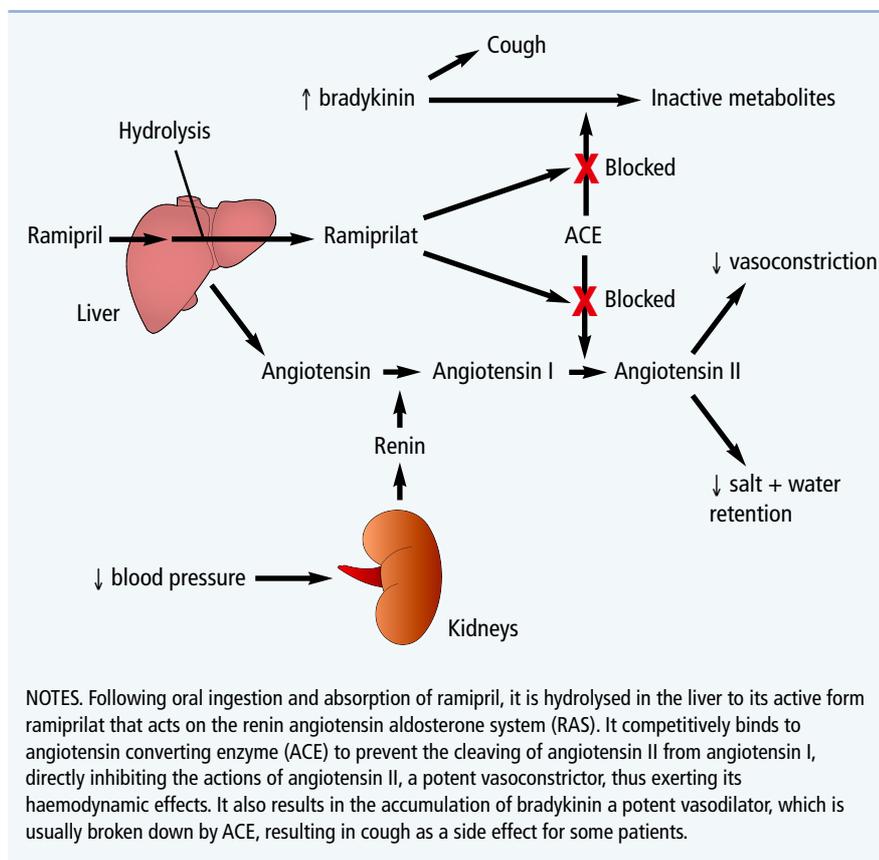


# Ramipril



**Figure 1.** Pharmacological action of ramipril

## Introduction

Angiotensin converting enzyme (ACE) inhibitors are used for the treatment of cardiovascular disease in people with diabetes. Ramipril is a second-generation ACE inhibitor, and is prescribed in patients with diabetes for several clinical indications including the management of hypertension, following myocardial infarction (MI), in chronic heart failure, in diabetic nephropathy and in patients with increased cardiovascular risk, where it has been shown to reduce the risk of death and cardiovascular events.

## Pharmacology

Figure 1 outlines the pharmacological action of ramipril, a monoethyl ester prodrug. Following oral ingestion and absorption, it is hydrolysed in the liver to its active form ramiprilat. This active metabolite exerts the haemodynamic effects associated with ACE inhibition, and has a higher affinity for angiotensin

converting enzyme than the active forms of enalapril and captopril.

Ramiprilat acts on the renin angiotensin aldosterone system (RAS) by competitively binding to ACE to prevent the cleaving of angiotensin II from angiotensin I, directly inhibiting the actions of angiotensin II, a potent vasoconstrictor.

ACE is normally responsible for metabolising the potent vasodilator peptide bradykinin. ACE inhibitors catalyse the degradation of bradykinin, the accumulation of which can be associated with a troublesome cough, an unwanted side effect of ACE inhibitors. Bradykinin also stimulates nitric oxide production, improving endothelial function and reducing peripheral vascular resistance.

ACE inhibitors reduce vascular smooth muscle cell proliferation, enhance fibrinolysis, have an inhibitory effect on platelet aggregation, and have a role in atherosclerotic plaque stabilisation. By inhibiting the

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formation of angiotensin II, ACE inhibitors reduce the secretion of aldosterone, with a resulting reduction in sodium and water reabsorption in the renal collecting duct.

Ramiprilat reaches its peak plasma concentration at approximately 3 hours. It has an extended elimination half-life when compared to captopril or enalapril, and can be administered once daily, although for some indications the clinical evidence is based on twice-daily dosing.

The large majority of ramipril and its active metabolites are excreted via the renal route in the urine (approximately 60%) with the remainder of the drug being excreted in faeces. Patients with renal impairment should have a reduced dose to avoid accumulation of ramiprilat.

There are few significant interactions between ramipril and other drugs, but care should be taken in those co-prescribed diuretics or in renal impairment. The main adverse effect is cough, which similar to other ACE inhibitors is dose dependent and would normally result in drug withdrawal in less than 10% of patients.

### **Trials of safety and efficacy**

**Cardiovascular risk.** The Heart Outcomes Prevention Evaluation (HOPE) study provides evidence for the use of ramipril in the management of cardiovascular risk.<sup>1</sup> In this large multicentre trial, 9297 subjects were randomly assigned to ramipril 10mg once daily or placebo and either vitamin E or placebo according to a two-by-two factorial design. Patients were included if they were at high cardiovascular risk (age  $\geq 55$  years, existing vascular disease or diabetes and at least one cardiovascular risk factor) but with no evidence of heart failure. The study demonstrated a 22% relative risk reduction for the primary endpoint, which was a composite of MI, stroke or death from cardiovascular causes.

The HOPE-TOO study, an extension of HOPE, looked at an additional 2.6 years of follow up and found that the benefits were maintained and more pronounced over this longer follow up.<sup>2</sup>

In the Study to Evaluate Carotid Ultrasound Changes in patients treated with ramipril and vitamin E (SECURE), 732 patients were

randomly assigned to receive ramipril 2.5mg or 10mg daily and followed up for 4.5 years.<sup>3</sup> Reduced progression of carotid artery atherosclerosis with ramipril treatment was demonstrated by B mode carotid ultrasound, and this benefit remained statistically significant after adjustment for hypertension and blood pressure (BP) changes, suggesting a direct vascular protective effect with ramipril treatment. However, this was not confirmed in another similar study.<sup>4</sup>

**Heart failure and post myocardial infarction.** In the Acute Infarction Ramipril Efficacy (AIRE) study, 2006 patients with clinical or radiological evidence of heart failure were randomised to ramipril 5mg twice daily or placebo within 2–9 days of an acute MI.<sup>5</sup> A 27% reduction in all-cause mortality was observed with ramipril compared to placebo at 15 months. The benefit on survival was notable as early as 30 days post treatment and was apparent across a wide range of subgroups.

AIRE Extension (AIREX) was a follow-up study occurring three years after the closure of AIRE, investigating long-term survival with a mean follow-up period of 59 months in 603 patients from UK centres previously involved in AIRE.<sup>6</sup> The survival benefit in patients with heart failure persisted with time and a 36% reduction in all-cause mortality was observed with ramipril treatment.

In APRES (the Angiotensin-converting Enzyme Inhibition Post Revascularization Study), patients with chronic stable angina pectoris and asymptomatic moderate left ventricular dysfunction (ejection fraction 30–50% with no evidence of clinical heart failure) were randomised to ramipril or placebo following revascularisation and followed up for a median of 33 months.<sup>7</sup> Treatment with ramipril significantly reduced the risk of the triple composite endpoint of cardiac death, acute MI or clinical heart failure by 58% compared to placebo.

The survival benefit observed with ramipril in patients with heart failure is consistent with evidence from other large trials investigating the role of other ACE inhibitors in this condition, making this group of medications the first-line therapy in patients with heart

failure. In addition to improving survival, ACE inhibitors reduce hospitalisation rates and improve symptoms.

**Hypertension.** Ramipril is frequently used to treat hypertension, but there is a lack of randomised control trials with hard cardiovascular endpoints using ramipril for this indication.

In HOPE, a very small reduction in BP in patients treated with ramipril was observed (mean reduction 3/2mmHg). This is probably an underestimate as the majority of subjects were normotensive at baseline (mean BP 139/79mmHg).

One study of ramipril in patients with essential hypertension suggested that ramipril may have beneficial effects on cardiac structure and function.<sup>8</sup> Ramipril 5mg was superior to felodipine 5mg in preventing left ventricular hypertrophy at three years in patients with recent onset of mild hypertension despite similar effects on BP reduction (32/9mmHg and 31/7mmHg respectively), and also prevented increases in left ventricular mass.

**Renal impairment.** The African American Study of Kidney Disease and Hypertension (AASK) assessed the effect of ramipril compared with metoprolol and amlodipine on glomerular filtration rate (GFR) in 1094 patients with hypertensive renal disease.<sup>9</sup> The study examined the effects of the three classes of antihypertensives on the rate of change in GFR, and on a composite of: reduction in GFR by 50% or more (or  $\geq 25$ ml/min per 1.73m<sup>2</sup>) from baseline, end-stage renal disease, or death. Although no significant differences were observed in BP reduction between the three different antihypertensive agents, ramipril was associated with 22% and 38% risk reductions in the composite outcome compared with metoprolol and amlodipine respectively.

### **Specific evidence for use in diabetes**

**Cardiovascular risk.** In the MICRO-HOPE sub-study, 3577 people with diabetes from HOPE were included, and the risk reduction in the combined primary outcome (MI, stroke or cardiovascular death) was 25%.<sup>10</sup> Ramipril reduced the risk of MI by 22%, stroke by 33%, cardiovascular

death by 37%, total mortality by 24%, revascularisation by 17% and overt nephropathy by 24% in patients with diabetes.

**Hypertension.** Ramipril lowered diastolic BP by a mean of 11mmHg at eight weeks in a multicentre parallel group trial of 837 patients with hypertension and diabetes mellitus who were randomised to either ramipril 10mg or aliskiren 300mg or both.<sup>11</sup>

**Diabetic nephropathy.** ATLANTIS (ACE Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects) compared standard (5mg) and low (1.25mg) dose ramipril treatment to placebo in 140 normotensive patients with type 1 diabetes and persistent microalbuminuria.<sup>12</sup> Subjects in the ramipril group were more likely to regress to normoalbuminuria (20% in the 5mg/day ramipril, 11% in the 1.25mg/day ramipril and 4% in the placebo group;  $p=0.05$ ), and urinary albumin excretion was significantly reduced in the combined-ramipril treatment groups compared to the placebo group at two years ( $p=0.013$ ). No differences were observed in GFRs between the ramipril and placebo groups over the two-year period.

In the DIABHYCAR study (type 2 DIABetes, HYPertension, CArdiovascular events and Ramipril), 4912 patients with type 2 diabetes, hypertension and microalbuminuria or proteinuria were randomised to either low-dose ramipril (1.25mg) or placebo in addition to their regular medications.<sup>13</sup> Cardiovascular and renal outcomes were compared in the two groups over a four-year follow-up period. Low-dose ramipril did not significantly reduce the incidence of cardiovascular death, non-fatal MI, stroke, heart failure leading to hospital admission, or end-stage renal failure. Low-dose ramipril lowered systolic and diastolic BP by 2.4mmHg and 1.1mmHg respectively after two years compared to placebo.

The effect of ramipril (5mg) vs nitrendipine (20mg) on renal function and urinary albumin excretion was examined over two years in a study of 51 male patients with type 2 diabetes, hypertension and renal impairment.<sup>14</sup> Urinary albumin excretion decreased significantly in

both groups, but the effect was more notable and achieved earlier in the ramipril group. There was no difference between the groups in the rate of progression to renal insufficiency as measured by reduction in creatinine clearance.

**Prevention of diabetes.** In HOPE, there was a 34% reduction in the incidence of diabetes with ramipril compared to placebo. HOPE-TOO facilitated further passive follow up of this cohort, and over the combined total follow-up period of 7.2 years there was an overall 31% relative risk reduction in new onset of diabetes. The diagnosis of diabetes was ascertained by self-reporting and was not a pre-specified outcome so these findings must be interpreted with caution.

A suggestion that use of ACE inhibitors may prevent the development of diabetes mellitus in people with increased cardiovascular risk was not supported by the findings of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial.<sup>15</sup> In this double-blind randomised trial, over 5269 subjects with impaired glucose tolerance testing were assigned to either treatment with ramipril or placebo and there was no significant reduction in the incidence of death or diabetes between the groups.

### Discussion

ACE inhibitors have a well-established role in the management of patients with cardiovascular disease.

Patients with increased cardiovascular risk due to a combination of increased age, vascular disease, diabetes and other cardiovascular risk factors, may benefit from treatment with ramipril as detailed by the HOPE study, where significant reductions in mortality and cardiovascular morbidity were demonstrated. In routine clinical practice, however, ramipril is rarely prescribed for cardiovascular risk alone and is more often used to treat hypertension, heart failure or diabetic nephropathy.

ACE inhibitors are considered as first-line agents in hypertensive patients <55 years and with diabetes. Although ramipril is one of the most commonly prescribed antihypertensives, it is not the most effective agent available for the treatment of essential

### Key points

- Ramipril is an angiotensin converting enzyme inhibitor, which is safe and effective for use in patients with hypertension, heart failure, and recent myocardial infarction to reduce the risk of death and further cardiac events
- The benefits of ramipril extend to patients with diabetes mellitus, and ramipril may have a role in preventing the development and progression of diabetic nephropathy
- Ramipril can be used once daily for all indications at the highest tolerated dose, except in patients with congestive cardiac failure where it is used twice daily as in the AIRE study

hypertension and has quite a modest BP lowering effect.

Ramipril treatment is associated with a significant survival benefit in patients with clinical or radiological evidence of heart failure following acute MI as reported in AIRE, and this benefit on mortality occurs within a few weeks of commencing treatment and persists over time. The benefit of ramipril is also apparent in patients with chronic stable angina and subclinical heart failure who have received revascularisation through beneficial effects on reducing left ventricular wall thickness and improving left ventricular ejection fraction.

In patients with diabetes, ramipril reduces urinary albumin excretion and improves renal endothelial function, which may contribute to improvements in renal and cardiovascular function. When combined with the renal results from the HOPE study this may explain the frequent use of ramipril in diabetic patients with chronic kidney disease.

### Declaration of interests

SG none. GMcK has received funding for attendance at conferences and has been paid for advisory boards by Sanofi. MF was an events adjudicator for the HOPE and HOPE-TOO studies, and was on the Steering Committee of HOPE-TOO. He has received payment for lectures and advisory boards from Sanofi.

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