Manuscript

Individual and combined relationship between reduced eGFR and/or Increased Urinary Albumin Excretion Rate with mortality risk among Insulin Treated Patients with Type 2 Diabetes in Routine Practice

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Abstract

Background: Low estimated glomerular filtration rate (eGFR) and increased urinary albumin-to-creatinine ratio (ACR) are well-recognised prognostic markers of cardiovascular (CV) risk, but their individual and combine relationship with CV disease and total mortality among insulin-treated Type 2 Diabetes (T2D) patients in routine clinical care is unclear.

Methods: We analysed data for insulin users with T2D from UK general practices between 2007 and 2014 and examined the association between mortality rates and CKD [categorised by low eGFR (<60mL/min/1.73 m^2); high eGFR (≥60mL/min/1.73 m^2); low ACR (<300mg/g); and high ACR (≥300mg/g) at insulin initiation] after a 5-year follow-up period using Cox proportional hazard models.

Results: A total of 18,227 patients were identified (mean age: 61.5±13.8 years, mean HbA1c: 8.6±1.8%). After adjusting for confounders, when compared to adults on insulin therapy with an eGFR <60 and an ACR ≥300 (low eGFR + high ACR) after a follow up period of 5 years, patients with an eGFR <60 and an ACR <300 (low eGFR + low ACR) had a 6% lower mortality rate (aHR: 0.94; 95%CI: 0.79 to1.12); those with an eGFR >60 and an ACR ≥300 (high eGFR + high ACR) had a 20% lower mortality rate (aHR: 0.80; 95%CI: 0.68 to 0.96); and those with an eGFR >60 and an ACR <300 (high eGFR + low ACR) had the lowest death rate (28% less; aHR: 0.72; 95%CI: 0.59 to 0.87).

Conclusion: This study shows that among a large cohort of insulin-treated T2D patients in routine practice, the combination of reduced eGFR with increased ACR was associated with the greatest risk of premature death, followed closely by those with reduced eGFR and normal ACR levels. Adoption of aggressive CV risk management strategies to reduce mortality in patients with a low eGFR and albuminuria is essential in these high risk patients with T2D.

Introduction

Several high impact studies have identified the elevated risk of end stage renal disease (ESRD) and cardiovascular (CV) disease conferred by albuminuria in addition to estimated Glomerular Filtration Rate (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. Estimated Glomerular Filtration Rate (eGFR) is a key indicator of renal function and is mathematically derived based on a patient's serum creatinine level, age, sex and race and calculated using the well validated formulae derived from the Modification of Diet in Renal Disease (MDRD) CKD-EPI equations [8]. "Normal" eGFR is usually >90 ml/min/1.73m2, corrected for body surface area "per 1.73m2" which is important for certain patient groups, e.g. amputees, extremes of body habitus, but in the absence of any marker of kidney damage, eGFR is only classified as CKD if its value is <60 ml/min/1.73m2 [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]. 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 *per se* 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 heterogenous, challenging group of patients, many of whom have significant comorbidities and high CV disease risk. No studies have assessed the relative strength of increments in urinary ACR and/or decrement in eGFR in predicting total mortality among insulin treated patients with T2D in routine clinical care.

Methods

Study Design

We conducted a retrospective cohort study using the UK primary care electronic database called The Health Improvement Network (THIN) Database.

THIN comprises longitudinal records which were obtained from about 587 General Practices and updated periodically. It contains medical information of over 12.4 million patients in which approximately 3.61 million are active users. Trained doctors and specialist nurses systematically enter routine clinical information into this database. These range from specialist medical consultations, diagnoses, laboratory results, prescriptions, referrals, hospital admissions, immunisations and clinical measurements as body weight, height and body mass index (BMI). It also has data on the patients' demography, lifestyle characteristics (e.g. alcohol use and smoking), socio-economic status (Townsend deprivation scores), ethnicity, religion and more recently, ethnicity/languages. It has been validated and shown it to be demographically representative of the UK population in terms of disease demography - prevalence and mortality [21]. Like many others, our research group has extensively used it in evaluating diabetes-related outcomes in routine clinical practice [22,23]

Study Participants

We obtained routine clinical data on 18,227 people with a diagnosis of T2D who met our inclusion criteria. These must be aged 18 years and above; commenced insulin therapy between December 2006 and May 2014; and with recorded values of albumin-creatinine ratio (ACR)

and e-GFR on insulin initiation. Patients with type 1, gestational diabetes, or other forms of diabetes; and those with no continuous records of regular insulin prescriptions were excluded.

Follow-up and Endpoints

The baseline (insulin initiation) ACR (mg/g) and eGFR (mls/min/1.73m^2) levels were used to categorise the patients into four treatment groups:

Group 1: Low eGFR + High ACR – those with eGFR <60 and an ACR ≥300

Group 2: Low eGFR +Low ACR – those with eGFR <60 and an ACR <300

Group 3: High eGFR + High ACR – those with eGFR ≥60 and an ACR ≥300

Group 4: High eGFR + Low ACR – those with eGFR ≥60 and an ACR <300

The primary endpoint was all-cause mortality. Secondary endpoints were the risks of cardiovascular events (non-fatal stroke and myocardial infarction) and a 3-point composite of MACE (Major Adverse Cardiovascular Event - all-cause mortality, non-fatal myocardial infarction, and stroke).

From the baseline period, these groups were followed up till the first of the occurrence of death or loss to follow-up; or discontinuation of insulin therapy; or at the end of the 5-year follow-up period.

Baseline and endpoint characteristics

We also obtained data on important clinical covariates that confound the association between the exposure and outcome variables. This is based on a priori knowledge and from the tests of association. Significant covariates were fitted in the final model in order to adjust for their possible confounding effects. Therefore, data were extracted for 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 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. These were included in our univariate analysis models from which significant covariates (those which

had a significant association with both the exposure and outcomes) were added to the final Cox models.

Statistical Analysis

Subjects with missing values for eGFR and ACR at baseline were further excluded. A small proportion of HbA1c, eGFR, weight, SBP and DBP records at baseline 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. Differences between the baseline categorical and continuous variables within the four groups were compared using Pearson's chi-squared test and linear regression respectively.

Mortality rates were presented as 5-year Kaplan-Meier estimates. Cox proportional hazard model was used to estimate the marginal and adjusted mortality ratios (HRs) with 95% confidence intervals, comparing the mortality in all the groups to Group 1 (Low eGFR + High ACR). In our multivariate Cox regression models in which we evaluated the association between poor renal function and all-cause mortality, the identified significant baseline covariates were included.

We did further Cox regression analysis to explore the risk of cardiovascular events (non-fatal stroke and myocardial infarction) and a 3-point composite of MACE (Major Adverse Cardiovascular Event) including all-cause mortality, non-fatal myocardial infarction and stroke; in the patient groups.

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 15.

Ethical Approval:

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

Results

Patient Characteristics.

Only 18,227 patients in the dataset met our inclusion criteria in which group 2 had the least number of patients (13.8%). The overall mean age was 61.5±14 years. Slightly above half (53.2%) of the population were males. The overall mean HbA1c and BMI were 8.7±1.8% (72mmol/mol) and 32.5±6.9kg/m^2 respectively. These are summarised in Table 1.

The mean eGFR was 62.9±21.2 and this significantly increased from group 1 to 4 ($p < 0.001$). Systolic BP slightly reduced across the groups ($p = 0.04$) but diastolic BP increased ($p = 0.01$). No significant differences were found in weight, duration of diabetes or lipid profiles ($p > 0.05$). On the other hand, there were significant difference in gender ($p < 0.001$); socio-economic status ($p<0.001$); smoking and alcohol status ($p<0.001$); and BMI ($p=0.018$) between the study groups (Table 1).

Primary Endpoint – Risk of All-cause Mortality and Cardiovascular (CV) Events

Crude Mortality Rates: There were 1025 deaths in the study population after a 5-year follow up period, with a total follow-up time of 71,624 person-years. The proportion of mortality significantly decreased across the group from 8.5% in group 1to 3.2% in group 4 (p-value for trend = 0.012). Similarly, the 5-year probability of survival for all-cause mortality was significantly lower in group 1 (89%) than in group 2 (90%), group 3 (95%) and group 4 (96%) (Log rank test p-value < 0.001) (Figure 1). The overall crude mortality rate was 14.3 per 1000person-years (95% CI: 13.5 to 15.2) with the greatest mortality rate in group 1 - 21.7 per 1000 person-years (95% CI: 19.8 – 23.7) and the least in group 4 - 8.1 per 1000 person-years (95% CI: 6.9 – 9.5) (Figure 2).

Risk of All-cause Mortality: Compared to group 1 (patients with low eGFR + high ACR), the risk of all-cause mortality was 6% lesser (aHR: 0.94; 95%CI: 0.79 to1.12) in group 2; 20%

lesser (aHR: 0.80; 95%CI: 0.68 to 0.96) in group 3; and 28% lesser; (aHR: 0.72; 95%CI: 0.59 to 0.87)in group 4, following adjustment for confounders (see Table 2).

Secondary Endpoints – Risk of Composite MACE and Cardiovascular Events.

Crude Event Rates: As shown in Table 2, a total of 1,794 composite events of MACE occurred after a 5-year follow up period, amounting to 63,698 person-years. This signified a crude event rate of 28 per 1000 person-years (95%CI: 27 – 30). Group 1 had the greatest proportion of the events (Table 2), as well as the lowest probability of survival (80%) compared to 83%, 90% and 91% in groups 2, 3 and 4 respectively, after 5 years (Log rank test p-value < 0.001, Figure 3A).

Similarly, a total of 764 cardiovascular events were recorded after 5 years (Crude event rate: 12 per 1000 person-years; within a total of 63,746 person-years. The crude incidence rates of CV events significantly decreased from Group 1 to 4 (p-value for trend <0.001).Similarly, the 5-year survival curve showed the same pattern (Log rank test p-value < 0.001, Figure 3B)

Risk of Composite MACE and Cardiovascular Events: Table 2 also shows that the risk of composite MACE was 7% lesser (aHR: 0.93; 95%CI: 0.82 to1.07) in group 2; 18% lesser (aHR: 0.82; 95%CI: 0.72 to 0.93) in group 3; and 27% lesser; (aHR: 0.73; 95%CI: 0.63 to 0.84) in group 4 compared to group 1 patients (with low eGFR + high ACR) following adjustment for confounders.

Similar pattern was shown in the risk of cardiovascular events in which there were 7%, 40% and 46% reductions in the risk of stroke and MI in groups 2, 3 and 4 respectively, compared to group 1 (Table 2)

Discussion

In this study of 18,227 patients with insulin treated T2D, we found that the combination of reduced eGFR with increased ACR was associated with the greatest risk of premature death, followed closely by those with reduced eGFR and normal ACR levels. This observation demonstrates that quantitative information about eGFR and albuminuria status is an independent predictor of total mortality, thus expanding prior observations and supporting the hypothesis that eGFR and ACR provides synergistic insight into the association between diabetic kidney disease and total mortality risk, even in this cohort of insulin treated T2D, which by definition is at high risk of CV disease and mortality. Interestingly we observed that individuals with reduced eGFR but normal ACR has a higher risk of mortality compared with those with normal eGFR but raised ACR.

While it had long been recognised that individuals with reduced eGFR had high rates of cardiovascular disease, [24] it was not until 2004 when Go and colleagues demonstrated a large exponential increase in the age-standardised rate for all-cause mortality and cardiovascular events over a three-year period in subjects with eGFR <60 mL/min. Subsequently, CKD Prognosis Consortium [25] provided a more comprehensive evidence about the prognostic impact of eGFR and albuminuria on mortality and kidney outcomes. In addition to eGFR, proteinuria, either measured as total urinary protein or as urine albumin, is also a potent predictor of mortality and cardiovascular risk [1,2]. This was again supported by the observation from the CKD Prognosis Consortium which demonstrated a linear increase in the risk of all-cause and cardiovascular mortality as urine albumin-to-creatinine ratio increases [25]. This increase in risk is independent of eGFR such that there is an additive effect of proteinuria on the risk of death or events at any level or stage of GFR.

While both eGFR and albuminuria independently associate with increased risk of cardiovascular disease, a key question for the practising clinician is whether they add anything to improve mortality prediction above the known traditional risk factors for cardiovascular disease such as age, hypertension or hyperlipidaemia among individuals who are already at high risk of premature death – as is the case in our insulin treated cohort here. To this end, our analysis for eGFR and albuminuria as a predictor of total mortality, has indeed independently adjusted for conventional cardiovascular risk factors. In contrast to our study, in the analysis of 27,000 patients in the TRANSCEND and ONTARGET randomised clinical trial who were at high cardiovascular risk, the addition of eGFR and albuminuria did not amount to a reduction in the number of subjects classified into the intermediate risk group [26]. Finally the PREVEND study group assessed the value of kidney measure to predict a composite endpoint of all-cause and cardiovascular mortality as well as incident cardiovascular events [27]. In this study, both eGFR and albuminuria were assessed separately against a model using Framingham cardiovascular risk factors. Albuminuria but not eGFR was associated with improved risk prediction. Of note, none of these studies were conducted specifically in people with T2D. Thus, mortality prediction in people with T2D, specifically those who are on insulin, represent a unique patient cohort, where combining eGFR and albuminuira offers additional prognostication for mortality outcome. However, whether increased ACR or reduced eGFR is a cause or simply a risk marker of mortality risk such that reducing ACR or increasing eGFR would improve mortality outcomes remains unclear and is beyond the remit of this present study. Nonetheless, in the context of albuminuria in people with T2D, recent data suggest that in addition to Renin Angiotensin System inhibitors, several glucose lowering treatment such as sodium-glucose cotransporter-2 inhibitors [28,29], and glucagon-like peptide-1 agonist [30,31], have been shown to improve ACR, as well as CV mortality outcomes and induce

weight loss. While the mechanism for the reduction of mortality 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 was associated with reduced CV event and total mortality compared with insulin alone [23]. Thus identification of patients at high risk of CV events based on ACR and eGFR 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, albuminuria and CV outcomes.

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 [32]. It is a secondary form of focal and segmental glomerulosclerosis (FSGS) manifested as proteinuria and progressive renal dysfunction [33]. 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. [34].

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. 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, the combination of elevated levels of ACR and reduced eGFR, are independently associated with increased risk of all-cause mortality in insulin treated patients with T2D, even after adjusting for known CV risk factors. This risk of mortality is followed closely with the group who had reduced eGFR but normal ACR. In view of recent advances in the management of CV disease and proteinuria in people with T2D, 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.

Conflict of Interest statement: All authors declare no conflict of interest in relation to the content of this manuscript

Reference

Reference

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Legend

Table 1 - Baseline Characteristics

Table 2 - Comparison of number of events, incidence rate and risk of the Primary and Secondary endpoints between the treatment groups

Figure 1 - Kaplan-Meier survival analysis plot for the primary endpoint –all cause mortality (log-rank test p value < 0.001)

Figure 2 – Graph of the Crude Incidence rate for primary endpoint – All-cause mortality. (Group 1: Low eGFR + High ACR (eGFR <60 and ACR ≥300); Group 2: Low eGFR +Low ACR (eGFR <60 and ACR <300); Group 3: High eGFR + High ACR (eGFR ≥60 and ACR ≥300); and Group 4: High eGFR + Low ACR (eGFR ≥60 and ACR <300)

Figure 3 - Kaplan-Meier survival analysis plots for the secondary endpoint (A) 3-point composite of MACE (log-rank test p value < 0.001); (B) Cardiovascular Events (log-rank test p value < 0.001)

Table 1: Baseline characteristics

Categories (Number)	Low eGFR + High ACR (Group 1) (5,563)	Low eGFR + Low ACR (Group 2) (2,522)	Hi eGFR + Hi ACR (Group 3) (5,511)	Hi eGFR + Low ACR (Group 4) (4,631)	Total (18,227)
Demographics					
Age (yrs), Mean (SD)	67.1 (11.9)	66.7 (11.5)	57.7 (13.5)	56.8 (13.5)	61.5 (13.6)
Gender, No. (%)					
Male	2820 (51)	1219 (48)	3079 (56)	2577 (56)	9,695 (53.2)
Townsend deprivation, No. (%)					
Least deprived	1128 (21)	514 (21)	999 (19)	946 (21)	3587 (19.7)
2nd quintile	1093 (21)	481 (20)	1043 (20)	880 (20)	3497 (19.2)
3rd quintile	1142 (21)	519 (21)	1116 (21)	953 (21)	3730 (20.5)
4th quintile	1133 (21)	515 (21)	1160 (22)	955 (21)	3763 (20.7)
Most deprived	832 (16)	387 (16)	913 (17)	727 (16)	2859 (15.7)
Smoking status, No. (%)					
Non-smoker	2760 (50)	1237 (49)	2613 (47)	2251 (49)	8861 (48.6)
Ex-smoker	2175 (39)	997 (40)	1944 (35)	1625 (35)	6741 (37.0)
Current smoker	628 (11)	288 (11)	954 (17)	755 (16)	2625 (14.4)
Alcohol status, No. (%)					
Non-drinker	1919 (34)	875 (35)	1762 (32)	1360 (29)	5916 (32.5)
Ex-drinker	679 (12)	285 (11)	592 (11)	512 (11)	2068 (11.4)
Current drinker	2965 (53)	1362 (54)	3157 (57)	2759 (60)	10,243 (56.2)
Clinical Parameters, Mean (SD)					
HbA1c (%) [mmol/mol]	8.7 (1.8) [72]	8.5 (1.7) [67]	8.8 (1.9) [73]	8.6 (1.8) [70]	8.7 (1.8) [72]
BMI (kg/m^2)	32.7 (6.7)	32.6 (6.7)	32.4 (6.9)	32.3 (7.0)	32.5 (6.9)
Diabetes duration* (yrs)	4.9 (4.9)	4.9 (5.4)	3.9 (4.6)	3.7 (4.7)	4.3 (4.9)
Duration on insulin (yrs)	4.3 (6.8)	4.5 (6.5)	3.6 (5.9)	3.6 (6.1)	3.9 (6.4)
Weight (Kg)	91.0 (18.4)	89.7 (18.6)	92.2 (19.2)	91.4 (18.6)	91.3 (18.7)
Height (m)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
SBP (mmHg)	138.8 (23.6)	135.9 (22.6)	136.5 (23.0)	133.4 (22.3)	136.3 (23.0)

DBP (mmHg)	74.4 (10.9)	75.1 (10.9)	76.8 (10.7)	77.4 (10.6)	76.0 (10.8)
eGFR (mls/min/1.73m^2)	42.9 (12.7)	46.3 (10.8)	76.8 (12.8)	79.1 (14.0)	62.9 (21.2)
TC (mmol/l)	4.5 (1.3)	4.3 (1.2)	4.7 (1.4)	4.5 (1.3)	4.5 (1.3)
HDL (mmol/l)	1.2 (0.4)	1.2 (0.4)	1.2 (0.4)	1.3 (0.5)	1.2 (0.4)
LDL (mmol/l)	2.3 (1.1)	2.2 (1.0)	2.5 (1.1)	2.4 (1.1)	2.4 (1.1)
Triglyceride (mmol/L)	2.2 (1.2)	2.0 (1.2)	2.1 (1.2)	1.8 (1.2)	2.0 (1.2)
Albumin (g/L)	4.0 (0.4)	4.0 (0.4)	4.1 (0.4)	4.1 (0.4)	4.0 (0.4)
BMI Categories, No. (%)					
Normal	696 (13)	316 (13)	762 (14)	681 (15)	2455 (13.5)
Overweight	1315 (24)	594 (24)	1315 (24)	1119 (24)	4343 (23.8)
Obese	3552 (64)	1612 (64)	3434 (62)	2831 (61)	11,429 (62.7)
GLTs, No. (%)					
Metformin	4668 (83.9)	2105 (83.5)	4807 (87.2)	4013 (86.7)	15,593 (85.6)
Sulphonylurea	4339 (78.0)	1951 (77.4)	4129 (74.9)	3375 (72.9)	13,794 (75.7)
Thiazolidinedione	1696 (30)	755 (30)	1803 (33)	1500 (32)	5,754 (31.6)
GLP-1RA	454 (8)	194 (8)	732 (13)	563 (12)	1,943 (10.7)
SGLT2i	15 (0)	7 (0)	35 (1)	28 (1)	85 (0.5)
Glinides	262 (5)	108 (4)	238 (4)	182 (4)	790 (4.3)
DPP4i	735 (13)	289 (11)	840 (15)	705 (15)	2,569 (14.1)
Use of Medications, No. (%)					
Aspirin	5459 (98)	2468 (97)	5232 (96)	4348 (98)	17,507 (96.1)
Antihypertensive	5175 (95)	2332 (94)	4634 (89)	3795 (87)	15,936 (87.4)
- ACE inhibitors	4,616 (85)	2,073 (84)	4,043 (77)	3,291 (76)	14,023 (80)
- ARBs	1,865 (34)	814 (33)	1,501 (29)	1,185 (27)	5,365 (31)
- Calcium channel blockers	3,363 (62)	1,478 (60)	2,693 (52)	2,110 (49)	9,644 (55)
- Beta-blockers	3,085 (57)	1,352 (55)	2,421 (46)	2,020 (46)	8,878 (51)
LLTs	4955 (91)	2257 (91)	4799 (92)	3965 (91)	15,976 (87.7)
Comorbidities, No. (%) [c]					
CHD	2003 (36)	906 (36)	1393 (25)	1158 (25)	5,460 (30.0)
PAD	924 (17)	395 (16)	626 (11)	463 (10)	2,408 (13.2)
Heart Failure	1029 (18)	444 (18)	577 (10)	407 (9)	2,457 (13.5)
Hypoglycaemia	1147 (21)	497 (20)	831 (15)	710 (15)	3,185 (17.5)

***Diabetes duration is the period between the diagnosis of diabetes to the initiation of Insulin therapy*

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

	Low eGFR + High ACR (Group 1)	**Low eGFR + Low ACR (Group 2)**	**Hi eGFR + Hi ACR (Group 3)**	**Hi eGFR + Low ACR (Group 4)**	**Total**
	5,563	**2,522**	**5,511**	**4,631**	**18,227**
All-Cause Mortality					
No of events/person-years	471/21,747	195/9999	211/21,645	148/18,233	1025/71,624
Absolute rates[a] (95%CI)[b]	21.7 (19.8 – 23.7)	19.5 (17.0 – 22.4)	9.7 (8.5 – 11.2)	8.1 (6.9 – 9.5)	14.3 (13.5 – 15.2)
aHR[c] (95%CI)	**1 (reference)**	**0.94 (0.79 – 1.12)**	**0.80 (0.68 – 0.96)**	**0.72 (0.59 – 0.87)**	-
p-value	-	0.515	0.013	0.001	-
3-point Composite MACE					
No of events/person-years	773/18,604	324/8,681	400/19,638	297/16774	1794/63,698
Absolute rates[a] (95%CI)[b]	41.5 (38.7 – 44.6)	37.3 (33.5 – 41.6)	20.4 (18.5 – 22.5)	17.7 (15.8 – 19.8)	28.2 (26.9 – 29.5)
aHR[c] (95%CI)	**1 (reference)**	**0.93 (0.82 – 1.07)**	**0.82 (0.72 – 0.93)**	**0.73 (0.63 – 0.84)**	-
p-value	-	0.319	0.002	<0.001	-
Cardiovascular Events					
No of events/person-years	299/18,625	129/8,692	189/19,648	147/16779	764/63,746
Absolute rates[a] (95%CI)[b]	16.0 (14.3 – 18.0)	14.8 (12.5 – 17.6)	9.6 (8.3 – 11.1)	8.7 (7.5 – 10.3)	12.0 (11.2- 12.9)
aHR[c] (95%CI)	**1 (reference)**	**0.93 (0.76 – 1.14)**	**0.60 (0.50 – 0.71)**	**0.54 (0.45 – 0.66)**	-
p-value	-	0.486	<0.001	<0.001	-

[a] *Absolute Rate at 1000 person-years*

[b] *95% CI – 95% Confidence Interval*
[c] *aHR (Adjusted Hazard Ratio). Adjusted for age, gender, duration of diabetes, Systolic BP, diastolic BP, HbA1c and Socio-economic status*