Rebuttal: PRO Position

Should Microalbuminuria Ever Be Considered as a Renal Endpoint in Any Clinical Trial?

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Our opponent states that microalbuminuria should not be used as a renal endpoint. His arguments are based on two major points: in absence of microalbuminuria, one may observe progression of renal function loss, and decrease in microalbuminuria is not always associated with renal protection.

We disagree with our opponent that studies showing the development of renal disease in the absence of microalbuminuria form a sound reason to discard microalbuminuria as a valid renal endpoint. As already stated in our commentary, these studies only indicate that other factors than increased albuminuria can also promote progressive renal function loss (note: in the absence of hypertension, renal progression occurs; this does not disqualify high blood pressure as a renal surrogate). The question is whether the presence of microalbuminuria predicts renal outcomes. The answer to this question is undoubtedly yes!

We agree that only a limited number of trials have properly evaluated the effect of interventions on the change in albuminuria and the relationship with renal outcomes. However, the few clinical trials that tested the effect of intervention on progression of renal disease unquestionably show associations between the change in albuminuria and renal outcomes. Our opponent quotes the ACCOMPLISH trial in which this relation is not observed and similar findings were reported in the ON-TARGET trial. However, these are secondary analyses

from cardiovascular trials. Such trials are not specifically designed for renal outcomes, and may consequently not lend themselves to firm conclusions on the topic of the current debate [1, 2]. Indeed, the number of patients with microalbuminuria in these studies makes up such a small proportion of the total (approximately 25%) that one cannot answer any questions of changes in albuminuria and outcome by analyzing the total group. We will have to await analysis in the microalbuminuria subgroups which are underway. The most compelling argument to refute the results of these cardiovascular trials is the fact that other parameters could have changed and negatively influenced renal outcomes. As mentioned in our commentary, diuretics are illustrative for such a phenomenon. They lower blood pressure, but if they induce hypokalemia, they appear not to be cardioprotective, despite their blood pressure lowering ability. This has never been a reason to question the suitability of blood pressure as a surrogate for cardiovascular outcome; neither should it be a reason to abandon microalbuminuria as a surrogate for renal outcomes.

Having made these comments, we do agree with our opponent that there is indeed a need for more clinical trials to provide us with data that strengthen the fact that the lowering of albuminuria, independent of other renal or cardiovascular risk markers, is associated with renal protection.

Disclosure Statement

D. de Zeeuw is a consultant for Astra Zeneca, Abbott, Amgen, BMS, Hemocue, J&J, Merck, Novartis, Noxxon. H.J. Lambers Heerspink has no conflict of interest.

References

- 1 Sarafidis PA, Bakris GL: Renin-angiotensin blockade and kidney disease. *Lancet* 2008; 372:511–512.
- 2 Lambers Heerspink HJ, De Zeeuw D: Dual RAS therapy not ON TARGET, but fully alive. *Nephron Clin Pract* 2010, in press.