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Nonalbuminuric Diabetic Kidney Disease and Risk of All-Cause Mortality and Cardiovascular and Kidney Outcomes in Type 2 Diabetes: Findings From the Hong Kong Diabetes Biobank

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Abstract

Rationale & Objective: Nonalbuminuric diabetic kidney disease (DKD) has become the prevailing DKD phenotype. We compared the risks of adverse outcomes among patients with this phenotype compared to other DKD phenotypes.

Study Design: Multicenter prospective cohort study.

Settings & Participants: 19,025 Chinese adults with type 2 diabetes enrolled in the Hong Kong Diabetes Biobank.

Exposures: DKD phenotypes defined by baseline estimated glomerular filtration rate (eGFR) and albuminuria: no DKD (without decreased eGFR or albuminuria), albuminuria without decreased eGFR, decreased eGFR without albuminuria, and albuminuria with decreased eGFR.

Outcomes: All-cause mortality, cardiovascular disease events (CVD), hospitalization for heart failure (HHF), and CKD progression (incident end-stage kidney disease or sustained eGFR reduction ≥40%).

Analytic Approach: Multivariable Cox proportional or cause-specific hazards models to estimate the relative risks of death, CVD, HHF, and CKD progression. Multiple imputation was used for missing covariates.
**Results:** Mean age was 61.1 years; 58.3% were males; and mean diabetes duration was 11.1 years. During 54,260 person-years of follow-up, 438 deaths, 1,076 CVD, 298 HHF, and 1,161 episodes of CKD progression occurred. The subgroup with decreased eGFR without albuminuria (vs. no DKD) had higher risks of all-cause mortality (HR 1.59, 95% CI, 1.04, 2.44), HHF (HR 3.08, 95% CI 1.82, 5.21) and CKD progression (HR 2.37, 95% CI, 1.63, 3.43), while the risk of CVD was not significantly increased (HR 1.14, 95% CI, 0.88, 1.48). The risks of death, CVD, HHF, and CKD progression were higher in the setting of albuminuria with or without decreased eGFR. A sensitivity analysis that excluded participants with baseline eGFR <30 mL/min/1.73 m² yielded similar findings.

**Limitations:** Potential misclassification because of drug use.

**Conclusions:** Nonalbuminuric DKD was associated with higher risks of HHF, and CKD progression than no DKD, regardless of baseline eGFR.

**Index Words:** diabetic kidney disease; nonalbuminuric diabetic kidney disease; phenotype; prognosis; type 2 diabetes

**Plain Language Summary**
Nonalbuminuric diabetic kidney disease (DKD) has become the prevailing DKD phenotype and distinct clinicopathological characteristics have been reported. We assessed the risks of adverse outcomes (all-cause mortality, CVD, heart failure hospitalization, and kidney disease progression) among patients with nonalbuminuric DKD compared to patients with other DKD phenotypes in a
multicenter prospective cohort study of type 2 diabetes that included 19,025 individuals. We found that patients with nonalbuminuric DKD had an increased risk of death, hospitalization for heart failure and chronic kidney disease progression compared to those without DKD, while the risks of all adverse outcomes were higher among individuals with albuminuric DKD, after adjustment for a wide range of confounders. Further studies are warranted to explore possible mechanisms explaining these observations that will help tailor the clinical management of nonalbuminuric DKD.
Introduction

Diabetic kidney disease (DKD) develops in approximately 40% of people with type 2 diabetes (T2D),\(^1\) and is the leading cause of end-stage kidney disease (ESKD),\(^2\) contributing to half of the new cases of ESKD.\(^3\) Despite advancements in therapies and improvement in risk management, the incidence of ESKD has been increasing in Asian and other populations,\(^4\) highlighting the need for earlier risk stratification and treatment to prevent development and progression of DKD.

Traditionally, based on studies in type 1 diabetes, the natural course of DKD is believed to progress from normo- to micro- to macroalbuminuria in an approximately linear pattern, with subsequent development of impaired glomerular filtration. However, this model has been challenged as accumulating studies have reported significant heterogeneity in the manifestations of DKD in T2D: a proportion of individuals develop decreased eGFR (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m\(^2\)) in the absence of albuminuria (decreased eGFR only).\(^5\)-\(^9\) Moreover, this group has become the prevailing DKD phenotype.\(^10\) In our previous analysis, we also found heterogeneous trajectories in the progression to ESKD in individuals with T2D.\(^11\)

Patients with decreased eGFR only exhibit some distinct clinicopathological characteristics from those with albuminuria, including a higher proportion of females and nonsmokers, better risk factors profile, and normal or mild diabetic renal structural lesions on biopsy.\(^5,12-15\) With this group now becoming the prevailing DKD phenotype\(^10\) and an upward trend in mortality reported in this group\(^16\), more studies on the prognosis of this phenotype are warranted. However, current studies are limited, and have reported mixed results.\(^12,14-17\) Patients with decreased eGFR only have been found to be at increased risks of mortality\(^15,17\) and cardiovascular disease (CVD);\(^15\) by contrast, a
study reported comparable risks of mortality, CVD, and ESKD among decreased eGFR only group compared to those in people without DKD.\textsuperscript{14} Both eGFR and urinary albumin-creatinine ratio (UACR) have been associated with heart failure,\textsuperscript{18} but to the best of our knowledge, the risk of heart failure across different DKD phenotypes have not been well investigated. Accordingly, in a multicenter prospective cohort of Chinese patients with T2D, we aim to assess the risks of all-cause mortality, CVD, hospitalization for heart failure (HHF), and CKD progression in decreased eGFR only group in comparison with other DKD phenotypes.

**Methods**

**Study Design and Participants**

The Hong Kong Diabetes Biobank (HKDB) is a multicenter prospective cohort study coordinated by the Prince of Wales Hospital, the teaching hospital of the Chinese University of Hong Kong. A total of 11 diabetes centers at major public hospitals across Hong Kong participated in the study. The HKDB used similar enrollment and assessment methods to that of the Hong Kong Diabetes Registry (HKDR), established at the Prince of Wales Hospital since 1995 as a quality-improvement program, incorporating comprehensive and structured assessment of risk factors and diabetes complications.\textsuperscript{19} A territory-wide diabetes risk assessment programme was subsequently set up by the Hong Kong Hospital Authority in 2000 through establishing hospital-based diabetes centres and adopting a similar structured assessment of diabetes complications.\textsuperscript{20} The HKDB was initiated in 2014 to establish a multicenter diabetes registry and biobank for identification of novel biomarkers of diabetes and diabetes-related complications. Briefly, all participants were invited to take part in the study when attending a scheduled and standardized diabetes complication assessment based on the modified European DIABCARE protocol.\textsuperscript{21} The recruitment methods,
collection of anthropometric, lifestyle factors, as well as biochemical investigations have been
detailed previously.\textsuperscript{19,22} Once enrolled, the participant will be followed till death. A total of 19,789
Chinese with T2D were enrolled consecutively from 2014 to 2019 (Table S1). After excluding 460
participants with missing baseline eGFR or UACR, and 304 participants with prevalent ESKD,
19,025 participants were included in the analysis (Figure S1). All participants provided written
informed consent at the time of enrollment. Approvals were obtained from the Joint Chinese
University of Hong Kong- New Territories East Cluster Clinical Research Ethics Committee, as
well as the Clinical Research Ethics Committee of each participating hospital.

\textbf{Measurements}

Anthropometric measurements, clinical examination, and laboratory investigations were
performed at enrollment and sociodemographic data, medical and medication history were also
documented during face-to-face interviews.\textsuperscript{22} Body mass index (BMI) was calculated as weight
in kilograms divided by height in meters squared. Blood pressure (in millimeters of mercury) was
measured in both arms after at least 5 minutes of sitting and a mean value was taken for the analysis.
Blood samples after at least 8-hour overnight fasting were measured for glycated hemoglobin
(HbA\textsubscript{1C}), serum creatinine, and lipid profile with certificated routine assays at local laboratories.
Creatinine was measured using the Jaffé’s kinetic method\textsuperscript{19} and the Chronic Kidney Disease
Epidemiology Collaboration (CKD-EPI) equation was used for eGFR calculation.\textsuperscript{23} A random spot
urine sample was used for urinary albumin measurement using the immunoturbidimetry method.\textsuperscript{19}

Eye examination included visual acuity and retinal photography and the images were reviewed by
diabetologists. Retinopathy was defined by typical changes due to diabetes, laser scars, or a history
of vitrectomy. History of CVD was defined as coronary heart disease (CHD), stroke, and/or peripheral vascular disease (PVD).

According to the status of albuminuria (UACR ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women) and decreased eGFR (eGFR <60 mL/min/1.73 m²), participants were categorized into four DKD phenotypes: no DKD (without albuminuria or decreased eGFR), albuminuria only, decreased eGFR only, and albuminuria plus decreased eGFR.

**Outcomes**

The endpoints of this study were all-cause mortality, CVD, HHF, and incident ESKD or sustained ≥40% reduction in eGFR compared with baseline (composite renal outcome) defined by discharge or diagnostic codes based on the International Classification of Diseases, Ninth Revision (ICD-9, Table S2). CVD was defined as the first occurrence of CHD (myocardial infarction, ischemic heart disease, or angina pectoris), stroke (ischemic stroke except transient ischemic attack, hemorrhagic stroke, or acute but ill-defined cerebrovascular disease), or PVD (amputation, gangrene, or peripheral revascularization). HHF was defined as hospitalization for heart failure. ESKD was defined as the first occurrence of chronic dialysis, kidney transplant, and sustained eGFR ≤15 mL/min/1.73 m² in 90 days apart. Sustained eGFR reduction was confirmed by a ≥40% reduction in eGFR compared with baseline in 90 days apart. Participants were censored at time of the study outcome of interest, death, or 31 December 2019, whichever came first.

**Statistical Analysis**
Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) and differences were compared by ANOVA or Kruskal-Wallis test as appropriate. Categorical variables were presented as number (percentage) and compared by the Chi-squared test. Median follow-up time was estimated using the reverse Kaplan-Meier method based on time to mortality.24

With no DKD as the reference group, risks of all-cause mortality across DKD phenotypes were estimated using Cox proportional hazards models and risks of CVD, HHF, and CKD progression were estimated using cause-specific hazards models. Two models were built for each outcome: the unadjusted model, and the fully adjusted model adjusting for age, sex, ever smoking, diabetes duration, systolic blood pressure (SBP), BMI, HbA1c, ln(triglycerides), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL-C), oral antihyperglycemic drugs, insulin, antihypertensive drugs, lipid-lowering drugs, renin-angiotensin-system (RAS) blockers, statins, diabetic retinopathy (DR), and history of CVD and heart failure.

Missing baseline covariates were imputed with multiple imputation by chained equations using all variables in Table 1. Imputation was performed separately for each outcome to create 5 imputed datasets. Predictive mean matching was used for continuous variables, and logistic regression was used for binary variables.25 Parameter estimates were obtained by Rubin’s formula.26 Cumulative incidences were estimated with Kaplan-Meier method (all-cause mortality) or cumulative incidence function (the remaining outcomes), and differences across DKD phenotypes were compared by the log-rank or Gray’s test, respectively. Corresponding survival curves were generated from the fully adjusted Cox proportional (all-cause mortality) or sub-distribution (the
remaining outcomes) hazards models in the first imputed dataset. A two-tailed $P$ value $<0.05$ was considered statistically significant. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). R packages “mice” and “survival” were used for multiple imputation and Cox proportional or cause-specific hazards model, respectively.

**Sensitivity Analysis**

To explore the potential influence of baseline eGFR on the rates of progressing to outcomes, we repeated the analyses after further excluding participants with baseline eGFR $<30$ mL/min/1.73 m$^2$, without performing imputation.

**Results**

**Baseline Characteristics**

Table 1 summarized the baseline characteristics of the 19,025 participants included in the study. The mean (SD) age was 61.1 (11.2) years, 58.3% were male, and the mean diabetes duration was 11.1 (8.8) years. The frequencies of DKD phenotypes were 51% for no DKD, 29% for albuminuria only, 5% for decreased eGFR only, and 15% for albuminuria plus decreased eGFR. Participants with decreased eGFR only had lower levels of SBP, BMI, HbA$_{1C}$, and fewer prevalent DR compared with participants with albuminuric DKD (albuminuria only or plus decreased eGFR). Moreover, participants with decreased eGFR only were older, more likely to be females and have prevalent CVD, and included fewer smokers, and had lower levels of DBP, total cholesterol, and LDL-C than the remaining DKD phenotypes (no DKD, albuminuria only, and albuminuria plus decreased eGFR). The use of RAS blockers was similar among the 3 DKD phenotypes (decreased eGFR only, albuminuria only, and albuminuria plus decreased eGFR).
Risk of All-cause Mortality

During a median 3.06 (IQR [1.76, 4.24]) years of follow-up, 438 (event rate, 2.30%) participants died, corresponding to a mortality rate (95% CI) of 7.83 (7.12, 8.60) per 1,000-person years. The crude incidence was lowest for people with no DKD and highest for people with albuminuria plus decreased eGFR (Table 2 and Figure 1). The unadjusted Cox model showed a similar pattern (Table 2). In the fully adjusted Cox model, compared with people with no DKD, HRs (95% CIs) for participants with decreased eGFR only, albuminuria only, and albuminuria plus decreased eGFR were 1.59 (1.04, 2.44), 2.00 (1.52, 2.63), and 3.26 (2.43, 4.38), respectively (Table 2).

Risk of CVD and HHF

During the observation period, 1,076 (5.66%) participants developed CVD and 298 (1.57%) participants developed HHF, corresponding to an incidence rate (95% CI) of 19.91 (18.73, 21.13) and 5.38 (4.78, 6.02) per 1,000-person years, respectively. The crude incidences and HRs for CV outcome, CVD, and HHF were lowest for participants with no DKD and highest for participants with albuminuria plus decreased eGFR (Table 2 and Figure 1). After adjusting for confounders, HRs for HHF exhibited similar patterns to that of mortality (Table 2 and Figure S2). For CVD, compared with participants with no DKD, HRs were significantly higher for participants with albuminuria only or plus decreased eGFR (1.19 [1.02, 1.40] and 1.47 [1.23, 1.76], respectively), while not significantly different for participants with decreased eGFR only (1.14 [0.88, 1.48]) (Table 2 and Figure S2).

Risk of CKD Progression
A total of 1,161 (6.10%) participants developed CKD progression during follow-up (incidence rate [95% CI] 21.74 [20.50, 23.02] per 1,000-person years), including 414 ESKD and 899 with sustained ≥40% reduction in eGFR. People with decreased eGFR only had a lower incidence of CKD progression compared with persons with albuminuric DKD, whereas a higher incidence than those with no DKD (Table 2 and Figure 1). After accounting for confounders, similar results were found (Table 2 and Figure S2).

**Sensitivity Analyses**

After further excluding participants with baseline eGFR <30 mL/min/1.73 m² (n = 18,425 included in the analyses), the patterns of risks remained unchanged for HHF and CKD progression (Table 3). For mortality and CVD, compared with people with no DKD, HRs for participants with decreased eGFR only were rendered non-significantly different (1.45 [0.86, 2.42], 1.33 [0.997, 1.78], and 1.24 [0.90, 1.70], respectively), whereas remained significantly higher for participants with albuminuric DKD (Table 3).

**Discussion**

In a well-characterized prospective cohort of T2D, we assessed the prognosis of people with different DKD phenotypes. Compared people without DKD, those with decreased eGFR only exhibited a non-significantly increased risk of CVD and death when baseline eGFR was over 30 mL/min/1.73 m², however people in this group were at increased risks of HHF and CKD progression, regardless of baseline CKD stages.
The decreased eGFR only group appears to have some shared clinical characteristics across ethnicities which are different from other DKD phenotypes.\cite{14,15,17} People with decreased eGFR only tend to be older, of more females and nonsmokers when compared with people with no DKD and with albuminuric DKD. Moreover, people with decreased eGFR only have been reported to have a lower prevalence of DR than albuminuric DKD and a higher prevalence of CVD compared with people with albuminuria only.\cite{14,17} In the current study, we found better blood pressure and lipid control, and more prevalent CVD in people with decreased eGFR only compared with other DKD phenotypes including no DKD.

In line with previous studies,\cite{15,17} people with decreased eGFR only had a higher risk of death than those without DKD and it seems that this risk mainly lied in those with baseline eGFR <30 mL/min/1.73 m$^2$. Data from the Renal Insufficiency And Cardiovascular Events (RIACE) study found a higher risk of death in people with decreased eGFR only than in those with no DKD (HR 1.58 [1.43, 1.75]).\cite{17} Similarly, results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study suggested higher risks of mortality (HR 1.42 [1.14, 1.78]) and major cardiovascular events (myocardial infarction, stroke, and CV death; HR 1.44 [1.13, 1.84]) in people with decreased eGFR only compared with those without DKD.\cite{15} In the current study, we found a higher risk of HHF in people with decreased eGFR only. As baseline eGFR is associated with death and CVD in patients with diabetes,\cite{18,27} to address the possible influence of eGFR on the risk of outcomes, we further excluded participants with baseline eGFR <30 mL/min/1.73 m$^2$ and found non-significantly different risks of death and CVD in people with decreased eGFR only compared with people with no DKD; however, this phenotype was still at increased risk of HHF. In keeping with our result, an analysis that included participants with baseline eGFR $\geq$30
mL/min/1.73 m² from the Japan Diabetes Clinical Data Management (JDDM) study reported no significant differences in the risks of death (HR 1.46 [0.73, 2.92]) and CVD (CHD, stroke, PVD, and CV death; HR 1.06 [0.63, 1.79]) between people with decreased eGFR only and with no DKD.¹⁴

There are several potential explanations for a non-significantly different risk of CVD between decreased eGFR only and no DKD. First, studies found that there were more females, fewer smokers, and better glycemic and blood pressure control in T2D patients with decreased eGFR only,¹⁴,¹⁵,¹⁷ suggesting that reduced eGFR in the absence of albuminuria may represent a distinct DKD phenotype with a preferable profile of clinical characteristics and respond superiorly to risk factors management. This phenotype may be enriched with people who regressed to normoalbuminuria because of RAS blockers, thus a lower likelihood of CKD progression. However, our result showed that people with decreased eGFR only had a higher risk of CKD progression, even after adjustment for RAS blockers. Furthermore, after excluding participants on RAS blockers at baseline in decreased eGFR only group, we found a similar result, that people with decreased eGFR only had a higher risk of CKD progression (Table S3). The second possible explanation is the underlying pathological features. Among patients with biopsy-proven DKD, those without proteinuria typically have less advanced and typical glomerular classifications as well as less severe interstitial and vascular lesions.¹² Albuminuria is a biomarker of endothelial dysfunction and inflammation and has been associated with CVD in T2D;²⁸ thus people with decreased eGFR only may of less atherosclerotic burden. It seems that the risk of CVD was not significantly increased in decreased eGFR only compared with no DKD in the East Asian population,¹⁴ while the risk was significantly higher in the Western population.¹⁵ This can be
attributed to the differences in the prevalence of comorbidities, especially higher rates of obesity, hypertension, and CVD in the Western population. Although BMI, SBP, and history of CVD have been controlled for in the analysis from ACCORD study\textsuperscript{15} and our analysis, the mean BMI, SBP, and prevalence of CVD were lower in our cohort (32.2 vs 26.4 kg/m\textsuperscript{2}, 136.3 vs 134.8 mmHg, and 35.2% vs 24.5%, respectively).

Diabetes is a major risk factor for heart failure,\textsuperscript{29} and the consistent results of a reduced risk of HHF in patients on sodium glucose co-transporter 2 inhibitor (SGLT2i)\textsuperscript{30-32} highlights the cardioprotective effect of SGLT2i beyond its role in glucose lowering. The secondary analysis of the Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction (DECLARE-TIMI) 58 randomized clinical trial found no heterogeneity in the effect on HHF across DKD markers (eGFR <60 mL/min/1.73 m\textsuperscript{2} and albuminuria) and reported a larger effect in patients with albuminuria plus decreased eGFR.\textsuperscript{33} The current study demonstrated that participants with decreased eGFR only had a higher risk of HHF than participants without DKD, and the finding remained unchanged after excluding participants with baseline eGFR <30 mL/min/1.73 m\textsuperscript{2}. As the study combined patients with either reduced eGFR or albuminuria as one group,\textsuperscript{33} it remains to be confirmed how much patients with reduced eGFR in the absence of albuminuria would benefit from this drug.

In contrast to our result that participants with decreased eGFR only had a higher risk of ESKD or \geq40\% eGFR reduction compared with people without DKD, results from ACCORD study reported that the risk of ESKD in decreased eGFR only was not increased when compared with no DKD,\textsuperscript{15} although both studies found that the highest risk of kidney disease progression occurred in people
with albuminuria plus decreased eGFR. Analysis in participants with baseline eGFR ≥30 mL/min/1.73 m² from JDDM also found a non-increased risk of ≥30% eGFR decline compared with those without DKD. However, our result is not without support. Higher risk of progression to ESKD has been found in people with reduced eGFR only compared with people without albuminuria and decreased eGFR in a large population-based study. Analysis from the Action in Diabetes and Vascular disease: preterAx and diamicron-MR Controlled Evaluation (ADVANCE) study found that among patients with normoalbuminuria, the risk of renal events (renal death, kidney replacement therapy, or doubling of serum creatinine to >200 umol/L) was higher in patients with eGFR <60 mL/min/1.73 m² compared with those with eGFR ≥60 mL/min/1.73 m².

Previous randomized trials testing potential renoprotective drugs in T2D almost excluded patients with only reduced eGFR, making the treatment for this phenotype less clear. Findings in the current study suggest that this phenotype is at risk of CKD progression; hence more randomized trials including people with decreased eGFR only are needed.

The major strengths of the present study include a large sample size and sufficient number of events facilitating the analyses. However, interpretations should be made in the context of some limitations. As our study included only Chinese participants, further investigations in different populations are warranted to examine the generalizability of our findings. Given the observational nature of the study, residual confounding cannot be ruled out. Information on the use of SGLT2i was not considered. Therefore, we were not able to compare the differences in SGLT2i prescription among DKD phenotypes as well as its possible influence on the outcomes, especially HHF and CKD progression. However, SGLT2i prevents HHF and progression of CKD with evidence mainly in patients with overt albuminuria; and studies in participants with decreased eGFR
only are limited. Further, a recent territory-wide analysis from Hong Kong indicated that the use of SGLT2i was overall quite low at 0.4% in 2016, although the rates of use within HKDB would likely be higher, given the setting of specialist diabetes clinics. The definition of DKD was based on eGFR and UACR, rather than biopsy-proven one. We acknowledge that the renal lesions of clinically defined DKD may be attributable to non-diabetic kidney disease (NDKD), as a proportion of patients can have renal biopsies suggestive of NDKD. However, a study in people with biopsy-proven DKD found similar results: persons without proteinuria (UACR < 300 mg/g) had a lower risk of mortality than people with proteinuria.

In conclusion, in a prospective cohort of Chinese patients with T2D, we demonstrated that, decreased eGFR was associated with higher risks of HHF and subsequent progression of CKD when compared with people without DKD. Currently, therapeutic strategies and targets for this phenotype are less well defined. With this group becoming the prevailing DKD phenotype and showing distinct clinicopathological features as well as risks of adverse outcomes, more studies are needed to explore possible mechanisms and to tailor the management and interventions for this phenotype.

**Supplementary Material**

Table S1. Baseline characteristics of HKDB, DKD overall and subjects excluded.

Table S2. Definitions of outcomes based on diagnosis and procedure codes.

Table S3. Event/incidence rates and risks of mortality, CVD, HHF, and CKD progression in non-RAS blockers users at baseline in decreased eGFR only group.

Figure S1. Analysis flow in the Hong Kong Diabetes Biobank.
Figure S2. Adjusted survival curves for all-cause mortality, CVD, HHF, and CKD progression according to four DKD phenotypes.

Item S1. Members of the Hong Kong Diabetes Biobank Study Group.

**Article Information**

Hong Kong Diabetes Biobank Study Group: A list of the members of the Hong Kong Diabetes Biobank Study Group is in Item S1.

Authors’ Contributions: Research idea and study design: QJ, RCM; data acquisition: ESL, AOL, CHT, RO, CKL, HW, GJ, EYC, JKN, APK, BF, KFL, SCS, GH, CCT, KPL, JYL, MT, GK, ITL, JKL, VTY, EL, SL, SF, YLC, CCC, YH, HL, CCS, WYS, JC, RCM; data analysis/interpretation: QJ, ESL, AOL, HW, CHT, JC, RCM; statistical analysis: QJ, ESL, AOL, HW, RCM; funding acquisition: JC, RCM; supervision or mentorship: CKL, RO, WYS, JC, RCM. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual’s own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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References

21. Piwernetz K, Home PD, Snorgaard O, Antsiferov M, Staehr-Johansen K, Krans M. Monitoring the targets of the St Vincent Declaration and the implementation of quality


Table 1. Baseline characteristics of study population stratified by DKD phenotypes.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Overall (N=19,025)</th>
<th>No DKD (N=9,713, 51%)</th>
<th>Albuminuria only (N=5,457, 29%)</th>
<th>Decreased eGFR only (N=1,044, 5%)</th>
<th>Albuminuria plus decreased eGFR (N=2,811, 15%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>61.1 ± 11.2</td>
<td>58.6 ± 10.6</td>
<td>59.9 ± 11.0</td>
<td>69.3 ± 8.4</td>
<td>68.6 ± 9.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender</td>
<td>11,084 (58.3)</td>
<td>5,280 (54.4)</td>
<td>3,440 (63.0)</td>
<td>546 (52.3)</td>
<td>1,818 (64.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking, ever</td>
<td>6,452 (33.9)</td>
<td>3,026 (31.1)</td>
<td>2,055 (37.6)</td>
<td>308 (29.5)</td>
<td>1,063 (37.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing</td>
<td>8 (0.04)</td>
<td>4 (0.02)</td>
<td>3 (0.01)</td>
<td>0</td>
<td>1 (0.03)</td>
<td></td>
</tr>
<tr>
<td>Diabetes duration, years</td>
<td>11.1 ± 8.8</td>
<td>9.2 ± 8.0</td>
<td>11.1 ± 8.6</td>
<td>14.7 ± 9.5</td>
<td>16.2 ± 9.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.5 ± 1.5</td>
<td>13.8 ± 1.4</td>
<td>13.7 ± 1.5</td>
<td>12.8 ± 1.5</td>
<td>12.7 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (0.1)</td>
<td>1 (0.01)</td>
<td>6 (0.1)</td>
<td>1 (0.1)</td>
<td>1 (0.04)</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>134.8 ± 17.8</td>
<td>130.8 ± 16.4</td>
<td>138.2 ± 17.8</td>
<td>133.8 ± 16.4</td>
<td>142.4 ± 18.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74.8 ± 11.4</td>
<td>74.3 ± 10.8</td>
<td>77.1 ± 11.7</td>
<td>71.0 ± 10.7</td>
<td>73.8 ± 12.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>7.8 ± 2.6</td>
<td>7.6 ± 2.3</td>
<td>8.3 ± 2.9</td>
<td>7.5 ± 2.4</td>
<td>8.0 ± 3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1C, %</td>
<td>7.6 ± 1.5</td>
<td>7.4 ± 1.3</td>
<td>7.9 ± 1.6</td>
<td>7.5 ± 1.2</td>
<td>7.9 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1C, mmol/L</td>
<td>59.9 ± 16.0</td>
<td>57.6 ± 14.7</td>
<td>62.5 ± 17.3</td>
<td>58.8 ± 13.4</td>
<td>63.0 ± 17.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>79.6 ± 23.0</td>
<td>90.0 ± 14.3</td>
<td>86.5 ± 15.2</td>
<td>48.9 ± 9.2</td>
<td>41.6 ± 11.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UACR, mg/mmol</td>
<td>2.0 (0.7-9.4)</td>
<td>0.8 (0.5-1.4)</td>
<td>8.8 (4.7-23.4)</td>
<td>1.0 (0.6-1.8)</td>
<td>34.5 (9.9-123.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.3 (0.9-2.0)</td>
<td>1.2 (0.9-1.7)</td>
<td>1.4 (1.0-2.1)</td>
<td>1.4 (1.0-1.9)</td>
<td>1.6 (1.1-2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.3 ± 0.9</td>
<td>4.3 ± 0.9</td>
<td>4.3 ± 1.0</td>
<td>4.1 ± 1.0</td>
<td>4.2 ± 1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.4</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C, mmol/L</td>
<td>2.3 ± 0.8</td>
<td>2.4 ± 0.8</td>
<td>2.3 ± 0.8</td>
<td>2.1 ± 0.7</td>
<td>2.2 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medical history</td>
<td>Missing (%)</td>
<td>440 (2.3)</td>
<td>224 (2.3)</td>
<td>139 (2.5)</td>
<td>13 (1.2)</td>
<td>64 (2.3)</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>-------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td></td>
<td>4,259 (22.4)</td>
<td>1,634 (16.9)</td>
<td>1,473 (27.0)</td>
<td>253 (24.2)</td>
<td>899 (31.9)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>4,657 (24.5)</td>
<td>1,856 (19.1)</td>
<td>1,327 (24.3)</td>
<td>405 (38.8)</td>
<td>1,069 (38.0)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
<td>3,268 (17.2)</td>
<td>1,346 (13.9)</td>
<td>883 (16.2)</td>
<td>310 (29.7)</td>
<td>2,082 (74.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>1,623 (8.5)</td>
<td>582 (6.0)</td>
<td>496 (9.1)</td>
<td>131 (12.5)</td>
<td>414 (14.7)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td></td>
<td>236 (1.2)</td>
<td>42 (0.4)</td>
<td>73 (1.3)</td>
<td>23 (2.2)</td>
<td>98 (3.5)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td></td>
<td>706 (3.7)</td>
<td>173 (1.8)</td>
<td>193 (3.5)</td>
<td>82 (7.9)</td>
<td>258 (9.2)</td>
</tr>
</tbody>
</table>

| Medication history                    | Missing (%) | 13,781 (72.4) | 6,862 (70.6) | 4,165 (76.3) | 756 (72.4) | 1,998 (71.1) | <0.001  |
| Oral antihyperglycemic drugs          |             | 3,767 (19.8) | 2,068 (21.3) | 1,010 (18.5) | 198 (19.0) | 491 (17.5) |        |
| Insulin                               |             | 5,985 (31.5) | 2,304 (23.7) | 1,820 (33.4) | 376 (36.0) | 1,485 (52.8) | <0.001  |
| Lipid-lowering drugs                  |             | 13,039 (68.5) | 6,180 (63.6) | 3,768 (69.0) | 819 (78.4) | 2,272 (80.8) | <0.001  |
| Antihypertensive drugs                |             | 13,618 (71.6) | 5,666 (58.3) | 4,425 (81.1) | 900 (86.2) | 2,627 (93.5) | <0.001  |
| RAS blockers                          |             | 10,009 (52.6) | 3,702 (38.1) | 3,558 (65.2) | 662 (63.4) | 2,087 (74.2) | <0.001  |
| Statins                               |             | 12,268 (64.5) | 5,696 (58.6) | 3,562 (65.3) | 794 (76.1) | 2,216 (78.8) | <0.001  |

Data are expressed in mean ± SD, median (interquartile range), or number (percentage) as appropriate. P values for differences across DKD phenotypes were obtained by one-way ANOVA, or Kruskal-Wallis test or Chi-squared test as appropriate. Abbreviations: BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; RAS, renin-angiotensin system; SBP, systolic blood pressure; TC, Total cholesterol; UACR, urinary albumin-creatinine ratio.
Table 2. Event/incidence rates and risks of mortality, CVD, HHF, and CKD progression across four DKD phenotypes.

<table>
<thead>
<tr>
<th></th>
<th>DKD overall (N=19,025)</th>
<th>No DKD (N=9,713, 51%)</th>
<th>Albuminuria only (N=5,457, 29%)</th>
<th>Decreased eGFR only (N=1,044, 5%)</th>
<th>Albuminuria plus decreased eGFR only (N=2,811, 15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event (%)</td>
<td>438 (2.30)</td>
<td>103 (1.06)</td>
<td>124 (2.27)</td>
<td>30 (2.87)</td>
<td>181 (6.44)</td>
</tr>
<tr>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>7.83 (7.12, 8.60)</td>
<td>3.56 (2.90, 4.31)</td>
<td>7.83 (6.51, 9.33)</td>
<td>10.21 (6.89, 14.58)</td>
<td>22.14 (19.03, 25.61)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event (%)</td>
<td>1,076 (5.66)</td>
<td>369 (3.80)</td>
<td>318 (5.83)</td>
<td>73 (6.99)</td>
<td>316 (11.24)</td>
</tr>
<tr>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>19.91 (18.73, 21.13)</td>
<td>13.05 (11.76, 14.46)</td>
<td>20.79 (18.57, 23.21)</td>
<td>25.88 (20.28, 32.54)</td>
<td>41.21 (36.79, 46.02)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>HHF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event (%)</td>
<td>298 (1.57)</td>
<td>33 (0.34)</td>
<td>90 (1.65)</td>
<td>27 (2.59)</td>
<td>148 (5.27)</td>
</tr>
<tr>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>5.38 (4.78, 6.02)</td>
<td>1.14 (0.79, 1.60)</td>
<td>5.73 (4.61, 7.04)</td>
<td>9.32 (6.14, 13.56)</td>
<td>18.71 (15.82, 21.98)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td><strong>Composite renal outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event (%)</td>
<td>1,161 (6.10)</td>
<td>128 (1.32)</td>
<td>327 (5.99)</td>
<td>38 (3.64)</td>
<td>668 (23.76)</td>
</tr>
<tr>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>21.74 (20.50, 23.02)</td>
<td>4.46 (3.72, 5.31)</td>
<td>21.59 (19.31, 24.06)</td>
<td>13.27 (9.39, 18.22)</td>
<td>99.29 (91.90, 107.11)</td>
</tr>
<tr>
<td>Unadjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age, sex, ever smoking, diabetes duration, systolic blood pressure, body mass index, glycated hemoglobin, ln(triglycerides), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, oral antihyperglycemic drugs, insulin, lipid-lowering drugs, antihypertensive drugs, renin-angiotensin-system blockers, statins, diabetic retinopathy, and history of cardiovascular disease and congestive heart failure.

Abbreviations: CI, confidence interval; composite renal outcome, incident end-stage kidney disease or sustained eGFR reduction ≥40%; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio.
Table 3. Event/incidence rates and risks of mortality, CVD, HHF, and CKD progression across four DKD phenotypes after further excluding subjects with baseline eGFR <30 mL/min/1.73 m².

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>All-cause mortality</th>
<th>CVD</th>
<th>HHF</th>
<th>Composite renal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event (%)</td>
<td>Incidence per 1,000 person-years (95% CI)</td>
<td>Unadjusted HR (95% CI)</td>
<td>Adjusted HR (95% CI)</td>
</tr>
<tr>
<td>DKD overall (N=18,425)</td>
<td>376 (2.04)</td>
<td>6.94 (6.26, 7.68)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>No DKD (N=9,713, 52.7%)</td>
<td>103 (1.06)</td>
<td>3.56 (2.90, 4.31)</td>
<td>2.19 (1.69, 2.84)</td>
<td>1.88 (1.36, 2.59)</td>
</tr>
<tr>
<td>Albuminuria only (N=5,457, 29.6%)</td>
<td>124 (2.27)</td>
<td>7.83 (6.51, 9.33)</td>
<td>2.65 (1.74, 4.05)</td>
<td>1.45 (0.86, 2.42)</td>
</tr>
<tr>
<td>Decreased eGFR only (N=1,000, 5.4%)</td>
<td>27 (2.70)</td>
<td>9.56 (6.30, 13.91)</td>
<td>5.27 (4.05, 6.85)</td>
<td>2.78 (1.93, 3.99)</td>
</tr>
<tr>
<td>Albuminuria plus decreased eGFR (N=2,255, 12.2%)</td>
<td>122 (5.41)</td>
<td>18.61 (15.45, 22.22)</td>
<td>5.27 (4.05, 6.85)</td>
<td>2.78 (1.93, 3.99)</td>
</tr>
</tbody>
</table>

**Adjusted for age, sex, ever smoking, diabetes duration, systolic blood pressure, body mass index, glycated hemoglobin, ln(triglycerides), high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, oral antihyperglycemic drugs, insulin, lipid-lowering drugs, antihypertensive drugs, renin-angiotensin-system blockers, statins, diabetic retinopathy, and history of cardiovascular disease and congestive heart failure.**

Abbreviations: CI, confidence interval; composite renal outcome, incident end-stage kidney disease or sustained eGFR reduction ≥40%; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio.
Figure legends

**Figure 1.** Cumulative incidence curves for all-cause mortality, CVD, HHF, and CKD progression according to four DKD phenotypes. Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure. Please note the y-axis of each figure has been zoomed in.
**All-cause mortality**

Log-rank

\[ p < 0.001 \]

**Cardiovascular disease**

Gray's test

\[ p < 0.001 \]

**Hospitalization for heart failure**

Gray's test

\[ p < 0.001 \]

**Incident ESKD or ≥40% reduction in eGFR**

Gray's test

\[ p < 0.001 \]