Manuscript

Albuminuria Regression and All-cause Mortality among Insulin-treated Patients with Type 2 diabetes: Analysis of a Large UK Primary Care Cohort

Running Head: Albuminuria Regression and Total Mortality among Patients with Type 2 diabetes

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Abstract

Background

Overt albuminuria (urinary albumin-creatinine ratio (ACR) >300mg/g) is an established risk factor for progression of nephropathy and total mortality. However, whether, a reduction in ACR translates into a reduction in mortality and/or cardiovascular events among insulin-treated patients with Type 2 diabetes (T2D) in routine practice is currently not known.

Methods

We obtained data on a large cohort of insulin users with T2D and nephropathy (baseline ACR ≥ 300 mg/g) from UK general practices between 2007 and 2014. Their corresponding ACR values after one year of follow up were thereafter categorised into: (1) <300mg/g (i.e. albuminuria regression) or (2) >300mg/g (i.e. non-regression of albuminuria), and the cohort was followed up for 5 years for all-cause mortality and cardiovascular events. Cox proportional hazard models were fitted to estimate the risk of all-cause death.

Results

A total of 11,074 patients with insulin-treated T2D met the inclusion criteria. Their mean age was 62.3(13.6) years; mean HbA1c: 8.7(1.8) %; and 53% were male. 682 deaths occurred after a follow-up period of 43,393 person-years with a mortality rate of 16 per 1000 person-years. 5-year survival was markedly reduced in the group whose proteinuria persisted or progressed (91 vs 95%; log-rank p-value <0.001). Compared to patients whose ACR levels remained above 300mg/g, all-cause mortality and cardiovascular events were 31% and 27% lower in those whose albuminuria regressed to <300mg/g (aHR: 0.69; 95%CI: 0.52 to 0.91; p=0.008 and aHR: 0.73; 95%CI: 0.54 to 0.98; p=0.041) respectively.

Conclusion

In patients with insulin-treated T2D and nephropathy in routine practice, a regression in albuminuria (e.g. via better BP or glycaemic control) is associated with a significant reduction in all-cause mortality. Thus, albuminuria is not simply a risk marker of renal and cardiovascular disease, but also an independent target for therapy. Albuminuria reduction should be viewed as a goal for renal and cardiovascular protection.

Research in context:

What is already known about this subject?

- Albuminuria is a strong predictor of adverse renal and cardiovascular outcomes in patients with Type 2 Diabetes (T2D), hypertension and in the general population.
- Several therapeutic strategies are available to reduce ACR, namely via interruption of the Renin-Angiotensin system (RAS) with either angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor blocker; strategies to achieve tight glucose control; and the use of Sodium Glucose co-transporter (SGLT)-2 inhibitor.
- Previous sub-analysis of studies have shown that the reduction in albuminuria achieved in the first months of RAS blockade predicts long-term renal and cardiovascular risk reduction

What is the key question?

- Among patients with Insulin treated Type 2 diabetes with overt proteinuria (ACR>300g/g), undergoing routine treatment in primary care, does regression of proteinuria confer an associated reduction in cardiovascular events and total mortality compared with patients whose proteinuria did not regress?

What are the new findings?

- Among this cohort of patients with Insulin treated Type 2 diabetes, increased albuminuria is an independent marker for subsequent cardiovascular events and total mortality in real world setting.
- Regression of albuminuria as a result of multifactorial intervention in routine clinical care was associated with a further significant reduction in cardiovascular events and total mortality events compared with patients whose albuminuria did not regress.
- The beneficial impact of albuminuria regression appears to be stronger for total mortality than for cardiovascular endpoints, regression of albuminuria is not associated with a significant reduction in non-fatal myocardial infarction but, was associated with a significant reduction in stroke event, compared with the cohort whose albuminuria level either increased or did not regress.

How might this impact on clinical practice in the foreseeable future?

- Thus, levels of albuminuria should be considered not only as an important risk marker, but also an important therapeutic target for cardiovascular and mortality prevention in patients with T2D, and should be a key consideration when determining drug choice irrespective of blood pressure and glucose levels.

Introduction

Albuminuria is a strong predictor of adverse renal and cardiovascular outcomes in patients with Type 2 Diabetes (T2D), hypertension and in the general population. [1-4] Albuminuria is typically assessed by measuring urinary albumin to creatinine ratio (ACR). ACR levels between 30mg/g to 300mg/g represent moderately increased levels of albuminuria, known as microalbuminuria, while levels of more than 300mg/g are associated with overt proteinuria. Several therapeutic strategies are available to reduce ACR, namely via interruption of the Renin-Angiotensin system (RAS) with either angiotensin-converting enzyme (ACE) inhibitors or Angiotensin II receptor blocker [5,6]; strict BP control; strategies to achieve tight glucose control [7]; and more recently, the Sodium Glucose co-transporter (SGLT)-2 inhibitor [8,9]. While these strategies are also associated with improvement in renal and cardiovascular outcomes, the precise impact of ACR reduction, independent of conventional cardiovascular risk parameters, in mediating the beneficial effect of cardio-renal outcome remains unclear.

For many patients with T2D, insulin treatment will be required to control hyperglycaemia and to reduce the risk of long-term vascular complications in patients with T2D. [10-12]. 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 also 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, potential adverse effects of iatrogenic hyperinsulinemia as well as a surrogate marker of increased diabetes duration

[19,20]. Thus, a cohort of insulin-treated patients with T2D, represents a complex heterogeneous challenging group of patients, many of whom have significant comorbidities and high CV disease risk.

Although previous studies have shown that the reduction in albuminuria achieved in the first months of RAS blockade predicts long-term renal and cardiovascular risk reduction [21, 22] - implying a causal association between albuminuria with cardio-renal risks [23], no previous study has been performed to investigate the independent effects of reduction in albuminuria on cardiovascular events and total mortality among insulin-treated patients with T2D in real-world primary care, given that insulin initiators usually have poor glycaemic control, longer disease duration or may be more advanced in age, and a reduction in ACR amongst them could be associated with marked reduction in these events.

Methods

Study Design

Using a large UK Primary Care database – The Health Improvement Network (THIN) Database – we conducted a historic cohort study among patients with T2D currently on insulin. THIN is a large UK electronic Primary Care database with clinical details of over 12.4 million patients, of which about 3.61 million are active. Data are imputed with the longitudinal records from about 587 General Practices which are obtained and updated regularly.

The routine clinical information of these patients are constantly and systematically entered into this database by trained doctors and specialist nurses. Data of 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) as well as information on the patients' demography (e.g. age, and gender)

lifestyle characteristics (e.g. alcohol use and smoking), socio-economic status (measured by the Townsend deprivation scores) are also included.

THIN database has been validated by various studies and shown to be demographically representative of the UK population in terms of indices of diseases and patients' demography [24]. Our research group has extensively used the THIN database in evaluating diabetes-related outcomes in routine clinical practice [25,26].

Study Participants

We obtained routine clinical data on 11,074 patients with a diagnosis of T2D who met our inclusion criteria. These were adults (aged 18 years and above) who were on insulin therapy between December 2006 and May 2014, irrespective of the use of other glucose-lowering therapies (GLTs). These patients must have recorded values of ACR at baseline and one year after insulin initiation. Only those with those with nephropathy (ACR levels above 300mg/g) were included. Urinary ACR in the dataset was measured from a single voided urine sample by a central laboratory, with the lowest detectable and reportable level of 1.0mg/g.

Excluded from the study were those with missing baseline data of ACR and those 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 for more than 6 months.

Follow-up and Endpoints

The selected study participants with nephropathy at insulin initiation (baseline date) were followed up from this date for one year. Post-one year ACR levels were estimated and patients were grouped into two: those with ACR levels now <300mg/g vs those with ACR $\geq$ 300mg/g. Patients were then followed up from this point until occurrence of the primary or secondary endpoint, or loss to follow-up, or discontinuation of insulin therapy, or at the end of the 5-year follow-up period.

The primary endpoints were all-cause mortality and cardiovascular events (a composite of non-fatal myocardial infarction and stroke).

The secondary endpoint was a 3-composite of Major Adverse Cardiovascular Events (MACE) which includes all-cause mortality or non-fatal myocardial infarction or stroke; and the component parts of non-fatal myocardial infarction and stroke.

All these outcomes were identified using their appropriate Read Codes in the database.

Baseline and endpoint characteristics

To be able to adjust for the effect of possible *a priori* confounders on the study endpoints, data were also obtained on important baseline clinical covariates. Among these were demographic variables 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 HbA1c, 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. We computed the change in mean arterial pressure (MAP) and HbA1c after one year of insulin initiation; and alongside baseline covariates with significant differences between the two groups, these were adjusted for in the final Cox model.

Statistical Analysis

Multiple imputations using the chained equation (MICE) model were used to input missing data for some important baseline clinical covariates as weight, HbA1c, eGFR, weight, SBP and DBP which were found to be completely missing at random (MAR).

Baseline data were summarised for the two groups using mean with standard deviations for continuous variables; and absolute numbers with proportions (%) for categorical variables. The differences in baseline characteristics between the two groups were estimated using Pearson's chi-squared test for categorical, and Student t-test for continuous variables.

Kaplan-Meier survival curves were estimated separately for both treatment groups. From these survival functions, we calculated the absolute reduction in the probability of an event occurring within the 5-year follow-up period.

Using the Cox regression model, the marginal Hazard Ratios (HRs) were estimated in order to quantify the adjusted hazard (aHR) of an event occurring in the "ACR below 300mg/g"

group compared with the “ACR 300mg/g and above” group. We tested for violations of the proportional hazard assumption of the Cox regression model, by adding an interaction term of the predictor; and by log-minus-log survival curves; and finally confirmed the proportional hazards assumptions were through Schoenfeld residuals test.

Point estimates were computed with 95% confidence intervals (CI) at the conventional statistical significance level of 0.05. Stata Software version 15 was used for all the analyses.

Ethical Approval:

This was obtained from the South-East Research Ethics Committee, UK

Results

Patient Characteristics.

A total of 11,074 new insulin initiators met our inclusion criteria. Of this, 1552 (14%) had reduction in albuminuria, as against 9522 (86%) who had persistent or progressive albuminuria after one year of intensive glucose control with insulin.

Their overall mean age was 62.3 ± 14 years, mean baseline HbA1c and eGFR were $8.7 \pm 1.8\%$ and $59.9 \pm 21.2 \text{ ml/min/1.73m}^2$ respectively. Table 1 is a summary of the baseline characteristics of the study participants, stratified by the two treatment groups.

From Table 1, it can be seen that at baseline, those with their post-one year ACR less than 300mg/g were younger ($p < 0.001$); less obese and overweight ($p = 0.002$); had less comorbidities ($p < 0.05$); shorter duration of diabetes before insulin initiation ($p = 0.004$); higher eGFR ($p < 0.001$); and lower systolic and diastolic BP ($p < 0.05$). Conversely, the use of other GLTs, baseline HbA1c and lipid profile were similar in both groups (all $p \geq 0.05$).

Primary Endpoint

i. All-Cause Mortality: Survival analyses at 5 years were 91% vs 95% for patients with ACR above 300mg/g (group 1) vs those with ACR below 300mg/g (group 2); log-rank test p-value <0.001 (Figure 1). Overall, there were 682 deaths with a crude incidence rate of 15.7 per 1000 person-years (95%CI: 14.6 to 17.0) within a total follow-up period of 43,393 person-time. There were 621 vs 61 deaths in group 1 vs 2, with an unadjusted mortality rates of 16.7 vs 9.7 per 1000 person-years (Table 2).

In the unadjusted model, the risk of all-cause mortality was 43% less (aHR: 0.57, 95%CI: 0.44 to 0.75, p <0.001) in group 2 compared to group 1. Following adjustment for change in HbA1c and Mean arterial pressure (MAP) and other significantly different baseline covariates in Table 1, this reduced to 31% (aHR: 0.69, 95%CI: 0.52 to 0.91, p=0.008) (Table 2)

ii. Cardiovascular (CV) Events: After a total follow-up period of 38,274 person-time, the 5-year survival probabilities for CV events were 94% vs 96% in group 1 vs group 2 (log-rank test p-value = 0.007); with an overall event rate of 12.6 per 1000 person-years (95%CI: 11.7 to 13.9) - 13.4 vs 5.6 per 1000 person-years in group 1 vs 2 respectively (Table 2). The risk of CV events was 27% less in group 1 (aHR: 0.73, 95%CI 0.54 to 0.98, p = 0.041) compared to group 2, even after adjustment.

Secondary Endpoint

i. Composite MACE: The probability of survival for composite MACE fell from 98% in both groups at year 1 to 84% vs 90% in group 1 and 2 respectively at 5 years (log-rank p-value <0.001) Figure 3A. Overall, there were 1,173 composite MACE (1,062 in group 1 vs 111 in group 2) with a crude event rate of 30.7 per 1000 person-years (95%CI: 30.0 to 32.5). See Table 3. The risk of MACE in the adjusted Cox model was 27% less in group 2 compared to group 1 (aHR: 0.737, 95%CI: 0.59 to 0.89, p = 0.002).

ii. Non-fatal Myocardial Infarction (MI) and Non-fatal Stroke: For non-fatal MI, there were no differences in survival between both groups (log-rank test p-value = 0.086), unlike in non-fatal stroke in which the survival probabilities fell from 99% at the first year to 94% vs 96% at 5 year (log-rank test p-value = 0.03). These are shown in the Kaplan-Meier curves in

Figures 3B and C. In both groups, there was a total of 69 and 419 events of non-fatal MI and stroke respectively (Event rates = 1.6 vs 10.6 per 1000 person-years). The events between the two treatment groups are summarised in Table 3.

There was no statistically significant difference in the risk of non-fatal MI between the treatment groups (aHR = 0.66, 95%CI: 0.26 to 1.70, $p = 0.387$) while for stroke, patients whose proteinuria regressed to $<300\text{mg/g}$ (group 2) had a 30% reduction (aHR = 0.72; 95%CI: 0.52 to 0.97; $p = 0.032$) in risk compared to those with persistent or progressive proteinuria (group 2).

Discussion

The present study showed that albuminuria is an independent marker for subsequent cardiovascular events and total mortality in insulin-treated patients with T2D. Regression of albuminuria as a result of multifactorial intervention in routine clinical care was associated with a further significant reduction in cardiovascular events and total mortality events. This association appears to be marginally stronger for total mortality than for cardiovascular endpoints. In addition, we found that regression of albuminuria was associated with reduction in non-fatal myocardial infarction (though not statistically significant) but, interestingly, was associated with a significant reduction in stroke event, compared with the cohort whose albuminuria level either increased or did not regress. Thus, levels of albuminuria should be considered not only as an important risk marker, but also an important therapeutic target for cardiovascular and mortality prevention in patients with T2D, and should be a key consideration when determining drug choice irrespective of blood pressure and glucose levels.

Albuminuria has long been recognised to be a risk marker for the severity of kidney disease. Although early opinion suggests that albuminuria is simply a surrogate marker of renal injury, evidence in the last 12 years however, have shown the cause-effect relationship between albuminuria and progressive kidney damage [21-23]. Our present study, obtained in a large retrospective cohort of patients with insulin-treated T2D undergoing routine care in UK general practices, shows that this phenomenon may also apply to cardiovascular event and total mortality. This is akin to the impact of blood pressure and serum cholesterol, where therapeutic strategies have been designed and with the aim to lower blood pressure and serum cholesterol respectively. Indeed, there are recognised therapeutic strategies that can

reduce the degree of albuminuria – namely antihypertensive agents such as ACE inhibitor and Angiotensin-2 receptor blocker [5,6], tight glucose control [7], SGLT2 inhibitors [8,9], and low protein diet [27]. Since RAS blockade and SGLT2 inhibitor also lower blood pressure, it remained speculative whether the changes in albuminuria *per se* affect the cardiovascular/mortality endpoints independently of blood pressure. However, individual variations to RAS blockade is well described – i.e. patients can have a systolic blood pressure reduction without a simultaneous reduction in albuminuria or vice versa [28]. This discordance in response to RAS blockade has been reported in clinical trial [29] as well as in population treated in routine clinical practice [30], and that the beneficial impact of albuminuria reduction was reported to be independent of blood pressure reduction. A particularly important finding from this present study was the fact that the cardiovascular and total mortality reduction was not observed in the cohort whose albuminuria did not regress, following adjustment for conventional cardiovascular factors. The current study for the first time shows on a large scale, in a real-world practice that the degree of albuminuria reduction is directly related to the subsequent cardiovascular and mortality protection in a high risk group of patients with T2D.

In the absence of a prospectively-designed clinical study, with appropriate treatment arms and robust endpoints, the mechanism linking albuminuria and excess mortality remains speculative. The Steno hypothesis suggested that urinary protein excretion reflects generalised vascular endothelial dysfunction [31] – e.g. increased circulating von Willebrand Factor (vWF) antigen released [32] and nitric oxide inhibition [33] in response to endothelial cell damage. In addition to vWF, soluble vascular cell adhesion molecule, fibrinogen, high platelet adhesiveness, erythrocytes aggregation and tissue plasminogen activator have been found to correlate with urinary albumin excretion [34], especially in patients with diabetes,

indicating increased thrombosis risk. Proteinuria is also linked with insulin resistance, a recognised marker and mediator of atherogenesis [35]. More recently, a key mechanism that contributes to the link between albuminuria and adverse cardiovascular outcome relates to the loss of the glycocalyx--a polysaccharide gel that lines the luminal endothelial surface and that normally acts as a barrier against albumin filtration [36]. Degradation of the glycocalyx in response to endothelial activation can lead to albuminuria and subsequent vascular inflammation, thus providing a pathophysiological framework for the clinical association of albuminuria with renal and cardiovascular disease progression.

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 which also enabled the component endpoints to be studied. It 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. 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. Lastly, changes after baseline in medications were not evaluated in this analysis and therefore cannot account for any differences that might influence the association between ACR and outcomes.

In summary, the findings of this study extend the cause-effect relationship between albuminuria and cardiovascular risks and that suppressing albuminuria should be an important target of therapy to achieve optimal cardiovascular protection in high risk individuals with T2D. While further prospective interventional studies are required to clarify the cause effect relationship, we would suggest that cardiovascular risk reduction guidelines on patients with T2D should not only view albuminuria as an important risk factor/marker, but should also define albuminuria regression as a target for therapy, similar to lipids, blood pressure and glucose targets.

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Legend

Table 1 - Baseline Characteristics of Study Participants

Table 2: Comparison of number of events, Event rate and Hazard Ratio of the Primary Outcomes between the treatment groups.

Table 3: Comparison of number of events, Event rate and Hazard Ratio of the Secondary Outcomes between the treatment groups.

Figure 1 - Kaplan-Meier survival analysis plot for All-cause Mortality between the two treatment groups (log-rank test p value < 0.001).

Figure 2 - Kaplan-Meier survival analysis plot for Cardiovascular Events between the treatment groups (log-rank test p value = 0.007).

Figure 3 - Kaplan-Meier survival analysis plot for (A) 3-point Composite Endpoint (log-rank test p value = 0.006). (B) Non-fatal Acute Myocardial Infarction (log-rank test p-value =0.086). (C) Non-Fatal Stroke (log-rank test p value = 0.03).

Table 1: Baseline Characteristics

Baseline Variables	Post One-year ACR Categories			p-value
	≥300mg/g (n = 9,522)	<300mg (n = 1,552)	Total (n = 11,074)	
Demographics				
Age (yrs), Mean (SD)	62.8 (13.5)	59.8 (13.5)	62.3 (13.6)	<0.001
Gender, No. (%)				
Male	5070 (53)	829 (53)	5899 (53)	0.901
Townsend deprivation, No. (%)				
Least deprived	1809 (20)	318 (21)	2127 (19)	0.734
2nd quintile	1835 (20)	301 (20)	2136 (19)	
3rd quintile	1948 (21)	310 (21)	2258 (20)	
4th quintile	1980 (22)	313 (21)	2293 (21)	
Most deprived	1504 (17)	241 (16)	1745 (16)	
Clinical Parameters, Mean (SD)				
HbA1c (%)	8.8 (1.8)	8.7 (1.8)	8.7 (1.8)	0.417
[mmol/mol]	73 (20)	72 (20)	72 (20)	
ACR (mg/g)	118.1 (62.8)	58.8 (24.1)	110.7 (62.5)	<0.001
BMI (kg/m²)	32.7 (6.8)	31.9 (6.8)	32.6 (6.8)	<0.001
Diabetes duration (yrs)	4.5 (4.8)	4.0 (4.7)	4.4 (4.8)	<0.001
Duration on insulin (yrs)	4.0 (6.4)	3.6 (6.1)	4.0 (6.4)	0.004
Weight (Kg)	91.7 (18.8)	91.0 (18.9)	91.6 (18.8)	0.131
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	0.104
SBP (mmHg)	138.4 (23.3)	132.9 (22.8)	137.6 (23.3)	<0.001
DBP (mmHg)	75.7 (10.9)	75.0 (10.6)	75.6 (10.9)	0.008
eGFR (mls/min/1.73m²)	59.0 (21.2)	65.6 (20.4)	59.9 (21.2)	<0.001
TC (mmol/l)	4.6 (1.3)	4.6 (1.2)	4.6 (1.3)	0.715
HDL (mmol/l)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	0.364
LDL (mmol/l)	2.4 (1.1)	2.4 (1.1)	2.4 (1.1)	0.574
Triglyceride (mmol/L)	2.2 (1.2)	2.0 (1.2)	2.1 (1.2)	<0.001
Albumin (g/L)	4.0 (0.4)	4.1 (0.4)	4.0 (0.4)	<0.001
Smoking status, No. (%)				
Non-smoker	4633 (49)	740 (48)	5373 (49)	0.219
Ex-smoker	3551 (37)	568 (37)	4119 (37)	
Current smoker	1338 (14)	244 (16)	1582 (14)	
Alcohol status, No. (%)				
Non-drinker	3194 (34)	487 (31)	3681 (33)	0.235
Ex-drinker	1091 (11)	180 (12)	1271 (11)	
Current drinker	5237 (55)	885 (57)	6122 (55)	
BMI Categories, No. (%)				
Normal	1223 (13)	235 (15)	1458 (13)	0.002
Overweight	2231 (23)	399 (26)	2630 (24)	
Obese	6068 (64)	918 (59)	6986 (63)	
GLTs, No. (%)				
Metformin	8163 (86)	1312 (85)	9475 (86)	0.216
Sulphonylurea	7316 (77)	1152 (74)	8468 (76)	0.025
Thiazolidinedione	3005 (32)	494 (32)	3499 (32)	0.831
GLP-1RA	1007 (11)	179 (12)	1186 (11)	0.258
SGLT2i	40 (0)	10 (1)	50 (0.5)	0.222
Glinides	428 (4)	72 (5)	500 (5)	0.800
DPP4i	1353 (14)	222 (14)	1575 (14)	0.921
Use of Medications, No. (%)				
Aspirin	9213 (99)	1478 (99)	10691 (99)	0.138

Antihypertensive	8493 (92)	1316 (89)	9809 (92)	<0.001
- ACE inhibitors	7505 (81)	1154 (78)	8659 (81)	0.002
- ARBs	2957 (32)	409 (28)	3366 (31)	0.001
- Calcium channel blockers	5302 (56)	754 (51)	6056 (57)	<0.001
- Beta-blockers	4807 (52)	699 (47)	5506 (51)	<0.001
- Diuretics	9214 (96)	1479 (95)	10693 (94)	0.001
LLTs	8407 (91)	1347 (91)	9754 (91)	0.834
Comorbidities, No. (%) ^c				
CHD	2992 (31)	404 (26)	3396 (31)	<0.001
PAD	1365 (14)	185 (12)	1550 (14)	0.011
Heart Failure	1433 (15)	173 (11)	1606 (15)	<0.001
Hypoglycaemia	1711 (18)	267 (17)	1978 (18)	0.465

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); HbA1c (hemoglobin 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); ACEi (Angiotensin Converting Enzyme Inhibitors); ARBs (Angiotensin II Receptor Blockers); SD (standard deviation)

Table 2: Comparison of number of events, Event rate and Hazard Ratio of the Primary Outcomes between the treatment groups.

Primary End Points	Post One-year ACR		
	≥300mg/g (n = 9522)	<300mg (n = 1552)	p-value
All-Cause Mortality			
Number of deaths	621	61	
Death rates (95%CI)	16.7 (15.5 – 18.1)	9.7 (7.6 – 12.5)	
HR (95%CI)	1 (reference)	0.57 (0.44 – 0.75)	<0.001
aHR ^a (95%CI)	1 (reference)	0.69 (0.52 – 0.91)	0.008
Cardiovascular Events^b			
Number of events	438	50	
Event rates (95%CI)	13.4 (12.2 – 14.7)	9.0 (6.8 – 11.8)	
HR (95%CI)	1 (reference)	0.67 (0.50 – 0.90)	0.007
aHR (95%CI)	1 (reference)	0.73 (0.54 – 0.98)	0.041

Abbreviations: HR, hazard ratio; aHR, Adjusted Hazard Ratio; ACR, albumin to creatinine ratio.
^a Hazard ratio in both all-cause mortality and CV events was adjusted for age, BMI, duration of diabetes, gender, Socio-economic status, change in HbA1c, Systolic and Diastolic BP, Change in Mean Arterial Pressure (MAP), Lipid profile, Use of antihypertensive medications and comorbidities as Heart failure, CHD and PAD.
^b Cardiovascular Events – Composite of non-fatal Myocardial Infarction and Stroke

Table 3: Comparison of number of events, Event rate and Hazard Ratio of the Secondary Outcomes between the treatment groups.

Secondary End Points	Post One-year ACR		
	≥300mg/g (n = 9522)	<300mg/g (n = 1552)	p-value
Composite Outcome^a			
Number of events	1062	111	
Event rates ^b (95%CI)	32.5 (30.6 - 34.5)	19.9 (16.5 - 24.0)	
HR (95%CI)	1 (reference)	0.61 (0.50 – 0.74)	<0.001
aHR ^c (95%CI)	1 (reference)	0.73 (0.59 – 0.89)	0.002
Non-fatal Myocardial Infarction			
Number of events	64	5	
Event rates (95%CI)	1.8 (1.4 – 2.3)	0.8 (0.3 – 2.0)	
HR (95%CI)	1 (reference)	0.46 (0.18 – 1.14)	0.094
aHR (95%CI)	1 (reference)	0.66 (0.26 – 1.70)	0.387
Non-fatal Stroke			
Number of events	374	45	
Event rates (95%CI)	11.1 (10.0 – 12.3)	7.9 (5.9 – 10.6)	
HR (95%CI)	1 (reference)	0.71 (0.52 – 0.97)	0.030
aHR (95%CI)	1 (reference)	0.72 (0.52 – 0.97)	0.032

Abbreviations: HR, hazard ratio; aHR, Adjusted Hazard Ratio; ACR, albumin to creatinine ratio.
^a Composite Outcome – Composite of All-cause mortality, non-fatal Myocardial Infarction and Stroke
^b Rates are expressed per 1000 person-years

^cHazard ratio in all the secondary endpoints was adjusted for age, BMI, duration of diabetes, gender, Socio-economic status, change in HbA1c, Systolic and Diastolic BP, Change in Mean Arterial Pressure (MAP), Lipid profile, Use of antihypertensive medications and comorbidities as Heart failure, CHD and PAD.

Unadjusted Kaplan-Meier estimates for All-cause Mortality

No at risk (failure)

ACR 300 & above	9522 (14)	9032 (187)	7827 (140)	6880 (153)	5983 (127)	5171
ACR below 300	1552 (2)	1484 (15)	1322 (14)	1180 (20)	1052 (10)	925

Unadjusted Kaplan-Meier estimates for Cardiovascular Events

No at risk (failure)

ACR 300 & above	8564	(120)	8012	(105)	6899	(82)	6020	(66)	5205	(65)	4493
ACR below 300	1409	(17)	1331	(8)	1177	(13)	1039	(9)	921	(3)	817

A

No at risk (failure)

ACR 300 & above	8564	(134)	8003	(293)	6890	(222)	6009	(220)	5200	(193)	4486
ACR below 300	1409	(19)	1329	(23)	1177	(27)	1039	(29)	920	(13)	817

B

No at risk (failure)

ACR 300 & above	9309	(15)	8822	(20)	7630	(9)	6699	(8)	5815	(12)	5024
ACR below 300	1524	(2)	1457	(0)	1297	(2)	1156	(1)	1030	(0)	906

C

No at risk (failure)

ACR 300 & above	8777	(105)	8231	(85)	7105	(73)	6212	(58)	5378	(53)	4647
ACR below 300	1437	(15)	1360	(8)	1202	(11)	1063	(8)	944	(3)	836