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ESC Expert consensus document

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease

The Task Force on ACE-inhibitors of the European Society of Cardiology

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Preamble

Guidelines and Expert Consensus documents aim to present all the relevant evidence on a particular issue in order to help physicians to weigh the benefits and risks of a particular diagnostic or therapeutic procedure. They should be helpful in everyday clinical decision-making.

A great number of Guidelines and Expert Consensus Documents have been issued in recent years by the European Society of Cardiology (ESC) and by different organisations and other related societies. This profusion can put at stake the authority and validity of guidelines, which can only be guaranteed if they have been developed by an unquestionable decision-making process. This is one of the reasons why the ESC and others have issued recommendations for formulating and issuing Guidelines and Expert Consensus Documents.

In spite of the fact that standards for issuing good quality Guidelines and Expert Consensus Documents are well defined, recent surveys of Guidelines and Expert Consensus Documents published in peer-reviewed journals between 1985 and 1998 have shown that methodological standards were not complied with in the vast majority of cases. It is therefore of great importance that guidelines and recommendations are presented in formats that are easily interpreted. Subsequently, their implementation programmes must also be well conducted.

The *ESC Committee for Practice Guidelines (CPG)* supervises and coordinates the preparation of new *Guidelines* and *Expert Consensus Documents* produced by Task Forces, expert groups or consensus panels. The chosen experts in these writing panels are asked to provide disclosure statements of all relationships they may have which might be perceived as real or potential conflicts of interest. These disclosure forms are kept on file at the European Heart House, headquarters of the ESC. The Committee is also responsible for the endorsement of these Guidelines and Expert Consensus Documents or statements.

The Task Force has classified and ranked the usefulness or efficacy of the recommended procedure and/or treatment and the Level of Evidence as indicated in the tables below:

Classes of recommendations

Class I	Evidence and/or general agreement that a given procedure/treatment is beneficial, useful and effective.
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the procedure/treatment.
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III*	Evidence or general agreement that the treatment is not useful/effective and in some cases may be harmful.

*Use of Class III is discouraged by the ESC.

Levels of evidence

Level of Evidence A	Data derived from multiple randomised clinical trials or meta-analyses.
Level of Evidence B	Data derived from a single randomised clinical trials or non-randomised studies.
Level of Evidence C	Consensus of opinion of the experts and/or small studies.

Introduction

The renin-angiotensin system plays a major role in cardiovascular disease and during the past decade extensive research investigated the possible clinical benefit of the use of angiotensin converting enzyme inhibitors (ACE-I) in different clinical conditions. Accordingly, these agents have been recommended for the treatment of heart failure, hypertension, and acute and chronic myocardial infarction. The aim of this document is to review the rationale and clinical evidence for the use of ACE-I in patients with cardiovascular disease.

The Task Force members for the Angiotensin Converting Enzyme Inhibitors in Cardiovascular Disease were nominated by the Committee for Practice Guidelines (CPG) of the European Society of Cardiology (ESC). A specific literature search was carried out for original articles in peer review journals included in Medline. In addition, the ESC as well as the American Heart Association/American College of Cardiology guidelines with reference to the use of ACE-I were carefully reviewed. Most of the previously made recommendations were maintained; some were updated and a few are new according to recent evidence in the literature.

Using recommendations which are graded provides a simple method for guidance. Classes of recommendation are derived from clinical trials, conducted in selected groups of patients that may not be representative of broader populations; in fact, patients with contraindications are excluded from clinical trials. Besides, the same strength of evidence may reflect different clinical benefit: mortality, morbidity, clinical symptoms or combined end-points; large or small benefit albeit statistically significant; easily obtained or only observed, or lost, after several years of treatment. Finally, in individual cases the recommended therapy may only be a treatment option and other alternatives may be equally acceptable or even more appropriate. An effort was made to include this information in a relatively short document.

The document prepared by the Task Force was circulated among a review board appointed by the ESC and approved by the Committee for Practice Guidelines of the ESC. The final document was sent to the European Heart Journal for a formal peer review.

This consensus document represents the views of the ESC and was arrived at after careful consideration of the available evidence. Health professionals are expected to take them fully into account when exercising their

clinical judgement. This consensus document does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with that patient, and where appropriate and necessary the patient's guardian or carer.

Pharmacology

Definition

Angiotensin converting enzyme inhibitors (ACE-I) competitively inhibit the angiotensin converting enzyme.[1–3] ACE is a non-specific enzyme involved in the metabolism of many small peptides, including the conversion of angiotensin I, an inactive octapeptide, into angiotensin II. Kininase, an enzyme that catalyses the degradation of bradykinin and other potent vasodilator peptides, is also competitively inhibited by ACE-I. The major effects of angiotensin-II are summarized in Table 1.

ACE-Inhibitor classification

ACE-I are classified in three categories according to the group that binds the zinc atom of the ACE molecule into those containing a sulfhydril, a carboxyl or a phosphoryl group as zinc ligand (Table 2).[4]

Pharmacokinetic profile

The absorption is highly variable among ACE-I (25—75%) and food either has no effect or reduces the rate, but not the extent of absorption. Some ACE-I are pro-drugs and they remain inactive until they are converted into active metabolites by hydrolysis in the liver or in the gastrointestinal tissue.[1–3] The peak plasma drug concentrations are reached 1—4 h after ingestion. Pro-drugs are more

Table 1 Effects of angiotensin-II

Vessels	Vasoconstriction Stimulates noradrenaline, aldosterone, vasopressin and endothelin-1 release
Heart	Inotropic and chronotropic effects Coronary vasoconstriction
Adrenal gland	Aldosterone and adrenaline release
Brain	Vasopressin release Substance P, LHRH and ACTH release Stimulation of the thirst center Increased sympathetic activation
Kidney	Vasoconstriction (efferent $>$ afferent arteriole) Contraction of mesangial cells Increased Na reabsorption in the proximal tubule Increased K excretion in distal nephron Decreased renin release
Platelets	Stimulates platelet adhesion and aggregation
Endothelial cells	Inactivation of NO (inhibits endothelial nitric oxide synthase) Expression of endothelial oxLDL receptor (LOX-1)
Sympathetic outflow	Enhancement of peripheral noradrenergic neurotransmission Catecholamine release from the adrenal medulla
Fibrinolysis	Increased expression of PAI-1 and 2
Inflammation	Activation and migration of macrophages Increased expression of adhesion molecules (VCAM-1, ICAM-1, P-selectin), chemotactic proteins (MCP-1) and cytokines (IL-6)
Trophic effects	Hypertrophy of cardiac myocytes Stimulation of vascular smooth muscle migration, proliferation and hypertrophy Stimulates proto-oncogenes (fos, myc, jun) and MAPKs (ERKs, JNK) Increased production of growth factors (PDGF, bFGF, IGF-1, TGFβ1) Increased synthesis of extracellular matrix proteins (fibronectin, collagen type-I and III, laminin-β1 and β2) and metalloproteinases
Atherosclerosis	Stimulation of NADH/NADPH oxidase activity and superoxide anion production, lipid peroxidation

ACTH: adrenocorticotropin hormone; bFGF: basic fibroblast growth factor; ERKs: extracellular-signal regulated protein kinases; JNK: Jun N-terminal kinases; LHRH: luteinizing hormone-releasing hormone; ICAM: intracellular adhesion molecule; IGF-1: Insulin-like growth factor; IL-6: interleuking-6; LOX-1: lipoxygenase-1; MCP-1: Monocyte chemo-attractant protein-1; MAPKs: mitogen-activated protein kinases; PDGF: platelet-derived growth factor; NADH/NADPH: nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate; NO: Nitric oxide; PAI: plasminogen activator inhibitor; TGF: Transforming growth factor; VCAM: vascular cell adhesion molecule.

Table 2 Pharmacological properties of various ACE-I

Drug	Elimination half-life	Renal elimination (%)	Dose (mg) standard regiment	Dose (mg) regiment in renal failure CrCl 10—30 ml/min
Sulfhydryl-containing inhibitors				
Benazepril*	11	85	2.5—20 b.i.d.	2.5—10 b.i.d.
Captopril	2	95	25—100 t.i.d.	6.25—12.5 t.i.d.
Zofenopril*	4.5	60**	7.5—30 b.i.d.	7.5—30 b.i.d.
Carboxyl-containing inhibitors				
Cilazapril	10	80	1.25—5 daily	0.5—2.5 daily
Enalapril*	11	88	2.5—20 b.i.d.	2.5—20 b.i.d.
Lisinopril*	12	70	2.5—10 daily	2.5—5 daily
Perindopril*	>24	75	4—8 daily	2 daily
Quinapril*	2—4	75	10—40 daily	2.5—5 daily
Ramipril*	8—14	85	2.5—10 daily	1.25—5 daily
Spirapril	1.6	50**	3—6 daily	3—6 daily
Trandolapril	16—24	15**	1—4 daily	0.5—1 daily
Phosphinyl-containing inhibitors				
Fosinopril*	12	50**	10—40 daily	10—40 daily

CrCl: creatinine clearance.
*Prodrug.
**Significant hepatic elimination.

lipophylic and they have a better access to the target tissue where they are converted to the active compound. Most ACE-I and their metabolites are mainly excreted by the renal route, whereas fosinopril, zofenopril, trandolapril and spirapril display balanced elimination through hepatic and renal routes.[5] Captopril is eliminated more rapidly from the body, which accounts for its brief duration of action (<6 h), whereas ramiprilat (the active metabolite of ramipril) and specially tandrolaprilat are eliminated more slowly than other ACE-I (Table 2).

In patients with congestive heart failure reduced absorption and biotransformation may delay the onset of effect. Due to diminished renal perfusion, renal excretion may be reduced, leading to elevated maximum drug plasma levels and prolonged duration of action. Thus, dose reductions are required in the presence of impaired renal function (when creatinine clearance falls to $\leqslant 30$ ml/min).[5] Fosinopril, spirapril, trandolapril and zofenopril are excreted in both the urine and bile, so that their clearance is not significantly altered by renal impairment (Table 2).

Mechanism of action

ACE-I competitively block the conversion of angiotensin-I into angiotensin-II reducing the circulating and local levels of angiotensin-II. ACE-I also reduce aldosterone and vasopressin secretion and decrease sympathetic nerve activity as well as the trophic effects of angiotensin-II. However, they do not inhibit the actions of angiotensin-II mediated via the activation of AT1 and AT2 receptors and they do not interact directly with other components of the renin—angiotensin system.[1–4,6,7] In addition, ACE-I may also inhibit kininase II and increase bradykinin levels, which in turn stimulates the B2 receptors leading to the release of nitric oxide NO, and vasoactive prostaglandins (prostacyclin and prostaglandin E2).[8,9]

Inhibition of plasma ACE appears to be less important during chronic administration. At this time, inhibition of ACE in different tissues (i.e., vessels, kidney, heart) may be more important in determining their pharmacological effects.[10]

Since the mechanism of action of ACE-I is the same, their effects are attributed to the class as a whole. Nevertheless, there are important differences in the binding affinity to tissue ACE and individual pharmacokinetic properties of individual drugs, which may result in marked differences in tissue concentration and in differential clinical effects. However, the clinical relevance of such differences has never been demonstrated. In fact, all currently available ACE-I can be considered equally effective at lowering blood pressure. Therefore, the choice and dose of the ACE-I should be based on the results of clinical trials where the benefit has been demonstrated.

Effects of ACE-inhibitors

Haemodynamic effects

ACE-I decrease total peripheral vascular resistances, promote natriuresis but cause little change in heart rate.[1–4] Local inhibition of ACE and angiotensin-II formation in specific target organs, such as the vascular wall, is involved in these responses.

In normotensive and hypertensive patients without congestive heart failure, ACE-I have little effect on cardiac output or capillary wedge pressure. In contrast to other vasodilators, no reflex tachycardia is observed, possibly due to an effect on baroreceptor sensitivity, vagal stimulation and/or reduced stimulation of sympathetic nerve activity. Changes in heart rate during exercise or postural changes are not impaired.[11] ACE-I reverse cardiac hypertrophy in hypertensive patients[12] and reduce endothelial dysfunction in normotensive

patients with coronary artery disease, hypertension, non-insulin-dependent diabetes mellitus and heart failure.[6,13–15] Improvement in endothelial function is related to attenuation of vasoconstriction and to the increased bradykinin-induced production of endothelium-derived NO.[14,15]

In patients with congestive heart failure ACE-I induce venous and arterial vasodilatation.[1–4] Venous vasodilatation increases peripheral venous capacitance, reduces right atrial pressure, pulmonary arterial pressure, capillary wedge pressures and left ventricular filling volumes and pressures, producing a rapid relief of pulmonary congestion. The arterial vasodilator effect reduces peripheral vascular resistances and increases cardiac output.

ACE-I improve cardiac relaxation and distensibility acutely and their long-term use reduces hypertrophy and blood pressure in hypertension.[3,4,6]

Neurohormonal effects

Short-term treatment with ACE-I is accompanied by a decrease in angiotensin-II and aldosterone levels and an increase in renin release and angiotensin I levels.[16,17,18] Since angiotensin-II increases peripheral and central sympathetic outflow and stimulates the release of catecholamines from the adrenal medulla,[7] ACE-I reduce the plasma levels of epinephrine, norepinephrine and vasopressin. In addition, the increase in angiotensin I levels may result in an increased production of bradykinin,[1–7] which exhibits vasodilator properties, and in the synthesis of angiotensin-II via non-ACE mediated pathways, (i.e., chymase).[19] During chronic ACE inhibition, angiotensin-II and aldosterone levels tend to return to pretreatment values due to the activation of alternative pathways (aldosterone "escape" phenomenon).[20] Aldosterone secretion is maintained by other steroidogenic stimuli, such as hyperkalemia, hypermagnesemia and adrenocorticotropic hormone.[21,22] On the other hand, ACE-I increases kinins, prostacyclin and NO levels, which may, in part, explain their vasodilator, antithrombotic and antiproliferative effects.

Antiproliferative effects

ACE-I also exhibit antiproliferative effects (reduction of vascular and cardiac hypertrophy and extracellular matrix proliferation) and reduce ventricular remodelling after myocardial infarction.[23,24] They reverse ventricular remodelling by reducing ventricular preload/afterload, preventing the proliferative effects of AII and sympathetic nerve activity and by inhibiting the aldosterone-induced cardiac hypertrophy and interstitial and perivascular fibrosis.[11,12] In the hypertrophied heart ACE-I reduce cardiac hypertrophy and improve diastolic function. ACE-I also prevent apoptosis of cardiac myocytes in pressure-overloaded hearts.

Renal effects

ACE-I decrease renal vascular resistances and increase renal blood flow and promote Na^+ and water excretion. Nevertheless, the Glomerular Filtration Rate (GFR) remains unchanged or falls slightly, and thus, filtration fraction is decreased. This is due to the relatively greater effect in dilating postglomerular efferent than afferent arterioles, leading to a reduction in glomerular capillary hydrostatic pressure and GFR.[25] Natriuresis is due to the improvement of renal haemodynamics, a decreased release of aldosterone and bradykinin that exert direct tubular effects and inhibition of the direct renal effects of angiotensin-II. ACE-I prevent progression of microalbuminuria to overt proteinuria,[26] attenuate the progression of renal insufficiency in patients with a variety of non-diabetic nephropathies[27] and prevent or delay the progression of nephropathy in patients with insulin-dependent diabetes mellitus.[28]

Other effects

The renin-angiotensin system plays an important role in the pathogenesis and progression of atherosclerosis.[6] In animal models, ACE-I can retard the development of atherosclerosis.[29,30] These antiatherogenic properties can be related to the inhibition of angiotensin-II formation, bradykinin potentiation and increased NO release, resulting in decreased migration and proliferation of vascular smooth muscle cells, decreased accumulation and activation of inflammatory cells, decreased oxidative stress and improved endothelial function.

The Survival And Ventricular Enlargement (SAVE)[31] and the Studies Of Left Ventricular Dysfunction (SOLVD)[32] trials as well as a large meta-analysis clinical trials[33] showed that ACE-I reduced by 20—25% the risk of unstable angina and recurrent myocardial infarction in patients with left ventricular dysfunction or congestive heart failure. The Heart Outcomes Prevention Evaluation (HOPE) study[34] demonstrated that ramipril decreased morbidity and mortality in patients at increased risk of atherothrombotic cardiovascular events. The study to evaluate carotid ultrasound changes in patients treated with ramipril and vitamin E (SECURE) study, a substudy of HOPE, showed that long-term ACE-I treatment retards the progression of carotid atherosclerosis in patients with vascular disease or diabetes, but without heart failure or left ventricular dysfunction.[35]

Effects on fibrinolytic balance

ACE-I also modulate vascular fibrinolytic balance by decreasing angiotensin-II, a potent stimulus for plasminogen activator inhibitor type 1 (PAI-1) synthesis and by increasing bradykinin levels a potent stimulus for tissue plasminogen activator.[36] Thus, ACE-I lower plasminogen activator inhibitor type 1 (PAI-1) concentrations and the molar ratio of PAI-1 to tissue plasminogen activator. ACE-I also counteract the platelet aggregation induced by angiotensin-II since they increased the production of NO and prostacyclin.

Side-effects

In most patients ACE-I are well tolerated, however, several adverse reactions may occur.[1,2,37]

Hypotension. Symptomatic hypotension due to the withdrawal of angiotensin-II mediated vasoconstrictor tone can occur, especially after the first dose of an ACE-I,

particularly in patients with high plasma renin activity (e.g., salt-depleted patients due to high doses of diuretics or with congestive heart failure).

Dry cough appears in 5% to 10% of patients[38–40] and it is not always easy to distinguish that resulting from pulmonary congestion or concomitant diseases, e.g., respiratory disease.[41] The aetiology is unknown, but it may be related to increased levels of bradykinin and/or substance P in the lungs. Cough is not dose-dependent, is more frequent among women and in Asian populations, it usually develop between 1 week and a few months of treatment and sometimes requires treatment discontinuation, even if some patients may tolerate re-institution of the ACE-I after a drug-free period. Once therapy is stopped, cough usually disappears within 3-5 days. There are no differences in the propensity of cough among the different ACE-I.

Hyperkalemia due to a decrease in aldosterone secretion is rarely found in patients with normal renal function but it is relatively common in those with congestive heart failure and in the elderly. Hyperkalemia is more frequent in patients with renal impairment, diabetes, receiving either K^+ or potassium K^+-sparing diuretics, heparin or Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).[42,43]

Acute renal failure. ACE-I can increase blood urea nitrogen or creatinine levels. In most patients creatinine levels either will remain stable or decrease towards pretreatment values during continued treatment. Acute renal failure is more frequent in patients with volume depletion due to high doses of diuretics, hyponatremia, bilateral renal artery stenosis, stenosis of the dominant renal artery or a single kidney and renal transplant recipients. Under these circumstances renin release increases leading to an increase in angiotensin-II levels that produces a selective efferent arteriolar constriction and helps to maintain the glomerular filtration rate. ACE-I reduce angiotensin-II levels, produce efferent arteriolar vasodilatation and reduce glomerular filtration, leading to an increase in creatinine levels. Older patients with congestive heart failure are particularly susceptible to ACE-I induced acute renal failure. However, in nearly all patients recovery of renal function occurs after discontinuation of ACE-I.[44]

Proteinuria. ACE-I can produce proteinuria. However, pre-existing proteinuria is not a contraindication for ACE-I, as they have been found to exert nephroprotective effects in renal diseases associated with proteinuria (i.e., diabetic nephropathy).

Angioedema is a rare but potentially life-threatening side-effect. Symptoms range from mild gastrointestinal disturbances (nausea, vomiting, diarrhoea, colic) to severe dyspnoea due to larynx oedema and death. It is more frequent within the first month of therapy, and among black patients. It disappears within hours after cessation of the ACE-I.[41,45] The mechanism appears to involve an accumulation of bradykinin and its metabolite des-arginin-bradykinin and inhibition of complement-1 esterase inactivator.

Teratogenic effects. When administered during the second or third trimester of pregnancy, ACE-I can cause foetal abnormalities (i.e., oligohydramnios, pulmonary hypoplasia, foetal growth retardation, renal dysgenesis neonatal anuria and neonatal death).[46]

Other side-effects, not related to ACE inhibition include ageusia and other taste disturbances (especially in the elderly); neutropenia; and maculopapular rash. Neutropenia is rare and occurs more frequently in patients with renal or collagen vascular disease.

Contraindications

History of angioneurotic oedema, allergy and bilateral renal artery stenosis are absolute contraindications for initiation of ACE-I treatment. Although ACE-I are not contraindicated in women of reproductive age, they should be discontinued as soon as pregnancy is suspected or diagnosed.[4,46–48] Low blood pressures (systolic blood pressure $<$90 mmHg) during ACE-I treatment are acceptable if the patient is asymptomatic. If potassium rises to $>$6.0 mmol/L or creatinine increases by $>$50% or to above 3 mg/dL (256 mmol/L) the administration of ACE-I should be stopped. Moderate renal insufficiency (serum creatinine 3 mg/dL or up to 265 μmol/L), mild hyperkalemia ($\leqslant$ 6.0 Mmol/L) and relatively low blood pressure (systolic blood pressure as low as 90 mmHg) are not contraindications to ACE-I treatment, but therapy should be maintained with renal function carefully monitored. The risk of hypotension and renal dysfunction increases with high doses, in elderly patients or in patients with severe heart failure, those treated with high doses of diuretics, with renal dysfunction or hyponatremia. ACE-I, as well as other vasodilators, should also be avoided in patients with dynamic left ventricular outflow tract obstruction.[49]

Drug interactions

Antacids may reduce the availability of ACE-I. Non-steroidal anti-inflammatory drugs may reduce the vasodilator effects of ACE-I. K^+-sparing diuretics, K^+ supplements or low salt substitutes with a high K^+ content may exacerbate ACE-I induced hyperkalemia and thus, these combinations should be avoided. However, with careful monitoring, the combination of an ACE-I and spironolactone may be advantageous. If urea or creatinine levels rise excessively, discontinuation of concomitant nephrotoxic drugs (e.g., NSAIDs, cyclosporin) should be considered. ACE-I may increase plasma levels of digoxin and lithium. Patients taking diuretics may be particularly sensitive to the vasodilator effects of ACE-I. In some studies, the concomitant administration of salicylate reduced the effectiveness of ACE-I in patients with congestive heart failure. However, in a recent meta-analysis including over 20,000 patients there is little evidence for the reduction of the benefit of ACE-inhibition in the presence of aspirin.[47]

Dosing

The dose of the ACE-I varies with the clinical setting and individual clinical response. Table 2 indicates the average

daily doses of different agents and Table 4 the initial and target doses in patients with chronic heart failure.

Clinical efficacy and practical use

The benefits of and clinical indications to the ACE-I have been clearly defined in many cardiovascular conditions and agreement as to their potential usefulness has been established in chronic heart failure, asymptomatic left ventricular dysfunction, acute myocardial infarction, hypertension and in patients with high risk for cardiovascular events. The presence of diabetes in the aforementioned conditions identifies a subgroup of particular benefit. General recommendations for the use of ACE-I include the control of blood pressure, renal function and serum K^+; the starting dose should be low and progressively increased, especially in patients with hypotension or heart failure.

Heart failure

ACE-I are indicated as first-line therapy in patients with a reduced left ventricular systolic function (left ventricular ejection fraction <40–45%, with or without heart failure symptoms, in absence of contraindications (Class I indication, level of evidence A) (Table 3).[50,51] The clinical benefit includes a reduction in mortality, rehospitalisation and progression of heart failure and was observed in men and women, white and black patients, diabetics and non-diabetics, although the benefit is less in women.[52,53] ACE-I should not be titrated based on symptomatic improvement alone but uptitrated to the dosages shown to be effective in the large, controlled trials in heart failure and left ventricular dysfunction (Table 4) (Class I, level of evidence A).[50,51] Although there is a class effect, not all ACE-I were tested in heart failure and the appropriate dosing is not always known.

Two pivotal trials, the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)[54] and SOLVD[55] showed that ACE-I increase survival in patients with chronic heart failure of all degrees of severity (New York Heart Association (NYHA) classes I–IV). Both sudden death and death due to progressive heart failure are reduced in symptomatic patients with heart failure. In the CONSENSUS trial,[54] patients in NYHA class IV were followed for an average of 188 days. Mortality at 6 months was significantly reduced in the ACE-I group (enalapril) (44% vs. 26%). In SOLVD,[55] patients in NYHA class II and III were followed for a mean of 3.45 years. The cumulative mortality was 39.7% in the placebo group compared to 35.2% in the active treatment group. This equates to 45 fewer deaths per 1000 patients treated or a number needed to treat for one year to save one life (NNT) of 22 for 3.5 years to prevent or postpone one premature death. In the large trials, ACE-I clearly reduced hospital admission rates (admissions for all causes but particularly those related to worsening heart failure). For example, in SOLVD, the NNT was 4.5 for 3.5 years to prevent one hospitalisation for heart failure and 3.0 for all-cause hospitalisation.

In the second Vasodilator Heart Failure Trial (VheFT-II)[56] the effect of enalapril was compared with that of a combination of hydralazine and isosorbide dinitrate in men with heart failure. Mortality after two years was significantly lower in the enalapril arm than in the hydralazine-isosorbide dinitrate arm (18% vs. 25%). The lower mortality in the enalapril arm was attributable to a reduction in the incidence of sudden death, and this beneficial effect was more prominent in patients with less severe symptoms (NYHA class I or II). In contrast, body oxygen consumption at peak exercise was increased only by hydralazine-isosorbide dinitrate treatment.

In patients with clinical heart failure early after acute myocardial infarction (AMI) the effect of ramipril was investigated in the Acute Infarction Ramipril Efficacy (AIRE) Trial,[57] demonstrating a significant reduction in mortality that was observed very early after the initiation of the study.

In summary, there is clear evidence that ACE-I prolong survival, reduce progression of heart failure and improve quality of life, but improvement in the functional class has not been consistently demonstrated. In most of the placebo controlled studies, ACE-I therapy was associated with an increase in exercise capacity and improvement of symptoms;[58,59] however, this benefit was not observed in all studies,[60,61] indicating that the long term effect of ACE-inhibition in heart failure is probably explained by different mechanisms that do not necessarily play an important role in the control of symptoms and in the improvement of functional capacity.

Target dose

These trials had high target doses of ACE-I (Table 4) and dosing varied considerably from one patient to another. It should be emphasized that the dose regimens used in the large clinical trials should also be used in every day clinical practice. Another large outcome study, the Assessment of Treatment with Lisinopril And Survival (ATLAS),[62] further explored the dose issue by comparing low dose to high dose ACE inhibitor treatment in patients with NYHA class II–IV. All cause mortality was not dif-

Table 3 Use of ACE-I in heart failure: guidelines

Setting/indication	Class	Level	Ref.
All patients with symptomatic heart failure and reduced LVEF, functional class II–IV	I	A	50, 51
LVSD with/without symptoms after AMI	I	A	50, 51
LVSD (reduced LVEF, <40–45%) without symptoms, no previous MI	I	A	50, 51
Diastolic heart failure	IIa	C	50, 51

AMI: Acute Myocardial Infection; LVSD: Left Ventricular Systolic Dysfunction.

Table 4 Practical guidance on using ACE-I in heart failure[64]

Who should receive ACE-I
- All patients with heart failure or asymptomatic left ventricular dysfunction.
- Without contraindications (history of angioneurotic oedema, pregnancy, bilateral renal artery stenosis)
- With caution in:
  - Significant renal dysfunction (creatinine >2.5 mg/dl or >221 μmol/L)
  - Hyperkalemia ($K > 5.0$ mmol/L)
  - Symptomatic hypotension (systolic blood pressure <90 mmHg)
- Drug interactions to look out for: K supplements, K sparing diuretics (including spironolactone), "low salt" substitutes with high K content, NSAIDS, angiotensin receptor blockers

What to promise the patients
The primary reason for adhering to drug therapy should be a prophylactic indication — avoiding death and hospitalisations. The patient may or may not experience improved functional class and exercise tolerance.

When to start
- As soon as possible after diagnosis and exclusion of contraindications

ACE-I and dosing

	Starting dose (mg)	Target dose (mg)	Reference
Captopril	6.25/t.i.d.	50 — 100/t.i.d.	31
Enalapril	2.5/b.i.d.	10 — 20/daily	54—56
Lisinopril	2.5 — 5/daily	30 — 35/daily	62
Ramipril	2.5/daily	5/b.i.d. or 10/daily	57
Trandolapril	1.0/daily	4/daily	73

- Start with a low dose
- Double dose at 2 week intervals (faster titration in asymptomatic LV dysfunction, mild heart failure, hypertensives and in hospitalised patients
- Aim for targed dose, or highest tolerated dose

Monitoring
- Clinical status, blood pressure at frequent intervals during the titration phase
- Renal function: creatinine and serum K
- Inform patient of benefits
- Advise patient to report adverse events: dizziness, symptomatic hypotension, cough

Problem solving
Symptomatic hypotension
- Reconsider need for other blood pressure lowering drugs: nitrates, calcium channel blockers, other vasodilators
- If no fluid retention, consider reducing, discontinuing diuretics
- Reduce dose

Cough
- Exclude other causes of cough (lung/bronchial disease, pulmonary oedema)
- If very troublesome and recurrent after discontinuing ACE-I and rechallenge, consider angiotensin receptor blocker

Worsening renal function
- Some creatinine <3 mg/dL (266 μmol/L) and K (<6 mmol/L) rise is expected at the beginning of treatment. No action if small and asymptomatic. Continue monitoring
- Reconsider stopping concomitant nephrotoxic drugs (NSAIDs), K supplements, K sparing diuretics. If no signs of congestion, reduce diuretics
- If high creatinine/K levels persist, halve doses of ACE-I. Recheck. Seek specialist advice

NSAIDS: non-steroidal antiinflammatory drugs. ACE-i dosing is indicated only for drugs used in large heart failure, placebo controlled trials. Other ACE-i have also been approved for use in heart failure in some european countries.

ferent in the two treatment groups, but the combined end-point of all-cause death and all-cause hospitalisation was significantly less common in patients receiving high dose treatment, as was the overall number of hospitalisations (24% reduction). For this reason, the higher target doses of ACE-I selected in the key clinical trials are also recommended in clinical practice, although there is probably only a small benefit when comparing intermediate and high doses of ACE-I.

In the NETWORK trial[63] patients with NYHA class II-IV heart failure were randomised to receive enalapril 2.5 mg twice daily, 5 mg twice daily, or 10 mg twice daily. However, no relationship was found between the dose of enalapril and the clinical outcome during 24 weeks follow-up. Deaths in each group were 4.2%, 3.3% and 2.9%, respectively (ns). The combined end-point of death, heart failure related hospitalisation or worsening heart failure was also similar (12.3%, 12.9% and 14.7%, respectively; ns) in each group.

It is notable that neither the ACE-I ATLAS or NETWORK trials showed differences in end-points between intermediate and high dose. In conclusion, clinicians should aim to achieve the targed dose defined in the relevant clinical trials, providing the dose is well tolerated.

Practical guidance on using ACE-I in heart failure is given in Table 4.[64]

ACE-I compared with angiotensin receptor blockers

The clinical efficacy of ACE-I has been compared with that of direct angiotensin-II receptor antagonists in several trials. In most of the studies, the angiotensin-II inhibitors were not superior to the comparator ACE-I. In the second losartan in heart failure survival study (ELITE-2)[65] mortality in 3152 patients with chronic heart failure was similar in losartan and captopril allocated groups, after a follow-up of 555 days (11.7% vs. 10.4%, respectively). In the Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL)[66] 5447 patients with heart failure after infarction were randomly allocated to receive losartan or captopril. Mortality after 2.7 years of follow-up was similar in both treatment groups (18% and 16% respectively). In the Valsartan in Acute Myocardial Infarction (VALIANT) trial[67] 15,703 patients with myocardial infarction complicated by left ventricular systolic dysfunction, heart failure or both were randomised to receive captopril valsartan or the combination of both drugs. During the 24.7 moths follow-up, no differences were found between the three groups with regard to mortality or other clinical outcomes. On the contrary, in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity (CHARM)-added trial,[68] the addition of candesartan to an ACE-I lead to a clinical important reduction in relevant cardiovascular events, although mortality was not reduced.

Since no differences have been demonstrated to date between ACE-I and angiotensin-II blockers, ACE-I should remain the first-choice treatment in patients with heart failure. Ongoing clinical research in new subgroups of patients, as well as in heart failure with preserved systolic function, will further define the relative role of the two groups of drugs in patients with heart failure.

Similarly, ACE-I were compared with omapatrilat in the treatment of chronic heart failure. In the large Omapatrilat Versus Enalapril Randomised Trial of Utility in Reducing Events (OVERTURE) study,[69] the clinical outcomes of 5,570 patients treated with enalapril or omapatrilat (a drug with a combined effect inhibiting the ACE and the neutral endopeptidase) were compared. After a follow-up of 14.5 months, no significant difference could be demonstrated between omapatrilat and enalapril in reducing the primary combined end-point of death or hospitalisation for heart failure.

Asymptomatic left ventricular systolic dysfunction

Patients with asymptomatic left ventricular systolic dysfunction (left ventricular ejection fraction $<40-45\%$ should receive ACE-I, in absence of contraindications (class I, level of evidence A) (Table 3).[50,51]

One large trial, the prevention arm of SOLVD (SOLVD-P),[70] randomised patients with a low left ventricular ejection fraction ($\leqslant 0.35$), but no signs of overt heart failure, to placebo or enalapril. Most patients had coronary heart disease and prior MI. After an average of 3.12 years of follow-up, active therapy reduced the risk of death or hospitalisation for new or worsening heart failure from 24.5% to 20.6%. There were approximately 70 fewer hospitalisations for worsening heart failure per 1000 patients treated (NNT for 3 years = 14). The risk of developing heart failure was reduced from 38.6% to 29.8% and the median length of time to the development of heart failure increased from 8.3 months in the placebo group to 22.3 months in the ACE-I group. Neither all cause death nor hospitalisations from any cause were reduced significantly by ACE-I treatment in SOLVD-P original follow-up of 3.2 years. However Jong et al.[71] recently reported a significant decrease in mortality (50.9% vs. 56.4%) during an 11.3 years extension of follow-up of the SOLVD-P. Interestingly, enalapril significantly reduced the incidence of diabetes in patients with left ventricular dysfunction, especially those with impaired fasting plasma glucose levels.[72]

The effects of ACE-I in patients with left ventricular dysfunction early after myocardial infarction were studied in two large trials, the Survival And Ventricular Enlargement (SAVE)[31] and the Trandolapril Cardiac Evaluation (TRACE),[73,74] demonstrating a reduction in mortality and rehospitalisation in patients receiving captopril and trandolapril, respectively.

Diastolic failure

Controversy exists regarding pharmacological therapy in diastolic heart failure, mainly due to the lack of studies in this form of heart failure.[75,76] ACE-I may improve relaxation and cardiac distensibility, and a further benefit may be obtained from reduction of neuroendocrine activation and regression of left ventricular hypertrophy during long-term therapy[77–79] Accordingly, ACE-I are recommended for the treatment of patients with symptoms of heart failure and preserved systolic ventricular function (class IIa, level of evidence C) (Table 3).[50,51] Angiotensin II receptor blockers seems to be an alternative option, supported by the recently reported benefit of candesartan in this population (CHARM-preserved trial.[80]) In any case, more information from ongoing studies is needed to define the role of different treatment options in patients with diastolic heart failure.

Acute myocardial infarction

Oral ACE-I are beneficial in AMI patients when administered within 36 h of the event (class IIa, level of evidence A), especially in the presence of anterior infarcts, impaired ejection fraction or mild-moderate heart failure (class I, level of evidence A) (Table 5).[81,82] Following AMI, patients with clinical heart failure or asymptomatic left ventricular dysfunction should be treated long term with ACE-I (class I, level of evidence A), as well as patients at high risk or with diabetes (class I, level of evidence A)[50,51,81,82] (Table 5). The benefit of ACE-I after AMI appears to be particularly beneficial in diabetic patients.[83]

Table 5 Use of ACE-I in myocardial infarction: guidelines

Setting/indication	Class	Level	Ref.
AMI, first 24 h			
High risk, (heart failure, LVD, no reperfusion, large infarcts)	I	A	81, 82
All patients	IIa	A	81, 82
Evolving AMI (>24h), Post MI			
Clinical heart failure, Asymptomatic LVD (LVEF<45%)	I	A	81, 82
Diabetes or other high risk patients	I	A	81

AMI: Acute Myocardial Infarction; LVD: Left Ventricular Dysfunction; LVEF: Left Ventricular Ejection Fraction.

Two types of large outcome trials have been carried out with ACE-I in patients with AMI: early and late intervention trials. A number of short term treatment trials with early interventions enrolled relatively unselected patients: the 2nd Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS-2),[84] the 4th International Study of Infarct Survival (ISIS 4),[85] the 3rd Study of the Gruppo Italiano per lo Studio della Sopravivenza (GISSI-3),[86] the 1st Chinese Cardiac Study (CCS-1).[87] Conversely, other randomised studies selected, high risk, patients with treatment initiated later and given long term: the Survival and Ventricular Enlargement (SAVE) trial,[31] the Acute Infarction Ramipril Efficacy (AIRE) trial[57] and the Trandolapril Cardiac Evaluation (TRACE) study.[73] In these latter trials, patients were selected to be at higher risk according to the presence of clinical signs of heart failure (AIRE) or evidence of left ventricular systolic dysfunction (SAVE, TRACE). Both types of trials showed that ACE-I may reduce mortality after MI.

Early intervention trials (<24–36 h) reported a small mortality benefit, probably reflecting the lower risk of the unselected patients recruited and the short treatment period. It is arguable if this benefit is clinically significant enough to recommend the use of ACE-I in large groups of low risk, unselected patients.

In the ISIS 4 trial 58,050 patients were treated within a median 8 h after the onset of suspected AMI with captopril or placebo.[85] During the first 5 weeks mortality was slightly but significantly lower in the captopril group (7.2% vs. 7.7%), corresponding to an absolute difference of 4.9 fewer deaths per 1000 patients treated with captopril for 1 month). The benefits of treatment seemed to persist at least one year (5.4 fewer deaths per 1000), with a small non-significant benefit after the first month. The absolute benefits appeared to be larger in certain higher-risk groups, such as those presenting with a history of previous MI (18 fewer deaths per 1000) or with clinical heart failure (14 fewer deaths per 1000) and patients with anterior myocardial infarction. On the contrary no benefit was observed when the location of the infarct was other than anterior. Rates of reinfarction, post infarction angina, cardiogenic shock and stroke were similar in both groups. Captopril was associated with an increase in hypotension considered severe enough to require termination of study treatment (10.3% vs. 4.8%).

The GISSI-3 study[86] enrolled 19,394 patients randomly distributed to receive lisinopril or placebo. Mortality at 6 weeks was lower in the lisinopril group (6.3% vs. 7.1%) and this difference was maintained at 6 months. Rates of reinfarction, post infarction angina, cardiogenic shock and stroke did not differ between lisinopril patients and controls.

In the CCS-1 study[87] 13,634 patients with AMI were randomised to received captopril or placebo. A trend toward 35-day mortality reduction (9.1% vs. 9.6%; ns) was observed.

In the CONSENSUS-2 trial,[84] 6,090 patients were randomised to receive enalapril or placebo within 24 h of the onset of AMI. Therapy was initiated with an intravenous infusion of enalapril followed by oral enalapril. Mortality rates in the two groups at one and six months were not significantly different (6.3% and 10.2% in the placebo group vs. 7.2% and 11.0% in the enalapril group). Early hypotension occurred in 12% of the enalapril group and 3% of the placebo group. Thus, it was concluded that enalapril therapy started within 24 h of the onset of acute myocardial infarction does not improve survival during the 180 days after infarction.

Finally, in the Survival of Myocardial Infarction Long term Evaluation (SMILE) trial[88] 1556 patients were enrolled within 24 h after the onset of symptoms of acute anterior myocardial infarction without thrombolysis, and they were randomised to receive zofenopril or placebo. The incidence of death or severe congestive heart failure at six weeks was significantly lower in the zofenopril group (7.1% vs. 10.6%), with a non-significant reduction in mortality. However, after one year, mortality was significantly lower in the zofenopril group (10.0% vs 14.1%).

In the meta-analysis of the ACE-I in Myocardial Infarction Collaborative Group, including over 100,000 patients,[89] mortality at 30 days was reduced from 7.6% in the placebo group to 7.1% in the ACE-I group. This equates to about 5 fewer deaths per 1000 patients treated for 4–6 weeks (NNT to prevent 1 death = 200). The benefit was greater (up to 10 lives saved per 1000) in certain higher risk groups, such as those presenting with heart failure or anterior infarct. On the contrary, no benefit was observed in low risk groups including patients with inferior MI without heart failure and only a trend for benefit was observed in diabetic patients. ACE-I also reduced the incidence of non-fatal cardiac failure (14.6% vs. 15.2%), but not reinfarction or stroke and ACE-I were associated with an excess of persistent hypotension (17.6% vs 9.3%) and renal dysfunction (1.3% vs. 0.6%). The overview also confirmed that most of the benefit was observed during the first week; of the total 239 lives saved by early treatment, 200 were saved in the first week following AMI.

These data suggest that ACE-I may have a role in early management as well as in the convalescence phase of acute MI but only in high risk groups. If treatment is initiated early, i.v. enalapril should be avoided; the initial dose should be low and increased progressively within 48 h with monitoring of blood pressure and renal function.

Late intervention trials. The trials including selected high risk patients with treatment initiated later (>48) after AMI and continued long term demonstrated a greater benefit obtained from the treatment with ACE-I.

In the SAVE study[31] 2230 patients with a LVEF <40% were randomised 3 to 16 days after infarction to receive captopril or placebo. Mortality at an average follow-up of 42 months was lower in the captopril group (20% vs. 25%). In addition, the incidence of fatal or non-fatal major cardiovascular events was also reduced in the captopril group, including the risk for developing heart failure, hospitalisation and reinfarction. These benefits were observed in patients who received thrombolytic therapy, aspirin, or β-blockers, as well as those who did not.

The TRACE study[73] included 1749 patients with left ventricular systolic dysfunction (LVEF <35%), with or without heart failure, to receive oral trandolapril or placebo 3–7 days after AMI. During the follow-up of 24–50 months mortality was lower in the trandolapril group (34.7% vs. 42.3%; $p < 0.001$). Trandolapril was also associated with a reduction in the risk of sudden death and progression to severe heart failure, but not with the risk of reinfarction. Long-term mortality was also investigated after a minimum of 6 years of inclusion.[74] The life expectancy of patients was 4.6 years for those given placebo versus 6.2 years for those on trandolapril. Thus, the median lifetime was increased by 15.3 months or 27% in patients allocated to trandolapril during the study period, indicating that treatment during a critical period is associated with a long term benefit.

In the AIRE study,[57] 1986 patients with clinical evidence of heart failure at any time after AMI were randomised to receive ramipril or placebo on day three to day 10 after AMI. Follow-up was continued for a minimum of 6 months and an average of 15 months. Mortality was significantly lower in patients receiving ramipril (17% vs. 23%). A reduction in the combined endpoint of death, severe/resistant heart failure, myocardial infarction, or stroke was also observed. This benefit was apparent as early as 30 days and was consistent across a range of subgroups.

In a meta-analysis of these late trials,[53] mortality was reduced from 29.1% to 23.4% with ACE-I therapy after an average follow-up of 2.6 years. This equates to 57 fewer deaths per thousand patients treated (or a NNT of 18, for approximately 2.5 years, to prevent or postpone 1 premature death). These trials also showed that ACE-I reduce the risk of developing heart failure and requiring hospitalisation for heart failure. With ACE-I treatment, the risk of reinfarction was reduced from 13.2% to 10.8% and the risk of heart failure hospitalisation from 15.5% to 11.9%.

As a result of these trials there was debate about how ACE-I should be used in MI. One approach advocated the treatment of all patients initially, with continued treatment only in those with clinical evidence of heart failure or left ventricular systolic dysfunction. Others argued that the small benefit of acute therapy in unselected patients was actually concentrated in high risk patients and that only these should be treated, though treatment should be given indefinitely. This debate has been superseded following completion of the Heart Outcomes Protection Evaluation (HOPE) study[34] and the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease EUROPA trial,[90] both showing benefit from ACE-inhibition in patients with established atherosclerotic arterial disease (or at high risk of arterial disease) (See secondary prevention section).

Hypertension

ACE-I are indicated in the treatment of hypertension (class I, level of evidence A). (Table 6).[91] Current guidelines strongly recommend reduction of blood pressure to different levels according to the risk profile (the higher the risk the lower the ideal blood pressure).[91,92] The primary objective in hypertensive patients is the control of blood pressure levels, that can be achieved with different drugs that also reduce cardiovascular morbidity during long term treatment: diuretics, β-blockers, ACE-I, calcium channel blockers and angiotensin II antagonists. Blood pressure control may only be achieved with a combination of drugs. A number of large, long-term follow-up trials compared different therapeutic strategies and could not demonstrate an unequivocal difference in favour of a particular treatment. These studies have to be interpreted with caution; some are not powered for the purpose of the study, small differences in blood pressure at randomisation may have a significant impact on the outcome and treatment of hypertension varies during the long-term follow-up. Based not only on the results of studies in hypertension but also on the information available from other sources (e.g., heart failure, myocardial infarction etc), the selection of a specific drug can be based on the patient profile.[92] Thus, ACE-I may be considered as the first choice therapy in patients with

Table 6 Use of ACE-I in hypertension: guidelines

Setting/indication	Class	Level	Ref.
To control blood pressure	I	A	91, 92
Patients with heart failure, systolic left ventricular dysfunction, diabetics, previous MI or stroke, high coronary disease risk	I	A	91, 92

heart failure, reduced systolic left ventricular ejection fraction or diabetes, previous myocardial infarction or stroke and patients with high coronary disease risk, based on the efficacy of these drugs in these patient populations[91–93] (Table 6).

In the second Swedish Trial in Old Patients with hypertension (STOP-2)[94] 6,614 patients aged 70—84 years with hypertension were randomly assigned conventional antihypertensive drugs (atenolol, metoprolol, pindolol, or hydrochlorothiazide plus amiloride) or newer drugs (enalapril or lisinopril, or felodipine or isradipine). Blood pressure was decreased similarly in all treatment groups. The primary combined end-point of fatal stroke, fatal myocardial infarction, and other fatal cardiovascular disease was similar in the different treatment groups. The combined end-point of fatal and non-fatal stroke, fatal and non-fatal myocardial infarction, and other cardiovascular mortality was also similar.

One of the secondary objectives of the Appropriate Blood pressure Control Diabetes (ABCD) trial[95] was to compare nisoldipine with enalapril as a first-line antihypertensive agent in terms of the prevention and progression of complications of diabetes throughout five years of follow-up in 470 patients. Using a multiple logistic-regression model with adjustment for cardiac risk factors, nisoldipine was associated with a higher incidence of fatal and non-fatal myocardial infarctions than enalapril, but the number of infarct episodes was simply too low to reach any conclusion. Mortality was similar in both groups.

The Captopril Prevention Project (CAPPP)[96] compared the effects of ACE-inhibition and conventional therapy (diuretics, β-blockers) on cardiovascular morbidity and mortality in 10,985 patients with hypertension. Captopril and conventional treatment did not differ in efficacy in preventing cardiovascular morbidity (a combination of myocardial infarction, stroke and cardiovascular mortality) but the incidence of stroke was higher in the captopril group. Conversely, the incidence of diabetes during the follow-up was lower in the captopril group. Also, in the subgroup of diabetic patients the combined cardiovascular end-point was favourable to the use of the ACE-I.

The UK Prospective Diabetes Study (UKPDS)[97,98] was a randomised controlled trial comparing an angiotensin converting enzyme inhibitor (captopril) with a β-blocker (atenolol) in patients with type 2 diabetes. Captopril and atenolol were equally effective in reducing blood pressure and the risk of macro vascular end points including mortality, but the study was probably underpowered. Similar proportions of patients in the two groups showed deterioration in retinopathy after nine years and developed albuminuria. The proportion of patients with hypoglycaemic attacks was not different between groups. It was concluded that blood pressure lowering with captopril or atenolol was similarly effective in reducing the incidence of diabetic complications. This study provided no evidence that either drug has any specific beneficial or deleterious effect, suggesting that blood pressure reduction in itself may be more important than the treatment used.

In the Perindopril Protection against Recurrent Stroke Study (PROGRESS)[99] 6,105 hypertensive and non-hypertensive patients with a history of stroke or transient ischaemic attack, were randomly assigned active treatment (perindopril, with the addition of indapamide at the discretion of treating physicians) or placebo. The primary outcome was total stroke. After a follow-up of 4 years active treatment reduced the incidence of stroke (10% vs. 14%) and also the risk of total major vascular events. The reduction of stroke was similar in hypertensives and normotensives. Combination therapy with perindopril and indapamide produced larger blood pressure reductions and larger risk reductions (43%) than did single drug-therapy with perindopril alone. Single-drug therapy produced a clinically relevant reduction in the risk of stroke.

In a meta-analysis by the blood pressure lowering treatment trialists' collaboration,[100] the overview of placebo-controlled trials of ACE-I (four trials, 12,124 patients, mostly with coronary heart disease) revealed reductions in stroke 30%, coronary heart disease (20%), and major cardiovascular events (21%). There is weaker evidence of differences between treatment regimens of differing intensities and of differences between treatment regimens based on different drug classes. In the trials comparing ACE-I-based regimens with diuretic-based or β-blocker-based regimens, there were no detectable differences between randomised groups in the risks of any of the outcomes studied. Only two trials directly compared ACE-based and calcium-antagonist-based regimens, the STOP-2 and the ABCD trial hypertensive subgroup. The combined analysis suggested a reduced risk of coronary-heart-disease events among the patients assigned ACE-I based therapy, but there was not any clear evidence of differences between randomised groups in the risks of stroke, cardiovascular death, or total mortality. For heart failure, there was a trend of borderline significance towards reduced risk among those assigned ACE-I-based therapy.

In another meta-analysis[101] including nine randomised trials comparing old drugs (diuretics and β-blockers), calcium-channel blockers and ACE-I in 62,605 hypertensive patients, no differences were found in the outcome between ACE-I and β-blockers or calcium channel blockers.

The second Australian national blood pressure study (ANBP-2)[102] assessed the clinical outcomes of 6083 hypertensive patients randomised to receive an ACE-I (enalapril) or a diuretic (hydrochlorothiazide). The addition of β-blockers, calcium-channel blockers, and α-blockers was recommended in both groups for the correct control of blood pressure through the study. Blood pressure reduction was identical, but after a follow-up period of 4.1 years, the cumulative rate of death and cardiovascular events was lower in the group receiving ACE-I (56.1 vs 59.8 per 1000 patient-years), mainly due to a decrease in myocardial infarction, while the incidence of stroke was similar.

Different results were observed in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT),[103] a randomised clinical trial in

33,357 hypertensives with at least one other cardiovascular risk factor. Patients were divided into 3 groups to receive chlorthalidone, amlodipine or lisinopril. The primary outcome was cardiovascular death or non-fatal myocardial infarction. Secondary outcomes included all-cause mortality, stroke, and different combined cardiovascular outcomes including coronary revascularisation, angina with hospitalisation, heart failure and peripheral vascular disease). The follow-up period was 4.9 years. Although the primary outcome failed to demonstrate a difference between treatments, and all cause mortality was also similar for lisinopril vs. chlorthalidone. Lisinopril had higher 6-year rates of combined cardiovascular disease (33.3% vs. 30.9%); stroke (6.3% vs. 5.6%); and HF (8.7% vs. 7.7%), and this brings into question use of ACE-I as first line therapy in hypertensive patients without high risk profile or heart failure.

In summary, it seems that the level or blood pressure reduction is more important than the specific treatment, although the evidence from trials in other cardiovascular conditions indicate superiority for ACE-I in patients with heart failure, diabetes or at high-risk from cardiovascular disease.

Secondary prevention and high-risk of cardiovascular disease

Long-term treatment with ACE-I in patients without heart failure is beneficial in patients with known cardiovascular disease or diabetes and some other risk factors (class I, level of evidence A) (Table 7).

Whether ACE-I also provide benefit to patients with coronary artery disease in the absence of congestive heart failure via an antiatherosclerotic mechanism has been investigated in several studies. In the PART-2 study,[104] in 600 patients with coronary, cerebrovascular or peripheral vascular disease, ramipril compared to placebo slightly reduced blood pressure (6 mmHg) and left ventricular mass, but not common carotid wall thickness or major cardiovascular events during a follow-up of 2 years. These results suggest that lowering blood pressure may be more important than other ACE-I actions to explain the possible clinical benefit. In the Quinapril Ischemic Event Trial (QUIET)[105] patients with normal left ventricular function undergoing coronary angiography were randomised to quinapril or placebo and followed for 3 years for cardiac end-points. No differences were found in the progression of coronary artery lesions in angiographic studies. The trial, including 1750 patients without heart failure, was not powered to show differences in terms of clinical events. The Simvastatin/enalapril Coronary Atherosclerosis (SCAT) Trial[106] evaluated the effects of cholesterol lowering (simvastatin) and ACE inhibition (enalapril) on coronary atherosclerosis in 460 normocholesterolemic patients. Enalapril failed to reduce the severity of coronary lesions as compared with placebo.

Several large multicenter trials were designed to test whether an ACE-I reduces major cardiovascular events in populations selected for coronary or other vascular diseases, including the Heart Outcomes Prevention Evaluation Study (HOPE), the EURopean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA), the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) and the telmisartan alone and in combination with ramipril global endpoint trial (ONTARGET) trials.

The HOPE trial[34,107–109] enrolled 9297 men and women with either confirmed arterial disease (known coronary heart disease, peripheral arterial disease, stroke) or diabetes and one other risk factor (hypertension, cigarette smoking, microalbuminuria or dyslipidaemia). Of note, 80% of patients had coronary heart disease, 55% had a history of angina, 52% prior MI, 43% peripheral arterial disease, 25% prior unstable angina, 26% previous coronary artery bypass grafting, 18% past percutaneous coronary revascularisation and 11% a stroke or transient ischaemic attack. Almost half had a history of hypertension and nearly 40% diabetes mellitus. Patients were randomised to placebo or an ACE-I (ramipril) and followed for a mean of 5 years. The primary end-point (death from cardiovascular causes, MI or stroke) was reached in 17.8% of placebo treated patients and 14.0% of ACE-I treated i.e., 38 fewer primary events per 1000 patients treated (NNT for 5 years = 26.3). Each of the components of this end-point was reduced by active therapy, as were a wide range of secondary end-points, including all cause mortality (from 12.2% to 10.4% in 5 years), need for revascularisation, diabetic complications, onset of new diabetes, cardiac arrest, worsening angina or heart failure. Interestingly, the reduction of blood pressure in the ramipril group was relatively small (3.3 mmHg, systolic), and the benefit in outcomes could not be attributed to blood pressure reduction alone.[110]

Further evidence for the long-term use of an ACE-I in secondary prevention comes from the EUROPA trial.[90] In this study, a large population of 13,655 relatively low risk patients with stable coronary heart disease without heart failure received perindopril or placebo during a mean follow-up of 4.2 years. Patients on perindopril group experienced less cardiovascular events, (cardiovascular mortality, myocardial infarction and sudden death), the 8% vs. 10% difference during the treatment period equivalent of 50 patients need to be treated over a period of 4.2 years to prevent one major cardiovascular event. The benefits of ACE-I were seen across all subgroups examined.

Taken in conjunction with the trials in heart failure and after myocardial infarction, the HOPE and EUROPA studies argue persuasively for a general vascular pro-

Table 7 Use of ACE-I in secondary prevention: guidelines

Setting/indication	Class	Level	Ref.
High-risk patients (evidence of cardiovascular disease or diabetes and one other risk factor)	I	A	34, 90

Table 8 Use of ACE-I to prevent sudden death: guidelines

Setting/indication	Class	Level	Ref.
Patients with heart failure	I	A	112, 113
Patients with previous MI	I	A	112, 113
Patients with dilated cardiomyopathy	I	B	112, 113

MI: myocardial infarction.

tective effect of ACE-I in patients with coronary and other forms of atherosclerotic arterial disease.

Along the same lines of HOPE and EUROPA, the PEACE trial is testing the efficacy of ACE-I (trandolapril) in the prevention of cardiovascular events in patients with documented coronary artery disease with preserved systolic function. Ongoing research also includes the comparison and combination of ACE-I with angiotensin-II receptor blockers (telmisartan alone and in combination with ramipril global end-point trial (ONTARGET).[111]) The results of these large ongoing trials will provide a better understanding for the treatment of patients at high risk of complications from atherosclerosis.

Prevention of sudden cardiac death

The use of ACE-I to prevent sudden cardiac death in patients with left ventricular dysfunction or heart failure after MI is considered as a class I indication, level of evidence A (Table 8).[112,113] In patients with asymptomatic left ventricular dysfunction, moderate and advanced heart failure treatment with ACE-I resulted in a reduction in mortality from sudden cardiac death. This reduction varied from 20% to 54% and was statistically significant in some heart failure studies, although sudden cardiac death was not the primary end-point in these trials.[112,113]

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