Impact of~~Cardiovascular Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus and Associated~~ Cardio-Renal-Metabolic Comorbidities on Cardiovascular Outcomes and Mortality in Type 2 Diabetes Mellitus

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Short Title: Cardiovascular outcomes in T2DM pts with cardio-renal-metabolic comorbidities (77 characters; limit: 80 characters, including spaces)

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Abstract

~~Introduction~~Background**:** We evaluated the incremental contribution of chronic kidney disease (CKD) to the risk of major adverse cardiovascular events (MACE), heart failure (HF), and all-cause mortality (ACM) in type 2 diabetes mellitus (T2DM) patients and its importance relative to the presence of other cardio-renal-metabolic comorbidities.

Methods: Patients (≥40 years) were identified at the time of T2DM diagnosis from US (Humedica/Optum) and UK (Clinical Practice Research Datalink) databases. Patients were monitored post-diagnosis for modified MACE (myocardial infarction, stroke, ACM), HF, and ACM. Adjusted hazard ratios were obtained using Cox proportional-hazards regression to evaluate the relative risk of modified MACE, HF, and ACM due to CKD. Patients were stratified by presence or absence of atherosclerotic cardiovascular disease (ASCVD) and age.

Results: Between 2011–2015, of 227,224 patients identified with incident T2DM, 40,063 (17.64%) had CKD. Regardless of prior ASCVD, CKD was associated with higher risk of modified MACE, HF, and ACM; this excess hazard was more pronounced in older patients with prior ASCVD. In time-to-event analyses in the overall cohort, patients with T2DM + CKD or T2DM + CKD + hypertension + hyperlipidemia had increased risks for modified MACE, HF and ACM versus patients with T2DM and no cardio-renal-metabolic comorbidities. Patients with CKD had higher risks for and shorter times to modified MACE, HF, and ACM than those without CKD.

Conclusion~~s~~: In T2DM patients, CKD presence was associated with higher risk of modified MACE, HF, and ACM. This may have risk-stratification implications for T2DM patients based on background CKD and highlights the potential importance of novel renoprotective strategies.

Introduction

Diabetes mellitus is the most common cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) [1], with up to 33.2% of patients with type 2 diabetes mellitus (T2DM) developing CKD over a 4-year follow-up [2]. In addition to a strong association with diabetes, the prevalence of CKD increases with other cardiovascular (CV) risk factors such as hypertension (HTN), hyperlipidemia (HPLD), and heart failure (HF) [3-6]. Common underlying mechanisms and relationships between these diseases are increasingly being recognized as part of various sets of cardio-renal-metabolic ("CaReMe") comorbidities [7]. CaReMe comorbidities are highly prevalent in adults with T2DM [7], with >80% of patients with T2DM having HTN and HPLD and 20% having CKD, illustrating the need to target multiple risk factors in a coordinated fashion in these patients. Although much focus has been placed on risk factors of HTN and HPLD, the contribution of CKD to the risk of mortality and CV complications, including HF, is incompletely understood in patients with T2DM [8].

From a clinical perspective, the presence of CKD and its essential role in perpetuating the development of adverse CV outcomes has not yet gained as wide an appreciation among clinicians as other traditional risk factors, such as HTN or hypercholesterolemia. This paradigm, however, may be changing, given that kidney disease is being used to identify patients at high CV risk in recent CV outcomes trials. Furthermore, recent clinical trials with sodium-glucose cotransporter-2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP1) receptor agonists, and other agents in patients with T2DM have demonstrated improvements in kidney and CV outcomes, further emphasizing a critical link between heart and kidney disease [9-12]. It is therefore important to understand the relative contribution of CKD to major adverse CV events (MACE), HF, and all-cause mortality (ACM) in patients with T2DM, both to improve risk stratification of patients and, potentially, to guide treatment options. Accordingly, we assessed the incremental relationship of CKD with the risk of MACE, HF, and ACM in a large real-world international cohort of patients with T2DM.

Material and Methods

Databases and study design

The analyses were performed using data from Humedica/Optum, Clinical Practice Research Datalink (CPRD), and the combined data from both databases. The Humedica/Optum database includes electronic health records (EHR) from medical groups, integrated delivery networks, and hospital systems and linked outpatient, inpatient, and pharmaceutical claims and laboratory data from privately insured patients across the United States (US). EHR data are available for approximately 30

million individuals across 38 states in the US and claims data are available for 12–14 million patients annually across all 50 states [13, 14].

The CPRD primary care database is a robust data source that includes demographics, symptoms, tests, diagnoses, therapies, health-related behaviors, and secondary-care referrals. It comprises anonymized medical records from general practitioners that cover more than 11.3 million patients from 674 general practices in the United Kingdom (UK). Approximately 6.9% of the UK population is included with 4.4 million active (alive and currently registered) patients meeting the quality criteria [15]. In summary, the patient populations in both Humedica/Optum and CPRD databases broadly represent the demographic and geographic breakdown of the respective populations in the US and UK. De-identified patient data were integrated with claims, prescription, and practice management data to generate a comprehensive and longitudinal perspective of clinical care. No informed consent was required according to CPRD and Humedica standard operating procedures.

Read codes in the CPRD and International Classification of Diseases, Ninth Revision (ICD-9) codes in Humedica/Optum were used to identify diagnoses and procedures. Index T2DM diagnoses were identified as one inpatient diagnosis of T2DM or two outpatient diagnoses for T2DM within 365 days (latter date served as the index), or two of the following criteria (latter date of the two served as the index): 1) Outpatient diagnoses for T2DM, 2) Use of a non-insulin antihyperglycemic agent, 3) Abnormal laboratory test of fasting blood glucose >6.94 mmol/L (125 mg/dL) or glycated hemoglobin (HbA_{1c}) ≥48 mmol/mol (6.5%). CKD was identified by ICD-9/Read codes. If a patient had diagnoses for multiple CKD stages during the baseline period, the highest stage was recorded. HF in the baseline period was identified as any HF diagnosis. HF outcomes in the follow-up period were identified as HF hospitalizations (hHF). In the CPRD, hHF was identified by inpatient healthcare records with a primary diagnosis of HF. In Humedica EHR data, hHF was identified as an admitting diagnosis for HF, whereas in the Humedica claims data hHF was identified as a primary inpatient diagnosis of HF (first diagnosis field).

For the study cohort, the major inclusion criterion was patients with index T2DM events between January 1, 2011, and March 31, 2015. The exclusion criteria were: 1) Patients with a diagnosis of type 1 diabetes mellitus prior to the index event, 2) Gestational diabetes within 1 year prior to the index event, 3) Less than 365 days of enrollment prior to the index event, 4) Less than 18 years old at the index event, 5) Use of insulin before the index date event, 6) History of solid organ transplantation.

Outcome measures

Patients were followed post-T2DM diagnosis for modified MACE, HF, and ACM. Modified MACE components were defined as myocardial infarction (MI; the presence of one inpatient diagnostic code for MI), stroke (the presence of one inpatient diagnostic code for hemorrhagic or ischemic stroke), and ACM (the presence of one diagnostic code for a discharge status of death and diagnostic codes for coronary artery disease or cerebrovascular disease).

Statistical analyses

Patients with T2DM were stratified according to the presence of CaReMe comorbidities at the time of T2DM diagnosis (T2DM only; HTN and HPLD; CKD; or CKD, HTN, and HPLD). The cumulative probability of time to event was presented with Kaplan–Meier plots. Patients aged ≥40 years with T2DM were included in the analysis and were additionally stratified based on presence or absence of prior atherosclerotic CV disease (ASCVD) and by age: 40 to <65 years, 65 to <75 years, and ≥75 years. Adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) were obtained by a stratified Cox proportional-hazards regression model, adjusting for age at index, sex, race, and comorbidities (MI, stroke, transient ischemic attack, atrial fibrillation, dysrhythmia, alcoholic fatty liver disease, hepatitis B, hepatitis C, HIV, peripheral artery disease, cancer) at baseline. Age and sex were forced into the model and other covariates (which could differ for each model) with *p*-values <0.1 were retained in the final model. Smoking status, body mass index, systolic blood pressure, HbA_{1c}, and low-density lipoprotein cholesterol were not included in the models because of the high percentage of missing values for these variables. All analyses were done using SAS v9.4 (SAS Institute, Cary, NC).

Results

Study cohort

Between 2011–2015, a total of 227,224 patients met eligibility criteria, of whom 17.64% had prevalent CKD (9.54% stage 2, 6.33% stage 3, 1.1% stage 4, 0.67% stage 5) at the time of T2DM diagnosis (Figure 1). The demographic and clinical characteristics shown for the four CaReMe combinations are shown in Table 1, with further details shown in Supplementary Tables 1–2.

Overall (based on CPRD data), patients with T2DM and CKD were older, a higher proportion were women, and had better glycemic control versus those with either T2DM alone or T2DM + HTN + HPLD. A greater proportion of patients with T2DM and CKD had a prior history of MI,

stroke/transient ischemic attack, HF, dysrhythmia/atrial fibrillation, or peripheral artery disease compared with patients in the T2DM alone or T2DM + HTN + HPLD cohorts (Table 1). The median follow-up times for patients with T2DM alone, T2DM + CKD, and T2DM + HTN + HPLD were 3.2 years, 2.7 years, and 3.0 years, respectively.

Missing data were much higher in the Humedica database than in the CPRD database and therefore the combined missing values were closer to those in the Humedica database. In Humedica, among patients with T2DM only, greater than 90% of values were missing for systolic blood pressure, body mass index, HbA_{1c}, and estimated glomerular filtration rate (eGFR). In patients with T2DM + HTN + HPLD these values were missing for more than 75% of patients. In patients with CKD with or without HTN + HPLD, missing data were less than 35% for these laboratory measurements and was less than 20% for eGFR.

CaReMe comorbidities, CV outcomes, and mortality

In unadjusted analyses (Figure 2), patients who had CKD as one of their CaReMe comorbidities had shorter times to modified MACE, HF, and ACM than did patients without CKD. After controlling for potential confounders, the presence of T2DM + CKD was associated with higher risks of modified MACE, HF, and ACM versus patients with T2DM alone, and when compared with patients with background T2DM + HTN + HPLD (Table 2).

Subgroup analyses of patients with and without established ASCVD

In patients with and without established ASCVD the presence of T2DM + CKD + HTN + HPLD was generally associated with a higher risk of modified MACE and ACM compared with patients that had T2DM only. In both subgroups the rate of hHF generally increased with age and with CKD stage, although CIs of unadjusted rates overlapped (Supplementary Tables 3–4). For all outcomes, CKD stage 4 conveyed a much higher risk than all other cohorts. Adjusted hazard ratios (95% CI) for modified MACE, HF, and ACM for CKD stage 4 patients relative to T2DM-only patients were 2.44 (2.23, 2.67), 3.83 (3.33, 4.40), and 3.06 (2.70, 3.48) without ASCVD and 1.58 (1.38, 1.81), 1.86 (1.57, 2.21), and 2.54 (2.12, 3.04) in patients with ASCVD, respectively. In general (across all ages and patients with or without prior ASCVD), the presence of CKD—regardless of the presence of HTN and HPLD—was associated with higher risks of modified MACE, HF, and ACM, compared with patients with T2DM only.

Discussion

In this analysis of two large databases, patients with prevalent CKD at the time of T2DM diagnosis had higher risks of modified MACE, HF, and ACM. The additional presence of CKD was associated with higher risks of modified MACE, HF, and ACM versus the presence of HTN and/or HPLD without CKD. Although previous epidemiological studies have reported a relationship between CKD and CV outcomes, these studies did not generally focus on patients with diabetes [8, 16, 17], and very little, until now, had been published in incident T2DM cohorts. Our findings emphasize the magnitude of this risk and suggest the possible importance of identifying novel strategies to augment renal protection in patients with T2DM.

Over the past 20 years, rates of MI and stroke have declined in patients with T2DM, possibly because of better pharmacological control of CV risk factors, such as with the use of statins [18]. However, CKD and end-stage kidney disease rates have remained essentially stable, and renal complications are highly prevalent. These rates are even higher in patients with CVD [19], illustrating the important relationship between CKD and CVD. From a mechanistic perspective, complex and overlapping pathways have been implicated in the pathogenesis of CV and renal complications in T2DM, and the overlap between these conditions. Accordingly, treatment of HF, ischemic CVD, and CKD in the presence of diabetes has focused on blockade of the renin–angiotensin–aldosterone system (RAAS) [20]. Reducing hyperglycemic burden in patients with T2DM has failed to reduce CV or HF risk, and only has a modest effect on CKD progression [21]. Advances in the treatment of patients with T2DM around reducing CV and renal risk have been made more recently with SGLT2 inhibitors and GLP1 receptor agonists, although end-organ protective effects appear to be largely independent of glucose-lowering effects.

Heart failure is one of the most common CV complications observed in patients with CKD, occurring more frequently than CV death [22]. Moreover, co-existent HF and CKD in the setting of T2DM is associated with an adverse prognosis [23]. For example, in previous adjusted analyses, patients with T2DM and CKD and HF had a 56% higher risk of ACM and a 44% higher risk of CV mortality compared with patients diagnosed with HF only [23]. Whereas previous work has reported a significant interaction between general CKD and HF risk [24], little is known about this interaction in the setting of multiple CaReMe comorbidities. In the current analysis, patients with T2DM and CKD were at higher risk for the development of HF, regardless of background HTN and HPLD. Furthermore, the relationship between CKD and higher HF risk increased with advanced CKD stage. This “cardiorenal” interaction is therefore important epidemiologically, and also appears to be important therapeutically because several therapies preferentially benefit both HF and CKD outcomes in

patients with diabetes, including RAAS inhibitors and SGLT2 inhibitors, as reflected by changes in recent clinical practice guidelines [25].

From a therapeutic perspective, preventing the development and progression of CKD in patients with T2DM is an important goal of care that involves treating multiple risk factors in addition to hyperglycemia. CV outcomes trials with SGLT2 inhibitors, have, for example, shown reductions in both CV outcomes and CKD progression even in the absence of significant kidney disease at baseline, and independent of glucose lowering, while previous intensive glycemic-control studies have principally only demonstrated benefits on surrogates of microvascular risk such as new onset of microalbuminuria [26]. Similarly, there have been a number of trials of various agents targeting pathways common to both kidney disease and CVD, including mineralocorticoid antagonists, which may indicate a place for the use of these compounds to take advantage of mechanisms of action that mitigate risk for CVD and CKD, independent of blood pressure lowering or control of other CV risk factors [9, 27, 28]. Indeed, some of these emerging therapies are thought to reduce cardiorenal risk by suppressing inflammation or profibrotic pathways that have until now not been a major consideration or therapeutic target.

Beyond considering CKD and HF in isolation, it is also important to account for additional CaReMe comorbidities that can impact CV risk and mortality. The approach used in the current analysis—examining interactions with multiple CaReMe comorbidities—is clinically relevant because CaReMe comorbidities are common in patients with T2DM, with 51% having three or more CaReMe comorbidities [7]. The confluence of comorbidities is important because patients with conditions such as CKD are at high risk of CV complications and ACM [29], an interaction that is partly independent of albuminuria and metabolic control[30]. In the current analysis, rather than the absolute number of CaReMe comorbidities leading to worse outcomes, the presence of CKD was a dominant determinant of CV risk. Although this does not mean that other risk factors should be ignored, it highlights the potential importance of reducing CKD progression in patients with T2DM [30]. Observations in previous datasets have reported a relationship between CKD and CV events, but have not been restricted to patients with T2DM; it has been generally hypothesized that T2DM is a risk factor for combined CV and renal risk, but this relationship has not been examined directly [31, 32].

Despite the large sample size, this analysis has important limitations. First, beyond the impact of incident CKD, we recognize that decline in kidney function is also associated with incident HF risk.

Because of the nature of the dataset, we were unable to include changes in eGFR over time in the analysis, nor were we able to account for the impact of specific intercurrent CV events such as revascularization procedures, which are also strongly linked with adverse outcomes in CKD patients with diabetes [33]. Claims data depend on accurate coding and on patients visiting a physician (perhaps well after a condition is manifest) and misclassification of the nature and timing of diagnoses is possible. However, the CaReMe conditions are well recognized and may be less subject to misclassification. Deaths not associated with a claim, and under-reporting of deaths, could underestimate the mortality rate. Due to large amounts of missing data, several important confounding factors could not be included in the statistical analyses. Finally, because of limitations of the available data, we were also unable to distinguish between HF with reduced and with preserved ejection fraction. Nonetheless, a unique strength of the current analysis is that we assessed the incremental contributions of various CaReMe comorbidities, such as HTN, HPLD, and CKD, to the risk of modified MACE, HF, and ACM in an incident cohort of patients with T2DM stratified by the presence or absence of prior ASCVD and by age.

In conclusion, in this large cohort study involving patients with T2DM, CKD was the key CaReMe comorbidity associated with increased risks of modified MACE, HF, and ACM. Beyond HTN and HPLD, there is a need to better diagnose, treat, and prevent renal complications in patients with T2DM, which may reduce morbid CV and renal complications. Furthermore, development of care models that emphasize comprehensive risk reduction in patients T2DM and CaReMe comorbidities (especially CKD) is needed.

Statements

Acknowledgments

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Statement of Ethics

No informed consent was required according to CPRD and Humedica standard operating procedures.

Disclosure Statement

D.Z.I.C. has received honoraria from Boehringer Ingelheim-Lilly, Merck, AstraZeneca, Sanofi, Mitsubishi-Tanabe, AbbVie, Janssen, Bayer, and Prometic and has received operational funding (research grants) for clinical trials from Boehringer Ingelheim-Lilly, Merck, Janssen, Sanofi, and AstraZeneca. D.C.W. has acted as a consultant and/or received honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Janssen, Napp, Mitsubishi Tanabe, Mundipharma, and Vifor Fresenius. S.V.A. has nothing to declare. E.R., P.R.H., and H.C. are employees of AstraZeneca. S.M. is employed by Evidera, which was contracted to provide support for the study. J.V. is a contractor to AstraZeneca in the capacity of Chief Medical Advisor for Cardiovascular, Renal and Metabolic therapeutic areas. M.K. has received grants, honoraria, and other research support from AstraZeneca during the conduct of the study, and, outside the submitted work, grants, honoraria, and other research support from AstraZeneca, grants and honoraria from Boehringer Ingelheim, and honoraria from Amarin, Amgen, Applied Therapeutics, Bayer, Eisai, GlaxoSmithKline, Glytec, Intarcia, Janssen, Merck, Novartis, Novo Nordisk, and Sanofi.

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The study was funded by AstraZeneca. The sponsor was involved in the study design; collection, analysis and interpretation of data; report writing; and the decision to submit the manuscript for publication.

Author Contributions

DC made substantial contributions to the design of the work and analysis and interpretation of data and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ER contributed to the rationale and concept of the study. DCW was involved in the design of the analysis. SVA contributed to the research question and analytic plan, and interpreting the analysis.

SM contributed substantially to the analysis and interpretation of the data. PRH participated in the conception and design of the study and the acquisition, analysis, and interpretation of the data. HC was involved in the design of the study and the analysis and interpretation of the data. JV contributed to the initiation of idea for the study, and interpretation of data and subsequent analysis. MK contributed to developing the research question and analytic plan and interpreting the analysis. All authors contributed to the drafting of the manuscript, reviewed the manuscript for important intellectual content, and approved the final version to be published.

Data Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Figure Legends

Fig. 1. Patient disposition and classification as per ICD-9 codes (combined)

The last row shows patients who were included in the analysis. Patients who do not fulfill any of these criteria are not shown; i.e., the numbers do not sum up to the previous row's N. It is possible for individual patients to be included in all of the last 3 groups; i.e., the 3 groups are not mutually exclusive.

Abbreviations: CKD, chronic kidney disease; CPRD, Clinical Practice Research Datalink; HPLD, hyperlipidemia; HTN, hypertension; ICD-9, International Classification of Diseases, Ninth Revision; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Fig. 2. Kaplan–Meier plots for the overall group of (A) time to modified MACE, (B) time to HF, (C) time to ACM

Abbreviations: ACM, all-cause mortality; CKD, chronic kidney disease; DM, type 2 diabetes mellitus; HF, heart failure; HPLD, hyperlipidemia; HTN, hypertension; MACE, major adverse cardiovascular events.