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# The Relationship between Urinary Albumin Excretion, Cardiovascular Outcomes and Total Mortality among Large Cohort of Insulin-Treated Patients with Type 2 Diabetes in Routine Primary Care Practices

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## Abstract

### Introduction

Albuminuria is a recognised diagnostic and prognostic marker of chronic kidney disease (CKD) and cardiovascular (CV) risk but the well-known relationship between increments in urinary albumin-creatinine ratio (ACR) and CV outcomes and mortality has not been fully explored in insulin treated patients with Type 2 Diabetes (T2D) in routine clinical care.

### Methods

We investigated data for insulin users with T2D from UK general practices between 2007 and 2014. Urinary ACR at the time of insulin initiation was measured and categorised as: <10mg/g; 10 to 29mg/g; 30 to 300mg/g; and >300mg/g. Patients were followed up for 5 years or the earliest occurrence of all-cause mortality, non-fatal myocardial infarction (MI) or stroke. Cox proportional hazard models were fitted to estimate the risk of a composite of these events.

### Results

A total of 12,725 patients with T2DM (mean age: 58.6±13.8 years, mean $HbA_{1c}$: 8.7±1.8) initiating insulin therapy between 2007 and 2014 met the inclusion criteria. Compared to patients whose ACR levels at insulin initiation were below 10mg/g, the adjusted risk of the 3-point composite endpoint was 9%, 30% and 98% higher in those with ACR levels between 10-29mg/g; 30-300mg/g and >300mg/g, respectively, after a follow up period of 5 years. ACR category on its own did not predict risk of all-cause mortality.

### Conclusion

This study shows that in patients with T2D on insulin therapy, increased urinary ACR is independently associated with an increased risk of major adverse CV events and all-cause mortality.

## Introduction

Several landmark studies have identified the elevated risk of end stage renal disease (ESRD) and cardiovascular (CV) disease conferred by albuminuria in addition to estimated GFR (eGFR). [1-4] These two distinct but complimentary methods to assess for the presence of chronic kidney disease (CKD) are widely used in routine clinical practice, with CKD due to diabetic nephropathy affecting 30-40% of patients with type 2 diabetes (T2D) [5]. Albuminuria is typically assessed by urinary albumin to creatinine ratio (ACR). Elevated ACR denote the presence of CKD, independent of eGFR categories [6,7]. ACR levels between 30mg/g to 300mg/g, represent moderately increased levels of albuminuria, known as microalbuminuria, while levels of more than 300mg/g is associated with frank proteinuria. In healthy adults, UACR is typically less than 10, but even small elevation in ACR between 10 mg/g and 29 mg/g have been shown to be associated with progression of renal disease and mortality. [8,9]

For many patients with T2D, insulin treatment will be required to control hyperglycaemia an to reduce the risk of long-term vascular complications in patients with T2D. [10-12]. Typically, this will involve the initiation of a basal or a biphasic insulin regimen, with some patients requiring multiple daily insulin injections with basal and prandial insulin. However, insulin therapy is known to induce ~4-9 kg weight gain in the first year of treatment. [13] This is relevant within the context of diabetic nephropathy since obesity is a significant risk factor for the appearance of proteinuria and ESRD. [14] Furthermore, recent evidence from randomized controlled trial, epidemiological and observational studies have implicated insulin therapy in patients with T2D with increased CV risk and mortality of [15-18],

possibly due to weight gain, recurrent hypoglycaemia, other potential adverse effects such as iatrogenic hyperinsulinemia as well as a surrogate marker of increased diabetes duration [19.20]. Thus, a cohort of insulin treated patients with T2D, represent a complex heteregenous, challenging group of patients, many of whom have significant comorbidities and high CV disease risk. The well-known relationship between increments in urinary ACR and CV outcomes and mortality has not been fully explored in insulin treated patients with Type 2 Diabetes (T2D) in routine clinical care.

## Methods

### Study Design:

This was a historic cohort study with UK primary care database - The Health Improvement Network (THIN) Database

THIN is a large UK electronic Primary Care database in which longitudinal records are obtained and updated from about 587 General Practices. It has details of over 12.4 million patients with about 3.61 million active users. Routine clinical information are constantly systematically entered into this database by trained doctors and specialist nurses. Data ranging from specialist or Primary Care consultations, diagnoses, laboratory results, prescriptions, referrals, hospital admissions, immunisations to important clinical measures such as body weight, height and body mass index (BMI). Also, information on the patients' demography, lifestyle characteristics (e.g. alcohol use and smoking), socio-economic status (Townsend deprivation scores), ethnicity, religion and languages are also included. THIN database has been validated and shown it to be demographically representative of the UK population in terms of demography, disease prevalence and mortality [21]. We have published extensively in our research group, using the THIN database in evaluating diabetes-related outcomes in routine clinical practice [22,23].

**Study Participants**

Routine clinical data on 12,725 people with a diagnosis of T2D; age >18 years; on insulin therapy between December 2006 and May 2014; and with recorded values of UACR .independent of e-GFR were obtained. We excluded patients with medical codes for type 1 or gestational diabetes, or other forms of diabetes, alongside those with no continuous regular prescriptions for insulin in their records.

**Follow-up and Endpoints**

From the point of insulin initiation (baseline date), the participants were divided based on the recorded Urinary albumin-to-creatinine ratio (UACR) from their medical records. UACR is usually measured from a single voided urine sample by a central laboratory, with the lowest detectable and reportable level of 1.0mg/g. In line with this, we categorized the patients based on their UACR level thus: less than10mg/g; 10mg/g to 29mg/g; 30mg/g to 300mg/g; and greater than 300mg/g.

The primary endpoint was a composite of the first occurrence of Major Adverse CV Events (MACE: all-cause mortality or non-fatal myocardial infarction or stroke). Participants were followed up from baseline date to either the primary endpoint or loss to follow-up; or discontinuation of insulin therapy; or at the end of the 5-year follow-up period. The secondary endpoint was the first occurrence of the components of the composite primary endpoint as defined above. All these outcomes were identified by their appropriate Read Codes in the database.

**Baseline and endpoint characteristics**

Data on important clinical covariates were also obtained in order to adjust for the possible confounding effects by the differences in their baseline characteristics. These included demographic variables such as age, gender, socioeconomic status, alcohol and smoking status; important clinical measures such as body weight, height, SBP and DBP; biochemical parameters, e.g. baseline $HbA_{1c}$, lipid-profile, use of other medications including other glucose-lowering therapies (GLTs); as well as comorbidity status, duration of diabetes treatment, and duration of insulin use. These were included in our univariate analysis models

from which significant covariates (those which had a significant association with both the exposure and outcomes and changed the measure of effect by 10%) were added to the final Cox models.

**Statistical Analysis**

There were some missing data in some important baseline categories like $HbA_{1c}$, eGFR, weight, SBP and DBP at baseline. A small proportion of these values were completely missing at random (MAR). These missing values were then computed using multiple imputations using the chained equation (MICE) model.

We computed summary data for the mean, standard deviations and proportions of the baseline characteristics. Baseline categorical variables within the UACR categories were compared using Pearson's chi-squared test and continuous variables with linear regression.

Event rates were presented as 5-year Kaplan-Meier estimates. For the endpoint of composite of MACE, Cox proportional hazard model was used to estimate the marginal and adjusted hazard ratios (HRs) with 95% confidence intervals, comparing the outcomes in all other baseline UACR categories to the <10mg/g category. Multivariate Cox regression models evaluating the association between UACR and the defined clinical endpoints were adjusted for the identified significant baseline covariates. Also, UACR was analysed as continuous variables based on the defined endpoints.

We tested for violations of the proportional hazard assumption of the Cox regression model, first by adding an interaction term of the predictor; secondly by log-minus-log survival curves; and thirdly by Schoenfeld residuals tests.

All the point estimates were computed with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05, using Stata Software version 14.

**Ethical Approval:**

We obtained ethical approval for this study was obtained from the South-East Research Ethics Committee.

## Results

### Patient Characteristics.

A total of 12,725 new insulin users with T2D with a mean age 58.6±14 years met our inclusion criteria. Among these, 29% (n = 3727) had UACR value <10mg/g while half (n = 7519) were within 30 to 300mg/g (Table 1). Baseline $HbA_{1c}$ increased gradually by increasing UACR levels (p = 0.02); while eGFR decreased with increasing UACR (p = 0.002). Similarly, UACR levels were worse with increasing obesity (p = 0.01) and in those on antihypertensive (p < 0.001). Table 1 summarises the baseline characteristics of the study participants.

### Baseline UACR vs Major Adverse Cardiovascular Events (3-point MACE)

**Crude Event Rates:** Table 2 show the proportion of the 3-point composite event, as well as the component events of all-cause mortality, non-fatal stroke and MI after a 5-year follow up period. It shows a stepwise increase in the incidence of all CV events according to baseline UACR categories and this was significant got the primary composite endpoint and all-cause mortality (p <0.001).

Similarly, the 5-year probability of survival for the 3-point composite endpoint was significantly lower (90% vs 90% vs 88% vs 83%) with increasing UACR categories of <10mg/g; 10 to 29mg/g; 30 to 300mg/g and >300mg/g (log rank test p-value = 0.0006) (Figure 1A).

For the components of all-cause mortality, non-fatal stroke and MI, Figures 1B to 1D showed the same trend of 5-year survival in the Kaplan-Meier plots shown.

**Composite Cardiovascular Outcomes:** Table 3 also shows a stepwise increase in the incidence and hazard of the composite endpoint according to baseline UACR categories. With UACR as a continuous variable in the adjusted multivariable Cox regression model, UACR was significantly associated with the risk of the 3-point composite endpoint, such that each unit increase in UACR was associated with a 14% increase in risk (p < 0.001). Similarly, for all-cause mortality, a unit increase in UACR was associated with an 18%

increase in the risk of all-cause mortality ($p < 0.0001$). However, this was not significant for non-fatal stroke ($p = 0.219$) or MI ($p = 0.101$).

In the UACR categories, worsening levels (above 300mg/g) were significantly associated with almost a two-fold (aHR = 1.98; 95% CI: 1.12 – 3.56) increase in the risk of the 3-point composite endpoint. However, this risk was non-significantly 95% higher (aHR=1.96; 95%CI: 0.88 – 4.42) for all-cause mortality; 3-fold greater (aHR=3.14; 95%CI: 0.49 – 13.5) for non-fatal MI and 70% higher (aHR=1.70; 95%CI: 0.58 – 3.21) for non-fatal stroke. (Table 3)

## Discussion

In this study of 12,725 patients with insulin-treated T2D, we found that increased urinary ACR is independently associated with an increased risk of major adverse CV events such as non-fatal myocardial infarction, stroke and all-cause mortality. This observation demonstrates that quantitative information about albuminuria status independently enhances prediction of CV morbidity and mortality, thus expanding prior observations and supporting the hypothesis that ACR provides complementary insight into the association between diabetic kidney disease and CV and total mortality risk, even in this cohort of insulin treated T2D, which by definition is at high risk of CV disease and mortality. Currently, urinary ACR testing is recommended for all patients with T2D to assess for chronic kidney disease. Urinary ACR could therefore readily be used as a more formal tool for CV risk prognostication so as to tailor individualised aggressive CV risk management strategy for insulin treated T2D.

In patients with T2D, increased levels of urinary albumin is an early marker of microvascular disease due to diabetic nephropathy. Traditionally, a cut point of 30mg/g has been used to diagnosed microalbuminuria, at which point, patients should be commenced on a renin-angiotensin system (RAS) blocker in order to retard the progression of albuminuria and diabetic nephropathy. Our study showed that, even low level elevations in ACR (10-29mg/dl) are associated with increased CV risk when compared with patients with ACR of less than 10 mg/g. Findings from this study therefore is clinically relevant and that ACR status will successfully identify high-risk patients at risk of CV events. However, whether increased ACR is a cause or simply a risk marker of CV risk such that reducing ACR would improve CV outcomes remains unclear and is beyond the remit of this present study. Nonetheless,

recent data suggest that in addition to RAS inhibitors, several glucose lowering treatment such as sodium-glucose cotransporter-2 inhibitors [24,25], and glucagon-like peptide-1 agonist [26,27], have been shown to improve ACR, as well as CV outcomes and induce weight loss. While the mechanism for the reduction of CV outcome remains unclear, concurrent use of these glucose lowering therapy with insulin are used widely. In a previous study within this same population cohort, we showed that the use of GLP-1 with insulin is associated with reduced cardiovascular event and total mortality compared with insulin alone. [23] Thus identification of patients at high risk of CV events based on ACR status, would not only trigger application of aggressive CV reduction strategy, but also concurrent use of appropriate glucose lowering therapies with favourable effects of weight, albuminuric and CV outcomes.

The association between albuminuria and CV mortality and end-stage kidney disease are well described in patients with T2D as well as in large heterogenous populations with multiple aetiologies of CKD. [28,29,30] However, none of these studies have been conducted specifically on insulin treated patients with T2D receiving routine care in primary care practices. While it is likely that the majority of patients within this cohort have CKD due to diabetic nephropathy, it is conceivable that other underlying aetiologies of albuminuria associated with CKD are also present. Specifically, Obesity-related glomerulopathy (ORG) has increasingly been reported in more and more obese patients without overt diabetes and pre-existing renal diseases [31]. It is a secondary form of focal and segmental glomerulosclerosis (FSGS) manifested as proteinuria and progressive renal dysfunction [32]. This is relevant within this cohort, due to the well recognised association between insulin treatment with adverse weight outcomes. Furthermore, previous studies have shown that weight loss intervention benefited remission of proteinuria in patients with ORG. [33]

The main strength of our study derives from the inclusion of a large cohort of patients with T2D receiving insulin therapy in a real-world population which is largely representative of the UK population. This implies that our findings will be generalizable to various population that share similar demographics. The large cohort of patients studied here provides adequate statistical power and also contains information on other time-varying covariates to adjust for possible confounders. We adjusted for a large set of factors that could have differed at the baseline. Nevertheless, some residual confounding in our study could persists. For example, our classification of albuminuria was largely based on a single measurement, in contrast to current recommendation, in which at least two measurements are required. Nonetheless, a single measure of urinary albumin within a large patient cohort provides a great deal of predictive information. In addition, as is the case in all studies of CV or ESRD risk associated with eGFR and albuminuria, the effect of competing hazards may bias estimates of risk. This is because elevated ACR and low eGFR are also risk factors for non-renal diseases, associated differential mortality in high-risk individuals may confound hazard ratio estimates for CV events. Although our rates of micro- (59%) and macroalbuminuria (0.6%) seemed higher and a lower respectively as previously reported, our findings were in keeping with patterns seen in similar studies. [34] Similarly, the lower rate of the first occurrence of stroke before MI in this study could reflect some possible way in which these were coded in the dataset. Nonetheless, our data were a true reflection of similar studies. Lastly, changes after baseline in medications and subsequent changes in glycaemic indices or blood pressure were not evaluated in this analysis and therefore cannot account for any differences that might influence the association between ACR and outcomes.

In conclusion, elevated levels of ACR, even within the normoalbuminuric range, are independently associated with increased risk of CV event and all-cause mortality in insulin treated patients with T2D, even after adjusting for known CV risk factors and eGFR. In view of recent advances in the management of CV disease and proteinuria, beyond conventional CV risk management strategy, this information will provide useful information to identify and prognosticate high risk patients with T2D patients who are in insulin to receive additional cardio-protective management strategy.

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## Legend

Table 1 - Baseline Characteristics

Table 2 - Proportion of endpoint events by the UACR categories (5-year Kaplan-Meier Estimates)

Table 3 - Risk of Composite Endpoints Events per Levels of UACR

Figure 1 - Kaplan-Meier survival analysis plot for (A) 3-point Composite Endpoint (log-rank test p value = 0.006). (B) All-cause Mortality (log-rank test p value = 0.007). (C) Non-fatal Acute Myocardial Infarction (log-rank test p value = 0.554). (D) Non-Fatal Stroke (log-rank test p value = 0.264).

Table 1: Baseline Characteristics

| Baseline Variables | UACR Category | | | | |
|---|---|---|---|---|---|
| | <10mg/g (n = 3727) | 10 to 29mg/g (n = 1401) | 30 to 300mg/g (n = 7519) | >300mg/g (n = 78) | Total (n = 12,725) |
| **Demographics** | | | | | |
| Age (yrs), Mean (SD) | 57.3 (13.8) | 57.8 (13.6) | 59.4 (13.8) | 62.4 (13.5) | 58.6 (13.8) |
| Gender, No. (%) | | | | | |
| Male | 1886 (51) | 674 (48) | 3743 (50) | 42 (54) | 6345 (50) |
| Townsend deprivation, No. (%) | | | | | |
| Least deprived | 805 (22) | 264 (20) | 1470 (21) | 15 (20) | 2554 (21) |
| 2nd quintile | 719 (20) | 287 (21) | 1448 (20) | 17 (23) | 2471 (20) |
| 3rd quintile | 787 (22) | 294 (22) | 1581 (22) | 15 (20) | 2677 (22) |
| 4th quintile | 742 (21) | 295 (22) | 1514 (21) | 19 (25) | 2570 (21) |
| Most deprived | 545 (15) | 207 (15) | 1157 (16) | 9 (12) | 1918 (16) |
| **Clinical Parameters, Mean (SD)** | | | | | |
| $HbA_{1c}$ (%) [mmol/mol] | 8.5 (1.8) [69] | 8.6 (1.8) [70] | 8.8 (1.9) [73] | 9.0 (1.3) [75] | 8.7 (1.8) [72] |
| BMI ($kg/m^2$) | 32.3 (7.0) | 33.1 (6.9) | 32.8 (6.9) | 32.6 (8.1) | 32.7 (6.9) |
| Diabetes duration (yrs)* | 3.7 (5.1) | 3.4 (4.6) | 3.9 (4.8) | 3.0 (5.6) | 3.8 (4.9) |
| Duration on insulin (yrs)** | 3.5 (6.3) | 3.1 (5.8) | 3.6 (6.4) | 2.8 (4.8) | 3.5 (6.3) |
| Weight (Kg) | 90.7 (18.7) | 91.8 (18.5) | 91.8 (18.9) | 89.8 (22.0) | 91.5 (18.8) |
| Height (m) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) | 1.7 (0.1) |
| SBP (mmHg) | 133.8 (22.5) | 134.9 (22.7) | 137.5 (23.3) | 142.0 (21.0) | 136.1 (23.1) |
| DBP (mmHg) | 77.4 (10.8) | 76.6 (10.6) | 76.2 (10.9) | 73.4 (11.0) | 76.6 (10.9) |
| eGFR ($mls/min/1.73m^2$) | 70.3 (20.5) | 68.1 (19.3) | 62.0 (21.3) | 55.1 (20.7) | 65.1 (21.2) |
| TC (mmol/l) | 4.5 (1.3) | 4.5 (1.2) | 4.6 (1.3) | 4.4 (1.1) | 4.6 (1.3) |
| HDL (mmol/l) | 1.3 (0.5) | 1.3 (0.4) | 1.2 (0.4) | 1.1 (0.4) | 1.3 (0.5) |
| LDL (mmol/l) | 2.4 (1.1) | 2.4 (1.0) | 2.4 (1.1) | 2.2 (1.0) | 2.4 (1.1) |
| Triglyceride (mmol/L) | 1.9 (1.2) | 1.9 (1.2) | 2.1 (1.2) | 2.2 (1.2) | 2.0 (1.2) |
| Albumin (g/L) | 4.1 (0.4) | 4.1 (0.4) | 4.1 (0.4) | 4.1 (0.5) | 4.1 (0.4) |
| Smoking status, No. (%) | | | | | |
| Non-smoker | 1967 (53) | 724 (52) | 3953 (53) | 42 (54) | 6686 (53) |
| Ex-smoker | 1207 (32) | 462 (33) | 2481 (33) | 27 (35) | 4177 (33) |

| | | | | | |
|---|---|---|---|---|---|
| Current smoker | 553 (15) | 215 (15) | 1085 (14) | 9 (12) | 1862 (15) |
| Alcohol status, No. (%) | | | | | |
| Non-drinker | 1109 (30) | 427 (30) | 2479 (33) | 30 (38) | 4045 (32) |
| Ex-drinker | 403 (11) | 171 (12) | 874 (12) | 5 (6) | 1453 (11) |
| Current drinker | 2215 (59) | 803 (57) | 4166 (55) | 43 (55) | 7227 (57) |
| BMI Categories, No. (%) | | | | | |
| Normal | 548 (15) | 157 (11) | 952 (13) | 8 (10) | 1665 (13) |
| Overweight | 898 (24) | 334 (24) | 1769 (24) | 21 (27) | 3022 (24) |
| Obese | 2281 (61) | 910 (65) | 4798 (64) | 49 (63) | 8038 (63) |
| **GLTs, No. (%)** | | | | | |
| Metformin | 3195 (86) | 1168 (83) | 6413 (85) | 55 (71) | 10831 (85) |
| Sulphonylurea | 2705 (73) | 984 (70) | 5592 (74) | 43 (55) | 9324 (73) |
| Thiazolidinedione | 1212 (32) | 417 (30) | 2405 (32) | 20 (26) | 4054 (32) |
| GLP-1RA | 431 (12) | 172 (12) | 920 (12) | 8 (10) | 1531 (12) |
| SGLT2i | 23 (0.6) | 8 (0.6) | 40 (0.5) | 0 (0) | 71 (0.6) |
| Glinides | 162 (4) | 56 (4) | 341 (5) | 3 (4) | 562 (4) |
| DPP4i | 558 (15) | 160 (11) | 1115 (15) | 8 (10) | 1841 (14) |
| **Use of Medications, No. (%)** | | | | | |
| Aspirin | 3470 (99) | 1329 (100) | 7148 (98) | 75 (100) | 12022 (100) |
| Antihypertensive | 2992 (86) | 1152 (87) | 6321 (88) | 73 (97) | 10538 (88) |
| LLTs | 3122 (90) | 1196 (90) | 6422 (90) | 67 (89) | 10807 (90) |
| **Comorbidities, No. (%)** | | | | | |
| CHD | 401 (11) | 153 (11) | 902 (12) | 9 (12) | 1465 (12) |
| PAD | 212 (6) | 89 (6) | 515 (7) | 7 (9) | 823 (6) |
| Heart Failure | 175 (5) | 71 (5) | 461 (6) | 6 (8) | 713 (6) |
| Hypoglycaemia | 607 (16) | 227 (16) | 1292 (17) | 11 (14) | 2137 (17) |

***Abbreviations:***
*GLP-1RA (Glucagon-like peptide-1 receptor agonist); SGLT2i (Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors); DPP4i (Dipeptidyl-peptidase 4 inhibitors); GLTs (Glucose Lowering Therapies); BMI (body mass index); SBP (systolic blood pressure); DBP (diastolic blood pressure); $HbA_{1c}$ (haemoglobin A1c); HDL (high-density lipoprotein); LDL (low-density lipoprotein); TC (total cholesterol); eGFR (estimated glomerular filtration rate); LLTs (lipid lowering therapies); PAD (peripheral arterial disease); CHD (coronary heart disease); ACR (albumin creatinine ratio); SD (standard deviation)*
**Diabetes duration (yrs) is the period between the diagnosis of diabetes and the initiation of insulin (baseline date)*
***Duration on insulin (yrs) is the mean duration of insulin use within the data collection period of Dec 2006 and May 2014*

Table 2. Proportion of the composite events by the UACR categories (5-year Kaplan-Meier Estimates)

| Characteristic | UACR Category, No. (%)[a] | | | | | |
|---|---|---|---|---|---|---|
| | <10mg/g (n = 3727) | 10 to 29mg/g (n = 1401) | 30 to 300mg/g (n = 7519) | >300mg/g (n = 78) | Total (n = 12,725) | p-value |
| Primary Composite Outcome[b] | 270 (7.2) | 111 (7.9) | 703 (9.3) | 11 (14.1) | 1095 (8.6) | < 0.001 |
| All-Cause Mortality | 144 (3.9) | 51 (3.7) | 393 (5.2) | 6 (7.7) | 595 (4.7) | < 0.001 |
| Non-fatal Myocardial Infarction | 15 (0.4) | 7 (0.5) | 42 (0.6) | 1 (1.3) | 65 (0.5) | 0.554 |
| Non-fatal Stroke | 110 (3.0) | 54 (3.9) | 267 (3.6) | 4 (5.1) | 435 (3.4) | 0.264 |

[a] *No of events (Percentage)*
[b] *Composite outcome is a three-point MACE including all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.*

Table 3: Risk of Composite Endpoints Events per Levels of UACR

| End Points | Log of UACR as Continuous[a] | | UACR as Categorical Adjusted HR[b] (95% CI)[c] | | | | |
|---|---|---|---|---|---|---|---|
| | Adjusted HR (95% CI) | p-value | <10mg/g (n = 3727) | 10 to 29mg/g (n = 1401) | 30 to 300mg/g (n = 7519) | >300mg/g (n = 78) | p-value |
| Composite Outcome[d] | | | | | | | |
| Absolute rates[e] (95%CI) | 22.1 (20.8 – 23.5) | | 18.6 (16.5- 30.0) | 20.0 (16.6-24.0) | 29.1 (22.4 – 26.0) | 35.8 (19.8 – 64.7) | |
| aHR (95%CI) | **1.14 (1.07-1.22)** | **<0.001** | **1 (reference)** | **1.09 (0.84 – 1.36)** | **1.30 (1.10 – 1.59)** | **1.98 (1.12 – 3.56)** | **0.0008** |
| All-Cause Mortality | | | | | | | |
| Absolute rates (95%CI) | 11.7 (10.8 – 12.7) | | 9.7 (8.3 – 11.5) | 8.6 (6.5 – 11.4) | 13.2 (11.9 – 14.6) | 19.0 (8.5 – 42.3) | |
| aHR (95%CI) | **1.18 (1.08-1.29)** | **<0.001** | **1 (reference)** | **0.88 (0.68 – 1.24)** | **1.36 (1.12 – 1.66)** | **1.96 (0.88 – 4.42)** | **0.0001** |
| Non-fatal Myocardial Infarction | | | | | | | |
| Absolute rates (95%CI) | 1.3 (1.0 – 1.6) | | 1.0 (0.6 – 1.7) | 1.2 (0.6 – 2.6) | 1.4 (1.04 – 1.90) | 3.2 (0.4 – 22.5) | |
| aHR (95%CI) | **1.18 (0.90-1.56)** | **0.219** | **1 (reference)** | **1.32 (0.71 – 3.014)** | **1.52 (0.84 – 2.60)** | **3.14 (0.49 – 13.5)** | **0.415** |
| Non-fatal Stroke | | | | | | | |
| Absolute rates (95%CI) | 8.8 (8.0 – 9.6) | | 7.6 (6.3 – 9.1) | 9.7 (7.4 – 12.6) | 9.1 (8.1 – 10.3) | 13.0 (4.9 – 34.7) | |
| aHR (95%CI) | **1.09 (0.98-1.21)** | **0.101** | **1 (reference)** | **1.26 (0.96 – 1.82)** | **1.18(0.62 – 1.27)** | **1.70 (0.58 – 3.21)** | **0.481** |

***Abbreviations:*** *HR, hazard ratio; UACR, urinary albumin to creatinine ratio.*

[a] *Per log (SD) is 1 (1.76).*

[b] *HR - Hazard ratio was adjusted for age, gender, duration of diabetes, Systolic BP, $HbA_{1c}$ and eGFR*

[c] 95% CI – 95% Confidence Interval

[d] Composite Outcome is *a three-point MACE including all-cause mortality, non-fatal acute myocardial infarction (AMI) and non-fatal stroke.*

[e] Absolute rates per 1000 person-years