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-dia-
tes 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
V.K. and C.W. have received institutional grant/research support from the University of Oxford, and C.W. has received speaker honoraria from Astellas Pharma and Merck Sharp & Dohme.

REFERENCES

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

The Fourth Dimension: Associations of Change in Albuminuria over Time

Conall M. O’Seaghdha*†‡§ and Caroline S. Fox*†‡**
*National Heart, Lung, and Blood Institute’s Framingham Offspring Study and the Center for Population Studies, Framingham, Massachusetts; †Division of Intramural Research, National Heart, Lung, and Blood Institute, Bethesda, Maryland; ‡Renal Division and Division of Endocrinology, Brigham and Women’s Hospital, Boston, Massachusetts; §Renal Division, Massachusetts General Hospital, Boston, Massachusetts; and **Division of Endocrinology, Harvard Medical School, Boston, Massachusetts

Albinumina is a powerful predictor of cardiovascular disease and death in health and a variety of disease states.1,2 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 in-
tervention.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Caroline S. Fox, National Heart, Lung, and Blood Insti-
tute’s Framingham Heart Study, 73 Mount Wayte Avenue Suite #2, Framing-
ham, MA 01702. Phone: 508-935-3447; Fax: 508-626-1262; E-mail: foxca@nhlbi.nih.gov

Copyright © 2011 by the American Society of Nephrology
In this issue of *JASN*, Schmieder et al.\(^3\) 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 AssessmeNt Study in ACE INtolerant subjects with cardiovascular Disease (TRANSCEND) and the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET). This was primarily a study of 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.\(^4,5\) The first used data from Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL), a placebo-controlled trial of losartan in diabetic nephropathy. Reductions in albuminuria during the first 6 months were associated with fewer subsequent cardiovascular events, and risk estimates were similar to the study by Schmieder *et al.*\(^3\): A halving in albuminuria was associated with an 18% reduction in risk for cardiovascular disease.\(^4\) The second used data from 8206 patients who had hypertension and electrocardiographic left ventricular hypertrophy and were drawn from the Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial of losartan versus atenolol.\(^5\) Again, decreases in albuminuria during the first 6 months of the study were associated with a lower cardiovascular event rate. The analysis by Schmieder *et al.*\(^3\) corroborates these earlier findings but is also novel in that it was adequately powered to identify a mortality association. Although mutually supportive results from three independent studies seem encouraging, some caution must be exercised in their interpretation.

At a time when novel cardiovascular risk factors are rapidly identified and proposed, assessing and quantifying the incremental yield of a new biomarker becomes paramount. Demonstration of a statistically significant risk association is only the starting point. The added predictive ability of a biomarker, in this case Δ albuminuria, has traditionally been assessed by measuring the area under the receiver operating characteristic curve. However, this approach has been criticized as overly stringent because a novel biomarker must have very strong independent associations with the outcome to improve on models already possessing good discrimination. As such, the net reclassification index (NRI)\(^6\) has been proposed. Applied to the present example, reclassification tables would categorize study participants into cardiovascular or renal risk categories on the basis of predicted risks using models with and without Δ albuminuria. The NRI is the sum of differences in proportions of individuals correctly reclassified as higher risk minus the proportion incorrectly reclassified by the inclusion of Δ albuminuria in the model. Hence, the NRI identifies the *additional* percentage of individuals correctly identified as being at increased cardiovascular risk by Δ albuminuria while also capturing loss in model performance as a result of its inclusion, thus better defining its predictive power as a biomarker. This approach has proved useful in identifying novel markers of renal and cardiovascular risk\(^6,7\) and should be considered for inclusion in future analyses of this type.

Another major challenge of this type of analysis is to disentangle the strong signal from albuminuria at baseline from any additional, independent association with Δ albuminuria that may be present. Dissecting out independent signals may prove difficult when exposures are highly correlated, such as 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.\(^5,8\) Adjusting for baseline albuminuria, as was done in the study by Schmieder *et al.*,\(^3\) may not be sufficient to tease apart the independent signals.\(^9\) 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,\(^8\) multiple assays are usually needed to capture precisely the variability component.\(^10\) 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.
REFERENCES
