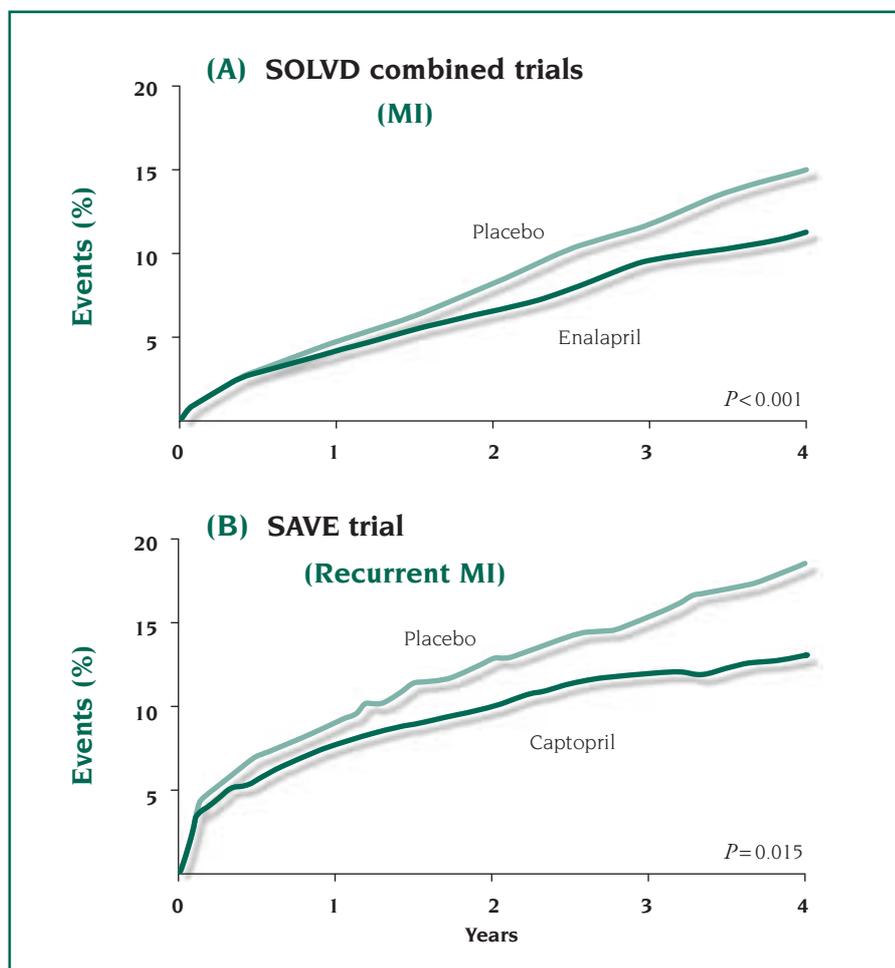


Figure 1. (A) Cumulative incidence of myocardial infarction (MI) in the combined Studies Of Left Ventricular Dysfunction (SOLVD). (B) Incidence of recurrent myocardial infarction in the Survival And Ventricular Enlargement (SAVE) trial. In both studies, differences in the incidence of myocardial infarction between ACE-inhibitor- and placebo-treated patients started to become apparent after 6 to 12 months of therapy and continued to widen thereafter.

Figure 1(A) is adapted with permission from ref 44: Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. *Lancet*. 1992;340:1173-1178. Copyright ©, 1992, The Lancet. Figure 1(B) is adapted with permission from ref 45: Rutherford JD, Pfeffer MA, Moya LA, et al, on behalf of the SAVE investigators. Effects of captopril on ischemic events after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. *Circulation*. 1994;90:1731-1738. Copyright © 1994, American Heart Association, Inc.

ACE inhibitors in the prevention of restenosis following percutaneous transluminal coronary angioplasty

ACE inhibitors have the theoretical potential to prevent restenosis after percutaneous transluminal coronary angioplasty (PTCA) in view of the demonstrated potent antiproliferative action of these drugs on vascular smooth muscle cells and supportive data from animal studies.⁴⁰ Clinical trials, including the Multicenter European Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis (MERCATOR) and the Multicenter American Research trial with Cilazapril after Angioplasty to prevent Transluminal coronary Obstruction and Restenosis (MARCATOR), using different doses of cilazapril, failed, however, to demonstrate a clear benefit for the use of ACE inhibitors in the prevention of restenosis post-PTCA.^{41,42} It is likely that the very potent and complex wound healing process after angioplasty may differ in responsiveness to ACE inhibitors compared with

coronary artery disease not affected by invasive interventions. Furthermore, these clinical trials started ACE-inhibitor therapy after angioplasty, as opposed to the animal experiments, where treatment preceded balloon injury to the vessel wall. A more recent study by Yamabe et al⁴³ where cilazapril was used 7 days before PTCA reported a significant reduction in restenosis rates. This was, however, a relatively small study, with only 128 patients completing follow-up and repeat quantitative coronary angiography, and its results require further confirmation. At the present time, ACE inhibitors cannot be recommended as a means of preventing restenosis following PTCA.

The role of ACE inhibitors in the prevention of myocardial infarction, stroke, and cardiovascular death

The potential for ACE inhibitors to prevent major acute ischemic events has been brought into focus by the results of the Studies Of Left Ventricular Dysfunction



(SOLVD) and SAVE, which separately demonstrated a significant reduction in the incidence of acute myocardial infarction in patients with documented cardiovascular disease and low ejection fraction treated with ACE inhibitors for approximately 40 months (Figure 1).^{44,45} Pooled results of the SOLVD Treatment trial, the SOLVD Prevention trial, SAVE, AIRE, and TRACE indicate a 21% RRR (95% CI, 11%-29%; $P=0.001$) for myocardial infarction associated with ACE-inhibitor therapy. In addition, other major ischemic end points, specifically, hospitalizations for unstable angina in the combined SOLVD trials (RRR=20%; 95% CI, 9%-29%, $P=0.001$) and revascularization procedures in the SAVE trial (RRR=24%, 95% CI, 6%-39%; $P=0.014$), were also significantly reduced in patients treated with enalapril and captopril, respectively.

It is unlikely that the observed reduction in ischemic events can be explained by the blood pressure-lowering action of ACE inhibitors alone, since the magnitude of risk reduction was substantially larger than that expected from short-term, modest reductions in blood pressure. In a recent meta-analysis of 14 randomized clinical trials of antihypertensive therapy, diastolic blood pressure reductions of 5 to 6 mm Hg for about 4 to 5 years resulted in a 14% reduction in fatal and nonfatal coronary heart disease events.⁴⁶ In the combined SOLVD trials, diastolic blood pressure was reduced by an average of 4 mm Hg, and this was associated with a 23% reduction in fatal or nonfatal myocardial infarction and a 21% reduction in cardiac deaths. Moreover, the risk reductions in ischemic events were similar in patients with different levels of systolic and diastolic blood pressure at baseline, and while there was a trend toward larger reductions in the risk for myocardial infarction and unstable angina among those with a greater reduction in blood pressure, this did not reach statistical significance. These considerations suggest that the reduction in major ischemic events observed with ACE-inhibitor therapy is at least in part due to mechanisms unrelated to the hypotensive effects of these drugs.

The effects of ACE inhibitors on myocardial infarction risk in major clinical trials are summarized in Table I (see next page), which emphasizes the importance of prolonged therapy in attaining benefits. The observed time course for the reduction of acute ischemic events (with a 6- to 12-month lag) resembles the results of trials of other interventions that would be expected to delay the natural course of atherosclerosis, such as cholesterol lowering, and suggests that the mechanism for the observed anti-ischemic action of ACE

inhibitors is unlikely to be related solely to the beneficial hemodynamic effect of these drugs, which is generally noticed immediately and not expected to increase with time (Figure 1). These observations derived from clinical trials, along with observations derived from animal experimentation and from mechanistic studies in human subjects, led to a number of hypotheses regarding potential "anti-ischemic" mechanisms of action of ACE inhibitors, including the prevention of coronary atherosclerosis progression and/or stabilization of atherosclerotic plaques, restoration of endothelial integrity and function, and prevention of thrombotic events. Furthermore, these findings support the intriguing possibility that the reduction in ischemic events noted in the SOLVD and SAVE trials may occur in a broader group of high-risk patients, such as those with evidence of cardiovascular disease and *preserved left ventricular ejection fraction*. Patients without left ventricular systolic dysfunction may not have significant increases in systemic levels of renin and angiotensin, although activation of the local tissue angiotensin system may occur in response to atherosclerotic vascular injury.

The effects of prolonged ACE-inhibitor therapy on the anatomical progression of atherosclerotic lesions were studied in the recently presented Prevention of Atherosclerosis with Ramipril Therapy-2 (PART-2) trial and the Simvastatin Coronary Atherosclerosis Trial (SCAT). Preliminary reports from these trials evaluating atherosclerosis progression by B-mode carotid ultrasound of the extracranial carotid arteries and by quantitative coronary angiography, respectively, suggest no clear retardation of the anatomic progression of atherosclerotic lesions with ACE inhibitors (MacMahon S et al and Teo KK et al, personal communications). However, both studies reported significant reductions in major clinical end points; thus in the PART-2 study conducted in over 600 patients with known cardiovascular disease treated with ramipril or placebo for an average of about 4 years, there was a reduction in cardiovascular deaths in the active treatment group ($P=0.045$), and in the SCAT trial, which included over 400 patients allocated to treatment with enalapril or placebo for an average of 5 years, there was a reduction in the combined end point of myocardial infarction, stroke, and death in the enalapril arm ($P=0.043$).

A number of ongoing trials are expected in the near future to provide further data regarding the effects of ACE inhibitors on the anatomic progression of atherosclerosis. These include the Study to Evaluate Carotid Ultrasound changes in patients treated with

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Ramipril and vitamin E (SECURE), assessing ramipril and vitamin E effects on carotid atherosclerosis using noninvasive quantitative B-mode carotid ultrasound techniques in 732 high-risk patients with established cardiovascular disease or diabetes and additional risk factors, and the Plaque HYPertension Lipid-Lowering Italian Study (PHYLLIS), assessing blood pressure and cholesterol-lowering effects on carotid intimal-medial thickness.^{47,48} If these studies confirm the results of the PART-2 and SCAT trials, in that there is no effect of ACE inhibitors on the anatomic extent of atherosclerotic lesions, and other large trials indicate a reduction in clinical events, then mechanisms independent of an effect on the extent of atherosclerosis need to be considered. Recent studies point towards a potential important role for the effects of ACE inhibitors on improving endothelial function and the balance of

thrombotic and fibrinolytic processes, although other complex mechanisms may also be essential. The Trial on Reversing Endothelial Dysfunction (TREND) is the first trial of an ACE inhibitor to demonstrate improved endothelial function in humans. In this trial, a total of 105 patients with established coronary artery disease were randomized to 6 months of treatment with quinapril 40 mg/day or placebo. Endothelial function, evaluated by the change in luminal diameter of coronary arteries in response to intracoronary infusion of acetylcholine, an effect mediated by endothelial production of nitric oxide, improved significantly in the quinapril group.⁴⁹ While the relative contributions of blockade of angiotensin II synthesis versus the prevention of bradykinin breakdown in restoring endothelial function and in improving clinical outcomes remain uncertain, studies using selective bradykinin

Mean duration of treatment	Patient characteristics	No. of MI (% of patients)		RRR (%)	P
		ACEI	Placebo	95% CI	
Trial(s)					
≤6 months					
CONSENSUS II	Unselected patients with acute MI	271(8.9)	268(8.8)	-1(-21, 15)	NS
GISSI-3	Unselected patients with acute MI	303(3.2)	292(3.1)	-4(-23, 12)	NS
ISIS-4	Unselected patients with acute MI	1162(4.0)	1101(3.8)	-6(-15, 3)	NS
CCS-1	Unselected patients with acute MI	Not reported		-	-
SMILE	Acute anterior MI; not eligible for thrombolysis	8(1.0)	5(0.6)	37(-20, 80)	NS
OVERALL				-5(-10, 2)	
15 months					
AIRE	Clinical evidence of HF early post-MI	81(8.0)	88(8.9)	9(-22, 35)	NS
26.5 months					
TRACE	EF ≤ 35% early post MI	97(11.1)	111(12.7)	14(-10, 31)	NS
38-42 months					
SOLVD Prevention	EF ≤ 35% without HF	161(7.6)	204(9.1)	24(6, 38)	0.01
SOLVD Treatment	EF ≤ 35% with HF	127(9.9)	158(12.3)	23(2, 39)	0.02
SAVE	EF ≤ 40% early post-MI	133(11.9)	170(15.2)	25(5, 40)	0.05
OVERALL				23(11, 32)	0.001
ACEI	angiotensin-converting enzyme inhibitor	EF	(left ventricular) ejection fraction	RRR	relative risk reduction
CI	confidence interval	HF	heart failure	Trials	see Trial Acronyms box
		MI	myocardial infarction		

Table 1. Effects of ACE inhibition on myocardial infarction—impact of duration of treatment.



receptor antagonists in humans support an important role for bradykinin potentiation, presumably through increased release of nitric oxide and endothelium-derived hyperpolarizing factor.⁵⁰ The Healing and Early Afterload Therapy (HEART) study conducted in 120 subjects assigned to treatment with ramipril or placebo within 24 hours of the onset of symptoms of myocardial infarction study and a prior smaller study in patients with recent infarction reported a significant decrease in plasminogen activator inhibitor-1 (PAI-1) levels following administration of an ACE inhibitor, confirming the experimental work that suggested an important role for the renin-angiotensin system in the regulation of endogenous fibrinolysis and the potential for ACE inhibitors to interrupt this regulatory pathway, thus contributing to their clinical benefit.^{51,52} It remains unclear whether this effect is important outside the early post-infarction period, and this question is addressed in the ongoing Mechanisms Of Reduced End points in the Heart Outcomes Prevention Evaluation (MORE-HOPE) study.

A number of recently completed and ongoing randomized large clinical trials evaluate the effects of ACE inhibitors on major clinical end points in patients with preserved left ventricular function.¹⁷ The QUinapril Ischemia Event Trial (QUIET) included 1750 normotensive, nonhyperlipidemic patients with coronary artery disease and normal left ventricular systolic function treated with low-dose (20 mg/day) quinapril or placebo for 3 years.⁵³ There was a 13% trend toward fewer major vascular events, which did not reach statistical significance. This trial has several limitations. Patients enrolled were overall at low risk for major adverse vascular events, which occurred at a frequency of about 2% per year, the sample size was too small to reliably detect or exclude moderate effects (ie, 15% - 20% RRR) that are plausible; if there is a "lag" in the development of benefit, longer trials are needed; the dose of drug used was low and there was little lowering of blood pressure. Furthermore, study drug compliance was poor, which further limits the power of the study. Therefore, it is likely that the limitations in the design and conduct of QUIET may have led to a considerable underestimation of the real effects of ACE inhibitors.

The HOPE study was conducted in 9541 high-risk patients with evidence of cardiovascular disease or diabetes and additional risk factors. Patients were randomly allocated to receive ramipril 10 mg/day or placebo and for an average of about 4.5 years. The study was recently stopped on the recommendations of the Data Safety and Monitoring Board prior to the

anticipated termination date due to overwhelming evidence of a reduction in major vascular events associated with ACE-inhibitor therapy.⁵⁴ Results of this landmark study will be published in the near future and are expected to greatly widen the indications for use of these drugs. Furthermore, the HOPE study is expected to provide important data on treatment effects in various predefined subgroups of interest. Thus, the study has randomized 2545 women, 4422 hypertensives, 52 101 individuals over age 65, and 3658 diabetics. A second large trial that is currently evaluating the same hypothesis is the Prevention of Events with ACE inhibitors (PEACE) study, which aims to randomize 8000 patients with coronary artery disease and LVEF of >40% to trandolapril 4 mg or placebo with a planned follow-up of about 5 years. The primary outcome is the composite of cardiovascular death, myocardial infarction, and revascularization. A third large trial addressing the potential for ACE inhibitors to reduce major cardiac outcomes in patients without significant left ventricular dysfunction is the EUROpean trial of Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), which will examine the effects of long-term administration of perindopril on myocardial ischemic events in about 10 500 patients with coronary artery disease, irrespective of baseline ventricular function, but without clinical manifestations of heart failure.⁵⁵ An additional large study is planned in patients with prior coronary bypass graft surgery following encouraging data from the small Effects of QUinapril On Vascular ACE and Determinants of ISchemia (QUO VADIS) study in 149 patients, in which treatment with quinapril was associated with a significant reduction in clinical ischemic events (18% in the placebo arm, versus 4% in the quinapril arm; $P=0.03$). The potential for ACE inhibitors to prevent strokes is under evaluation in the Perindopril pROtection aGainst REcurrent Stroke Study (PROGRESS) in 6000 individuals.

CONCLUSIONS

ACE inhibitors are currently well established and accepted agents in the treatment of patients with heart failure, left ventricular dysfunction without overt heart failure symptoms in the setting of recent myocardial infarction or chronic ischemic cardiac disease, hypertension, and acute myocardial infarction. These drugs have also been clearly shown to reduce the progression of renal disease in insulin-dependent diabetes mellitus with proteinuria.

Promising information supported by basic research, epidemiologic and genetic links, as well as clinical trials in patients with low LVEF, suggest a potential new emerging role for ACE inhibitors in reducing the risk for myocardial infarction and other major ischemic events, in a broader range of high-risk patients with *preserved left ventricular function*. Ongoing clinical trials will clearly answer these hypotheses over the next few years and will also provide insight into the impact of prolonged ACE-inhibitor therapy on the atherosclerotic process itself. The findings of these clinical investigations will potentially impact on a large number of patients with coronary artery disease and could therefore have important public health implications.

THREE KEY QUESTIONS

Ongoing research is also expected to answer important questions examined in the following Expert Answers section regarding the mechanisms of action of ACE inhibitors that account for clinical benefit, such as **“Is bradykinin important for the clinical outcome?”** (Tiziana Bachetti); **“Is the endothelium an important therapeutic target?”** (Ruddi Busse and Ingrid Fleming; and **“ACE inhibition in ischemic heart disease: what is the relevance of the control of the neuroendocrine response?”** (Willem J. Remme). Answers to such questions are extremely relevant in defining the role of ACE-inhibitor therapy and of other drugs that act via different pathways in modulating the renin-angiotensin-aldosterone system.

Note: Recent data from the HOPE trial (published after completion of this manuscript) confirm significant benefits for treatment with ramipril in patients with preserved left ventricular systolic function.⁵⁶ This large trial demonstrated a significant 22% relative risk reduction in the primary study end points, the composite of myocardial infarction, stroke, and cardiovascular death, for high-risk patients treated with ramipril. Treatment with ramipril also reduced the rates of death from cardiovascular causes, myocardial infarction, stroke, death from all causes, heart failure, and complications related to diabetes.

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ACE in Ischemic Heart Disease

Expert Answers to Three Key Questions

①

Is bradykinin important for the clinical outcome?

T. Bachetti

②

Is the endothelium an important therapeutic target?

R. Busse, I. Fleming

③

ACE inhibition in ischemic heart disease: what is the relevance of the control of the neuroendocrine response?

W.J. Remme



Is bradykinin important for the clinical outcome?

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Reduction in the synthesis of the potent vasoconstricting agent angiotensin II has long been considered as the principal mechanism accounting for angiotensin-converting enzyme inhibition and the ensuing limitation in the progression of a variety of cardiovascular diseases. Recently, a new mechanism of action of these relatively old drugs has been proposed, ie, the increased availability of bradykinin. This kinin, which is broken down by angiotensin-converting enzyme, has a potent vasodilator effect resulting from the stimulation of specific receptors on endothelial cells and the release of nitric oxide, prostacyclin, and the endothelium-derived hyperpolarizing factor. The recent development of a specific bradykinin-receptor blocking agent, icatibant, has allowed better understanding of the beneficial properties of angiotensin-converting enzyme inhibitors on endothelial dysfunction, both in experimental and clinical studies.

Keywords: angiotensin-converting enzyme inhibitor; bradykinin-receptor blocking agent; icatibant; endothelial dysfunction

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Angiotensin-converting enzyme (ACE) inhibitors undoubtedly represent a milestone in cardiovascular therapy. ACE inhibitors are known to delay the progression of coronary artery disease (CAD) by interrupting the series of events that lead to end-stage ischemic heart disease. Moreover, in patients with

severe congestive heart failure (CHF), ACE inhibitors, quite surprisingly, reduce the recurrence of angina pectoris and myocardial infarction, the rate of hospitalization for ischemic heart disease, and the rate of coronary artery bypass surgery or angioplasty.¹⁻⁴ More recently, ACE inhibitors have been shown to reduce vascular hypertrophy, attenuate

SELECTED ABBREVIATIONS AND ACRONYMS

AIRE	Acute Infarction Ramipril Efficacy
ALLHAT	Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack
AT I, II	angiotensin I, II
CAD	coronary artery disease
CONSENSUS	CoOperative North Scandinavian ENalapril SURvival Study
ecNOS	endothelial constitutive nitric oxide synthase
EDHF	endothelium-derived hyperpolarizing factor
EUROPA	EUropean trial on 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 Outcome Prevention Evaluation
ISIS 4	Fourth International Study of Infarct Survival
NO	nitric oxide
PEACE	Prevention of Events with ACE inhibitors
QUIET	QUinapril Ischemic Event Trial
SAVE	Survival And Ventricular Enlargement
SCAT	Simvastatin and enalapril Coronary Atherosclerosis Trial
SOLVD	Studies Of Left Ventricular Dysfunction
TRACE	TRAndolapril Cardiac Evaluation
TREND	Trial on Reversing ENdothelial Dysfunction
VCAM-1	vascular cell adhesion molecule-1

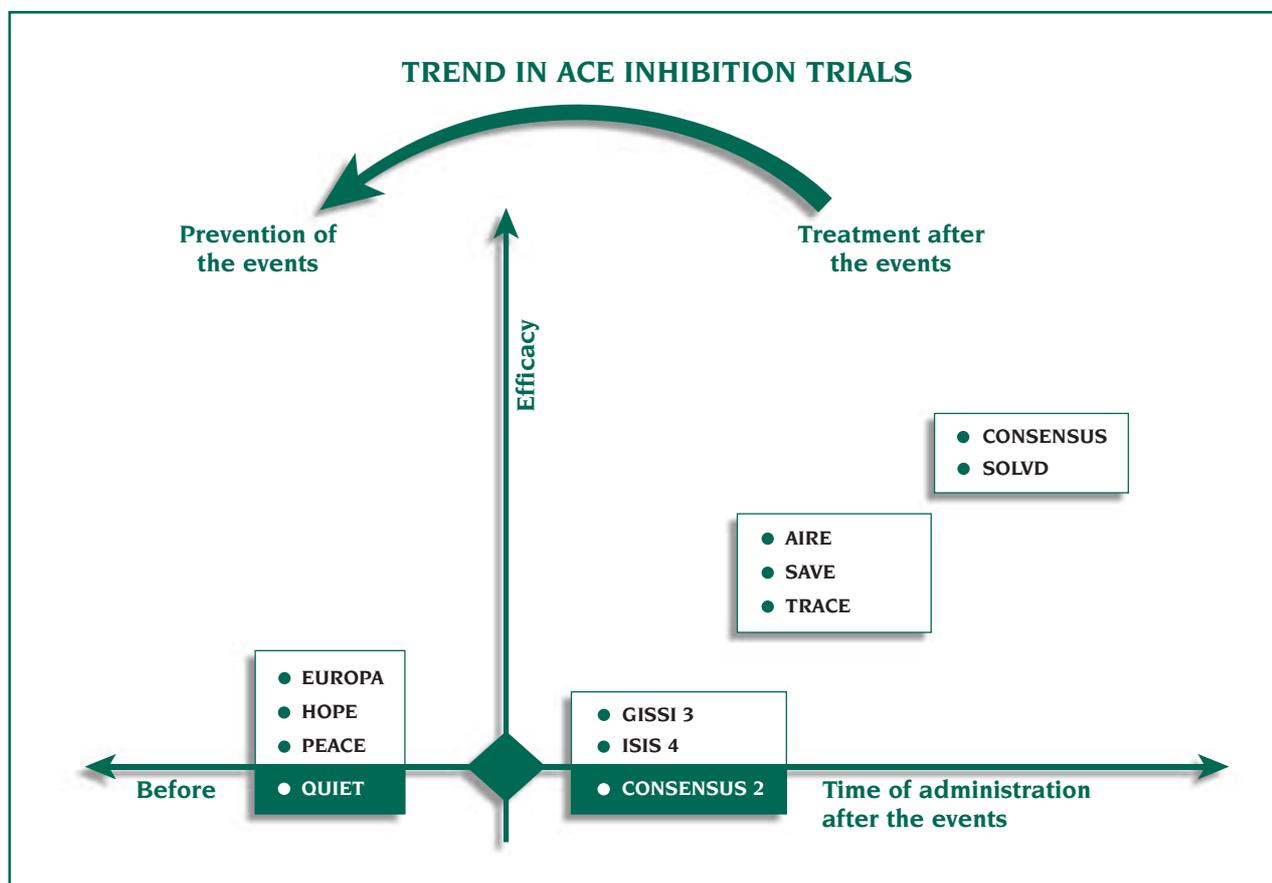


Figure 1. The plot shows the efficacy profile of clinical trials on angiotensin-converting enzyme (ACE) inhibitors, given as therapeutic or preventive treatment. Study acronyms: see box at beginning of article.

atherosclerosis, and influence mortality and hospitalization when used in patients with left ventricular dysfunction without CHF.⁵

ACE ACTIVITY AND EXPRESSION

These encouraging results have led researchers to propose that alteration in ACE activity, particularly in tissues, may be an important factor in the development and progression of CAD. Epidemiological, genetic, and experimental studies support this hypothesis.⁶ Indeed, increased ACE activity is associated with damage to the ventricle and vasculature. Local tissue synthesis of ACE is secondary to its gene expression, which is induced by hypertension, ischemia, cardiac pressure overload,

and CHF, resulting in an increased local production of angiotensin II.⁷ As a consequence of the induction of tissue ACE expression, long-term regulation of cardiovascular homeostasis also occurs via degradation of bradykinin.⁸ This may result in secondary permanent structural changes, such as myocardial and vascular remodeling. In addition, a genetic variant of the ACE gene has been associated with increased risk for cardiovascular disease.

ACE INHIBITORS IN THE PREVENTION OF ATHEROSCLEROSIS

Interestingly, in the last decade, clinical trials have shown that the use of ACE inhibitors reduced mortality, in parallel with a trend toward re-

ducing the time interval of start of treatment after an acute event. Nowadays, the rationale for the use of ACE inhibitors has even become prevention (Figure 1).^{4,9} Thus, trials such as the Heart Outcome Prevention Evaluation (HOPE), the Simvastatin and enalapril Coronary Atherosclerosis Trial (SCAT), the Antihypertensive and Lipid-Lowering treatment to prevent Heart ATtack (ALLHAT), the EUropean trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), and the Prevention of Events with ACE inhibitors study (PEACE), are now studying the effects of the ACE inhibitors, either administered alone or in combination with other drugs, on the progression of CAD as well as on CAD-related morbidity and mortality.⁵



Recently, ACE inhibitors have also been proposed as having an anti-atherogenic action, as they have been shown to exert such an action in several experimental models of atherosclerosis.^{10,11} This action is complex and includes protection of the endothelium, antimitogenic effects, antithrombotic and plaque-stabilizing effects, and possibly antioxidant properties. However, clinical studies have not confirmed the encouraging experimental results: cilazapril administered after angioplasty failed to prevent restenosis in humans,¹² and quinapril failed to show reduction in mortality or recurrence of angina pectoris after angioplasty.¹³ This lack of effect in humans may be due to the low doses of ACE inhibitors used in these studies, as the doses required to inhibit the neointimal development are higher than the usual antihyper-

tensive ones. ACE inhibitors are believed to exert their antiatherosclerotic activity through indirect mechanisms, ie, reduction in vascular smooth muscle growth and proliferation. In fact, angiotensin II (AT II) induces the expression of proto-oncogenes, such as *c-fos*, *c-myc*, and *c-jun*, resulting in vascular remodeling. Other proposed mechanisms are the stabilization of the endothelium, by inhibiting the synthesis of neutrophil chemoattractants and enhancing accumulation of kinins. As far as endothelial function is concerned, another clinical study, the Trial on Reversing Endothelial Dysfunction (TREND), showed that, after ACE inhibition with quinapril, the abnormal vasoconstrictor response to intracoronary infusion of acetylcholine was significantly reduced and, in some cases, reversed to a vasodilator

response in patients with established coronary artery atherosclerosis.¹⁴ The contribution of bradykinin to this beneficial effect of quinapril on coronary artery endothelial dysfunction has been postulated, but is still to be defined.

ACE INHIBITION IMPROVES ENDOTHELIAL FUNCTION VIA BRADYKININ — EXPERIMENTAL EVIDENCE

ACE is present as a circulating enzyme (1%-10%) as well as a cardiac and vascular tissue factor (90%-99%). Indeed, ACE is mainly located in the cell membrane of the endocardium and endothelial cells.¹⁵ As shown in *Figure 2*, ACE converts the less active peptide angiotensin I (AT I) into the powerful vasoconstrictor angiotensin II (AT II). Therefore, ACE inhibitors induce peripheral

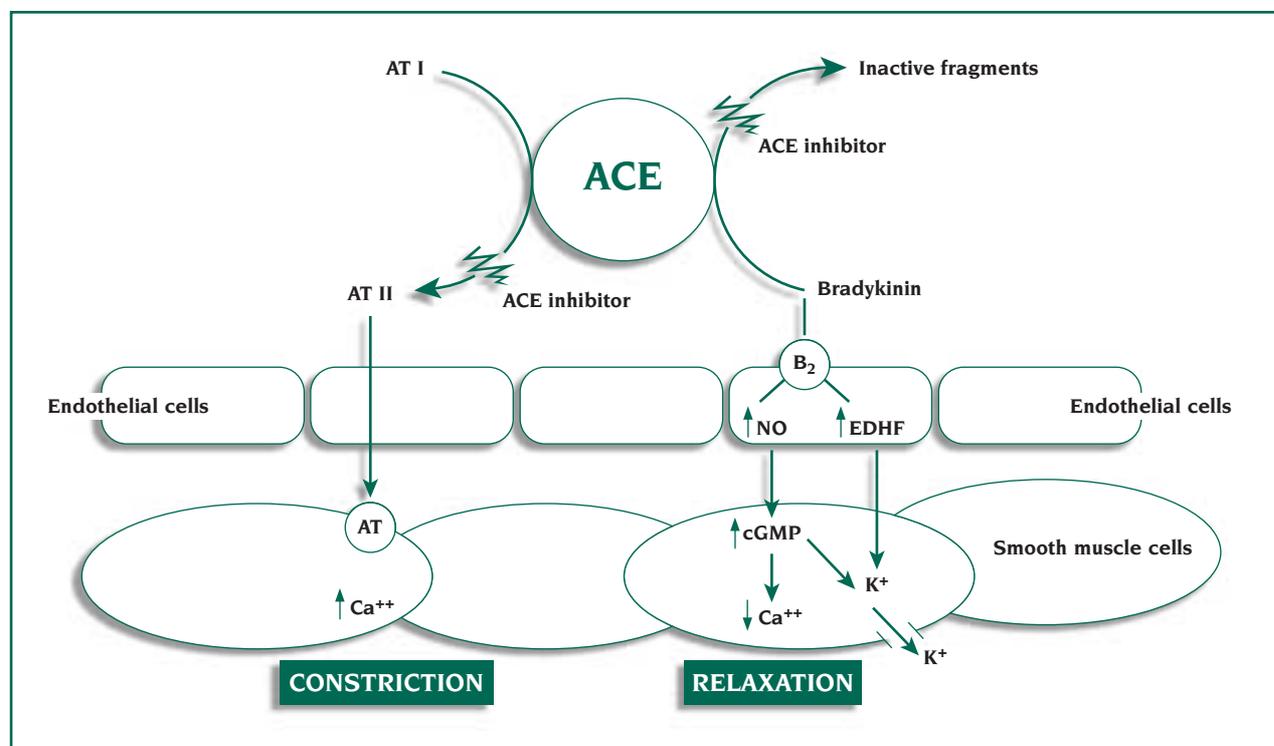


Figure 2. Activity of angiotensin-converting enzyme (ACE)/kininase: the same enzyme catalyzes the synthesis of angiotensin II (AT II) from angiotensin I (AT I), and the breakdown of bradykinin into inactive fragments. AT II interacts with AT receptors on smooth muscle cells, causing calcium-dependent vasoconstriction. Bradykinin acts on endothelial bradykinin receptors causing the release of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF), leading to vasorelaxation. ACE inhibitors have a double mechanism of action: (i) inhibition of the ACE-dependent synthesis of AT II; and (ii) inhibition of the kininase-dependent breakdown of bradykinin. cGMP, cyclic guanosine monophosphate.

vasodilatation by reducing the synthesis of AT II. Moreover, ACE catalyzes the breakdown of bradykinin into inactive fragments: for this activity, ACE is known as kininase II. It follows that the vasodilating effects of ACE inhibitors are also due to increased local bio-availability of bradykinin. Bradykinin, released from its substrate kininogen by kallikrein, is a potent vasodilator peptide. It acts on specific endothelial bradykinin receptors, thus causing activation of the arachidonic acid cascade and elevation of intracellular calcium concentration, which, in turn, stimulates the release of prostacyclin, endothelium-derived hyperpolarizing factor (EDHF) and endothelium-derived relaxing factor (EDRF) or nitric oxide (NO), leading to smooth muscle relaxation (Figure 2).

Experimental studies demonstrated that ACE-inhibitor-mediated vasorelaxation is bradykinin-dependent, since selective B₂-kinin receptor antagonists, eg, HOE 140, reduce the release of NO and the endothelium-dependent hyperpolarizing effect.¹⁶ In addition, ACE inhibitors potentiate the endothelial release of NO via potentiation of bradykinin.¹⁷ Furthermore, we observed that chronic treatment of rats with quinapril resulted in an upregulation of the expression of endothelial constitutive NO synthase (ecNOS), the enzyme responsible for NO synthesis, in the aortic tissue, with a parallel increase in its enzymatic activity, suggesting an increased production of NO. These effects were partially abolished when rats were cotreated with quinapril and HOE 140, suggesting that bradykinin plays an essential role in the ACE-inhibitor-induced modulation of the NO pathway (Figure 3). Thus, the ACE inhibitors that are particularly effective in blocking bradykinin degradation, eg, perindopril, are more likely to influence the rate of

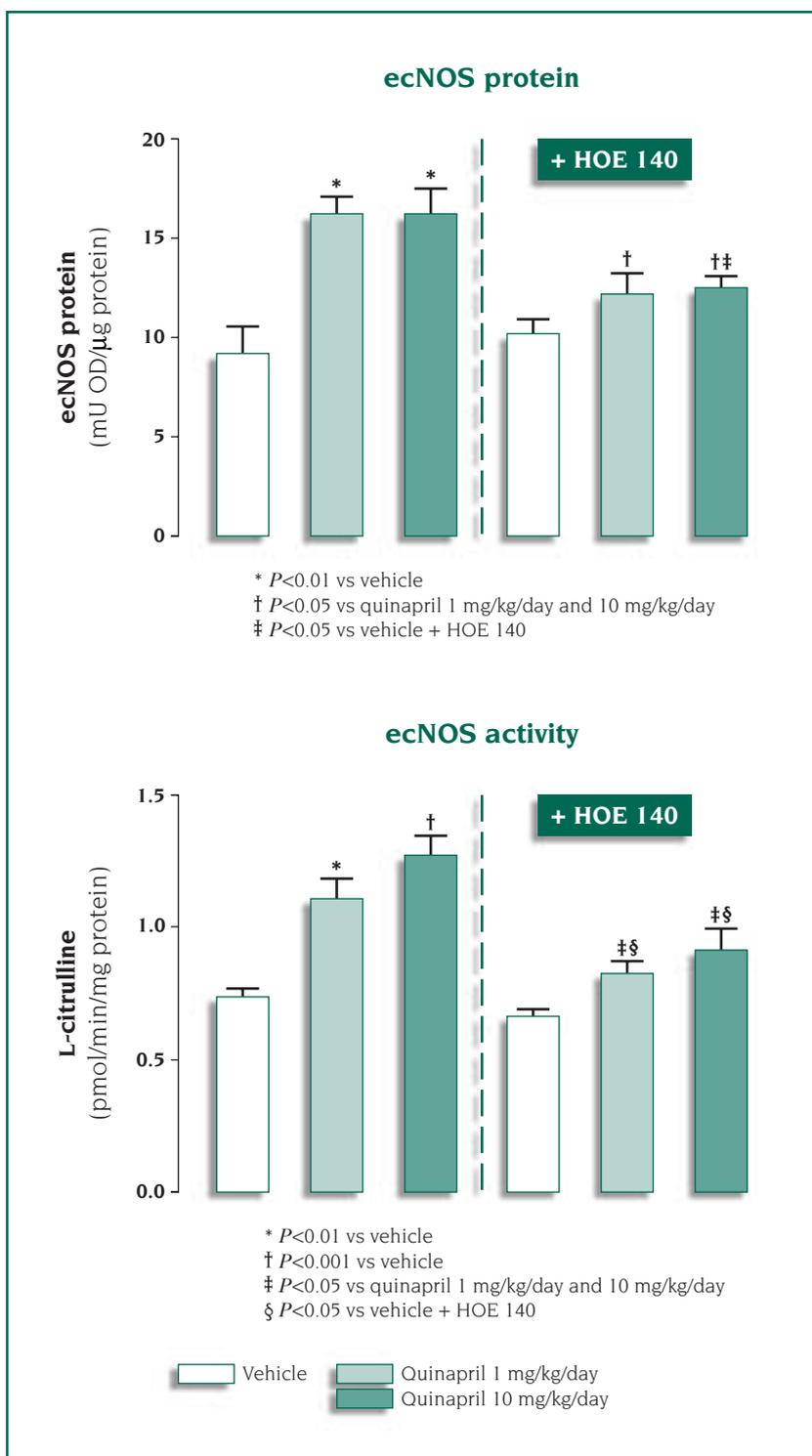


Figure 3. Endothelial constitutive nitric oxide synthase (ecNOS) protein expression (upper panel) and activity (lower panel), measured as L-citrulline production, in the rat aorta. Animals were treated with saline and quinapril, in combination with HOE 140, a bradykinin-receptor antagonist. An increase in both ecNOS protein expression and activity was observed after 7 days of quinapril treatment. This effect was partially reversed by the cotreatment with quinapril and HOE 140, suggesting that bradykinin plays an essential role in the ACE-inhibitor-induced modulation of NO production. OD, optical density (upper panel).



NO synthesis and eventually restore the impaired endothelium-dependent vasodilatation.

ACE INHIBITION IMPROVES ENDOTHELIAL FUNCTION VIA BRADYKININ—CLINICAL EVIDENCE

Chronic treatment with ACE inhibitors has a twofold benefit: it decreases the ratio of plasma AT II to AT I and increases the plasma level of bradykinin,¹⁶ resulting in improvement in vascular function. However, accurate measurement of bradykinin levels is technically difficult, due to its short half-life and high instability *ex vivo*. Therefore, the definition of the role of bradykinin in explaining the mechanism of action of ACE inhibitors has only recently been possible with the availability of the specific bradykinin B₂-receptor antagonist icatibant acetate, formerly known as HOE 140. Using icatibant, Hornig et al¹⁸ demonstrated that the flow-dependent endothelium-mediated vasodilatation of the radial artery induced in healthy volunteers by quinaprilat was indeed mainly related to an increase in endogenous bradykinin levels, confirming the hypothesis that accumulation of endogenous kinins is the major determinant for the hypotensive effect of ACE inhibitors. This effect is of particular importance only under flow-stimulated conditions, ie, during physical activity, as no beneficial effect was seen on radial artery diameter under resting conditions. However, in other vascular beds, ie, coronary resistance and epicardial conduit arteries, bradykinin has been shown to play a role in the regulation of the baseline tone, suggesting a different role of bradykinin throughout the vascular tree in humans and a possible mechanism for the benefit of ACE inhibitors in CAD.

A clinical study conducted in previously untreated patients with essential hypertension has demonstrated that perindopril normalized the remodeling process in subcutaneous small arteries, reducing the media-to-lumen ratio.¹⁹ Indeed, in such patients, the vascular structure of resistance vessels is known to be altered and an optimized treatment should consist not only in lowering blood pressure, but also in normalizing vascular structure. ACE-inhibitor treatment with perindopril caused an increase in lumen diameter of the small arteries, while the β -blocker atenolol had no effect, both drugs being effective in reducing blood pressure. A recent clinical study has demonstrated that bradykinin contributes to the short-term effects of ACE inhibition on systemic blood pressure in both normotensive and hypertensive subjects.²⁰ Indeed, the hypotensive effect of captopril was significantly attenuated after 4 hours by the coadministration of icatibant, and was similar to that obtained after the administration of losartan, an AT II subtype 1-receptor antagonist. In addition, icatibant significantly counteracted the increase in plasma renin activity observed in response to ACE inhibition, suggesting that increased bradykinin also plays a role in the renin response to captopril.

In patients with CHF, chronic ACE-inhibitor treatment has been shown to revert the impaired vasodilatation of peripheral vessels, improving skeletal muscle blood flow during physical exercise.²¹ An increase in local tissue levels of bradykinin and the consequent stimulation of NO release have been proposed as mechanisms mediating the reversal of endothelial dysfunction. In addition, an acetylcholine-induced increase in forearm blood flow was observed after 3 months of treatment with perindopril in patients

who improved clinically.²² In the same study, another marker of endothelial activation, the soluble vascular cell adhesion molecule-1 (VCAM-1), was significantly reduced after long-term ACE-inhibition.

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Is the endothelium an important therapeutic target?

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The vascular endothelium modulates vascular tone and the expression of a number of vascular genes mainly by producing vasoactive autacoids such as nitric oxide (NO) and the superoxide anion (O₂⁻). Hypertension, arteriosclerosis, and ischemic heart disease are all associated with dysregulation of endothelial cell function. This is related to an imbalance in the production of endothelial NO and vascular O₂⁻, which results in the shutdown or inactivation of intrinsic antiatherogenic processes. Clinical and experimental evidence indicates that angiotensin-converting enzyme (ACE: kininase II) inhibitors are able to halt the development of endothelial dysfunction, and, in certain situations, to restore the balance in vascular autacoid production.

Keywords: endothelium; endothelial dysfunction; angiotensin II; bradykinin; nitric oxide; atherosclerosis; ischemic heart disease; hypertension; ACE inhibitor

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The vascular endothelium plays a crucial role in the modulation of vascular tone, a function that is accomplished mainly by the synthesis and release of a number of vasoactive dilating substances, including NO, prostacyclin, and the endothelium-derived hyperpolarizing factor, as well as vasoconstricting substances, such as endothelin-1, prostaglandin H₂, and O₂⁻. It can be assumed that, in the healthy vasculature, a certain level of each of these compounds contributes to the maintenance of vascular tone. In vascular disease this delicate balance is disturbed, so that a decrease in the production of a vasodilator autacoid, such as NO, or an overproduction of a vasoconstrictor substance is thought to promote resetting of vascular tone to a permanently elevated level. While this simple model contains some degree of truth, the situation is more complicated, as endothelial autacoids, especially NO and O₂⁻, modulate the expression of genes that are implicated in the atherogenic process. For example, the expression of adhesion molecules (such as E-selectin, P-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1) and the chemokine monocyte chemoattractant factor-1, which are prerequisites for monocyte infiltration into the vascular wall, is suppressed by NO. A decrease in NO bioavailability in vivo is thought to occur mainly through an increase in the vascular production of O₂⁻, which scavenges NO, although a reduction in endothelial nitric oxide

synthase (eNOS) expression and elevated circulating levels of an endogenous eNOS inhibitor have also been reported (for review see ref 1).

ACE INHIBITORS AND NO/O₂⁻

On the basis of these considerations, it is evident that the development of a therapy that halts the development of endothelial dysfunction and/or restores the balance in vascular production of NO and O₂⁻ would be of considerable interest for the treatment of cardiovascular diseases. Accumulating experimental evidence suggests that angiotensin-converting enzyme (ACE) inhibitors are able to do just that. Moreover, recent evidence suggests that they possess additional properties that may modulate at least the acute effects of this class of compounds on the cardiovascular system.

SELECTED ABBREVIATIONS AND ACRONYMS

CHO	Chinese hamster ovary
eNOS	endothelial nitric oxide synthase
Erk	extracellularly regulated kinase
HOPE	Heart Outcomes Prevention Evaluation
QUIET	QUinapril Ischemic Event Trial
TREND	Trial on Reversing ENdothelial Dysfunction

ACE INHIBITORS AND ANGIOTENSIN II

Angiotensin II is one of the most potent endogenously produced vasoconstrictors and can accentuate its effects by stimulating the production of three additional vasoconstrictors, endothelin-1, prostaglandin H_2 , and O_2^- . Regarding vascular sources of O_2^- , both the endothelium and vascular smooth muscle contain membrane-bound oxidase(s) that utilize reduced nicotinamide adenine dinucleotide (NADH) and reduced nicotinamide adenine dinucleotide phosphate (NADPH) as substrates for electron transfer to molecular oxygen. These enzymes are, to a certain extent, similar to the neutrophil NADPH oxidase, with the exception that the vascular NADH/NADPH oxidase is a basally active, low-output enzyme, which does not exhibit bursts of activity following cell activation. The expression of NADH/NADPH oxidase in vascular smooth muscle cells is known to be increased within a few hours by subnanomolar concentrations of angiotensin II.² The subsequent increase in O_2^- underlies endothelial dysfunction (diminished vasodilator responsiveness to acetylcholine) in rats made hypertensive with angiotensin II, as the infusion of superoxide dismutase to inactivate O_2^- generated within the vasculature restores endothelium-dependent dilator responses.³ It is therefore tempting to suggest that ACE inhibitors could exhibit a beneficial effect by breaking this angiotensin II/ O_2^- potentiating loop. A decrease in vascular O_2^- production would, in turn, be expected to increase the half-life of endothelium-derived NO and give the appearance of restoring endothelial NO production. ACE inhibitors influence eNOS expression, and chronic ACE inhibitor therapy has been shown to enhance

eNOS expression and NO production in normotensive and spontaneously hypertensive rats. The mechanism underlying this effect is currently unknown, as little information is available regarding the effects of altered vascular O_2^- production on the expression of eNOS mRNA and protein. Interestingly, the massive increase in eNOS expression (in this case more than threefold) observed in rats treated with ramipril for 2 years was also associated with an increase in O_2^- production, an effect which may be the consequence of endothelial depletion of the essential eNOS cofactor tetrahydrobiopterin (H_4B).^{4,5} Such depletion of a cofactor may arise either as a consequence of the generation of peroxynitrite (the reaction product of NO and O_2^-), which is able to oxidize H_4B to dihydrobiopterin. Indeed, in the absence of H_4B , eNOS produces O_2^- rather than NO, and the administration of H_4B to hypercholesterolemic patients is reported to restore endothelial function.⁶ This mechanism may also be involved in the genesis of endothelial dysfunction, as H_4B alters O_2^- and NO release (and, therefore, probably ONOO⁻) in spontaneously hypertensive rats prior to the development of manifest hypertension.⁷

ACE INHIBITORS AND BRADYKININ

It is important to note that comparison of the effects of angiotensin II antagonists, renin inhibitors, and ACE inhibitors in the isolated working heart shows that only the ACE inhibitor is able to increase coronary blood flow.⁸ These and many other observations tend to suggest that it is the effect of ACE inhibition on bradykinin metabolism that underlies their beneficial effects on blood flow and NO production.⁹ Indeed, experimental evidence

has demonstrated that bradykinin and related kinins are continuously formed in the isolated heart and that ACE inhibitors elicit an approximately fivefold increase in kinin levels.¹⁰ This effect of ACE inhibitors on the heart is, as expected, dependent on kininogenase activity, and the source of this coronary bradykinin appears to be the endothelial cell layer, as its removal markedly attenuates basal and ACE inhibitor-induced kinin release.⁹ From the points mentioned above, it is clear that by inhibiting kininase II, ACE inhibitors could augment the effect of bradykinin on the endothelial cell.⁹⁻¹¹ It is, however, debatable whether enough bradykinin is available at the endothelial cell surface in the presence of a continuous flow to make this effect possible. Indeed, even if ACE inhibitors increase the local concentration of vascular bradykinin, it is unclear how this can restore endothelium-dependent vasodilatation to acetylcholine, which is routinely used in experimental and clinical assessments of endothelial function.

NOVEL ACE-INDEPENDENT EFFECTS OF ACE INHIBITORS

While generally accepted to potentiate responses to bradykinin,⁹⁻¹¹ ACE inhibitors directly elicit responses in the isolated heart, arterial segments, and cultured endothelial cells.¹² Whether the differences observed reflect the rate of endogenous bradykinin generation in the various preparations is controversial, and additional factors may determine ACE-inhibitor responsiveness. One such factor is fluid shear stress, since ACE inhibitors such as ramiprilat and moexiprilat have been reported to elicit a relaxation in superfused coronary artery rings, although neither of these inhibitors affects the tone of arterial rings



incubated under static conditions in an organ chamber.¹³ In addition, a response to ACE-inhibitor application can be detected in otherwise nonresponding preparations if these were previously acutely exposed to bradykinin.¹⁴ Whether these observations indicate that ACE inhibitors are able to liberate bradykinin stored by, or on, endothelial cells remains to be elucidated, but the efficiency of ACE inhibitors in eliciting a relaxant response does appear to be dependent on a certain basal concentration of bradykinin in the vicinity of target cells. Whether the fluid shear stress present in the superfusion systems studied is a stimulus for the production of endothelium-derived bradykinin also remains to be clarified. Shear stress-induced NO production has indeed been proposed to be mediated by endothelium-derived bradykinin, which, in an autocrine loop, stimulates the B₂ receptor, thus increasing [Ca²⁺]_i and activating eNOS.¹⁵ However, the activation of eNOS by fluid shear stress is now known to be mediated by a completely different intracellular signaling pathway than that activated in endothelial cells by bradykinin.¹⁶ Much of the experimental evidence for a role for bradykinin in the response to shear stress was interpreted under the assumption that a specific activation of the B₂ kinin receptor could be antagonized by the B₂ receptor antagonist icatibant. However, the B₂ receptor has a constitutive or basal activity, and icatibant is actually an inverse agonist at this receptor, which means that its basal activity is inhibited and the receptor is stabilized in a totally inactive form.¹⁷ Thus, the effects of icatibant on cellular responses actually reflect both the inhibition of inherent receptor activity as well as that induced by an increase in agonist concentrations. This situation has

almost certainly led to false positive results, ie, a biological or physiological role for the bradykinin has been proposed on the basis of an observed response to icatibant. Recent experimental evidence suggests that a signaling cross-talk exists between ACE and the B₂ kinin receptor, such that ACE inhibitors can elicit icatibant-sensitive responses (inositol 1,4,5-trisphosphate production, increase in [Ca²⁺]_i, activation of eNOS, and vasodilatation) by a mechanism distinct from their ability to inhibit ACE.^{9,18,19} Although pharmacological studies using various vascular preparations suggested that ACE inhibitors may exert a direct effect on the B₂ kinin receptor, this has only recently been confirmed by monitoring the sequestration of the B₂ receptor into endothelial caveolae, which are specialized microdomains of the plasma membrane.¹⁹ The ACE inhibitor ramiprilat was found to attenuate the basal flux or cycling of the kinin receptor through caveolae as well as the bradykinin-stimulated sequestration into caveolae. This latter effect was distinct from enzyme inhibition, as the synthetic ACE substrate hippuryl-L-histidyl-L-leucine, at a concentration that blocks the degradation of bradykinin by ACE, failed to affect B₂ receptor sequestration.¹⁹ In addition to this effect on the physical translocation of the receptor protein, ACE inhibitors are able to reactivate endothelial B₂ receptors that have been desensitized by exposure to high concentrations of bradykinin, resulting in an immediate secondary increase in inositol 1,4,5-trisphosphate, [Ca²⁺]_i and the activation of the extracellularly regulated kinases Erk1 and Erk2.¹⁹ A similar reactivation of B₂ signaling by enalaprilat was recently reported in response to Chinese hamster ovary (CHO) cells transfected with both ACE and the B₂

receptor.¹⁸ As the expression of ACE is reported to be essential for ACE inhibitors to reactivate B₂ kinin receptor signaling, it seems likely that some form of cross-talk exists between ACE and the B₂ receptor. One possibility is that ACE inhibitors may act in the opposite manner to icatibant and stabilize the B₂ receptor in a G-protein-coupled or basally active form. While this hypothesis is at the moment purely speculative, ACE inhibitors and peptides, such as angiotensin,¹⁻⁷ which bind to either of the two active sites on ACE, enhance bradykinin-induced responses mediated by the Gα_i subunit of heterotrimeric G-proteins. Moreover, ACE inhibitors can also directly activate Gα_i in the absence of bradykinin (author's unpublished observation). Taken together, these data provide the first clear evidence that ACE inhibitors exert effects on endothelial cells that cannot be simply attributed to the inhibition of kinase II activity and the accumulation of locally produced bradykinin.

CLINICAL EVIDENCE THAT ACE INHIBITORS RESTORE ENDOTHELIAL FUNCTION

Perhaps the most convincing evidence to date for an effect of ACE inhibitors on the endothelium is the Trial on Reversing ENdothelial Dysfunction (TREND), in which 6 months treatment with quinapril was found to improve endothelial function in subjects who had a manifest single or double coronary artery disease.²¹ As ACE inhibitors have proven to be of clinical benefit in congestive heart failure, and endothelial dysfunction is thought to be of importance in the early stages of atherosclerosis and in the pathophysiology of myocardial ischemia, a clinical trial was designed to determine whether ACE inhibitors could reduce the inci-

dence of ischemic events in patients with established coronary artery disease. The Quinapril Ischemic Event Trial (QUIET) was the first prospective, double-blind, placebo-controlled trial to investigate the long-term antiatherosclerotic effects of ACE inhibition. Unfortunately, no significant beneficial effect of quinaprilat could be detected on either ischemic incident prevention or stenosis development.²² The outcome of QUIET is in contrast to the results of a number of smaller trials in which ACE inhibition was reported to selectively improve endothelium-dependent, but not endothelium-independent, dilation and to abolish abnormal epicardial vasomotion in patients with endothelial dysfunction related to heart failure and coronary artery disease.^{23,24} The latest clinical trial, Heart Outcomes Prevention Evaluation (HOPE), with ramipril, was such a resounding success that the trial was stopped prematurely in view of the significant decrease in incidence of cardiovascular events in patients deemed to be at high risk of myocardial infarct, stroke, and complications associated with diabetes.²⁵

IS THE ENDOTHELIUM AN IMPORTANT THERAPEUTIC TARGET?

The answer is yes, as the endothelium plays a central role in vascular homeostasis, and the balance in endothelial NO/O₂⁻ production is clearly involved in the regulation of pro- and antiatherogenic vascular gene expression. Despite the disappointing results obtained to date in some of the larger clinical trials, there is a wealth of experimental evidence showing that prolonged treatment with ACE inhibitors restores endothelial function and, in some cases, reverses medial thickening and the number of monocytes detected within the subintima.²⁶

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ACE inhibition in ischemic heart disease: what is the relevance of the control of the neuroendocrine response?

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Neuroendocrine systems are central to key heart disease processes such as cardiovascular remodeling, fibrosis, apoptosis, paradoxical coronary constriction, and salt-and-water retention. The neuroendocrine response to severe ischemia leads to increased arterial pressure and afterload, and compounds myocardial oxygen debt. Acute ACE inhibition in pacing-induced ischemia modulates vasoconstrictor hormone secretion, while chronic ACE inhibition appears to improve myocardial ischemia via long-term neurohormone-mediated structural effects. Thus, inhibition of angiotensin II formation itself inhibits the sympathetic system, and possibly also aldosterone and endothelin secretion. Crucially, it also reduces the breakdown of bradykinin. Long-term improvement in coronary structure and endothelial function during chronic ACE inhibition normalizes the paradoxical vascular response to neuroendocrine stimuli.

Keywords: angiotensin-converting enzyme; neuroendocrine response

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Neurohormonal activation is pivotal to the development of heart failure and its progression to end-stage cardiac disease. Although many different mechanisms underlie the development of the disease, circulating or local tissue neurohormonal systems are central to the more important processes, including cardiovascular remodeling, fibrosis, apoptosis, inappropriate vasoconstriction, and salt-and-water retention. In advanced stages, the picture of neurohormonal and peptide activation includes the sympathetic system, the renin-angiotensin system, aldosterone, vasopressin, endothelin, the natriuretic peptides, and cytokines. In the early stages of failure and in the preceding phase of asymptomatic ventricular dysfunction, an increase in circulating catecholamines, aldosterone, and natriuretic peptides is observed. Of these, the natriuretic peptides are the first to increase and, besides their hemodynamic effects, may serve to temporarily inhibit the activation of vasoconstriction and growth-promoting neurohormones, such as norepinephrine and angiotensin II.

It is as yet unclear whether this picture differs between ischemic and nonischemic cardiomyopathy, either in the symptomatic or asymptomatic phase of heart failure.

As there is now accumulating evidence that myocardial ischemia per se stimulates certain neurohormones, one might hypothesize that heart failure due to ischemic cardiomyopathy is accompanied by more intense neurohormonal activation.

WHAT IS THE EVIDENCE THAT MYOCARDIAL ISCHEMIA LEADS TO NEUROHORMONAL STIMULATION?

The sympathetic system

Global ischemia in a rodent Langendorff model results in progressive cardiac norepinephrine release, which starts approximately 10 minutes after the onset of ischemia.¹ This time interval corresponds with a reversal of the uptake-1 mechanism in nerve endings, from uptake

SELECTED ABBREVIATIONS AND ACRONYMS

CATS	Captopril And Thrombolysis Study
ANP	atrial natriuretic peptide
SAVE	Survival And Ventricular Enlargement Trial
SOLVD	Studies Of Left Ventricular Dysfunction



to release, under the influence of increased Na^+/H^+ exchange and sodium uptake in the nerve ending. Of interest, in the acute phase of ischemia, there is net uptake of norepinephrine by the heart due to prejunctional inhibition of norepinephrine release, most likely the result of increasing levels of adenosine. In humans, pacing-induced myocardial ischemia also leads to a reversal of cardiac norepinephrine release to net uptake during and immediately after the ischemic episode, at a time that hypoxanthine, a breakdown product of adenosine, is significantly increased in the venous effluent of the ischemic area.^{2,3}

With continued severe ischemia resulting in myocardial infarction, norepinephrine release from the infarcted area continues with, ultimately, a complete loss of cardiac norepinephrine levels during the first days of coronary occlusion.

In patients with an acute infarct, plasma and urinary catecholamine levels rise within 1 hour of the onset of symptoms, depending on the magnitude and severity of the insult. This observation appears to be relatively consistent and has been observed in several studies conducted from the sixties to the eighties.⁴⁻⁶

In contrast, whether circulating catecholamine levels, which reflect the activity of the sympathetic system, rise during exercise- or stress-induced ischemia, has been less clear for many years. Early studies did not find significantly elevated levels over and above those induced by exercise per se, possibly due to the low sensitivity of early analytic techniques.

However, more recently, marked increases in circulating norepinephrine levels have been observed, correlat-

ed with the severity of ischemia, and significantly higher than circulating catecholamine levels in patients with coronary artery disease who, despite similar exercise levels, did not become ischemic.

Similar observations have been made in patients who developed myocardial ischemia during incremental atrial pacing (*Figure 1, see next page*). Whereas this form of testing does not affect circulating catecholamines in the absence of ischemia, patients who developed severe ischemia significantly increased arterial and coronary venous norepinephrine and epinephrine levels, by 70% and 40%, respectively, whereas patients with less ischemia also activated their sympathetic system, but to a lesser extent and for a shorter period.⁷ Importantly, changes were not due to the stress of anginal pain, as similar levels of ischemia resulted in equal increases in norepinephrine in both symptomatic and asymptomatic patients.⁸

The renin-angiotensin system

In the same studies, more severe ischemia also activated the renin-angiotensin system. In patients with severe ischemia, arterial angiotensin II levels rose by 50% (*Figure 1*).⁷ No changes were observed in the coronary venous effluent. Neither was angiotensin II affected in milder forms of ischemia. Activation of the renin-angiotensin system has been reported minutes after coronary occlusion, with progressive increases in both renin and angiotensin II.^{9,10} Nephrectomy prevented this neurohormonal activation. Whether a reduction in cardiac output and renal perfusion in severe ischemia or the concomitant sympathetic stimulation causes this activation of the renin-angiotensin system is unknown. The direct effect

is a significant increase in the strong vasoconstrictor neurohormone angiotensin II. As the sympathetic system is activated simultaneously, arterial vasoconstriction is likely to occur.

Natriuretic peptides

In the model of pacing-induced ischemia, both arterial and coronary venous atrial natriuretic peptide (ANP) levels increase markedly, and cardiac ANP release is augmented.¹¹ Cardiac ANP release is most pronounced 1 minute after pacing, when the effect of fast atrial contractions can be discarded, suggesting a direct effect of ischemia and ischemia-induced left ventricular (LV) filling pressures. Increased ANP levels also accompany exercise-induced stress in patients with ischemic LV dysfunction and significantly correlate with ischemia-induced changes in ejection fraction.¹² As such, ANP could be a marker of ischemic cardiac dysfunction. Whether it has additional effects, counteracting the vasoconstricting effects of norepinephrine or angiotensin II, is unclear.

ISCHEMIA-INDUCED NEUROHORMONAL ACTIVATION AND VASOCONSTRICTION

In humans, neurohormonal stimulation such as that occurring during short periods of stress- or exercise-induced ischemia definitely results in systemic vasoconstriction, leading to increased arterial pressures and afterload. As such, it is likely to increase myocardial oxygen demand, further augmenting the ischemic episode that initiated the neurohormonal response. Importantly, simultaneous, extensively enhanced cardiac ANP release and subsequent increased arterial ANP do not counteract this vasoconstrictive effect.

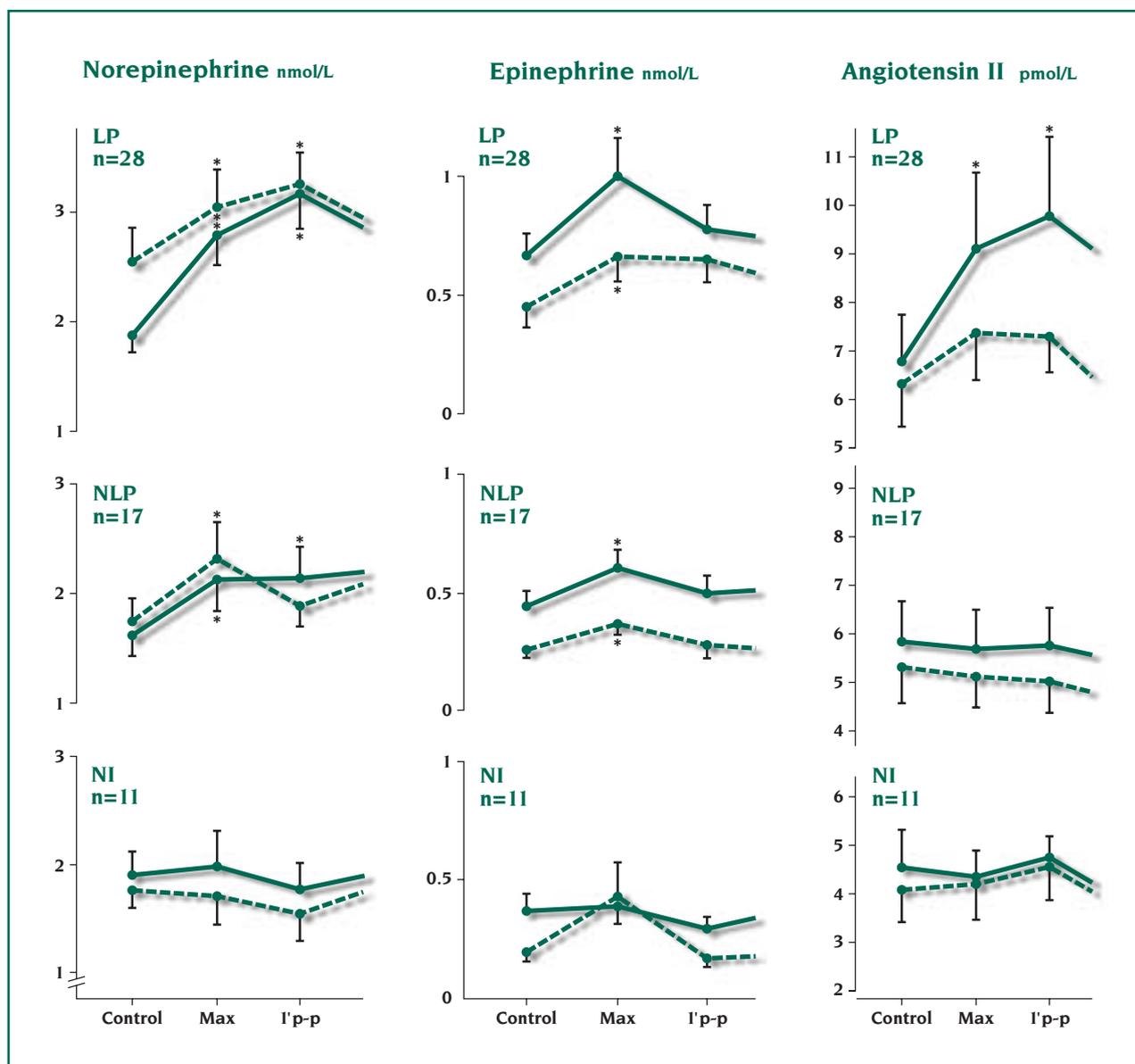


Figure 1. Effect of incremental atrial pacing on arterial (solid line) and coronary venous (broken line) norepinephrine, epinephrine, and angiotensin II in patients who develop severe ischemia (LP), mild ischemia (NLP), and patients who, despite similar pacing levels, do not become ischemic (NI). In the latter group, pacing does not affect neurohormones. In contrast, in both mild and severe ischemia, norepinephrine and epinephrine levels are significantly increased and, in severe ischemia, arterial angiotensin II levels are also increased. * $P < 0.05$ vs control; Max, maximal pacing heart rates; 1'p-p, 1 minute post pacing.

Modified from ref 7: Remme WJ, Kruissen HACM, Look MP, Bootsma M, De Leeuw PW. Systemic and cardiac neuroendocrine activation and severity of myocardial ischemia in humans. *J Am Coll Cardiol.* 1994;23:82-91. Copyright © 1994, The American College of Cardiology.

Indirect evidence also suggests that coronary vasoconstriction ensues following myocardial ischemia. During exercise and angina, the lesion area of stenotic coronary arteries constricts, whereas normal coronary segments dilate. The presence of abnormal endothelial function, as

demonstrated by vasoconstriction after intracoronary acetylcholine, appears to be a prerequisite. Although in these studies neurohormonal activation was not measured, the observation that other stimuli that activate the sympathetic system—such as the cold pressor

test—also result in vasoconstriction in coronary segments with abnormal endothelial function, whereas normal coronary segments dilate, strongly suggests the involvement of neurohormonal, ie, sympathetic, activation.¹³ That sympathetic activation indeed underlies coronary



vasoconstriction during ischemia is suggested by an enhanced coronary vasoconstricting response to acute β -blockade in these circumstances, most likely the result of sympathetic activation of unopposed α -adrenergic receptors.¹⁴

PREVALENCE OF ISCHEMIA-INDUCED NEUROHORMONAL ACTIVATION

As neurohormonal activation and its sequelae depend on the severity of ischemia, this becomes more of an issue in clinical conditions in which severe ischemia predominates. Thus, severe ischemia during stress or exercise leads to greater activation and more pronounced systemic vasoconstriction.

Cardiac sympathetic nervous activity is increased in patients with unstable angina compared with those with stable angina.¹⁵ One might speculate that this increase leads to enhanced sympathetically induced coronary vasoconstriction and contributes to progressive myocardial ischemia in these patients.

Neurohormonal activation is also more pronounced in patients with LV dysfunction compared with patients with normal function, despite a similar degree of myocardial ischemia,¹⁶ as measured by myocardial lactate production and ischemic electrocardiographic changes. During pacing-induced ischemia, the increase in arterial and coronary venous norepinephrine and epinephrine levels is approximately two times greater in LV dysfunction, and so is the effect on systemic vascular tone. Moreover, in LV dysfunction, arterial angiotensin II levels increase, even in moderate ischemia, but not in patients with normal function. Is this observation clinically relevant?

ACE INHIBITION AND MYOCARDIAL ISCHEMIA—EFFECTIVE IN PATIENTS WITH HEART FAILURE AND/OR ASYMPTOMATIC LV DYSFUNCTION

Several large, controlled studies, such as the Survival And Ventricular Enlargement trial (SAVE) and Studies Of Left Ventricular Dysfunction (SOLVD), designed to evaluate the long-term effect of angiotensin-converting enzyme (ACE) inhibition on mortality and morbidity in patients with heart failure or asymptomatic LV dysfunction, observed a significant, unexpected effect on myocardial ischemia in terms of reduction in the frequency of myocardial infarction and unstable angina.^{17,18} It is tempting to consider at least a partial anti-ischemic effect of the ACE inhibitors through modulation of neurohormonal activation and prevention of secondary systemic and coronary vasoconstriction during ischemia, as the latter is pronounced in this patient group, at least during stress-induced myocardial ischemia. Unfortunately, in SAVE and SOLVD, the anti-ischemic effect occurred relatively late after the institution of therapy, on average after 6 to 12 months. This suggests different mechanisms are involved through which ACE inhibitors reduce ischemia. Rather than acute, hemodynamically linked properties, long-term structural effects seem more likely. That this may indeed be the case is suggested by a large array of animal and human studies, indicating that ACE inhibitors: (i) have antiproliferative and antiatherogenic effects on the vascular wall; (ii) improve abnormal endothelial function; (iii) restore abnormal fibrinolytic balance in coronary artery disease; and (iv) prevent cardiac remodeling and dilatation following an insult or pressure overload, thereby restoring

myocardial wall stress and reducing oxygen demand. Alone or in concert, these properties may eventually lead to a structural, anti-ischemic effect and potentially to secondary prevention of coronary artery disease. Where do neurohormones fit in?

ACE INHIBITORS REDUCE MYOCARDIAL ISCHEMIA THROUGH NEUROHORMONAL MODULATION

ACE inhibition affects different neurohormonal systems. First, the conversion of angiotensin I to angiotensin II is inhibited. The resultant reduction in angiotensin II has a marked inhibitory effect on the sympathetic system at different levels. Potentially, the reduction in angiotensin II should further reduce aldosterone and endothelin secretion. However, the relevance of these neurohormones in acute ischemia is not well known.

In addition to the effect on angiotensin II, ACE inhibition also reduces the breakdown of bradykinin, which in broad terms may be viewed as the counterpart of angiotensin II, having antigrowth effects, improving endothelial dysfunction, and inducing marked vasodilation. Bradykinin appears pivotal to the improvement of abnormal endothelial function by ACE inhibitors, as these effects are prevented by concomitant administration of a bradykinin B₂ receptor antagonist.¹⁹ Similarly, the antiremodeling effect of ACE inhibition in cardiac models of hypertrophy is counteracted by bradykinin receptor antagonists.²⁰ Whether bradykinin interferes with ACE inhibitor modulation of ischemia-induced neurohormonal activation is less clear. Immediately following full ACE inhibition (eg, by 90% to 95%), sympathetic activation initially increases, as measured by

ACE and neuroendocrine response - Remme

circulating norepinephrine levels. This effect does not seem temporarily related to ACE inhibitor-induced vasodilation, which suggests a bradykinin-related effect. Effects are small and of short duration, however, with a peak effect after 5 to 10 minutes, tapering off thereafter. To test the acute effect of ACE inhibition on ischemia-induced neurohormonal activation, a model of incremental atrial pacing was used, with two identical tests, the first in the untreated condition and the

second, approximately 1 hour later, 15 minutes after intravenous administration of the ACE inhibitor under study or placebo. This allows the effects to be studied under stable, resting, and supine conditions, and reproducible hemodynamic, metabolic, and neurohormonal effects to be obtained.²¹ With sufficient ACE inhibition achieved (approximately 90% and an approximate 50% reduction in circulating angiotensin II levels), several ACE inhibitors, eg, perindo-

prilat and enalaprilat, significantly modulated the increase in arterial norepinephrine and epinephrine levels and resulted in a change from cardiac norepinephrine uptake to the normal net release pattern (Figure 2).^{11,16,22} In addition, in those studies in which an increase in arterial angiotensin II was found during the untreated pacing test, this was similarly prevented following ACE inhibition. Moreover, ACE inhibition reduced ANP release during ischemia (Figure 3).¹¹ In contrast,

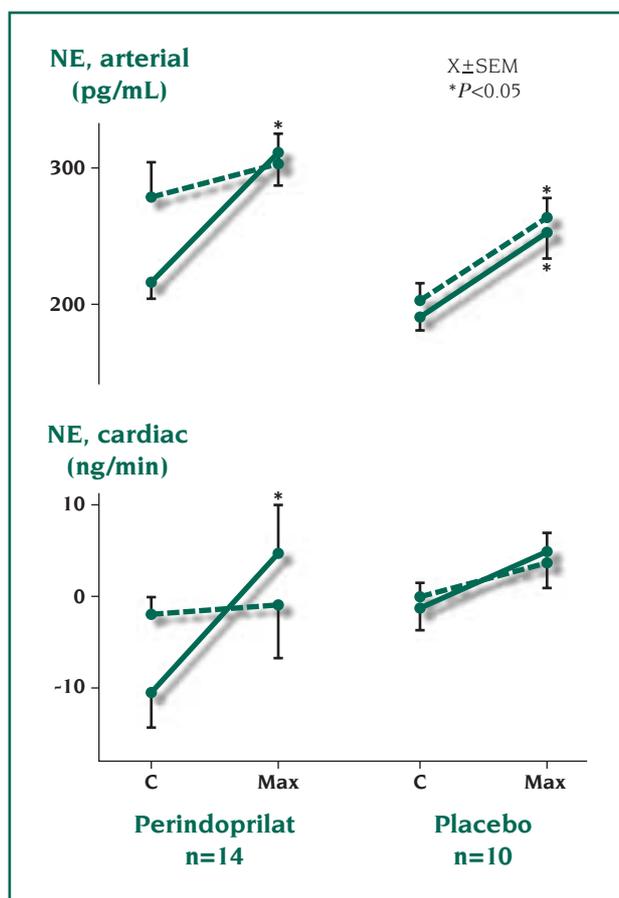


Figure 2. Effect of ACE inhibition with perindoprilat on arterial norepinephrine (NE) levels and cardiac NE balance during two sequential incremental atrial pacing stress tests, the first before intervention (solid line), the second after intervention (broken line). Ischemia-induced neurohormonal activation, ie, increase in arterial norepinephrine, is identical during pacing before and after placebo. In contrast, perindoprilat significantly reduces the increase in arterial norepinephrine levels. C, control; Max, maximal pacing. Values are $x \pm SEM$; * $P < 0.05$.

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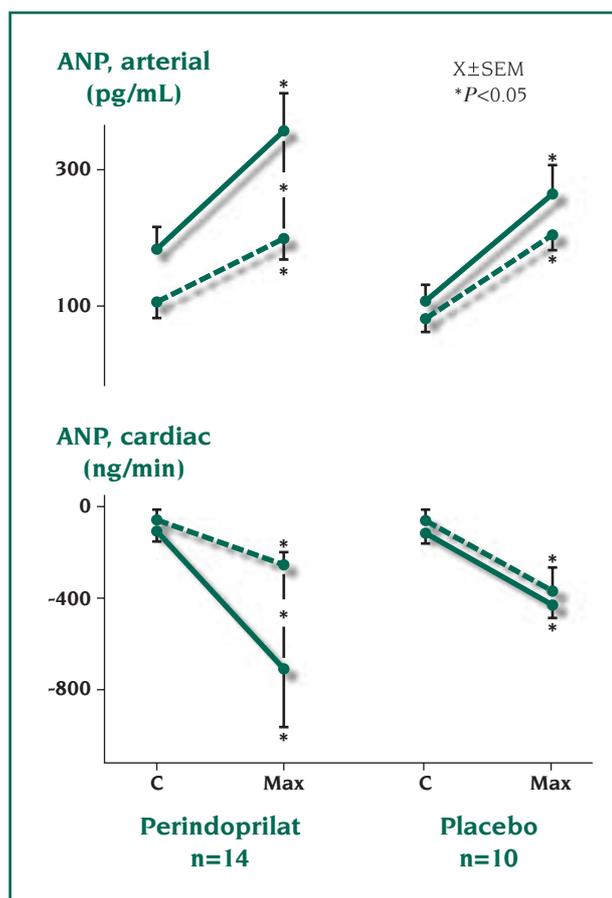


Figure 3. Effect of ACE inhibition with perindoprilat on arterial atrial natriuretic peptide (ANP) levels and cardiac ANP balance during two sequential incremental atrial pacing stress tests, the first before intervention (solid line), the second after intervention (broken line). Ischemia-induced neurohormonal activation, ie, increases in arterial ANP, is identical during pacing before and after placebo. In contrast, perindoprilat significantly reduces the increase in arterial ANP levels. C, control; Max, maximal pacing. Values are $x \pm SEM$; * $P < 0.05$.

Reproduced from ref 11: Remme WJ. Effect of ACE inhibition on neurohormones. Eur Heart J. 1998;19(suppl J):J16-J23. Copyright © 1998, The European Society of Cardiology.



activation of these neurohormones and peptides was reproducible in placebo-treated patients. Consequently, this modulation of vasoconstricting neurohormones prevented the systemic vasoconstriction observed during the control test. In a similar type of study, ACE inhibition has also been shown to reduce ischemia-induced coronary vasoconstriction.²³

As, therefore, myocardial oxygen demand is less, and supply is improved, ACE inhibition should result in less ischemia. This is indeed what has been observed in those studies in which ACE inhibition was sufficient, ie, approximately 90%, but not observed or observed to a lesser extent when the acute inhibition of ACE was smaller.

Of note, the anti-ischemic effect of ACE inhibition under these conditions is more pronounced in patients with LV dysfunction than in those with normal function, and follows a more pronounced reduction in circulating neurohormones and subsequent greater reduction in systemic vasoconstriction and myocardial oxygen demand, despite a similar degree of ischemia under baseline stress conditions.²⁴

THE ANTI-ISCHEMIC EFFECTS OF ACE INHIBITION— IS THE CONTROL OF NEUROENDOCRINE RESPONSE RELEVANT?

Ischemia reduction through modulation of neurohormonal activation very likely contributes to the overall anti-ischemic profile of ACE inhibitors. When and to what extent is difficult to assess, as neurohormonal measurements during ACE-inhibitor intervention are required, but are unlikely to be carried out under normal clinical conditions.

Clinical studies in which neurohormones were determined during ischemia and ACE-inhibitor therapy other than with the agents mentioned above are not available. Hence, we can only speculate. As there appears to be no short-term benefit from orally administered ACE inhibitors in patients with stable angina, it is unlikely that significant neurohormonal modulation during ischemia and subsequent prevention of systemic and coronary vasoconstriction play an important role under these conditions.

be related to a reduction in ventricular volumes. However, in that study, anti-ischemic effects were already apparent after 3 months at a time when changes in volumes were moderate, which suggests that mechanisms other than an effect on wall stress are involved. Modulation of ischemia-induced neuroendocrine activation may play a role in patients with persistent ischemia after myocardial infarction, particularly as ventricular dysfunction is present. It is tempting to speculate that over time this modulation

Placebo-controlled study	ACE inhibitor	Objective criteria	Angina
Daly et al, 1985 ²⁵	captopril	+	+
Strozzi et al, 1987 ²⁶	captopril	+	+
Jackson et al, 1987 ²⁷	cilazapril	-	-
Rietbrock et al, 1988 ²⁸	enalapril	+	?
Vogt et al, 1988 ²⁹	enalapril	-	-
Gibbs et al, 1989 ³⁰	enalapril	-	-
Odenthal et al, 1991 ³¹	benazepril	-	-
Van den Heuvel et al, 1995 ³²	enalapril	-	-

Table I. Variable anti-ischemic efficacy of short-term ACE inhibition in stable angina.

Several studies have been performed comparing an ACE inhibitor versus placebo for only a few weeks (2-6 weeks), and using exercise tests or 24-hour Holter recordings to test the anti-ischemic properties of the ACE inhibitor under study. Nearly all were negative in the sense that there were neither ischemic electrocardiographic changes nor were anginal symptoms reduced (*Table I*).²⁵⁻³² In contrast, Sogaard et al demonstrated that long-term treatment with ACE inhibition in patients with persistent ischemia after myocardial infarction significantly reduced the frequency of ischemic events and improved exercise tolerance.³³ These authors suggested that the reduction in ischemic events could

might lead to progressively less vasoconstriction, as, concomitantly, endothelial function improves. Of interest, in the long-term follow-up of the Captopril And Thrombolysis Study (CATS),³⁴ in which late anti-ischemic effects were reported, when the double-blind medication was stopped after 1 year, more ischemic events were reported in patients who were previously on captopril compared with placebo-treated patients. Again, this could be due to an abnormality in cardiovascular structure and function, eg, a repeated disturbance of endothelial function or a rebound phenomenon resulting from interrupted modulation of neurohormonal activation during ischemia.

However, since neurohormones were not measured in these studies, the latter can only be assumed. Nevertheless, the possibility remains that modulation of neurohormonal activation and subsequent improvement in coronary and systemic vasomotor tone during ischemia may be one of the mechanisms through which chronic ACE inhibition improves myocardial ischemia. It is postulated that this effect gains in importance over time following a long-term improvement in coronary structure and endothelial function during chronic ACE inhibition, which then leads to normalization of the abnormal vascular response to neurohormonal stimuli.

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Surfing the Heart

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 European Agency for the
Evaluation of Medicinal Products

www.eudra.org/emea.html

This is the official site of the **European Agency for the Evaluation of Medicinal Products** (EMA), and offers a wealth of resources and material, organized in a simple and user-friendly way. The design and graphics are far more advanced than those of its American counterpart, the Food and Drug Administration site (www.fda.gov). One of the site's strong points is the timely availability of information, in particular of assessments of new drugs and reports of ad hoc committees, accessed in the *Documents* section. The home page also provides links to a *What's New* section, featuring the latest publications and a calendar of EMA events; an *Other Sites* section with an extensive list of European and worldwide related sites, and even a *Forum* where regulatory issues can be discussed. For the lazy surfer, a box at the top left of the screen automatically scrolls announcements of coming events.



Centers for Disease Control
and Prevention

www.cdc.gov

Although infectious diseases are the main activity of the **Centers for Disease Control and Prevention**, the site also focuses on other topics. The possibility of downloading the guidelines produced by the CDC as material free for public use is what makes this site distinctive. Although the graphic appearance of the downloaded documents may appear unsophisticated (ie, pure unenriched text), its scientific value is indisputable! Furthermore, the guidelines can be searched by topic, title, etc. Of particular interest is the section dedicated to the surveillance and prevention of chronic diseases and individual risk factors, in which cardiovascular diseases are prominently featured.

 The Internet Drug Index
www.RxList.com

RxList - The Internet Drug Index provides information on more than 4000 drugs. These can be looked up by name, pharmaceutical category, manufacturer, and even US prescription code. The information provided encompasses pharmacological and clinical data and key characteristics of drugs. A "virtual" textbook that every physician should bookmark!



Reuters Health

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Reuters is one of the biggest press agencies in the world, with a first-rate internet coverage of news related to medicine and health. Articles are listed by category including clinical cases, epidemiology, and public health. All news items have their sources clearly indicated. All drugs cited have a hypertext link to the Reuters Clinical Pharmacology Database, for further information. This database can also be accessed through a powerful search engine at the bottom of the screen, alongside with a MEDLINE search engine. Part of the information is only accessible by subscribed members of the press. Although the actual scientific relevance of this service to physicians is probably modest, occasional surfing of the *Medical News*, *Industry Briefing*, and consumer-oriented *Health eLine* sections will provide useful insights into the perception of health problems by the nonspecialist press agencies.

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Icons of Cardiology

Starling's other observations

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Ernest Henry Starling (1866-1927) is best known to cardiologists for his "Law of the Heart," which describes the dependence of cardiac performance on end-diastolic volume. Starling's research addressed a then puzzling observation, that stroke volume remains constant when afterload and heart rate are varied over a wide range.^{1,2} This led to the discovery that end-diastolic volume controls the work of the heart,^{3,4} which was the centerpiece of Starling's Linacre Lecture given at Cambridge University in 1915.⁵

The clinical impact of Starling's Law of the Heart is seen in the 1917 Lumleian Lecture, published by Sutherland,⁶ which cites Starling's work in describing how moderate dilatation of the heart, by increasing output, is "advantageous." This marked a paradigm shift in cardiology because the great clinician scientists of the 19th century had emphasized the maladaptive features of the cardiac dilatation found in patients who died of heart failure.⁷ Sutherland writes: "*Usually... dilatation has been ascribed to weakness of the wall of the left ventricle; but on the other hand, it may simply be an attempt on the part of the heart to overcome the... difficulties of the circulation.*"⁶ Starling's original research reports on

the heart,¹⁻⁴ include four additional observations that are usually attributed to later investigators (*Table I*). One reason that these descriptions of important physiological principles were overlooked for several decades is that they are contained within textual passages, not illustrated by figures, and in some cases buried in footnotes.

STARLING'S OTHER OBSERVATIONS

1. Application of the Law of Laplace to the heart
2. Unloading of the ventricle during ejection
3. The instability of the descending limb of the Starling Curve
4. The "family" of Starling Curves

Table I.

THE LAW OF LAPLACE

The direct proportionality between wall stress and ventricular radius (the Law of Laplace), had been overlooked by most physiologists until the early 1950s.⁸ Starling, however, clearly understood this relationship when he wrote: "*If the cavity of each ventricle were perfectly spherical the tension on each muscle fiber would be greater the greater capacity of the sphere, assuming the intracardiac pressure to remain constant.*"³ This statement is in a footnote, which suggests that the Law of Laplace was well known at the time.

UNLOADING OF THE VENTRICLE DURING EJECTION

Commenting on the functional consequences of the relationship between cavity radius and wall stress described above, Starling notes that the walls of the ventricle are unloaded during ejection; he writes: "*Since under normal circumstances the capacity of the heart cavities becomes less during the contraction of the ventricle, a constant tension on the muscle fibers would tend to produce a pressure in the heart cavities that would increase steadily as the emptying proceeded and their capacity became smaller. If this were the case, a plateau, ie, a period of constant pressure in the ventricular cavities, would be associated with a gradually diminishing load off the individual muscle fibers as they contracted, a condition which would be favorable for obtaining the maximum mechanical performance out of the contracting muscle.*"³

The energetic consequences of decreased wall stress during ejection became apparent the following year when Starling's student, C. Lovatt Evans, found that less extra oxygen is consumed when stroke volume is increased than during a proportional increase in ejection pressure.⁹ One mechanism for this difference is that the fall in wall stress during ejection allows potential energy stored in the series elasticity to be used to eject blood under pressure into the aorta and pulmonary artery. This is a major reason for the low energy cost of ejec-

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Starling in his laboratory (1924). Photos by Louis N. Katz. Reproduced courtesy of: Katz AM. *Molecular biology in cardiology, a paradigmatic shift*. *J Mol Cell Cardiol*. 1988;20:355-366. Copyright © 1988, Academic Press.

tion because this energy would have been degraded to heat had the heart not been allowed to empty. The clinical relevance of this phenomenon was not recognized until the mid-1950s, when cardiac energy expenditure and oxygen consumption were observed to depend on heart rate and ejection pressure, but to be virtually independent of stroke volume.^{10,11}

INSTABILITY OF THE DESCENDING LIMB

For more than 40 years after Starling published his Law of the Heart, the failing heart was generally assumed to operate on the descending limb, where increasing venous return decreases ejection.^{12,13} Starling, however, recognized that this is an unstable situation, writing: *“So long as the heart continues to beat and maintain a circulation, its output must be equal to the venous inflow... It is evident that the heart could not continue to throw out more blood than it received, and if it threw out less blood, each beat would leave the heart fuller than before, so that in a very short time the heart*

*would be overdilated and the circulation would come to an end.”*³

Although the impossibility of achieving a steady state on the descending limb of the Starling curve was restated in 1965,¹⁴ some textbooks and educators continued to teach that heart failure is due to overstretching of cardiac fibers into the mid 1980s, an error that provided a model for the *“insidious tendency of misconceptions to compound each other within a general climate of oversimplification.”*¹⁵

THE FAMILY OF STARLING CURVES

The “modern” description of the shift from one Starling curve to another, now referred to as a change in myocardial contractility, is generally attributed to Sarnoff.¹⁶ However, length-independent changes in cardiac performance had been documented since the beginning of the 20th century, and were well known to Starling. He points out, for example, that inadequate coronary flow reduces the work of the heart at any end-diastolic volume. In discussing the deterioration of the isolated heart-

lung preparation, which Starling calls *fatigue*, he writes: *“In the fatigued heart a greater diastolic distension is necessary to produce a given output of blood at each systole than is required in the fresh heart beating at the same rate.”*³ Starling's awareness of the “family” of curves is apparent in his statement: *“We may assume that (during fatigue) the liberation of chemical substances responsible for the tension change becomes less either from diminution of their concentration within the cell or deficient building up between each contraction... But the relation between the length of the muscle fiber and the tension set up at its contraction remains as before.”*⁴ Starling even describes a hypothetical experiment in which a skeletal muscle generates two length-tension curves: a normal curve, and a curve that is depressed because of “moderate fatigue.”

CONCLUSIONS

It is interesting to speculate as to why the concepts listed in *Table I*, all of which are clearly mentioned in

Starling's other observations - Katz

Starling's original research reports, came to be overlooked by his immediate successors. Perhaps the major cause is the overarching importance of the Law of the Heart, which showed that dilatation not only has maladaptive consequences (now called "remodeling"), but is also an adaptive physiological mechanism that adjusts cardiac output to equal the venous return. Starling's appreciation of the Law of Laplace may have been overlooked by his successors because application of this Law to the heart was once so obvious as to need no mention; as a result, later workers overlooked this important relationship altogether. Decreased wall stress during ejection was known to physiologists during the middle of the 20th century. I recall Louis N. Katz, my father, mentioning this to me in 1953; however, he was not aware that utilization of energy stored in the series elasticity to pump blood is an important reason for the low energy cost of ejection, even though this explained the greater efficiency of increasing ejection than increasing pressure, a topic that we explored together in the early 1950s.¹⁷ I became aware of this fact a few years ago, during a conference with first-year medical students.

The commonly held view that the failing heart operates on the descending limb illustrates the unfortunate human tendencies for oversimplification and excessive reliance on authority.¹⁵ More puzzling is the failure of Starling's successors to recognize the interplay between length-dependent changes in cardiac performance and changes in myocardial contractility (the "family" of Starling curves), which Starling had understood and described. This failure of later scientists to see what was obvious to Starling is a reminder of how easy it is to lose one's way in science and medicine. One can only wonder what is being overlooked today.

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ACE in Ischemic Heart Disease

Summaries of Ten Seminal Papers

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①

Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension

M.H. Alderman and others. *N Engl J Med.* 1991

②

Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions

S. Yusuf and others. *Lancet.* 1992

③

The emerging concept of vascular remodeling

G.H. Gibbons, V.J. Dzau. *N Engl J Med.* 1994

④

Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection

E.M. Lonn and others. *Circulation.* 1994

⑤

Effects of captopril on ischemic events after myocardial infarction. Results of the Survival And Ventricular Enlargement trial

J.D. Rutherford and the SAVE Investigators. *Circulation.* 1994

⑥

Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease

F. Diet and others. *Circulation.* 1996

⑦

Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND Study

G.B. Mancini and others. *Circulation.* 1996

⑧

Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. HEART Study Investigators

D.E. Vaughan and others. *Circulation.* 1997

⑨

Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials

The ACE Inhibitor Myocardial Infarction Collaborative Group. *Circulation.* 1998

⑩

Angiotensin-converting enzyme inhibitors

N.J. Brown, D.E. Vaughan. *Circulation.* 1998

Selection of seminal papers by

S. Yusuf, MBBS, Dphil, FRCPC, FACC; E. Lonn, MD, FRCPC, FACC
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Highlights of the years by **P.B. Garlick**

Division of Radiological Sciences - Guy's Hospital -
London SE1 9RT - UK

Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension

M.H. Alderman, S. Madhavan, W.L. Ooi, H. Cohen, J.E. Sealey, J.H. Laragh

N Engl J Med. 1991;324:1098-1104

This was one of the first prospective human studies to suggest an important role of the renin-angiotensin system in the etiology of myocardial infarction. Consequently, it has been in the forefront of the discussion of a number of angiotensin-converting enzyme (ACE) inhibitors trials that have postdated this investigation. The rationale was based on the numerous animal experiments that had detailed the cerebral, cardiac, renal, and vascular damage caused by infusions of angiotensin II.

Alderman and colleagues determined the pretreatment renin-sodium profiles of 1717 subjects (mean age 53 years; 36% white; 67% men) with mild-to-moderate hypertension and followed them up for 8.3 years. The renin-sodium profile of each individual was obtained by plotting plasma renin-sodium activity against urinary excretion of sodium. Renin-sodium profiles were classified as either high (12.3%; 211 patients), normal (55.9%; 960 patients), or low (31.8%; 546 patients). Those with a high renin-sodium profile had a slightly higher diastolic blood pressure and were more likely to be young, male, and white. Other baseline characteristics were reported as being identical. The antihypertensive treatment being given consisted of diuretics and β -blockers with no significant difference in mean blood pressure between treatments. No ACE inhibitors were prescribed.

During the 8.3 years of follow up there were 27 myocardial infarctions. The incidence per 1000 person-years was 13 among the subjects with a high renin-sodium profile, 5.3 among those with a normal profile, and 3.3 among those with a low profile. The independent relationship between the renin-sodium profile and the risk of myocardial infarction was confirmed by multivariate analysis that controlled for concomitant factors known to influence the rate of infarction. Renin-sodium profile remained an independent predictor of outcome in a best-fit model of risk factors important in the development of myocardial infarction. Somewhat surprisingly, blood pressure lost its independent predictive value under these circumstances. The principal finding that patients with high renin-sodium profiles were at a greater risk of myocardial infarction, with

greatest discriminative value among men, whites, and otherwise low-risk patients, gained little acceptance in routine clinical care. Principal among the reasons for this was the fact that the investigation was not powered to adequately look at the occurrence of myocardial infarction (total of just 27 events). However, at the time of publication, β -blockers had just been shown both to reduce plasma renin activity and also to be useful in secondary prevention of myocardial infarction. Consequently, one of the important questions raised in this paper speculated as to the potential efficacy of ACE-inhibitors in preventing myocardial infarction.

The publication of the Studies Of Left Ventricular Dysfunction (SOLVD) trial 18 months later showed that high-risk patients with left ventricular impairment had a reduced incidence of myocardial infarction as a result of ACE inhibition, which was significantly greater than might be predicted on the basis of blood pressure-lowering effects alone. In previous trials of antihypertensive therapy, a 5-to-6-mm Hg reduction in diastolic blood pressure (DBP) was associated with a 14% reduction in acute coronary events. In the SOLVD trial, the reduction in DBP with treatment was just 4 mm Hg, yet a 23% reduction in myocardial infarction was observed. Nevertheless, this analysis, coupled with an associated evaluation of the Survival And Ventricular Enlargement (SAVE) trial in patients after myocardial infarction treated with captopril, was essentially retrospective. The first prospective data in this area have just emerged from the Heart Outcome Prevention Evaluation (HOPE) study, which confirmed the ability of ramipril therapy to prevent myocardial infarction in a wide range of high-risk patients.

1991

Antarctica is declared to be a
“continent for peace and science”;
Mike Powell leaps into the record books with
an 8.95-m-long jump; and the British actress
Dame Peggy Ashcroft dies, aged 83



Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions

S. Yusuf, C.J. Pepine, C. Garces, H. Pouleur, D. Salem, J. Kostis, C. Benedict, M. Rousseau, M. Bourassa, B. Pitt

Lancet. 1992;340:1173-1178

In this article, the Studies Of Left Ventricular Dysfunction (SOLVD) trial investigators address the issue as to whether ACE inhibition reduces the risk of the development of acute coronary events in high-risk patients with low ejection fractions. While most ACE-inhibitor trials of that time were focusing on the hemodynamic and structural effects of treatment, few were concerned with possible antithrombotic or antiatherosclerotic benefits.

Eligible patients without overt heart failure and not requiring therapy were entered into the SOLVD Prevention trial (4228 patients); those with overt heart failure requiring treatment, but without preexposure to ACE inhibitors were entered into the Treatment trial (2569 patients). Patients were then randomized to receive double-blind treatment with either enalapril (titrated up to 10 mg twice daily) or placebo, and followed for an average of 40 months. The primary outcome measures of death and hospital admission for heart failure indicated significant benefits in the active treatment groups of each study arm. The predefined secondary end point of myocardial infarction appeared to be reduced, leading to a detailed post-hoc evaluation of a variety of related end points, including some that had not been predefined, such as unstable angina.

Risk reductions for myocardial infarction were similar in both trials separately as well as in combination, where 362 (10.6%) patients in the placebo group had a myocardial infarction as compared to 288 (8.5%) in the enalapril group (risk reduction 23%; 95% confidence interval [CI] 11%-34%; $P < 0.001$). There were also significant reductions in admissions for unstable angina observed in both trials combined; 595 (17.5%) patients in the placebo group were admitted compared with 499 (14.7%) in the enalapril group (risk reduction 20%; 95% CI 9%-29%; $P < 0.001$). These differences showed a trend towards benefit by 6 months, with the event curves widening to a significant difference with long-term follow-up.

Yusuf et al's paper demonstrated significant reductions in acute coronary events and cardiac mortality in patients with low ejection fractions treated with enalapril. The risk

of major ischemic events was reduced by about 22%. Development of unstable angina or myocardial infarction in this group of patients significantly increased the risk of death and hospital admission for heart failure. This study suggests that preventing major ischemic events should be integral in the management of patients with heart failure, whether overt or subclinical. Previous trials had reported conflicting results on the effects of ACE inhibitors on the severity of stable angina. These trials were small and of very short duration. While the beneficial effects of enalapril on cardiac failure are seen early on, the effect on acute coronary episodes is unlikely to be due to an immediate effect such as a reduction in preload or afterload. The delay in the reduction of events more closely parallels that seen with statin therapy, where plaque stabilization and other nonhypcholesterolemic effects seem to occur after some months.

The benefits of reduction in acute coronary events could not be explained solely by the lowering of blood pressure, suggesting that ACE inhibitors might block other adverse effects of raised angiotensin II. These may include coronary vasoconstriction, an antiproliferative effect on vascular smooth muscle, prevention of progression of atherosclerosis and myocardial hypertrophy, and favorable effects on blood clotting and endothelial function. The SOLVD data suggested that other populations of high-risk patients might also benefit from ACE inhibition, as later confirmed by Yusuf in the prospectively designed and conducted Heart Outcome Prevention Evaluation (HOPE) study.

1992

Fidel Ramos is elected
President of the Philippines;
Margaret Thatcher visits the Falklands on the
10th anniversary of the end of the conflict;
and the Argentinian composer
Astor Piazzolla dies, aged 70

The emerging concept of vascular remodeling

G.H. Gibbons, V.J. Dzau

N Engl J Med. 1994;330:1431-1438

An accompanying review (*see page 115*) relates to a paper dealing with the structural and hemodynamic remodeling of the heart that follows acute myocardial infarction. The authors of this paper, being at that time at the forefront of research into many aspects of vascular remodeling, describe the central role of the endothelium as a pathophysiological organ. Vascular remodeling is identified as an active and adaptive process dependent on a dynamic interaction of locally produced factors and hemodynamic stimuli. Furthermore, as the endothelium is constantly exposed to these factors, it is proposed as having a key role in the development of vascular pathologies. Wall shear stress is the tractive force on the endothelial cells induced by blood flow, and relates both to the flow velocity and luminal diameter. The vessel remodels itself to maintain a constant level of shear stress, reshaping vessel wall diameter as necessary. Different pathways mediate the response of the endothelium to shear stress or pressure, activating metabolic ion channels and, subsequently, intracellular mechanisms involving gene transcription for factors such as nitric oxide (NO) synthase and platelet-derived growth factor. This suggests potential mechanisms by which increased arterial pressure may promote vascular hypertrophy. Endothelial cells thus mediate vascular tone, in addition to hemostasis, inflammation, lipid metabolism, cell growth, programmed cell death, and migration. The interactions between the endothelial cells and the structural matrix in which they are embedded have also been shown to be important in vascular remodeling. This, therefore, involves a counterbalance of deconstruction and reconstruction, with the endothelial cell in a central regulatory role.

Vascular remodeling may also have an important role in a wide spectrum of other cardiovascular disorders. Vein grafts, used in coronary artery bypass grafting, suffer two traumas. They are removed from a low-pressure system, and placed in a high-pressure system, as well as sustaining injury from tissue ischemia and surgical handling. High intraluminal pressure results in wall thickening, while shear stress is reduced by dilatation (arterialization of vein grafts). This increased shear stress is paralleled by an increase in

endothelial production of factors such as transforming growth factor β 1 (TGF- β 1) and NO. Any cause of pulmonary hypertension results in a similar remodeling response of the pulmonary vasculature. Following endothelial cell injury in other arterial beds, vessels develop thickening of the smooth muscle medial layer. There is also increased production of matrix proteins within the vessel wall. A thickened media, reduced luminal diameter, and an increased extracellular matrix are also features of hypertensive vessels in the systemic circulation. All of these (mal-)adaptive responses can be inhibited in animal models using inhibitors of elastase and collagen synthesis as well as endothelin-receptor antagonists. These drugs, among which bosentan, are close to completing phase III clinical trials and may soon be available for clinical use.

Atherosclerosis most frequently develops in areas of disturbed flow (or high shear stress), such as at the bifurcations from which subsidiary arterial branches emerge. Vascular remodeling influences the natural history of atherosclerotic lesions by regulating the infiltration of mononuclear cells. The authors postulate that vascular stenoses increase shear stress, which in turn induces an increase in vessel radius to normalize the shear stress. If this compensatory mechanism fails, the lesion may progress in an unstable way, with a resulting acute vascular syndrome, eg, myocardial infarction or stroke. The process of vascular remodeling is thus considered to be fundamental to many vascular diseases. This paper firmly relegates to the past the notion of the endothelium as a passive or minimally active vascular lining.

1994

Iceland celebrates 50 years as
an independent republic;

A 79-year-old US golfer drops dead in
Massachusetts after shooting his first hole-in-one;

The British actor and playwright John Osborne
dies, aged 65 years



Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection

E.M. Lonn, S. Yusuf, P. Jha, T.J. Montague, K.K. Teo, C.R. Benedict, B. Pitt

Circulation. 1994;90:2056-2069

Angiotensin-converting enzyme (ACE) inhibitors have found an increasing role in the management of a variety of cardiovascular disorders. By blocking the renin-angiotensin (RAS) system, ACE inhibitors have cardiovascular protective effects that reduce the risk of ischemic events in patients at high risk of developing major vascular events. This paper looked at the proposed mechanisms of these cardioprotective and vasculoprotective effects and goes on to examine genetic and epidemiological studies and evidence from randomized clinical trials.

ACE inhibition of angiotensin II reduces afterload and preload and, subsequently, ventricular wall stress. In the context of myocardial infarction, this translates to a reduction in early infarct expansion and hence wall stress. With blockade of angiotensin II-mediated vasoconstriction, there is increased coronary blood flow, improving myocardial oxygen supply and demand. Activation of the RAS results in cardiac myocyte and vessel wall hypertrophy and a restructuring of the extracellular matrix, increasing left ventricular mass. Inhibition of ACE can reverse this left ventricular hypertrophy. ACE inhibition also prevents angiotensin II-mediated vascular smooth muscle cell growth and proliferation and migration of inflammatory cells, processes that are involved in atherogenesis. However, improvement of endothelial function, as well as potential antithrombotic effects, may also be mediated by potentiating the effects of bradykinin and nitric oxide. Other potential benefits of ACE inhibitors may include effects on myocardial ischemic preconditioning, potential antiarrhythmic effects, protection from plaque rupture, and antioxidant properties.

Lonn et al, citing the study by Alderman et al (*see accompanying review*) in men with mild-to-moderate hypertension, stress the 5.3-fold increase in relative risk of myocardial infarction among subjects with high vs low renin-sodium profiles after 8.3 years. Furthermore, early studies of the deletion polymorphism of the ACE gene suggested that homozygous individuals have higher ACE levels and an associated increased risk of myocardial infarction. This association, has however, not been substantiated in much

larger studies recently presented at the European Society of Cardiology Congress. The Survival And Ventricular Enlargement (SAVE) study and the Studies Of Left Ventricular Dysfunction (SOLVD) retrospectively looked at the use of ACE inhibitors in patients with impaired left ventricular function, both symptomatic and asymptomatic, and found that the incidence of acute coronary events (myocardial infarction and unstable angina) was significantly reduced. The need for revascularization procedures for patients treated with captopril in the SAVE trial was also reduced. The magnitude of the reduction in these major ischemic events was substantially larger than that expected from a short-term, modest reduction in blood pressure, suggesting ACE inhibitor therapy has beneficial properties above and beyond the established hemodynamic effects of these agents.

Lonn et al point out that the Acute Infarction Ramipril Efficacy (AIRE), Fourth International Study of Infarct Survival (ISIS-4), and (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-III) GISSI-3 trials have all provided evidence of beneficial effects of ACE inhibitors initiated early in the course of myocardial infarction, but also suggested that the short duration of follow up did not permit useful conclusions as to whether major ischemic events might be prevented. In this context, later data from the AIRE Extension study demonstrated that patients randomized to ramipril had significantly fewer fatal myocardial infarctions after 5 years of follow-up. This observation is now supported by the positive findings of the Heart Outcome Prevention Evaluation (HOPE) study.

1994

Tomiichi Murayama becomes Japan's first socialist Prime Minister since 1948; Belgian Willy Claes is appointed Secretary-General of NATO; and US teenager Michael Fay gets four strokes of the cane in Singapore, for vandalism

Effects of captopril on ischemic events after myocardial infarction. Results of the Survival And Ventricular Enlargement trial. SAVE Investigators

J.D. Rutherford, M.A. Pfeffer, L.A. Moye, B.R. Davis, G.C. Flaker, P.R. Kowey, G.A. Lamas, H.S. Miller, M. Packer, J.L. Rouleau, et al.

Circulation. 1994;90:1731-1738

The effects of the angiotensin-converting enzyme (ACE) inhibitor captopril on total mortality after myocardial infarction (MI) was first assessed among the 2331 patients recruited to the Survival And Ventricular Enlargement (SAVE) trial, all of whom had an ejection fraction of <40% on radionuclide scanning, but no symptoms of heart failure. After a relatively long follow-up period of 42 months, a relative risk reduction of 19% was observed. Furthermore, the use of captopril was reported to result in a reduction in further major ischemic events.

The current paper is a retrospective analysis focused on these recurrent ischemic events, their impact on subsequent mortality, and the effect of captopril on this clinical end point. A requirement for revascularization at any time after randomization was also compared between the two groups. Univariate determinations of risk factors for recurrent MI were ascertained using a Cox proportional-hazard model. Analysis revealed that 14% of the patients had a recurrent (fatal or nonfatal MI) and also that this was the strongest predictor of subsequent mortality, conferring an approximate sevenfold increased risk. Captopril therapy resulted in a significant 25% relative reduction in risk of recurrent MI (95% confidence interval [CI], 5%-40%) and attenuated the risk of death from recurrent MI by 32% (95% CI, 4%-51%). It was also observed that the recurrence of MI was independent of baseline left ventricular function, which therefore suggested a mechanism of action that was not purely hemodynamic. An important limitation of these data concerned the definition of myocardial infarction that was prespecified as the occurrence of a new Q-wave, being later changed to an end point—committee-validated event (based on history, ECG, and enzyme changes). Ultimately, neither of these definitions formed the basis for the analysis, but rather a third clinical item (opinion of attending physician) was used. Importantly, the two earlier definitions failed to demonstrate a statistically significant effect of therapy.

Additional support for the concept advanced in this paper came from the review of cardiac revascularization rates. Captopril conferred a 24% relative risk reduction in the

need for revascularization, thereby suggesting a direct anti-ischemic effect. However, there was no impact observed on recurrent hospitalization for unstable angina, which may have related to the difficulty in defining this end point retrospectively. These findings correlate with post-hoc data from the SOLVD trials (*see accompanying review*). As the benefits reported by the SAVE Investigators on the prevention of MI was evident despite the use of other concomitant therapies, this suggests a novel mechanism of protection. Given our current understanding of the triggers of acute MI and the role played by fragile plaque rupture, it is suggested that in addition to the known antihypertensive effects of ACE inhibitors, improvement in endothelial function and fibrinolytic activity may also be of importance.

As with the SOLVD retrospective analysis of the occurrence of acute coronary events, these data should be viewed more as hypothesis-generating rather than as firm evidence of benefit. The dependence of the conclusions on reclassification of events represents an important limitation. Nevertheless, this study was important as it advanced the case for prospective randomized trials specifically designed to evaluate the ability of ACE inhibitors to prevent myocardial infarction. Three trials (Heart Outcome Prevention Evaluation [HOPE], European trial on Reduction Of cardiac events with Perindopril in stable coronary Artery disease [EUROPA], and Prevention of Events with ACE inhibitors [PEACE]) have each sought to evaluate patients without left ventricular dysfunction. Of these, only the results of the HOPE study are currently known, demonstrating impressive benefit from ramipril in prevention of death, myocardial infarction, stroke, and the need for revascularization.

1994

Russian tanks and artillery roll into Chechnya;
Iran's production of caviar falls by 10%
due to pollution and poaching;
and US actor Telly Savalas, alias Kojak,
dies, aged 70



Increased accumulation of tissue ACE in human atherosclerotic coronary artery disease

F. Diet, R.E. Pratt, G.J. Berry, N. Momose, G.H. Gibbons, V.J. Dzau

Circulation. 1996;94:2756-2767

Diet et al's descriptive histological study was designed to demonstrate how tissue angiotensin-converting enzyme (ACE) might be implicated in the atherosclerotic process. Immunohistochemical techniques were used to detect ACE in 100 coronary artery segments taken from recently explanted hearts at the time of cardiac transplantation. A fluorometric assay was used for quantifying ACE activity. Coronary artery segments were categorized in accordance with the American Heart Association vascular lesion classification system (Class I, nonatheromatous; Class II, fibro-fatty plaque; Class III, fibrous plaque; Class IV, advanced lesion). The histological features of the plaques were described with particular attention to areas of relatively high ACE immunoreactivity.

Advanced plaques showed evidence of increased vascularization, with the endothelium of these vasa vasorum microvessels demonstrating prominent ACE immunoreactivity. Numerous macrophages with high ACE immunoreactivity were also apparent in the advanced atherosclerotic plaques. Diet et al concluded that because macrophages were a major cell type containing ACE, the enzyme was implicated in the chronic inflammatory process evident in advanced plaques. They also demonstrated that angiotensin II immunoreactivity colocalized with ACE in areas of high macrophage content, and therefore appeared to be implicated in the inflammatory process. However, this particular analysis was only carried out on 1 patient (who was not on ACE-inhibitor therapy). Expression of ACE was also seen to be greater in macrophages that had transformed to lipid-laden foam cells. This was further evaluated *in vitro* by treatment of THP-1 cells with phorbol, which induced differentiation into adherent macrophage-like cells, and in turn correlated with a threefold increase in ACE activity. A further twofold increase in ACE activity was observed following treatment with phorbol plus acetylated low-density lipoprotein (LDL). This suggests a role of oxidized LDL in the activation of ACE expression. The study concluded that intimal endothelial cells express ACE as would be expected, but, in addition, inflammatory cells and plaque neovasculature (both of which are features of more advanced

atherosclerotic lesions) express ACE to an even greater degree. Clearly, further additional mechanisms are involved in plaque destabilization and rupture, and indeed the role of ACE in this situation may in fact be beneficial. The authors discuss potential pathological mechanisms by which angiotensin II may promote the development of atherosclerosis: (i) stimulation of the expression of adhesion molecules by endothelial cells, an important first step in the progression to atherosclerosis; (ii) chemotactic properties (it stimulates the growth and migration of smooth muscle cells); and (iii) formation of superoxide radicals *in vitro*. While offering no real data on the implication of angiotensin II, this paper implies a pathological role for ACE, suggesting favorable effects from its inhibition. ACE inhibitors may have a further beneficial role in the modulation of endothelial function by potentiating the effects of bradykinin, nitric oxide, and prostacyclin. Possibly the two most interesting developments in the last few years have been the recognition of the importance of inflammatory mechanisms in triggering acute coronary events, coupled with therapeutic efforts to produce plaque stabilization. This paper suggests a plausible mechanism by which ACE inhibitors might beneficially interact with the inflammatory process to prevent the occurrence of myocardial infarction. Nevertheless, these observations remain imperfect in themselves despite the attractiveness of the story. The exact mechanism(s) by which ACE inhibition is able to prevent acute myocardial infarction is likely to remain as much a mystery as is the mechanism by which these and other drugs save lives after myocardial infarction.

1996

A Thai monk convicted of killing a
British backpacker is sentenced to death;
Susan Sarandon wins a Best Actress Oscar for her
role in "Dead Man Walking";
and Haing Ngor, Cambodian star of "The Killing
Fields," is shot dead in Los Angeles

Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease: the TREND* Study

G.B. Mancini, G.C. Henry, C. Macaya, B.J. O'Neill, A.L. Pucillo, R.G. Carere, T.J. Wargovich, H. Mudra, T.F. Lüscher, M.I. Klibaner, H.E. Haber, A.C. Uprichard, C.J. Pepine, B. Pitt

Circulation. 1996;94:258-265. Published erratum appears in *Circulation*. 1996;84:1490

Mancini and colleagues hypothesized that angiotensin-converting enzyme (ACE) inhibitors might confer a beneficial effect on coronary ischemic events, by influencing endothelial function in favor of vasodilation. In a randomized, parallel-group, placebo-controlled, double-blind study including 129 patients, they then sought to test this hypothesis. Quantitative angiography was used to measure the vasodilator / vasoconstrictor response to intracoronary acetylcholine infusion following 6 months of quinapril therapy and to compare responses with those seen following 6 months administration of placebo. This test is designed to detect endothelial dysfunction that results in failure of the normal endothelial cell muscarinic receptor-stimulated release of nitric oxide (that would have induced vasodilatation), thereby unmasking direct muscarinic stimulation of vascular smooth muscle cells, and hence coronary vasoconstriction.

The mean difference in the vasoconstrictor response at 6 months for patients randomized to placebo or quinapril was first compared. Thereafter, the changes in response in the two groups over 6 months were also contrasted. To aid the analysis, two categorical responses were also defined, representing either a 5% improvement in response or a >5% deterioration in response. Following both doses of acetylcholine, quinapril therapy resulted in a significantly lower occurrence of the vasoconstrictor response at 6 months ($P < 0.014$). The net change from baseline improved in the quinapril group, whereas there was no net change in the placebo group ($P < 0.002$). The categorical responses also demonstrated an attenuation of vasoconstriction in the treatment group.

Other predictors of improved endothelial function were included in a logistic regression model, including smoking status, stenosis severity, blood pressure, sex, initial response to acetylcholine, and lipid values. Interestingly, quinapril therapy was the only significant predictor of a vasoconstrictor response demonstrated. These results support the role of ACE inhibitors in the modification of endothelial function and are consistent with a reduced

level of angiotensin II, shifting the balance of endothelial constrictors and dilators in favor of vasoconstriction. Angiotensin II is implicated in the activation of endothelin I and also bradykinin degradation, resulting in reduced nitric oxide and prostacyclin levels. Harmful endothelial effects may also be mediated through the production of superoxides, which is stimulated in vitro by angiotensin II.

With good reason the authors apply their findings to explain the action of ACE inhibitors in reducing ischemic events even though endothelial dysfunction is often viewed as early evidence of atheroma formation, and plaque rupture as a much later development. To be consistent with the timing of observations from the Survival And Ventricular Enlargement (SAVE), Studies Of Left Ventricular Dysfunction (SOLVD), and Heart Outcome Prevention Evaluation (HOPE) trials, it would be necessary to postulate a plaque-stabilizing effect resulting from improved endothelial function. Alternatively, one might postulate that coronary artery spasm was acting as a trigger for the development of acute myocardial infarction in at least a proportion of patients, or that global improvement of endothelial function throughout the body through blood pressure reduction was indirectly resulting in less plaque rupture. However, repeated suggestions that prevention of myocardial infarction by ACE inhibition is achieved by mechanisms above and beyond blood pressure reduction focus interest on other novel effects such as those described here.

*Trial on Reversing ENdothelial Dysfunction.

1996

WHO sets up a task force
to combat worldwide obesity;
3 billion television viewers watch Muhammad Ali,
aka Cassius Clay, open the Atlanta Olympics;
and Marcel Carné, the French film director,
dies, aged 90



Effects of ramipril on plasma fibrinolytic balance in patients with acute anterior myocardial infarction. HEART Study Investigators

D.E. Vaughan, J.L. Rouleau, P.M. Ridker, J.M. Arnold, F.J. Menapace, M.A. Pfeffer

Circulation. 1997;96:442-447

Vaughan and colleagues wished to evaluate the theory that angiotensin-converting enzyme (ACE) inhibitors might have a favorable effect on fibrinolytic balance. If shown to be true, this might represent one of the many potential mechanisms by which this therapeutic class helps to prevent acute coronary events. Fibrinolytic balance is influenced by the relative quantities and activities of tissue plasminogen activator (TPA) and plasminogen activator inhibitor (PAI-1), which are continuously being synthesized and metabolized by vascular endothelial and smooth muscle cells. Epidemiological data suggest that elevated levels of PAI-1 in the period immediately after a myocardial infarction (MI) are an indicator of future coronary risk. Consequently, if ACE inhibitors were shown to be able to attenuate this rise in PAI-1, this would offer support to the concept that treatment would attenuate thrombotic events. Of further interest in this regard is the observation that PAI-1 levels appear to correlate with plasma aldosterone and renin activity. Activation of the renin-angiotensin axis may therefore be seen as an appropriate reaction to blood loss, as clot formation is enhanced and blood pressure is supported.

The Healing and Early Afterload Reduction Therapy (HEART) study was a double-blind placebo-controlled trial designed to examine the effect on ventricular remodeling after anterior MI of different dosages and timings of ACE-inhibitor therapy. Patients were randomized within 24 h to placebo or either low-dose ramipril (0.625 mg per day) or full-dose ramipril (1.25 mg to 10 mg per day). At day 14, placebo patients were also started on ramipril therapy based on the perceived need for this agent in all patients. Importantly, recruitment to the study was stopped early when additional trial data indicated benefits from early initiation of full-dose ACE inhibition. However, this study also constituted a prospective investigation of the effect of ramipril on fibrinolytic balance. To facilitate this, blood samples were obtained on day 1 and 14 following the index infarction from which TPA and PAI-1 levels plus activity were measured. For comparison, paired blood samples were also obtained from 120 healthy volunteers.

At day 14 after MI, PAI-1 antigen levels and PAI-1 activity were lower than at day 1. However, PAI-1 antigen levels were 44% lower in the ramipril group as compared with the placebo group ($P=0.004$), paralleling PAI-1 activity, which was 22% lower ($P=0.02$). Plasma TPA antigen showed a similar though statistically not significant trend. When the molar ratios of these two proteins were compared, the ramipril group demonstrated a balance favoring lysis in comparison with placebo. In fact, the molar ratio of PAI-1/TPA did not change significantly in the treatment group, whereas the ratio increased in the placebo group. A dose-dependent effect of ramipril was not observed.

As the magnitude of reduction in PAI-1 observed in the treatment group was comparable with the differences in PAI-1 activity associated with increased risk of MI, the authors conclude that this mechanism may explain the beneficial effect of ACE inhibitors of recurrent MI. However, the study was not designed to explore the chronic effects of ACE inhibitors on thrombolytic balance. Perhaps the most persuasive aspect of the hypothesis proposed by this work is the advantages that would result from linked reflex systems responding to the adverse effects of hemorrhage. Enhanced clotting would limit blood loss, vasoconstriction and tachycardia support blood pressure acutely, while salt-and-water retention both supports blood pressure and replaces the blood volume lost. As these same linked systems appear to confer a harmful influence on cardiac disease, their inhibition with drugs such as β -blockers and ACE inhibitors makes sense intuitively and suggests the mechanisms through which benefits result.

1997

India celebrates 50 years
of independence from Britain;

The Booker Prize is awarded to Arundhati Roy
for "The God of Small Things";
and the philosopher Sir Isaiah Berlin dies, aged 88

Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials

The ACE Inhibitor Myocardial Infarction Collaborative Group

Circulation. 1998;97:2202-2212

This meta-analysis summarized the data from five randomized trials—the Second COoperative North Scandinavian ENalapril SURvival Study (CONSENSUS-II), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-III (GISSI-3), Fourth International Study of Infarct Survival (ISIS-4), Chinese Cardiac Study (CCS-1), and Survival of Myocardial Infarction: Long-term Evaluation (SMILE) trial—of angiotensin-converting enzyme (ACE)-inhibitor therapy started early (<36 h) in the acute phase following myocardial infarction (MI). In addition, the authors set out to explore patient subgroups in which the absolute benefit from ACE inhibition appeared to be greater. This collectively provided data on almost 100 000 patients, ie, 98% of all patients randomized to this type of study.

Important for a correct interpretation was the appreciation of the heterogeneity of the different trials included in the meta-analysis. Thus, the CONSENSUS-II trial evaluated the effects of immediate intravenous enalapril and observed a trend towards increased mortality. The GISSI-3 trial was not blinded and employed a definition of progressive heart failure that was unusual as it included the need for non-trial ACE-inhibitor therapy. Given the open design, patients allocated lisinopril were less likely to have required initiation of an alternate ACE inhibitor than were the untreated control group. These differences aside, the overall results favored the use of an ACE inhibitor in the early postinfarct period. The overview demonstrated that 7.1% deaths occurred in the treatment group (3501 deaths) and 7.6% (3740) in the control arm, consistent with an absolute 0.5% and a relative 7% risk reduction (95% confidence interval [CI]: 2% to 11%). This represents approximately 5 fewer deaths per 1000 patients treated. Furthermore, 85% of survival benefit was observed within the first week, 40% being within the first 48 hours.

The authors therefore advocated the introduction of ACE-inhibitor therapy within the first 24 hours after MI in most patients and a reevaluation of all untreated patients prior to hospital discharge to maximize benefits. However, the subgroup analysis suggested an alternative approach in

which patients are targeted according to their predicted risk profile. The study identified a similar proportional mortality reduction in all risk groups, thereby confirming an increased absolute mortality benefit in the high-risk patients. Certain patient characteristics were associated with a greater benefit, including anterior MI, higher heart rates, prior MI, hypertension, and diabetes. Treating these particular patients would prevent most, but not all deaths, deaths prior to 30 days. As these trials did not continue treatment long-term, they recommend reference to the trials of ACE inhibition in heart failure to inform clinical decisions regarding maintenance therapy.

Although no single subgroup could be identified in which therapy proved harmful, there was a greater incidence of persistent hypotension and renal dysfunction in those aged 75 or more, and, furthermore, no survival advantage was identified among these patients. It is noteworthy that systolic pressure <100 mm Hg and cardiogenic shock were contraindications to trial recruitment. This early survival benefit of ACE inhibitors was founded on various hypotheses regarding the potentially favorable effects of this group of agents. The well-established ventricular remodeling process seemed unlikely to be the sole mechanism, and the authors suggest an early effect on infarct expansion, neurohormonal effects, and alterations in collateral blood flow as possible alternate explanations. Overall, this series of studies was very disappointing, as three out of the five trials were unable to demonstrate a survival benefit beyond 30 days, and the remaining two failed to do so also at 30 days. Other studies with other designs were to evidence the survival benefit with ACE inhibitors.

1998

Finn Mila Hakkinen wins the Japanese Grand Prix—and the World Championship; “Eternity and a Day,” directed by Angelopoulos, wins the Palme d’Or at Cannes; and the artist Victor Passmore dies, aged 89



Angiotensin-converting enzyme inhibitors

N.J. Brown, D.E. Vaughan

Circulation. 1998;97:1411-1420

The angiotensin-converting enzyme (ACE) inhibitors collectively represent one of the major advances in cardiovascular therapeutics over the past 20 years. After emphasizing some important differences in their pharmacology, this review describes some of their clinical uses. All ACE inhibitors reduce the formation of the vasoconstricting, salt-retaining angiotensin II, while simultaneously decreasing the degradation of bradykinin, thus enhancing its vasodilatory and salt-depleting effects. However, the structural, pharmacodynamic, and pharmacokinetic differences that are described question the appropriateness of the "class effect." ACE inhibitors differ in their basic chemical structure and also in their active moieties. In vitro studies suggest that those with a sulfhydryl group (eg, captopril) may have additional effects on prostaglandins and free-radical scavenging. This may, in turn, be related to a higher incidence of adverse effects, including neutropenia, nephrotic syndrome, and skin rash with this type of ACE inhibitor. Notably, these are some of the effects that result from the venom of the Brazilian arboreal viper *Bothrops jararaca* from which captopril was originally derived.

The antihypertensive effects correlate better with tissue levels of ACE than with plasma levels. Significant differences in relative tissue affinities of ACE inhibitors have been demonstrated by Fabris et al in the rat heart model. The acute antihypertensive effects of ACE inhibitors correlate well with pretreatment plasma renin activity. With chronic therapy, this correlation disappears and more patients achieve a decrease in blood pressure. This suggests alternative, nonrenin-related effects, possibly involving bradykinin. In black men, ACE inhibitors are less effective antihypertensives, one explanation being that these individuals have low renin levels more often than whites. Drugs that increase renin activity (eg, diuretics), when used concomitantly, appear to abolish this racial difference in response to ACE inhibitors.

ACE inhibitors produce their vasodilatory effects without a reflex tachycardia and without impairment of the heart-rate response to exercise or posture. The authors emphasized

that, at the time of press, no studies demonstrated a reduction of end-organ damage or mortality, and, therefore, that ACE inhibitors could not be recommended as first-line antihypertensives. However, this is likely to change with strongly significant benefits above and beyond the blood pressure effects seen with the treatment of high-risk patients in the recent Heart Outcome Prevention Evaluation (HOPE) study. Several large trials have demonstrated benefits for their use in clinical (systolic) heart failure, but their role in treating diastolic heart failure is much less clear. Nevertheless, diastolic dysfunction represents a significant component of congestive cardiac failure due to hypertensive left ventricular hypertrophy (LVH), which is responsive to ACE inhibitor therapy.

The renoprotective effects of ACE inhibitors in patients with progressive diabetic nephropathy are also emphasized, being independent of severity of baseline renal dysfunction. Interestingly, polymorphisms in the ACE gene may have important implications in deciding which patients may most benefit from ACE inhibition. At this stage, as with many genetic association studies, conflicting results between different investigators exist, with no firm conclusions possible. Clearly, the benefit of ACE inhibition has applications beyond its original use for treatment of hypertension. Primary prevention of myocardial infarction in high-risk patients represents a Holy Grail that has recently been attained following completion of the HOPE study. This completes a remarkable journey from poison to panacea.

1998

Terrorists bomb the US embassies in
Nairobi and Dar-es-Salaam;
the remains of Russia's last czar, Nicholas II,
are interred in the family vault;
and Pol Pot, the Cambodian dictator, dies, aged 73

ACE in Ischemic Heart Disease

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