Therapeutic Approaches in Lowering Albuminuria: Travels Along the Renin-Angiotensin-Aldosterone-System Pathway

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Achieving optimal blood pressure and albuminuria control is a major therapeutic treatment goal in patients with renal insufficiency. Angiotensin-converting enzyme-inhibitors (ACEIs) and angiotensin-receptor blockers (ARB) are the mainstay of therapy in these patients. However, despite these therapies many patients remain at high risk of renal or cardiovascular disease that shows a relationship with albuminuria. Various approaches have been tested to maximize the efficacy of ACEI and ARB.

Increasing the dose of an ACEI or ARB beyond the maximal registered antihypertensive dose causes a distinct decrease in albuminuria without additional effects on blood pressure. The combination of an ACEI and ARB is another possibility to further reduce albuminuria. However, the alleged beneficial effects on hard renal and cardiovascular outcome are not unambiguously demonstrated. Adding a direct renin inhibitor to an ACEI or ARB has been shown to lower albuminuria in patients with and without diabetes. Long-term trials are currently under way to determine the effects of direct renin inhibition on clinical outcomes. Volume excess has been shown to blunt the blood pressure and albuminuria response to ACEI or ARB therapy. Intervening in volume status by means of restricting dietary sodium intake or diuretic therapy has convincingly been shown to lower blood pressure and albuminuria. Whether this strategy translates into a reduction in the risk of renal or cardiovascular events has not (yet) been investigated in prospective randomized trials.

Various options are at hand which have been shown to maximize the blood pressure and albuminuria response to ACEI and ARB treatment. However, long-term studies supporting the benefits of these strategies on hard renal and cardiovascular outcomes are warranted.

Key Words: Albuminuria, Microalbuminuria, Renin-Angiotensin-Aldosterone-System, Angiotensin converting enzyme, Angiotensin receptor blocker, Aldosterone, Nephropathy, Cardiovascular disease, Sodium

Achieving optimal blood pressure and albuminuria control is a major therapeutic treatment goal in patients with renal insufficiency. Angiotensin converting enzyme-inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are the mainstay of therapy because of their proven efficacy to lower blood pressure and albuminuria, both important risk markers for renal and cardiovascular disease progression.

The additional renoprotective effects of agents intervening in the renin-angiotensin-aldosterone-system (RAAS) as compared with other conventional blood pressure lowering treatments are well established, both in the nondiabetic and diabetic population. In the late 90s, the results of the REIN trial showed that in patients with nondiabetic nephropathies, ramipril 10 mg/day conferred renoprotection relative to conventional antihypertensive therapy at equal level of blood pressure control.[1] Bjorck et al showed that in patients with type 1 diabetes and nephropathy, RAAS inhibition (RAASi) with enalapril reduce the rate of renal function loss more than antihypertensive treatment with metoprolol at a similar level of blood pressure control.[2] These results were confirmed by the Collaborative Study Group Trial demonstrating that captopril delays renal function loss in the type 1 diabetic population at similar blood pressure control.[3] Eight years after the publication of the Collaborative Study Group Trial, the blood pressure-independent renoprotective effects of ARBs were reported in patients with type 2 diabetes by both the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) and Irbesartan Diabetic Nephropathy Trial (IDNT) trials.[4,5]

Next to the reduction in blood pressure, the reduction in albuminuria achieved with ACEIs or ARBs may be the critical step in achieving renal (and cardiovascular) protection. Initially, Rossing et al and Apperloo et al demonstrated in patients with and without diabetes, respectively, that the magnitude of change in proteinuria during the initial months of the therapy strongly correlated with long-term glomerular filtration rate decline: the more the albuminuria/proteinuria was initially lowered by the instituted therapy, the slower the rate of subsequent renal function decline.[6,7] Subsequently, analyses from large randomized controlled trials confirmed the strong independent relationship between initial reductions in albuminuria achieved within the first months after initiation of ARB therapy and the long-term risk of renal and cardiovascular events.[8-10] Such analyses imply that lowering of albuminuria may serve as an independent target for renal and cardiovascular protective therapy. However, it should be noted that these analyses were conducted post hoc and were no longer based on

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1548-5595/$36.00

doi:10.1053/j.ackd.2011.04.001

randomized comparisons. Although the association between changes in albuminuria and outcome were adjusted for a range of potential confounding factors, theoretically it could still be possible that the observed association was caused by other factors unrelated to treatment effects. To avoid this type of bias, it is necessary to associate the treatment effects on albuminuria with the treatment effects on the hard endpoint. This approach requires a combined analysis of multiple randomized controlled trials and is referred to as the "trial-level" approach. The clear advantage of the trial-level approach is that the estimated treatment effects on albuminuria and the hard endpoint are based on randomized data. Thus, the trial-level approach reduces the chance of bias which may have been present in the correlation analyses of changes in albuminuria and outcomes in single trials. A joint analysis of multiple randomized clinical trials investigating the effects of RAASi on renal disease progression illustrates the clear association between the treatment effects on albuminuria and the treatment effects on hard renal endpoint: the larger the reduction of albuminuria in a trial, the larger the treatment effect on the hard renal endpoint (Table 1 and Fig 1). These results support the evidence that albuminuria may be a separate target for renoprotective therapy.

Despite proven efficacy in the overall population, it is known that the long-term effects of RAASi show marked variability between patients which is closely linked to a similar between-patient heterogeneity in the risk factors for renal and cardiovascular disease, such as blood pressure and albuminuria. Thus, despite RAASi treatment, considerable high residual blood pressure and albuminuria is present in a substantial number of patients.[17] Several therapeutic approaches along the RAAS pathway have been tested to optimize the treatment response to RAASi so as to further lower albuminuria and attenuate the risk for renal and cardiovascular disease. These therapeutic approaches will be reviewed in this article.

CLINICAL SUMMARY

- The initial reduction in albuminuria during renin-angiotensin-aldosterone-system inhibition is associated with long-term renoprotection: the larger the reduction in albuminuria, the larger the long-term renal risk reduction.
- Despite proven efficacy at a group level, the long-term renoprotective effects of RAASi show a marked between-patient variability which is closely linked to a similar between-patient heterogeneity in its risk factors, such as blood pressure and albuminuria. This results in high residual albuminuria levels in a substantial number of patients despite optimal therapy.
- Strategies to further lower the residual albuminuria include uptitration of the dose of a RAASi beyond the recommended antihypertensive dose, addition of a DRI or aldosterone antagonist to the therapeutic regimen, or importantly, reduction of dietary sodium intake.

Selecting the Optimal Dose of ACEI or ARBs

To optimize the antialbuminuric response to ACEI or ARB therapy, one first needs to ascertain that the optimal dose for reduction in albuminuria is used. Because ACEIs and ARBs are registered as antihypertensive drugs, the dose frequently used in clinical studies (and clinical practice) is the maximum recommended dose for blood pressure reduction. However, the optimal dose for reduction in albuminuria exceeds the dose which is used for blood pressure reduction.[18] Many studies are available to show that increasing the dose of an ACEI or ARB will further lower the albuminuria or proteinuria in the presence or absence of further changes in blood pressure[19-21] (Fig 2). The most recent large study on this topic is the Supra Maximal Atacand Renal Trial. The authors compared ultra-high dosages of candesartan, that is, 64 and 128 mg/day with candesartan 16 mg/day, which was the maximum recommended dose for blood pressure reduction in patients with proteinuria >1g/day.[22] After 30 weeks of therapy, 24-hour proteinuria was 17% and 33% lower with candesartan 64 mg/day and 128 mg/day, respectively as compared with candesartan 16 mg/day (Fig 2). However, the follow-up of these studies was too short to determine whether the additional antialbuminuric effects achieved with supramaximal doses of RAASi resulted in additional end-organ protection. Only one study followed up patients long enough to determine whether uptitrating the dose of ACEI or ARB beyond the maximum recommended dose for blood pressure reduction conferred additional renoprotection. Hou et al compared the optimal antiproteinuric and tolerable dose of an ACEI (benazepril) or ARB (losartan) versus the conventional dose of these agents in nondiabetic patients with nephropathy. In about 50% of the patients, the optimal antiproteinuric dose was reached with benazepril 20 mg or losartan 100 mg, whereas the other patients required a dose of benazepril up to 40 mg or losartan 200 mg. Uptitrating the dose of either of these agents resulted in additional reduction in albuminuria and a marked reduction in the risk of ESRD of 50% during 3.7 years of follow-up.[13] Thus, an approach of dose titration with single RAASi beyond the maximum recommended dose of blood pressure reduction results in the additional reduction in albuminuria and leads to enhanced end-organ protection. Additional studies exploring this concept and focusing on safety issues may justify this therapeutic treatment strategy.