

Management of proteinuria: blockade of the renin–angiotensin–aldosterone system

SUMMARY

Proteinuria, in particular albuminuria, is a potentially significant modifiable risk factor for cardiovascular disease and the progression of kidney disease.

Current treatment guidelines for albuminuria recommend a single renin–angiotensin–aldosterone inhibitor. This can be an ACE inhibitor or an angiotensin receptor antagonist.

The routine use of combined renin–angiotensin–aldosterone inhibition for albuminuria is not supported by current evidence. Combination therapy is associated with higher rates of adverse events such as hyperkalaemia and progressive renal impairment.

Introduction

Proteinuria, defined as all urinary proteins including albumin, is associated with an increased risk of coronary heart disease and cerebrovascular disease.^{1–3} Moderately increased albuminuria (microalbuminuria) increases the risk of coronary heart disease by 50% and stroke by 70%. Severely increased albuminuria (macroalbuminuria) more than doubles the risk of both coronary heart disease or stroke.^{2,4} Table 1 shows the degrees of albuminuria.

Albuminuria has also been associated with an increased risk of gastrointestinal haemorrhage⁵ and progression of kidney disease.⁶ Increased urinary albumin over time has been associated with a greater risk of major renal events, including dialysis, transplantation and death.⁷

Albuminuria is an important target for intervention. In addition to treating the specific cause of albuminuria, other management approaches are frequently used to reduce the degree of albuminuria. These therapies include inhibitors of the renin–angiotensin–aldosterone system. However, their optimum use has been a source of discussion and controversy.

Guidelines for treating proteinuria

The current Kidney Disease Improving Global Outcomes (KDIGO) guideline, published in 2013, recommends the use of either an ACE inhibitor or an angiotensin receptor antagonist (sartan) in all adults with albuminuria over 300 mg/day.⁸ It also suggests one of these drugs is used in patients with diabetes and moderately increased albuminuria.⁸ There was insufficient evidence for the guideline to recommend combining an ACE inhibitor with an angiotensin receptor antagonist for preventing the progression of chronic kidney disease, regardless of albuminuria.

In 2015 the Kidney Health Australia publication Chronic Kidney Disease Management in General Practice recommended a 50% reduction in albuminuria as a target of treatment. It advised against combination ACE inhibitor and angiotensin receptor antagonist therapy,⁹ as did the NICE guidelines in the UK.¹⁰

Efficacy

Multiple trials have reported that ACE inhibitors are effective at reducing proteinuria in both diabetic and non-diabetic populations.^{11–13} ACE inhibitors also reduce the rate of progression of kidney disease, and the risk of dialysis or transplantation by up to 50% in patients with proteinuria.^{11–13}

The angiotensin receptor antagonists are effective for reducing proteinuria in diabetic and non-diabetic populations.¹⁴ Major trials have also reported that they slow the progression of kidney disease.^{15–17} During the first 6–12 months of treatment, a 50% reduction in proteinuria is associated with a 40–50% reduction in the risk for progression of kidney disease.¹⁸

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Table 1 Albuminuria excretion rates

Diagnostic test	Normal	Moderately increased albuminuria (microalbuminuria)	Severely increased albuminuria (macroalbuminuria)
24-hour urine albumin collection (mg/24 hours)	<30	30–300	>300
Urine albumin:creatinine ratio (mg/mmol)	<3	3–30	>30

Rationale behind combination therapy

Combined inhibition of the renin–angiotensin–aldosterone system was first evaluated on the basis of three pathophysiological considerations.¹⁹ First, any renin–angiotensin–aldosterone inhibition with an ACE inhibitor or angiotensin receptor antagonist is incomplete due to substantial redundancy built into human physiological systems. Second, studies have shown that chronic treatment with ACE inhibitors or angiotensin receptor antagonists results in aldosterone escape with plasma concentrations reaching pre-treatment levels within 6–12 months in up to 40% of patients.²⁰ Third, given that treatment with an ACE inhibitor or angiotensin receptor antagonist alone does not completely eliminate proteinuria, adding a second renin–angiotensin–aldosterone inhibitor may provide further reduction.²⁰

Combination with angiotensin receptor antagonists

There have been numerous studies of treatment with an ACE inhibitor and an angiotensin receptor antagonist (Table 2). The ONTARGET trial evaluated combination treatment with telmisartan and ramipril against either drug alone.²¹ Combination treatment was associated with increased harms including hyperkalaemia, renal impairment, hypotension and syncope.²¹ However, interpretation of these data in the clinical management of patients with albuminuria is potentially complicated for multiple reasons.

First, most participants in the ONTARGET trial did not have chronic kidney disease or albuminuria, therefore any clinical benefits for patients with albuminuric chronic kidney disease were unlikely to be detected.²² Second, the doses of both drugs were doubled following a short run-in period, resulting in an increased likelihood of overtreatment and adverse effects.²² In practice, it is likely that doses would be adjusted according to clinical need and response, rather than doubled. During the trial, albuminuria increased during the follow-up period. The increase in albuminuria over time was statistically lower in the telmisartan alone and combination groups, than with ramipril alone. There was no significant difference in albuminuria between telmisartan alone and combination treatment.²³ In addition, the rates of cardiovascular events were not statistically different between the three groups.²¹

The VA NEPHRON-D trial evaluated losartan alone and in combination with lisinopril. This trial was stopped early due to an increased incidence of acute kidney injury and hyperkalaemia with combination therapy.²⁴

In 2018, the LIRICO and VALID trials failed to demonstrate any significant cardiovascular or renal

benefits with combination treatment. Neither trial found increased harms such as those seen in the ONTARGET or VA NEPHRON-D trials, however it is important to note that both the LIRICO and VALID trials were limited by a lack of statistical power and small sample sizes.^{25,26}

Combination with direct renin inhibitors

The ALTITUDE trial studied aliskirin, a direct renin inhibitor, added to an ACE inhibitor or an angiotensin receptor antagonist for reducing cardiovascular and renal events. This trial was terminated early due to an increased incidence of hyperkalaemia and renal impairment.²⁷ A similar trial in patients with heart failure also showed increased harm with the addition of aliskirin to an ACE inhibitor.²⁸ Direct renin inhibitors are no longer marketed in Australia.

Combination with aldosterone antagonists

Aldosterone antagonists have known antiproteinuric effects. A systematic review found that adding an aldosterone antagonist to an ACE inhibitor or angiotensin receptor antagonist reduced proteinuria in patients with chronic kidney disease. Currently, it is unknown whether this combination reduces the risk of end-stage kidney disease or major cardiovascular events in patients with proteinuric chronic kidney disease. Treatment with an aldosterone antagonist increased the risk of gynaecomastia and doubled the risk of hyperkalaemia.²⁹

The RALES trial studied spironolactone, an aldosterone antagonist, added to an ACE inhibitor in patients with heart failure. The trial ended early due to the overwhelming mortality benefit associated with adding spironolactone.³⁰ Importantly however, this combination was associated with increased rates of hyperkalaemia and hyperkalaemia-associated morbidity and mortality.^{31,32}

The ASPIRANT trial reported that in patients with resistant hypertension, adding an aldosterone antagonist such as spironolactone to standard therapy may be beneficial in reducing systolic blood pressure.³³

Implications for clinical practice

Proteinuria, in particular albuminuria, is a strong predictor of adverse renal and cardiovascular events. Screening for albuminuria is recommended in all adults with one or more risk factors for chronic kidney disease such as diabetes, hypertension, obesity, current smoking, cardiovascular disease, family history of chronic kidney disease and Aboriginal or Torres Strait Islander people.³⁴

Appropriate recognition and treatment of albuminuria, even in patients who are normotensive, can reduce patient morbidity and mortality. Treatment of

Table 2 Summary of randomised controlled trials of combination ACE inhibitor and angiotensin receptor antagonist treatment

Study	Patients	Entry criteria	Treatment arms	Outcomes	Follow-up period (median)	Results
ONTARGET ²¹	25,620	Vascular disease or high-risk diabetes	1. Telmisartan 2. Ramipril 3. Telmisartan + ramipril	Composite cardiovascular outcome (death, myocardial infarction, stroke and hospitalisation)	56 months	No statistically significant difference in cardiovascular events between groups Higher incidence of hyperkalaemia, renal impairment, hypotension and syncope with combination treatment
VA NEPHRON-D ²⁴	1448	Type 2 diabetes and random urine ACR >33 mg/mmol	1. Losartan + placebo 2. Losartan + lisinopril	First change in eGFR or decline of ≥50% in eGFR, or end-stage kidney disease or death	26 months	Terminated early due to higher incidence of hyperkalaemia and acute kidney injury with combination treatment
LIRICO ²⁵	1243	Diabetes, ≥1 cardiovascular risk factor and a urine ACR >3.4 mg/mmol	1. ACE inhibitor* 2. Angiotensin receptor antagonist* 3. ACE inhibitor + angiotensin receptor antagonist	Composite cardiovascular outcome (death, myocardial infarction, stroke and hospitalisation) Doubling of serum creatinine or progression to end-stage kidney disease	32 months	No statistically significant differences in cardiovascular or renal outcomes between groups No statistically significant differences in adverse outcomes between groups
VALID ²⁶	103	Type 2 diabetes, serum creatinine 159–309 micrommol/L and urine ACR >56 mg/mmol	1. Benazepril 2. Valsartan 3. Benazepril + valsartan	Progression to end-stage kidney disease	41 months	Reduced progression to end-stage kidney disease in valsartan alone group No statistically significant differences in adverse outcomes between groups

ACR albumin:creatinine ratio

eGFR estimated glomerular filtration rate

* any commercially available drug

comorbidities and cardiovascular risk factors should always accompany treatment of albuminuria.

Gradually increasing to the maximum tolerated dose of an ACE inhibitor or angiotensin receptor antagonist is likely to yield the greatest benefit. This dose titration will depend on the patient's tolerance and may be limited by adverse events such as hypotension, dizziness, cough or hyperkalaemia.

Although data supporting a combination renin-angiotensin-aldosterone inhibitor are lacking for the treatment of albuminuria, there may be specific circumstances such as heart failure or refractory hypertension when it may be appropriate. However, this should only occur with close monitoring due to the higher rate of adverse events such as hyperkalaemia, acute kidney injury, progressive chronic kidney disease, hospitalisation and death.^{31,32}

ACE inhibitors, angiotensin receptor antagonists and cancer risk

A recently published large population-based cohort study suggested that treatment with an ACE inhibitor was associated with a small but significant increase in the risk of lung cancer compared with angiotensin receptor antagonists. It further found that the risk of lung cancer was higher with longer durations of treatment.³⁵ However, a meta-analysis of randomised controlled trials also found an increased risk of lung cancer with angiotensin receptor antagonists.³⁶

At present, given the conflicting data and lack of long-term prospective evidence, it is not possible to claim that an ACE inhibitor is safer than an angiotensin receptor antagonist or vice versa. Instead, the choice of drug should be based on patient factors, tolerability and clinician experience.

Conclusion

Combining renin-angiotensin-aldosterone drugs to increase blockade of the system reduces proteinuria, but has been consistently associated with a higher incidence of adverse events including

hyperkalaemia and acute kidney injury without clear benefits. Combination therapy should not be routinely prescribed to patients with proteinuria. The recommended treatment is monotherapy with either an ACE inhibitor or an angiotensin receptor antagonist. ◀

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