Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON

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OBJECTIVE

To assess the association between 2-year changes in urine albumin–to–creatinine ratio (UACR) and the risk of clinical outcomes in type 2 diabetes.

RESEARCH DESIGN AND METHODS

We analyzed data from 8,766 participants in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation Post-Trial Observational Study (ADVANCE-ON). Change in UACR was calculated from UACR measurements 2 years apart, classified into three groups: decrease in UACR of ≥30%, minor change, and increase in UACR of ≥30%. By analyzing changes from baseline UACR groups, categorized into thirds, we repeated these analyses accounting for regression to the mean (RtM). The primary outcome was the composite of major macrovascular events, renal events, and all-cause mortality; secondary outcomes were these components. Cox regression models were used to estimate hazard ratios (HRs).

RESULTS

Over a median follow-up of 7.7 years, 2,191 primary outcomes were observed. Increases in UACR over 2 years independently predicted a greater risk of the primary outcome (HR for ≥30% UACR increase vs. minor change: 1.26; 95% CI 1.13–1.41), whereas a decrease in UACR was not significantly associated with lower risk (HR 0.93; 95% CI 0.83–1.04). However, after allowing for RtM, the effect of "real" decrease in UACR on the primary outcome was found to be significant (HR 0.84; 95% CI 0.75–0.94), whereas the estimated effect on an increase was unchanged.

CONCLUSIONS

Changes in UACR predicted changes in the risk of major clinical outcomes and mortality in type 2 diabetes, supporting the prognostic utility of monitoring albuminuria change over time.

Albuminuria is a strong predictive marker for adverse cardiovascular and renal outcomes among patients with diabetes (1–3). Accordingly, albuminuria has an important role in the stratification of risk for adverse outcomes in diabetes and has been incorporated in the definition and staging of chronic kidney disease (CKD), a widely recognized microvascular complication of diabetes. However, there is ongoing controversy as to whether changes in albuminuria accurately reflect changes in the risk of adverse long-term outcomes (4,5). In other words, is albuminuria an appropriate therapeutic target in clinical practice, and can it be used as a surrogate marker for cardiovascular and renal outcomes in clinical trials?

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A number of recent studies have suggested good correlation between early changes in albuminuria and the subsequent risk of clinical outcomes in diabetes. However, these studies have been generally small in size (e.g., 216 to 1,647 patients [6–10]), had relatively short durations of follow-up for outcomes (<3 years [11,12]), or have been limited to evaluating the association between albuminuria change and subsequent long-term adverse kidney outcomes without assessments for cardiovascular disease, the primary cause of morbidity and mortality among patients with type 2 diabetes (12–15). In addition, although some studies have shown positive linear associations between albuminuria change and subsequent clinical outcomes (11,13), a recent study in type 1 diabetes found no association between albuminuria remission and subsequent renal events (16). No previous study has adequately investigated the role of regression to the mean in these associations.

Thus, based on data from the Action in Diabetes and Vascular disease: Preterax and Diamicron MMR Controlled Evaluation (ADVANCE), a randomized controlled trial in patients with type 2 diabetes and its posttrial follow-up (ADVANCE Post-Trial Observational Study [ADVANCE-ON]), we evaluated the associations among 2-year changes in urine albumin–to–creatinine ratio (UACR) and major cardiovascular events, major renal events, and all-cause mortality.

RESEARCH DESIGN AND METHODS

Study Design and Population

ADVANCE was a 2 × 2 factorial randomized controlled trial evaluating the effects of blood pressure (BP)–lowering and intensive blood glucose–lowering treatment on vascular outcomes in patients with type 2 diabetes. A detailed description of the design has been published previously (17–19). In brief, a total of 11,140 individuals with type 2 diabetes aged ≥55 years at high risk of cardiovascular events were recruited from 215 centers in 20 countries. After a 6-week active run-in period, participants were randomly assigned to either a fixed-dose combination of perindopril (4 mg) and indapamide (1.25 mg) or matching placebo and also to either a gliclazide-based (modified release) intensive glucose control regimen aiming to achieve a hemoglobin A_{1c} ≤6.5% or standard glucose control based on local guidelines. There were no inclusion or exclusion criteria related to BP or glomerular filtration rate; however, the presence of albuminuria was one of a number of eligibility criteria for inclusion. The median durations of follow-up for the BP- and glucose-lowering trial interventions were 4.4 and 5.0 years, respectively. The ADVANCE-ON study was a posttrial follow-up study, comprising 8,494 of the 10,082 surviving participants at the end of the randomized treatment phase (20). The median total follow-up period (i.e., including both ADVANCE and ADVANCE-ON) was 9.9 years. Approvals for the original trial and the posttrial follow-up phase were obtained from the institutional review board of each center, and all participants provided written informed consent.

Participants with UACR measurements at study registration and 2 years after randomization were eligible for inclusion into the current study. Patients with major macrovascular or renal events or death during the first 2 years, those with missing UACR values at study registration (at the beginning of the 6-week run-in period prior to randomization) or 2 years after randomization, or those with missing covariate information were excluded.

Study Outcomes and Follow-up

The primary outcome for this study was the composite of major macrovascular events (defined as nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, or other cardiovascular death), major renal events (defined as requirement for chronic dialysis or kidney transplantation or renal death), and all-cause mortality. Secondary outcomes included the individual components of the primary outcome: *1*) major macrovascular events, *2*) major renal events, and *3*) all-cause mortality. Participants were followed from their 2-year visit until the earliest of the first study event, death, or the end of follow-up (Supplementary Fig. 1). Study events recorded during the randomized treatment phase were reviewed and validated by an independent end point adjudication committee. Outcomes occurring during posttrial follow-up were reported by the study centers using the standardized definitions adopted during the trial, without central adjudication (20).

Statistical Methods

UACR was measured (in micrograms per milligram) at ADVANCE trial registration, 2 and 4 years after randomization, and at the end of follow-up based on single-spot urine samples taken at a random time of day. We assessed change in UACR from study registration (hereafter referred to as the "first UACR") to 2 years after randomization. Change in UACR was defined by grouping UACR as in previous reports (6,15) as: decrease in UACR of ≥30%, minor change in UACR (decrease of UACR <30% to increase <30%), and increase in UACR of ≥30%. We also assessed change continuously based on fold changes in UACR.

However, it is a fact of nature that someone who has a high value at baseline will tend to have a lower value on a subsequent measurement and vice-versa: so-called regression to the mean (RtM) (21). To allow for this, we repeated our categorical analyses, but only considered anyone in the highest or middle thirds of UACR at baseline whose value went up by ≥30% or experienced minor change for the highest third at 2 years to have a "real" increase; that is, a residual increase after accounting for RtM. Similarly, only patients in the middle or lowest thirds whose values went down by ≥30% or who experienced minor change for the lowest third were considered to have a "real" residual decrease, over and above RtM (Supplementary Fig. 2). We computed the regression dilution coefficient using the MacMahon-Peto method (21) and evaluated the effect of the first ACR on clinical outcomes with and without use of adjustment by this coefficient.

Continuous variables are reported as means with SD for variables with approximately symmetric distributions. UACR and triglycerides values are presented as median and interquartile interval (IQI) because of their skewed distributions and were transformed into natural logarithms before analysis. Linear trends across categories were tested by linear regression analysis and logistic regression analysis, as appropriate. Cox regression models were used to estimate hazard ratios (HRs) and their corresponding 95% CIs for change in UACR adjusting for age, sex, region (Asia or other) of residence, ADVANCE trial treatment allocation (BP and glucose-lowering), baseline UACR duration of diabetes, history of macrovascular disease, current smoking, current alcohol consumption, BMI, hemoglobin A_{1c}, total cholesterol, triglyceride, estimated glomerular filtration rate (eGFR; calculated using the CKD-EPI creatinine

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equation [22] and grouped into KDIGO eGFR categories [23]), systolic BP, and percent 2-year changes in eGFR and systolic BP. We assessed continuous change in UACR using restricted cubic spline regression models for a log-transformed fold change of UACR with knots placed at 0.25-, 0.5-, 1- (stable UACR), 2-, and 4-fold change.

We explored potential modification of the association between change in UACR and major macrovascular events according to subsets of participants grouped by sex, age, region of residence (Asia vs. Eastern Europe, or Established Market Economies), duration of diabetes, age at completion of education, baseline history of cardiovascular disease, ADVANCE randomized treatment allocation, UACR (<30, 30–300, or >300 μg/mg), systolic BP (<120, 120–140, or >140 mmHg), and eGFR (<60 or ≥60 mL/min/1.73 m^2) levels. We conducted sensitivity analysis in which we repeated the assessment of the association between overall categorical UACR change and outcomes after imputing missing UACR (*n* = 1,496 patients) and covariate (*n* = 227 patients) values for 1,723 patients.

Statistical analyses were performed with SAS 7.11 (SAS Institute, Cary, NC) and Stata software (release 13; StataCorp, College Station, TX). A two-sided *P* value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of the 11,140 participants in the ADVANCE trial, 8,766 participants (78.7%) who were followed in ADVANCE-ON were eligible for inclusion in the present analysis. The mean age of the cohort was 66 years (SD 6), 43% were female, and the mean duration of diabetes was 7.8 years at baseline (SD 6.3) (Table 1).

Changes in UACR

Among patients with UACR <30 μg/mg at the time of the first UACR measurement (*n* = 6,194), 24% (*n* = 1,485) and 47.3% (*n* = 2,928) experienced a decrease in UACR ≥30% and an increase in UACR, respectively. Overall, in those with UACR <30 μg/mg, UACR levels increased by a median of 1.8 μg/mg (IQI −2.7 to 9.7 μg/mg) over the initial 2-year period. Conversely, in patients with UACR levels 30–300 μg/mg (*n* = 2,285), 55.3% (*n* = 1,263), and 24.3% (*n* = 555) experienced a decrease in UACR ≥30% and an increase in UACR, respectively. Overall, in those with UACR levels 30–300 μg/mg, UACR levels decreased by a median of −21 μg/mg (interquartile range −53 to 18 μg/mg). Finally, among patients with UACR >300 μg/mg (*n* = 287), 74.2% (*n* = 213) and 8.7% (*n* = 25) experienced a decrease in UACR ≥30% and an increase in UACR, respectively, with an overall decrease of −315 (IQI −471 to −121). Overall, at the 2-year follow-up, 33.8% (2,961/8,766) experienced a UACR decrease of ≥30%, 26.2% (2,297/8,766) experienced minor change, and 40.0% (3,508/8,766) experienced an increase in UACR of ≥30%.

Clinical Events During Follow-up

During a median 9.7 years (IQI 5.9–10.8) follow-up after the first UACR was measured, higher levels of baseline UACR were, as expected, associated with an increased risk of the primary composite outcome, as well as its individual components (Supplementary Fig. 3).

During a median 7.7 years (IQI 3.9–8.8) following the 2-year period in which change in UACR was measured, 2,191 patients (25.0%) developed the primary composite outcome (1,457 events during ADVANCE-ON). There were 1,392 major macrovascular events (15.9%), 108 major renal events (1.2%), and 1,416 deaths (16.1%). The annual event rates were 2.4, 0.2, and 2.3%, respectively.

Overall, we observed a strong positive linear association between change in UACR and the risk of the primary and secondary outcomes (Figs. 1*A* and 2). Compared with patients who experienced a minor change in UACR (<30% up or down), the risk of the primary outcome was significantly higher among those with an increase in UACR of ≥30% (HR 1.26; 95% CI 1.13–1.41), whereas a decrease in UACR was not significantly associated with a lower risk of the composite outcome (HR 0.93; 95% CI 0.83–1.04). An increase in UACR was significantly associated with a 20% (95% CI 5–38), 67% (95% CI 2–273), and 40% (95% CI 22–60) higher risk of major macrovascular events, major renal events, and all-cause mortality, respectively, compared with minor change (Fig. 1*A*). Assessment of the relationship between fold changes in UACR and the risk of study outcomes showed similar linear associations for the primary outcome, as well as the secondary outcomes of major macrovascular and renal events, although statistical significance was not reached for comparisons with decreasing UACR (Fig. 2). For the outcome of all-cause mortality, whereas an increase in UACR was predictive of higher risk, the association was flat for decreasing UACR.

RtM

As expected, there was strong evidence of RtM (Supplementary Fig. 4): the regression dilution coefficient was 2.01. Every one-SD increase in baseline UACR was associated with a 21% higher risk of the primary outcome (95% CI 17–25) and correction for regression dilution increased this estimate to 46% (95% CI 36–57) (Supplementary Fig. 2). After accounting for RtM, the effects of a decrease in UACR were greater, but the effects of an increase were similar (Fig. 1*B*). A decrease in UACR beyond RtM was associated with a significantly lower risk of the primary outcome (HR 0.84; 95% CI 0.75–0.94) and also major macrovascular events (HR 0.84; 95% CI 0.73–0.97) and all-cause mortality (HR 0.81; 95% CI 0.70–0.93).

Subgroup and Sensitivity Analysis

Subgroup analyses by baseline levels of UACR showed similar associations across the clinical outcomes assessed (Fig. 3). Additional analysis by eGFR and systolic BP (Supplementary Fig. 5), sex, age, region of residence, duration of diabetes, age at completion of education, history of cardiovascular disease, and randomized treatment allocation (BP- and glucose-lowering) (Supplementary Fig. 6) showed similar positive linear associations between UACR change and major macrovascular events across all assessed patient groups (p for heterogeneity 0.19–0.98). Results remained unchanged when missing UACR and covariates values were imputed for those excluded in the primary analysis (Supplementary Fig. 7).

CONCLUSIONS

In a cohort of 8,766 patients with type 2 diabetes, we observed an overall positive linear association between 2-year changes in UACR and the future risk of major clinical outcomes. Increases in UACR over 2 years were independently predictive of greater adverse cardiovascular and renal outcomes as well as all-cause mortality, although decreased UACR did not significantly predict lower risk of clinical outcomes. However, after accounting for RtM, associations between decreases in

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Table 1—Characteristics of study participants

		UACR change over 2 years			
	Study registration (baseline)	Decrease in UACR ≥30%	Minor change in UACR (decrease <30% to increase <30%)	Increase in UACR ≥30%	*P* value for trend
Number of participants	8,766	2,961	2,297	3,508	—
Demographic factors					
Age (years)	66 (6)	66 (6)	66 (6)	66 (6)	0.50
Female [*n* (%)]	3,730 (43)	1,235 (42)	961 (42)	1,534 (44)	0.10
Residence in Asia [*n* (%)]	3,522 (40)	1,230 (42)	928 (40)	1,364 (39)	0.03
Medical and lifestyle history					
Duration of diabetes (years)	7.8 (6.3)	7.9 (6.3)	7.5 (6.1)	7.9 (6.4)	0.57
History of macrovascular disease at baseline [*n* (%)]	2,703 (31)	900 (30)	681 (30)	1,122 (32)	0.15
Current smoking [*n* (%)]	1,288 (15)	418 (14)	341 (15)	529 (15)	0.28
Current alcohol drinking [*n* (%)]	2,596 (30)	875 (30)	712 (31)	1,009 (29)	0.44
Risk factors					
SBP (mmHg)	145 (21)	146 (22)	144 (21)	144 (21)	<0.001
DBP (mmHg)	81 (11)	81 (11)	80 (11)	80 (11)	<0.001
Heart rate (bpm)	74 (12)	75 (12)	74 (12)	74 (12)	0.02
Hemoglobin A_{1c} (%)	7.48 (1.54)	7.51 (1.56)	7.47 (1.51)	7.46 (1.52)	0.15
Hemoglobin A_{1c} (mmol/mol)	58.2 (16.8)	58.6 (17.1)	58.1 (16.5)	58.0 (16.7)	—
Total cholesterol (mmol/L)	5.2 (1.2)	5.2 (1.2)	5.2 (1.2)	5.2 (1.2)	0.07
Triglycerides* (mmol/L)	1.6 (1.2–2.3)	1.7 (1.2–2.4)	1.6 (1.2–2.3)	1.6 (1.2–2.3)	0.17
BMI (kg/m^2)	28.2 (5.2)	28.3 (5.3)	28.1 (5.1)	28.2 (5.2)	0.32
Randomized treatments [*n* (%)]					
Perindopril-indapamide	4,356 (50)	1,641 (55)	1,132 (49)	1,583 (45)	<0.001
Intensive blood glucose control	4,458 (51)	1,581 (53)	1,162 (51)	1,715 (49)	0.001
Blood glucose–lowering treatments [*n* (%)]					
Oral hypoglycemic agents^	7,954 (91)	2,695 (91)	2,067 (90)	3,192 (91)	0.98
Insulin	125 (1)	46 (2)	29 (1)	50 (1)	0.69
BP-lowering treatments [*n* (%)]					
β-Blocker	2,112 (24)	666 (22)	540 (24)	906 (26)	0.002
Calcium-channel blocker	2,666 (30)	957 (32)	635 (28)	1,074 (31)	0.18
Diuretics†	2,014 (23)	637 (22)	500 (22)	877 (25)	<0.001
ACE inhibitors†	3,706 (42)	1,194 (40)	960 (42)	1,552 (44)	0.001
Angiotensin II receptor blockers	441 (5)	158 (5)	114 (5)	169 (5)	0.35
Other antihypertensive agents	1,088 (12)	373 (13)	278 (12)	437 (12)	0.88
Any BP-lowering agents†	6,522 (74)	2,223 (75)	1,653 (72)	2,646 (75)	0.65
Changes in risk factors					
First UACR* (μg/mg)	14.1 (7.1–37.1)	29.8 (14.1–79.6)	12.2 (7.1–26.5)	8.8 (4.4–19.4)	<0.001
Second UACR* (μg/mg)	—	8.8 (4.4–19.4)	12.0 (6.9–26.5)	26.4 (11.6–72.5)	<0.001
First eGFR (mL/min/1.73 m^2)	75 (17)	76 (18)	76 (17)	75 (17)	0.09
Second eGFR (mL/min/1.73 m^2)	—	72 (18)	72 (18)	72 (17)	0.79
First SBP (mmHg)	145 (21)	146 (22)	144 (21)	144 (21)	<0.001
Second SBP (mmHg)	—	136 (18)	137 (18)	139 (19)	<0.001

Mean values and their corresponding SDs are presented for continuous variables unless otherwise noted. Categorical variables are presented as numbers and percentages [*n* (%)]. DBP, diastolic BP; SBP, systolic BP. *Median values (IQI) are presented for triglycerides and UACR. ^Randomized treatment with gliclazide was not included. †Randomized treatment with perindopril-indapamide was not included.

UACR and study outcomes were much stronger and reached significance for all outcomes but major renal events. Overall findings were consistently observed across various patient subgroups including those defined by baseline UACR, kidney function, and systolic BP. Our results suggest that clinically meaningful changes in UACR, up or down, may translate to corresponding changes in the risk of future major clinical outcomes and death in people with type 2 diabetes.

Cardiovascular disease remains the leading cause of morbidity and mortality in type 2 diabetes (24), whereas diabetes is the primary cause of end-stage kidney disease (ESKD) (25,26), a condition that places a heavy burden on patients as well as health care systems. As such, improved strategies for the prevention and/or delay of cardiovascular and kidney disease in diabetes are needed. Albuminuria has been proposed as a potentially useful therapeutic target and surrogate for long-term risk of clinical outcomes based on: *1*) evidence showing a strong, graded association between baseline levels of albuminuria and cardiovascular and renal outcomes (27,28), *2*) the early time point at which it frequently occurs on the spectrum of disease progression, and *3*) the simple and inexpensive nature of its measurement in routine clinical practice. There are also plausible pathophysiologic processes that explain the underlying relationship between albuminuria and cardiovascular and renal events including dysfunction of the vascular endothelium (29,30) and chronic, low-grade inflammation. However, although the link between albuminuria and cardiovascular disease has been well reported (2,27), data on

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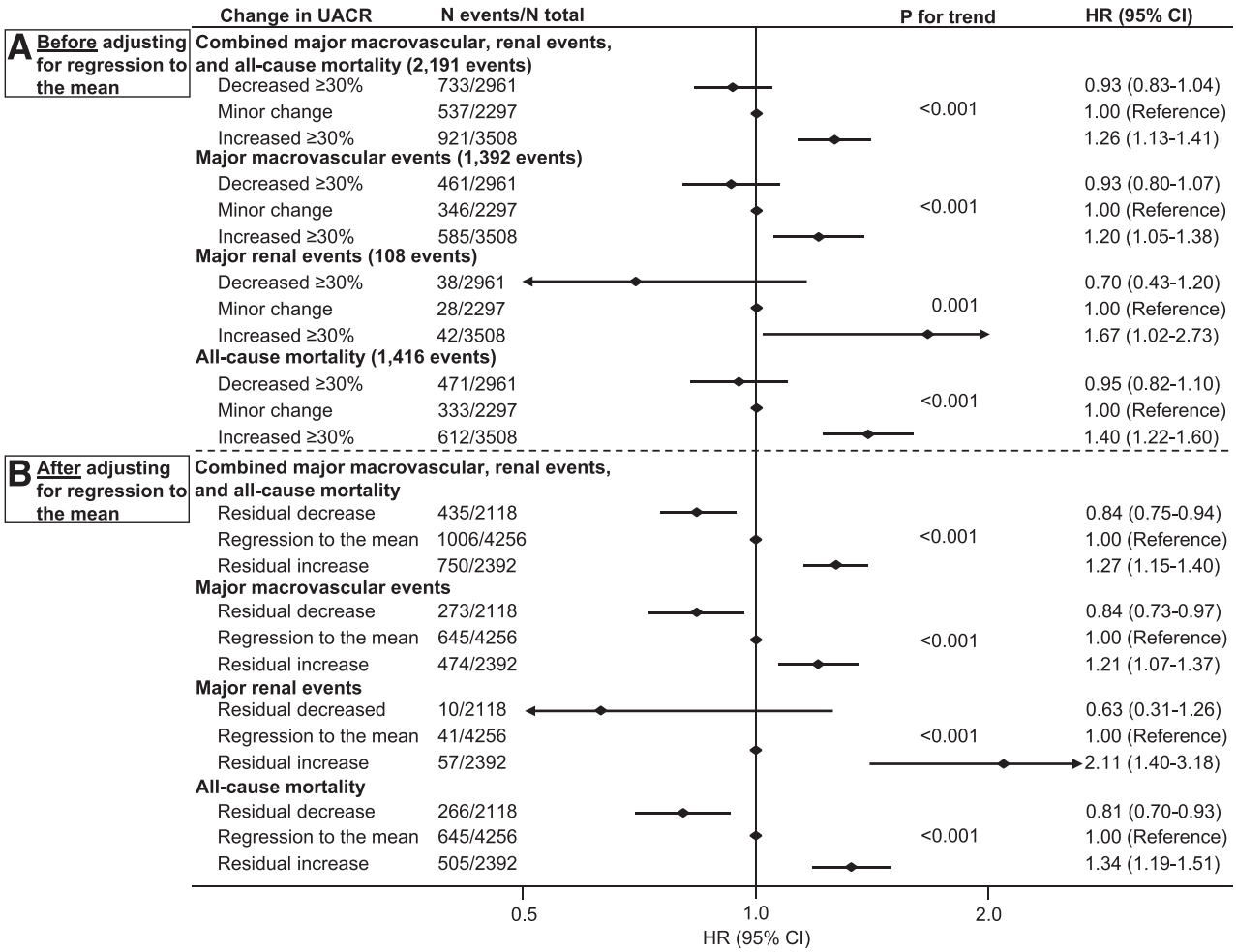

Figure 1—Adjusted HRs and 95% CIs for study outcomes according to categorical change in UACR, before and after adjustment for RtM. *A*: Adjustments were for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, BMI, hemoglobin A_{1c}, total cholesterol, log-transformed triglycerides, eGFR, systolic BP, log-transformed baseline UACR, change in systolic BP, change in eGFR, and ADVANCE trial treatment allocations (randomized BP lowering and glucose control). *B*: Adjustments were for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, BMI, hemoglobin A_{1c}, total cholesterol, log-transformed triglycerides, eGFR, systolic BP, change in systolic BP, change in eGFR, and ADVANCE trial treatment allocations (randomized BP lowering and glucose control).

the predictive ability of UACR change for cardiovascular outcomes have been limited and conflicting. In particular, although there is accumulating evidence to support the predictive value of UACR increase in determining future risk, whether UACR reduction subsequently translates to lower risk of clinical outcomes remains less certain (4). For example, a recent study in type 1 diabetes showed that although progression to macroalbuminuria was associated with higher risk of cardiovascular events (HR 2.65; 95% CI 1.68–4.19) compared with normoalbuminuria, remitted microalbuminuria was also associated with an increased cardiovascular risk (HR 2.62; 95% CI 1.68–4.07) (16). In contrast, in an analysis of two prospective trials (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET] and the Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease [TRANSCEND]), ≥50% decline and ≥100% increase in albuminuria over 2 years compared with those who experienced minor change was subsequently associated with lower (HR 0.85; 95% CI 0.76–0.95) and higher (HR 1.38; 95% CI 1.26–1.51) cardiovascular risk, respectively (11).

In our study, although we observed an overall positive linear trend between change in UACR and clinical outcomes, the association was generally flat for UACR decrease. However, our results accounting for UACR decrease beyond levels attributed to RtM showed that decreases in UACR significantly predicted a lower risk of the primary outcome and major macrovascular events. It seems likely that natural variation in UACR has led to an underestimation of the association between UACR change and clinical outcomes in our study. To our knowledge, no previous study has accounted for RtM comprehensively, and this may explain some situations in which decreases in UACR have not led to decreases in event rates (16).

In addition to cardiovascular events, there has been particular interest in the utility of albuminuria change as a surrogate for ESKD in high-risk groups including those with diabetic nephropathy, given the often slowly progressing nature of CKD, which leads to practical challenges in the development of novel management strategies. Indeed, compared with other fields of internal medicine, nephrology has the lowest number of interventional studies testing potential therapies (31). Surrogates that reliably predict clinically meaningful long-term outcomes

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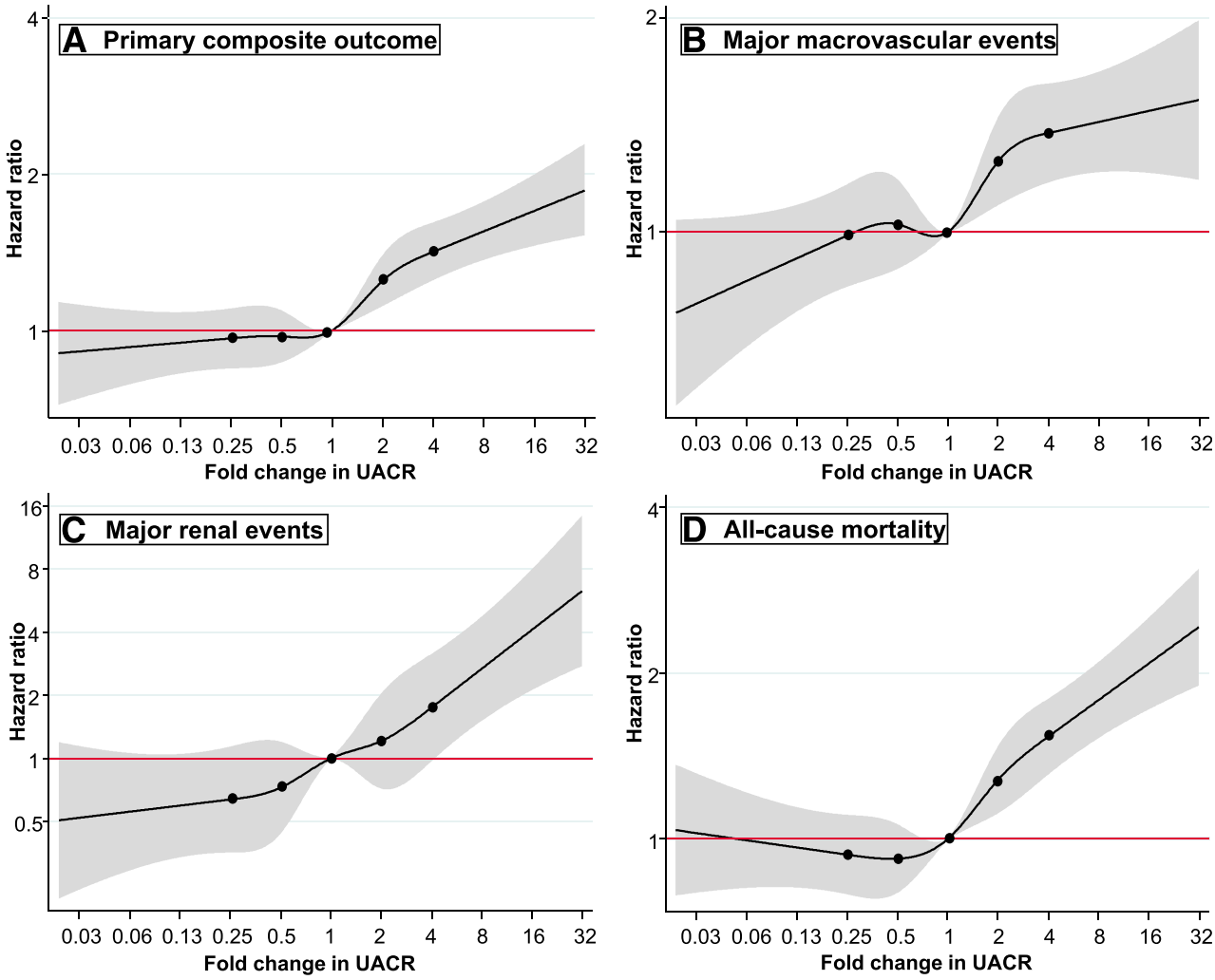

Figure 2—Adjusted HRs and 95% CIs for study outcomes associated with 2-year fold changes in UACR. Adjustments as for Fig. 1*A*. *A*: Composite of major macrovascular and renal events and all-cause mortality. *B*: Major macrovascular events. *C*: Major renal events. *D*: All-cause mortality. The circles represent the points at which knots were placed (0.25-, 0.5-, 1-, 2-, and 4-fold change). The areas shaded in grey represent the 95% CIs.

(e.g., ESKD) could be used in such settings to reduce the need for lengthy follow-up and large sample sizes in planning new studies. Although a significant association between UACR decline and lower risk of major renal events was not observed (possibly because of the relatively low ESKD event rate of 0.2% per year), our results showing a positive linear relationship between change in UACR and subsequent ESKD are largely consistent with two recent studies. A cohort study (n = 19,897 [13]) based on data on health care users in Stockholm, Sweden, showed that ≥4-fold decreases and ≥4-fold increases in UACR were associated with lower (HR 0.34; 95% CI 0.26–0.45) and higher (HR 3.08; 95% CI 2.59–3.67) ESKD risk, respectively, when compared with stable levels of UACR. Similarly, in the ONTARGET/TRANSCEND-based study, ≥50% decline and ≥100% increase in albuminuria compared with those who experienced minor change were subsequently associated with a 27% decrease and a 40% increase in ESKD risk, respectively (11). Taken together, our results add to a growing list of observational studies that suggest that an increase in albuminuria may be an effective surrogate for risk of ESKD.

The strengths of our study include: *1*) the assessment of the relationship between change in UACR and clinically important outcomes based on multiple approaches including one accounting for RtM, *2*) the large and diverse participant population (including Asia [40%], Australasia [14%], Europe [43%], and North America [3%]) derived from an international, multicenter randomized trial, and *3*) the long follow-up period that included the 5-year posttrial phase. Our study, however, has limitations. First, our calculation of the percent change in UACR was based on two UACR measurements at baseline and 2 years after the initial measurement (using single recordings at each time point). UACR measurements are associated with substantial within-person variability, and although our analyses of UACR change as a continuous variable showed consistent overall results, the possibility for misclassification of UACR change remains (32). We acknowledge the possibility that the use of multiple UACR measurements at each time interval might have reduced misclassification of the magnitude of UACR change. However, the consistency of our study methodology (pertaining to the frequency of UACR measurement and quantification of its change) and overall study conclusions

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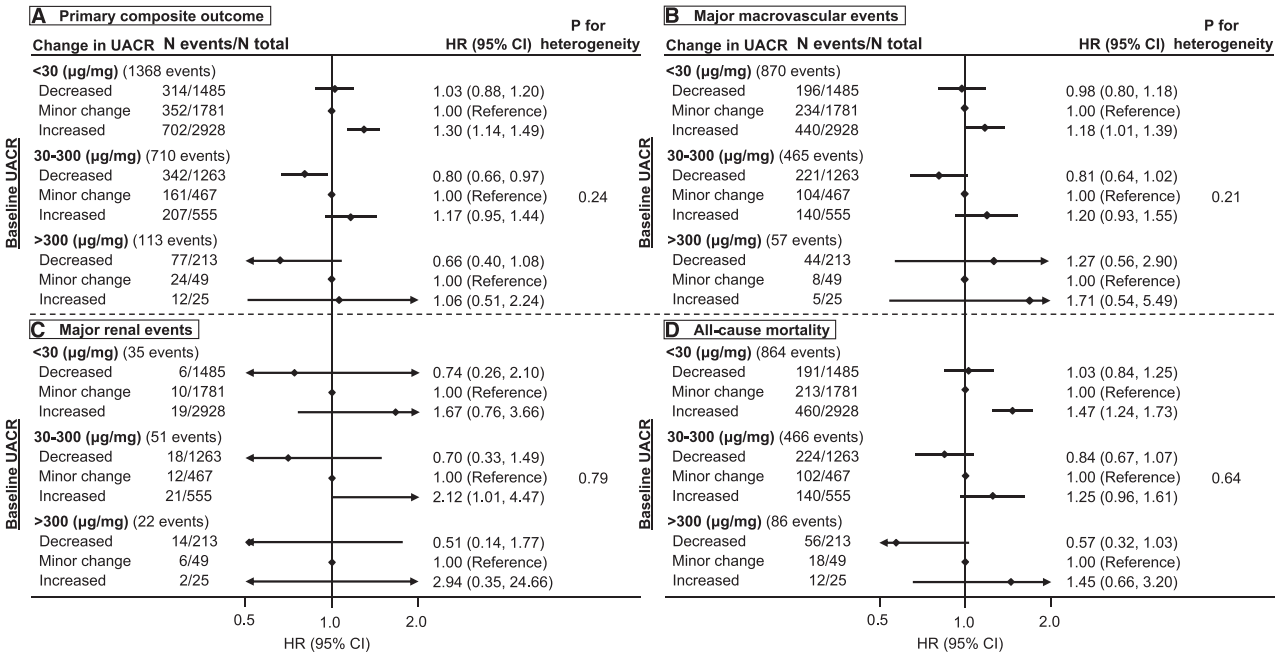

Figure 3—Adjusted HRs and 95% CIs for study outcomes according to baseline UACR levels. Adjustments as for Fig. 1*A*.

compared with prior studies (8,11) assessing the relationship between UACR change and clinical outcomes supports the robustness of our study findings. Second, although we have sought to explore the impact of RtM in our overall findings, our grouping of patients to define residual UACR decrease and increase is arbitrary and suggests the need for further research. Third, our study cohort was derived from a randomized trial of patients with type 2 diabetes, and therefore, the results have limited generalizability to broader populations. Fourth, only 84% of the participants alive at the end of ADVANCE were enrolled in the posttrial follow-up (ADVANCE-ON). However, patient baseline characteristics of those included in ADVANCE-ON were similar to those of the entire trial population (20). Fifth, the ESKD event rate in ADVANCE/ADVANCE-ON was relatively low (0.2% per year) compared with prior studies that have included people with diabetes (0.7–6.6% per year [11,33,34]), which may explain the lack of a significant association between UACR decline and lower risk of major renal events. Finally, despite our best efforts to adjust for clinically relevant characteristics, because of the nature of observational study design, the possibility of residual confounding remains.

In conclusion, 2-year changes in UACR were linearly associated in a positive fashion with the risk of study outcomes, including major clinical outcomes as well as all-cause mortality. Our results suggest that change in UACR may have important prognostic utility as a surrogate for clinically important outcomes in type 2 diabetes.

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Duality of Interest. S.Z. reports past participation in advisory boards and/or receiving honoraria from Amgen Australia, AstraZeneca/Bristol-Myers Squibb Australia, Janssen-Cilag, Merck Sharp & Dohme (Australia), Novartis Australia, Sanofi, Servier Laboratories, and Takeda Pharmaceutical Company Australia. S.C. reports receiving fees for serving on advisory boards and lecture fees from Servier Laboratories. G.M. reports personal fees from Servier Laboratories, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini Group, Recordati, and Takeda Pharmaceutical Company. M.M. received personal fees from Novo Nordisk, Sanofi, Eli Lilly and Company, Merck Sharp & Dohme, Abbott, Novartis, Servier Laboratories, and AstraZeneca and grant support from Novo Nordisk, Sanofi, Eli Lilly and Company, Merck Sharp & Dohme, and Novartis. D.M. has received personal fees from Servier Laboratories. N.P. received honoraria from Servier Laboratories, Takeda Pharmaceutical Company, Menarini Group, and Pfizer; grant support from Servier Laboratories and Pfizer; and personal fees from Servier Laboratories, Takeda Pharmaceutical Company, Menarini Group, and Pfizer. B.W. reports personal fees from Servier Laboratories, Novartis, Boehringer Ingelheim, and Merck Sharp & Dohme. A.R. receives salary in part from George Health Enterprises, the social enterprise arm of The George Institute for Global Health (George Health Enterprises has received investment to develop fixed-dose combinations containing aspirin, statin, and BP-lowering drugs). V.P. reports honoraria for scientific lectures from Boehringer Ingelheim, Merck Sharp & Dohme, AbbVie, Roche, AstraZeneca, and Servier Laboratories and serves on steering committees and/or advisory boards supported by AbbVie, Astellas Pharma, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Pfizer. J.C. received research grants from Servier Laboratories for the ADVANCE trial and ADVANCE-ON posttrial follow-up and honoraria for speaking about these studies at scientific meetings. M.W. reports consultancy fees from Amgen. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. M.J., T.O., J.C., and M.W. contributed to the concept and rationale for the study and interpretation of the results and drafted the manuscript. M.J. and T.O. conducted statistical analysis with advice from M.W. M.J., T.O., S.Z., S.C., G.M., M.M., D.M., N.P., B.W., A.R., V.P., J.C., and M.W. contributed to discussion and reviewed and edited the manuscript. M.W. and J.C. are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the

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integrity of the data and the accuracy of the data analysis.

References

1. Matsushita K, van der Velde M, Astor BC, et al.; Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010;375:2073–2081
2. Perkovic V, Verdon C, Ninomiya T, et al. The relationship between proteinuria and coronary risk: a systematic review and meta-analysis. PLoS Med 2008;5:e207
3. Smink PA, Lambers Heerspink HJ, Gansevoort RT, et al. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Am J Kidney Dis 2012;60:804–811
4. Fried LF, Lewis J. Albuminuria is not an appropriate therapeutic target in patients with CKD: the con view. Clin J Am Soc Nephrol 2015;10:1089–1093
5. Lambers Heerspink HJ, Gansevoort RT. Albuminuria is an appropriate therapeutic target in patients with CKD: the pro view. Clin J Am Soc Nephrol 2015;10:1079–1088
6. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309–2320
7. Atkins RC, Briganti EM, Lewis JB, et al. Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 2005;45:281–287
8. Imai E, Haneda M, Chan JC, et al. Reduction and residual proteinuria are therapeutic targets in type 2 diabetes with overt nephropathy: a post hoc analysis (ORIENT-proteinuria). Nephrol Dial Transplant 2013;28:2526–2534
9. Pavkov ME, Knowler WC, Hanson RL, Bennett PH, Nelson RG. Predictive power of sequential measures of albuminuria for progression to ESRD or death in Pima Indians with type 2 diabetes. Am J Kidney Dis 2008;51:759–766
10. Yuyun MF, Dinneen SF, Edwards OM, Wood E, Wareham NJ. Absolute level and rate of change of albuminuria over 1 year independently predict mortality and cardiovascular events in patients with diabetic nephropathy. Diabet Med 2003;20:277–282
11. Schmieder RE, Mann JF, Schumacher H, et al.; ONTARGET Investigators. Changes in albuminuria predict mortality and morbidity in patients with vascular disease. J Am Soc Nephrol 2011;22:1353–1364
12. Inker LA, Levey AS, Pandya K, Stoycheff N, Okparavero A, Greene T; Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Early change in proteinuria as a surrogate end point for kidney disease progression: an individual patient meta-analysis. Am J Kidney Dis 2014;64:74–85
13. Carrero JJ, Grams ME, Sang Y, et al. Albuminuria changes are associated with subsequent risk of end-stage renal disease and mortality. Kidney Int 2017;91:244–251
14. Lea J, Greene T, Hebert L, et al. The relationship between magnitude of proteinuria reduction and risk of end-stage renal disease: results of the African American study of kidney disease and hypertension. Arch Intern Med 2005;165:947–953
15. Heerspink HJ, Kröpelin TF, Hoekman J, de Zeeuw D; Reducing Albuminuria as Surrogate Endpoint (REASSURE) Consortium. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. J Am Soc Nephrol 2015;26:2055–2064
16. de Boer IH, Gao X, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Albuminuria changes and cardiovascular and renal outcomes in type 1 diabetes: the DCCT/EDIC Study. Clin J Am Soc Nephrol 2016;11:1969–1977
17. ADVANCE Management Committee. Study rationale and design of ADVANCE: Action in Diabetes and Vascular Disease–Preterax and Diamicron MR Controlled Evaluation. Diabetologia 2001;44:1118–1120
18. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
19. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
20. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406
21. MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1, Prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. Lancet 1990;335:765–774
22. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
23. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the evaluation and management of chronic kidney disease. Kidney Int 2013;(Suppl. 3):1–150
24. Australian Institute of Health and Welfare. Deaths from diabetes [Internet], 2014. Available from https://www.aihw.gov.au/reports/diabetes/diabetes-compendium/contents/deaths-from-diabetes. Accessed 15 May 2017
25. Afkarian M, Zelnick LR, Hall YN, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016;316:602–610
26. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864–2883
27. Ninomiya T, Perkovic V, de Galan BE, et al.; ADVANCE Collaborative Group. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 2009;20:1813–1821
28. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 1997;157:1413–1418
29. Stehouwer CD. Endothelial dysfunction in diabetic nephropathy: state of the art and potential significance for non-diabetic renal disease. Nephrol Dial Transplant 2004;19:778–781
30. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989;32:219–226
31. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. J Am Soc Nephrol 2004;15:411–419
32. Selvin E, Juraschek SP, Eckfeldt J, Levey AS, Inker LA, Coresh J. Within-person variability in kidney measures. Am J Kidney Dis 2013;61:716–722
33. Brenner BM, Cooper ME, de Zeeuw D, et al.; RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–869
34. Appel LJ, Wright JT Jr, Greene T, et al.; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 2010;363:918–929

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