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

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We thank the editors for the opportunity to write a rebuttal to Dr. Lambers Heerspink's and Dr. Gansevoort's pro side of the debate of whether albuminuria is an appropriate therapeutic target. There are a few areas in which we agree with their argument. Albuminuria does predict poor outcomes, and the presence of albuminuria identifies individuals who are at high risk of progression. Increases in albuminuria also predict poor outcomes. However, the review of the analyses of change in albuminuria in trials missed that this association is seen in both the treated and placebo groups (1,2). A change in albuminuria is telling us something about the disease state (*i.e.*, is a marker) and is not necessarily a treatment effect. This latter distinction is important because treatments that lower albuminuria may cause more harm than good. Indeed, even with the most established therapy to slow the progressive loss of renal function, inhibition of the renin-angiotensin system, dual inhibitors of the renin-angiotensin-aldosterone system lowered proteinuria further but caused more harm than good to the participants (3–6). As cited in the Biomarker-Surrogacy Evaluation Schema (7), the main danger of the use of surrogates is that they may not capture the combined risk/benefit of a treatment. Although Drs. Lambers Heerspink and Gansevoort may argue that exceptions to the rule that treatments that lower albuminuria decrease the risk of ESRD do not invalidate the rule, we would argue that exceptions mean that each treatment needs to be studied individually to determine whether it is both safe and effective. Because some therapies that lower albuminuria do decrease the risk of progression, change in proteinuria in earlier phase studies could help identify potentially effective agents. However, the treatments should then be tested in fully powered studies before they are approved and used in patients.

Drs. Lambers Heerspink and Gansevoort further argue that the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend targeting proteinuria and thus we should not need to further debate this issue. Of course, our experience in the renal community with the recommendations from guidelines on the early use of erythropoietin-stimulating agents later being established in multiple well designed clinical trials to be harmful should teach us that guidelines are often opinions and do not trump data. Furthermore, in reading the clinical practice guideline for GN again, one needs to say "not quite" to the authors' representation of the message from KDIGO. The GN guidelines primarily use proteinuria as a guide for which patients to treat with disease-modifying agents (8). That is, proteinuria identifies individuals at increased risk for progression and could be used as a guide for which patients to treat. This is not unreasonable and would be analogous to stating that individuals with diabetes and overt proteinuria are at increased risk and should be treated with an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB). It is not the same as saying that proteinuria is a target. The guideline section on IgA nephropathy does recommend uptitrating ACEIs or ARBs to target proteinuria <1 g/d as tolerated, which is the only recommendation in this guideline that specifically targets proteinuria (recommendation 10.2.3). This is somewhat ironic, because the body of evidence for any specific treatment for IgA nephropathy is weak. However, we also point to recommendation 5.4.2, which states the following: "We suggest that, for the initial episode of nephrotic syndrome associated with minimal change disease (MCD), statins not be used to treat hyperlipidemia, and ACEI or ARBs not be used in normotensive patients to lower proteinuria." Thus, the recommendation for treatment of proteinuria is not universal and is not a settled question. Furthermore, we point out that both of these recommendations were graded as level 2D, which indicates that the evidence is very low.

We also have some concerns regarding the meta-analysis and whether it can be used for evidence of surrogacy. The meta-analysis states that for multiple interventions, a 30% reduction in albuminuria correlates with a 23.7% decreased risk of ESRD (9). With the exception of ACEIs and ARBs, none of the other included interventions have been shown to slow progression to ESRD in randomized studies. As Drs. Lambers Heerspink and Gansevoort cite in their editorial, a valid surrogate would require at least three randomized studies in three drug classes and we do not have that for albuminuria. Among the other interventions that they discuss in their editorial, protein reduction has not been shown to prevent the need for dialysis (the patient-centered outcome), nor has pentoxifylline. The biomarker-surrogacy argument fails their generalizability argument.

We read the Biomarker-Surrogacy Evaluation Schema with interest and think that the results are not as clear cut

Table 1. Biomarker-Surrogacy Evaluation Schema applied to albuminuria

Domain	Points	Criteria	Albuminuria
Study design criterion	0	Evidence from *in vitro or* animal studies *or* case reports *or* cross- sectional observational *or* retrospective observational cohorts studies evaluating the relationship between marker and target	3: Two RCTs in the same drug class [RENAAL, IDNT (10,11)]
	1	At least one nonpopulation-based prospective observational study with collection of all covariates needed to adjust for known confounding and effect modification evaluating the relationship between marker and target	
	2	At least one population-based prospective observational study with collection of all covariates needed to adjust for known confounding and effect modification evaluating the relationship between marker and target *or* one RCT of the same drug class of an intervention evaluating the relationship between marker and target	
	3	Two RCTs of the same drug class of an intervention evaluating the relationship between marker and target	
	4	Two RCTs in each of two drug classes and of an intervention evaluating the relationship between marker and target	
	5	Three RCTs in each of three known drug classes of an intervention that can evaluate the relationship between marker and target *or* three randomized biomarker-target trials	
Target outcome criterion	0	Target(s) is a biomarker and reversible	4: ESRD
	1	Target(s) is a biomarker and irreversible	
	2	Target(s) is a clinical end point of reversible mild organ morbidity or reversible mild burden of disease	
	3	Target(s) is a clinical end point of reversible severe organ morbidity or reversible severe burden of disease or irreversible mild organ morbidity or irreversible mild burden of disease	
	4	Target(s) is a clinical end point of irreversible severe organ morbidity or irreversible severe burden of disease	
	5	Target(s) is death	
Statistical evaluation criterion	0	Evidence of poor to fair prognostic validity *or* very poor overall surrogate statistical validity	We have not redone the analysis; for the sake of argument, we will accept the score of 4
	1	Evidence of good to excellent prognostic validity *or* poor overall surrogate statistical validity	
	2	Fair overall surrogate statistical validity	
	3	Good overall surrogate statistical validity	
	4	Very good overall surrogate statistical validity	
	5	Excellent overall surrogate statistical validity	

Table 1. (Continued)

Domain	Points	Criteria	Albuminuria
Penalties		Biology, epidemiology , and success in clinical trials	−2: Studies have shown opposite effect [ACCOMPLISH (12)]
	−1	Evidence of no surrogacy validity in at least one adequately powered RCT	
	−1	Evidence of one epidemiologic study that supports opposite assertion	
	−1	Evidence of no effect in at least one adequately powered epidemiologic study	
	−1	Biomarker remote from clinical end point	
	−1	No animal model evidence to support surrogacy validity of therapeutic response	
	−1	No prospective epidemiologic evidence to support surrogacy validity	
	−2	Evidence of one adequately powered RCT that supports opposite assertion	
	−2	Application of the schema used <90% of adequately powered existing trials	
		Generalizability	−2: Has only been shown in studies of diabetic nephropathy
	−2	No evidence to support surrogacy validity of therapeutic response from clinically heterogeneous study populations by age, sex, comorbidity, and disease stage	
		Risk-benefit	−3: Studies of combination renin angiotensin system blockade show harm (3,4,13)
	−3	One RCT that demonstrates use of marker confers patient harm	
	−3	Does not meet the threshold criterion of a rank of 3 in at least one domain if score is ≥7	

Domains and criteria are from Lassere (7). RCT, randomized controlled trial; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan; INDT, Irbesartan Diabetic Nephropathy Trial; ACCOMPLISH, Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension.

when applied to albuminuria as the pro position would propose (7). In addition to points for the various criteria, there are penalties for evidence that does not support the particular surrogate. The authors did not apply these penalties. We have redone the table using the schema in the original published document (Table 1). In this schema (7), a level 1 surrogate would require a score of 13–15 and a level 2 surrogate would require a score of 10–12. Subtracting the penalties decreases the score from 11 to 4, which is not adequate to serve as a surrogate end point for treatment.

We therefore reiterate our conclusion that albuminuria is a risk factor but is not a surrogate end point or target for treatment. We may be doing our patients more harm than good by targeting albuminuria. However, we await further studies to prove or disprove this hypothesis.

Disclosures

None.

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