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The relationship between acute kidney injury and chronic kidney disease in patients with Type 2 Diabetes: an observational cohort study

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Significance Statement

There is currently a limited understanding of the interplay between AKI and CKD in people with type 2 diabetes and how this compares to the non-diabetic population. Through development of an algorithm which can be applied to routinely collected biochemistry data, this study has quantified the risk of AKI in patients with diabetes and how this relates to CKD. These findings have both important epidemiological and clinical implications demonstrating that the risk of AKI and associated adverse outcomes in this population of patients is currently underestimated. Increasing awareness may allow for implementation of simple interventions which prevent the occurrence of AKI thereby improving patient outcomes.

Abstract

Background

Type 2 diabetes is one of the leading causes of chronic kidney disease (CKD) and an independent risk factor for Acute Kidney Injury (AKI). This study aims to evaluate rates of AKI and how this relates to CKD status and further renal function decline in patients with and without type 2 diabetes using electronic healthcare records.

Methods

Study design was a retrospective cohort study. The negative-binomial model for counts with follow-up time as offset, adjusted for sex and age was used to evaluate AKI rates in people with and without diabetes depending on CKD status. A mixed effect linear model adjusted for demographic characteristics and co-morbidities was developed to evaluate decline in glomerular filtration rate (GFR) before and after an AKI event depending on diabetes and CKD status.

Results

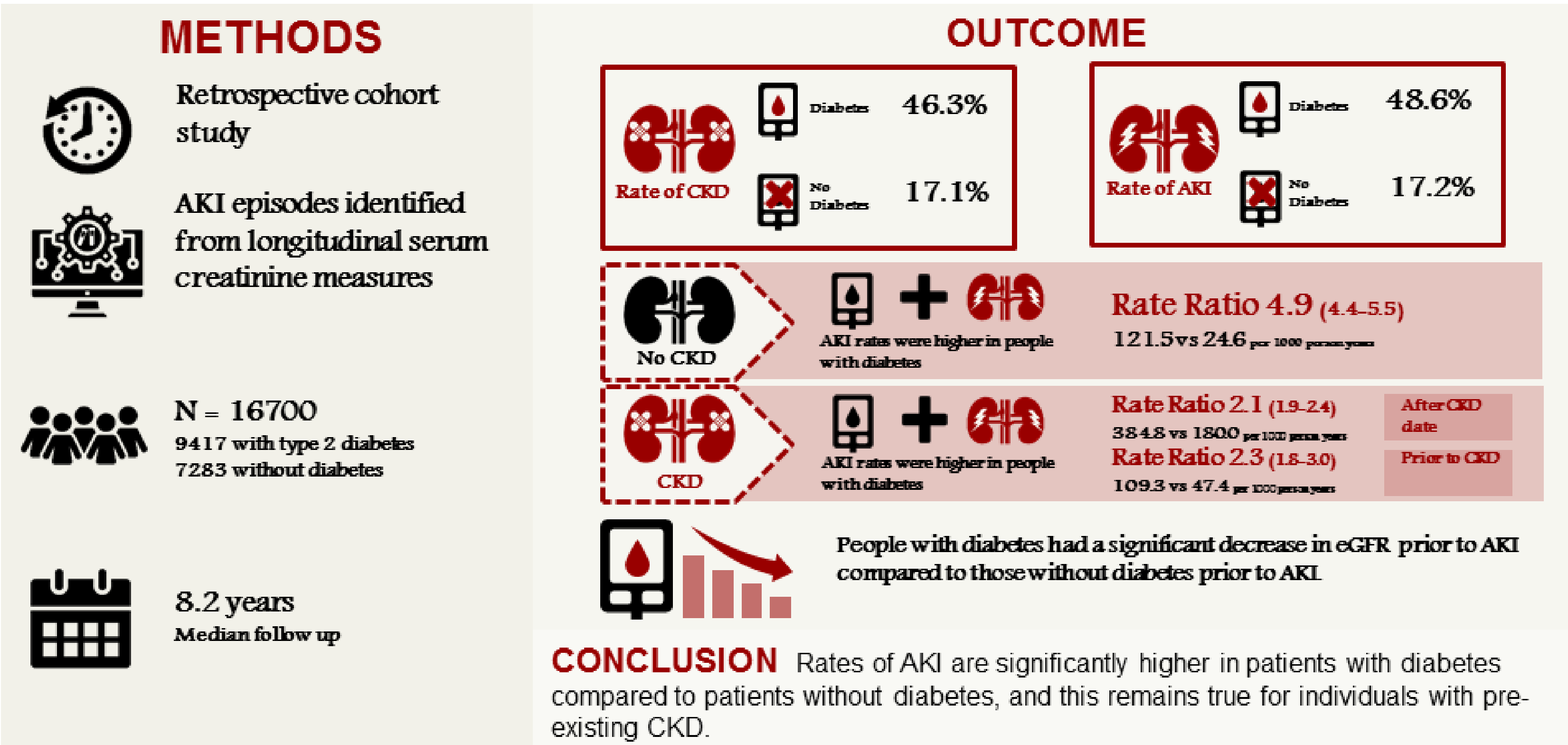
The cohort was formed of 16700 participants with a median follow-up of 8.2 years. 9417 of these had type 2 diabetes and 7283 had no diabetes. 48.6% (N=4580) of participants with diabetes developed AKI compared to 17.2% (N=1257) of controls. 46.3% (N=4359) of those with diabetes had CKD vs 17.1% (N=1251) of controls. In the absence of CKD, AKI rate was five times higher in people with diabetes than controls (121.5 vs 24.6 per 1000 person-years, Rate Ratio RR=4.9, 95% CI 4.4-5.5), whereas for people with CKD, rate of AKI was twice higher in people with diabetes than controls (384.8 vs 180.0 per 1000 person-years, RR=2.1, 95% CI 1.9-2.4 after CKD date and 109.3 vs 47.4 per 1000 person-years, RR=2.3, 95% CI 1.8-3.0 prior to CKD). Fall in eGFR slope before AKI was steeper in people with diabetes compared to those without diabetes. After AKI episodes, loss of eGFR became steeper in people without diabetes, but did not increase in those with diabetes and pre-existing CKD.

Conclusion

Rates of AKI are significantly higher in patients with diabetes compared to patients without diabetes, and this remains true for individuals with pre-existing CKD.

Keywords: acute kidney injury; chronic kidney disease; type 2 diabetes; epidemiology; incidence.

The relationship between AKI and CKD in patients with T2DM



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Introduction

Type 2 diabetes is one of the leading causes of chronic kidney disease (CKD) and end-stage renal disease worldwide [1]. A large proportion of patients who develop CKD experience prior episodes of acute kidney injury (AKI), with evidence suggesting that kidney function does not fully recover following the AKI event[1]. Moreover, CKD is a well-known risk factor for AKI, with recent studies suggesting that there is a considerable overlap between the pathophysiology underlying the two conditions [2]. However the relationship is likely to be complex and remains poorly understood.

Type 2 Diabetes (T2D) has been reported as an independent risk factor for AKI in previous observational studies [3,4] and progressive decline in kidney function has also been well described in this population [1]. Both AKI and CKD have been identified as risk factors for cardiovascular disease [5], which is the most frequent complication in T2D. Despite the increased access to routinely collected health care data, there are few observational studies evaluating the risk of AKI in people with T2D [6,7], and even fewer simultaneously investigating AKI and CKD in this population [1]. As a result, there is a limited understanding of the interplay between AKI and CKD in people with T2D and how this compares to the non-diabetic population. [8] Previously, quantification of AKI from routine health care data was limited to the use of hospitalization and death using International Classification of Diseases (ICD) coding [6]. More recently, the Kidney Disease Improving Global Outcome (KDIGO) definition for AKI based on changes in serum creatinine (SCr) has been universally adopted which has enabled a more uniform approach [9,10]. However, this approach comes with its challenges, which mainly relate to the application of the KDIGO definition. In clinical practice AKI can only be identified when previous tests within a time window are available for comparison, which may not be the case when blood testing is infrequent. To overcome this, various time windows to define baseline creatinine have been proposed, including the use of both prior and post index values [11–16]. Despite the numerous definitions, the variation in the intensity of blood sampling may still lead to misclassification between AKI and CKD [10]. This highlights the importance of accurate definitions for both AKI and CKD that can be used in database studies to help understand the contribution of AKI to CKD and CKD progression, as well as the risk of developing AKI in patients with CKD.

The aim of this study was to develop an algorithm to examine rates of AKI in patients with and without T2D depending on CKD status using routinely collected healthcare data, and to investigate whether the association between AKI on GFR decline is different in people with T2D compared to people without diabetes.

Methods

Study population

The design is a retrospective cohort study of people from the Tayside region of Scotland (n = 402641 on 1 January 2012) which represents about 8% of the Scottish population. People with and without type 2 diabetes that were matched by age, sex and general practice were recruited in the Genetic of Diabetes Audit and Research in Tayside Study (GoDARTS) from December 1998 to October 2012 which includes either at diabetes or eye screening clinics or through their GP [17]. About 50% of the patients with T2D at that time from Tayside region were recruited into GoDARTS [8]. Participants attended a clinic at recruitment, where a serum sample was collected to allow a number of routine biochemical measures to be measured. Recruitment was treated as the baseline for this study with participants being followed up until May 2017 using comprehensive electronic records.

The current study includes participants from GoDARTS with type 2 diabetes at baseline to form the diabetic group and patients with no diabetes to form the control group. To allow for an accurate estimation of AKI rate in patients without diabetes, patients from GoDARTS who develop diabetes later during the follow-up time were not included in the study. Also, patients without SCr measures on or after recruitment were not included. For the eGFR slope analysis, patients with three or more SCr values with at least one-year gap between the first and last measure prior to the first AKI episode (if applicable) and three or more SCr measures after the AKI episode with at least 90 days gap between the first and last of these measures were included. Patients with an AKI event prior to analysis were excluded.

Datasets and variables

The GoDARTS study was linked through an individual-specific anonymised identifier to the following clinical datasets: information on diabetes including type of diabetes and date of diagnosis was acquired from the Scottish Care Information – Diabetes Collaboration (SCI-DC) Diabetes Summary and Longitudinal data [18]. SCr values were obtained from the laboratory biochemistry system, comprising of SCr measures from both primary and secondary care. The Scottish Renal Registry was used to identify patients receiving renal replacement therapy (RRT) and date of therapy initiation [19]. The Scottish Morbidity Records 01 (SMR01) for hospital admission was used to evaluate patient comorbidities including coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease and liver disease based on ICD-10 codes at admissions prior to recruitment. The community prescribing data was used to assess whether the patient have been prescribed any of the following classes of anti-hypertensive drugs: diuretics, angiotensin converting enzyme (ACE) Inhibitors, angiotensin receptor blockers (ARBs), beta-blockers and calcium channel blockers [20]. The demographics dataset was used to determine participant sex and date of birth which was used to calculate age at recruitment. Patients who had moved out of Tayside health board were treated as lost to follow-up. The Community Health Index death dataset (CHI - the NHS Scotland population register) was used to obtain date of death. Follow-up time was defined as the time from recruitment until May 2017, or date of RRT, or date of death, or date the patient moved out of Tayside health board, which ever occurred first.

Development of an algorithm to identify AKI episode from serum creatinine tests

SCr measures from Jan 1988 to May 2017 were used in the analysis; measures obtained after initiation of RRT were not included. All assays in the region are done in the same regional laboratory, and SCr measures were adjusted for changes in assays over time. AKI was defined based on the KDIGO criteria [9]. As testing was infrequent with large time gaps in some patients, leading to a lack of baseline being calculated , we developed an algorithm to calculate baseline creatinine incorporating both prior and post index creatinine measurements in the definition of baseline (Table 1). Severity of AKI (Stages 1-3, Table 1) was defined using KDIGO criteria [9]. To identify AKI episodes, SCr that were within seven days apart were grouped into single episodes of care. Within the episode of care, a 1.2-fold increase in creatinine from baseline was used to evaluate SCr values measured before and after each Scr value flagged as AKI case in order to assess AKI initiation and recovery and determine the start and the end of the AKI episode [21]. Furthermore, if two AKI episodes were within seven days apart then the two episodes and SCr values in-between were grouped into one AKI episode [21]. The length of AKI episode was calculated based on start and end dates of the AKI episode and was used to assess whether AKI had progressed to Acute Kidney Disease (AKD), defined as an AKI lasting more than seven days [22]. The highest AKI stage within the episode was used to define the stage of the AKI episode.

Estimated Glomerular filtration rate (eGFR) and CKD status

The CKD-EPI formula was used to estimate glomerular filtration rate (eGFR) from serum creatinine [23]. Development of CKD was defined according to the CKD-KDIGO guideline as eGFR < 60 ml/min per 1.73m^2 present on at least two occasions at least 90 days apart [23]. To avoid misclassification between AKI and CKD, eGFR values contained within AKI episodes were first removed from the longitudinal data. The variation in the intensity of blood sampling, led to eGFR estimates either too distant (in healthy individuals) or too dense over time (in sicker patients). As a result a median smoother was applied to the remaining eGFR values based on a set of rules derived from the CKD-KDIGO definition as follows; for each date of index blood test, three eGFR baseline values were calculated using the median eGFR for the period 365 to 91 days prior to the index date, then 7 days prior to 7 days after index, and 91 to 365 days after index date respectively. CKD diagnostic date was established when at least two of the three medians were below 60 ml/min per 1.73m^2 (Table 2).The CKD date was then compared against recruitment date to determine whether participants had prevalent CKD at recruitment or they developed incident CKD during follow-up.

Primary and secondary outcomes

The primary outcome was the number of AKI episodes per person during follow-up, which was used to calculate AKI episode rates per 1000 patients per year (including recurrent events) and AKI rate ratios in people with type 2 diabetes vs non-diabetes depending on CKD status. The secondary outcome was eGFR decline over time calculated as the eGFR slope of the linear regression model per one-year unit increase. Other outcomes were number of patients experiencing AKI during follow-up, length of AKI episodes and AKI stage.

Statistical methods to analyse AKI rates depending on CKD status

Counts and proportions for categorical variables and mean and standard deviation (SD) or median and inter-quartile range (IQR) for quantitative data were used to describe the demographic characteristics. These were reported in people with and without diabetes and by CKD status (no-CKD at recruitment or during follow-up, pre-CKD to account for the period prior to CKD development for those that developed CKD during follow-up, and post-CKD to include the post- CKD period for those that had CKD at recruitment or developed CKD during follow-up. The difference between two independent proportions were calculated based on Wilson's method [24]. The negative-binomial model for counts with log-link and follow-up time as offset was used to analyse the primary outcome and to estimate rates of AKI episodes in cases and controls depending on CKD status. The relationship between the outcome and the explanatory variable (sex, age and diabetes status) was assumed linear via the log-link function [25]. Un-adjusted AKI rates and rates adjusted for age and sex were provided together with the corresponding rate ratios (RRs) for association. Further adjustment for co-morbidities at recruitment was performed to investigate how much of the effect of diabetes on AKI incidence rates can be explained by pre-existing co-morbidities. The chi-square test was used to investigate the association between diabetes and AKI stage and the non-parametric Mann-Whitney test was used to investigate differences in the length of AKI episodes between the T2D vs control groups.

Sensitivity analyses was conducted to evaluate and compare incidence rates for stages 2 and stage 3 AKIs, and AKIs longer than 48 hrs respectively, as well as for AKIs occurring during hospital admission in people with diabetes vs controls.

Statistical methods to analyse of longitudinal eGFR data

EGFR values measured during AKI episodes were first removed from the data and replaced at the start of the episode with a baseline eGFR calculated as the median eGFR for the seven days prior to the AKI episode if measures were available, otherwise the median eGFR of values measured between 365 and 8 days prior to the start of the AKI episode was used. A linear-mixed effect model was used to analyse the association between AKI and eGFR decline from the longitudinal eGFR data. AKI was included into the model as a time-varying factor with three levels: no AKI for patient with no AKI event during the follow-up, pre-AKI for patient with an AKI event during follow-up for the period prior to the AKI and post-AKI for the period after the AKI episode [26]. To identify significant changes in eGFR slope pre and post AKI event and whether these changes differ between people with T2D and controls an interaction term between AKI, T2D status and time was accommodated into the model. Baseline variables such as sex, age (treated as age groups) and presence of cardiovascular diseases were fitted into the model with both fixed intercept and slope. An interaction between these variable and T2D was also included and Akaike Information Criterion (AIC) was used for variable selection. Given the strong interaction effects between AKI, diabetes and CKD status, the analysis was conducted separately for people with no CKD at recruitment and those that had an established CKD diagnosis prior to recruitment. The mixed model was fitted with both random intercept and slope per individual before and after the AKI episode (when applicable), assuming an unstructured covariance matrix for the random effects.

Data linkage and analysis was carried out using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

The cohort

A total of 18306 participants were recruited into the GoDARTS cohort, of which 16700 met the selection criteria. 9417 of patients had type 2 diabetes at recruitment and 7283 did not have diabetes at recruitment nor developed it later and formed the control group. 1606 patients were excluded from the current study, of which 681 had other types of diabetes, 720 developed diabetes after recruitment and 205 did not have SCr tests on or after recruitment (Figure 1). Table 3 shows baseline characteristics of the cohort. People within type 2 diabetes were older than controls (66.9 vs 60.8 years old, difference 6.0 years, 95% CI 5.7-6.4) and 44.0% were females compared to 51.4% in the control group (difference 7.4%, 95% CI 5.8-8.9). People with T2D had a lower eGFR at baseline compared to controls (76.6 vs 84.3, difference 7.7, 95% CI (7.1-8.29), 26.6% of people with T2D had CKD at recruitment compared to only 9.1% in the control group (difference 17.5%, 95% CI (16.3-18.6), and there was a higher percentage of people with cardiovascular disease in the diabetic group compared to control (Table 3). The mean (SD) follow-up time from recruitment was 8.2 (3.5) years for people with type 2 diabetes vs (2.4) for controls.

AKI and AKI episodes

Table 4 shows summary statistics of SCr measures from recruitment and describes the frequency of AKI in the two groups. A total of 512615 SCr tests were recorded from recruitment; of those 387657 (75.6%) were from patients with type 2 diabetes. The median (IQR) number of SCr measures per individual during the follow-up were 31 (19-51) in type 2 diabetes vs 11 (4-21) in controls. Including post AKI creatinines in order to calculate a baseline value increased the yield of AKI cases from 28306 to 40567. A breakdown of AKI cases identified using the different baseline SCr definitions using pre and post Index SCr measures is shown in Table S1 in the supplementary material. After grouping successive tests into episodes, a total of 13928 AKI episodes were identified from recruitment until end of follow-up. Of these 11647 were experienced by patients with diabetes. AKI occurred in 5837 patients representing 48.6% (N=4580) of patients with type 2 diabetes vs 17.2% (N=1257) of controls (difference 31.4%, 95% CI 30.0-32.7). More than 50% of patients with diabetes experiencing AKI had recurrent AKI, whereas the majority of patients in the control group with AKI had only one episode of AKI during follow-up (Table 5). Overall 54.2% of AKI episodes lasted no more than two days, a further 26.5% between 2 to 7 days, and the remaining 19.3% of AKI episodes were longer than 7 days resulting in AKD. Less than five AKI/AKD episodes were greater than 90 days, however after inspection it was revealed that these occurred during hospitalisation due to other complications. 76.3% of AKI episodes were stage 1 with the rest being stage 2 or 3. Diabetes was significantly associated with increased AKI episode length (p-value <0.001) but not significantly associated with AKI stage (p-value=0.737).

AKI and CKD

Figure S1 illustrates the complex interplay between AKI/AKD and CKD and the many trajectories evolving during the course of the disease. The way AKI initiates and develops can take many forms ranging from one acute kidney insult which improves rapidly with full recovery within seven days (figure a2) to one or more acute kidney insults during the course of the disease which progress to AKD requiring more than seven days to resolve. There are also cases when serum creatinine does not fully reverse after an AKI episode leading to the development of CKD (Figure d2). This further shows that, while some patients fully recover following an episode of AKI and never develop CKD (Figure a1-a3), others may experience a rapid kidney decline following an AKI episode (figure d1-d3). At the same time there is also the possibility to develop CKD without prior AKI episodes, and only experience AKI later as superimposed on CKD (figures b1-b3, c1-c3).

Table 6 describes the characteristics of people with diabetes vs controls in terms of their sex, age and follow-up time as well as frequency of AKI during follow-up depending on CKD status. 26.6% (N=2504) of people with diabetes had CKD at recruitment and further 19.7% (n=1855) developed the condition during follow-up leading to a total of 46.3% (n=4359) people with CKD in the diabetic group compared to 17.1% (n=1251) in the control group (difference 29.2%, 95% CI 27.8-30.4). In people with diabetes and CKD, 50.3% were female (n=2192) compared to only 38.6% (n=1954) in those without CKD (difference 11.7%, 95% CI 9.7-13.7). Also, people with diabetes developed CKD at a younger age compared to people in the control group (mean age 74.1 vs 77.6 years, difference 3.5 years, 95% CI 3.0-4.0) 66.1% (n=2883) of people with diabetes who developed CKD experienced AKI superimposed on CKD in the diabetic group compared to 45.5% (n=569) in the control group (difference=20.6%, 95% CI 17.5-23.8). Additionally, 26.6% (n=493) of people with diabetes who developed CKD after recruitment had at least one episode of AKI prior to development of CKD, the corresponding figure in the control group being 9.9% (n=58, difference 16.7%, 95% CI 13.3-19.8). The proportion of people experiencing AKI was significantly higher in the diabetic group compared to the control group for those patients who did not have CKD at recruitment nor develop it later; 31.7% (n=1602) vs 10.8% (n=651) in the control group (difference 20.9%, 95% CI 19.4-22.4).

Estimating AKI episode rates in people with and without diabetes

Table 6 shows estimates of AKI episode incidence rates and rate ratios for people with diabetes vs control un-adjusted and adjusted for sex and age at recruitment. Regardless of CKD status, adjusted AKI rates were 4.7 times higher in people with diabetes compared to controls (adjusted rate 179.0 vs 38.4 per 1000 person-years, RR=4.7, 95% CI 4.3-5.0). In particular, people with diabetes and no CKD experienced AKI at a rate almost five times higher than people with no diabetes (adjusted rate 121.5 vs 24.6 per 1000 person-year, RR=4.9, 95% CI 4.4-5.5), whereas in people with CKD rate of AKI for those in the diabetic groups was twice higher than in the corresponding control (adjusted rate 384.8 vs 180.0 per 1000 person-year, RR=2.1, 95% CI 1.9-2.4). Similarly, people with diabetes who develop CKD after recruitment experience episodes of AKI at a rate twice higher than those in the control group (adjusted rate 109.3 vs 47.4 per 1000 person-year, RR=2.3, 95% CI 1.8-3.0). It is noteworthy that the AKI rate in people with diabetes in the absence of CKD was very close to AKI rate prior to development of CKD (121.5 vs 109.0 per 1000 person year).

Additional model adjustment for other co-morbidities at baseline only partially reduced the association between diabetes and AKI incidence rates (Table S4 in Supplementary material, RR=3.85, 95%CI 3.44-4.32 in people with no CKD at recruitment or during follow-up, and RR=2.01 95%CI 1.82-2.22 in people with CKD at recruitment or during follow-up time).

Sensitivity analysis for the AKI rate analysis

The sensitivity analysis conducted to estimate rates for stage 2 and 3 AKIs show consistent results with the main analysis (Tables S2 in the supplementary material). The results show that people with diabetes and no CKD experience stage 2 and 3 AKIs at a rate that is over five time higher than people in the control group (adjusted mean rate 30.6 vs 5.5 per 1000 person-year, RR=5.5, 95% CI 4.6-6.6) whereas in people with CKD rate of AKI for those in the diabetic groups was twice higher than in the corresponding control group (adjusted mean rate 76.5 vs 38.9 per 1000 person-year, RR=2.1, 95% CI 1.8-2.5). Similarly, analysis of rates of AKIs lasting over 48hrs or AKIs during hospital admission show consistent results with the main analysis (Table S3 and Table S4).

Estimating the effect of AKI on eGFR slope over time

Of the 16700 people included in the initial analysis, there were 3250 people with AKI prior to recruitment which were not included in the eGFR analysis. A further 2558 people did not meet the selection criteria of which 1324 had an AKI post recruitment (738 with T2D and 386 with no diabetes). As a result a total of 10892 people with 279391 SCr measures were included in the eGFR longitudinal data analysis. Of these 5665 had T2D and 5227 were from the control group (Figure 1, Tables S6 and S7 in the supplementary material). Of the 10892, 2470 people experienced an AKI during follow-up of which 1859 had T2D and 611 had no diabetes. People with no CKD at recruitment had a significant higher decline in eGFR in the period pre-AKI compared to no-AKI regardless of diabetes status, but rate of decline was significantly higher in people with diabetes (Figure 2, Table S6 in the supplementary material: eGFR slope pre-AKI vs no-AKI =-1.14, 95% CI (-1.24 to -1.03) in people with T2D and -0.29, 95%CI (-0.45 to -0.11) in controls, slope difference=-0.85, 95%CI (-1.05 to -0.65)). A further decrease in rate was observed in the control group in the period post-AKI compared to pre-AKI in both T2D and control groups, the increase in rate of decline was only marginally significant in people with T2D (eGFR slope post-AKI vs pre-AKI =-0.29, 95% CI (-0.59 to 0.01)), whereas it was significant in the control group (eGFR slope post-AKI vs pre-AKI =-0.55, 95% CI (-1.08 to -0.03)), however the difference between T2D group and control was not significant (slope difference=0.26, 95%CI (-0.34 to 0.86)). Sex was significantly associated with eGFR with males having a higher mean eGFR than females in people with T2D and lower in control. No change in eGFR slope was observed between male and females in any of the subgroups. An increase in age was associated with a reduction in eGFR at baseline regardless of diabetes status, but significant differences in eGFR slope among the different age groups were observed only in people with T2D. Furthermore, people with peripheral vascular disease and hypertension had a significant further decline in eGFR slope regardless of diabetes status.

People with CKD at recruitment show a higher rate decline in eGFR in the period pre-AKI compared to no-AKI and this result was significant in the T2D group and marginally significant in the control group, but the difference between the two groups was not significant (Figure 2,Table S7 in the supplementary material: eGFR slope pre-AKI vs no AKI =-0.79, 95% CI (-1.05 to -0.52) in people with T2D and -0.40, 95%CI (-0.85 to 0.05) in controls, slope difference=-0.38 (-0.90 to 0.14)). The decline in eGFR rate post AKI compared to pre-AKI did not change in people with T2D diabetes (eGFR slope post AKI vs pre AKI=0.23, 95% CI (-0.24 to 0.71)), whereas AKI was associated with further eGFR decline post AKI compared to pre AKI period in controls (eGFR slope post AKI vs pre AKI =-0.84, 95% CI (-1.73 to 0.06)), with the post-AKI effect being significantly different between T2D and control groups (slope difference=1.07, 95%CI (0.06 to 2.08)). There was no significant eGFR difference between males and females in people with CKD at recruitment regardless of diabetes status. An increase in age was associated with a reduction in eGFR at baseline regardless of diabetes status, and older people with diabetes appeared to have a lower eGFR decline than younger ones. None of the cardiovascular diseases were significantly associated with eGFR at baseline or eGFR slope, however their effect was an important one as reflected in the model AIC and therefore they were retained in the model.

Discussion

In our study, we have quantified rates of AKI in patients with and without diabetes demonstrating the extent of the risk. Rates of AKI are significantly higher in patients with type 2 diabetes compared to those without with a 4.7 fold increase in AKI rate. In people with diabetes and preserved renal function, rate of AKI is 4.9 fold higher than people without diabetes whereas in people with CKD rate of AKI for those in the diabetic group is 2 fold higher than in non-diabetics. More than 50% of the patients with diabetes who develop AKI will suffer from recurrent events. Rates of CKD are also higher in patients with Type 2 diabetes with 46.3% developing CKD compared to 17.1% in those without diabetes.

Fall in eGFR slope before AKI was steeper in people with diabetes compared to those without diabetes. After AKI episodes, loss of eGFR became steeper in people without diabetes, but did not increase in those with diabetes and pre-existing CKD.

In comparison to other studies, progressive decline leading to CKD has been well described in people with type 2 diabetes [1], but AKI in diabetes mellitus have been less investigated [6,7,27,28]. Girman et al examined 119 966 patients with diabetes and 1 794 516 patients without diabetes from the General Practice Research Database. AKI incidence was markedly higher in their cohort: 198 per 100,000 person-years in patients with Type 2 diabetes compared with 27 per 100,000 patients-years among patients without diabetes (crude hazard ratio 8.0, 95% CI 7.4-8.7) [6]. They did not utilise a biochemical definition for AKI relying on clinical coding which can lead to significant under ascertainment [29] . In addition, a meta-analysis by James et al showed that the hazards rations for AKI were higher in participants with diabetes compared to those without diabetes at any level of eGFR [30]. Once again, the definition for AKI relied on administrative codes in these studies thereby under estimating milder forms of AKI. There are very few studies that have examined AKI and CKD simultaneously and recurrent AKI in this group of patients [31].

Our results are consistent with existing evidence indicating that diabetes is an independent risk factor for AKI [3,6,27]. However, reported AKI rates in people with diabetes vary greatly depending on the population studied (e.g. different specialist settings, age range) and the methods used for AKI identification (e.g. medical history, ICD10 coding or changes in SCr) [10]. Most of the prior studies have reported AKI incidence of new AKI cases within a given time window and therefore estimates relate to number of patients experiencing AKI. The algorithm developed in this study allows quantification of AKI rates based on number of AKI episodes including recurrent AKI. Our findings have important clinical implications. AKI is associated with adverse patient outcomes including increased mortality, future development of CKD and increased length of hospital stays [3,32,33]. It therefore places a significant financial burden on healthcare resources [34]. In our study over 75% of AKI were Stage 1 reflecting a mild, transient increase in serum creatinine. This may be of clinical significance as there is an increasing evidence showing that even mild, transient (lasting less than 24 hours) AKI is associated with poorer long term outcomes [35,36] compared to those who do not have AKI. There are currently no effective treatments for AKI once it is established and so earlier detection and prevention is vital. It is, however, important to note that there may be misclassification of chronic decline in renal function in patients with diabetes accounting for some of the observed increased rates of AKI. We have shown that rates of AKI are higher in patients with diabetes both with and without CKD with more than half developing recurrent episodes. To our knowledge, there has been no previous work looking at eGFR slopes prior to developing AKI. We found that those who develop AKI with diabetes have a greater decline in eGFR slope prior to developing AKI than those who do not. These findings are expected as a declining kidney would be more susceptible to episodes of AKI. However, it is surprising that there is less additional decline in eGFR in those with diabetes compared to those without following an episode of AKI compared to prior to an AKI episode. It remains unclear what the mechanism underlying AKI is in diabetic patients. A predisposing factor in these patients may be generalised or intrarenal atherosclerosis. In addition, patients with diabetes are likely to have glomerular hyperfiltration which is masking structural renal damage thereby rendering them more susceptible to AKI than those without diabetes due to their reduced repair capacity and so are susceptible to fluctuations in serum creatinine. A further suggested mechanism is that tubular growth in response to hypergylcemia promotes inflammation, senescence, and tubulointerstitial fibrosis which enhance the susceptibility of the diabetic kidney to episodes of AKI [37]. It also remains unclear whether prevention of AKI in these patients would prevent or delay progression of CKD. However, it would seem sensible that these patients are more closely monitoring during intercurrent illnesses with a greater awareness of avoiding high risk medicines such as non-steroidal anti-inflammatories and aminoglycosides. There is currently a lack of awareness among patients with diabetes of the risk of AKI and so patient education on the importance of hydration may play an important in role. We have also shown that in patients with both hypertension and diabetes, there is an additional decline in eGFR highlighting the importance of blood pressure control in addition to ensuring good glycaemic control in this patient group.

An important strength of the study is the refinement of KDIGO definition enabling a more sensitive estimation of AKI rates which has allowed us to demonstrate the high risk of AKI in patients with diabetes regardless of CKD status. We developed an algorithm to identify AKI episodes from SCr measures. A number of definitions to detect AKI cases based on changes in SCr have been used previously [16], and NHS England has implemented an algorithm which applies the KDIGO definition to routinely collected SCr tests to automatically produce AKI alerts to support clinical investigations [15]. This algorithm, defines baseline creatinine levels based on SCr one year prior to the index date, potentially leading to undetected AKI when such measurements are not available. The proposed algorithm utilises SCr values both prior and after the index date. Whilst this may not be useful for AKI detection in clinical practice, it may improve AKI detection for epidemiological purpose when applying to routinely collected datasets allowing for a more sensitive estimation of AKI incidence. Our study shows that at least one third of AKI cases remains undetected when baseline creatinine is only based on tests prior to the index date. Previous epidemiological studies of AKI from routinely collected SCr reported AKI cases in isolation, with episodes being defined using either fixed time periods such as 30 days [14] or admission and discharge dates for hospitalized patients [31]. The current study is novel through the development of an algorithm which examines consecutive SCr measures to detect the start and the end of an AKI episode, which can be used to calculate the length of the episode and further assess whether the AKI has resolved quickly or it has progressed to AKD. The grouping of AKI cases into AKI episodes was particularly important to allow an accurate estimate of AKI rates when applied to routinely collected data. Identification of the AKI episode start and end dates was also used in the study to clean the SCr data in order to allow assessment of CKD status and correctly determine the CKD onset date, which represents another strength of the study. Another important strength of the study is the development of a statistical framework for the analysis of the eGFR longitudinal data to evaluate decline in eGFR before and after an AKI event depending on diabetes and CKD status.

One of the main limitations of the study relates to the nature of routine healthcare data where blood measurements are infrequent, which makes it difficult to calculate baseline creatinine for assessment of AKI. As a result some of the AKI in the longitudinal data might remain undetected leading to misclassification between AKI and progressive CKD. This variation in the intensity of blood sampling may also lead to ascertainment bias in AKI estimation due to more tests that are being performed in sicker patients. In our study, blood tests were performed on average three times more often in people with diabetes than people in the control group. This may partially explain the high AKI rate in people with diabetes compared to controls. It could however be argued that increased testing was performed in response to clinical indication and similarly lack of testing in those who were deemed well. The possibility that the increased AKI is being driven by the increased testing rather than the other way round is diminished by the analysis of more severe (stage 2 and stage 3) AKIs and AKIs lasting more than 48hrs, for which a high AKI rate ratio between people with diabetes compared to controls in the absence of CKD were obtained. In addition, diabetes status confers a substantially increased risk for AKI in individuals with pre-existing CKD, where the testing rate is high regardless of diabetes status. These results demonstrates a profoundly increased clinical burden of acute kidney disease in diabetes patients. Another limitation of the study is the potential of selection bias due to the use of consented data from the GoDARTs cohort, a characteristic of most observational studies using consented data, which may lead to AKI rate estimates that are not generalizable. Furthermore calculation of slopes required a number of creatinine measures over a specified time period and so a significant number of patients were excluded from the analysis. This could introduce selection bias which may have affected our findings. However, it is difficult to eliminate this issue when examining eGFR slopes using observational data.

In conclusion, we have quantified the risk of AKI in patients with diabetes and its relationship as both a precursor and a consequence of CKD. The risk of AKI in this population of patients is currently underestimated and associated adverse outcomes following AKI are not well understood. Further work to evaluate the pathogenesis for AKI and the risk factors associated with the increased AKI rate in patients with diabetes such as use of medication is required to allow for development and implementation of interventions which both prevent the occurrence of AKI and reduce decline in eGFR thereby improving patient outcomes.

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Disclosure Statement

The authors have nothing to disclose

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Ethics approval and consent to participate

The GoDARTS study was approved by the Tayside Medical Ethics Committee with informed consent being obtained for all participants (REC reference 053/04). Data provision and linkage was carried by the University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic), with analysis of anonymised data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service and consent for this study was obtained from the NHS Fife Caldicott Guardian.

Author Contributions

S.H. design the study, conducted the data processing and analysis and wrote and revised the manuscript. M.K.S., R.S.Y.K., S.M., A.S.F.D., and E.R.P., contributed to the interpretation of the data and the revision of the manuscript. S.B. and C.N.A.P. contributed to study design, the interpretation of the data and the writing and revision of the manuscript. S.H and C.N.A.P. are 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.

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Table 1. Definition of AKI cases, AKI episodes and AKI stages

Definition of AKI cases using the NHS algorithm (one of the three criteria) **(19):**	
Criterion 1:	Serum creatinine ≥ 1.5 times higher than median of all creatinine measures in the 8-365 days prior to index.
Criterion 2:	Serum creatinine ≥ 1.5 times higher than the lowest creatinine in the 7 days prior to index.
Criterion 3:	Serum creatinine > 26 µmol/L higher than the lowest creatinine in the 48 hours prior to index.
Definition of AKI cases using the modified algorithm (one of the four criteria):	
Criterion 1:	Serum creatinine ≥ 1.5 times higher than median of all creatinine measures in the 8-365 days prior to index
Criterion 2:	Serum creatinine ≥ 1.5 times higher than the lowest creatinine in the 7 days prior to or post index
Criterion 3:	Serum creatinine > 26µmol/L higher than the lowest creatinine in the 2 days prior to or post index
Criterion 4:	Serum creatinine ≥ 1.5 times higher than median of all creatinine measures in the 8-365 days post index
Definition of AKI episode: grouping AKI cases into episodes	
Step 1:	Serum creatinine tests measured within 7 days were grouped into episodes of care
Step2:	If any value within an episode of care was flagged as AKI then the whole episode was flagged as AKI
Step3:	Within each episode of care Serum creatinine values before and after an AKI case that were greater that 1.2 fold increase in baseline were included in the AKI episodes and used to determine the start and the end of the AKI episode
Step 4	AKI episodes occurring within 7 days further linked to assess AKD
Step 5:	AKD of length greater than 90 days flagged as potential CKD
Classification criteria for AKI stages **(19)*:***	
Stage 1	Rise in creatinine > 26µmol/L within 48 h (2 days) or 1.5≤index/baseline<2
Stage 2	2 ≤ index/baseline < 3
Stage 3	index/baseline ≥ 3

Table 2. Establishing CKD date and CKD status from the longitudinal eGFR data.

Implementation of the median smoother to the eGFR data to ascertain CKD

Step 1:	eGFR values contained within AKI episodes were removed from the data
Step 2:	Calculate the median eGFR for the 91 to 365 days prior to index: $Median_{91\text{-}365d\ prior}$.
Step 3:	Calculate the median eGFR for the 7 days prior to 7 days post index: $Median_{7d\ prior\text{-}7d\ post}$.
Step 4:	Calculate the median eGFR for the 91 to 365 days post index: $Median_{91\text{-}265d\ post}$.
Sept 5:	Define $Median_{eGFR}$ as the median of the three medians defined in steps 2-4
Step 6:	CKD date establish when at least two of the medians in steps 2-4 are available and less than 60 ml/min per 1.73m^2

Definition of CKD status

No CKD	At recruitment or during follow-up.
Pre-CKD	The period from recruitment until development of CKD, for those people that developed CKD later.
Post-CKD	The period after recruitment, for those that had CKD at recruitment, or post CKD, for those that developed the condition later, until end of follow-up.

Figure 1: Flow chart of patient selection in the current study

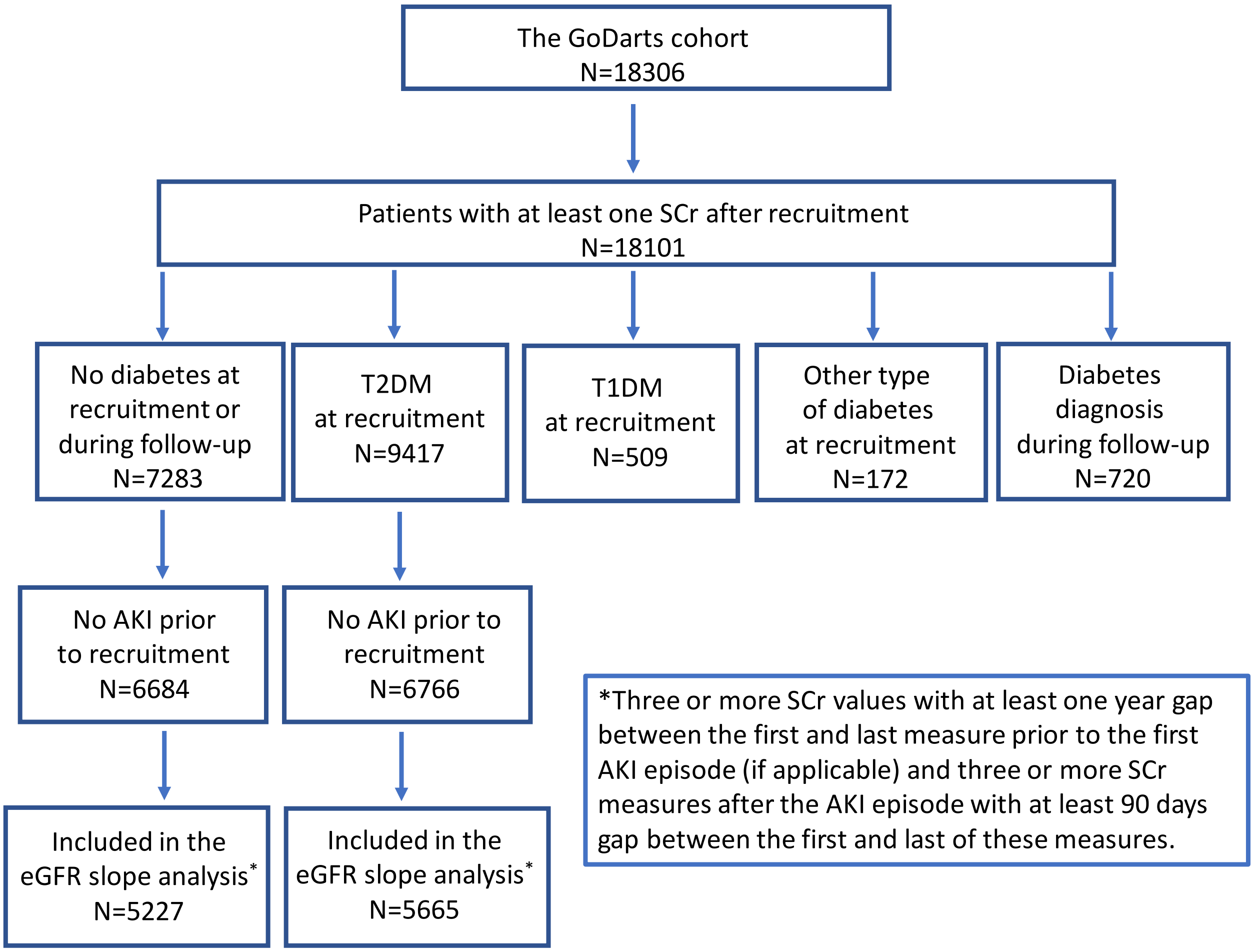
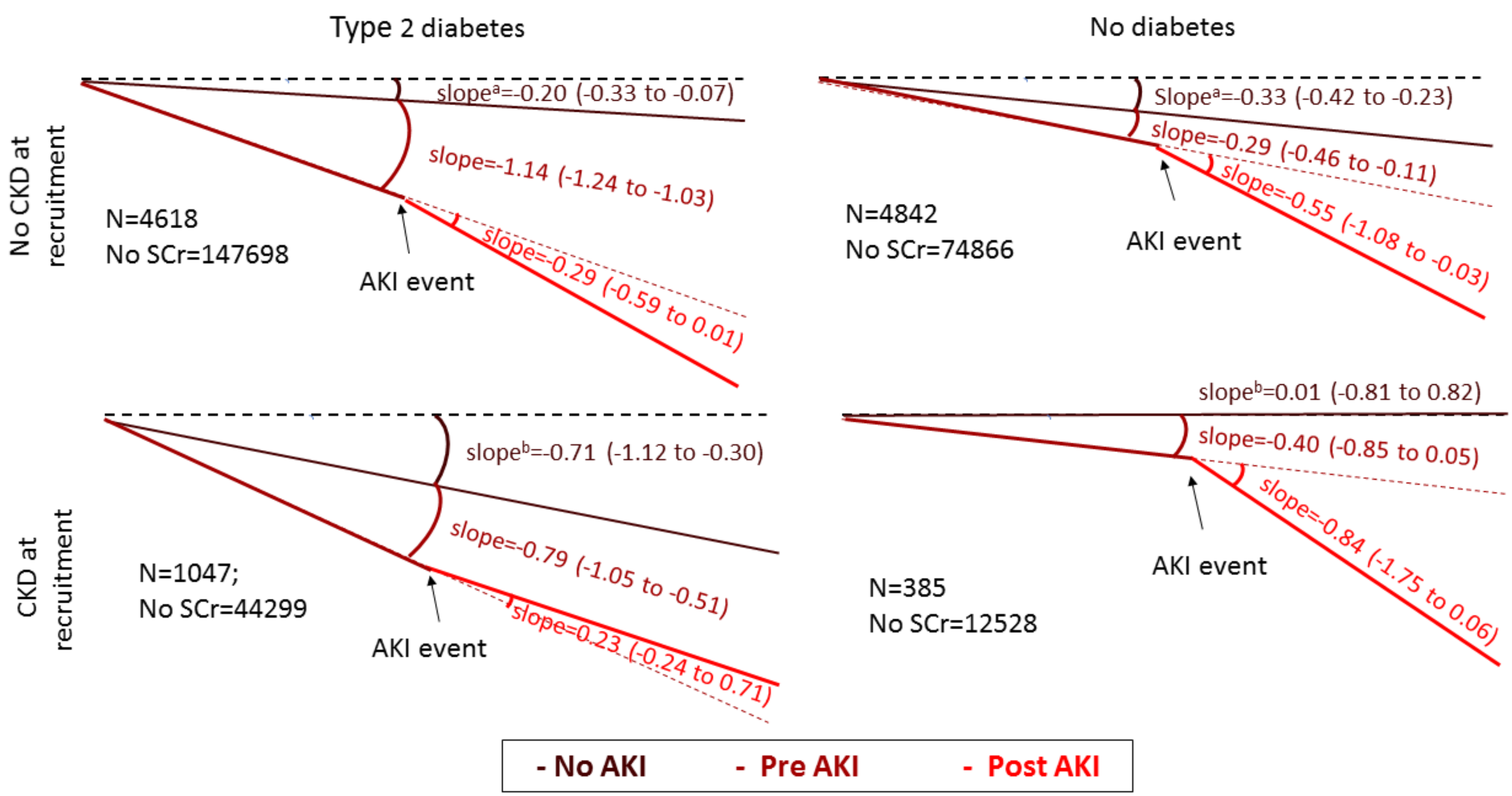


Figure 2: Visual representation of the eGFR slope estimates in people without AKI (No AKI), prior to the AKI (Pre AKI) and after the AKI event (Post AKI) depending on diabetes status and CKD status at recruitment ([a]Reference group includes: No AKI during follow-up, female, 49 and below, no cardiovascular disease; [b]Reference group includes: No AKI during follow-up, female, 50 to 64, no cardiovascular disease)



	All patients (N=16700)	T2DM (N=9417)	Control (N=7283)
Sex: Female N (%)	7888 (47.2)	4146 (44.0)	3742 (51.4%)
Age at recruitment: mean (SD)	64.3 (12.5)	66.9 (11.3)	60.8 (13.3)
eGFR at recruitment: mean (SD)[a]	79.9 (19.7)	76.6 (21.0)	84.3 (16.9)
CKD at recruitment: N(%)[b]	3168(18.9)	2503 (26.6)	665 (9.1)
Cardiovascular disease at recruitment			
Coronary Artery Disease (CAD): N (%)	3271 (19.6)	2489 (26.4)	782 (10.7)
Congestive Heart Failure (CHF): N (%)	670 (4.0)	587 (6.2)	83 (1.1)
Peripheral Vascular Disease (PVD): N (%)	636 (3.8)	540 (5.7)	95 (1.3)
Cerebrovascular Disease (CD): N (%)	786 (4.7)	644 (6.8)	142 (1.9)
Hypertension: N (%)	9863 (59.1)	7271 (77.2)	2592 (35.6)

[a]eGFR at recruitment was missing for 145 people

[b] 2442 additional participants developed CKD during follow-up

Table 3. Baseline characterises of the cohort broken down by diabetes status

	All patients (N=16700)	Type 2 diabetes (N=9417)	Control (N=7283)
Number of SCr tests	512615	387657	124958
Number of SCr tests per patient: median (IQR)	22 (10-39.5)	31 (19-51)	11 (4-21)
Number of SCr tests flagged as AKI			
Old algorithm (retrospective tests)	28306	24257	4049
Modified algorithm (retrospective and prospective tests)	40567	34469	6098
Number of AKI episodes	13928	11647	2281
Number of SCr tests within AKI episodes	65316	55401	9915
Number of patients with AKI during follow-up	5837	4580 (48.6)	1257 (17.2)
Number of episodes per person: median (IQR)	2 (1-3)	2 (1-3)	1 (1-2)
Length of AKI episode: median (IQR)	3 (1-7)	3 (1-7)	3 (1-6)
AKI episode ≤ 2days	7544 (54.2)	6237 (53.6)	1307 (57.3)
AKI episode> 2days and ≤ 7days	3697 (26.5)	3114 (26.7)	583 (25.6)
AKI episode > 7days	2687 (19.3)	2296 (19.7)	392 (17.2)
AKI stages			
Stage 1	10633 (76.3)	8895 (76.4)	1738 (76.2)
Stage2	2285 (16.4)	1901 (16.3)	387 (16.8)
Stage 3	1010 (7.3)	851 (7.3)	159 (7.0)

Table 4. Descriptive statistics showing number of SCr tests from recruitment, number of SCr test flagged by AKI using the NHS England algorithm vs the modified algorithm, number of AKI episodes and number of patients experiencing AKI during the follow-up time as well as characteristics of the AKI episodes in terms of length and severity in the diabetic and control groups.

Patients' groups	Sex Female number (%)	Age at recruitment	Follow-up time (years) Mean (SD)	Number of SCr tests per patient per year: median (IQR)	AKI patients N (%)	Number of AKI episodes
All patients (N=16700)	7888 (47.2)	64.3 (12.5)	8.8 (3.2)*	2.6 (1.2-5.2)	5837(35.0)	13928
Control (N=7282)	3742 (51.4)	60.8 (13.3)	9.6 (2.4)	1.1 (0.4-2.3)	1257 (17.3)	2281
Type 2 diabetes (N=9417)	4146 (44.0)	66.9 (11.3)	8.2 (3.5)	3.8 (2.4-7.4)	4580 (48.6)	11647
No CKD (N=11090)	5089 (45.9)	59.9 (11.8)	9.2 (2.9)*	1.8 (0.8-3.2)	2263 (20.4)	3952
Control (N=6032)	3135 (52.0)	57.9 (12.1)	9.8 (2.3)	0.9 (0.4-1.7)	651(10.8)	951
Type 2 diabetes (N=5058)	1954 (38.6)	62.4 (11.0)	8.4 (3.4)	2.9 (2.0-4.7)	1602 (31.7)	3001
CKD (N=5610)	2799 (49.9)	72.8 (8.9)	8.1 (3.4)*	5.1 (3.0-9.4)	3584 (63.9)	9976
Control (N=1251)	607 (48.5)	75.3 (8.1)	8.7 (3.0)	3.3 (2.0-6.4)	606 (48.4)	1330
Type 2 diabetes (N=4359)	2192 (50.3)	72.1 (9.0)	8.0 (3.5)	5.7 (3.4-10.3)	2978 (68.3)	8646
Prior to CKD diagnosis (N=2442)	1114 (45.6)	69.2 (8.9)	4.42 (3.1)†	2.9 (1.8-4.6)	571 (23.4)	942
Control (N=587)	273 (46.5)	72.7 (8.2)	4.7 (2.9)	1.8 (1.1-3.3)	58 (9.9)	120
Type 2 diabetes (N=1855)	841 (45.3)	68.2 (8.9)	4.3 (3.1)	3.2 (2.2-5.0)	493 (26.6)	822
Post CKD diagnosis (N=5610)	2799 (49.9)	74.9 (8.3)§	6.2 (3.5)‡	5.7 (3.2-11.1)	3352 (59.8)	9034
Control (N=1251)	607 (48.5)	77.6 (7.7)	6.5 (3.5)	4.0 (2.3-7.5)	569 (45.5)	1210
Type 2 diabetes (N=4359)	2192 (50.3)	74.1 (8.3)	6.1 (3.5)	6.3 (3.6-12.0)	2883 (66.1)	7824

*from recruitment until end of follow-up (RRT/death/out with HB/May 2017 whichever happened first).
†from recruitment until development of CKD.
‡from development of CKD/recruitment, whichever happened last, until end of follow-up.
§Age at recruitment or development of CKD, whichever happened last.

Table 5. Descriptive statistics showing sex, age, follow-up time and number of SCr tests as well as number of patients experiencing AKI and number of AKI episodes in the diabetic vs control groups depending on CKD status.

Patients' groups	AKI episodes per 1000 person-years			
	Un-adjusted		Adjusted for age and sex	
	Mean rate (SE)	Rate ratio (95%CI)	Mean rate (SE)	Rate ratio (95% CI)
All patients (N=16700)	131.6 (126.8-136.6)	-	114.8 (110.5-119.5)	-
Control (N=7282)	38.2 (36.0-40.5)	1.0	38.4 (36.2-40.8)	1.0
Type 2 diabetes (N=9417)	204.8 (196.4-213.6)	5.4 (5.0-5.8)	179.0 (171.5-186.9)	4.7 (4.3-5.0)
No CKD (N=11090)	54.6 (51.4-58.0)	-	66.3 (61.1-72.1)	-
Control (N=6032)	18.0 (16.6-19.6)	1.0	24.6 (22.3-27.2)	1.0
Type 2 diabetes (N=5058)	101.1 (93.9-108.8)	5.6 (5.0-6.3)	121.5 (111.0-133.0)	4.9 (4.4-5.5)
CKD (N=5610)	276.0 (265.1-187.3)	-	267.0 (252.1-282.8)	-
Control (N=1251)	148.5 (135.8-162.3)	1.0	130.1 (117.7-143.8)	1.0
Type 2 diabetes (N=4359)	312.6 (299.2-326.6)	2.1 (1.9-2.3)	299.3 (282.4-317.2)	2.3 (2.1-2.5)
Prior to CKD diagnosis (N=2442)	93.8 (85.4-108.0)	-	92.9(81.0-106.1)	-
Control (N=587)	45.8 (36.7-57.2)	1.0	47.4 (37.2-60.5)	1.0
Type 2 diabetes (N=1855)	109.9 (99.3-121.6)	2.4 (1.9-3.1)	109.3 (94.8-126.1)	2.3 (1.8-3.0)
Post CKD diagnosis (N=5610)	337.2 (323.3-351.7)	-	350.8 (321.8-382.5)	-
Control (N=1251)	187.3 (170.5-205.8)	1.0	180.0 (159.1-203.8)	1.0
Type 2 diabetes (N=4359)	379.2 (362.1-397.1)	2.0 (1.8-2.2)	384.8 (353.1-419.3)	2.1 (1.9-2.4)

Table 6. AKI episode rates and rate ratios in the diabetic and non-diabetic groups depending on the CKD status