

Inhibition of the renin–angiotensin system

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GUIDELINES

In patients with hypertension associated with renovascular disease, pharmacological inhibition of the renin–angiotensin system effectively and safely lowers blood pressure in most patients (Level II evidence).

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **In patients with established evidence-based indications for inhibition of the renin–angiotensin system, for example congestive cardiac failure or chronic kidney disease with proteinuria, this treatment should not generally be withheld on the basis of renovascular disease.**
- **When an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) are used in patients with renovascular disease, renal function should be monitored regularly. This is especially important in patients with high-grade (>70%) bilateral renal artery stenosis or high-grade renal artery stenosis to a solitary functioning kidney. As a guide, following initiation of this treatment in patients with renovascular disease, serum creatinine and electrolytes should be checked after 1 and 4 weeks, and then at least every 3 months thereafter.**
- **A significant increase in serum creatinine (>20%) following initiation of treatment with an ACE inhibitor or ARB correlates with the presence of renovascular disease and may be an indication for investigation for this condition.**
- **Patients with atherosclerotic renovascular disease have a high risk of experiencing cardiovascular events and management should be optimized to reduce this risk. This includes the use of statins to lower lipids, antiplatelet therapy, smoking cessation and the control of blood pressure.**

IMPLEMENTATION AND AUDIT

The systematic monitoring of renal function and the incidence of acute renal failure following the commencement of an ACE inhibitor or ARB in patients at high risk of renovascular disease or with known renovascular disease should be done.

BACKGROUND

This guideline subtopic addresses the role of blockade of the renin–angiotensin system in the management of patients with renovascular disease, which is defined as stenotic lesions affecting the main renal arteries. The effect of renin–angiotensin system blockade in intrarenal vascular disease is not specifically addressed in this document. The term renovascular disease includes patients with either unilateral or bilateral renal artery stenosis of any cause. This document does not address the situation of renal artery stenosis in a transplanted kidney. As with other guideline subtopics in this section, terminology regarding severity of renal artery stenosis is defined as high grade (>70%), intermediate grade (50–69%) and low grade (<49%).

Activation of the renin–angiotensin system in patients with renovascular disease promotes the development of hypertension, and is also likely to contribute to other adverse events such as the development of left ventricular hypertrophy and poor cardiovascular outcomes.¹ Blockade of the renin–angiotensin system by either ACE inhibitors or ARBs is potentially attractive therefore as a rational therapy for patients with renovascular disease.² There has been some reluctance, however, to use these therapies in patients with renovascular disease because of the risk of precipitating acute renal failure, especially in patients with bilateral disease.³

The clinical effects of renal artery stenosis include renovascular hypertension and ischaemic nephropathy leading to chronic kidney disease. In addition, patients with atherosclerotic renal artery stenosis are at a markedly increased risk of coronary events, stroke, heart failure and death.^{4,5} The risk of these events is significantly greater than the risk of progressing to end-stage kidney disease.^{4,5} While the immediate clinical objectives of treatments for renal artery stenosis are to control blood pressure and to preserve renal function, the long-term objectives of treatment are to reduce both overall and cardiovascular morbidity and mortality.

There is a high incidence of coexisting cardiovascular conditions in patients who have atherosclerotic renal artery stenosis. For example, in a sample of elderly patients with chronic systolic heart failure, the prevalence of atherosclerotic renal artery stenosis was 34%.⁶ Atherosclerotic renal artery stenosis is also associated with coronary artery disease,^{5,7-9} stroke,^{9,10} peripheral vascular disease,¹¹ diabetes¹² and smoking.¹³ There are a number of large randomized controlled trials (RCTs) demonstrating benefits from treatment with either ACE inhibitors or ARBs in patients at high risk of adverse cardiovascular or renal outcomes. For example, these classes of medications have been shown to reduce cardiovascular mortality in patients with systolic heart failure,¹⁴ left ventricular hypertrophy¹⁵ and high cardiovascular risk.¹⁶ In addition, ACE inhibitors or ARBs have been found to slow progression in both diabetic and non-diabetic patients with proteinuric chronic kidney disease.¹⁷⁻¹⁹ Significantly, because of the associations between atherosclerotic renal artery stenosis and other comorbidities, it is not uncommon for patients with renovascular disease to have other evidence-based indications for medications that block the renin-angiotensin system. In addition, because renovascular disease is often asymptomatic and not routinely screened for, many patients with undiagnosed renovascular disease are likely to be commenced on medications that block the renin-angiotensin system for the treatment of hypertension, renal disease or cardiovascular indications. Specific studies to address the question of whether or not the presence of renal artery stenosis affects the benefits of renin-angiotensin system blockade in patients who have established indications for these therapies are lacking. Despite renovascular disease being a relatively common condition, it is not standard practice to screen patients for its presence before ACE inhibitors or ARBs are commenced. In patients who have clearly established indications for renin-angiotensin system blockade and who are also known to have renovascular disease, a relevant clinical question is whether possible concerns about the effects of ACE inhibitors or ARBs on renal function are sufficient to justify withholding these treatments.

Another important clinical question concerns the effectiveness of renin-angiotensin system blockade, compared with other alternatives for the treatment of hypertension in patients with renovascular disease. It is also important to consider the possible effects on renal function of renin-angiotensin system blockade in patients with renovascular disease. In this regard, there are risks of both harm, caused by a critical reduction in renal perfusion and glomerular filtration rate, and potential for benefit, caused by improvements in blood pressure and proteinuria, as well as inhibition of pro-fibrotic pathways.²⁰

This subtopic reviews current knowledge of the effect of medications that inhibit the renin-angiotensin system on outcome in patients with renovascular disease. Specifically reviewed are the effects of renin-angiotensin system blockade in patients with renovascular disease on: (1) the control of hypertension; (2) cardiovascular morbidity and mortality; and (3) renal function, especially the risk of causing acute

renal failure. The role of other medical therapy in the management of patients with renovascular disease is briefly summarized here but is not reviewed in detail.

SEARCH STRATEGY

Databases searched: MeSH terms and text words for ACE inhibitors and ARBs were combined with MeSH terms and text words for renovascular disease and combined with MeSH terms and text words for renal function, blood pressure, cardiovascular events and mortality. The search was performed in Medline. The search was repeated again in May 2009 with the addition of the search terms 'statins', 'aspirin' and 'anti-platelet therapy'. The Cochrane Central Register of Controlled Trials and Database of Systematic Reviews (via the Cochrane Library) were searched for trials and reviews not indexed in Medline. In addition, the reference lists of manuscripts retrieved by the above method were manually reviewed for additional studies.

Date of searches: 28 August 2008, 2 April 2009, 11 May 2009.

WHAT IS THE EVIDENCE?

Blood pressure control

Randomized controlled trials

Franklin and Smith randomized 75 patients with documented renovascular hypertension to the ACE inhibitor enalapril plus the thiazide diuretic hydrochlorothiazide or triple therapy combination consisting of hydralazine, timolol and hydrochlorothiazide (Table 1).^{21,22} The latter combination was a commonly used regimen at that time for resistant hypertension. Renovascular hypertension was defined in this study by the simultaneous presence of a significant stenosis demonstrated by arteriography and a positive functional test. The definition of what was regarded as a significant stenosis by arteriography in the study was not stated. The study design consisted of a 15-day dose titration phase followed by a 6-week maintenance phase and the outcome was blood pressure control after the 6-week maintenance phase. There was a 12 mmHg greater decrease in supine systolic blood pressure in the enalapril-treated group compared with the triple-drug therapy-treated group ($P < 0.05$). A significant increase in serum creatinine (>0.3 mg/dL) was observed in 20% of patients assigned to enalapril treatment but no cases of severe acute renal failure occurred. A smaller study of only 18 patients by Reams and Bauer also randomized patients with renovascular disease to either enalapril and hydrochlorothiazide or triple-drug therapy consisting of hydrochlorothiazide, timolol and hydralazine.²³ Effective control of blood pressure, defined as supine diastolic blood pressure less than 90 mmHg, was achieved in all patients assigned enalapril in combination with hydrochlorothiazide and no adverse effects were observed. In contrast, 5/9 (56%) of patients on the triple-drug combination either had uncontrolled hypertension or

developed significant side effects. Patients who were uncontrolled or intolerant of the triple-drug combination were well controlled by enalapril and hydrochlorothiazide. In summary, these two small trials suggest that an ACE inhibitor based-regimen appears to control blood pressure better in patients with renovascular hypertension than some other therapies. Significant limitations of these studies include their small size, the outdated nature of the comparator treatment and the lack of long-term follow up for hard end-points.

Observational studies

Tullis *et al.* performed a cross-sectional analysis of the effect of usage *vs* non-usage of different classes of antihypertensive medication on blood pressure control in a population of 139 hypertensive patients with atherosclerotic renal artery stenosis demonstrated by renal artery duplex ultrasonography (Table 2).²⁴ The study found ACE inhibitor usage *vs* non-usage was associated with significantly lower systolic (157 ± 27 *vs* 169 ± 22 mmHg; $P = 0.03$) and diastolic (79 ± 9 *vs* 85 ± 9 mmHg; $P = 0.001$) blood pressure. In contrast, usage *vs* non-usage of beta-blockers or calcium channel blockers did not have any significant effect on blood pressure. Blood pressure was actually slightly higher in users of diuretics compared with non-users. The observed beneficial effect of ACE inhibitor use on blood pressure was confined to those patients with at least one high-grade (>60%) renal artery stenosis lesion and was more pronounced in those with unilateral rather than bilateral high-grade disease. A multiple regression analysis model predicted an 11.2 mmHg reduction in mean arterial pressure in patients with high-grade unilateral renal artery stenosis who were taking an ACE inhibitor, compared with those who were not. In summary, this study supports the concept that using medications that block the renin-angiotensin system provides superior control of blood pressure than do alternative agents in patients with renovascular hypertension. This study is limited, however, by its cross-sectional observational design and its lack of data regarding either renal function or clinical outcomes.

Several open label studies have found that ACE inhibitors can successfully control blood pressure in a high proportion (82–96%) of patients with renovascular hypertension (Table 3). This is a contrast to the era before ACE inhibitors were available, when renovascular hypertension was commonly refractory to the available medical therapies.²⁵ In addition, in a review of 269 patients with documented renovascular hypertension treated with captopril in worldwide hypertension trials, Hollenberg reported that control of hypertension (diastolic pressure < 95 mmHg) was achieved in 74% of patients.²⁵ Renal failure necessitating cessation of captopril only occurred in 5% of these patients. The response of renovascular hypertension to captopril has also been reported to be predictive of the effectiveness of surgical revascularization in improving blood pressure.^{26,27} Hodsman *et al.* treated 20 patients with renovascular hypertension with enalapril and was able

to successfully lower blood pressure in all 20 patients with no significant adverse effects.²⁸ Jackson *et al.* also reported that enalapril (\pm diuretic) was able to achieve a satisfactory reduction in blood pressure in a high proportion (75%) of patients with proven renovascular hypertension.²⁹ The ACE inhibitor delapril has been reported to effectively lower blood pressure by $\geq 20/10$ mmHg in 80% (8/10) of patients with renovascular hypertension.³⁰ In 30% of cases, the reduction of blood pressure with delapril was $\geq 30/15$ mmHg. Although these open label studies are inherently limited by their design, generally the results appear favourable when compared with the experience of earlier treatments with agents such as diuretics, direct vasodilators and inhibitors of the sympathetic nervous system, when rates of effective blood pressure control for renovascular hypertension were reported to be of the order of 35–45%.^{2,25} The widespread availability of dihydropyridine calcium channel blockers has possibly also increased the ability of clinicians to control renovascular hypertension with medical therapy, although formal studies evaluating the role of these medications in renovascular disease are lacking.

Cardiovascular mortality and long-term renal outcomes

Randomized controlled trials

There are no RCTs directly examining the effect of renin-angiotensin system blockade on long-term clinical outcomes in a population of patients with known renovascular disease.

Observational studies

Losito *et al.* performed a long-term (up to 189 months) follow-up study of 195 patients with atherosclerotic renal artery stenosis, as defined by a luminal narrowing of greater than 50% on arteriogram³¹ (Table 2). Renal artery angioplasty was performed in 136 of these patients, with the remainder receiving only medical therapy. Multivariate Cox regression analysis showed use of ACE inhibitors to reduce overall mortality with a hazard ratio of 0.24 (95% confidence interval (CI): 0.08–0.71, $P = 0.0098$). The Kaplan-Meier survival for patients treated or not treated with ACE inhibitors produced a significant log rank test: 9.07, $P = 0.0026$. The effect was more significant in patients treated medically ($P = 0.015$) than in those treated with revascularization ($P = 0.05$). In addition, the multivariate regression analysis also found that use of ACE inhibitors was associated with a reduced risk of worsening impairment of kidney function, as defined by an increase in serum creatinine of more than one third. In this case, the use of ACE inhibitors, was associated with a reduced risk with a hazard ratio of 0.29 (95% CI: 0.09–0.92, $P = 0.036$). The Kaplan-Meier analysis of survival time, free of confounding by serum creatinine, revealed a significant difference between those treated with ACE inhibitors and those not treated (log rank test = 6.75, $P = 0.009$). Interestingly, this study was unable to detect any effect of revascularization on cardiovascular

mortality in patients with renovascular disease. The principal strength of this study is the length of follow up for hard clinical end-points. Because it is an observational study, however, it cannot be regarded as definitive, as the possibility of confounding by indication cannot be excluded. A reduction in patient mortality with the use of ACE inhibitors in the treatment of renovascular disease is consistent, nonetheless, with numerous animal studies that have consistently demonstrated that when compared with other therapies, both ACE inhibitors and ARBs reduce mortality in animal models of renal artery stenosis.^{2,32–35}

The risk of blockade causing acute renal failure in patients with renovascular disease

Randomized controlled trials

The RCT described above by Franklin and Smith also evaluated the short-term effect of combination therapy with enalapril and hydrochlorothiazide on renal function in patients with renovascular hypertension.^{21,22} A significant increase in serum creatinine (>0.3 mg/dL) was observed in 20% of patients assigned to enalapril treatment (Table 4). All patients in whom a significant rise in serum creatinine was observed with enalapril had a stenosis of 80% or more in at least one kidney. In these patients, renal function stabilized without any progressive worsening of kidney function. No patients developed oliguric acute renal failure, including 18 patients who were known to have bilateral renal artery stenosis on arteriography. The incidence of enalapril-induced renal dysfunction did not differ between patients with unilateral (23%) or bilateral (17%) renal artery stenosis. In the comparator group treated with hydralazine, timolol and hydrochlorothiazide, only one patient developed significant reduction of renal function.

Observational studies

Treatment with ACE inhibitors has been reported to induce acute renal failure in patients with bilateral renal artery stenosis or renal artery stenosis with a solitary kidney.³ ACE inhibitors and ARBs can also cause acute renal failure in patients with mild renovascular disease if there is coexisting volume depletion or severe intrarenal renovascular disease. In the community, volume depletion is a more common precipitant of ACE inhibitor-associated acute renal failure than is renovascular disease.³⁶ As noted in the trials discussed above, many patients with renovascular disease tolerate renin–angiotensin system blockade without any increase in serum creatinine, and many of the increases in serum creatinine that are observed are relatively minor.^{21,22,29} In addition, acute renal dysfunction caused by pharmacological blockade of the renin–angiotensin system is rapidly reversed when the offending medication is ceased.²⁹ In open label studies using ACE inhibitors for the treatment of renovascular hypertension, the rates of discontinuation because of rising serum creatinine were fairly low, ranging from 0.0% to 12.5% (Table 4).^{28–30,37}

The risk of renin–angiotensin system blockade causing acute renal failure in a population at high risk of renovascular disease has been most thoroughly evaluated by van de Ven *et al.*³⁸ (Table 4). This study included 108 patients at high risk of atherosclerotic renal artery stenosis; by arteriography 52 patients had severe bilateral renovascular disease or renal artery stenosis affecting a solitary functioning kidney, 21 had less severe bilateral renovascular disease, 20 had unilateral renovascular disease and 15 had no apparent renovascular disease. All patients were administered enalapril at a high dose (10 mg b.i.d.) and blood pressure and creatinine were measured after 4 days and at 2 weeks. A greater than 20% rise in serum creatinine was seen in 26 patients (24%) after 4 days and in an additional 31 patients (28.7%) after 2 weeks. In more than half of these high-risk patients, enalapril was ceased because of an increase in serum creatinine. In all cases, however, renal function recovered after enalapril was ceased. A good correlation was observed between the increase in serum creatinine and the severity of renovascular disease ($r = 0.53$, $P < 0.001$). The authors of this study concluded that controlled exposure to ACE inhibitors in this population was safe, and that ACE inhibitor-induced increases in serum creatinine are a sensitive detector of severe bilateral renovascular disease in a high-risk population.

The risk of progressive ischaemia in the post-stenotic kidney

In patients with renal artery stenosis, an additional concern is the risk of long-term loss of renal mass and function in the post-stenotic kidney. Data on whether or not renin–angiotensin system blockade increases the risk of this event are inconsistent. In a prospective study performed by Caps *et al.* 204 kidneys with renal artery stenosis were followed prospectively for the development of renal atrophy by ultrasound performed every 6 months for 2 years.³⁹ The predictors of increased risk of developing renal atrophy were found to be the severity of the renal artery stenosis observed by duplex ultrasound, a systolic blood pressure greater than 180 mmHg, a renal artery peak systolic velocity > 400 cm/s, and a renal cortical end diastolic volume ≤ 5 cm/s. Interestingly, the use of ACE inhibitors did not appear in this study to impact on the risk of developing renal atrophy (relative risk (RR) 1.1, 95% CI: 0.5–2.5). In contrast, others have reported that in patients with unilateral renal artery stenosis, ACE inhibitors improve renal function in the unaffected kidney, while hastening ischaemic atrophy on the stenotic side.^{40–43} This is consistent with some animal studies on the subject.⁴⁴ In summary, there are variable data suggesting that in renal artery stenosis, renin–angiotensin system inhibition could accelerate renal atrophy in the post-stenotic kidney. In unilateral disease, this appears to be counterbalanced, however, by protection to the non-stenosed kidney, with no net adverse effect on renal function overall. The beneficial effects of renin–angiotensin system blockade in unilateral renal artery stenosis on blood pressure control and cardiovascular risk potentially, however, outweigh this possible adverse effect of renin–angiotensin system blockade on the function of the post-stenotic kidney.

In contrast to the situation of unilateral renal artery stenosis, in the case of severe bilateral renal artery stenosis or severe renal artery stenosis to a solitary functioning kidney, there is a more clinically relevant risk of an overall loss of renal function resulting from reduced perfusion to the total functioning renal mass. It is very important therefore that if renin–angiotensin system blockade is used in these patients that renal function is carefully monitored.

Other medical therapy in patients with atherosclerotic renovascular disease – cardiovascular risk reduction

As discussed above, patients with atherosclerotic renovascular disease have markedly increased cardiovascular morbidity and mortality.^{7–13} In addition to the control of blood pressure and the preservation of kidney function, a central goal of management is to reduce overall cardiovascular risk. Optimal medical therapy for renovascular disease is not clearly defined but is frequently suggested to include antiplatelet therapy, angiotensin inhibition, blood pressure control, lipid management, blood glucose control in diabetics, smoking cessation, diet and exercise.⁴⁵

The optimal blood pressure target for patients with renovascular disease has not been defined. In general, however, a blood pressure target of less than 140/90 mmHg is recommended for uncomplicated hypertension and a target of less than 130/80 mmHg hypertension associated with diabetes or renal disease.⁴⁶ Aiming for these targets remains appropriate in patients with renovascular disease. Achieving these targets often requires combination therapy and the need to use up to a four-drug combination is not unusual.⁴⁶ In addition to agents that block the renin–angiotensin system, other appropriate medications for the control of blood pressure in patients with renovascular disease include diuretics, calcium channel blockers and beta-blockers.⁴⁶

There are no prospective trials specifically examining the role of lipid-lowering therapy in patients with atherosclerotic renovascular disease. Retrospective studies have, however, reported that use of statins appears to reduce progression of renal insufficiency, slow the progression of stenosis and lower overall mortality.^{47,48} For example, Cheung *et al.*⁴⁸ found that patients who had been treated with a statin had a reduced risk of progression of renal artery stenosis (RR 0.28, 95% CI: 0.10–0.77) and a higher rate of regression of renal artery stenosis. In addition, atherosclerosis is a systemic process and a high proportion of patients with atherosclerotic renovascular disease have detectable vascular disease in the coronary, peripheral or cerebral circulations.^{5,7–13} The 2005 Position Statement on Lipid Management from the National Heart Foundation of Australia recommends that patients with clinical evidence of vascular disease are at high absolute risk of a vascular event and are included in the group of patients most likely to benefit from lipid-lowering therapy. Despite the lack of specific trials in patients with renovascular disease, this general recommendation for treatment in patients with clinical evidence of vascular disease is applicable to patients with clinical renovascular disease.⁴⁹ Statins are the first line agent for lipid-lowering therapy but other agents such as

fibrates or ezetimibe can also have a role. The treatment targets for lipid-lowering therapy in patients with renovascular disease have not been specifically defined but probably should be the same as for other patients with clinical vascular disease. According to the 2005 position statement of the National Heart Foundation, the recommended targets for patients with atherosclerotic vascular disease are serum low density lipoprotein of less than 2.0 mmol/L, high density lipoprotein greater than 1.0 mmol/L and triglycerides of less than 1.5 mmol/L.⁴⁹

There are no studies specifically examining the role of antiplatelet therapy in atherosclerotic renovascular disease. There are, however, a number of studies showing a beneficial effect of aspirin in those patients with either established cardiovascular or cerebrovascular disease or in patients at high cardiovascular risk.⁵⁰ A meta-analysis of trials examining the use of aspirin following myocardial infarction showed an overall reduction in the risk of a serious vascular event of approximately 25% and a reduction in the risk of vascular mortality of 13%.⁵⁰ Aspirin therapy for the prevention of cardiovascular events has been recommended for patients in whom the benefit in terms of cardiovascular risk reduction outweighs the risk of bleeding complications.⁵¹ In general, this criterion applies to most patients with established evidence of vascular disease because these patients are at an increased absolute risk of vascular events. On this basis, it is reasonable to recommend that patients with atherosclerotic renovascular disease be treated with low dose aspirin for cardiovascular risk reduction, unless there are contraindications such as an increased bleeding risk. Other antiplatelet agents such as clopidogrel and ticlopidine have not been studied in patients with atherosclerotic renovascular disease but are not contraindicated if there are other indications for their use. Antiplatelet therapy in patients with renal artery stents *in situ* is probably also appropriate, although this has not been well studied.

SUMMARY OF THE EVIDENCE

Prospective and retrospective studies both find that the use of agents that block the renin–angiotensin system (ACE inhibitors and ARBs) achieve better control of blood pressure in patients with renovascular disease than alternative agents. Prospective studies for other clinical end-points of this treatment in patients with renovascular disease are not available. Retrospective data, however, suggest that the use of ACE inhibitors is associated with lower mortality in patients with renovascular disease compared with other agents. It is important to consider that many patients with atherosclerotic renovascular disease have associated comorbidities such as cardiac failure, left ventricular hypertrophy or proteinuric chronic kidney disease that are associated with documented benefits from renin–angiotensin system inhibition. Agents that block the renin–angiotensin system can cause acute renal failure in patients with bilateral high-grade renovascular disease, unilateral high-grade renal artery stenosis to a solitary functioning kidney or volume depletion, however, this risk is relatively low (range

0–12.5%) and the effect is reversible when the medication is ceased. Renal function should be monitored regularly when ACE inhibitors or ARBs are given to patients with renovascular disease. Patients with renovascular disease are at high risk of poor cardiovascular outcomes. Optimal control of hypertension in patients with renovascular disease often requires the combined use of multiple blood pressure-lowering medications.

WHAT DO THE OTHER GUIDELINES SAY?

Kidney Disease Outcomes Quality Initiative: No recommendation.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

American College of Cardiology/American Heart Association, 2005⁵²

1. AEC inhibitors are effective medications for treatment of hypertension associated with unilateral renal artery stenosis. (Level of evidence: A)
2. ARBs are effective medications for treatment of hypertension associated with unilateral renal artery stenosis. (Level of evidence: B)

SUGGESTIONS FOR FUTURE RESEARCH

1. Consideration should be given to performing a large multicentre RCT of blockade of the renin–angiotensin system vs dihydropyridine calcium channel blocker in patients with proven renovascular disease. Patients enrolled should have high grade (>70%) renal artery stenosis and not have other definite indications or contraindications to renin–angiotensin system blockade. The proposed primary outcome would be composite cardiovascular events. Important secondary outcomes include blood pressure control and the risk of acute renal failure.
2. Future research should aim to better define the subset of patients with renovascular disease who are most at risk of developing acute renal failure following blockade of the renin–angiotensin system. In addition to appropriately designed trials, better definition of this group of patients is likely to be enhanced by regular prospective audit and advances in understanding of pathophysiology and diagnostic techniques.

CONFLICT OF INTEREST

Peter Mount has a Level II b conflict of interest according to the conflict of interest statement set down by CARI.

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APPENDICES

Table 1 Randomized controlled trials comparing renin–angiotensin system blockade with other medical treatment in patients with renovascular hypertension

Study ID	N	Intervention (experimental group)	Intervention (control group)	Blinding	Intention to treat analysis	Outcome and follow up	Results
Franklin and SmitEh (1985, 1986) ^{21,22}	74	Enalapril (E) and hydrochlorothiazide (HCT)	Timolol (T), Hydralazine (H), Hydrochlorothiazide (HCT)	Double blind	Yes	Change in supine BP (6 weeks) Change in standing BP (6 weeks)	E and HCT –32/–20 mmHg T, H, HCT –20/–18 mmHg (<i>P</i> < 0.05) E and HCT –14/–18 mmHg T, H, HCT –5/–14 mmHg (<i>P</i> < 0.05)
Reams and Bauer (1985) ²³	18	Enalapril (E) and hydrochlorothiazide (HCT)	Timolol (T), Hydralazine (H), Hydrochlorothiazide (HCT)	Double blind	Yes	Supine diastolic blood pressure < 90 mmHg on treatment (6 weeks)	E and HCT 100% T, H, HCT 44.4% (<i>P</i> not stated)

BP, blood pressure.

Table 2 Observational studies comparing renin–angiotensin system blockade with other medical treatment in the management of patients with atherosclerotic renovascular disease

Study ID	N	Intervention	Comparator	Outcome and follow up	Results
Tullis <i>et al.</i> (1999) ²⁴	139	ACE inhibitor use	ACE inhibitor non-use	BP (control of hypertension)	Systolic BP 157 ± 27 vs 169 ± 22 mmHg (<i>P</i> = 0.03) Diastolic BP 79 ± 9 vs 85 ± 9 mmHg (<i>P</i> = 0.001)
Losito <i>et al.</i> (2005) ³¹	195	ACE inhibitor use (n = 62)	ACE inhibitor non-use (n = 133)	Mortality 54.4 ± 40.4 months	Hazard ratio 0.24 (95% CI: 0.08–0.71) (<i>P</i> = 0.0098) Log rank test: 9.07 (<i>P</i> = 0.0026)

ACE, angiotensin-converting enzyme; BP, blood pressure; CI, confidence interval.

Table 3 Non-randomized observational studies of ACE inhibitors for the treatment of hypertension in patients with renal artery stenosis

Study ID	N	Treatment	Outcome and follow up	Results
Case <i>et al.</i> (1982) ⁵³	21 (7 unilateral 14 bilateral)	Captopril 50–400 mg daily (±additional agents)	Supine BP. Mean follow up 24 months.	Unilateral RAS Mean baseline BP 197/115 mmHg After treatment 139/85 mmHg ($P < 0.01$) Bilateral RAS Mean baseline BP 193/116 mmHg After treatment 139/82 mmHg ($P < 0.001$)
Schwietzer <i>et al.</i> (1982) ³⁷	9	Captopril 25–150 mg 3 times/day	Supine BP after 3 months of treatment	Mean baseline BP 204/124 mmHg After treatment 145/89 mmHg ($P < 0.01$)
Hodsmen <i>et al.</i> (1983) ²⁸	Group 1 ($n = 10$) – unilateral renal artery stenosis and normal renal function Group 2 ($n = 10$) – unilateral or bilateral renal artery stenosis and very severe or resistant hypertension	Enalapril 10–40 mg daily as monotherapy (after 14 day washout) Enalapril 10–40 mg daily as add on to existing previous therapy	Supine BP after 3 months of treatment	Mean baseline BP 196/104 mmHg After treatment 150/92 mmHg ($P < 0.001$) Mean baseline BP 204/110 mmHg After treatment 154/88 mmHg ($P < 0.01$)
Jackson <i>et al.</i> (1986) ²⁹	16	Enalapril 5–77.5 mg daily ± diuretic (HCT or frusemide)	Supine BP after 3 months of treatment	Mean baseline BP 179/106 mmHg After treatment 160/90 mmHg ($P < 0.05$) Diastolic BP < 95 mmHg in 12/16 (75%) of patients
Ogihara <i>et al.</i> (1991) ³⁰	10	Delapril 15–120 mg daily	Reduction of BP by $>20/10$ mmHg after 12 weeks	Effective treatment in 8/10 (80%) of patients

ACE, angiotensin-converting enzyme; BP, blood pressure; HCT, hydrochlorothiazide; RAS, renal artery stenosis.

Table 4 Studies reporting the risk of deterioration of renal function caused by renin–angiotensin system blockade in patients with known renovascular disease

Study ID	N	Treatment	Study type	Outcome and follow up	Results
Hodsman <i>et al.</i> (1983) ²⁸	Group 1 (n = 10) – unilateral RAS and normal renal function	Enalapril 10–40 mg daily as monotherapy (after 14 day washout)	Prospective open label uncontrolled trial	Overall change in serum creatinine (3 months)	Baseline 103.0 ± 8.0 μmol/L After treatment 127 ± 10.0 μmol/L (P < 0.001)
	Group 2 (n = 10) – unilateral (5) or bilateral (5) RAS and very severe or resistant hypertension	Enalapril 10–40 mg daily as add on to existing previous therapy	Prospective open label uncontrolled trial	Overall change in serum creatinine (3 months)	Baseline 142 ± 34 μmol/L After treatment 145 ± 35 μmol/L
Franklin and Smith (1985) ^{21,22}	49	Enalapril and hydrochlorothiazide	Randomized controlled trial	Increase in serum creatinine of ≥0.3 mg/dL	10/49 (20.4%)
Jackson <i>et al.</i> (1986) ²⁹	16	Enalapril ± diuretic	Prospective open label uncontrolled trial	Increase in serum creatinine (undefined)	4/16 (25%)
van de Ven <i>et al.</i> (1998) ³⁸	93 (severe bilateral RAS in 52)	Enalapril 10 mg b.i.d.	Prospective open label uncontrolled trial	Increase in serum creatinine of ≥20% (2 weeks)	57/93 (61.3%)

RAS, renal artery stenosis.