Rebuttal of the Con View: Albuminuria Is an Appropriate Therapeutic Target in Patients with CKD

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Abstract

Our opponents in this debate state that there are insufficient data to consider albuminuria as a valid target for therapy in patients with CKD. They base their opinion predominantly on two arguments: first, a decrease in albuminuria is not always associated with renoprotection, and second, no prospective randomized controlled trial has been conducted that really targeted albuminuria.

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Our opponents illustrate their first argument with examples from cholesterol studies and bisphosphonate studies demonstrating that either raising HDL cholesterol or bone mineral density does not translate in a reduction in cardiovascular outcomes or fractures. Of course examples of surrogates that failed exist, but exceptions can always be found. BP reduction, for example, is an accepted surrogate; however, clinical trial data are available showing that a BP reduction is not always associated with cardiovascular protection. For example, the Action to Control Cardiovascular Risk in Diabetes trial, that compared intensive BP control (systolic BP <120 mmHg) with conventional BP control (systolic BP <140 mmHg), failed to show benefit for the primary cardiovascular end point despite a 14 mmHg difference in BP between the two treatment arms (1). Such data have never been reason to question the validity of BP reduction as surrogate for cardiovascular risk reduction. Similarly, exceptions to the rule should also not be reason to disqualify albuminuria as a target for therapy in patients with CKD.

In addition, we have to realize that most drugs are relatively unselective in their effects. Although drugs are registered as primarily BP- or cholesterol-lowering drugs, many have multiple off-target treatment effects that will influence their overall effect on the outcome measure under study. Our opponents quote a number of trials, including the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) and Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) trials, where these phenomena occurred. Intervention in the renin-angiotensin-aldosterone system (RAAS) exerts many effects. Some of these effects are beneficial and organ protective, such as BP lowering and albuminuria lowering. However, RAAS blockade may also decrease hemoglobin concentration or lead to hypotension, which may actually increase renal and cardiovascular risk. Although the additional albuminuria-lowering effect of intensive RAAS inhibition may have been beneficial in these trials, the harmful effects of this treatment were apparently strong enough that they counterbalanced the beneficial effects. Therefore, these trials should not be used to disqualify albuminuria as valid target for treatment. They only show that the balance between beneficial and harmful effects determines overall outcome.

As their second argument, our opponents state that no trial has properly evaluated whether albuminuria is a valid target for renoprotective therapy. Our opponents quote the Renoprotection of Optimal Anti-Protienuric Doses trial and argue that this trial actually compared suboptimal versus optimal RAAS inhibition dose and thereby is confounded. We kindly disagree with this interpretation. This trial was designed to target albuminuria. Importantly, it showed that at equal BP control an approximate 30% difference in albuminuria between the low- and high-dose RAAS inhibition groups resulted in an approximate 50% reduction in the incidence of the composite end point of doubling of serum creatinine, ESRD, or death. This trial therefore convincingly shows that titrating RAAS inhibition on albuminuria response beyond the BP effect of this intervention results in renoprotection. Therefore, the results of this trial are the quintessential evidence that albuminuria is a valid target for therapy in patients with CKD.

Having made these comments, we do agree that further trials are required to further strengthen the case that targeting albuminuria, independent of BP and other renal and cardiovascular risk factors, is important to achieve optimal renoprotection in patients with CKD.

Disclosures

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