ADIS DRUG EVALUATION

Drugs 2002; 62 (2): 339-385
0012-6667/02/0002-0339/$27.50/0

Quinapril

A Further Update of its Pharmacology and Therapeutic Use in Cardiovascular Disorders

Christine R. Culy and *Blair Jarvis*

Adis International Limited, Auckland, New Zealand

Various sections of the manuscript reviewed by:

T.J. Anderson, Foothills Hospital/The University of Calgary, Division of Cardiology, Calgary, Alberta, Canada; ***J. Flack***, Wayne State University, Department of Internal Medicine, Detroit, Michigan, USA; ***A.G. Kontopoulos***, Aristotelian University, Hippocration Hospital, Department of Cardiology, Thessaloniki , Greece; ***J. Mancini***, Vancouver Hospital and Health Sciences Centre, UBC Department of Medicine, Vancouver, Canada; ***C.M. White***, Hartford Hospital, Department of Pharmacy, Hartford, Connecticut, USA.

Data Selection

Sources: Medical literature published in any language since August 1994 on quinapril, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'quinapril' or 'quinapril hydrochloride'. EMBASE search terms were 'quinapril' or 'quinapril hydrochloride' or 'CI 906'. AdisBase search terms were 'quinapril' or 'quinapril-hydrochloride' or 'CI-906'. Searches were last updated 20 Dec 2001.

Selection: Studies in patients with hypertension, congestive heart failure or coronary artery disease who received quinapril. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Quinapril, hypertension, congestive heart failure, coronary artery disease, pharmacodynamics, pharmacokinetics, therapeutic use.

Contents

Summary

Abstract

Quinapril is rapidly de-esterified after absorption to quinaprilat (the active diacid metabolite), a potent angiotensin converting enzyme (ACE) inhibitor. Quinapril produces favourable haemodynamic changes, and improves ventricular and endothelial function in patients with various cardiovascular disorders; these effects are mediated through the binding of quinaprilat to both tissue and plasma ACE.

Quinapril 10 to 40 mg/day provided effective blood pressure control in most patients with essential hypertension in clinical trials, but some patients required dosages of 80 mg/day and/or concomitant diuretic therapy. In general, quinapril provided similar blood pressure control to other standard antihypertensive therapies including other ACE inhibitors, calcium antagonists and β-adrenoceptor antagonists in comparative clinical trials. Combined therapy with quinapril and hydrochlorothiazide had a significantly greater antihypertensive effect than either drug as monotherapy in two well designed studies. Quinapril has also been shown to reduce microalbuminuria in patients with hypertension and/or diabetes mellitus.

In patients with congestive heart failure, quinapril ≤40 mg/day produced beneficial haemodynamic and echocardiographic changes and improved exercise tolerance, symptoms and functional class. Effects of quinapril on survival have not been investigated, but quinapril 10 to 20 mg/day showed comparable efficacy to captopril 25 to 50mg twice daily in two well designed trials.

In patients with coronary artery disease, quinapril 40 mg/day significantly reduced the incidence of ischaemic events after coronary artery bypass grafting

(CABG) in a well controlled study (n = 148). However, a lower dosage of quinapril (20 mg/day) showed no effect on ischaemic events or atherosclerotic progression with 3 years of treatment in a similarly designed study involving 1750 patients undergoing coronary angioplasty.

The tolerability of quinapril is similar to that of other ACE inhibitors. In placebo-controlled trials, cough occurred in 2 and 4.3% and hypotension occurred in <1 and 2.9% of quinapril recipients with hypertension or congestive heart failure, respectively. No increase in adverse events was observed when the dosage was increased from 10 to 40 mg/day.

Conclusion: Quinapril is now firmly established as an effective and well tolerated ACE inhibitor for the treatment of patients with hypertension and congestive heart failure. Quinapril 40 mg/day also significantly reduced the incidence of ischaemic events in patients undergoing CABG in one study; however, a lower dosage of quinapril (20 mg/day) had no effect on ischaemic events in patients undergoing coronary angioplasty in another trial. Additional trials in patients with coronary artery disease receiving optimal dosages of quinapril (40 mg/day) would be useful.

Overview of Pharmacodynamic Properties

Quinapril is a non-sulfhydryl angiotensin converting enzyme (ACE) inhibitor prodrug which is metabolised to quinaprilat, the active diacid metabolite. As with all ACE inhibitors, quinaprilat exerts its therapeutic effect by inhibiting the conversion of angiotensin I to angiotensin II; ACE inhibitors also prevent the degradation of bradykinin, but whether increased levels of bradykinin play a role in the therapeutic effects of these agents is still uncertain. Quinaprilat binds with a high affinity to both plasma and tissue ACE. In humans, a single dose of quinapril 20mg provides >50% inhibition of plasma ACE over 24 hours. Quinapril has also been shown to inhibit angiotensin II formation in human vasculature following several weeks of administration. In humans, the hypotensive effect of exogenous bradykinin is potentiated by ACE inhibitor therapy, and the bradykinin antagonist icatibant reduces the hypotensive effect of ACE inhibitors in humans. Similar effects have been demonstrated with quinapril in animal studies.

In patients with hypertension, once-daily administration of quinapril 10 to 40mg provided good 24-hour blood pressure control as assessed by ambulatory blood pressure monitoring in some, but not all studies. Generally, quinapril had no significant effect on heart rate, cardiac output or left ventricular (LV) ejection fraction. In patients with moderate to severe congestive heart failure, quinapril produced a number of favourable haemodynamic effects including improved cardiac output and reduced systemic vascular resistance and pulmonary capillary wedge pressure, without an increase in heart rate.

Quinapril ≤40 mg/day reduced LV hypertrophy in patients with hypertension or chronic valvular regurgitation, and reduced progressive ventricular remodelling in patients with distant myocardial infarction in one small investigation.

Quinapril 10 to 40mg once daily improved endothelial function (as measured by improved flow-mediated dilation or reduced vasoconstrictive response to acetylcholine) in patients with coronary artery disease and hypertension over 2 to 6 months of therapy; improved endothelial function was also observed in patients with congestive heart failure receiving a single infusion of quinaprilat. In contrast, the angiotensin II antagonist losartan (50 mg/day), calcium antagonists amlodipine (5 mg/day) and nitrendipine (10 mg/day), and the ACE inhibitor enalapril (10 mg/day) did not improve endothelial function.

Quinapril 5 to 10 mg/day increased heart rate variability and reduced sympathetic overactivity after myocardial infarction in patients with coronary artery disease.

In general, quinapril showed neutral or beneficial effects on lipid profiles, glycaemia and renal haemodynamics.

Overview of Pharmacokinetic Properties

Following oral administration of quinapril in healthy volunteers, approximately 60% of the dose is absorbed and peak plasma concentration (C_{max}) is reached within 1 hour. Quinapril then undergoes rapid de-esterfication to quinaprilat, the active diacid metabolite, which reaches C_{max} within 2 hours. Both quinapril and quinaprilat are highly bound to plasma proteins (≈97%), and mean elimination half-lives are ≈1 and 2 hours, respectively. Quinaprilat has a long terminal half-life of ≈25 hours, which may be associated with its slow release from ACE. The main route of elimination is via the kidney: quinaprilat accounts for 30% of the oral dose recovered in the urine, quinapril accounts for 3% and two other inactive metabolites account for 6% each. The remainder of the oral dose is eliminated in the faeces as unabsorbed quinapril or by biliary excretion of quinapril and its metabolites.

The pharmacokinetics of quinapril and quinaprilat are affected by renal and hepatic impairment. In addition, elimination of quinapril may be reduced in patients with congestive heart failure and/or advanced age; however, this reduction is typically a result of decreased renal function in these patients. In lactating mothers receiving a 20mg dose of quinapril, only 1.6% of the maternal dose was estimated to reach the infant.

Therapeutic Efficacy

Hypertension

The antihypertensive efficacy of quinapril is well documented, with dosages of 10 to 80 mg/day consistently producing significant reductions in blood pressure in patients with mild to moderate hypertension (patients with DBP 95 to 120mm Hg and/or SBP >140mm Hg) in placebo-controlled trials.

In comparative, randomised clinical trials, quinapril (10 to 80 mg/day) displayed similar antihypertensive efficacy to other ACE inhibitors captopril (25 to 200 mg/day) and enalapril (10 to 80 mg/day), but inconsistent results have been reported in studies comparing quinapril with lisinopril (2.5 to 20 mg/day). Quinapril 20 to 40mg once daily showed similar efficacy to β-adrenoceptor antagonist atenolol 50 to 100 once daily; however, lower dosages of quinapril (10 to 20 mg/day) did not appear to be as effective as atenolol 50 to 100 mg/day in patients with a history of moderate to severe hypertension. Quinapril 10 to 40 mg/day produced similar response rates to metoprolol 50 to 200 mg/day in patients with hypertension, but quinapril 20 mg/day was slightly less effective than metoprolol 100 mg/day in reducing diastolic blood pressure in patients with type 2 diabetes mellitus in another study. Quinapril (5 to 40 mg/day) also showed similar antihypertensive efficacy to twice-daily sustained release nifedipine (20 to 80 mg/day), once-daily amlodipine (5 to 10 mg/day) and once-daily nitrendipine (10 to 40 mg/day).

The addition of a diuretic [usually hydrochlorothiazide (HCTZ)] to quinapril monotherapy increases the response rate from ≥50% to ≈70 to 90% in patients with hypertension. Two large, randomised, double-blind studies showed that quinapril and HCTZ combination therapy was significantly more effective at lowering blood pressure than either drug as monotherapy over 8 weeks of treatment in patients with moderate to severe hypertension.

Quinapril 10 to 40 mg/day reduced urinary albumin excretion rate (UAE) to a similar extent as captopril 50 to 150 mg/day and metoprolol 100 mg/day, and was significantly better than atenolol 50 to 100 mg/day and/or HCTZ 25 to 50 mg/day at reducing UAE in randomised, comparative trials. Quinapril 10 to 40 mg/day also significantly decreased UAE in patients with hypertension with or without type 2 diabetes mellitus in two noncomparative studies.

Congestive Heart Failure

In patients with congestive heart failure, quinapril ≤40 mg/day produced favourable haemodynamic and echocardiographic parameters and improved symptoms, exercise tolerance and disease severity. These favourable effects have been maintained for up to 1 year of nonblind therapy. Although the effect of quinapril on survival in patients with congestive heart failure has not been determined, treatment with other ACE inhibitors has resulted in improved mortality rates, and a recent meta-analysis suggests a class effect for these agents in reducing morbidity and mortality in these patients.

In two recent double-blind, randomised, placebo-controlled investigations (n = 131 and 146), quinapril 10 to 20mg once daily showed comparable efficacy to captopril 25 to 50mg twice daily in reducing symptoms of heart failure (e.g. dyspnoea, ventricular gallop or pulmonary congestion), improving echocardiographic parameters (e.g. LV ejection fraction or LV diastolic/systolic diameters) and improving exercise tolerance in patients with mild to moderate congestive heart failure [New York Heart Association (NYHA) functional classes I to III] over 10 or 12 weeks of treatment. In one study, NYHA functional class was also improved with both therapies but quinapril had a greater effect than captopril in patients with more severe disease. Similar effects were observed in another study in elderly patients (aged ≥65 years) with NYHA functional class II or III with an aetiology of ischaemic heart disease.

Coronary Artery Disease

The results of two large, double-blind, placebo-controlled, randomised trials investigating the potential use of quinapril in patients with coronary artery disease have recently become available: the effects of QUinapril On Vascular Ace and Determinants of Ischemia (QUO VADIS) study and the QUinapril Ischemic Event Trial (QUIET).

In the QUO VADIS trial (n = 148), a significant reduction in cardiac events was observed in patients receiving quinapril 40 mg/day versus placebo for 1 year following coronary artery bypass surgery. In contrast, in the QUIET trial, treatment with quinapril 20 mg/day over 3 years had no significant effect on reducing cardiac events or the progression of atherosclerosis in 1750 normolipidaemic, normotensive patients with normal LV function (LV ejection fraction >40%) following coronary angioplasty. Flaws in the design of the QUIET investigation, including insufficient sample size, inadequate quinapril dosage and use of lipid-lowering therapy, may have contributed to the lack of effect seen with quinapril in this study. In other investigations in patients undergoing coronary angioplasty and/or coronary stent implantation, quinapril has shown some efficacy in reducing restenosis; however, additional trials are necessary to define the role of quinapril in these patients.

Tolerability

Quinapril is generally well tolerated and adverse experiences are usually mild and transient and seldom require treatment withdrawal. In placebo-controlled trials in patients with hypertension or congestive heart failure, discontinuation of

quinapril therapy because of adverse events was required in 4.7 and 6.8% of patients, respectively. The most commonly occurring adverse events seen in these studies were dizziness, headache, cough and fatigue, each occurring in <8% of patients. ACE inhibitor class-specific cough occurred in 2% of patients with hypertension and 4.3% of patients with congestive heart failure. Hypotension rarely occurred in patients with hypertension but was reported in 2.9% of patients with congestive heart failure in placebo-controlled trials. Angioedema was seen in 0.1% of patients.

Quinapril shows similar tolerability to other ACE inhibitors. In a large meta-analysis of comparative clinical trials, 12% of 1819 patients receiving quinapril experienced a treatment-related adverse event compared with 15% of 339 enalapril recipients and 16% of 186 captopril recipients. Treatment withdrawal because of adverse events in these studies was less common in quinapril recipients (3.7%) than those receiving enalapril (8.0%) or captopril (6.4%). In addition, quinapril 10 to 40 mg/day showed similar tolerability to metoprolol 50 to 200 mg/day in a large comparative study.

Elderly patients (aged >65 years) tolerated quinapril as well as younger patients (aged <65 years), and addition of a diuretic to quinapril therapy induced little change in incidence of adverse events.

Dosage and Administration

In patients with hypertension, quinapril therapy is initiated at a once-daily dose of 10 or 20mg and titrated according to blood pressure response to a maximum of 80 mg/day. Twice-daily administration may be required in patients whose blood pressure control diminishes towards the end of a once-daily dosage interval.

Because of the risk of hypotension, caution is advised when quinapril is added to diuretic therapy. European prescribing information recommends a low initial dose of quinapril (2.5mg) in patients already receiving diuretic therapy. US prescribing information recommends that patients should discontinue diuretic therapy 2 to 3 days prior to beginning quinapril treatment; if this is not feasible, the recommended initial dose of quinapril is 5mg. Lower starting dosages of quinapril are also recommended for elderly hypertensive patients (aged ≥65 years) and those with renal impairment. The quinapril dosage should then be gradually titrated to blood pressure control.

In patients with congestive heart failure, quinapril is indicated for use as an adjunctive therapy in combination with diuretics and/or digitalis. The initial dose of quinapril recommended in the US and Europe is 5mg and 2.5mg, respectively. The quinapril dosage should then be titrated up to a maximum of 40 mg/day to achieve an effective dose or until the appearance of undesirable adverse events. In Europe, medical supervision is recommended during initiation of quinapril in patients with severe/unstable congestive heart failure, patients receiving high dose loop diuretics (e.g. >80mg furosemide), multiple diuretics or high dose vasodilator therapy, patients with hypovolaemia, hyponatraemia (serum sodium <130 mgEq/L), systolic blood pressure <90mm Hg or serum creatinine >150 μmol/L and those aged ≥70 years. In the US, it is recommended that all patients with congestive heart failure be supervised for at least 2 hours following the initial dose of quinapril to monitor for the development of hypotension.

1. Introduction

Quinapril is an angiotensin converting enzyme (ACE) inhibitor which, like other members of its class, is a well established treatment option for patients with hypertension and congestive heart failure. In addition, recent clinical research suggests that ACE inhibitors may also provide protection against adverse cardiovascular events in patients with atherosclerotic disease without high blood pressure or left ventricular (LV) dysfunction.[1]

This article provides an overview of the use of quinapril in patients with hypertension and heart failure (which have previously been extensively reviewed in *Drugs* in 1990[2] and 1994[3]), and also reviews recent experimental and clinical studies investigating the role of quinapril in patients with coronary artery disease.

2. Overview of Pharmacodynamic Properties

Quinapril is a non-sulfhydryl ACE inhibitor prodrug. The active diacid metabolite, quinaprilat, is responsible for the pharmacodynamic effects observed following oral administration of quinapril.

Since the pharmacodynamic properties of quinapril have previously been extensively reviewed, this section focuses on human data and the most significant findings published since the previous review of quinapril in *Drugs*.[3]

2.1 Mechanism of Action

Quinapril exerts its therapeutic effect through the inhibition of ACE, a key component of the renin-angiotensin-aldosterone system (RAS) [see figure 1].[4,5] ACE is present in both tissue and plasma where it acts as a catalyst in the conversion of angiotensin I to angiotensin II. In addition to being a potent vasoconstrictor, angiotensin II stimulates aldosterone secretion by the adrenal cortex which promotes renal conservation of sodium and a subsequent increase in extracellular volume. Angiotensin II also stimulates vasopressin secretion from the brain (promoting further fluid retention), activates the sympathetic nervous system[6,7] and exerts a number of effects in cardiac and vascular tissue[8] (figure 1) which are thought to contribute to the pathogenesis of congestive heart failure[9] and/or coronary artery disease.[8]

ACE inhibitors also influence the kallikrein-kinin-prostaglandin system (see figure 1). Since ACE is structurally identical to kininase II, one of the enzymes responsible for the transformation of bradykinin into inactive peptides, inhibition of ACE reduces bradykinin degradation.[10] Bradykinin is a potent vasodilator that is thought to exert its vasodilatory action through the release of endothelium-derived prostacyclin, nitric oxide (NO) and endothelium-derived hyperpolarising factor.[11] Bradykinin also stimulates secretion of plasminogen activator,[12,13] which may result in increased fibrinolysis.[5]

2.1.1 Effects on ACE

Quinaprilat binds with a high affinity to both tissue and plasma ACE.[14] In *in vitro* analyses of the binding of various ACE inhibitors, the order of potency (assessed by radioinhibitor-binding displacement) was quinaprilat = ramiprilat > perindoprilat > enalaprilat > captopril > quinapril in human plasma[15] and spiraprilat > benazeprilat > quinaprilat = cilazaprilat > ramiprilat > lisinopril > enalaprilat > perindoprilat > captopril in human heart membrane preparations.[16] In addition, quinaprilat has a much slower dissociation from human heart ACE than lisinopril or enalaprilat *in vitro*,[17] These properties are likely to account for the long pharmacodynamic/therapeutic effects of quinaprilat relative to its short half-life (see section 3).

It is generally thought that the therapeutic effects of ACE inhibitors correlate better with tissue ACE inhibition than with circulating ACE;[14,18] however, differences between ACE inhibitor binding affinities have not been shown to impact on clinical outcomes.[4]

In humans, quinapril administration decreases plasma ACE activity, increases plasma renin activity, decreases pressor response to angiotensin I, decreases plasma angiotensin II levels and decreases plasma aldosterone levels (reviewed by Plosker & Sorkin).[3] In healthy volunteers, single doses of

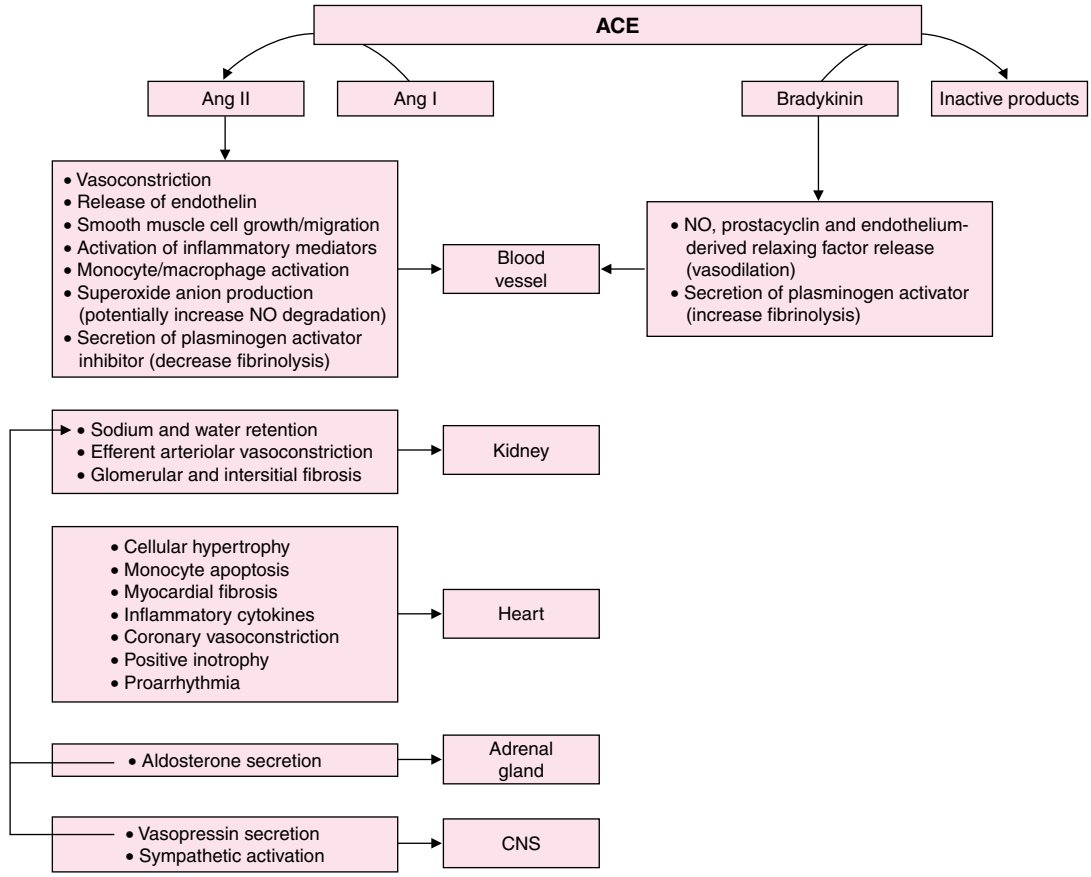

Fig. 1. Role of angiotensin-converting enzyme (ACE) in the renin-angiotensin-aldosterone and kallikrein-kinin-prostaglandin systems and the effects of angiotensin (Ang) II and bradykinin.[4,5] **NO** = nitric oxide.

quinapril 2.5 to 20mg provided >50% inhibition of plasma ACE over 24 hours[19] and reduced angiotensin I pressor response by up to 90%.[19,20] Quinapril has also been shown to inhibit vascular ACE in humans.[21] In a recent randomised, placebo-controlled, double-blind study,[21] 187 patients with coronary artery disease received placebo, quinapril 40mg once daily or captopril 50mg three times daily for ≈4 weeks before undergoing coronary artery bypass grafting (CABG). Local angiotensin II formation assessed in mammary arteries extracted during CABG was significantly reduced in patients treated with quinapril versus those receiving placebo. Angiotensin II was also decreased in captopril recipients but this change was not statistically different from that in placebo recipients.[21]

2.1.2 Effects on Bradykinin

There is a growing body of evidence which suggests that increased levels of bradykinin may contribute to the therapeutic effects of ACE inhibitors; however, this is still a matter of debate.[5] In humans, ACE inhibitor therapy potentiated the action of exogenous intravenous bradykinin by ≈50-fold.[22,23] In addition, coadministration of the bradykinin antagonist icatibant (HOE 140) significantly attenu-

ated the hypotensive effect of captopril in humans.[24] Similar effects have been shown with quinapril in animal studies. In spontaneously hypertensive rats, coadministration of icatibant significantly attenuated the hypotensive effect of quinapril.[25] Furthermore, the reduction in experimentally induced ventricular hypertrophy observed with quinapril treatment was prevented by icatibant,[26] as were reductions in myocardial injury[27] and improvements in cardiac performance and reduced LV weight[28] seen with quinapril in experimental models of myocardial infarction.

The potential role of bradykinin in modifying endothelial function is discussed in more depth in section 2.4. It is generally accepted that the effects of ACE inhibitors on bradykinin also contribute to some of the adverse effects of these agents, such as cough and angioedema.[29]

2.2 Effects on Blood Pressure and Haemodynamics

In patients with hypertension, quinapril 10 to 80 mg/day in single or divided doses induces significant and sustained reductions in mean systolic (SBP) and diastolic blood pressure (DBP) [see section 4.1]. Despite the fact that quinapril and quinaprilat have such short elimination half-lives (see section 3), once-daily administration of quinapril 10 to 40mg has been shown to provide good 24-hour blood pressure control as assessed using ambulatory blood pressure monitoring.[30,31] In one randomised, placebo-controlled study including 66 patients with hypertension receiving a single daily dose of quinapril 20 to 40mg, 50% of the peak effect remained at the trough;[31] however, other studies suggest that the peak to trough ratio of once-daily quinapril therapy may be slightly lower (30 to 40%),[32,33] indicating that some patients may be better maintained with twice-daily therapy.[29] In general, doses of 40 to 80mg were more effective at trough than 10 to 20mg doses, and twice-daily administration was more effective than the same dose given once daily.[29]

Quinapril had no significant effect on heart rate, cardiac output or LV ejection fraction in patients with hypertension in the majority of clinical trials; however, quinapril 10 mg/day did reduce heart rate from 77.1 ± 4.4 to 68.1 ± 6.0 beats/min ($p < 0.001$) in one study in 23 patients with mild to moderate hypertension over 8 weeks of therapy.[34]

In patients with moderate to severe congestive heart failure, single-dose administration of quinapril 2.5 to 10mg consistently produced a number of favourable effects, including improved cardiac output and reduced systemic vascular resistance and pulmonary capillary wedge pressure, without an increase in heart rate (reviewed in Wadworth & Brogden[2] and Plosker & Sorkin[3]).[35-41] A recent study investigating the neurohormonal and haemodynamic effects of increasing dosages of quinapril (2.5 to 10mg twice daily) suggested that these positive effects may be dose-related.[42]

2.3 Effects on Left Ventricular Modelling and Function

2.3.1 In Patients with Hypertension

In addition to its antihypertensive effects, quinapril has also been shown to reduce LV hypertrophy, improve diastolic function and reduce left atrial enlargement in patients with hypertension and LV hypertrophy;[43-47] however, no randomised, comparative studies are available.

In the largest study,[43] 2 years of treatment with quinapril 10 to 40 mg/day (with or without chlorthalidone 25 to 50 mg/day) significantly reduced LV hypertrophy and improved diastolic function in 122 patients with mild to moderate hypertension. As assessed by echocardiography, 58 patients were considered to have a normal left ventricle at baseline while the other 64 patients had LV hypertrophy (LV mass ≥131 or ≥100 g/m^2 for men or women, respectively) and/or a high ratio of LV posterior wall thickness to diastolic diameter (RWT; >0.45). After 2 years of quinapril treatment, LV mass was significantly reduced by a mean of 12 to 15% in patients with baseline hypertrophy ($p < 0.001$). Significant ($p < 0.001$) reductions in LV mass were also observed in patients who had no evidence of LV hypertrophy at baseline, and none of these patients progressed towards

hypertrophy over the course of the study. In addition, reductions in LV mass were similar in patients receiving quinapril monotherapy to those observed in patients receiving quinapril combined with chlorthalidone. By the end of the trial, the number of patients with a normal LV geometric pattern had increased from 58 to 87 (48 to 71%), and the number of patients with elevated RWT (>0.45) had decreased from 40 to 1 (33 to 0.8%). Changes in LV geometry during the 2-year period of quinapril treatment were paralleled by significant improvements in Doppler indices of LV diastolic function.

Similar results were found in another study including 98 patients with mild to moderate hypertension receiving 4 months of treatment with quinapril 20 mg/day with or without concomitant hydrochlorothiazide (HCTZ) 12.5 mg/day.[45] At the end of the treatment, LV mass index was reduced by a mean of 6.85 g/m^2 ($p = 0.0003$). The greatest reductions in LV mass index were observed in the 59 patients (60%) who had LV hypertrophy at baseline (–11.27 g/m^2; $p = 0.0001$) whereas the mean reduction was nonsignificant for those in whom LV hypertrophy was not detected at baseline (–0.16 g/m^2; $p = 0.94$). Analysis of the changes in LV mass between patients receiving combination treatment with HCTZ (28%) and those receiving monotherapy showed that treatment with the diuretic had no effect on reducing LV mass index. Although no changes in diastolic or systolic LV dimensions were observed, both interventricular and posterior wall thickness was significantly reduced by quinapril as measured during diastole and systole.

In two small studies including patients with hypertension and LV hypertrophy (n = 15[44] and 23[47]), 4 to 6 months of quinapril 10 to 40 mg/day reduced mean LV mass index from 174 to 161 g/m^2 ($p < 0.05$)[44] and from 138 to 120 g/m^2 ($p < 0.001$),[47] respectively.

Quinapril continues to reduce LV hypertrophy over long-term treatment. In a recent study, 23 patients with previously untreated hypertension and LV hypertrophy receiving quinapril 10 or 20 mg/day (five patients received concomitant therapy with HCTZ 25 mg/day) were followed for 3 years.[46] After a mean treatment period of 7.5 months, a significant ($p < 0.001$) decrease of 17.5% in LV mass index was observed, and a complete regression of LV hypertrophy was achieved in 38.1% of patients. LV mass continued to decrease with ongoing quinapril treatment and after a mean of 38.3 months LV mass index was 38.6% lower than pretreatment values, with 90.5% of patients achieving complete regression (see figure 2). Indeed, a lower than normal LV mass index of ≤95 g/m^2 was observed in 61.9% of patients by the end of the study. Significant improvements in diastolic function and left atrial size were also observed with quinapril treatment (figure 2).

Where reported,[45-47] no significant relationship between blood pressure and LV mass reduction was observed in these studies, suggesting that other factors are likely to play a role in reduction of LV mass. Diez & Laviades[48] suggested that the ability of ACE inhibitors such as quinapril to reduce LV mass index in hypertensive patients with LV hypertrophy may be related to their ability to reduce insulin-like growth factor-1 (IGF-1), which is present in high levels in these patients. Indeed, in their investigation involving 87 patients, regression of LV hypertrophy occurred only in patients

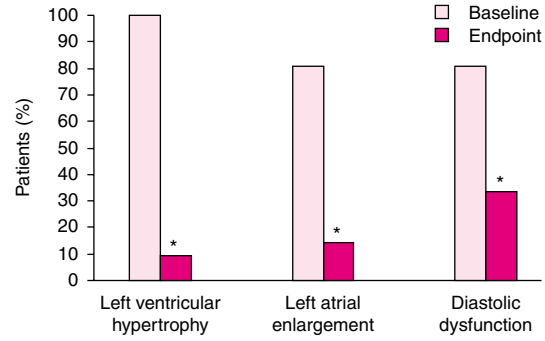

Fig. 2. Effects of quinapril in patients with left ventricular hypertrophy. The percentage of patients (n = 23) with left ventricular hypertrophy (left ventricular mass index >125 g/m^2 for men or >110 g/m^2 for women), diastolic dysfunction (ratio of early diastolic and late diastolic Doppler filling velocities <1) and left atrial enlargement (left atrial dimension >40mm) at baseline and after a mean of 38.3 months of treatment with quinapril 10 or 20 mg/day; * $p \leq 0.001$.[46]

whose enhanced baseline IGF-1 levels were normalised after treatment with quinapril, captopril or lisinopril.[48] Additional factors are also likely to be involved.

2.3.2 In Patients with Chronic Valvular Regurgitation

Quinapril also helps to improve LV function in patients with chronic valvular regurgitation.[49,50] Over 1 year of treatment in a noncomparative trial, quinapril 10 to 20 mg/day decreased the regurgitation fraction in patients with moderate to severe chronic aortic (n = 12) and mitral (n = 12) regurgitation by 27 and 42%, respectively ($p = 0.001$ for both).[50] Significant reductions in LV end-systolic ($p < 0.0001$) and end-diastolic volume ($p \leq 0.005$) were also observed in both groups. Furthermore, LV mass was reduced by 35% in patients with aortic regurgitation, and LV hypertrophy (present in all patients at baseline) was completely reversed in these patients. In patients with mitral regurgitation, LV mass index was reduced by 15%, and septal wall thickness (an indication of borderline hypertrophy) was normalised following 1 year of quinapril treatment. These results suggest that quinapril treatment may help delay surgical intervention in these patients.[50]

2.3.3 Effects on Remodelling Post-Myocardial Infarction

In patients who survive myocardial infarction, structural remodelling occurs in both the infarcted and non-infarcted regions of the myocardium.[51] LV dilation is an important characteristic of remodelling and, in the early stages after a myocardial infarction, helps restore depressed cardiac function.[51] However, in approximately 20% of patients with healed myocardial infarction, LV dilation continues to progress over the years and long-term survival in these patients is reduced.[51,52]

Quinapril appears to prevent progression of LV dilation and remodelling in patients with healed myocardial infarction; however, evidence is currently limited to one study.[53] In this double-blind, randomised, placebo-controlled trial, 25 patients who had experienced an acute myocardial infarction >1.5 years previously and who had progressive asymptomatic LV dilation (end-diastolic volumes >80 ml/m^2) were randomised to receive placebo or quinapril 10 to 40 mg/day for 1 year. Progressive dilation continued in patients receiving placebo but not in those receiving quinapril: mean end-diastolic volume (as assessed by gated single-photon emission computed tomography) increased by 24.6 ml/m^2 ($p < 0.05$ *vs* baseline) in placebo recipients and only 4.1 ml/m^2 in quinapril recipients ($p < 0.05$ *vs* placebo).

No significant change in ejection fraction or pulmonary wedge pressure at rest was observed in either treatment group over 1 year of treatment; however, mean pulmonary wedge pressure during bicycle exercise tended to increase in patients receiving placebo (from 21.3 to 24.3mm Hg) and decrease in patients receiving quinapril (from 20.2 to 17.4mm Hg), although no significant difference between groups or versus baseline was found. At the end of the study, heart rate was significantly lower during exercise in patients receiving quinapril than in those receiving placebo (91 ± 2 *vs* 108 ± 6 beats/min).[53]

2.4 Effects on Endothelial Dysfunction

ACE inhibitors are thought to modify the endothelium in a number of ways. In addition to reducing the proliferative and prothrombotic effects of angiotensin II (figure 1),[8] ACE inhibition may also increase NO bioavailability by reducing production of superoxide anions that degrade NO[54-56] while simultaneously promoting bradykinin-dependent induction of endothelial NO production.

NO is an important endothelium-dependent vasodilator which also exerts potent antiatherogenic and thromboresistant properties by preventing platelet aggregation and cell adhesion.[8] However, the endothelium-derived NO system appears to be impaired in patients with cardiovascular disorders. Flow-mediated dilation (FMD), an endothelium-derived NO-dependent phenomenon, is reduced in patients with coronary artery disease.[57,58] Furthermore, coronary arteries in patients with atherosclerosis may paradoxically constrict in the presence

of acetylcholine (ACh), an indication of NO deficiency.[59-62]

Endothelial function is also impaired in patients with hypertension, congestive heart failure, diabetes mellitus and hyperlipidaemia.[63] Indeed, endothelial dysfunction is thought to play an important role in the genesis and development of cardiovascular diseases[63-65] and is associated with an increased risk of cardiovascular events.[66,67]

The effects of quinapril or quinaprilat on FMD or ACh-induced vasoconstriction have been investigated in healthy volunteers (section 2.4.1), as well as in patients with coronary artery disease (section 2.4.2), hypertension (section 2.4.3) and congestive heart failure (section 2.4.4). The effects of quinapril/quinaprilat on endothelial function have also been compared with other agents including the angiotensin II antagonist losartan,[68,69] calcium antagonists amlodipine and[69] nitrendipine[70] and the ACE inhibitor enalapril[69] in randomised, comparative studies.

2.4.1 In Healthy Volunteers

ACE inhibition with quinapril had a greater effect than the angiotensin II inhibitor losartan in modulating FMD in a recent randomised, double-blind, placebo-controlled, crossover study involving 30 healthy volunteers.[68] In this study, the effect of 2 weeks of quinapril (40 mg/day), losartan (50 mg/day) or placebo treatment on pre- and postprandial endothelial function was assessed. During placebo treatment, ingestion of an oral fat load significantly decreased preprandial FMD from 6.2 to 4.2% ($p < 0.05$). In contrast, pre- and postprandial FMD were not significantly altered during treatment with quinapril (6.4 *vs* 6.3%) or losartan (7.1 *vs* 5.4%) therapy; however, the difference between pre- and post-prandial FMD was significantly smaller during quinapril therapy than that observed during losartan therapy ($p < 0.05$). Measurements of postprandial triglyceride concentrations showed that there was an inverse relationship between triglyceride concentration and FMD during placebo treatment, but not during quinapril or losartan therapy. These results suggest a direct effect of angiotensin II inhibition (via quinapril or losartan) on endothelial function, possibly due to down-regulation of the expression of membrane oxidases resulting in decreased production of lipid-induced superoxides that degrade NO.[68,71] However, since the effects of quinapril were significantly greater than those of losartan ($p < 0.05$), other mechanisms independent of angiotensin II inhibition (e.g. bradykinin) may be involved.

In a nonrandomised study in ten healthy volunteers,[72] an infusion of quinaprilat (1.6 μg/min for 5 minutes) increased radial artery FMD over baseline by 46%. However, when quinaprilat was co-infused with the bradykinin antagonist icatibant (90 μg/min for 5 minutes) this effect was abolished, suggesting that bradykinin-dependent mechanisms are involved. It is likely that these effects are due to bradykinin-induced NO release, since bradykinin-induced prostaglandin release was inhibited by administration of 250mg of aspirin administered intravenously 30 minutes before measurement.

In another nonrandomised study measuring arterial blood flow in 44 healthy volunteers,[73] increases in blood flow observed following bradykinin administration were potentiated by co-infusion with quinaprilat (3.9 nmol/min for 10 minutes). When these agents were infused together, there was a substantial and significant ($p < 0.02$) shift of the bradykinin dose-response curve towards lower concentrations. The increase in blood flow observed with quinaprilat was abolished by specific inhibition of NO synthase by *N*-monomethyl-L-arginine (L-NMMA), indicating a direct effect of quinaprilat on NO. Similar significant effects were not observed when enalaprilat (13 nmol/min for 10 minutes) was infused with bradykinin.[73]

2.4.2 In Patients with Coronary Artery Disease

In patients with coronary artery disease, quinapril has been shown to attenuate ACh-induced vasoconstriction[74] and improve FMD.[69,75]

In the largest and longest running investigation [the Trial in Reversing ENdothelial Dysfunction (TREND)],[74] 6 months of quinapril treatment (40mg once daily) resulted in a significant reversal of endothelial dysfunction in normotensive patients with coronary artery disease, preserved LV func-

tion and minimal dyslipidaemia. In this randomised, double-blind, placebo-controlled study, 129 patients received quinapril (n = 64) or placebo (n = 65) after undergoing clinically indicated coronary revascularisation; 105 patients were available for evaluation after 6 months of treatment. All patients had evidence of endothelial dysfunction in at least one non-intervened coronary artery at baseline.

At baseline, vasoconstriction in response to the highest dose of ACh (10^{-4} mmol/L) was 9.4 ± 2.3 and 14.3 ± 2.5% in the placebo and quinapril treatment groups, respectively (nonsignificant difference between treatment groups). At the end of 6 months of treatment, the response to ACh 10^{-4} mmol/L in the quinapril group had decreased by 12% to 2.3 ± 2.5% ($p < 0.002$) [figure 3], whereas no change was observed in the placebo group. These responses were sustained even after cessation of oral therapy for 72 hours, and were observed without any significant effect of quinapril on systemic blood pressure. The vasodilatory response to nitroglycerin (NO agonist) did not change during the study, indicating that endothelium-independent vasodilation was not affected by quinapril treatment.

Recently, the effects of smoking status[77] and hyperlipidaemia[76] in patients involved in the TREND study were evaluated. In the quinapril group, the mean change in ACh (10^{-4} mmol/L)-induced response after 6 months of treatment was 16.6 and 10.5% in patients who were classified as smokers (n = 15) and nonsmokers (n = 36), respectively; in quinapril recipients with hyperlipidaemia [low-density lipoprotein cholesterol (LDL-C) >130 mg/dl; n = 31], the mean percentage change in response was 13.2% compared with 10.5% in patients with LDL-C <130 mg/dl (n = 19)[76] [figure 3]. These results suggest that smokers or patients with hyperlipidaemia may derive more benefit from quinapril therapy.

Quinapril also improved impaired endothelium-dependent FMD in patients with coronary artery disease in one randomised[69] and one nonrandomised investigation.[75]

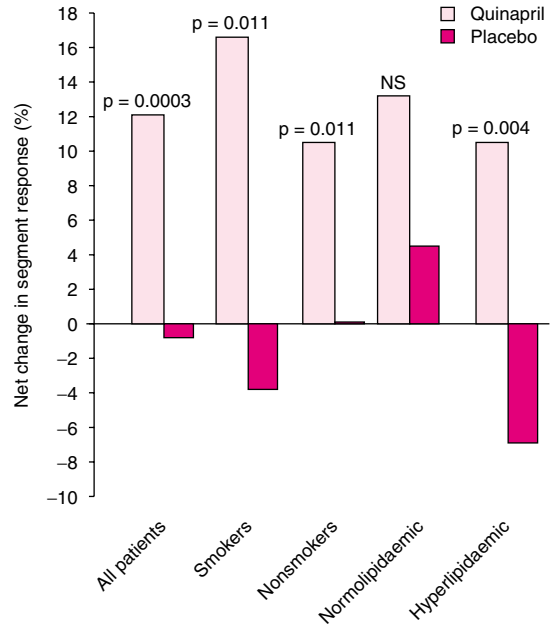

Fig. 3. Changes in endothelial function in patients with coronary artery disease after 6 months of treatment with quinapril 40 mg/day or placebo in a randomised, double-blind trial.[74] Endothelial function was assessed according to the mean change in coronary artery diameter in response to acetylcholine 10^{-4} mmol/L (segment response); the net change in segment response after 6 months is provided for all patients as well as subgroups of patients who were smokers, nonsmokers, normolipidaemic [low-density lipoprotein cholesterol (LDL-C) <130 mg/dl] or hyperlipidaemic (LDL-C >130 mg/dl).[74,76,77]

In the Brachial Artery Normalization of Forearm Function (BANFF) study,[69] 80 patients with coronary artery disease (>50% stenosis in at least one major coronary artery) were randomised to once-daily therapy with quinapril 20mg, enalapril 10mg, the calcium antagonist amlodipine 5mg or the angiotensin II antagonist losartan 50mg. In this nonblind, crossover study, each patient received three of the four study drugs for 8 weeks each, with a 2-week washout period between treatments. At baseline, mean FMD was 7.3 ± 0.6% with no significant differences between treatment groups. At the end of the study, FMD was significantly increased by 1.8 ± 1.0% ($p < 0.02$) with quinapril

treatment whereas no change was observed with losartan (0.8 ± 1.1%; p = 0.57), amlodipine (0.3 ± 0.9%; p = 0.97) or enalapril (–0.2 ± 0.8%; p = 0.84) [no significant differences between treatment groups]. There was no significant effect on nitroglycerin-mediated (endothelium-independent) dilation in any group.

The improvements in FMD observed in quinapril recipients appeared to be related to the presence of the insertion (I) allele of the ACE genotype. Improvements in FMD were observed only in patients with ID and II genotypes (3.3 ± 1.2 and 3.2 ± 1.9%, respectively; $p < 0.05$ *vs* baseline for both), whereas patients with the DD ACE genotype showed no significant improvement (0.5 ± 2.1%).

Similar positive effects of quinapril on FMD were observed in another study involving ten patients with coronary artery disease who received quinapril 20 to 40 mg/day for 8 weeks.[75] At the end of the study, FMD had increased from 2.4 ± 0.4 to 10.8 ± 2.2% ($p < 0.001$). Interestingly, quinapril reduced baseline serum nitrate/nitrite levels by 19 ± 17% from 58.2 ± 19.0 to 46.0 ± 13.3 μmol/L ($p < 0.01$ *vs* baseline). Serum nitrate/nitrite levels are thought to reflect, in part, luminal release of NO;[78] therefore, an increase in serum nitrate/nitrite levels might have been expected if NO synthesis was increased by bradykinin-dependent mechanisms. The effects of quinapril on endothelial function in this study may be related to a reduction in NO degradation resulting from reduced intracellular production of superoxide anions.[56] With reduced NO degradation, a negative feedback system may reduce NO synthesis [79] which would account for reduced serum nitrate/nitrite levels.

2.4.3 In Patients with Hypertension

Quinapril has also been shown to improve FMD in patients with hypertension in one small randomised study.[70] In this investigation, 26 patients with mild to moderate hypertension received 3 months of once-daily treatment with quinapril 20mg (n = 15) or nitrendipine 10mg (n = 11). Although treatment was not blinded, the investigators analysing the ultrasound images were blinded to the study phase and treatment assignments.

At baseline, FMD in the brachial artery was similar for patients in the quinapril treatment group to that for patients in the nitrendipine treatment group at baseline (1.7 ± 2.8 and 1.1 ± 3.3%, respectively), as was nitroglycerin-induced dilation (12.3 ± 4.8 and 11.0 ± 5.2%, respectively). After 3 months of treatment, FMD had increased to 5.8 ± 4.7% in patients receiving quinapril ($p < 0.005$ *vs* baseline) but was unchanged in patients receiving nitrendipine (1.1 ± 3.9%; $p < 0.01$ *vs* quinapril). No changes in brachial artery diameter, flow ratio or nitroglycerin-induced dilation were observed during the course of the study. Plasma bradykinin levels in the quinapril treatment group increased over 3 months (from 9.7 ± 2.8 to 11.7 ± 1.9 pg/ml; $p < 0.05$) whereas these levels remained stable during nitrendipine therapy (from 10.3 ± 2.9 to 11.4 ± 1.9 pg/ml). Increases in bradykinin did not appear to correlate with the increase in FMD observed in these patients (r = 0.14). Likewise, increases in FMD in the quinapril group did not correlate with a reduction in blood pressure (r = 0.20); indeed, both quinapril and nitrendipine decreased blood pressure to a similar extent.

2.4.4 In Patients with Congestive Heart Failure

The effects of quinaprilat, the active metabolite of quinapril, on endothelial dysfunction in patients with congestive heart failure were investigated in one randomised trial.[73] In this study, 40 patients with congestive heart failure [New York Heart Association (NYHA) functional class II] received an intra-arterial infusion of quinaprilat (1.6 μg/min; n = 15), enalaprilat (5 μg/min; n = 15) or placebo (n = 10). These dosages were previously found to be equipotent in inhibiting the formation of angiotensin II from angiotensin I in the human forearm circulation.[73] FMD was assessed both before and during administration of L-NMMA, an inhibitor of endothelial synthesis of NO.

Following quinaprilat treatment, FMD increased from 6.9 ± 0.6 to 10.2 ± 0.6% ($p < 0.01$). In contrast, enalaprilat had no effect on FMD, even when it was infused twice in the same dose (5 μg/min) or increased up to 30 μg/min; likewise, no change was observed with placebo. When L-NMMA (7 μmol/

min) was administered alone, FMD was reduced. The proportion of FMD inhibited by L-NMMA (the proportion mediated by NO) was significantly increased with quinaprilat treatment, from 2.5 ± 0.5 to 5.61 ± 0.6% ($p < 0.01$), but not with placebo or enalaprilat.

2.5 Effects on Autonomic Function

Angiotensin II is known to interact with the sympathetic nervous system by potentiating the release and increasing reuptake of norepinephrine by the sympathetic nerve terminals.[7] Therefore, ACE inhibitors may reduce sympathetic hyperactivity, a hallmark of progressive heart disease.[6]

Studies in normotensive and hypertensive individuals showed that sympathetic and parasympathetic mediation of heart rate and blood pressure were not affected[80,81] or were only slightly affected[82] by quinapril. However, recent studies suggest that quinapril may have a role in reducing sympathetic hyperactivity following myocardial infarction.[83-86] In these patients, quinapril appears to enhance heart rate variability recovery.[84,85] This may help to improve prognosis in these patients since decreased heart rate variability after myocardial infarction is recognised as a strong predictor of arrhythmic events, sudden death and total mortality.[87]

In one study,[84] 60 patients with uncomplicated acute myocardial infarction were randomised to receive quinapril 5 to 10 mg/day (n = 25), metoprolol 25 to 100 mg/day (n = 25) or placebo (n = 10) for ≈1 month following acute myocardial infarction; patients with stable coronary artery disease (n = 20) and age-matched healthy volunteers (n = 20) were included as controls. Using power spectral analysis, heart rate variability indexes were assessed 5 days after the onset of uncomplicated myocardial infarction (baseline) and again after 30 days of treatment. As expected, baseline heart rate variability was significantly decreased in patients with myocardial infarction compared with the control groups. By the end of the study, both the time and frequency domain heart rate variability indices were significantly improved in patients receiving quinapril or metoprolol versus those receiving placebo ($p < 0.05$ *vs* placebo; no significant differences were observed between quinapril and metoprolol treatment groups). In addition, a significant reduction in the ratio of low- to high-frequency power was seen with both treatments, which signifies a restoration in sympathetic-parasympathetic balance. The effects of quinapril and metoprolol appeared to peak during the late morning and evening hours, when autonomic function was most adversely affected. [83]

Similar results were found in another randomised study by the same investigators evaluating the effects of various ACE inhibitors on heart rate variability.[85] Compared with patients receiving placebo (n = 15), those receiving quinapril (10 mg/day; n = 15), captopril (37.5 mg/day; n = 15) and lisinopril (10 mg/day; n = 15), but not enalapril (10 mg/day; n = 15) or cilazapril (2.5 mg/day; n = 15) showed significant improvements in post-myocardial infarction heart rate variability over 30 days of treatment.[85]

In another randomised investigation,[86] quinapril improved cardiopulmonary baroreflex (CPB) control of sympathetic activity and reduced sympathetic hyperactivity in patients with uncomplicated myocardial infarction. CPB provocation was performed 5 days after the onset of acute myocardial infarction in 30 patients who then received quinapril 10mg once daily or placebo for 5 days. At day 10, CPB sensitivity had increased in both groups, from 14.0 ± 6.0 to 34.0 ± 12.6% in placebo recipients and from 17.1 ± 7.4 to 58.2 ± 36.4% in patients receiving quinapril ($p < 0.05$ *vs* baseline for both groups). However, CPB sensitivity at the end of the study was significantly higher in patients receiving quinapril than that observed in those receiving placebo ($p < 0.05$), as was the mean change in CPB sensitivity (41 ± 35% *vs*20 ± 10%; $p < 0.05$). In addition, the mean plasma norepinephrine level was significantly decreased in patients receiving quinapril (from 416 ± 200 to 331 ± 170 pg/ml; $p < 0.05$) but these levels did not change in patients receiving placebo.[86]

Quinapril has also shown beneficial effects in improving sympathetic-parasympathetic balance in patients with diabetic autonomic neuropathy.[88,89]

2.6 Renal Effects

In patients with hypertension, quinapril ≤40 mg/day reduced renal vascular resistance with little or no effect on renal blood flow or glomerular filtration rate (GFR)[29] [reviewed by Plosker & Sorkin].[3] However, a neutral effect on GFR has not been demonstrated in all clinical studies. In one noncomparative study, GFR was significantly increased in 17 patients with mild to moderate hypertension receiving 20 weeks of quinapril 5 to 20 mg/day.[90] In contrast, GFR and filtration fraction significantly decreased in 19 patients with hypertension who received quinapril 10 to 40 mg/day for 1 year in another study; renal plasma flow remained constant.[91]

Quinapril has also been shown to reduce albumin urinary excretion rate (UAE) in patients with diabetes mellitus and/or hypertension in clinical trials (discussed in section 4.1.3). The antiproteinuric action of ACE inhibitors appears to be unrelated to their blood pressure-lowering effects.[92] This is possibly a result of reduced glomerular capillary pressure seen with ACE inhibitor treatment, which improves glomerular membrane selectivity.[93]

In patients with congestive heart failure, quinapril increased renal and hepatic blood flow and reduced renal and hepatic vascular resistance without changing GFR.[29,94]

2.7 Metabolic Effects

Unlike other antihypertensive agents such as diuretics and β-adrenoceptor antagonists,[95] quinapril treatment either has no effect on[96] or improves the lipid profile in patients with hypertension or congestive heart failure. In one noncomparative study investigating the effect of quinapril on blood lipids, 16 weeks of quinapril 10 to 40 mg/day significantly decreased total cholesterol and LDL-C by 3.3 and 5.1% and increased high-density lipoprotein cholesterol (HDL-C) by 5.9% in 98 patients with mild to severe hypertension; a nonsignificant reduction in triglyceride levels was also observed.[97] In another study including 15 patients with hypertension and dyslipidaemia receiving quinapril 20 mg/day for 6 months in combination with a low lipid diet, mean total cholesterol, triglycerides and LDL-C levels were reduced by 44, 29 and 39 mg/dl, respectively ($p < 0.002$ for all).[98] Improvements in blood lipids have been observed in other clinical trials in patients with hypertension.[34,99-101]

In addition, quinapril ≤40 mg/day has shown neutral or positive effects on glycaemic endpoints in patients with hypertension[100,102,103] and/or diabetes mellitus.[103,104] In one randomised, double-blind study in patients with type 2 diabetes mellitus (n = 60) [also discussed in section 4.1.1],[104] quinapril 20mg once daily had no effect on blood glucose levels, oral glucose tolerance and C-peptide and insulin responses, whereas these parameters significantly worsened in patients receiving metoprolol 100mg once daily over 24 weeks of therapy. A small, but significant increase in glycosylated haemoglobin (HbA_{1c}) was observed in both treatment groups, although the absolute increase tended to be lower in the quinapril group (nonsignificant difference).[104]

Quinapril may actually increase insulin sensitivity in patients with hypertension. Following 3 months of quinapril treatment (10 to 20 mg/day) vascular insulin sensitivity was significantly increased in 11 patients with hypertension;[105] however, in another study,[106] 12 weeks of quinapril treatment (20 mg/day) had no significant effect on insulin sensitivity, glucose effectiveness or β-cell function in 17 obese men with mild to moderate hypertension.

3. Overview of Pharmacokinetic Properties

The pharmacokinetic properties of quinapril have previously been extensively reviewed,[2,3] so this section provides a brief overview. The pharmacokinetics of quinapril and quinaprilat in healthy volunteers are outlined in table I.

Table I. Pharmacokinetics of quinapril and quinaprilat in 12 healthy male volunteers receiving single oral doses[108]

Parameter	Quinapril dose (mg)				
	2.5	10	20[a]	40	80
C_{max} (μg/L)					
Quinapril	ND	65	153	207	536
Quinaprilat	41	223	607	923	1760
t_{max} (h)					
Quinapril	ND	0.7	0.8	1.4	0.9
Quinaprilat	2.1	1.6	1.9	2.3	1.5
$AUC_{0-\infty}$ (μg/L • h)					
Quinapril	ND	93	265	373	677
Quinaprilat	167	803	2423	3386	6212
$t_{½}$ (h)					
Quinapril	ND	0.78	0.88	0.92	0.83
Quinaprilat	2.1	1.8	2.2	1.9	1.9
UE_{0-72h} (%)					
Quinapril	ND	3.7	3	3.1[b]	3.4
Quinaprilat	25	29	29	27[b]	29

a From a separate group of four volunteers.

b Urinary excretion was evaluated up to 24 hours after administration.

$AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; **C_{max}** = maximum plasma concentration; **ND** = not determined owing to low concentrations; **t_{max}** = time to reach C_{max}; **$t_{½}$** = elimination half-life; **UE_{0-72h}** = urinary excretion from time 0 to 72 hours after administration.

After oral administration of quinapril in healthy volunteers, approximately 60% of the dose is absorbed and peak plasma concentrations (C_{max}) are observed within 1 hour. Following absorption, quinapril undergoes rapid de-esterification, primarily in the liver, to its major active diacid metabolite, quinaprilat (≈40% of oral dose),[29] and two minor, inactive diketopiperazine metabolites.[107] Peak plasma concentrations of quinaprilat occur within approximately 2 hours (table I).[107-109] Both the parent drug and its metabolite show dose-related increases in C_{max} after single (table I) or repeated oral doses of quinapril 2.5 to 80mg;[107] however, wide interindividual variation in C_{max} has been reported.[2] No accumulation of quinapril or quinaprilat was noted in healthy volunteers receiving quinapril 20 mg/day over 7 days, and steady state plasma concentrations were achieved within 3 days.[107] In contrast to those of other ACE inhibitors captopril and moexipril,[110] C_{max} values of quinapril and quinaprilat are not affected by coadministration of food, although time to reach C_{max} may be increased by ≈30 minutes.[107,111] Quinapril and its metabolites are highly bound to plasma proteins (≈97%).[29,107]

Following oral or intraperitoneal administration, [^{14}C]quinapril distributed rapidly and extensively to all tissues except the brain in animal studies.[29,112] This extensive tissue distribution is short lived in all tissues except those rich in ACE such as the lungs and kidney.[112]

The mean elimination half-life of quinapril is 1 hour, whereas the mean elimination half-life of quinaprilat is ≈2 hours. As observed with other ACE inhibitors, the terminal elimination phase of quinaprilat is prolonged (≈25 hours),[29,113] presumably because of the slow release of quinaprilat from ACE.[107] The primary route of elimination is via the kidney: quinaprilat accounts for 30% of the oral dose recovered in the urine, quinapril accounts for 3% and the two diketopiperazine metabolites account for 6% each. The remainder of the oral

dose is eliminated in the faeces as unabsorbed quinapril or by biliary excretion of quinapril and its metabolites.[107]

3.1 Special Populations

The pharmacokinetics of quinapril have been investigated in various populations including patients with renal[114-119] or hepatic[120] insufficiency, elderly patients,[121] patients with congestive heart failure[41,122] and lactating mothers.[120]

Both renal and hepatic impairment have been shown to affect the pharmacokinetic properties of quinapril and quinaprilat. Compared with that in volunteers with normal renal function,[114] quinaprilat half-life was prolonged in patients with renal dysfunction (2.3 *vs* 11.3 hours), and quinaprilat C_{max} and area under the concentration-time curve (AUC) were increased (481 *vs* 1616 μg/L and 1856 *vs* 18700 μg • h/L). Similar changes were observed for quinapril.[114] In volunteers with varying degrees of renal impairment, the half-life of quinaprilat increased as creatinine clearance (CL_{CR}) decreased.[115-117] Chronic haemodialysis[119] or continuous ambulatory peritoneal dialysis[118] had little effect on the elimination of quinaprilat in patients with end-stage renal failure, with only a small amount of quinaprilat being excreted in dialysate (5.4 and 2.6% of the total quinapril dose, respectively).

In a group of patients with hepatic insufficiency resulting from cirrhosis,[120] mean quinaprilat C_{max} and AUC values were 70 and 50% lower, respectively, than those observed in patients with normal hepatic function, presumably because of a reduced rate and extent of quinapril metabolism to the active moiety quinaprilat.[120]

Elimination of quinapril and quinaprilat may be reduced in patients with congestive heart failure [41,122] and in elderly patients.[112,121] However, these reductions appear to be related to a reduction in renal function. In a study involving 12 patients with congestive heart failure,[122] CL_{CR} was found to be the major determinant of quinaprilat clearance and the presence or severity of congestive heart failure had a minimal effect. Similar results were observed in studies in elderly patients.[112,121] In a review of two unpublished studies,[112] quinaprilat C_{max} and AUC were 27 and 50% higher, respectively, in elderly patients with mild hypertension (mean age 73 years) than those in younger individuals (mean age 25 years). These results were consistent with the fact that CL_{CR} was lower in elderly than in younger subjects (mean of 62 *vs* 99 ml/min).[112] In another study involving eight elderly patients (mean age of 76 years) with hypertension,[121] a small increase in quinaprilat AUC was observed over 8 days of quinapril 10mg administration: AUC increased from 1650 μg • h/L after the first quinapril dose to 1823 μg • h/L on day 8 ($p < 0.05$); however, the investigators considered this difference small and of no clinical significance.

A recent study in breast-feeding human mothers showed that the quinapril dose reaching the infant is very low. In this study (n = 6 lactating mothers), only 1.6% of the maternal quinapril dose (20mg) reached the infant. The milk to plasma concentration ratio for quinapril was 0.12 [95% confidence interval (CI): 0.009 to 0.14], and no quinapril was detected in the milk after 4 hours. Furthermore, no quinaprilat was detected in any of the milk samples. These results suggest that quinapril may be used during breast-feeding;[123] however, the effect of such small doses of quinapril on the developing infant are not known so caution is advised when this drug is given to nursing women.[29]

3.2 Drug Interactions

The pharmacokinetics of quinapril are not affected by concomitant administration of HCTZ, propranolol or cimetidine. In addition, quinapril did not affect the pharmacokinetics of digoxin or HCTZ or the anticoagulant effect of warfarin.[29] However, coadministration of quinapril and tetracycline can result in reduced oral absorption of the latter, possibly due to binding of tetracycline with magnesium in the quinapril tablet formulation;[29] this interaction can be avoided if tetracycline is administered 2 to 3 hours before or after quinapril.[124]

4. Therapeutic Efficacy

The therapeutic efficacy of quinapril was extensively reviewed in *Drugs* in 1990 [2] and in 1994.[3] Several studies have since been published confirming the efficacy of quinapril in patients with hypertension (section 4.1) and congestive heart failure (section 4.2); two large studies have also investigated the role of quinapril in patients with coronary artery disease (section 4.3).

4.1 Hypertension

In general, clinical studies investigating the antihypertensive effects of quinapril monotherapy (section 4.1.1) included patients with mild to moderate hypertension (patients with DBP 95 to 120mm Hg and/or SBP >140mm Hg following a 2- to 6-week washout period), whereas patients with more severe disease received combination therapy with quinapril plus a diuretic, usually HCTZ (section 4.1.2). In the majority of trials, dosages were titrated to response at intervals of 2 to 6 weeks, although dosages were fixed in some studies. Most trials investigated once-daily dosages over the range of 10 to 40mg; however, twice-daily dosing up to 80 mg/day was used in some studies, and a diuretic was added if blood pressure remained elevated in some investigations. Quinapril was administered orally in all clinical studies.

Patients responding to treatment were usually defined as those with a DBP of ≤90mm Hg and/or a reduction of ≥10mm Hg from baseline.

4.1.1 Monotherapy

As reported in the previous reviews of quinapril in *Drugs*,[2,3] quinapril 10 to 80 mg/day consistently produced statistically and clinically significant reductions in blood pressure in patients with mild to moderate hypertension in randomised, placebo-controlled trials. In the largest of these studies (n = 270),[125] SBP/DBP was reduced by a mean of 17.1/11.1mm Hg in patients receiving quinapril 20 to 80mg once daily over 12 weeks compared with 0.4/1.2 in those receiving placebo, with 58 *vs* 11% of patients showing a response ($p < 0.05$ *vs* placebo).[2,3,125]

The efficacy of quinapril in patients with mild to moderate hypertension has since been further established in a number of randomised and non-comparative investigations (see later in this section).

Comparative Trials

To date, the antihypertensive efficacy of quinapril in patients with mild to moderate hypertension has been compared with that of other ACE inhibitors (enalapril,[126-128] captopril[129,130] and lisinopril[32,34,100,131]) as well as other classes of agents including β-adrenoceptor antagonists (atenolol and [132,133] metoprolol[104,134]) and calcium antagonists (nifedipine,[135] amlodipine[136] and nitrendipine[137]). Quinapril has also been compared with captopril and enalapril in patients with moderate to severe hypertension who were receiving concomitant diuretic therapy (discussed in section 4.1.2).[138-140]

Many of these investigations have been discussed in depth in the previous reviews of quinapril;[2,3] however, a brief synopsis of these older trials, in addition to the results of recent studies (shown in table II) are discussed below.

As outlined in the previous reviews, once-daily treatment with the same dosages of quinapril or enalapril (10 to 40 mg/day) produced similar reductions in DBP and SBP over 12 to 28 weeks of treatment in three randomised, double-blind studies (n = 53 to 258).[126-128] Similarly, quinapril 10 to 40 mg/day once or twice daily was at least as effective as captopril 25 to 150 mg/day twice or three times daily in reducing DBP in two, 12-week randomised, placebo-controlled trials (n = 40 and 403).[129,130] Quinapril 10mg once daily was also shown to produce superior blood glucose lowering effects to lisinopril 10mg once daily in a 12-week, randomised, double-blind study in patients with mild to moderate hypertension (n = 47);[34] however, quinapril (20 to 40mg once daily) was not as effective as lisinopril (10 to 20mg once daily) in another 8-week, randomised, nonblind investigation involving 23 patients with mild to moderate hypertension.[32] Since the previous review of quinapril was published in 1994,[3] two additional

Table II. Recent clinical trials[a] comparing the antihypertensive efficacy of quinapril (Q) monotherapy with other antihypertensive agents in patients (pts) with mild to moderate hypertension[b]

Reference (study design)	No. of evaluated pts	Dosage regimen (duration of treatment)	Mean reduction in baseline SBP/DBP (mm Hg) [type of measure]	Response rate (%)[c]
Compared with lisinopril (L)				
Langan et al.[132][d]	36	Q 5-40mg od (26 wks)	22/14.3*** [sitting]	75
(r, db, pl, mc)	39	L 2.5-20mg od (26 wks)	21.1/15.5*** [sitting]	69.2
Montero Carrasco et al.[101][e]	25	Q 10-20mg od (8 wks)	24.6***/18*** [sitting] 10.6*/3.5* [24h ABP]	NR
(r, nb, pl)	25	L 10-20mg od (8 wks)	20***/18.8*** [sitting] 30.8***/11.6*** [24h ABP]	NR
Compared with β-adrenoceptor antagonists				
Ostman et al. [105][f]	26	Q 20mg od (24 wks)	15***/10*** [supine]	77
(r, db, pl, mc)	34	M 100mg od (24 wks)	11**/14***† [supine]	85
Rosenthal et al.[135][g] (r, db, pl)	5053	Q 10-40mg od (12 wks)	NR	62.3/62.9 (men/women)[h]
	506	M 50-200mg od (12 wks)	NR	65.8/62.6 (men/women)[h]
Compared with calcium antagonists				
Ding et al.[137]	27	Q 10-40mg od (10 wks)	10***/6*** [24h ABP]	NR
(r, db, co)		A 5-10mg od (10 wks)	15***/9*** [24h ABP]	NR
Schulte et al.[138] [i]	52	Q 10-40mg od (24 wks)	14**/13** [sitting]	70
(r, db, pl, mc)	50	N 10-40mg od (24 wks)	15**/11**† [sitting]	63

a Published since the last review of quinapril.[3]

b Classified as DBP 90 to 109;[101,137] 95 to 114;[135,138] or 100 to 120mm Hg.[132]

c Patients whose DBP was reduced to ≤90mm Hg or by ≥10mm Hg.

d Study in elderly patients (aged 60 to 75 years; mean ≈67 years).

e Article in Spanish.

f Patients with type 2 diabetes mellitus and hypertension (severity of hypertension not stated); this study also evaluated glycaemic control (discussed in section 2.7) and changes in urinary albumin excretion (section 4.1.3).

g Primary endpoint in this study was incidence of adverse events.

h Based on the results of 4846 patients (87%) who completed the entire 12 weeks of treatment.

i Article in German.

A = amlodipine; **ABP** = ambulatory blood pressure; **co** = crossover; **db** = double-blind; **DBP** = diastolic blood pressure; **M** = metoprolol; **mc** = multicentre; **N** = nitrendipine; **nb** = nonblind; **NR** = not reported; **od** = once daily; **pl** = parallel group; **r** = randomised; **SBP** = systolic blood pressure; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ *vs* baseline; † $p < 0.05$ between treatment-group difference, $p < 0.05$ *vs* Q.

studies have compared the antihypertensive efficacy of quinapril (5 to 40mg once daily) with lisinopril (2.5 to 20mg once daily) in mild to moderate hypertension (table II).[100,131] In both these investigations, reductions in sitting or clinical blood pressure were similar between treatment groups; however, lisinopril produced slightly greater reductions in mean 24-hour ambulatory blood pressure than quinapril in one study[100] (table II).

In previous double-blind, randomised comparisons with the β-adrenoceptor antagonist atenolol (50 to 100mg once daily), quinapril (20 to 40mg once daily) showed similar efficacy to this agent in patients with mild to moderate hypertension in one study (n = 50);[133] however, lower doses of quinapril (10 to 20mg once daily) appeared to be less effective in controlling 24-hour ambulatory blood pressure than atenolol (50 to 100mg once daily) in patients with moderate to severe hypertension in another trial (n = 44).[132] Quinapril has since been been compared with another β-adrenoceptor antagonist metoprolol in two studies (table II).[104,134] In the larger of these studies,[134] patients with mild to moderate hypertension were randomised to receive

once-daily therapy with quinapril 10 to 40mg (n = 5053) or metoprolol 50 to 200mg (n = 506) in a double-blind fashion for 12 weeks. Although antihypertensive efficacy was not the primary endpoint in this study (tolerability was), responder rates were similar for both the quinapril and metoprolol treatment arms (62.3 and 65.8% for men and 62.9 and 62.6% for women in an intent-to-treat analysis). No data on specific changes in blood pressure values were reported in this trial.

In the other investigation,[104] 72 patients with type 2 diabetes mellitus and hypertension (mean baseline SBP/DBP 163 to 171/98mm Hg) were randomised to receive quinapril 20mg or metoprolol 100mg for 6 months. SBP and DBP were significantly reduced from baseline in both treatment groups, but the reduction in DBP was more pronounced ($p < 0.05$) with metoprolol (table II). In contrast with quinapril, metoprolol was associated with a worsening of glycaemic control (section 2.7).

Quinapril also shows similar antihypertensive efficacy to various calcium antagonists.[135-137] As outlined in the previous review,[3] once-daily quinapril (5 to 20 mg/day) produced comparable reductions in SBP and DBP levels to twice-daily therapy with sustained-release nifedipine (20 to 80 mg/day) in patients with mild to moderate hypertension over 16 weeks in a large randomised, double-blind study (n = 339).[135] In addition, recent studies indicate that once-daily quinapril (10 to 40 mg/day) has similar antihypertensive efficacy to once-daily amlodipine (5 to 10 mg/day)[136] and nitrendipine (10 to 40 mg/day)[137] in patients with mild to moderate hypertension (table II).

Noncomparative/Observational Trials

In recent large noncomparative investigations,[141-143] quinapril 10 to 80 mg/day produced pronounced reductions in blood pressure over 2 to 6 months of treatment in patients with mild to moderate hypertension, and showed similar efficacy in elderly patients and/or those with diabetes mellitus.

In the largest, fully published investigation (the EUREKA study),[141] 8 weeks of once-daily therapy with quinapril 40mg significantly improved blood pressure control in 6082 patients with poorly controlled hypertension. Overall, blood pressure was reduced by a mean of 25/15mm Hg ($p < 0.001$ *vs* baseline for SBP and DBP). As shown in figure 4, significant improvements in SBP and DBP were observed regardless of previous treatment. Control of DBP (≤90mm Hg) was achieved in 90% of patients, adequate control of SBP (≤140mm Hg) was achieved in 56% of patients and 54% achieved adequate control of both DBP and SBP. Significant improvements were also observed in a subgroup of 1266 hypertensive patients with diabetes mellitus. At the start of the trial, fewer than 1% of these patients had blood pressure levels ≤135/85mm Hg but after quinapril treatment, 65% had achieved DBP ≤85mm Hg, 21% had SBP ≤135mm Hg and 19% had achieved both. Overall, blood pressure was reduced by a mean 25/14mm Hg in these patients [$p < 0.0001$ *vs* baseline].

Similar results were found in another noncomparative study investigating the antihypertensive efficacy of quinapril 10 to 80 mg/day in 10 782 patients with mild to moderate hypertension (the ASCEND study).[143-145] This trial has not yet been published in full, but results from a mod-

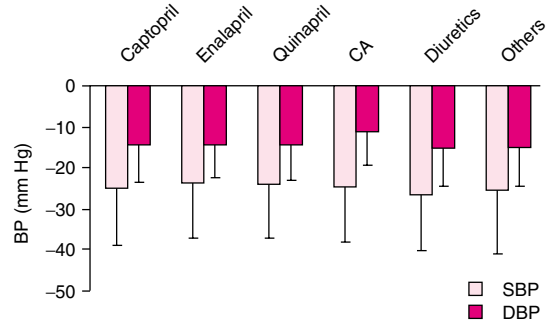

Fig. 4. Mean reduction from baseline in systolic (SBP) and diastolic blood pressure (DBP) after treatment with quinapril 40 mg/day in patients with poorly controlled hypertension previously treated with captopril (mean dosage 72 mg/day, n = 611), enalapril (mean dosage 23 mg/day, n = 634), quinapril (mean dosage 23 mg/day, n = 354), calcium antagonists (CA) [n = 679], diuretics (n = 591), or others (n = 1224) in a noncomparative trial. All values are significantly different from baseline ($p < 0.0001$).[141]

ified intent-to-treat population (n = 9384) treated for 12 weeks are available in abstract form. Overall, blood pressure was reduced by 22/12.5mm Hg and blood pressure control (SBP/DBP ≤140/90mm Hg) was achieved in 54.2% of the intent-to-treat population. In the 5367 patients who completed 12 weeks of therapy, blood pressure control was achieved in ≈72%. This study also evaluated the response to quinapril treatment in various subpopulations. As illustrated in figure 5, elderly (aged 65 to 74 years) and very elderly (aged ≥75 years) patients achieved comparable control rates to those seen in younger patients, which is consistent with results observed in previous studies.[146-148] In addition, no gender bias was found, and patients with diabetes mellitus had similar control rates to that in the total population (figure 5). However, control rates in African-American patients were slightly lower than those in Caucasians (figure 5). Indeed, a reduced antihypertensive response in African-American versus Caucasian patients is a common finding with ACE inhibitor therapy.[149]

In another study, 752 patients with mild to moderate hypertension received quinapril 10 to 40 mg/day for 12 weeks.[150] Overall, mean SBP/DBP decreased by a mean of 28/19mm Hg ($p < 0.0001$) and 67.1% of the 711 patients completing the study showed a response (SBP/DBP <140/90mm Hg or a reduction in SBP of ≥20mm Hg). By the end of the trial, 395 patients required 10 mg/day, 260 required 20 mg/day and only 56 patients (7.9%) required 40 mg/day.

In another investigation, the antihypertensive efficacy of once-daily quinapril 10 to 40mg was maintained over 6 months of treatment in 3742 patients with mild to moderate hypertension. In this study,[142] patients who received quinapril either as a monotherapy (78%) or in combination with other therapy (22%) had their blood pressure reduced from 161/98mm Hg to 145/88mm Hg at 3 months and to 144/87mm Hg at 6 months.

Most large-scale clinical trials have been ≤6 months in duration, but available data in a limited number of patients show that the blood pressure-lowering efficacy of quinapril is maintained over 1,[91,99,134,151] 2[43] or 3[46] years of treatment.

Effect of Dose-Titration Interval

The dosage titration interval may influence the antihypertensive response to quinapril. As previously reviewed by Wadworth & Brogden,[2] the response rate to quinapril 10 to 20mg was reportedly >70% when the titration interval was 4 weeks and 60 to 70% when the interval was shorter. Similar results were found in a recent large, random-

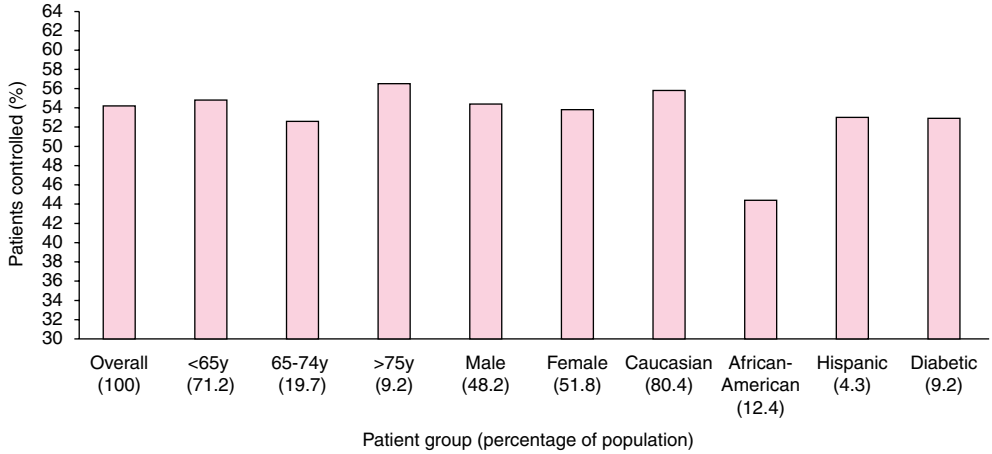

Fig. 5. Effect of age, sex, ethnicity and diabetic status on blood pressure (BP) control rate in a large, prospective, noncomparative trial involving 9384 patients receiving quinapril 10 to 80 mg/day for 12 weeks.[143] BP control was defined as systolic/diastolic BP ≤140/90mm Hg.

ised, prospective study comparing fast (every 2 weeks) versus slow (every 6 weeks) titration of quinapril in 2935 patients with mild to moderate hypertension.[152]

In this investigation, therapy with quinapril was initiated at a dose of 20mg once daily; this dose was then doubled over two clinic visits until blood pressure was <140/90mm Hg or a dose of 80mg was reached. By the third clinic visit (week 6 for the fast titration group and week 18 for the slow titration group), the mean reduction in SBP and DBP and the blood pressure response and control rates were significantly greater in the slow- versus fast-titration group (figure 6). However, a greater proportion of patients randomised to the fast titration sequence were still on quinapril treatment at visit three (73.7 *vs* 64.5%).[152]

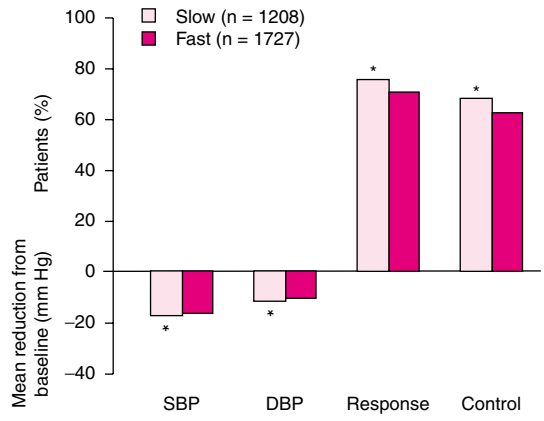

Fig. 6. Slow versus fast titration of quinapril. Mean reductions from baseline in systolic (SBP) and diastolic blood pressure (DBP), and response and control rates in patients undergoing slow (every 6 weeks) or fast (every 2 weeks) titration of quinapril (10 to 80mg once daily). A response was defined as a reduction of ≤10mm Hg in SBP or SBP/DBP ≤130/85mm Hg and blood pressure control was defined as SBP/DBP <140/90mm Hg; final measures were taken after three visits (week 18 and week 6 for slow and fast titration, respectively); * $p < 0.05$ *vs* fast titration.[152]

4.1.2 Combination Therapy

A large percentage of patients with hypertension require a combination of antihypertensive drugs to achieve the recommended targets for blood pressure control. Indeed, it is estimated that fewer than half of all patients with hypertension achieve adequate control with monotherapy and ≈33% require three or more drugs.[153-155]

As with other ACE inhibitors, concomitant therapy with a thiazide diuretic enhances the antihypertensive efficacy of quinapril. Results of previous clinical trials show that the addition of a diuretic (usually HCTZ) to quinapril monotherapy increases the response rate from ≥50% to ≈70 to 90% in patients with hypertension (reviewed by Plosker & Sorkin[3] and Wadworth & Brogden[2]).

As reported in the previous reviews,[2,3] quinapril 10 to 40mg twice daily was at least as effective as other ACE inhibitors captopril (50 to 200mg twice daily)[139]and enalapril (10 to 40mg twice daily)[138] at reducing DBP when these agents were added to diuretic therapy (HCTZ or chlorthalidone 25 mg/day) in patients with moderate to severe hypertension (DBP ≥105mm Hg during diuretic therapy or ≥115mm Hg during placebo treatment) in two randomised, double-blind trials (n = 170 and 172). Indeed, once-daily quinapril (10 to 40 mg/day) produced similar reductions in DBP to twice-daily captopril (50 to 200 mg/day) in another randomised, double-blind study in patients (n = 195) with moderate to severe hypertension receiving concomitant HCTZ (25 mg/day).[138]

More recently, two randomised, double-blind trials have compared the antihypertensive efficacy of quinapril and HCTZ monotherapy with that of these agents combined.[102,156] In both these studies, quinapril and HCTZ combination therapy was significantly more effective at lowering blood pressure than either drug as monotherapy over 8 weeks of treatment in patients with moderate to severe hypertension (DBP ≥105 and ≤120mm Hg at the end of a 2- to 4-week placebo baseline period during which other antihypertensive medication was withdrawn) [table III].

4.1.3 Renoprotective Effects

Microalbuminuria (abnormally elevated UAE) is considered to be a marker of glomerular damage that strongly predicts the development of overt proteinuria and progressive renal dysfunction.[93,157]

Table III. Antihypertensive efficacy of quinapril (Q) combined with hydrochlorothiazide (HCTZ) versus that of either drug as monotherapy in two randomised, double-blind, placebo-controlled trials in patients (pts) with moderate to severe hypertension[a]

Reference	No. of evaluated pts	Dose regimen (duration of treatment)	Mean reduction in baseline SBP/DBP (mm Hg)[b]	Response rate (%)[c]
Lenz et al.[159][d]	101	Low-dose: Q 10mg od (4 wks) High-dose: Q 20mg od (4 wks)	Low-dose: 13.1*/12.1* High-dose: 19.7*/17*	66
	109	Low-dose: HCTZ 12.5mg od (4 wks) High-dose: HCTZ 25mg od (4 wks)	Low-dose: 11.6*/12.5* High-dose: 20.4**/17.2**	70
	108	Low-dose: Q 10mg + HCTZ 12.5mg (4 wks) High-dose: Q 20mg + HCTZ 25mg (4 wks)	Low-dose: 17.7/14.6 High-dose: 27.1/19.5	72
Romero et al.[103]	96	Q 20mg od (8 wks)	13.2*/12.1*	65
	96	HCTZ 12.5mg od (8 wks)	12.4*/11.0*	53*
	99	Q 20mg + HCTZ 12.5mg (8 wks)	17.6/14.4	69

a Patients with supine DBP ≥105mm Hg and ≤120mm Hg after 2 to 4 weeks of placebo treatment; baseline SBP/DBP for all patients ranged from 167 to 173/109 to 110mm Hg.

b Supine blood pressure at trough.

c Patients whose DBP was reduced by ≥10mm Hg at last evaluable visit.

d All patients received low-dose therapy for the first 4 weeks and then 88% received high-dose therapy (forced titration) for the following 4 weeks (91 patients in Q monotherapy group; 94 in HCTZ monotherapy group and 99 in combination group).

DBP = diastolic blood pressure; **od** = once daily; **SBP** = systolic blood pressure; * $p < 0.05$, ** $p < 0.001$ *vs* same-dose combination therapy.

In patients with hypertension and/or diabetes mellitus, elevated UAE is also associated with a greater incidence of cardiovascular events.[157,158]

Lowering blood pressure reduces UAE in patients with hypertension; however, it is thought that ACE inhibitors have additional antiproteinuric effects that go beyond their blood pressure-lowering action.[92,159] ACE inhibitors have been shown to reduce UAE and slow the progression of overt nephropathy in patients with diabetic or nondiabetic nephropathy to a greater extent than other antihypertensive agents, despite a similar blood pressure-lowering effect.[92,93,159,160] ACE inhibitors have also produced greater reductions in UAE than other commonly used antihypertensive agents in patients with hypertension,[161-165] but this has not been demonstrated in all trials.[157,166]

The effects of quinapril on UAE in patients with hypertension and/or diabetes mellitus are discussed below.[91,167]

Comparative Trials

The effect of quinapril on UAE in patients with hypertension was similar to that of captopril[167] and metoprolol[104] and greater than that of HCTZ and/or atenolol[91] in three small randomised comparative trials.

In the first of these investigations,[167] quinapril 10 to 40mg once daily and captopril 25 to 75mg twice daily produced significant and comparable reductions in UAE in patients with mild to moderate hypertension over 12 weeks of treatment. Mean baseline UAE was reduced from 79.2 to 47.5 mg/24h ($p = 0.031$) and from 85 to 59 mg/24h ($p = 0.025$) in patients receiving quinapril (n = 17) or captopril (n = 17), respectively.

In another randomised, double-blind study,[104] (also discussed in section 2.7 and section 4) the effect of 6 months of once-daily quinapril 20mg or metoprolol 100mg on UAE in patients with type 2 diabetes mellitus was evaluated in a small group of individuals with baseline microalbuminuria (UAE 30 to 300 mg/24h) or macroalbuminuria (UAE >300 mg/24h). In these patients, baseline UAE was reduced from 11 to 7 mg/24h in quinapril recipients (n = 7) and from 14.8 to 8 mg/24h in metoprolol recipients (n = 11) [nonsignificant difference from baseline in both treatment groups].

In another study,[91] the effects of quinapril on renal function were compared with those of HCTZ

and/or atenolol in a group of 40 patients with hypertension. Patients who had already achieved adequate blood pressure control with diuretics and/or β-adrenoceptor antagonists but had an elevated UAE (30 to 300 mg/24h) were randomised to continue with their previous therapy with HCTZ (25 to 50 mg/day) and/or atenolol (50 to 100 mg/day) or switch to quinapril therapy (10 to 40mg once daily). After 1 year of treatment, both treatment groups showed similar and significant improvements in blood pressure control: mean baseline blood pressure was reduced by a mean of 17/12mm Hg ($p < 0.01$) in patients receiving HCTZ and/or atenolol and by 23/17mm Hg ($p < 0.01$) in patients receiving quinapril. However, significant reductions in UAE were observed only in the quinapril group. In quinapril recipients, UAE decreased from 68.5 to 47.2 mg/24h ($p = 0.05$ *vs* baseline), whereas UAE increased in patients receiving HCTZ and/or atenolol from 59.1 to ≈78 (endpoint estimated from graph). GFR and filtration fraction were also significantly reduced in quinapril recipients ($p < 0.05$) and renal plasma flow remained unchanged in both groups.[91]

Noncomparative Trials

Quinapril also significantly reduced blood pressure and UAE in patients with hypertension, including some patients with type 2 diabetes mellitus, in two noncomparative investigations.

In the largest of these studies,[168] 213 patients with mild to moderate essential hypertension (without evidence of diabetes mellitus) received quinapril 10 to 40 mg/day or quinapril 20 mg/day plus HCTZ 12.5 mg/day. After 12 weeks of treatment, blood pressure was reduced by a mean of 11/10mm Hg (from 155/102 to 144/92mm Hg; $p = 0.001$). This decrease was accompanied by a significant reduction of 6.1 mg/24h in UAE (from 20.6 to 14.5 mg/24h; $p = 0.0001$) in patients whose UAE was <300 mg/24h at baseline (n = 165 of 175 evaluable patients). UAE was most consistently decreased in patients who were considered proteinuric (UAE >300 mg/24h; n = 10) or microalbuminuric (UAE 30 to 300 mg/24h; n = 34) at baseline, although UAE was also reduced in patients with normal renal function (UAE <30 mg/24h; n = 131): reductions in UAE were observed in 90, 79 and 60% of these patients, respectively. Mean reductions in UAE for these patient groups are shown in figure 7. Overall, 19 patients who were microalbuminuric at baseline experienced a decrease in UAE to within the normal range; six patients in the normal range became microalbuminuric and one microalbuminuric patient shifted to the proteinuric range. No significant changes in plasma creatinine or CL_{CR} were evident in patients with UAE <300 mg/24h.[168]

Reductions in baseline UAE were seen in all dosage groups (34.3% reduction in patients receiving 10 to 20 mg/day, 29.5% in those receiving 40 mg/day and 14.0% in those receiving combination therapy) and all age groups (11.8% reduction in patients aged <45 years, 29.8% in those aged 46 to 64 years and 37.5% in those aged >65 years).

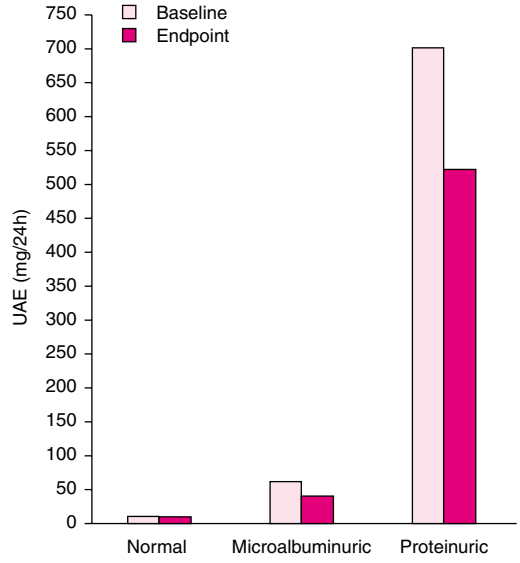

Fig. 7. Mean change in urinary albumin excretion rate (UAE) with quinapril in patients with varying renal status. Data are from 175 patients [131 with normal UAE (<30 mg/24h); 34 with microalbuminuria (30 to 300 mg/24h); 10 with proteinuria (>300 mg/24h] for whom urinary data are available at both baseline and endpoint; patients received quinapril 10 to 40 mg/day or quinapril 20 mg/day plus 12.5 mg/day hydrochlorothiazide for 12 weeks.[168]

In the other investigation,[103] the effect of once-daily quinapril 10 to 40mg on blood pressure, UAE and glucose profiles was investigated in 30 patients with hypertension and 24 patients with hypertension and type 2 diabetes mellitus. Following 8 weeks of treatment, the mean reduction in baseline SBP/DBP was similar for patients with hypertension and those with hypertension and diabetes mellitus (22/20 and 22/18mm Hg, respectively; $p = 0.01$ *vs* baseline for both). In addition, mean UAE was significantly reduced from 39.6 to 16.7 mg/24h ($p < 0.05$) in patients with hypertension and from 46.8 to 21.2 mg/24h ($p < 0.05$) in patients with hypertension and diabetes mellitus. At baseline, 63% of patients had normal UAE (<21 mg/24h), 31% were microalbuminuric (UAE >21 to 216 mg/24h) and 6% had proteinuria (UAE >216 mg/24h). The reduction in UAE observed with quinapril was directly correlated with baseline UAE ($r = 0.706$; $p < 0.05$) and was not correlated with changes in SBP, DBP or mean arterial blood pressure in either group of patients. Quinapril had no effect on insulin sensitivity, as indicated by the integrated insulin and glucose responses to an oral glucose load, and by the plasma glucose/plasma insulin index.

4.2 Congestive Heart Failure

Numerous studies have demonstrated that quinapril ≤40 mg/day, either alone or as an add-on to existing therapy, produces beneficial haemodynamic[35-39] and echocardiographic changes[39,40] and improves exercise tolerance,[35,37,39,40,169,170] symptoms[37,171] and disease severity[170,171] in patients with congestive heart failure, including those who were resistant to previous digitalis and/or diuretic therapy. Beneficial effects of quinapril were maintained for up to 1 year of continued treatment (reviewed by Wadworth & Brogden[2] and Plosker & Sorkin[3]). The beneficial effects of quinapril on exercise tolerance appear to be dose related, and improvements in exercise duration generally require dosages of 20 to 40 mg/day.[29]

Although beneficial effects of quinapril on survival have not been demonstrated, the beneficial effects of other ACE inhibitors in reducing morbidity and mortality in patients with congestive heart failure[172-175] or LV dysfunction after myocardial infarction[176-180] are well established. Furthermore, available evidence suggests that there are no differences among available ACE inhibitors in their effects on symptoms, clinical status, mortality or disease progression.[181,182] In a meta-analysis of >30 published and unpublished randomised, placebo-controlled trials investigating the effects of ACE inhibitor therapy in >7000 patients (including five trials with 875 patients using quinapril),[181] the rates of mortality and hospitalisations associated with congestive heart failure were consistent among the various ACE inhibitors.

Since the previous review, three studies have compared the effects of quinapril with another ACE inhibitor, captopril.[183-185]

Two of these studies were randomised, placebo-controlled, double-blind investigations which included 146[183] and 131[184] patients with mild to moderate congestive heart failure (NYHA functional classes I to III). After a 2-week placebo washout period during which other antihypertensive therapy (excluding existing diuretic and/or digitalis therapy) was discontinued, patients were randomised to receive quinapril 10 to 20mg once daily or captopril 25 to 50mg twice daily (typical maintenance dosages for these agents)[186] for a period of 10[184] or 12[183] weeks. In both studies, captopril and quinapril improved the signs and symptoms of heart failure and improved exercise capacity and echocardiographic parameters to a similar extent (table IV). Furthermore, in one study, NYHA functional class was improved with both agents (figure 8);[184] however, quinapril appeared to be more effective than captopril in reducing the number of patients with NYHA functional class III heart failure. One study also evaluated the effects of concomitant therapy with digoxin on LV function.[184] In patients receiving quinapril, an improvement in LV ejection fraction was observed regardless of whether they were receiving digoxin. However, in patients receiving captopril, significant improvements in LV ejection fraction were

Table IV. Changes in clinical symptoms, echocardiographic parameters and exercise tolerance in patients receiving quinapril 10 to 20mg once daily or captopril 25 to 50mg twice daily in two randomised, double-blind studies[a]

	Acanfora et al.[187]				Gavazzi et al.[186]			
	quinapril (n = 65)		captopril (n = 66)		quinapril (n = 68)		captopril (n = 62)	
	baseline	endpoint	baseline	endpoint	baseline	endpoint	baseline	endpoint
Number (%) of patients with clinical signs and symptoms[b]								
Dyspnoea at rest	7 (12%)	4 (7%)	10 (16%)	3 (5%)*	10 (13.3%)	2 (2.7%)	11 (15.7%)	6 (8.6%)
Dyspnoea at effort	42 (65%)	12 (9%)***	35 (54%)	15 (24%)**	74 (98.7%)	45 (60%)	66 (94.3%)	39 (55.7%)
PND	21 (34%)	8 (14%)*	28 (45%)	10 (16%)**	3 (4%)	0	2 (2.9%)	1 (1.4%)
Orthopnea	12 (19%)	3 (5%)*	14 (23%)	5 (8%)**	8 (10.7%)	4 (5.3%)	6 (8.6%)	2 (2.6%)
Oedema	24 (37%)	3 (5%)****	29 (44%)	5 (8%)	25 (33.3%)	7 (9.3%)	18 (25.7%)	7 (10%)
Lung congestion	44 (68%)	14 (23%)****	40 (61%)	14 (23%)****	22 (29.3%)	3 (4%)†	21 (30%)	9 (12.8%)
Ventricular gallop (S_3)	51 (79%)	27 (44%)****	54 (82%)	40 (66%)****	14 (18.7%)	4 (5.3%)	12 (17.1%)	6 (8.6%)
Atrial gallop (S_4)	15 (23%)	6 (10%)	13 (20%)	10 (16%)*	7 (9.3%)	6 (8%)	7 (10%)	6 (8.6%)
Hepatomegaly	21 (32%)	9 (15%)*	17 (26%)	10 (16%)	19 (25.3%)	16 (21.3%)	16 (22.9%)	14 (20%)
Echocardiographic parameters								
LVESD (mm)	49.6 ± 8.3	47 ± 7.9**	50.8 ± 9	48.4 ± 9**	45.2 ± 1.3	44.9 ± 1.3†	45.7 ± 1.3	43.7 ± 1.2
LVEDD (mm)	61.8 ± 7.4	59.9 ± 6.5**	62.9 ± 8.5	61.3 ± 8.8**	61.5 ± 1.1	61.3 ± 1.1	60.6 ± 1.1	59.6 ± 1.0
LVEF (%)	34.3 ± 6.6	39.3 ± 6.1**	34.6 ± 5.1	38 ± 7.2**	51.2 ± 1.6	52.4 ± 1.7	48.5 ± 1.6	51.6 ± 1.6
Exercise tolerance								
Exercise duration (s)	372	468**	354	426**	422.1	497.2*	451.7	519.0*

a Following a 2-week placebo washout period, patients were randomised to quinapril (10mg once daily) or captopril (25mg twice daily); these doses were doubled after 4 weeks (provided there were no major adverse reactions and if blood pressure was not <110/70mm Hg) and treatment was continued for a further 8[186] or 6[187] weeks.

b For the study by Gavazzi et al.[186] the endpoint was the number (%) of patients whose symptoms were unchanged or worsened; statistical differences between baseline and endpoint for clinical symptoms were not calculated in this trial.

LVEDD = left ventricular end diastolic diameter; **LVEF** = left ventricular ejection fraction; **LVESD** = left ventricular internal systolic diameter; **PND** = paroxysmal nocturnal dyspnoea; * $p < 0.05$, ** $p < 0.005$, *** $p < 0.001$, **** $p < 0.0001$ *vs* baseline; † $p < 0.05$ *vs* captopril.

observed only in patients who were not taking digoxin.

The other study comparing quinapril with captopril was a randomised, parallel-group study in elderly patients (aged ≥65 years) with NYHA class II or III with an aetiology of ischaemic heart disease receiving diuretic therapy.[185] Patients completing 18 to 24 weeks of treatment with quinapril 2.5 to 10mg once daily (n = 20) or captopril 6.25 to 25mg twice daily (n = 16) were included in the evaluation. At the end of the treatment, the distance walked in a 6-minute walking test was increased by 72.2 and 83.1m in patients receiving quinapril or captopril (no significant difference between treatments). However, neither treatment was shown to improve functional life scores (quantitative data not reported). In addition, analysis of the change in NYHA functional status from study entry to study end showed a statistically significant difference between the two groups in favour of quinapril ($p = 0.02$).[185]

In another recent investigation,[187] the efficacy of once-daily quinapril was shown to be similar to that of twice-daily therapy in a group of elderly patients (aged ≥60 years) with heart failure (NYHA class II or III). In this crossover trial, all patients underwent a 4-week run-in period where they received quinapril 5 to 10mg twice daily after which they were randomised to receive quinapril 20mg once daily or 10mg twice daily. After 8 weeks of treatment, patients then crossed over to receive the alternative regimen for another 8 weeks. At the end

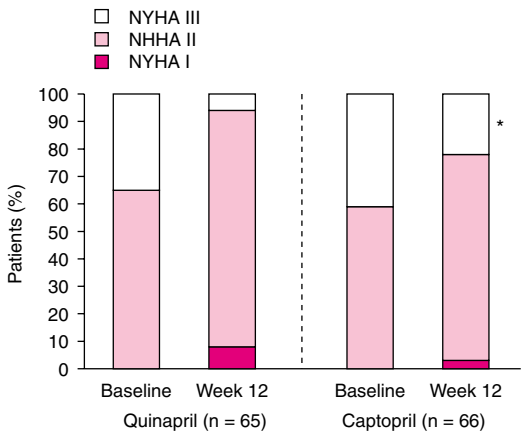

Fig. 8. Quinapril versus captopril in patients with congestive heart failure. New York Heart Association (NYHA) functional class at baseline and after 12 weeks of therapy with once-daily quinapril (10 to 20mg) or twice-daily captopril (25 to 50mg) in patients with congestive heart failure; * $p < 0.05$ *vs* quinapril.[184]

of the trial, mean 6-minute walking test results (378 and 377m), Cardiac Depression Scale scores (70.9 and 71.6) and Symptom Assessment Scale scores (14.8 and 14.7) were similar during once and twice daily therapy, respectively. Mean NYHA status, as assessed by the investigator, was also similar for both once- and twice-daily treatment (1.94 and 1.91). These results are consistent with those of an earlier crossover study (reported in the previous review),[169] which showed that once-daily quinapril (5 to 20mg) and twice-daily quinapril (2.5 to 10mg) each improved exercise time by approximately 60 seconds compared with placebo ($p < 0.01$).[169]

4.3 Coronary Artery Disease

Angiotensin II exerts a number of direct effects on the vasculature and the myocardium which may contribute to the processes of atherosclerosis, intimal hyperplasia and postinfarction remodelling (figure 1).[8] By reducing these effects, ACE inhibitors may theoretically reduce the frequency of ischaemic events in patients with coronary artery disease.[8]

Quinapril binds with high affinity to tissue ACE (section 2.1.1) and has been shown to significantly improve endothelial dysfunction in patients with coronary artery disease [see section 2.4 (TREND[74] and BANFF[69])].

Since the previous review, the results of two large randomised, double-blind, placebo-controlled trials investigating the role of quinapril in patients with myocardial ischaemia have become available: the effects of QUinapril On Vascular Ace and Determinants of Ischemia Study (QUO VADIS) [section 4.3.1] and the QUinapril Ischemic Event Trial (QUIET) [section 4.3.2]. The effect of quinapril on restenosis in patients undergoing coronary angioplasty and/or coronary stent implantation has also been investigated (section 4.3.3).

4.3.1 QUO VADIS

The QUO VADIS study was a randomised, double-blind, placebo-controlled study designed to evaluate the effect of 1 year of quinapril 40 mg/day on ischaemia and clinical ischaemic events in patients undergoing CABG.[188] Patients without evidence of severe hypertension or symptomatic heart failure who showed exercise-induced ischaemia were randomised to receive quinapril 40 mg/day (n = 75) or placebo (n = 73) 4 weeks before CABG and for 1 year thereafter. Concomitant treatment with diuretics, antiarrhythmics, digitalis, or tricyclic antidepressants was not permitted; however, all patients received low-dose aspirin after CABG.

At the end of the study, intent-to-treat analysis revealed that the number of patients experiencing a clinical ischaemic event (death, repeat CABG, percutaneous revascularisation, myocardial infarction, recurrence of angina pectoris, ischaemic stroke, or transient ischaemic attack) was significantly lower in patients receiving quinapril than those receiving placebo (4 *vs* 15%) [hazard ratio 0.23; 95% CI: 0.06 to 0.87, p = 0.02].[188] In addition, placebo was found to be an independent predictor of the occurrence of clinical ischaemic events in a multivariable regression model (p = 0.03). These effects were not related to differences in blood pressure, since SBP and/or DBP increased

equally in both treatment groups from randomisation up to 1 year after CABG.

The reduction in ischaemic events observed in the quinapril treatment group was not accompanied by improvements in exercise-induced ischaemia (the primary endpoint of this study). Total exercise time, as assessed during a bicycle test, was increased by a mean of 79 and 72 seconds in the placebo and quinapril treatment groups by the end of the study (nonsignificant difference between treatment groups); however, this test was performed 24 hours after the last dose of study medication was administered, which may explain the lack of effect. In addition, the number of patients experiencing at least one ischaemic episode during 48-hour Holter monitoring was similar between treatment groups at the end of the study.[188]

4.3.2 QUIET

The QUIET study was a randomised, double-blind, multicentre, placebo-controlled study designed to assess the effects of 3 years of quinapril 20 mg/day on the incidence of cardiac ischaemic events and/or the progression of coronary artery atherosclerosis in patients undergoing coronary angioplasty.[189] A total of 1750 normolipidaemic, normotensive patients with normal LV function (LV ejection fraction >40%) were randomised to receive quinapril 20mg (n = 878) or placebo (n = 872) within 12 to 72 hours after undergoing successful coronary angioplasty or atherectomy; all patients had at least one coronary artery not previously subjected to mechanical revascularisation at baseline. The primary endpoints in this study were occurrence of first cardiac event (cardiac death, resuscitated cardiac arrest, nonfatal myocardial infarction, revascularisation or hospitalisation for angina pectoris) and time to first cardiac event, based on an intent-to-treat analysis. In addition, an angiographic study evaluating atherosclerotic changes in nonintervened vessels was conducted in a randomly selected subgroup of 453 patients.[190]

A summary of cardiac events occurring during the trial and the results of the angiographic study are outlined in table V. No significant reductions in the frequency of major cardiac events were observed between patients receiving quinapril or placebo; however, the number of patients requiring coronary angioplasty of nonintervened vessels was significantly lower in the quinapril group (table V). In addition, there was no significant difference between treatment groups in the time to first major cardiac event. The relative risk for early (within the first 6 months) and late (during months 7 to 36) ischaemic events were 1.06 (95% CI: 0.87 to 1.29; p = 0.55) and 0.95 (95% CI: 0.78 to 1.16; p = 0.58). Furthermore, no significant differences in angiographic changes were observed in patients receiving quinapril and placebo (table V).

In retrospect, a number of concerns have been raised as to whether the QUIET study was a suitable test of the effects of quinapril on atherosclerosis. Indeed, this study has several limitations which may have contributed to the lack of observed effect with quinapril. One of the most significant limitations was the sample size. The study was powered to detect a 25% reduction with 95% confidence in the total number of ischaemic events. However, the incidence of 'hard' ischaemic events (death, nonfatal myocardial infarction and resuscitated cardiac arrest) was approximately 2% per year, or 6% over the 3-year study, which meant that a sample size of 20 000 patients would have been necessary to detect a 25% reduction in these events with 95% confidence.[189]

Another concern is whether the dosage of quinapril (20 mg/day) was adequate to produce the desired effect. In the TREND study (see section 2.4[74]), a dosage of 40 mg/day was shown to successfully reduce endothelial dysfunction and was well tolerated. In addition, a significant reduction in post-CABG ischaemic events was shown with quinapril 40 mg/day in the QUO VADIS study after only 1 year of treatment (see section 4.3.1).

The use of lipid-lowering drugs in this study may have also influenced the results.[190] In the angiographic study, 75 patients (15.7%) took lipid-lowering medication for at least 12 months on-trial. When these individuals were removed from the angiographic analysis, progression rates decreased in the quinapril group and increased in the

Table V. Results of the QUIET trial: cardiac events and angiographic results

	Placebo	Quinapril 20mg	RR (95% CI)
Cardiac events[a]			
Cardiac death	13 (1.5%)	12 (1.4%)	NR
Nonfatal myocardial infarction	40 (4.6%)	36 (4.1%)	NR
Resuscitated cardiac arrest	4 (0.5%)	0	NR
All patients with any of the above serious events	54 (6.2%)	48 (5.5%)	0.87 (0.59 to 1.29)
Coronary artery bypass grafting	104 (11.9%)	116 (13.2%)	NR
Coronary angioplasty in any vessel	223 (26.7%)	233 (25.4%)	NR
Coronary angioplasty in previously nonintervened vessels	114 (13%)	79 (9%)*	NR
Hospitalised with unstable angina	45 (5.6%)	52 (5.9%)	NR
All patients with any event	329 (37.7%)	338 (38.5%)	1.04 (0.89 to 1.22)
All patients with any event at months 7 to 36	203 (23.3%)	189 (21.6%)	NR
Angiographic changes[b]			
Progression[c]	119 (49%)	111 (47%)	0.93 (0.64 to 1.35)
New stenosis development	44 (19%)	50 (22%)	NR
Change in lumen diameter index (mm)	–0.21 ± 0.003	–0.18 ± 0.003	NR
Change in percentage diameter stenosis index	5.1 ± 1.0	3.5 ± 1.0	NR

a Assessed in 878 and 872 patients randomised to quinapril and placebo, respectively.

b Assessed in 224 and 229 patients randomised to quinapril and placebo, respectively, for whom suitable baseline and follow-up data were available. An additional 24 patients (10 receiving quinapril and 14 receiving placebo) who had interim cardiac events (cardiac death, myocardial infarction or new vessel revascularisation) but no or inadequate follow-up angiogram were included in the analysis of progressors.

c Patients who had interim cardiac events or who showed angiographic evidence of progression defined as a diminution in minimum lumen diameter of ≥0.40mm in at least one nonintervened stenotic segment within the patient.

CI = confidence interval; **NR** = not reported; **QUIET** = QUinapril Ischemic Event Trial; **RR** = relative risk; * p = 0.018 *vs* placebo.

placebo group; however, the difference still did not achieve statistical significance for either minimum lumen diameter index (–0.23 *vs* –0.18mm; p = 0.175) or percent diameter stenosis (5.6 *vs* 3.4%; p = 0.056).[190]

It is impossible to determine in retrospect whether these factors contributed to the lack of effect of quinapril in this study and more data are necessary to determine the role of quinapril, and other ACE inhibitors for that matter, in these patients.

4.3.3 Restenosis in Patients Undergoing Angioplasty with or without Coronary Stent Implantation

It has been estimated that up to 40% of patients undergoing angioplasty develop clinically significant luminal narrowing of coronary arteries within 6 months after the procedure.[191] Treatment with intravascular stents may reduce this proportion to 20% in coronary arteries; however, this procedure may lead to an iatrogenic condition, in-stent restenosis, which is difficult to treat.[191] Although quinapril did not reduce stenosis in the QUIET trial, this agent has shown some efficacy in reducing restenosis in other investigations in patients undergoing coronary angioplasty and/or coronary stent implantation.

In the largest of these trials (reported as an abstract),[192] 255 patients undergoing successful coronary angioplasty with or without stent implantation were randomised to receive quinapril 10 to 20 mg/day or were assigned to a control group. After a follow-up period of 3 to 6 months, complete quantitative coronary angiographic results were available in 108 patients in the quinapril treatment group and 107 in the control group; approximately

50% of patients in each group had received stent. Compared with that in the control group, minimal lumen diameter at follow-up was significantly greater in the quinapril group (1.62 ± 0.72 *vs* 1.44 ± 0.7mm; $p < 0.05$) as was the net gain (1.12 ± 0.77 *vs* 0.87 ± 0.81mm; $p < 0.05$). In addition, restenosis per patient (34.3 *vs* 44.9%) and per lesion (30.6 *vs* 43.8%) were significantly lower in quinapril recipients than in the control group ($p < 0.05$ *vs* control for both).[192]

Similar results were shown in another randomised trial in patients undergoing coronary stent implantation.[193] In this study, 100 patients were assigned to receive quinapril 10 or 20mg once daily or no quinapril for 6 months after the procedure; all patients also received daily treatment with 200mg ticlopidine and 81mg aspirin for several days before the procedure and for the study duration. Quantitative coronary angiographic analysis showed that the minimal in-stent lumen diameter was higher and percentage diameter stenosis was lower in the quinapril group than in the control group after 6 months; however, these differences did not reach statistical significance. A significant reduction in restenosis in patients receiving quinapril was shown in a quantitative planar intravascular ultrasound analysis (performed in 31 and 36 patients in the quinapril and control group). Compared with that in the control group, the minimal lumen cross-sectional area was higher in quinapril recipients (4.48 *vs* 3.73 mm^2; $p < 0.05$) and the percentage area stenosis was lower (39.1 *vs* 50.4%; $p < 0.01$) at the end of the study. Volumetric intravascular ultrasound analysis also revealed a lower intimal hyperplasia volume (1.77 *vs* 2.53 mm^3/mm; $p = 0.014$) and higher in-stent lumen volume (6.04*vs* 5.29 mm^3/mm; $p = 0.045$) in patients receiving quinapril than those in the control group at the end of the trial.[193]

Quinapril does not appear to improve restenosis in patients with the ACE DD genotype.[194] In a randomised, placebo-controlled, double-blind study, 91 of these patients received quinapril 40 mg/day (n = 46) or placebo (n = 45). Treatment was initiated within 48 hours after stent implantation and continued for 6 months. At the end of the study, quantitative coronary angiography revealed a trend towards increased angiographic restenosis in patients receiving quinapril, and the primary endpoint of late loss in minimum lumen diameter was significantly higher in the quinapril group than in the placebo group (1.11 *vs* 0.76mm; $p = 0.018$).

5. Tolerability

Quinapril is generally well tolerated and adverse events are usually mild and transient and seldom require treatment withdrawal. In placebo-controlled trials in patients with hypertension or congestive heart failure, the most frequently reported adverse events were dizziness, headache, fatigue and cough (see figure 9). Overall, discontinuation of therapy because of adverse events was required in 4.7% of 1563 patients with hypertension and 6.8% of 585 patients with congestive heart failure.[29]

Adverse events that are specific to ACE inhibitors as a class include cough, hypotension, hyperkalaemia and, rarely, angioedema. As shown in figure 9, cough was observed in 2% of patients with hypertension (n = 1563) and 4.3% of patients with congestive heart failure (n = 585) receiving quinapril in placebo-controlled trials;[29] similar rates have been observed in other randomised, comparative clinical trials.[96,195] Excessive hypotension occurs rarely in patients with uncomplicated hypertension during treatment with quinapril. In controlled clinical trials, syncope was observed in 0.4% of 3203 patients receiving quinapril; this incidence was slightly lower than that observed in patients receiving captopril (1%) or enalapril (0.8%).[29] The risk of hypotension is higher in patients with congestive heart failure and this event was reported in 2.9% of these patients in placebo-controlled trials (figure 9).[29] Angioedema of the face, extremities, lips, tongue, glottis and larynx is another adverse event associated with ACE inhibition and has been observed in 0.1% of patients receiving quinapril.[29] The incidence of angioedema appears to be slightly higher in Black than in non-Black patients. In two

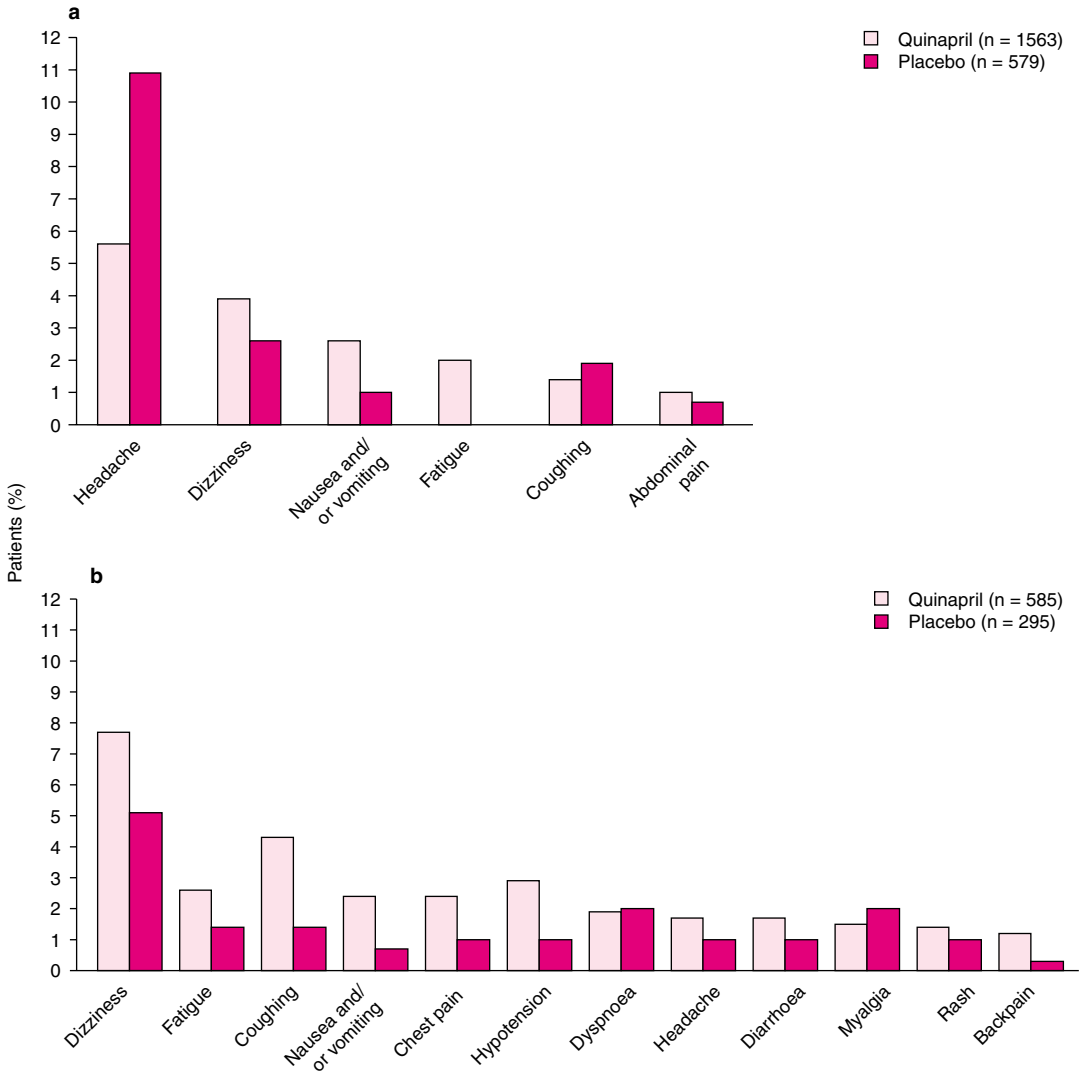

Fig. 9. Adverse events possibly or probably related to quinapril therapy occurring in >1% of patients with hypertension (**a**) or congestive heart failure (**b**) included in placebo-controlled trials.[29]

large US postmarketing trials, angioedema was reported in 0.3 to 0.55% of Black patients (n >3000) and 0.17 to 0.39% of non-Black patients (n >19 000).[29]

Hyperkalaemia (serum potassium ≥5.8% mmol/L) occurred in ≈2% of patients receiving quinapril in clinical trials; increases in potassium were transient in most cases and <1% of patients discontinued therapy because of this event.[29]

Quinapril has a similar tolerability to that of other ACE inhibitors. In a large meta-analysis of comparative clinical trials,[195] 12% of 1819 patients receiving quinapril experienced a treatment-related adverse event compared with 15% of 339

enalapril recipients and 16% of 186 captopril recipients. Treatment withdrawal because of adverse events in these studies was less common in quinapril recipients (3.7%) than those receiving enalapril (8.0%) or captopril (6.4%); quinapril recipients also showed a lower incidence of first-dose hypotension and orthostatic hypotension (0.4 and 6.1%) than either enalapril (1.5 and 9.4%) or captopril recipients (2.2 and 8.6%).

In a large randomised, double-blind study, quinapril 10 to 40 mg/day (n = 5053) showed comparable tolerability to metoprolol 50 to 200 mg/day (n = 506) over 12 weeks of treatment.[134] In this study, symptoms such as fatigue, dizziness and dyspnoea tended to occur more often in metoprolol recipients; the incidence of spontaneously reported cough was higher in quinapril recipients (2.7 *vs* 1.6%).

Elderly patients (>65 years) tolerated quinapril as well as younger patients in clinical trials.[96,146,195] Furthermore, combined therapy with quinapril and a diuretic produced little change in the incidence of adverse events compared with quinapril monotherapy,[102,156,195] although the incidence of first-dose hypotension appears to be increased with combined therapy.[29] The addition of quinapril to diuretic therapy may actually reduce adverse metabolic adverse effects associated with diuretics. In two double-blind, randomised trials,[102,156,195] coadministration of quinapril and HCTZ attenuated the potassium loss and the increase of uric acid levels compared with that in patients receiving HCTZ monotherapy.

The incidence and severity of adverse events did not increase with increased dosages of quinapril monotherapy over the dosage range of 10 to 40 mg/day in patients with hypertension.[142,196] However, the rapidity of dose escalation may influence the tolerability of quinapril. In a recent study,[152] patients with mild to moderate hypertension were randomised to receive either a slow (once every 6 weeks; n = 1208) or a fast (every 2 weeks; n = 1727) titration schedule (also see section 4.1.1). Quinapril was initiated at a dose of 20mg once daily and titrated to a maximum of 80 mg/day in both groups. Although the frequency of adverse events was similar in the fast- versus slow-titration groups (10.8 *vs* 10.7%), more patients in the fast-titration group experienced a severe event (21 *vs* 12%).[152]

6. Dosage and Administration

Quinapril is indicated for the treatment of hypertension and congestive heart failure. The approved US and UK indications and dosage recommendations are presented below.

6.1 Hypertension

In patients with hypertension, quinapril is indicated for use both as monotherapy and in combination with diuretics. The recommended starting dose for patients initiating monotherapy is 10 or 20mg once daily in the US[29] and 10mg once daily in the UK.[197] Depending on blood pressure response, the dosage may need to be increased. Dosage titration should be performed at ≥2-weekly intervals or over a sufficient period to allow adequate time for evaluation of response. Most patients require maintenance dosages of 20 to 40 mg/day given as a single dose or two divided doses, although some patients may require doses of up to 80 mg/day. In some patients, the antihypertensive effect of quinapril may diminish towards the end of a once-daily dosage interval such that twice-daily administration of the same daily dose may be needed.[29] Typically, greater efficacy is observed at the end of the dosing interval in patients receiving dosages of 40 to 80 mg/day and/or divided doses.[29]

Quinapril is also indicated for use in combination with a diuretic if blood pressure cannot be adequately controlled with quinapril or diuretic therapy alone. When quinapril is administered to a patient already receiving diuretic therapy, symptomatic hypotension can occasionally occur. To reduce this risk, a low initial dose of quinapril (2.5mg) in patients already receiving diuretic therapy is recommended in the UK;[197] this dose can then be titrated (as described above) to the optimal response. In the US,[29] patients are recommended

to discontinue diuretic therapy 2 to 3 days prior to beginning quinapril treatment to reduce the risk of hypotension. A diuretic may then be added if blood pressure is not adequately controlled with quinapril alone. If it is not possible to discontinue diuretic therapy before starting quinapril, the recommended initial dose of quinapril is 5mg and patients should be carefully monitored for several hours until blood pressure stabilises.[29]

In the UK,[197] elderly patients and those with renal impairment (CL_{CR} <40 ml/min) are recommended to receive an initial quinapril dosage of 2.5mg, followed by titration to optimal response. Monitoring of renal function in patients with renal insufficiency should be considered over the course of quinapril therapy; however, clinical experience suggests that renal function is unlikely to alter, and may actually improve, in the majority of patients.[197] In the US, the recommended initial dosage of quinapril in elderly patients (aged ≥65 years) is 10mg once daily, followed by titration to optimal response.[29] In patients with compromised renal function, the initial quinapril dosage should be adjusted based on CL_{CR}: 10 mg/day for patients with CL_{CR} >60 ml/min, 5 mg/day for those with CL_{CR} ranging from 30 to 60 ml/min and 2.5 mg/day for those with CL_{CR} ranging from 10 to 30 ml/min. In patients with CL_{CR} <10 ml/min there are insufficient data for dosage recommendations.[29] Depending on blood pressure response, these patients should then have their dosage titrated (as described above) to optimal response.[29]

6.2 Congestive Heart Failure

In patients with congestive heart failure, quinapril is indicated for use as an adjunctive therapy in combination with diuretics and/or digitalis. The initial dosage of quinapril recommended in the UK and US is 2.5 and 5 mg/day, respectively.[29,197] The quinapril dosage should then be titrated (up to a maximum of 40 mg/day) to achieve an effect or until the appearance of undesirable adverse events. In the UK and US, the usual maintenance dosages are given as 10 to 20 and 20 to 40 mg/day, respectively, administered in one or two divided doses.[29,197]

In the UK,[197] medical supervision is recommended for patients with severe/unstable congestive heart failure, patients receiving high-dose loop diuretics (e.g. >80 mg/day furosemide), multiple diuretics or high-dose vasodilator therapy, patients with hypovolaemia, hyponatraemia (serum sodium <130 mgEq/L), SBP <90mm Hg or serum creatinine >150 μmol/L and those aged ≥70 years. In these patients, quinapril therapy should be initiated in hospital.[197] In the US,[29] it is recommended that all patients with congestive heart failure be supervised for at least 2 hours following the initial dose of quinapril to monitor for the development of hypotension.

In patients with congestive heart failure and renal impairment, the initial dose of quinapril recommended in the US[29] is 5 mg/day in patients with CL_{CR} >30 ml/min and 2.5 mg/day for patients with CL_{CR} 10 to 30 ml/min. There are insufficient data in patients with CL_{CR} <10 ml/min to provide dosage recommendations.[29]

7. Place of Quinapril in the Management of Cardiovascular Disorders

Quinapril, like other ACE inhibitors, has a well established efficacy in the treatment of hypertension (see section 7.1) and congestive heart failure (see section 7.2). ACE inhibitors also appear to have anti-ischaemic effects that go beyond their effects on blood pressure and LV function; the results of experimental and clinical studies evaluating the potential role of quinapril and other ACE inhibitors in coronary artery disease are discussed in section 7.3.

7.1 Hypertension

Hypertension is a common disorder which, if not effectively treated, has high mortality and morbidity resulting from a greatly increased probability of coronary artery disease, congestive heart failure, stroke and renal failure. It has long been accepted that lowering blood pressure reduces

these risks. In a retrospective analysis of randomised trials,[198] lowering DBP by 5 to 6mm Hg and SBP by 10 to 14mm Hg was estimated to reduce the risk of coronary heart disease and stroke by 14 and 42%, respectively. However, the risk of cardiovascular disease in patients with hypertension is not only determined by the level of blood pressure control.[199] Other factors such as dyslipidaemia, diabetes mellitus, smoking and target organ damage (e.g. nephropathy, congestive heart failure, LV hypertrophy) also increase the risk of cardiovascular events, and all these factors should be taken into account when deciding how best to treat these patients.[199]

Current guidelines for the management of patients with hypertension vary slightly in their recommended blood pressure goals. The JNC-VI (The Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure),[199] BHS (British Hypertension Society)[155] and WHO-ISH (World Health Organization-International Society of Hypertension)[200] guidelines recommend reducing blood pressure to 140/90, 140/80 and 130/80mm Hg, respectively, with further reductions for high risk groups such as patients with diabetes mellitus and/or renal dysfunction.

While some patients may reach these targets with nonpharmacological interventions, the majority require drug therapy to maintain blood pressure control.[199] At present, there are six main classes of antihypertensive agents (ACE inhibitors, β-adrenoceptor antagonists, α-adrenoceptor antagonists, angiotensin II antagonists, diuretics and calcium antagonists) which all produce broadly similar clinically significant reductions in blood pressure.[199,200] Both the JNC-VI[199] and BHS[155] recommend thiazide diuretics or β-adrenoceptor antagonists as first-line drug therapy in otherwise healthy patients with hypertension. This is largely based on the large amount of evidence showing a reduction in cardiovascular morbidity and mortality with these agents. Indeed, recent findings from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) have now shown that not all antihypertensive agents produce similar effects on cardiovascular outcomes. This trial was designed to assess the relative effects of different hypertensive agents [diuretics (chlorthalidone), calcium antagonists (amlodipine), ACE inhibitors (lisinopril) or α-adrenoceptor antagonists (doxazosin)] on cardiovascular events in a cohort of >40 000 patients with hypertension.[201] The α-adrenoceptor antagonists arm of ALLHAT was discontinued early because the occurrence of combined cardiovascular events, a secondary endpoint, was 25% higher than that in patients receiving diuretic therapy, and these patients were twice as likely to be hospitalised for congestive heart failure.[202,203] Importantly, there was no difference in the risk of myocardial infarction or all-cause mortality (the primary endpoint in this study) between the two treatment groups.

In contrast, ACE inhibitors appear to be equally as effective as other treatments in preventing cardiovascular outcomes. In two large prospective randomised trials (the Captopril Prevention Project[204] and the Swedish Trial in Old Patients with Hypertension-2 study[205]; both n >6500), ACE inhibitors produced similar effects to conventional treatments (β-adrenoceptor antagonists or diuretics) in reducing cardiovascular mortality and morbidity.[204,205] The results of the ongoing arms of the ALLHAT study will provide more details on the effects of ACE inhibitors compared with other antihypertensive agents.

There are several compelling indications for ACE inhibitors in patients with hypertension. Unless otherwise contraindicated, JNC-VI,[199] BHS[155] and WHO[200] guidelines strongly recommend the use of ACE inhibitors in patients with heart failure, LV dysfunction (isolated or following MI) and type 1 diabetic nephropathy. Indeed, ACE inhibitors have shown clear benefits in reducing morbidity and mortality following myocardial infarction[206] and in patients with LV dysfunction or congestive heart failure[181] (see section 7.2), and these drugs reduce the onset and progression of renal failure in patients with type 1 diabetic nephropathy.[92,207]

JNC-VI and BHS guidelines also state that ACE inhibitors may offer particular benefit in patients with type 2 diabetic nephropathy or nondiabetic renal disease.[155,199] Renal dysfunction is a recognised cardiovascular risk factor in patients with diabetes mellitus and/or hypertension.[199] Lowering blood pressure can reduce the progression of renal disease; however, it is thought that ACE inhibitors confer additional benefits through mechanisms beyond their blood pressure-lowering effects.[92,93] ACE inhibitors have been shown to reduce proteinuria and prevent the progression of renal decline in patients with diabetic or nondiabetic nephropathy to a greater extent than other antihypertensive agents.[92,159,160] Some studies also show that ACE inhibitors reduce microalbuminuria (a predictor of end-stage renal disease and cardiovascular outcome)[157] to a greater extent than other antihypertensive agents in patients with hypertension.[157] Similar results have been observed with quinapril (section 4.1.3). In one randomised trial,[91] quinapril reduced blood pressure to a similar extent to conventional treatment (atenolol and/or HCTZ) over 1 year of therapy, but only quinapril was associated with significant reduction in microalbuminuria. The effects of ACE inhibitors such as quinapril on UAE may be important, considering up to 40% of patients with untreated hypertension have evidence of microalbuminuria.[208] However, whether reductions in UAE translate to a lesser incidence of cardiovascular or renal events remains to be determined.

ACE inhibitors significantly reduce the macrovascular and microvascular complications of diabetes mellitus.[1,209] Unlike other antihypertensive agents such as β-adrenoceptor antagonists and diuretics,[95,200] ACE inhibitors, including quinapril (see section 2.7), have shown limited effects on glucose homeostasis and lipid balance. In some prospective clinical trials in patients with diabetes mellitus, ACE inhibitors were associated with a reduced incidence of cardiovascular complications compared with diuretic or β-adrenoceptor antagonist treatment;[204,210] however, other studies suggest that these agents produce similar outcomes on morbidity and mortality in these patients[209,211] and further evidence is required to determine whether there are true differences between drug classes in their effects on cardiovascular events in patients with diabetes mellitus. Results from the recent Heart Outcomes Prevention Evaluation (HOPE) study show that ACE inhibitors may also reduce the onset of diabetes in high-risk individuals.[212] In this study, which included 5720 patients without known diabetes but with vascular disease (hypertension, coronary artery disease), 3.6% of patients receiving ramipril treatment developed diabetes compared with 5.4% of patients receiving placebo over a mean follow-up period of 4.5 years ($p < 0.001$). These results could have enormous clinical and public heath implications due to the huge health and economic impact of diabetes mellitus. However, although these data were collected prospectively, diagnosis of diabetes mellitus was not a primary or secondary endpoint in this study and these results require confirmation in a prospective trial.[212]

ACE inhibitors, including quinapril (see section 2.3.1), have also been shown to reduce LV hypertrophy, a strong blood pressure-independent cardiovascular risk factor in patients with hypertension.[213,214] Regression of LV hypertrophy reduces cardiac events and morbidity. In a recent echocardiographic study in 430 patients with essential hypertension,[215] those who experienced significant reductions in LV hypertrophy with antihypertensive therapy had a significantly lower risk of cardiovascular events over an 8-year follow-up period than patients who did not have regression of LV hypertrophy (1.78 *vs* 3.03 events per 100 person-years; $p = 0.029$); these effects were not related to differences in blood pressure control. ACE inhibitors appear to be better at reducing LV hypertrophy than other antihypertensive agents. In a recent meta-analysis,[214] LV mass decreased by 13% with ACE inhibitor therapy, 9% with calcium antagonists, 6% with β-adrenoceptor antagonists and 7% with diuretics after a mean treatment duration of 25 weeks ($p < 0.05$ for ACE inhibitors *vs* diuretics and β-adrenoceptor antagonists).

Regardless of which antihypertensive drug is used, most patients are not effectively controlled with monotherapy, even at high doses, and combination therapy is typically required in >50% of patients. [153-155] ACE inhibitors are usually used in combination with diuretics. In clinical studies, the combination of quinapril and HCTZ was significantly better at lowering blood pressure in patients with moderate to severe hypertension than either drug as monotherapy (section 4.1.2). In addition, combined therapy with quinapril and HCTZ reduced the adverse metabolic effects observed during HCTZ monotherapy (section 5).

7.2 Congestive Heart Failure

The benefits of ACE inhibitors in patients with congestive heart failure are well documented. These agents significantly improve survival, reduce the frequency of hospitalisation, relieve symptoms and slow the progression of the disease in patients with congestive heart failure.[173-175,181] In addition, ACE inhibitor therapy has been shown to prevent the occurrence or the progression of congestive heart failure in patients with asymptomatic heart failure[216] and those with reduced ejection fractions following myocardial infarction,[177,179] resulting in improved survival in these patients.

Both US[182] and UK[217,218] guidelines recommend that all patients with heart failure due to LV systolic dysfunction receive an ACE inhibitor unless they are intolerant of or have a contraindication to their use. These agents are also recommended in patients with asymptomatic LV systolic dysfunction and in patients with LV dysfunction following myocardial infarction.[182,217,218]

ACE inhibitors are usually used together with diuretics in patients with congestive heart failure. Diuretics are an important therapy for congestive heart failure, because they are the only reliable means of controlling fluid retention in these patients; however, survival benefits have not been demonstrated with these agents, so they should always be used in combination with ACE inhibitors.[182]

β-Adrenoceptor antagonists[219-222] and spironolactone[223] have been shown to provide significant reductions in mortality when added to ACE inhibitor therapy. Furthermore, the angiotensin II inhibitor valsartan[222] also significantly improved the combined endpoint of morbidity and mortality (but not overall mortality) in patients receiving baseline ACE inhibitor therapy; however, no benefits were observed in patients already receiving ACE inhibitors combined with β-adrenoceptor antagonists.[222] Current US guidelines[182] recommend β-adrenoceptor antagonists as adjunctive therapy to ACE inhibitors in patients with NYHA class II or III congestive heart failure whereas spironolactone is indicated for patients with more severe heart failure (NYHA class IV) [provided they are tolerated and there is no contraindication for their use].[182] However, recent clinical trial results suggest that β-adrenoceptor antagonist therapy (in particular, carvedilol)[222] may also be beneficial in patients with NYHA class IV heart failure; the role of angiotensin II antagonists are yet to be defined.

Digoxin is another well established treatment for patients with heart failure and is often used in combination with ACE inhibitors.[182] This agent reduces symptoms of heart failure, but failed to improve survival in a large prospective trial (n = 6800).[224]

Quinapril treatment has been shown to provide a number of positive effects in patients with congestive heart failure (section 4.2). Although there is no evidence supporting an effect of quinapril on survival, available data suggest that there are no differences among available ACE inhibitors in their effects on symptoms, clinical status, mortality or disease progression.[181] Quinapril has been compared with captopril (an ACE inhibitor shown to produce significant survival benefits)[177] in two large, well designed trials.[183,184] Although mortality was not assessed, quinapril was at least as effective as captopril in increasing LV ejection fraction, an important determinant of survival.[225,226]

Despite the proven benefits of ACE inhibitors, they remain substantially underprescribed in patients with congestive heart failure.[227-230] Indeed,

it is estimated that fewer than half of patients with heart failure receive ACE inhibitors, and up to 30% of patients who are taking these agents are not receiving dosages proven to reduce mortality in clinical trials.[228,229] Underutilisation of ACE inhibitor therapy increases the frequency of death and hospitalisations,[228] and could have important implications for the costs of caring for these patients.[227]

7.3 Coronary Artery Disease

In the setting of coronary artery disease, the use of ACE inhibitors has previously been limited to patients with LV dysfunction or heart failure following myocardial infarction.[231,232] However, there is a growing body of evidence that supports the use of ACE inhibitors in a broader range of patients with atherosclerotic disease or coronary risk factors.[1]

The potential anti-ischaemic effects of ACE inhibitors was first noted in patients with LV dysfunction, with or without previous myocardial infarction.[233] Analyses from the Survival and Ventricular Enlargement (SAVE) trial and the Studies of Left Ventricular Dysfunction (SOLVD) trials showed that ACE inhibitor therapy reduced the risk of myocardial infarction by >20% in these patients.[177,233,234] More recently, the results from the HOPE trial show that similar protective effects can also be achieved in a range of patients with normal LV function.[1] In this study (n >9000), ACE inhibition with ramipril significantly reduced the risk of death, myocardial infarction, stroke and revascularisation in a high-risk group of patients with pre-existing vascular disease who had no evidence of LV dysfunction or heart failure.[1] Beneficial effects of ACE inhibition were observed in all subgroups, including those with or without diabetes, pre-existing cardiovascular disease, previous myocardial infarction or hypertension at baseline. Benefits were also observed among patients already taking a number of effective treatments, including aspirin, β-adrenoceptor antagonists and lipid-lowering agents, indicating that ACE inhibition offers an additional approach to the prevention of atherothrombotic complications. The risk reduction appeared to be independent of the modest lowering of blood pressure (–3/2mm Hg), suggesting that ACE inhibition exerts additional effects on the vasculature that are independent of their blood pressure-lowering effects.[1]

The results of this trial have prompted changes to the recommendations of ACE inhibitor use in patients with coronary artery disease. The 2001 American Heart Association/American College of Cardiology Guidelines for Preventing Heart Attack and Death in Patients with Atherosclerotic Cardiovascular Disease now recommend that these agents be used in all patients following myocardial infarction and should be considered for all other patients with coronary or other vascular disease unless contraindicated.[235]

The precise mechanism through which ACE inhibitors might exert vasculoprotective effects is still uncertain, but potential mechanisms include regression of hypertrophy and fibrosis, decreased inflammation and oxidative stress, and increased fibrinolysis.[4] Modification of the endothelium, which plays an important role in modulating smooth muscle function and growth, is also likely to contribute. Endothelial dysfunction is a characteristic feature of patients with coronary artery disease, and is also present in high-risk patients such as those with hypertension, diabetes mellitus or hyperlipidaemia or smokers.[63,65] Two recent studies have demonstrated that endothelial dysfunction is associated with an increased risk of adverse cardiovascular events, which supports the concept that coronary endothelial dysfunction might play a role in the progression of coronary atherosclerosis.[66,67] Findings from a number of studies have indicated that ACE inhibitors improve endothelial dysfunction,[236] whereas other antihypertensive agents have shown limited or no effect.[237] Of all the ACE inhibitors, quinapril has demonstrated the most convincing evidence of a beneficial effect on endothelial function. This agent has been shown to significantly improve endothelial-dependent vasodilation in patients with coronary artery disease in two large randomised trials (TREND,[74] BANFF[69])

[section 2.4]. In contrast, the angiotensin II antagonist losartan and the calcium antagonist amlodipine showed no effect on endothelial function in the BANFF study;[69] enalapril also failed to show a significant effect in the BANFF trial, suggesting that differences may exist between ACE inhibitors in their ability to improve endothelial function. Quinapril, by virtue of its high tissue ACE affinity, may offer particular benefit in this setting.[69] Quinapril also improved endothelial function in patients with hypertension in one analysis;[70] these positive effects were not observed with nitrendipine and were independent of blood pressure reduction. However, whether or not improvements in endothelial function translate to a reduction in the incidence of ischaemic events remains to be determined.

The effects of quinapril in reducing ischaemic events in patients with coronary artery disease have been investigated in two large, randomised, double-blind, placebo-controlled trials: the QUO VADIS (section 4.3.1) and QUIET studies (section 4.3.2). Both these investigations included patients who did not have traditional indications for ACE inhibitor therapy: their blood pressure was controlled and they had no evidence of LV dysfunction[189] or symptomatic heart failure.[188]

In the QUIET study (n = 1750), quinapril 20 mg/day failed to show a significant effect on reducing ischaemic events or atherosclerotic progression over 3 years of treatment following coronary angioplasty. However, the lack of effect observed with quinapril in this trial is likely to be due to flaws in trial design such as insufficient sample size and/or insufficient dosage (discussed in section 4.3.2). Compared with the HOPE study, the dose of quinapril used in the QUIET trial was low. Whereas the HOPE investigators chose the maximum antihypertensive dose of ramipril (10 mg/day), the dosage of quinapril used in the QUIET study (20 mg/day) was at the lower end of the quinapril antihypertensive dosage range (10 to 80 mg/day).[186] Available evidence shows that higher dosages of quinapril are certainly feasible in patients with coronary artery disease. In the TREND[74] and QUO VADIS trials,[188] quinapril was well tolerated at twice the dose used in the QUIET study (40 mg/day). Importantly, quinapril 40 mg/day was shown to significantly reduce ischaemic events in the QUO VADIS trial.[188] In this study (n = 148), the incidence of ischaemic events was reduced by 70% in patients receiving quinapril compared with those receiving placebo over 1 year post-CABG. Risk reduction was observed in the combined event rates of myocardial infarction, recurrence of angina pectoris, transient ischaemic attack and ischaemic stroke, despite the small number of patients treated and the relatively short treatment period. However, quinapril did not reduce exercise-induced ischaemia or the incidence of ischaemia on 48-hour Holter monitoring (the primary endpoints of this study),[188] which is consistent with the results of other studies showing variable results with ACE inhibitor therapy on exercise-induced ischaemia in patients with stable angina pectoris.[238-240] The QUO VADIS was the second trial to demonstrate an anti-ischaemic effect of ACE inhibitor therapy following CABG. In a previous investigation in 159 patients with stable chronic angina and asymptomatic heart failure (the Angiotensin-converting enzyme Post REvascularisation study),[241] treatment with ramipril following CABG was also shown to significantly reduce cardiac death, myocardial infarction and congestive heart failure. The results of these trials suggest a potential role for ACE inhibitors following CABG. A reduction in ischaemic events in these patients would have important clinical and economic implications since CABG is one of the most frequently performed operations in the world;[242] further data showing the protective effects of ACE inhibitors in these patients would be useful.

The results of ongoing studies investigating the role of ACE inhibitors in patients with coronary artery disease, such as PEACE, EUROPA and IMAGINE, are awaited with interest.[14,243,244]

7.4 Conclusion

Quinapril is now firmly established as an effective and well tolerated ACE inhibitor for the treatment of patients with hypertension and congestive heart failure. Quinapril 40 mg/day also significantly reduced the incidence of ischaemic events in patients undergoing CABG in one study; however, a lower dosage of quinapril (20 mg/day) had no effect on ischaemic events in patients undergoing coronary angioplasty in another trial. Additional trials in patients with coronary artery disease receiving optimal dosages of quinapril (40 mg/day) would be useful.

References

1. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000 Jan 20; 342 (3): 145-53
2. Wadworth AN, Brogden RN. Quinapril: a review of its pharmacological properties, and therapeutic efficacy in cardiovascular disorders. Drugs 1991; 41 (3): 378-99
3. Plosker GL, Sorkin EM. Quinapril: a reappraisal of its pharmacology and therapeutic efficacy in cardiovascular disorders. Drugs 1994 Aug; 48 (2): 227-52
4. Givertz MM. Manipulation of the renin-angiotensin system. Circulation 2001 Jul 31; 104 (5): 14-8
5. Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation 1998 Apr 14; 97 (14): 1411-20
6. Cody RJ. The sympathetic nervous system and the renin-angiotensin-aldosterone system in cardiovascular disease. Am J Cardiol 1997 Nov 13; 80 (9B): 9-14
7. Zimmerman BG. Actions of angiotensin on adrenergic nerve endings. Fed Proc 1978 Feb; 37 (2): 199-202
8. Dzau VJ. Mechanism of protective effects of ACE inhibition on coronary artery disease. Eur Heart J 1998 Sep; 19 Suppl. J: 2-6
9. Ruffolo Jr RR, Feuerstein GZ. Neurohormonal activation, oxygen free radicals, and apoptosis in the pathogenesis of congestive heart failure. J Cardiovasc Pharmacol 1998; 32 Suppl. 1: 22-30
10. Erdös EG. The angiotensin I converting enzyme. Fed Proc 1977 Apr; 36 (5): 1760-5
11. Vanhoutte PM. Endothelium and control of vascular function. State of the Art lecture. Hypertension 1989 Jun; 13 (6 Pt 2): 658-67
12. Minai K, Matsumoto T, Horie H, et al. Bradykinin stimulates the release of tissue plasminogen activator in human coronary circulation: effects of angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2001 May; 37 (6): 1565-70
13. Brown NJ, Nadeau JH, Vaughan DE. Selective stimulation of tissue-type plasminogen activator (t-PA) in vivo by infusion of bradykinin. Thromb Haemost 1997 Mar; 77 (3): 522-5
14. Dzau VJ, Bernstein K, Celermajer D, et al. The relevance of tissue angiotensin-converting enzyme: manifestations in mechanistic and endpoint data. Am J Cardiol 2001 Nov 9; 88 Suppl.: 1-20
15. Fabris B, Chen BZ, Pupic V, et al. Inhibition of angiotensin-converting enzyme (ACE) in plasma and tissue. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 6-13
16. Vago T, Bevilacqua M, Conci F, et al. Angiotensin converting enzyme binding sites in human heart and lung: comparison with rat tissues. Br J Pharmacol 1992 Nov; 107 (3): 821-5
17. Kinoshita A, Urata H, Bumpus M, et al. Measurement of angiotensin I converting enzyme inhibition in the heart. Circ Res 1993; 73: 51-60
18. Dzau VJ. Mechanism of action of angiotensin-converting enzyme (ACE) inhibitors in hypertension and heart failure: role of plasma versus tissue ACE. Drugs 1990; 39 Suppl. 2: 11-6
19. Sedman AJ, Posvar E. Clinical pharmacology of quinapril in healthy volunteers and in patients with hypertension and congestive heart failure. Angiology 1989 Apr; 40 (4 Pt 2): 360-9
20. Breslin E, Posvar E, Neub M, et al. A pharmacodynamic and pharmacokinetic comparison of intravenous quinaprilat and oral quinapril. J Clin Pharmacol 1996 May; 36 (5): 414-21
21. Oosterga M, Voors AA, Buikema H, et al. Angiotensin II formation in human vasculature after chronic ACE inhibition: a prospective, randomized, placebo-controlled study. QUO VADIS Investigators. Cardiovasc Drugs Ther 2000 Feb; 14 (1): 55-60
22. Bönner G. The role of kinins in the antihypertensive and cardioprotective effects of ACE inhibitors. Drugs 1997; 54 Suppl. 5: 23-30
23. Bönner G, Preis S, Schunk U, et al. Hemodynamic effects of bradykinin on systemic and pulmonary circulation in healthy and hypertensive humans. J Cardiovasc Pharmacol 1990; 15 Suppl. 6: 46-56
24. Gainer JV, Morrow JD, Loveland A, et al. Effect of bradykinin-receptor blockade on the response to angiotensin-converting-enzyme inhibitor in normotensive and hypertensive subjects. N Engl J Med 1998 Oct 29; 339 (18): 1285-92
25. Benetos A, Levy BI, Lacolley P, et al. Role of angiotensin II and bradykinin on aortic collagen following converting enzyme inhibition in spontaneously hypertensive rats. Arterioscler Thromb Vasc Biol 1997 Nov; 17 (11): 3196-201
26. Holtz J, Allgeier J, Goetz R, et al. Bradykinin contributes to the cardiac reparation by quinapril in rats with hypertensive left ventricular hypertrophy. Eur Heart J 1992; 13 Suppl. 2: 252
27. Hoshida S, Yamashita N, Kawahara K, et al. Amelioration by quinapril of myocardial infarction induced by coronary occlusion/reperfusion in a rabbit model of atherosclerosis: possible mechanisms. Circulation 1999 Jan 26; 99 (3): 434-40
28. Hu K, Gaudron P, Anders H-J, et al. Chronic effects of early started angiotensin converting enzyme inhibition and angiotensin AT1-receptor subtype blockade in rats with myocardial infarction: role of bradykinin. Cardiovasc Res 1998 Aug; 39 (2): 401-12
29. Parke Davis Pharmaceuticals Ltd. Accupril® (quinapril hydrochloride tablets): prescribing information 2001. Available from URL: http://www.pfizer.com/hml/pi's/accuprilpi.pdf [Accessed 2001 Sep 20]
30. Portaluppi F, Montanari L, Pansini R. Effects of the converting ensyme inhibitor quinapril on the circadian rhythm of blood pressure and heart rate in essential hypertension. Curr Ther Res 1990 Oct; 48 (4): 613-22
31. Canter DA, Texter MJ, McLain RW. Short report: ambulatory blood pressure monitoring can play an integral role in patient selection, dosage adjustment and efficacy assessment in clinical trials of antihypertensive agents. J Hypertens 1994 Apr; 12 (4): 491-4

32. De Cesaris R, Ranieri G, Andriani A, et al. A comparative study of the effects of lisinopril and quinapril administered once a day in essential hypertension. [In Italian]. Minerva Med 1990 Jul-1990 31; 81 (7-8): 541-6
33. Zannad F. Duration of action of angiotensin converting enzyme inhibitors. Am J Hypertens 1995; 8 (10 Pt. 2): 75-81
34. Papageorgiou A, Karayiannis A, Athyros V, et al. A comparative study of the efficacy and safety of quinapril and lisinopril in patients with mild to moderate hypertension. Drug Invest 1994; 7 (1): 13-7
35. Banas Jr JS. Preliminary hemodynamic report of the efficacy and safety of quinapril in acute and chronic treatment of patients with congestive heart failure. Angiology 1989 Apr; 40 (4 Pt 2): 396-404
36. Holt P, Najm J, Sowton E. The acute haemodynamic effects of quinapril, a new non-sulfhydryl angiotensin converting enzyme inhibitor, in patients with severe congestive cardiac failure. Eur J Clin Pharmacol 1986; 31 (1): 9-14
37. Nieminen MS, Kupari M. The hemodynamic effects of ACE inhibitors in the treatment of congestive heart failure. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 36-40
38. Townend JN, West JN, Davies MK, et al. Effect of quinapril on blood pressure and heart rate in congestive heart failure. Am J Cardiol 1992 Jun 15; 69 (19): 1587-90
39. Kromer EP, Elsner D, Riegger GA. Digoxin, converting-enzyme inhibition (quinapril), and the combination in patients with congestive heart failure functional class II and sinus rhythm. J Cardiovasc Pharmacol 1990 Jul; 16 (1): 9-14
40. Sardu G. Treatment of mild-to-moderate congestive heart failure with the angiotensin converting enzyme inhibitor quinapril. Adv Ther 1991; 8: 124-32
41. Squire IB, Macfadyen RJ, Lees KR, et al. Haemodynamic response and pharmacokinetics after the first dose of quinapril in patients with congestive heart failure. Br J Clin Pharmacol 1994 Aug; 38 (2): 117-23
42. Nussberger J, Fleck E, Bahrmann H, et al. Dose-related effects of ACE inhibition in man: quinapril in patients with moderate congestive heart failure. Study Group on Neurohormonal Regulation in Congestive Heart Failure: Lausanne, Switzerland; Berlin, Dusseldorf, Munich, Germany. Eur Heart J 1994 Dec; 15 Suppl. D: 113-22
43. De Castro S, Pelliccia F, Cartoni D, et al. Effects of angiotensin-converting enzyme inhibition on left ventricular geometric patterns in patients with essential hypertension. J Clin Pharmacol 1996 Dec; 36 (12): 1141-8
44. Schartl M, Bocksch WG, Dreysse S, et al. Remodeling of myocardium and arteries by chronic angiotensin converting enzyme inhibition in hypertensive patients. J Hypertens 1994 Jul; 12 Suppl. 4: 37-42
45. Lavezzaro G, Raule G, Toppi R, et al. Angiotensin converting enzyme inhibition with quinapril and left ventricular mass in the hypertensive patient: a 4-month echocardiographic study. Drug Invest 1994; 8 (1): 38-48
46. Franz I-W, Tönnesmann U, Müller JFM. Time course of complete normalization of left ventricular hypertrophy during long-term antihypertensive therapy with angiotensin converting enzyme inhibitors. Am J Hypertens 1998 Jun; 11 (6 Pt 1): 631-9
47. Marceau M, Kouamé N, Lacourcière Y, et al. Vascular structure in the forearm and calf after 6 months of angiotensin converting enzyme inhibition in elderly hypertensive subjects with left ventricular hypertrophy. J Hypertens 1998 May; 16 (5): 673-9
48. Díez J, Laviades C. Insulin-like growth factor-1 and cardiac mass in essential hypertension: comparative effects of captopril, lisinopril and quinapril. J Hypertens Suppl 1994 Jul; 12 Suppl. 4: 31-6
49. Schön HR, Schroter G, Blomer H, et al. Beneficial effects of a single dose of quinapril on left ventricular performance in chronic mitral regurgitation. Am J Cardiol 1994 Apr 15; 73 (11): 785-91
50. Schön HR. Hemodynamic and morphologic changes after long-term angiotensin converting enzyme inhibition in patients with chronic valvular regurgitation. J Hypertens 1994 Jul; 12 Suppl. 4: 95-104
51. Gaudron P, Eilles C, Kugler I, et al. Progressive left ventricular dysfunction and remodeling after myocardial infarction. Potential mechanisms and early predictors. Circulation 1993 Mar; 87 (3): 755-63
52. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990 Apr; 81 (4): 1161-72
53. Gaudron P, Kugler I, Hu K, et al. Effect of quinapril initiated during progressive remodeling in asymptomatic patients with healed myocardial infarction. Am J Cardiol 2000 Jul 15; 86: 139-44
54. Griendling KK, Minieri CA, Ollerenshaw JD, et al. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. Circ Res 1994 Jun; 74 (6): 1141-8
55. Rajagopalan S, Kurz S, Munzel T, et al. Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation: contribution to alterations of vasomotor tone. J Clin Invest 1996 Apr 15; 97 (8): 1916-23
56. Rubanyi GM, Vanhoutte PM. Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor. Am J Physiol 1986 May; 250 (5 Pt 2): 822-7
57. Lieberman EH, Gerhard MD, Uehata A, et al. Flow-induced vasodilation of the human brachial artery is impaired in patients <40 years of age with coronary artery disease. Am J Cardiol 1996 Dec 1; 78 (11): 1210-4
58. Celermajer DS, Sorensen KE, Gooch VM, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet 1992 Nov 7; 340 (8828): 1111-5
59. Vita JA, Treasure CB, Nabel EG, et al. Coronary vasomotor response to acetylcholine relates to risk factors for coronary artery disease. Circulation 1990 Feb; 81 (2): 491-7
60. Egashira K, Inou T, Hirooka Y, et al. Impaired coronary blood flow response to acetylcholine in patients with coronary risk factors and proximal atherosclerotic lesions. J Clin Invest 1993 Jan; 91 (1): 29-37
61. El-Tamimi H, Mansour M, Wargovich TJ, et al. Constrictor and dilator responses to intracoronary acetylcholine in adjacent segments of the same coronary artery in patients with coronary artery disease. Endothelial function revisited. Circulation 1994 Jan; 89 (1): 45-51
62. Quyyumi AA, Dakak N, Andrews NP, et al. Nitric oxide activity in the human coronary circulation: impact of risk factors for coronary atherosclerosis. J Clin Invest 1995 Apr; 95 (4): 1747-55
63. Ruschitzka F, Corti R, Noll G, et al. A rationale for treatment of endothelial dysfunction in hypertension. J Hypertens Suppl 1999 Feb; 17 Suppl. 1: 25-35
64. Ambrosioni E, Bacchelli S, Esposti DD, et al. Anti-ischemic effects of angiotensin-converting enzyme inhibitors: a future

therapeutic perspective. J Cardiovasc Pharmacol 2001 Apr; 37 Suppl. 1: 3-9
65. Charbonneau F, Anderson TJ. Effects of antihypertensive agents on endothelial dysfunction: rationale for the brachial artery normalization of forearm function study. Am J Cardiol 1998; 82 (10 A): 34-6
66. Suwaidi JA, Hamasaki S, Higano ST, et al. Long-term follow-up of patients with mild coronary artery disease and endothelial dysfunction. Circulation 2000 Mar 7; 101 (9): 948-54
67. Schächinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease. Circulation 2000 Apr 25; 101 (16): 1899-906
68. Wilmink HW, Banga JD, Hijmering M, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor antagonism on postprandial endothelial function. J Am Coll Cardiol 1999 Jul; 34 (1): 140-5
69. Anderson TJ, Elstein E, Haber H, et al. Comparative study of ACE-inhibition, angiotensin II antagonism, and calcium channel blockade on flow-mediated vasodilation in patients with coronary disease (BANFF study). J Am Coll Cardiol 2000 Jan; 35 (1): 60-6
70. Uehata A, Takase B, Nishioka T, et al. Effect of quinapril versus nitrendipine on endothelial dysfunction in patients with systemic hypertension. Am J Cardiol 2001 Jun 15; 87 (12): 1414-6
71. Chin JH, Azhar S, Hoffman BB. Inactivation of endothelial derived relaxing factor by oxidized lipoproteins. J Clin Invest 1992 Jan; 89 (1): 10-8
72. Hornig B, Kohler C, Drexler H. Role of bradykinin in mediating vascular effects of angiotensin-converting enzyme inhibitors in humans. Circulation 1997 Mar 4; 95 (5): 1115-8
73. Haefeli WE, Linder L, Lüscher TF. Quinaprilat induces arterial vasodilation mediated by nitric oxide in humans. Hypertension 1997 Oct; 30 (4): 912-7
74. Mancini GBJ, Henry GC, Macaya C, et al. Angiotensin-converting enzyme inhibition with quinapril improves endothelial vasomotor dysfunction in patients with coronary artery disease. The TREND (Trial on Reversing ENdothelial Dysfunction) Study. Circulation 1996 Aug 1; 94 (3): 258-65
75. Koh KK, Bui MN, Hathaway L, et al. Mechanism by which quinapril improves vascular function in coronary artery disease. Am J Cardiol 1999 Feb 1; 83 (3): 327-31
76. Pitt B, Pepine C, O'Neill B, et al. Modulation of ACE inhibitor efficacy on coronary endothelial dysfunction by low density lipoprotein cholesterol. J Am Coll Cardiol 1997 Feb; 29 Suppl. A: 70
77. Schlaifer JD, Mancini GB, O'Neill BJ, et al. Influence of smoking status on angiotensin-converting enzyme inhibition-related improvement in coronary endothelial function. TREND Investigators. Trial on Reversing Endothelial Dysfunction. Cardiovasc Drugs Ther 1999 May; 13 (3): 201-9
78. Wennmalm Å, Benthin G, Edlund A, et al. Metabolism and excretion of nitric oxide in humans: an experimental and clinical study. Circ Res 1993 Dec; 73 (6): 1121-7
79. Buga GM, Griscavage JM, Rogers NE, et al. Negative feedback regulation of endothelial cell function by nitric oxide. Circ Res 1993 Nov; 73 (5): 808-12
80. Pörsti I, Arvola P, Säynävälammi P, et al. Effects of single doses of quinapril and atenolol on autonomic nervous function and exercise capacity in healthy volunteers. Eur J Clin Pharmacol 1990; 38 (6): 541-6
81. Portaluppi F, Montanari L, Vergnani L, et al. Effects of the converting enzyme inhibitor quinapril on autonomic function in normotensive and essential hypertensive subjects. Curr Ther Res 1991 Aug; 50 (2): 231-8
82. Fernandez PG, Snedden W. Converting enzyme inhibition attenuates the noradrenaline response to the Valsalva manoeuvre. Can J Cardiol 1991 Jun; 7 (5): 214-22
83. Kontopoulos AG, Athyros VG, Papageorgiou AA, et al. Effect of quinapril or metoprolol on circadian sympathetic and parasympathetic modulation after acute myocardial infarction. Am J Cardiol 1999 Nov 15; 84: 1164-9
84. Kontopoulos AG, Athyros VG, Papageorgiou AA, et al. Effect of quinapril or metoprolol on heart rate variability in post-myocardial infarction patients. Am J Cardiol 1996 Feb 1; 77 (4): 242-6
85. Kontopoulos AG, Athyros VG, Papageorgiou AA, et al. Effect of angiotensin-converting enzyme inhibitors on the power spectrum of heart rate variability in post-myocardial infarction patients. Coron Artery Dis 1997 Aug-1997 30; 8 (8-9): 517-24
86. Hikosaka M, Yuasa F, Yuyama R, et al. Effect of angiotensin-converting enzyme inhibitor on cardiopulmonary baroreflex sensitivity in patients with acute myocardial infarction. Am J Cardiol 2000 Dec 1; 86 (11): 1241-6
87. Kleiger RE, Miller JP, Bigger Jr JT, et al. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 1987 Feb 1; 59 (4): 256-62
88. Kontopoulos AG, Athyros VG, Didangelos TP, et al. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. Diabetes Care 1997 Mar; 20 (3): 355-61
89. Athyros VG, Didangelos TP, Karamitsos DT, et al. Long-term effect of converting enzyme inhibition on circadian sympathetic and parasympathetic modulation in patients with diabetic autonomic neuropathy. Acta Cardiol 1998; 53 (4): 201-9
90. De Caprio L, De Rosa ML, Di Palma A, et al. Regression of left ventricular hypertrophy and improvement of renal hemodynamics in hypertensive patients treated with quinapril. Cardiovasc Drugs Ther 1994 Oct; 8 (5): 735-40
91. Ruilope LM, Lahera V, Alcazar JM, et al. Randomly allocated study of the effects of standard therapy versus ACE inhibition on micro-albuminuria in essential hypertension. J Hypertens 1994 Jul; 12 Suppl. 4: 59-63
92. Lewis EJ, Hunsicker LG, Bain RP. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 1993 Nov; 329 (20): 1456-62
93. Salvetti A, Mattei P, Sudano I. Renal protection and antihypertensive drugs: current status. Drugs 1999 May; 57 (5): 665-93
94. Munger MA, Chance M, Nair R, et al. Evaluation of quinapril on regional blood flow and cardiac function in patients with congestive heart failure. J Clin Pharmacol 1992 Jan; 32 (1): 70-6
95. Ferrari P, Rosman J, Weidmann P. Antihypertensive agents, serum lipoproteins and glucose metabolism. Am J Cardiol 1991 Apr 22; 67 (10): 26-35
96. Frank GJ, Knapp LE, McLain RW. Overall tolerance and safety of quinapril in clinical trials. Angiology 1989 Apr; 40 (4 Pt 2): 405-15
97. Fogari R, Lusardi P, Mugellini A, et al. Effect of antihypertensive therapy with quinapril on blood lipids. Adv Ther 1994; 11 (3): 144-53
98. Cangelosi MM, Gaudio M, Brancati AM, et al. Blood lipid changes in hypertensive, dyslipidemic patients under long term quinapril treatment. Int Angiol 1994 Mar; 13 (1): 65-7

99. Koskinen P, Manninen V, Eisalo A. Quinapril and blood lipids. Br J Clin Pharmacol 1988 Oct; 26 (4): 478-80
100. Motero Carrasco J. A comparative study of the efficacy of lisinopril versus quinapril in controlling light to moderate arterial hypertension. A follow-up with ABPM spa. Rev Esp Cardiol 1995 Nov; 48 (11): 746-53
101. Manzato E, Capurso A, Crepaldi G. Modification of cardiovascular risk factors during antihypertensive treatment: a multicentre trial with quinapril. J Int Med Res 1993 Jan-1993 28; 21 (1): 15-25
102. Romero R, Castellote E, Ocón J, et al. Controlled multicenter study with quinapril, hydrochlorothiazide, and combination in patients with moderate to severe hypertension. J Cardiovasc Pharmacol 1995 Jul; 26 (1): 114-8
103. Dominguez LJ, Barbagallo M, Kattah W, et al. Quinapril reduces microalbuminuria in essential hypertensive and in diabetic hypertensive subjects. Am J Hypertens 1995 Aug; 8 (8): 808-14
104. Östman J, Asplund K, Bystedt T, et al. Comparison of effects of quinapril and metoprolol on glycaemic control, serum lipids, blood pressure, albuminuria and quality of life in non-insulin-dependent diabetes mellitus patients with hypertension. Swedish Quinapril Group. J Intern Med 1998 Aug; 244 (2): 95-107
105. Feldman RD, Schmidt ND. Quinapril treatment enhances vascular sensitivity to insulin. J Hypertens 2001 Jan; 19 (1): 113-8
106. Cabezas-Cerrato J, Garcia-Estevez DA, Araujo D, et al. Insulin sensitivity, glucose effectiveness, and b-cell function in obese males with essential hypertension: investigation of the effects of treatment with a calcium channel blocker (diltiazem) or an angiotensin-converting enzyme inhibitor (quinapril). Metabolism 1997 Feb; 46 (2): 173-8
107. Olson SC, Horvath AM, Michniewicz BM, et al. The clinical pharmacokinetics of quinapril. Angiology 1989; 40 (4 Pt 2): 351-9
108. Fukiyama K, Azuma J, Yoshida H, et al. A pharmacokinetic study of quinapril in normal Japanese men Japanese. Rinsho Iyaku 1993; 9 Suppl. 7: 3-16
109. Fukiyama K, Higashi J, Yoshida K, et al. A clinical phase I study of quinapril Japanese. Yakuri To Chiryo 1991; 19: 167-98
110. White CM. Pharmacologic, pharmacokinetic, and therapeutic differences among ACE inhibitors. Pharmacotherapy 1998; 18 (3): 588-99
111. Ferry JJ, Horvath AM, Sedman AJ, et al. Influence of food on the pharmacokinetics of quinapril and its active diacid metabolite, CI-928. J Clin Pharmacol 1987; 27 (5): 397-9
112. Vertes V, Haynie R. Comparative pharmacokinetics of captopril, enalapril, and quinapril. Am J Cardiol 1992; 69 (10): 8-16
113. Elliott HL, Macdonald NJ, Meredith PA, et al. Dose responses and pharmacokinetics for the angiotensin converting enzyme inhibitor quinapril. Clin Pharmacol Ther 1992; 51 (3): 260-5
114. Hovarth A, Olson S. Pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with renal insufficiency. J Clin Pharmacol 1988; 28: 908-9
115. Begg EJ, Robson RA, Bailey RR, et al. The pharmacokinetics and pharmacodynamics of quinapril and quinaprilat in renal impairment. Br J Clin Pharmacol 1990 Aug; 30 (2): 213-20
116. Onoyama K, Hirakata H, Okuda S, et al. Pharmacokinetics of quinapril in patients with renal dysfunction. Curr Ther Res 1993 Dec; 54 (6): 658-71
117. Wolter K, Fritschka E. Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. Eur J Clin Pharmacol 1993; 44 Suppl. 1: 53-6
118. Swartz RD, Starmann B, Horvath AM, et al. Pharmacokinetics of quinapril and its active metabolite quinaprilat during continuous ambulatory peritoneal dialysis. J Clin Pharmacol 1990 Dec; 30 (12): 1136-41
119. Blum RA, Olson SC, Kohli RK, et al. Pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients on chronic hemodialysis. J Clin Pharmacol 1990 Oct; 30 (10): 938-42
120. Hovarth A, Olson S, Ferry J, et al. Pharmacokinetics of quinapril and its active metabolite, quinaprilat, in patients with hepatic impairment. J Clin Pharmacol 1988; 28: 917
121. Sasaki M, Maeda A, Fujimura A. Pharmacokinetic alterations of quinapril during repeated treatment in elderly subjects. Eur J Clin Pharmacol 1998 Jun; 54 (4): 347-9
122. Begg EJ, Robson RA, Ikram H, et al. The pharmacokinetics of quinapril and quinaprilat in patients with congestive heart failure. Br J Clin Pharmacol 1994; 37 (3): 302-4
123. Begg EJ, Robson RA, Gardiner SJ, et al. Quinapril and its metabolite quinaprilat in human milk. Br J Clin Pharmacol 2001 May; 51 (5): 478-81
124. Bammert J, Posvar E, Sedman A, et al. A study to determine the relationship of the tetracycline-quinapril pharmacokinetic (PK) interaction with the timing of concurrent drug administration. Pharm Res 1991; 8 Suppl.: S293
125. Maclean D. Quinapril: a double-blind, placebo-controlled trial in essential hypertension. Angiology 1989 Apr; 40 (4 Pt 2): 370-81
126. Sánchez S, Luna A, Orozco R, et al. Quinapril versus enalapril in the treatment of mild-to-moderate essential hypertension. Clin Ther 1991 Sep 31; 13 (5): 651-5
127. Taylor SH. A comparison of the efficacy and safety of quinapril with that of enalapril in the treatment of mild to moderate essential hypertension. Angiology 1989 Apr; 40 (4 Pt 2): 382-8
128. Durante MYJ, Crisostomo M, et al. A parallel group double-blind study of once daily quinapril versus enalapril in the treatment of mild-to-moderate essential hypertension. Philipp J Int Med 1991; 29: 173-84
129. Taylor SH. The treatment of mild to moderate hypertension with ACE inhibitors. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 24-8
130. Anastacio RV, Mendoza CM, Katigbak-Gancayco B, et al. A parallel group double-blind study of once-daily quinapril versus twice-daily captopril in the treatment of mild to moderate essential hypertension. Philipp J Int Med 1993; 31: 41-52
131. Langan J, Laws D, Livingstone ED. Quinapril and lisinopril in elderly patients with mild-to-moderate hypertension: a randomised, double blind comparison. Br J Clin Res 1995; 6: 191-9
132. Lacourcière Y, Lefebvre J, Provencher P, et al. Comparison of quinapril and atenolol as single drugs or in combination with hydrochlorothiazide in moderate to severe hypertensives, using automated ambulatory monitoring. Br J Clin Pharmacol 1993 Feb; 35 (2): 121-7
133. Bahena JH, Estrella ME, Munoz M. Quinapril versus atenolol in the treatment of mild to moderate essential hypertension. Clin Ther 1992 Jul-1992 31; 14 (4): 527-36
134. Rosenthal J, Bahrmann H, Benkert K, et al. Analysis of adverse effects among patients with essential hypertension receiving an ACE inhibitor or a beta-blocker. Cardiology 1996 Sep 31; 87 (5): 409-14

135. Doel SR, Millar LJ, McEwan S. Quinapril and nifedipine in mild to moderate hypertension. A randomised, open, multicentre, parallel group comparison. Clin Trials Metaanal 1992 Jun; 28: 29-38
136. Ding Y-A, Chang S-M, Chou T-C. Comparison of amlodipine and quinapril on ambulatory blood pressure and platelet function in hypertension. J Hum Hypertens 1995 Aug; 9 (8): 637-41
137. Schulte K-L. Comparison of antihypertensive efficacy and tolerance of quinapril and nitrendipine German. Herz Kreisl 1994 Oct; 26: 332-6
138. Goldstein RJ. The treatment of moderate to severe hypertension with ACE inhibitors. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 29-35
139. Schnaper HW. Comparison of the efficacy and safety of quinapril vs. captopril in treatment of moderate to severe hypertension. Angiology 1989 Apr; 40 (4 Pt 2): 389-95
140. Frishman WH. The efficacy and safety of quinapril in the treatment of moderate to severe and severe hypertension: comparison to captopril. Clin Cardiol 1990 Jun; 13 (6) Suppl. 7: 26-31
141. Pueyo C, Diaz C, Sol JM, et al. Efficacy and safety of quinapril 40mg once daily as monotherapy for patients with poorly controlled hypertension: The EUREKA study. Clin Drug Invest 2000; 20 (2): 81-8
142. Larochelle P, Haynes B, Maron N, et al. A postmarketing surveillance evaluation of quinapril in 3742 Canadian hypertensive patients: the ACCEPT Study. Accupril Canadian Clinical Evaluation and Patient Teaching. Clin Ther 1994 Sep-1994 31; 16 (5): 838-53
143. Dzau V, Julius S, Weber M, et al. ASCEND (Accupril Study of Clinical, Economic, and Dose Titration End Points): demographics and special population results. Am J Hypertens 1996 Apr; 9 (Pt 2): 72
144. Dzau V, Julius S, Weber M, et al. ASCEND (Accupril Study of Clinical, Economic, and Dose Titration End Points): design, rationale, general results. Am J Hypertens 1996 Apr; 9 (Pt 2): 72
145. Dzau V, Julius S, Weber M, et al. ASCEND (Accupril Study of Clinical, Economic, and Dose Titration End Points): effect of up titration and compliance on response rate. Am J Hypertens 1996 Apr; 9 (Pt 2): 72
146. Forette B, Koen R, Vicaut E. Efficacy and safety of quinapril in the elderly hypertensive patient. Am Heart J 1992 May; 123 (5): 1426-32
147. Schnaper HW. The management of hypertension in older patients. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 56-61
148. Alcocer L, Parra J, Aguirre L, et al. The effectiveness of quinapril in hypertensive patients over 60 years old. Eur J Clin Res 1995; 7: 241-6
149. Richardson AD, Piepho RW. Effect of race on hypertension and antihypertensive therapy. Int J Clin Pharmacol Ther 2000 Feb; 38 (2): 75-9
150. Olvera S, Alcocer L, Novoa G. Usefulness of low-dose, once-daily quinapril as monotherapy for patients with hypertension. Clin Ther 1996; 18 (5): 864-73
151. Kuramoto K, Omae T, Ogihara T, et al. Efficacy and safety of quinapril in long-term treatment of essential hypertension Japanese. Rinsho Iyaku 1993; 9 Suppl. 7: 41-58
152. Flack JM, Yunis C, Preisser J, et al. The rapidity of drug dose escalation influences blood pressure response and adverse effects burden in patients with hypertension: the Quinapril Titration Interval Management Evaluation (ATIME) Study. ATIME Research Group. Arch Intern Med 2000 Jun 26; 160 (12): 1842-7
153. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998 Jun 13; 351 (9118): 1755-62
154. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 1998 Sep 12; 317: 703-13
155. Ramsay LE, Williams B, Johnston GD, et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. J Hum Hypertens 1999 Sep; 13: 569-92
156. Lenz T, Schulte K-L, Wagner B, et al. Quinapril, hydrochlorothiazide, and combination in patients with moderate to severe hypertension. Eur Heart J 1994 Jul; 15 (7): 940-6
157. Bianchi S, Bigazzi R, Campese VM. Microalbuminuria in essential hypertension: significance, pathophysiology, and therapeutic implications. Am J Kidney Dis 1999 Dec; 34 (6): 973-95
158. Gerstein HC, Mann JF, Yi Q, et al. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001 Jul 25; 286 (4): 421-6
159. Jafar TH, Schmid CH, Landa M, et al. Angiotensin-converting enzyme inhibitors and progression of nondiabetic renal disease: a meta-analysis of patient-level data. Ann Intern Med 2001; 135: 73-87
160. Kshirsagar AV, Joy MS, Hogan SL. Effect if ACE inhibitors in diabetic and nondiabetic chronic renal disease: a systematic overview of randomized placebo-controlled trials. Am J Kidney Dis 2000 Apr; 35 (4): 695-707
161. Bianchi S, Bigazzi R, Baldari G, et al. Microalbuminuria in patients with essential hypertension. Effects of an angiotensin converting enzyme inhibitor and of a calcium channel blocker. Am J Hypertens 1991 Apr; 4 (4 Pt 1): 291-6
162. Ranieri G, Andriani A, Lamontanara G, et al. Effects of lisinopril and amlodipine on microalbuminuria and renal function in patients with hypertension. Clin Pharmacol Ther 1994 Sep; 56 (3): 323-30
163. Ogawa Y, Haneda T, Hirayama T, et al. Effects of lisinopril and nitrendipine on urinary albumin excretion and renal function in patients with mild to moderate essential hypertension. Hypertens Res 2000 Nov; 23 (6): 607-12
164. Bianchi S, Bigazzi R, Baldari G, et al. Microalbuminuria in patients with essential hypertension: effects of several antihypertensive drugs. Am J Med 1992 Nov; 93 (5): 525-8
165. De Venuto G, Andreotti C, Mattarei M, et al. Long-term captopril therapy at low doses reduces albumin excretion in patients with essential hypertension and no sign of renal impairment. J Hypertens Suppl 1985 Nov; 3 Suppl. 2: 143-5
166. Erley CM, Haefele U, Heyne N, et al. Microalbuminuria in essential hypertension: reduction by different antihypertensive drugs. Hypertension 1993 Jun; 21 (6 Pt 1): 810-5
167. Puig JG, Mateos FA, Ramos TH, et al. Albumin excretion rate and metabolic modifications in patients with essential hypertension: effects of two angiotensin converting enzyme inhibitors. Am J Hypertens 1994 Jan; 7 (1): 46-51
168. Larochelle P. Effect of quinapril on the albumin excretion rate in patients with mild to moderate essential hypertension. Multicenter Study Group. Am J Hypertens 1996 Jun; 9 (6): 551-9

169. Northridge DB, Rose E, Raftery ED, et al. A multicentre, double-blind, placebo-controlled trial of quinapril in mild, chronic heart failure. Eur Heart J 1993 Mar; 14 (3): 403-9
170. Riegger GA. Effects of quinapril on exercise tolerance in patients with mild to moderate heart failure. Eur Heart J 1991 Jun; 12 (6): 705-11
171. Pflugfelder PW, Baird MG, Tonkon MJ, et al. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawal in chronic heart failure: a double-blind, placebo-controlled study of quinapril. Quinapril Heart Failure Trial Investigators. J Am Coll Cardiol 1993 Nov 15; 22 (6): 1557-63
172. Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988 Jan 22-1988; 259 (4): 539-44
173. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991 Aug 1; 325 (5): 303-10
174. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med 1991 Aug 1; 325 (5): 293-302
175. CONSENSUS Trial Study Group. Effect of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987 Jun 4; 316 (23): 1429-35
176. Gruppo Italiano per lo Studio della Sopravvivenza nell'infarto Miocardico. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Lancet 1994 May 7; 343 (8906): 1115-22
177. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. SAVE Investigators. N Engl J Med 1992 Sep 3; 327 (10): 669-77
178. Cleland JGF, Erhardt L, Murray G, et al. Effect of ramipril on morbidity and mode of death among survivors of acute myocardial infarction with clinical evidence of heart failure. A report from the AIRE Study Investigators. Eur Heart J 1997 Jan; 18 (1): 41-51
179. Køber L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med 1995 Dec 21; 333 (25): 1670-6
180. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. Survival of Myocardial Infarction Long-Term Evaluation (SMILE) Study Investigators. N Engl J Med 1995 Jan 12; 332 (2): 80-5
181. Garg R, Yusuf S. Overview of randomized trials of angiotensin-converting enzyme inhibitors on mortality and morbidity in patients with heart failure. Collaborative Group on ACE Inhibitor Trials. JAMA 1995 May 10; 273 (18): 1450-6
182. Anonymous. Consensus recommendations for the management of chronic heart failure. On behalf of the Steering Committee and the Membership of the Advisory Council to Improve Outcomes Nationwide in Heart Failure. Am J Cardiol 1999 Jan 21; 83 (2A): 1-38
183. Gavazzi A, Marioni R, Campana C, et al. Comparative trial of quinapril versus captopril in mild to moderate congestive heart failure. Quinapril/Captopril Congestive Heart Failure Study Group. J Hypertens 1994 Jul; 12 Suppl. 4: 89-93
184. Acanfora D, Furgi G, Trojano L, et al. Quinapril in patients with congestive heart failure: controlled trial versus captopril. Am J Ther 1997 May-1997 30; 4 (5-6): 181-8
185. Beynon JH, Pathy MS. An open, parallel group comparison of quinapril and captopril, when added to diuretic therapy, in the treatment of elderly patients with heart failure. Curr Med Res Opin 1997; 13 (10): 583-92
186. British Medical Association. British National Formulary (BNF 41). 2001
187. Krum H, Karrasch J, Hamer A, et al. Effect of angiotensin-converting enzyme inhibitor dosing interval on functional parameters in patients with chronic heart failure. Am Heart J 1998 Feb; 135 (2 Pt 1): 237-41
188. Oosterga M, Voors AA, Pinto YM, et al. Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study). QUinapril on Vascular Ace and Determinants of Ischemia. Am J Cardiol 2001 Mar 1; 87 (5): 542-6
189. Pitt B, O'Neill B, Feldman R, et al. The Quinapril Ischemic Event Trial (QUIET): evaluation of chronic ace inhibitor therapy in patients with ischemic heart disease and preserved left ventricular function. Am J Cardiol 2001 May 1; 87 (9): 1058-63
190. Cashin-Hemphill L, Holmvang G, Chan RC, et al. Angiotensin-converting enzyme inhibition as antiatherosclerotic therapy: no answer yet. QUIET Investigators. QUinapril Ischemic Event Trial. Am J Cardiol 1999 Jan 1; 83 (1): 43-7
191. Kester M, Waybill P, Kozak M. New strategies to prevent restenosis. Am J Cardiovasc Drugs 2001; 1 (2): 77-83
192. Okimoto T, Imazu M, Hayashi Y, et al. Quinapril with high affinity to tissue angiotensin-converting enxyme inhibitor reduces restenosis after percutaneous transcatheter coronary revascularization. J Am Coll Cardiol 2000 Feb; 35 (2) Suppl. A: 37
193. Kondo J, Sone T, Tsuboi H, et al. Effect of quinapril on intimal hyperplasia after coronary stenting as assessed by intravascular ultrasound. Am J Cardiol 2001 Feb 15; 87 (4): 443-56
194. Meurice T, Bauters C, Hermant X, et al. Effect of ACE inhibitors on angiographic restenosis after coronary stenting (PARIS): a randomised, double-blind, placebo-controlled trial. Lancet 2001 Apr 28; 357 (9265): 1321-4
195. Knapp LE, Frank GJ, McLain R, et al. The safety and tolerability of quinapril. J Cardiovasc Pharmacol 1990; 15 Suppl. 2: 47-55
196. Parra-Carillo JZ, Alcocer D-B, Olvera S, et al. Multicentric study of quinapril, an angiotensin converting enzyme inhibito in the treatment of mild to moderate essentional hypertension. Cur Ther Res 1992; 51: 185-95
197. Electronic Medicines Compendium. Accupro: summary of product characteristics (Parke-Davis). 2001 Aug 23 [online]. Available from URL: http://emc.vhn.net [Accessed 2001 Sep 10]
198. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2. Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. Lancet 1990 Apr 7; 335 (8693): 827-38
199. Anonymous. The Sixth Report of the Joint National Committee on prevention, detection, evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997 Nov 24; 157 (21): 2413-46
200. World Health Organization. 1999 World Health Organization-International Society of Hypertension Guidelines for the

Management of Hypertension. Guidelines Subcommittee. J Hypertens 1999 Feb; 17 (2): 151-83
201. Davis BR, Cutler JA, Gordon DJ, et al. Rationale and design for the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Research Group. Am J Hypertens 1996 Apr; 9 (4 Pt 1): 342-60
202. National Institutes of Health. NHLBI stops part of study: high blood pressure drug performs no better than standard treatment. National Heart, Lung, and Blood Institute. 2000 Mar
203. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2000 Apr 19; 283 (15): 1967-75
204. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. Lancet 1999 Feb 20; 353 (9153): 611-6
205. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999 Nov 20; 354 (9192): 1751-6
206. ACE Inhibitor Myocardial Infarction Collaborative Group. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100 000 patients in randomized trials. Circulation 1998 Jun 9; 97 (22): 2202-12
207. Lewis JB, Berl T, Bain RP, et al. Effect of intensive blood pressure control on the course of type 1 diabetic nephropathy. Am J Kidney Dis 1999 Nov; 34 (5): 809-17
208. Bigazzi R, Bianchi S, Campese VM, et al. Prevalence of microalbuminuria in a large population of patients with mild to moderate essential hypertension. Nephron 1992; 61 (1): 94-7
209. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 1998 Sep 12; 317 (7160): 713-20
210. Pahor M, Psaty BM, Alderman MH, et al. Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 2000 Jul; 23 (7): 888-92
211. Lindholm LH, Hansson L, Ekbom T, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. J Hypertens 2000 Nov; 18 (11): 1671-5
212. Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. JAMA 2001 Oct 17; 286 (15): 1882-5
213. van Zwieten PA. The influence of antihypertensive drug treatment on the prevention and regression of left ventricular hypertrophy. Cardiovasc Res 2000; 45 (1): 82-91
214. Schmieder RE, Martus P, Klingbeil A. Reversal of left ventricular hypertrophy in essential hypertension: a meta-analysis of randomized double-blind studies. JAMA 1996 May 15; 275 (19): 1507-13
215. Verdecchia P, Schillaci G, Borgioni C, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. Circulation 1998 Jan 6-1998; 97 (1): 48-54
216. SOLVD Investigattors. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992 Sep 3; 327 (10): 685-91
217. Task Force of the Working Group on Heart Failure of the European Society of Cardiology. The treatment of heart failure. Eur Heart J 1997 May; 18 (5): 736-53
218. Eccles M, Freemantle N, Mason J. North of England evidence based development project: guideline for angiotensin converting enzyme inhibitors in primary care management of adults with symptomatic heart failure. BMJ 1998 May 2; 316 (7141): 1369-75
219. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 1999 Jun 12; 353 (9169): 2001-7
220. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet 1999 Jan 2; 353 (9146): 9-13
221. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. US Carvedilol Heart Failure Study Group. N Engl J Med 1996 May 23; 334 (21): 1349-55
222. Thackray SDR, Witte KKR, Khand A, et al. Clinical trials update: highlights of the scientific sessions of the American Heart Association year 2000: Val HeFT, COPERNICUS, MERIT, CIBIS-II, BEST, AMIOVIRT, V-MAC, BREATHE, HEAT, MIRACL, FLORIDA, VIVA and the first human cardiac skeletal muscle myoblast transfer for heart failure. Eur J Heart Fail 2001 Jan; 3 (1): 117-24
223. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999 Sep 2; 341 (10): 709-17
224. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997 Feb 20; 336 (8): 525-33
225. Cohn JN. Overview of the treatment of heart failure. Am J Cardiol 1997 Dec 4; 80 (11A): 2-6
226. Cohn JN, Johnson GR, Shabetai R, et al. Ejection fraction, peak exercise oxygen consumption, cardiothoracic ratio, ventricular arrhythmias, and plasma norepinephrine as determinants of prognosis in heart failure. V-HeFT VA Cooperative Studies Group. Circulation 1993 Jun; 87 Suppl. VI: 5-16
227. Andersson F, Cline C, Rydén-Bergsten T, et al. Angiotensin converting enzyme (ACE) inhibitors and heart failure. The consequences of underprescribing. Pharmacoeconomics 1999 Jun; 15 (6): 535-50
228. Kermani M, Dua A, Gradman AH. Underutilization and clinical benefits of angiotensin-converting enzyme inhibitors in patients with asymptomatic left ventricular dysfunction. Am J Cardiol 2000; 86 (6): 644-8
229. Skrabal MZ, Stading JA, Behmer-Miller KA, et al. Advances in the treatment of congestive heart failure: new approaches for an old disease. Pharmacotherapy 2000; 20 (7 I): 787-804
230. Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. Arch Intern Med 2001; 161 (3): 342-52
231. Wood D, De Backer G, Faergeman O, et al. Prevention of coronary heart disease in clinical practice. Summary of recommendations of the Second Joint Task Force of European and other societies on coronary prevention. J Hypertens 1998 Oct; 16: 1407-14

232. Smith Jr SC, Blair SN, Criqui MH, et al. Preventing heart attack and death in patients with coronary disease. Circulation 1995 Jul 1; 92 (1): 2-4
233. Lonn EM, Yusuf S, Jha P, et al. Emerging role of angiotensin-converting enzyme inhibitors in cardiac and vascular protection. Circulation 1994 Oct; 90 (4): 2056-69
234. Yusuf S, Pepine CJ, Garces C, et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet 1992 Nov 14; 340 (8829): 1173-8
235. Smith Jr SC , Blair SN, Bonow RO, et al. AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. Circulation 2001 Sep 25; 104 (13): 1577-9
236. Mancini GBJ. Long-term use of angiotensin-converting enzyme inhibitors to modify endothelial dysfunction: a review of clinical investigations. Clin Invest Med 2000; 23 (2): 144-61
237. Higashi Y, Sasaki S, Nakagawa K, et al. A comparison of angiotensin-converting enzyme inhibitors, calcium antagonists, beta-blockers and diuretic agents on reactive hyperemia in patients with essential hypertension: a multicenter study. J Am Coll Cardiol 2000 Feb; 35 (2): 284-91
238. Simon J, Gibbs R, Crean PA, et al. The variable effects of angiotensin converting enzyme inhibition on myocardial ischaemia in chronic stable angina. Br Heart J 1989 Aug; 62 (2): 112-7
239. Steffensen R, Grande P, Madsen JK, et al. Short-term effects of captopril on exercise tolerance in patients with chronic stable angina pectoris and normal left ventricular function. Cardiology 1995; 86 (6): 445-50
240. Cleland JG, Henderson E, McLenachan J, et al. Effect of captopril, an angiotensin-converting enzyme inhibitor, in patients with angina pectoris and heart failure. J Am Coll Cardiol 1991 Mar 1; 17 (3): 733-9
241. Kjøller-Hansen L, Steffensen R, Grande P. The Angiotensin-converting Enzyme Inhibition Post Revascularization Study (APRES). J Am Coll Cardiol 2000 Mar 15; 35 (4): 881-8
242. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: executive summary and recommendations : A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 Guidelines for Coronary Artery Bypass Graft Surgery). Circulation 1999 Sep 28; 100 (13): 1464-80
243. Pfeffer MA, Domanski M, Verter J, et al. The continuation of the Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial. Am Heart J 2001 Sep; 142 (3): 375-7
244. Fox KM, Henderson JR, Bertrand ME, et al. The European trial on reduction of cardiac events with perindopril in stable coronary artery disease (EUROPA). Eur Heart J 1998 Sep; 19 Suppl. J: 52-5

Correspondence: *Christine R. Culy*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland, New Zealand.
E-mail: demail@adis.co.nz