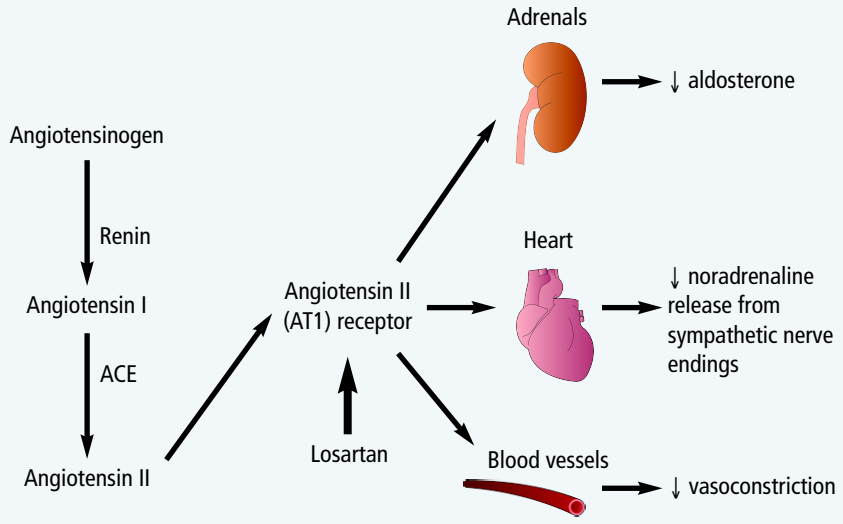
Losartan



NOTES. Losartan competitively and selectively binds to the angiotensin II (A1) receptor. This results in reduction in vasoconstriction, reduction in aldosterone secretion and thereafter reduced salt and water retention. There are also direct effects of losartan on the heart and vasculature mediated via antagonising sympathetic activity and reducing myocyte hypertrophy

Figure 1. The pharmacological actions of losartan

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Introduction

Losartan, an angiotensin II receptor blocker (ARB), is licensed for use for a number of clinical indications including chronic heart failure, diabetic nephropathy and hypertension (including reduction in stroke risk in hypertension with left ventricular hypertrophy [LVH]). In addition to potentially reducing the risk of cardiovascular events, it is often better tolerated than other classes of antihypertensive agents.

Pharmacology

Figure 1 outlines the pharmacological actions of losartan. The renin-angiotensin-aldosterone (RAAS) enzymatic cascade begins with the cleavage of angiotensinogen by renin to form the inactive decapeptide angiotensin-I. This is subsequently metabolised to angiotensin II by angiotensin converting enzyme (ACE).

The discovery of specific angiotensin II receptor antagonists has confirmed the existence of various subtypes of angiotensin II receptors. All known clinical effects of angiotensin II are mediated via the angiotensin II type 1 (AT1) receptors which are located in the heart, kidney, vascular smooth muscle cells, brain, adrenal gland, platelets, adipocytes and placenta. Activation of the AT1 receptor stimulates vasoconstriction, sodium retention, endothelin and vasopressin release as well as activating sympathetic activity, promoting myocyte hypertrophy and cardiac fibrosis, and suppressing plasma renin secretion. Losartan was the first orally active AT1 receptor antagonist licensed for use and has been shown *in vitro* to compete with binding of angiotensin II to AT1 receptors. EXP 3174 is the major active metabolite of losartan and mediates most of its effects.

Trials of safety and efficacy

Heart failure and post myocardial infarction. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) was a multinational, double-blind, randomised, parallel group study comparing losartan with the ACE inhibitor captopril on mortality in patients with acute myocardial infarction and evidence of left ventricular dysfunction.[1] In all, 5477 patients were randomly assigned treatment with losartan or captopril and titrated

to target dose (50mg losartan daily, 50mg captopril three times daily) as tolerated with mean follow up of 2.7 years. The primary endpoint was all-cause mortality. There was a non-significant difference in total mortality in favour of captopril but losartan was significantly better tolerated with fewer patients discontinuing study medication.

The Evaluation of Losartan in the Elderly (ELITE) study enrolled 722 patients aged 65 or more with NYHA class II–IV heart failure and ejection fractions of 40% or less.[2] Subjects were randomised to receive either losartan 50mg once daily or captopril 50mg three times daily for 48 weeks. The frequency of the primary endpoint of increases in serum creatinine was the same in both groups, although fewer losartan patients discontinued therapy for adverse events. Admissions with heart failure were the same in both groups and NYHA functional class improved significantly and to a comparable extent from baseline after long-term treatment with both losartan and captopril. Unexpectedly, death and/or hospital admission for heart failure were recorded in 9.4% of the losartan group and 13.2% of the captopril patients. This risk reduction was primarily due to a decrease in all-cause mortality observed with the losartan group because of an apparent reduction in sudden cardiac deaths. The ELITE-II study, a double blind, randomised controlled trial enrolling 3152 patients aged 60 or over with NHYA class II–IV heart failure and ejection fraction of 40% or less, failed to replicate these findings with no significant difference in all-cause mortality or sudden cardiac death identified between the two treatment groups.[3] However, ELITE-II did confirm the tolerability of losartan in comparison with captopril with significantly fewer patients discontinuing therapy because of adverse events.

The Heart Failure Endpoint evaluation of Angiotensin II Antagonist Losartan (HEAAL) study investigated whether higher doses of ARB could achieve improved clinical outcomes. A total of 3846 patients with NYHA II–IV heart failure, ejection fraction of 40% or less and intolerance to ACE inhibitors were randomly assigned to losartan 50mg or 150mg per day.[4] The primary endpoint was death or admission for heart failure. Higher-dose losartan reduced rates of death or admission for heart failure although adverse events such as renal dysfunction, hypotension and hyperkalaemia were more common in the 150mg treatment group.

A small study has investigated the effects of addition of ARB to ACE inhibitor therapy in patients with severe congestive heart failure.[5] This study showed that functional status improved by at least one NYHA class in 9 of 16 patients receiving losartan compared with 1 of 17 patients receiving placebo. There was also an improvement in peak VO_2 after six months' treatment in the group receiving losartan in addition to ACE inhibitor.

Renal impairment. Losartan has been shown to reduce albumin excretion in hypertensive patients with non-diabetic renal disease, an effect that occurred in the absence of a change in glomerular filtering properties.[6] A multicentre, open-label study evaluated the blood pressure lowering activity, tolerability and safety of losartan in 112 hypertensive patients with mild, moderate and severe chronic kidney disease.[7] Losartan was administered daily for 12 weeks either as monotherapy or in combination with another non-ACE inhibitor antihypertensive agent following a three-week placebo period. Losartan was shown to reduce systolic and diastolic blood pressure in groups with mild, moderate and severe renal dysfunction. Creatinine clearance and glomerular filtration rate remained stable after 12 weeks. Hyperkalaemia required discontinuation of therapy in only one patient.

Hypertension and cardiovascular risk. The Losartan Intervention for Endpoint reduction in hypertension (LIFE) study was a double-blind, randomised, parallel group trial with 9193 participants between 55 and 80 years of age with essential hypertension and LVH, an independent risk factor for cardiovascular morbidity and death.[8] Patients were randomised to once-daily losartan or atenolol based antihypertensive therapy for at least four years. Blood pressures were substantially reduced in both groups. There was a reduction in the primary composite endpoint in the losartan group (relative risk 0.87, 95% CI 0.77–0.98; p=0.021) and less fatal or non-fatal stroke (relative risk 0.75, 95% CI 0.63–0.89; p=0.001). Losartan also showed greater reduction of LVH compared with atenolol after four years of treatment.[9] There was also a lower rate of adverse events in the losartan group.

A multicentre, double-blind study randomised 407 patients to receive either losartan or enalapril for a 12-week period to evaluate the blood pressure lowering effects and tolerability of the drugs in patients with essential hypertension. Both drugs reduced systolic and diastolic blood pressure from baseline at six and 12 weeks of follow up. The only difference between the groups was that there was increased reporting of dry cough as a side effect in the group receiving ACE inhibitor therapy.[10] The benefits of combination treatment with losartan and hydrochlorothiazide have also been investigated in essential hypertension. Losartan was found to produce an additive reduction in systolic and diastolic blood pressures and was well tolerated among study subjects.[11]

Specific evidence for use in diabetes

Heart failure. Hospitalisation for heart failure was a secondary endpoint in the LIFE study; 1147 of 1195 patients with diabetes did not have a history of heart failure. Each case was reviewed and confirmed by the Endpoint Classification Committee using clinical or diagnostic findings. Losartan significantly reduced the first hospitalisations for heart failure compared with atenolol in patients with diabetes (hazard ratio 0.57, p=0.019).[12]

These findings were replicated in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study where 1413 of 1513 patients with diabetes did not have a diagnosis of heart failure.[13] Losartan significantly reduced the first hospitalisations for heart failure compared with losartan in this study.

Renal impairment. In a randomised, placebo controlled trial of 147 normotensive patients with type 2 diabetes and microalbuminuria, five weeks of treatment with losartan reduced

albumin excretion compared with placebo. Side effects did not differ between the treatment groups.[14]

The first major randomised controlled clinical trial evaluating the effects of losartan on progression of renal disease and death among patients with type 2 diabetes who were at high risk of developing endstage renal disease was the RENAAL study. At total of 1513 patients with diagnoses of type 2 diabetes and nephropathy were enrolled in this randomised, double-blind study and were allocated to receive either losartan or placebo in addition to conventional antihypertensive therapy for a mean of 3.4 years. The primary composite outcome included a doubling of serum creatinine from baseline, development of endstage renal disease and death. Secondary composite endpoints included a composite of cardiovascular morbidity and mortality, proteinuria and rate of progression of renal disease. There was a 16% reduction in the losartan group compared with the placebo group of patients reaching the primary endpoint. There was a 25% reduction in risk of doubling serum creatinine and a 28% risk reduction for development of endstage renal disease in the losartan group, but no significant difference in death rates between the two groups. The composite of cardiovascular morbidity and mortality was similar in both groups, but losartan significantly reduced rates of hospitalisation for heart failure.[12]

Hypertension and cardiovascular risk. The LIFE study included 1195 patients with diabetes, hypertension and left ventricular hypertrophy.[12] Subjects were randomised to receive either losartan or atenolol based therapy and followed up for at least four years. Mean blood pressure fell to a similar degree in both subgroups. The primary composite endpoint of cardiovascular death, stroke or myocardial infarction was reduced in the group receiving losartan-based therapy. In addition to this, all-cause mortality was significantly reduced in the losartan subgroup. Losartan was more effective than atenolol in reducing LVH.

Prevention of diabetes? Losartan was found to reduce the risk of development of diabetes by 25% in the 7998 patients without diabetes in the LIFE study compared with atenolol.[15] The results of a systematic review are not conclusive, but suggest that diabetes incidence is unchanged or decreased by treatment with ACE inhibitors and ARBs.[16]

Discussion

Taken together, the results of the OPTIMAAL and ELITE II studies suggest that losartan offers an alternative if ACE inhibitor therapy is not tolerated in chronic heart failure. The LIFE diabetes substudy confirmed that these benefits are also applicable to patients with diabetes. For the 2578 patients with diabetes included in the LIFE and HEAAL studies without a history of heart failure, losartan treatment was associated with significant risk reduction in hospitalisation for new-onset heart failure confirming its benefit in patients at high renal and cardiovascular risk. Focusing on renal disease, losartan has been shown to reduce albumin excretion in hypertensive patients with non-diabetic renal disease. Furthermore, in patients with varying degrees of renal insufficiency ranging from mild to severe, losartan was effective at lowering blood pressure and proteinuria. These benefits have been confirmed in patients with type 2 diabetes and microalbuminuria. It is well tolerated among patients with diabetic nephropathy. ARBs are an established therapeutic option in the management of hypertension and have been proven to reduce the frequency of cardiovascular death, including stroke, as well as reducing LVH in hypertensive populations. It is often better tolerated than other classes of antihypertensive agent, particularly ACE inhibitors and beta blockers.

Declaration of interests

GC, GMcK, HS: none. MF has received payments for lectures and advisory boards from Merck Sharp & Dohme.

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Key points

- Losartan, an angiotensin II receptor blocker, is safe and effective in the management of patients with chronic heart failure, renal impairment and hypertension where it may reduce the risk of cardiovascular events
- The benefits of losartan extend to patients with diabetes, and losartan may have a role in preventing the development and progression of diabetic nephropathy
- Losartan is often better tolerated than other classes of agents used for similar indications

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