lowered by an average of 33 mg/dl, which produced a reduction of 19% in total stroke (HR 0.81; 95% CI 0.66 to 0.99), driven by a 28% reduction in ischemic stroke. There was a NS excess of hemorrhagic stroke (HR 1.21; 95% CI 0.78 to 1.86). AURORA-diabetes showed an excess of hemorrhagic stroke as well (HR 5.21; 95% CI 1.17 to 23.3), but the result is not in keeping with the 4D study (eight versus five hemorrhagic strokes in placebo versus active), which included more patients with diabetes and followed them for longer. Is this a concern, and should this discourage the use of statins in dialysis patients? A recent meta-analysis suggested that statins might increase the risk for hemorrhagic stroke, but this increase is of the order of 20%, and because the risk for ischemic stroke in most populations is substantially higher, the absolute effect on all stroke is beneficial. Nevertheless, the small number of events (two versus 12) in this analysis means that this result should be interpreted with caution.

How does one resolve these issues? The evidence would be stronger if all of the available evidence were included in a meta-analysis of the individual data from AURORA, 4D, and the dialysis patients in SHARP. This might have enough events to assess reliably the effects of statin therapy in patients both with and without diabetes on coronary events as well as stroke. Such an analysis should resolve the questions raised by this study. If there is going to be a sunrise for statins in dialysis patients, this study so far is just the beginning of more to come.

DISCLOSURES

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See related article, “Rosuvastatin in Diabetic Hemodialysis Patients,” on pages 1335–1341.

The Fourth Dimension: Associations of Change in Albuminuria over Time

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Albinminuria is a powerful predictor of cardiovascular disease and death in health and a variety of disease states. However, once albuminuria has been detected, the value of monitoring changes in excretion rates over time is unclear and has not been tested rigorously. Furthermore, because no studies have directly assessed whether targeted reduction of albuminuria reduces future cardiovascular risk, controversy exists as to whether it may be considered a modifiable risk factor, suitable for clinical monitoring and specific intervention.

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In this issue of *JASN*, Schmieder et al. examine the utility of change in albuminuria over a 2-year interval (Δ albuminuria) to predict future cardiovascular and renal events in a post hoc analysis of 23,480 participants drawn from the Telmisartan Randomised Assessm ent Study in ACE iNtolerant subjects with Cardiovascular Disease (TRANS CEND) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This was primarily a study of a change in the microalbuminuric range conducted in a middle-aged population with atherosclerotic vascular disease or with diabetes and target organ damage and preserved kidney function. Associations of a doubling or halving in urinary albumin excretion and the development of cardiovascular disease, kidney disease, and mortality during the subsequent 3 years were examined. They observed a 15% reduction in mortality risk for patients whose albuminuria declined, compared with a 30% increase in cardiovascular events, a 40% increase in renal events, and a 50% increase in mortality in the group of patients who experienced an increase in albuminuria.

This article completes a triumvirate of studies that attempted to resolve the question of whether longitudinal changes in urinary albumin excretion independently predict cardiovascular and renal outcomes—all post hoc analyses of randomized trials of angiotensin blockade and all with near-identical results. The first used data from Reduction of End-stage Disease in Hypertension (RIDGE) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This analysis by Schmieder et al. examined the utility of change, as the exposure. This has the downside of overemphasizing fluctuations at the opposite end of the spectrum, potentially biasing results toward the null. A second potential source of bias relates to measurement of Δ albuminuria (halving or doubling), as opposed to absolute change in albuminuria, for which patients with the highest baseline values are more likely to have the greatest absolute change in albuminuria, as well as the highest cardiovascular risk. Adjusting for baseline albuminuria, as was done in the study by Schmieder et al, may not be sufficient to tease apart the independent signals. The investigators anticipate this problem by using relative change in albuminuria (halving or doubling), as opposed to absolute change, as the exposure. This has the downside of overemphasizing fluctuations at the opposite end of the spectrum, potentially biasing results toward the null. A second potential source of bias relates to measurement of Δ albuminuria itself. Because albuminuria measurements exhibit substantial variability, multiple assays are usually needed to capture precisely the variability component. Only two measures of albuminuria were used for this analysis, which is understandable because more frequent measures are rarely feasible in large-scale studies. The loss of precision introduced by this limitation would also be expected to bias results toward the null. Considering these two sources of bias, it is perhaps encouraging that evidence of association was nonetheless detected. However, a prospective study that uses multiple measures of albuminuria over time and specifically examines the effect of targeted albuminuria reduction on cardiovascular events will be required to characterize definitively and accurately the strength of association with cardiovascular and renal risk.

Albuminuria has the potential to be that most valuable of clinical tools—a biomarker that could be used to titrate BP, glycemic control, or other risk factors to the individual. Although questions of causality or modifiability are not addressable by this approach, this study should stimulate efforts to resolve definitively whether it can fulfill this potential.
DISCLOSURES
None.

REFERENCES
