

# **Changes in albuminuria and the risk of major clinical outcomes in diabetes: results from ADVANCE-ON**

\*Min Jun<sup>1</sup>, \*Toshiaki Ohkuma<sup>1</sup>, Sophia Zoungas<sup>1,2</sup>, Stephen Colagiuri<sup>3</sup>, Giuseppe Mancia<sup>4</sup>, Michel Marre<sup>5-7</sup>, David Matthews<sup>8</sup>, Neil Poulter<sup>9</sup>, Bryan Williams<sup>10</sup>, Anthony Rodgers<sup>1</sup>, Vlado Perkovic<sup>1</sup>, John Chalmers<sup>1</sup>, Mark Woodward<sup>1,11,12</sup>

On behalf of the ADVANCE Collaborative Group

\*Contributed equally

## Affiliations:

1. The George Institute for Global Health, University of New South Wales, Sydney, Australia
2. School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
3. Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, Sydney Medical School, University of Sydney, Sydney, New South Wales, Australia
4. Istituto Auxologico Italiano, University of Milan-Bicocca, Milan, Italy
5. INSERM, UMRS 1138, Centre de Recherche des Cordeliers, Paris, France
6. Department of Diabetology, Endocrinology and Nutrition, Assistance Publique-Hôpitaux de Paris, Bichat Hospital, DHU FIRE, Paris, France
7. Université Paris Diderot, Sorbonne Paris Cité, UFR de Médecine, Paris, France
8. University of Oxford, Oxford Centre for Diabetes, Endocrinology and Metabolism, UK
9. International Centre for Circulatory Health, Imperial College, London, UK
10. Institute of Cardiovascular Sciences, University College London (UCL) and National Institute of Health Research UCL Hospitals Biomedical Research Centre, London, U.K.
11. The George Institute for Global Health, University of Oxford, UK
12. Department of Epidemiology, Johns Hopkins University, Baltimore MD, USA

Corresponding author:

John Chalmers

The George Institute for Global Health, University of New South Wales, Sydney, Australia

Level 10, King George V Building

Royal Prince Alfred Hospital, Missenden Rd

Camperdown NSW 2050 Australia

Email: [chalmers@georgeinstitute.org.au](mailto:chalmers@georgeinstitute.org.au)

Phone: +61 2 8052 4586

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## ABSTRACT

**Objective:** To assess the association between two-year changes in urine albumin-to-creatinine ratio (UACR) and the risk of clinical outcomes in type 2 diabetes (T2DM).

**Research Design and Methods:** We analyzed data from 8766 participants in the ADVANCE-ON study. Change in UACR was calculated from UACR measurements two years apart, classified into three groups: decrease in UACR of  $\geq 30\%$ , minor change and increase in UACR of  $\geq 30\%$ . 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, 2191 primary outcomes were observed. Increases in UACR over two years independently predicted a greater risk of the primary outcome (HR for  $\geq 30\%$  UACR increase versus minor change: 1.26, 95% confidence interval [CI]: 1.13-1.41) while 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), whilst the estimated effect on an increase was unchanged.

**Conclusions:** Changes in UACR predicted changes in the risk of major clinical outcomes and mortality in T2DM, supporting the prognostic utility of monitoring albuminuria change over time.

**Keywords:** albuminuria, UACR, type 2 diabetes, cardiovascular events, end-stage renal disease

**Abbreviations:** ACR=albumin-to-creatinine ratio

Albuminuria is a strong predictive marker for adverse cardiovascular and renal outcomes among patients with diabetes.<sup>1-3</sup> 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.<sup>4,5</sup> 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?

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 1647 patients<sup>6-10</sup>), had relatively short durations of follow-up for outcomes (<3 years<sup>11,12</sup>) 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<sup>12-15</sup>. In addition, while some studies have shown positive linear associations between albuminuria change and subsequent clinical outcomes,<sup>11,13</sup> a recent study in type 1 diabetes found no association between albuminuria remission and subsequent renal events.<sup>16</sup> 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-MR Controlled Evaluation (ADVANCE), a randomized controlled trial (RCT) in patients with

type 2 diabetes and its post-trial follow-up (ADVANCE-ON), we evaluated the associations between two-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 2x2 factorial RCT 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.<sup>17-19</sup> In brief, a total of 11,140 individuals with type 2 diabetes aged  $\geq 55$  years at high risk of cardiovascular events were recruited from 215 centres 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 (modified release)-based intensive glucose control regimen aiming to achieve a hemoglobin A1c  $\leq 6.5$  %, or standard glucose control based on local guidelines. There were no inclusion or exclusion criteria related to blood pressure 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 blood pressure and glucose-lowering trial interventions were 4.4 and 5.0 years, respectively. The ADVANCE-Observational (ADVANCE-ON) study was a post-trial follow-up study, comprising 8494 of the 10,082 surviving participants at the end of the randomized treatment phase.<sup>20</sup> 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 post-trial follow-up phase were obtained from the institutional review board of each centre, and all participants provided written informed consent.

Participants with UACR measurements at study registration and two years after randomization were eligible for inclusion into the current study. Patients with major macrovascular or renal events or death during the first two years, those with missing UACR values at study registration (at the beginning of the 6-week run-in period prior to randomisation) or two 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 two-year visit until the earliest of the first study event, death or the end of follow-up (Supplemental Figure S1). Study events recorded during the randomized treatment phase were reviewed and validated by an independent end-point adjudication committee. Outcomes occurring during post-trial follow-up were reported by the study centres using the standardized definitions adopted during the trial, without central adjudication.<sup>20</sup>

### *Statistical methods*

UACR was measured (in  $\mu\text{g}/\text{mg}$ ) at ADVANCE trial registration, two and four 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 (hereinafter referred to as the “first UACR”) to two years after randomization. Change in UACR was defined by grouping UACR as in previous reports<sup>6,15</sup> as: decrease in UACR of  $\geq 30\%$ , minor change in UACR (decrease of UACR  $< 30\%$  to increase  $< 30\%$ ) and increase in UACR of  $\geq 30\%$ . 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).<sup>21</sup> 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 more, or experienced minor change for the highest third, at two 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 more were considered to have a “real” residual decrease, or experienced minor change for the lowest third, over and above RtM (Supplemental Figure S2). We computed the regression dilution coefficient using the MacMahon-Peto method<sup>21</sup> 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 standard deviation (SD) for variables with approximately symmetric distributions. UACR and triglycerides values are presented as median and interquartile interval (IQI) due to 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% confidence intervals (CIs) for change in UACR adjusting for age, sex and region (Asia or other) of residence, ADVANCE trial treatment allocation (BP and glucose-lowering), baseline UACR duration of diabetes mellitus, history of macrovascular disease, current smoking, current alcohol consumption, BMI, hemoglobin A1c, total cholesterol, triglyceride, estimated glomerular filtration rate [eGFR; calculated using the CKD-EPI creatinine equation<sup>22</sup> and grouped into KDIGO eGFR categories<sup>23</sup>], systolic BP and percent two-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 other), duration of diabetes, age at completion of education, baseline history of cardiovascular disease, ADVANCE randomized treatment allocation, UACR (<30, 30-300 or >300  $\mu\text{g}/\text{mg}$ ), systolic BP (<120, 120-140 or >140 mmHg) and eGFR (<60 or  $\geq 60$  ml/min/1.73m<sup>2</sup>) levels. We conducted sensitivity analysis where we repeated the assessment of



the association between overall categorical UACR change and outcomes after imputing missing UACR (n=1496 patients) and covariate (n=227 patients) values for 1723 patients.

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

## **Results**

### *Patient characteristics*

Of the 11,140 participants in the ADVANCE trial, 8766 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=6194), 24% (n=1485) and 47.3% (n=2928) experienced a decrease in UACR  $\geq$ 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 two-year period. Conversely, patients with UACR levels 30-300 µg/mg (n=2285), 55.3% (n=1263) and 24.3% (n=555) experienced a decrease in UACR  $\geq$ 30% and an increase in UACR, respectively. Overall, in those with 30-300 µg/mg, UACR levels decreased by a median of -21 µg/mg (IQR: -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  $\geq 30\%$  and an increase in UACR, respectively, with an overall decrease of -315 (IQI: -471 to -121  $\mu\text{g}/\text{mg}$ ). Overall, at the two-year follow up, 33.8% (2961/8766) experienced a UACR decrease of  $\geq 30\%$ , 26.2% (2297/8766) experienced minor change and 40.0% (3508/8766) experienced an increase in UACR of  $\geq 30\%$ .

#### *Clinical events during follow-up*

During a median 9.7 years (IQI: 5.9 to 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 (Supplemental Figure S3).

During a median 7.7 years (IQI: 3.9 to 8.8) following the two-year period in which change in UACR was measured, 2191 patients (25.0%) developed the primary composite outcome (1457 events during ADVANCE-ON). There were 1392 major macrovascular events (15.9%), 108 major renal events (1.2%) and 1416 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 (Figure 1A and 2). Compared with patients who experienced a minor change in UACR (less than 30% up or down), the risk of the primary outcome was significantly higher among those with an increase in UACR of  $\geq 30\%$  (HR 1.26, 95% CI: 1.13-1.41), while 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 to minor change (Figure 1A). 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 (Figure 2). For the outcome of all-cause mortality, while an increase in UACR was predictive of higher risk, the association was flat for decreasing UACR.

### *Regression to the mean*

As expected, there was strong evidence of RtM (Supplemental Figure S4): 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%; Supplemental Figure S2). After accounting for RtM the effects of a decrease in UACR were greater, but the effects of an increase were similar (Figure 1B). 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 (Figure 3). Additional analysis by eGFR and systolic BP (Supplemental Figure S5); sex, age, region of residence, duration of diabetes, age at completion of education, history of cardiovascular disease and randomized treatment allocation (blood pressure and

glucose-lowering; Supplemental Figure S6) 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 (Supplemental Figure S7).

## **Conclusions**

In a cohort of 8766 patients with type 2 diabetes, we observed an overall positive linear association between two-year changes in UACR and the future risk of major clinical outcomes. Increases in UACR over two years was 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 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<sup>24,25</sup> while diabetes is the primary cause of end-stage kidney disease (ESKD)<sup>26,27</sup>, a condition which places a heavy burden on patients as well as healthcare 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,<sup>28,29</sup> 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<sup>30,31</sup> and chronic, low-grade inflammation. However, while the link between albuminuria and cardiovascular disease has been well-reported,<sup>2,28</sup> data on the predictive ability of UACR change for cardiovascular outcomes have been limited and conflicting. In particular, while 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.<sup>4</sup> For example, a recent study in type 1 diabetes showed that while 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).<sup>16</sup> 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]),  $\geq 50\%$  decline and  $\geq 100\%$  increase in albuminuria over two 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.<sup>11</sup>

In our study, while 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 studies have accounted for RtM, and this may explain some situations where decreases in UACR have not led to decreases in event rates.<sup>16</sup>

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 lead 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.<sup>32</sup> Surrogates which reliably predict clinically meaningful long-term outcomes (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. Whilst a significant association between UACR decline and lower risk of major renal events was not observed (possibly due to 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=19897<sup>13</sup>) based on data on health care users in Stockholm, Sweden, showed that  $\geq 4$ -fold decreases and  $\geq 4$ -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,  $\geq 50\%$  decline and  $\geq 100\%$  increase in albuminuria compared with those who experienced minor change was subsequently associated with a 27% decrease and a 40% increase in ESKD risk, respectively.<sup>11</sup> Taken together, our results add to a growing list of observational studies which 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 which included the five-year post-trial phase. Our study, however, has limitations. First, our calculation of the percent change in UACR was based on two UACR measurements at baseline and two 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.<sup>33</sup> 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 compared with prior studies<sup>8,11</sup> assessing the relationship between UACR change and clinical outcomes supports the robustness of our study findings. Second, whilst 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 post-trial follow-up (ADVANCE-ON). However, patient baseline characteristics of those included in ADVANCE-ON were similar to those of the entire trial population.<sup>20</sup> Fifth, the ESKD event rate in ADVANCE/ADVANCE-ON was relatively low (0.2% per year) compared with prior studies which have included people with diabetes (0.7-6.6% per year<sup>11,34,35</sup>) 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, due to the nature of observational study design, the possibility of residual confounding remains.

In conclusion, two-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**

MW reports consultancy fees from Amgen. SZ 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 Australia. SC reports receiving fees for serving on advisory boards and lecture fees from Servier. GM reports personal fees from Servier, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Medtronic, Novartis, Menarini International, Recordati, and Takeda. MM received personal fees from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme, Abbott, Novartis, Servier and Astra-Zeneca, and grant support from Novo Nordisk, Sanofi, Eli Lilly, Merck Sharp and Dohme, and Novartis. NP received honoraria from Servier, Takeda, Menarini and Pfizer, and grant support from Servier and Pfizer. DRM has received personal fees from Servier. NP reports grants from Servier, Pfizer, DUK, BHF, and HTA, and personal fees from Servier, Takeda, Menarini, and Pfizer. BW reports personal fees from Servier, Novartis, Boehringer Ingelheim, and MSD. AR receives salary in part from George Health Enterprises, the social enterprise arm of The George Institute. George Health Enterprises has received investment to develop fixed dose combinations containing aspirin, statin and blood pressure lowering drugs. VP reports honoraria for scientific lectures from Boehringer Ingelheim, Merck, AbbVie, Roche, AstraZeneca, and Servier and serves on steering committees and/or advisory boards supported by AbbVie, Astellas, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, and Pfizer. JC received research grants from the National Health and Medical Research

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### **Author contributions**

MJ, TO, JC, and MW contributed to the concept and rationale for the study and interpretation of the results, and drafted the manuscript. MJ and TO conducted statistical analysis with advice from MW. All authors contributed to discussion and reviewed and edited the manuscript. MW and JC are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Table 1: Characteristics of study participants**

| Variable  | Study registration<br>(baseline) | UACR change                     |  |                                 | <i>P</i> value<br>for<br>trend |
|---|----------------------------------|---------------------------------|--|---------------------------------|--------------------------------|
|   |                                  | Decrease in<br>UACR $\geq 30\%$ | Minor change<br>in UACR<br>(decrease<br><30% to<br>increase<br><30%) | Increase in<br>UACR $\geq 30\%$ |                                |
| Number of participants                              | 8,766                            | 2,961                           | 2,297  | 3,508                           |                                |
| <b>Demographic factors</b>                          |                                  |                                 |  |                                 |                                |
| Age (years)   | 66 (6)                           | 66 (6)                          | 66 (6)   | 66 (6)                          | 0.50                           |
| Female (%)  | 3,730 (43)                       | 1,235 (42)                      | 961 (42)   | 1,534 (44)                      | 0.10                           |
| Residence in Asia (%)                               | 3,522 (40)                       | 1,230 (42)                      | 928 (40)   | 1,364 (39)                      | 0.03                           |
| <b>Medical and Lifestyle history</b>                |                                  |                                 |  |                                 |                                |
| Duration of diabetes mellitus<br>(years)            | 7.8 (6.3)                        | 7.9 (6.3)                       | 7.5 (6.1)  | 7.9 (6.4)                       | 0.57                           |
| History of macrovascular<br>disease at baseline (%) | 2,703 (31)                       | 900 (30)                        | 681 (30)   | 1,122 (32)                      | 0.15                           |
| Current smoking (%)                                 | 1,288 (15)                       | 418 (14)                        | 341 (15)   | 529 (15)                        | 0.28                           |
| Current alcohol drinking (%)                        | 2,596 (30)                       | 875 (30)                        | 712 (31)   | 1009 (29)                       | 0.44                           |
| <b>Risk factors</b>                                 |                                  |                                 |  |                                 |                                |
| 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 <sub>1c</sub>                          |                                  |                                 |  |                                 |                                |
| (%)   | 7.48 (1.54)                      | 7.51 (1.56)                     | 7.47 (1.51)  | 7.46 (1.52)                     | 0.15                           |
| (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                           |
| Body mass index (kg/m <sup>2</sup> )                | 28.2 (5.2)                       | 28.3 (5.3)                      | 28.1 (5.1)   | 28.2 (5.2)                      | 0.32                           |
| <b>Randomized treatments</b>                        |                                  |                                 |  |                                 |                                |
| Perindopril-indapamide                              | 4,356 (50)                       | 1,641 (55)                      | 1,132 (49)   | 1,583 (45)                      | <0.001                         |
| Intensive blood glucose<br>control                  | 4,458 (51)                       | 1,581 (53)                      | 1,162 (51)   | 1,715 (49)                      | 0.001                          |

### Blood glucose-lowering treatments

|   |            |            |            |            |      |
|---|------------|------------|------------|------------|------|
| Oral hypoglycemic agents <sup>^</sup> (%) | 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

|   |            |            |            |            |        |
|---|------------|------------|------------|------------|--------|
| β-blocker (%)   | 2,112 (24) | 666 (22)   | 540 (24)   | 906 (26)   | 0.002  |
| Calcium-channel blocker (%)                               | 2,666 (30) | 957 (32)   | 635 (28)   | 1074 (31)  | 0.18   |
| Diuretics <sup>†</sup> (%)                                | 2,014 (23) | 637 (22)   | 500 (22)   | 877 (25)   | <0.001 |
| Angiotensin-converting enzyme inhibitors <sup>†</sup> (%) | 3,706 (42) | 1,194 (40) | 960 (42)   | 1552 (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 <sup>†</sup> (%)                   | 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/1.73m <sup>2</sup> )  | 75 (17)         | 76 (18)          | 76 (17)         | 75 (17)          | 0.09   |
| Second eGFR (ml/min/1.73m <sup>2</sup> ) |                 | 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 standard deviations (SDs) are presented for continuous variables unless described otherwise; \*median values (interquartile interval [IQI]) are presented for triglycerides and urine albumin-creatinine-ratio (UACR), categorical variables are presented as number (%); eGFR=estimated glomerular filtration rate; SBP=systolic blood pressure; <sup>^</sup>Randomized treatment with gliclazide was not included; <sup>†</sup>Randomized treatment with perindopril-indapamide was not included

### Figure legend

Figure 1: Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes according to categorical change in UACR, before and after adjustment for regression to the mean. Adjustments were for age, sex, region of residence, duration of diabetes, history of macrovascular diseases, smoking habit, drinking habit, body mass index, HbA1c, total cholesterol, log-transformed triglycerides, estimated glomerular filtration rate (eGFR) systolic blood pressure (BP) and ADVANCE trial treatment allocations (randomized blood pressure lowering and glucose control).

Figure 2: Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes associated with two-year fold changes in UACR. Adjustments as for Figure 1.

Figure 3: Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for study outcomes according to baseline UACR levels. Adjustments as for Figure 1.

### Table legend

Table 1: Characteristics of study participants at registration according to change in UACR

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