Complete Summary

GUIDELINE TITLE

Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease.

BIBLIOGRAPHIC SOURCE(S)

Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004 Aug;25(16):1454-70. [113 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE
METHODOLOGY - including Rating Scheme and Cost Analysis
RECOMMENDATIONS
EVIDENCE SUPPORTING THE RECOMMENDATIONS
BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS
CONTRAINDICATIONS
QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES
IDENTIFYING INFORMATION AND AVAILABILITY
DISCLAIMER

SCOPE

DISEASE/CONDITION(S)

Cardiovascular disease including:

- Heart failure
- Asymptomatic left ventricular systolic dysfunction
- Diastolic failure
- Acute myocardial infarction
- Hypertension
- Sudden cardiac death

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Prevention
Treatment

CLINICAL SPECIALTY

Cardiology
Emergency Medicine
Family Practice
Internal Medicine
Preventive Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To review the rationale and clinical evidence for the use of angiotensin converting enzyme inhibitors (ACE-I) in patients with cardiovascular disease

TARGET POPULATION

- Patients with cardiovascular disease including those with:
    - Heart failure
    - Asymptomatic left ventricular systolic dysfunction
    - Diastolic failure
    - Acute myocardial infarction
    - Hypertension
- Patients at high risk of cardiovascular disease

INTERVENTIONS AND PRACTICES CONSIDERED

Monitoring

1. Blood pressure
2. Creatinine levels
3. Serum potassium levels
4. Patient reporting of adverse events

Treatment/Prevention

Angiotensin-converting enzyme inhibitor therapy

1. Sulfhydryl-containing inhibitors
    - Benazepril
    - Captopril
    - Zofenopril
2. Carboxyl-containing inhibitors

- Cilazapril
- Enalapril
- Lisinopril
- Perindopril
- Quinapril
- Ramipril
- Spirapril
- Trandolapril

3. Phosphinyl-containing inhibitors
    - Fosinopril

MAJOR OUTCOMES CONSIDERED

- Reduction in morbidity and mortality
- Decrease in blood pressure
- Myocardial infarction and reinfarction rate
- Hospitalisation rate
- Progression of heart failure
- Heart failure symptoms, quality of life, and New York Heart Association functional class
- Exercise capacity
- Occurrence of post infarction angina
- Incidence of cardiogenic shock
- Incidence of stroke
- Rate of diabetes complications
- Incidence of coronary heart disease
- Need for coronary revascularisation
- Severity of coronary lesions
- Onset of new diabetes

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A specific literature search was carried out for original articles in peer review journals included in Medline. In addition, the European Society of Cardiology (ESC) as well as the American Heart Association/American College of Cardiology guidelines with reference to the use of angiotensin-converting enzyme inhibitors were carefully reviewed.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

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

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Subgroups of the task force formulated drafts in specific areas, then presented the drafts to the entire task force to reach consensus.

Most of the recommendations made in previous European Society of Cardiology guidelines and in American Heart Association/American College of Cardiology guidelines on angiotensin-converting enzyme inhibitors were maintained; some were updated, and a few are new according to recent evidence in the literature.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Class 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 and/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 European Society of Cardiology.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The document prepared by the Task Force was circulated among a review board appointed by the European Society of Cardiology (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.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The class of recommendations (I-III) and level of evidence (A-C) are defined at the end of the "Major Recommendations" field.

Clinical Efficacy and Practical Use

The benefits of and clinical indications to the angiotensin-converting enzyme inhibitors (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 and 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 potassium (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 [LVEF] <4045%, with or without heart failure symptoms, in absence of contraindications (Class I indication, level of evidence A) (please refer to the table below entitled "Use of ACE-I in Heart Failure"). 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. 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 (Please refer to the table below entitled "Practical Guidance on Using ACE-I in Heart Failure") (Class I, level of evidence A). 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) and SOLVD showed that ACE-I increase survival in patients with chronic heart failure of all degrees of severity (New York Heart Association (NYHA) classes II-V). Both sudden death and death due to progressive heart failure are reduced in symptomatic patients with heart failure. In the CONSENSUS trial, 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, 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 1,000 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) 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, 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; however, this benefit was not observed in all studies, 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.

Use of ACE-I in Heart Failure: Guidelines

Setting/indication	Class	Level	References
All patients with	I	A	Remme et al., 2001; American College of

Setting/indication	Class	Level	References
symptomatic heart failure and reduced LVEF, functional class II-IV			Cardiology/American Heart Association (ACC/AHA) Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002
LVSD with/without symptoms after AMI	I	A	Remme et al., 2001; ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002
LVSD (reduced LVEF, <40-45%) without symptoms, no previous MI	I	A	Remme et al., 2001; ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002
Diastolic heart failure	IIa	C	Remme et al., 2001; ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2002

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

Target Dose

These trials had high target doses of ACE-I (Please refer to the table below entitled "Practical Guidance on Using ACE-I in Heart Failure") 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), 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 different 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 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 (not significant [ns]). The combined end-point of death, heart failure related hospitalization, 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 targeted 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 the table below entitled "Practical Guidance on Using ACE-I in Heart Failure."

Practical Guidance on Using ACE-I in Heart Failure

Who should receive ACE-I

- All patients with heart failure or asymptomatic left ventricular (LV) 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 micromoles/L)
    - Hyperkalemia (potassium [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, nonsteroidal anti-inflammatory drugs (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/three times a day(t.i.d.)	50-100/t.i.d.	Pfeffer et al., 1992
Enalapril	2.5/two times a day (b.i.d.)	10-20/daily	Effects of enalapril, 1987; Effect of enalapril on survival, 1991; Cohn et al., 1991
Lisinopril	2.5-5/daily	30-35/daily	Packer et al., 1999
Ramipril	2.5/daily	5/b.i.d. or 10/daily	Effect of ramipril on mortality, 1993
Trandolapril	1.0/daily	4/daily	Kober et al., 1995

- 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 targeted 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

- 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 micromoles/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: Nonsteroidal anti-inflammatory 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.

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) mortality in 3,152 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) 5,447 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 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 months 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, the addition of candesartan to an ACE-I lead to a clinically 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, 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 (LVEF <40-45%) should receive ACE-I, in absence of contraindications (class I, level of evidence A) (please refer to the table entitled "Use of ACE-I in Heart Failure").

One large trial, the prevention arm of SOLVD (SOLVDP), randomised patients with a low LVEF ($\leq$0.35), but no signs of overt heart failure, to placebo or enalapril. Most patients had coronary heart disease and prior myocardial infarction (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 1,000 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 one study 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.

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) and the Trandolapril Cardiac Evaluation (TRACE), 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. 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. 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) (please refer to the table entitled "Use of ACE-I in Heart Failure"). Angiotensin II receptor blockers seem to be an alternative option, supported by the recently reported benefit of candesartan in this population (CHARM-preserved trial). 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 acute myocardial infarction (AMI) patients when administered within 36 hours (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) (please refer to the table below entitled Use of ACE-I in Myocardial Infarction). 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) (please refer to the table below entitled "Use of ACE-I in Myocardial Infarction"). The benefit of ACE-I after AMI appears to be particularly beneficial in diabetic patients.

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), the 4th International Study of Infarct Survival (ISIS 4), the 3rd Study of the Gruppo Italiano per lo Studio della Sopravivenza (GISSI-3), the 1st Chinese Cardiac Study (CCS-1). Conversely, other randomised studies selected, high risk, patients with treatment initiated later and given long term: the Survival and Ventricular Enlargement (SAVE) trial, the Acute Infarction Ramipril Efficacy (AIRE) trial, and the Trandolapril Cardiac Evaluation (TRACE) study. 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. 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 1,000 patients treated with captopril for 1 month). The benefits of treatment seemed to

persist at least one year (5.4 fewer deaths per 1,000), with a small nonsignificant 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 1,000) or with clinical heart failure (14 fewer deaths per 1,000) 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 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 13,634 patients with AMI were randomised to receive captopril or placebo. A trend toward 35-day mortality reduction (9.1% vs. 9.6%; ns) was observed.

In the CONSENSUS-2 trial, 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 1,556 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 nonsignificant 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, 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 1,000 patients treated for 46 weeks (NNT to prevent 1 death = 200). The benefit was greater (up to 10 lives saved per 1,000) 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 nonfatal 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, intravenous (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 2,230 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 nonfatal major cardiovascular events was also reduced in the captopril group, including the risk for developing heart failure, hospitalization, and reinfarction. These benefits were observed in patients who received thrombolytic therapy, aspirin, or beta-blockers, as well as those who did not.

The TRACE study included 1,749 patients with left ventricular systolic dysfunction (LVEF <35%), with or without heart failure, to receive oral trandolapril or placebo 3 to 7 days after AMI. During the follow-up of 24 to 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. 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, 1,986 patients with clinical evidence of heart failure at any time after AMI were randomised to receive ramipril or placebo on day three to day ten 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, 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 and the European Trial On Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) trial, both showing benefit from ACE-inhibition in patients with established atherosclerotic arterial disease (or at high risk of arterial disease) (See Secondary Prevention section).

Use of ACE-I in Myocardial Infarction: Guidelines

Setting/indication	Class	Level	References
AMI, first 24 h			
High risk, (heart failure, LVD, no reperfusion, large infarcts)	I	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction, 1999
All patients	IIa	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction, 1999
Evolving AMI (>24h), Post MI			
Clinical heart failure, asymptomatic LVD (LVEF<45%)	I	A	Van de Werf et al., 2003; ACC/AHA Guidelines for the Management of Patients With Acute Myocardial Infarction, 1999
Diabetes or other high-risk patients	I	A	Van de Werf et al., 2003

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

Hypertension

ACE-I are indicated in the treatment of hypertension (class I, level of evidence A) (please refer to the table below entitled "Use of ACE-I in Hypertension"). 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). The primary objective in hypertensive patients is the control of blood pressure levels, which can be achieved with different drugs that also reduce cardiovascular morbidity during long term treatment: diuretics, beta-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, and 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), the selection of a specific drug can be based on the patient profile. Thus, ACE-I may be considered as the first choice therapy in patients with 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 (please refer to the table below entitled "Use of ACE-I in Hypertension").

In the second Swedish Trial in Old Patients with Hypertension (STOP-2), 6,614 patients aged 70 to 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 nonfatal stroke, fatal and nonfatal myocardial infarction, and other cardiovascular mortality was also similar.

One of the secondary objectives of the Appropriate Blood Pressure Control Diabetes (ABCD) trial 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 nonfatal 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) compared the effects of ACE-inhibition and conventional therapy (diuretics, beta-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) was a randomised controlled trial comparing an angiotensin converting enzyme inhibitor (captopril) with a beta-blocker (atenolol) in patients with type 2 diabetes. Captopril and atenolol were equally effective in reducing blood pressure and the risk of macrovascular 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) 6,105 hypertensive and nonhypertensive 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, 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 beta-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 including nine randomised trials comparing old drugs (diuretics and beta-blockers), calcium-channel blockers, and ACE-I in 62,605 hypertensive patients, no differences were found in the outcome between ACE-I and beta-blockers or calcium channel blockers.

The second Australian National Blood Pressure Study (ANBP-2) assessed the clinical outcomes of 6,083 hypertensive patients randomised to receive an ACE-I (enalapril) or a diuretic (hydrochlorothiazide). The addition of beta-blockers, calcium-channel blockers, and alpha-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 1,000 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), 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 nonfatal 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 heart failure (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 or diabetes or at high-risk from cardiovascular disease.

Use of ACE-I in Hypertension: Guidelines

Setting/indication	Class	Level	References
To control blood pressure	I	A	Prevention of coronary heart disease, 1998; Chobanian et al., 2003
Patients with heart failure, systolic left ventricular dysfunction, diabetics, previous MI or stroke, high coronary disease risk	I	A	Prevention of coronary heart disease, 1998; Chobanian et al., 2003

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) (please refer to the table below entitled Use of ACE-I in Secondary Prevention).

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, 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) 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 1,750 patients without heart failure, was not powered to show differences in terms of clinical events. The Simvastatin/Enalapril Coronary Atherosclerosis (SCAT) Trial 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 enrolled 9,297 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 revascularization, 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 1,000 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.

Further evidence for the long-term use of an ACE-I in secondary prevention comes from the EUROPA trial. 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 fewer 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 protective 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). The results of these large ongoing trials will provide a better understanding for the treatment of patients at high risk of complications from atherosclerosis.

Use of ACE-I in Secondary Prevention: Guidelines

Setting/indication	Class	Level	References

Setting/indication	Class	Level	References
High-risk patients (evidence of cardiovascular disease or diabetes and one other risk factor)	I	A	Yusuf et al., 2000; Fox, 2003

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 (please refer to the table below entitled "Use of ACE-I to Prevent Sudden Death"). 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.

Use of ACE-I to Prevent Sudden Death: Guidelines

Setting/indication	Class	Level	References
Patients with heart failure	I	A	Priori et al., 2001; Priori et al., 2003
Patients with previous MI	I	A	Priori et al., 2001; Priori et al., 2003
Patients with dilated cardiomyopathy	I	B	Priori et al., 2001; Priori et al., 2003

MI: myocardial infarction.

<u>Definitions</u>

Class 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 and/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 European Society of Cardiology (ESC)

Level of Evidence

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

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

References open in a new window

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for selected recommendations (see Major Recommendations).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of angiotensin-converting enzyme inhibitors (ACE-I) in patients with cardiovascular disease

POTENTIAL HARMS

Side Effects

- *Symptomatic hypotension* due to the withdrawal of angiotensin-II mediated vasoconstrictor tone can occur, especially after the first dose of an angiotensin-converting enzyme inhibitor (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 and it is not always easy to distinguish that resulting from pulmonary congestion or concomitant diseases (e.g., respiratory disease). 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, usually develops between 1 week and a few months of treatment, and sometimes requires treatment discontinuation, even if some patients may tolerate reinstitution of the ACE-I after a drug-free period. Once therapy is stopped, cough usually disappears within 3 to 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 potassium or potassium-sparing diuretics, heparin, or nonsteroidal anti-inflammatory drugs (NSAIDs).
- *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 arteriola 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.

- *Proteinuria*. ACE-I can produce proteinuria. However, preexisting 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. The mechanism appears to involve an accumulation of bradykinin and its metabolite desarginin-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).
- *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.

Drug Interactions

Antacids may reduce the availability of ACE-I. Nonsteroidal anti-inflammatory drugs may reduce the vasodilator effects of ACE-I. Potassium-sparing diuretics, potassium supplements, or low salt substitutes with a high potassium 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.

CONTRAINDICATIONS

CONTRAINDICATIONS

History of angioneurotic oedema, allergy, and bilateral renal artery stenosis are absolute contraindications for initiation of angiotensin-converting enzyme inhibitors (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. 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 micromoles/L), mild hyperkalemia (≤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, in patients with severe heart failure, in those treated with high doses of diuretics, and in those 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.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- 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.
- 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.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lopez-Sendon J, Swedberg K, McMurray J, Tamargo J, Maggioni AP, Dargie H, Tendera M, Waagstein F, Kjekshus J, Lechat P, Torp-Pedersen C. Expert consensus document on angiotensin converting enzyme inhibitors in cardiovascular disease. The Task Force on ACE-inhibitors of the European Society of Cardiology. Eur Heart J 2004 Aug;25(16):1454-70. [113 references] PubMed

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

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 European Society of Cardiology.

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This is the current release of the guideline.

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Print copies: Available from Elsevier Science Ltd. European Heart Journal, ESC Guidelines - Reprints, 32 Jamestown Road, London, NW1 7BY, United Kingdom. Tel: +44.207.424.4422; Fax: +44 207 424 4515; Web site: http://www.eurheartj.org/

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

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