Diabetes Ther (2022) 13:275–286
https://doi.org/10.1007/s13300-021-01191-y

ORIGINAL RESEARCH

Manifestation of Heart Failure and Chronic Kidney Disease are Associated with Increased Mortality Risk in Early Stages of Type 2 Diabetes Mellitus: Analysis of a Japanese Real-World Hospital Claims Database

Takashi Kadowaki · Issei Komuro · Naru Morita · Hiroki Akiyama · Yoko Kidani · Toshitaka Yajima

Received: November 4, 2021 / Accepted: December 7, 2021 / Published online: January 10, 2022

ABSTRACT

Introduction: To assess the initial manifestation of comorbidities and their impact on mortality risk in patients with type 2 diabetes mellitus (T2DM) without a history of cardiovascular or renal complications (i.e., in the early stages of T2DM) compared with patients without T2DM.

Methods: We performed a retrospective cohort study using a Japanese hospital claims database. The incidence rates of comorbidities (chronic kidney disease [CKD], heart failure [HF], myocardial infarction [MI], peripheral arterial disease [PAD], and stroke) and mortality risk were compared between patients with T2DM and age-/sex-matched patients without T2DM (matched 1:2).

Results: Among the comorbidities assessed in this study, CKD and/or HF was the most frequent initial manifestation in the patients with T2DM (n = 426,186) with an incidence rate 2.02 times greater than that in matched patients without T2DM (n = 1,018,609). The mortality risk was also greater in patients with T2DM than in patients without T2DM with a hazard ratio of 1.73. In both patients with and without T2DM, the presence of CKD or HF was associated with greater mortality risks compared with the presence of MI, PAD, or stroke.

Conclusions: The high incidence of CKD or HF manifestation can contribute to the augmented mortality risk in patients in the early stages of T2DM compared with patients without T2DM. These findings highlight the importance of early interventions for preventing/treating CKD and HF to improve the prognosis of patients with T2DM.

Keywords: Diabetes; Heart failure; Chronic kidney disease; Cardiorenal syndrome; Complications; Real-world data

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13300-021-01191-y.

T. Kadowaki
Toranomon Hospital, Tokyo, Japan

I. Komuro
Department of Cardiovascular Medicine, The University of Tokyo, Tokyo, Japan

N. Morita · H. Akiyama · Y. Kidani · T. Yajima (✉)
Cardiovascular, Renal, and Metabolism, Medical Affairs, AstraZeneca K.K., Tower B Grand Front Osaka, 3-1 Ofukacho, Kita-ku, Osaka 530-0011, Japan
e-mail: toshitaka.yajima@astrazeneca.com

Key Summary Points

Why carry out this study

Chronic kidney disease (CKD) and heart failure (HF) are early and frequent complications in patients with type 2 diabetes mellitus (T2DM), and history of prior CKD or HF is associated with increased mortality risk.

However, it remains unclear how much a background of diabetes augments the mortality risk and development of CKD and HF among patients in the early stages of T2DM compared with that in patients without T2DM.

What was learned from the study

CKD and/or HF was more frequent as the initial manifestation than atherosclerotic cardiovascular diseases in patients with T2DM with an incidence rate 2.02 times greater than that in matched patients without T2DM. The mortality risk was also greater in patients with T2DM than in patients without T2DM with a hazard ratio of 1.73.

The high incidence of CKD or HF may contribute to the augmented mortality risk in patients in the early stages of T2DM relative to that in patients without T2DM.

Early prevention and treatment of CKD and HF may improve the prognosis of patients with T2DM.

INTRODUCTION

It is estimated that more than 400 million people are living with diabetes worldwide with 4 million deaths each year [1, 2]. With aging of the population, the prevalence of diabetes is expected to increase to 578 and 700 million by 2030 and 2045, respectively [2], which will greatly exacerbate the healthcare burden of diabetes.

The vast majority of patients with diabetes have one or more complications. In a US cross-specialty diabetes registry [3], only 6% of patients had isolated type 2 diabetes mellitus (T2DM), whereas more than 50% of patients had at least three comorbidities, predominantly hypertension, hyperlipidemia, coronary artery disease, and chronic kidney disease (CKD). According to data from the Emerging Risk Factors Collaboration, the hazard ratio (HR) for all-cause death in patients with diabetes compared to patients without diabetes was 1.80 (95% confidence interval [CI] 1.71–1.90) after adjustment for age, sex, smoking status, and body mass index (BMI)[4]. Diabetes was also associated with greater risks of death from cardiovascular causes (HR 2.32; 95% CI 2.11–2.56) and renal diseases (HR 3.02; 95% CI 2.39–3.82) [4]. The development of comorbidities and its impact on mortality risk in patients with T2DM without history of cardiovascular or renal complications was recently examined using real-world databases in six countries, which included Japan [5]. It was reported that CKD or heart failure (HF) were more frequent initial manifestations than other comorbidities, such as myocardial infarction (MI), peripheral arterial disease (PAD), and stroke. Moreover, a history of CKD or HF was associated with increased mortality risk [5], suggesting the importance of early management of CKD and HF in patients with T2DM. However, it remains unclear how much the background of diabetes augments the mortality risk and the development of CKD and/or HF (hereafter referred to as CKD/HF) in the early stages of T2DM relative to that in patients without T2DM.

In this study, we compared the cumulative incidence rates of CKD, HF, and atherosclerotic cardiovascular diseases (ASCVDs; i.e., MI, PAD, and stroke) between patients with T2DM and patients without T2DM having no history of cardiovascular and renal complications, and determined the increase in mortality risk mediated by the background of T2DM. The results will demonstrate the real-world clinical significance of preventive or interventional

approaches targeting early comorbidities in patients with T2DM.

METHODS

Ethical Statement

This study was approved by the Non-Profit Organization MINS Institutional Review Board (D1690R00061). Because this study was a retrospective observational study with anonymized data collection, informed consent was not required.

Data Source and Study Population

The Medical Data Vision (MDV) database, a large-scale claims database covering approximately 23% of acute care hospitals in Japan, was used. The MDV includes inpatient and outpatient data, mainly from secondary care hospitals. The demographic characteristics, including the age and sex distributions of these patients, are similar to those of the Japanese national statistics, as explained in previous studies using the MDV database [6–8].

All individuals aged at least 18 years old with a recorded diagnosis of T2DM (10th revision of the International Statistical Classification of Diseases [ICD-10] codes E11 and E14) between April 1, 2008 and September 30, 2018 were extracted from the database. A separate cohort of patients without T2DM or other types of diabetes was extracted using the same period (hereafter described as patients without T2DM). Patients with T2DM were then matched with patients without T2DM by age and sex at a ratio of 1:2. The index date was set as follows: for patients with T2DM, the first visit after 1 year of the initial hospital records or the date of initial diagnosis of T2DM, whichever came later; for patients without T2DM, the first visit after 1 year of the initial hospital records. For the T2DM cohort, patients were excluded if they had a diagnosis of T1DM (ICD-10 codes E10 and O24.0) or gestational diabetes (ICD-10 code O24.4) up to 1 year before the index date, or if they lacked an age-/sex-matched patient without T2DM.

The T2DM and age-/sex-matched non-T2DM cohorts were further divided on the basis of their comorbidities. Patients without documented history of cardiovascular diseases (CVD), CKD, or HF at the index date were identified to investigate the development of comorbidities during the follow-up period. In this article, T2DM without a history of CVD, CKD, or HF is referred to as the early stages of T2DM. Additionally, patients with T2DM and patients without T2DM with a comorbidity (CKD, HF, MI, PAD, or stroke) at the index date were selected to evaluate the impact of these comorbidities on the mortality risk.

Disease Definition

Diseases were defined using the ICD-10 codes listed in Table S1 (Supplementary Material). The patients were considered to have CVD if they had a diagnosis of MI, PAD, stroke, atrial fibrillation (AF), unstable angina pectoris (UAP), or angina pectoris (AP) at the index date. Patients without an ICD-10 code for CKD were considered to not have CKD.

Statistical Analyses

Continuous variables (such as age and BMI) are described using the mean and standard deviation, and categorical variables are described using frequencies and percentages. The first manifestation of HF, CKD, MI, stroke, or PAD was identified as the first recorded diagnosis. In patients with multiple events after the index date, only the first event was counted. Data were retrieved throughout the follow-up period until the date of leaving the database, death, or September 2018, whichever came first. The mortality risk was assessed using the records for in-hospital death from any cause. The time-to-event endpoints were analyzed using Cox proportional hazard regression models in which the reference category was patients without history of T2DM, CVD, CKD, or HF. The results are presented as HRs with 95% CIs and corresponding *P* values. The crude HRs and the HRs

adjusted for age and sex are presented. Kaplan–Meier plots were used to determine the cumulative incidence of events (all-cause mortality, manifestation of CKD, HF, MI, PAD, and stroke).

Table 1 Baseline characteristics of patients with or without T2DM

	Patients with T2DM ***N*** **= 426,186**	**Patients without T2DM** ***N*** **= 1,018,609**
Age at index date (years)	66.54 ± 12.39	68.41 ± 11.87
Sex at index date		
Male	217,382 (51.0%)	537,454 (52.8%)
Female	208,804 (49.0%)	481,155 (47.2%)
Body weight[a], kg	*n* = 120,186	*n* = 177,728
	60.63 ± 14.35	57.86 ± 13.01
BMI[a], kg/m^2	*n* = 120,186	*n* = 177,728
	23.92 ± 8.81	22.78 ± 24.77
HbA1c[a], % (mmol/mol)	*n* = 18,414	*n* = 9991
	6.48 ± 1.26	5.29 ± 0.42
	(47 ± 13.8)	(34 ± 4.6)
CCI[a]	1.59 ± 2.05	0.94 ± 1.71
Severity of T2DM[a,b]		
0	346,490 (81.3%)	1,018,609 (100.0%)
1	72,629 (17.0%)	–
2	6549 (1.5%)	–
3	518 (0.1%)	–
HF status[a], absent	426,186 (100.0%)	1,018,609 (100.0%)
CKD status[a], absent	426,186 (100.0%)	1,018,609 (100.0%)
Comorbidities other than CKD or HF[a,c]	0	0
Follow-up (days)	945.19 ± 741.63	776.36 ± 717.00

Values are mean ± standard deviation or *n* (%) of patients

T2DM type 2 diabetes mellitus, *CKD* chronic kidney disease, *HF* heart failure, *BMI* body mass index, *CCI* Charlson comorbidity index, *MI* myocardial infarction, *UAP* unstable angina pectoris, *AP* angina pectoris, *AF* atrial fibrillation, *PAD* peripheral artery disease

[a]Recorded at any time in the patient's medical history (from first record to the index date); the value recorded closest to the index date was used

[b]The severity of T2DM was determined on the basis of the number of diabetes-related complications (i.e., diabetic nephropathy, neuropathy, and retinopathy)

[c]MI, UAP, AP, AF, stroke, or PAD

RESULTS

Baseline Patient Characteristics

During the study period, we extracted data on 2,635,633 patients with T2DM and 4,277,120 age-/sex-matched patients without T2DM from the database. After applying the inclusion criteria, there were 426,186 patients with T2DM and 1,018,609 patients without T2DM having no history of CVD, CKD, or HF (Supplementary Material Fig. S1). The patients with T2DM were younger (66.54 ± 12.39 years vs. 68.41 ± 11.87 years) and had a greater BMI (23.92 ± 8.81 kg/m^2 vs. 22.78 ± 24.77 kg/m^2) than the patients without T2DM (Table 1). The prevalence of hypertension was greater in the patients with T2DM than in the patients without T2DM (40.1% vs. 15.8%; Supplementary Material Table S2). Statins (17.6% vs. 4.1%) and fibrates (2.4% vs. 0.5%) were more frequently prescribed in the patients with T2DM, indicating a greater prevalence of hyperlipidemia compared with the patients without T2DM (Supplementary Material Table S2). The prevalence rates of comorbidities associated with an impact on prognosis, including cancer (23.7% vs. 21.0%) and COPD (1.2% vs. 1.2%) were balanced in both groups of patients (Supplementary Material Table S2). The follow-up durations were 945.19 ± 741.63 days and 776.36 ± 717.00 days for the patients with T2DM and patients without T2DM, respectively.

First Manifestation of Comorbidities During the Follow-up Period

Among patients with T2DM, the most frequent comorbidity recorded during the follow-up period was CKD/HF, with an incidence rate of 33.5/1000 person-years (Fig. 1a; Table 2). Individually, the incidence rates of HF and CKD were 20.7/1000 person-years and 15.8/1000 person-years, respectively. Stroke (11.1/1000 person-years), PAD (5.6/1000 person-years), and MI (2.1/1000 person-years) were less frequent (Fig. 1a; Table 2). We also evaluated the development of comorbidities in the patients without T2DM and found that CKD/HF (18.0/1000 person-years) was the most frequent comorbidity (Fig. 1b; Table 2). HF was the most frequent individual comorbidity (13.2/1000 person-years), followed by stroke (8.6/1000 person-years), CKD (5.9/1000 person-years), PAD (3.2/1000 person-years) and MI (1.1/1000 person-years) (Fig. 1b; Table 2). The adjusted HRs were greater in the patients with T2DM than in the age-/sex-matched patients without T2DM for all comorbidities examined (CKD/HF: HR 2.02, 95% CI 1.99–2.05; HF: HR 1.72, 95% CI 1.69–1.75; CKD: HR 2.84, 95% CI 2.77–2.90; MI: HR 2.11, 95% CI 1.99–2.24; stroke: HR 1.42, 95% CI 1.39–1.45; PAD: HR 1.87, 95% CI 1.80–1.93) (Table 2). We also compared the cumulative incidence of all-cause mortality between the two groups of patients. As shown in Fig. 1c, the mortality risk was significantly greater in the patients with T2DM than in the patients without T2DM (HR 1.73, 95% CI 1.70–1.77).

Impact of Each Comorbidity on Mortality Risk

We investigated the impact of a history of each comorbidity on mortality risks by determining the HRs in patients with T2DM or patients without T2DM with a history of CKD, HF, MI, PAD, or stroke at the index visit. For this analysis, the reference group comprised patients without T2DM having no history of CVD, CKD, or HF at baseline. The baseline characteristics of these groups of patients are shown in Tables S3 and S4 (Supplementary Material). The presence of a single ASCVD (i.e., MI, PAD, or stroke) was associated with increased mortality risk in the patients with T2DM (MI: HR 1.64, 95% CI 1.52–1.77; PAD: HR 1.88, 95% CI 1.73–2.04; stroke: HR 1.70, 95% CI 1.64–1.77) and the patients without T2DM (MI: HR 1.40, 95% CI 1.26–1.56; PAD: HR 1.26, 95% CI 1.15–1.38; stroke: HR 1.29, 95% CI 1.24–1.34); these risks were numerically greater in the patients with T2DM than in the patients without T2DM (Fig. 2). The presence of CKD or HF at baseline was associated with greater mortality risk than the presence of ASCVD in the patients with

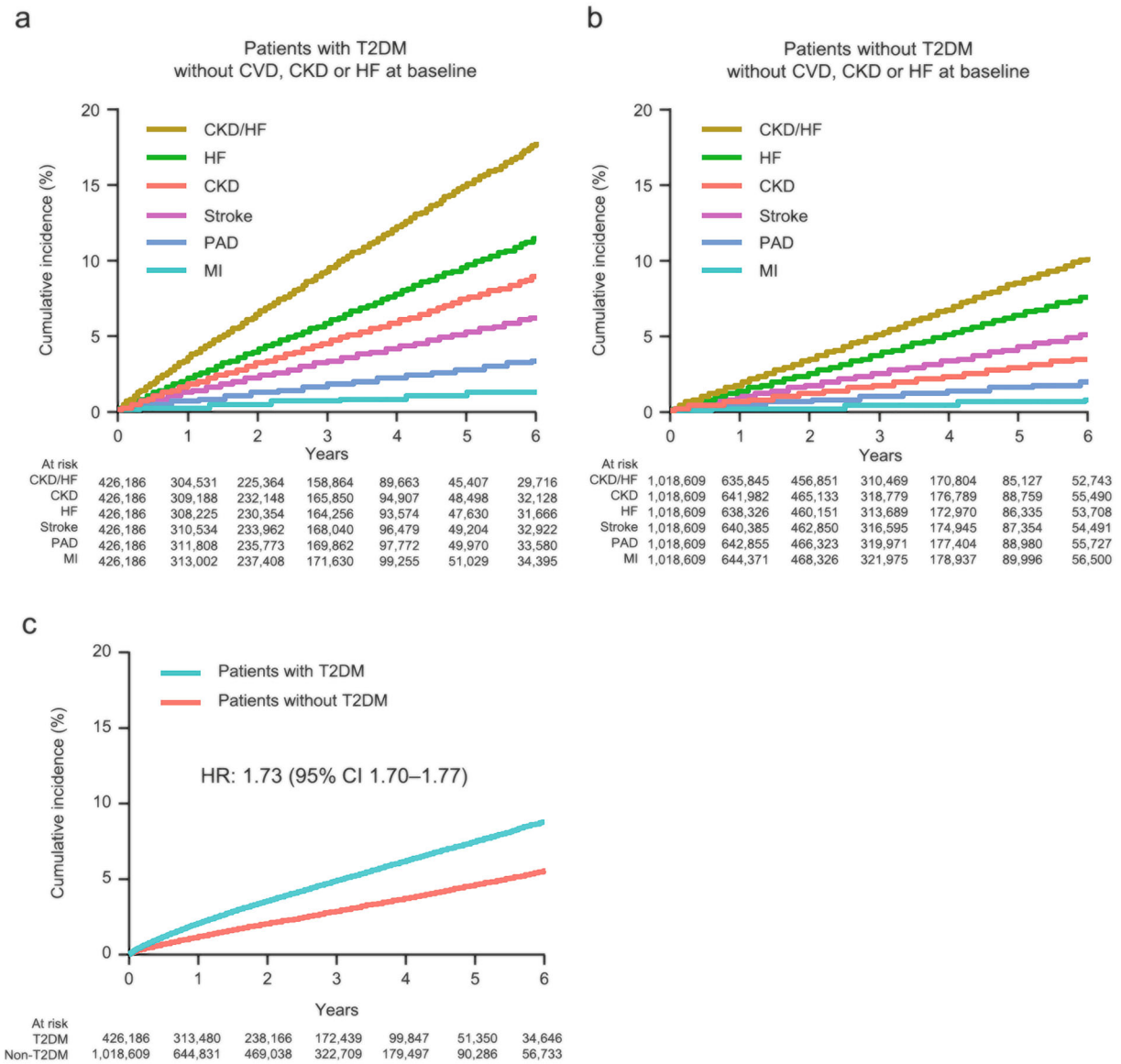

Fig. 1 Kaplan–Meier curves of the manifestation of comorbidities and all-cause mortality during the follow-up period in patients **a** with T2DM and **b** without T2DM having no history of CVD, CKD, or HF at baseline. **c** All-cause mortality in patients with T2DM and patients without T2DM. *CKD* chronic kidney disease, *CVD* cardiovascular disease, *HF* heart failure, *MI* myocardial infarction, *PAD* peripheral artery disease, *T2DM* type 2 diabetes

T2DM and patients without T2DM (T2DM with CKD: HR 2.59, 95% CI 2.49–2.69; non-T2DM with CKD: HR 2.50, 95% CI 2.37–2.64; T2DM with HF: HR 3.02, 95% CI 2.92–3.13; non-T2DM with HF: HR 2.69, 95% CI 2.59–2.79). The trend toward greater mortality risk was more prominent in patients with both CKD and HF among the patients with T2DM (HR 4.96, 95% CI 4.71–5.21) and the patients without T2DM (HR 5.42, 95% CI 5.04–5.84). Unlike ASCVD, there were no obvious differences in the mortality risks associated with HF or CKD between the patients with T2DM and patients without T2DM (Fig. 2).

Table 2 Event rates in T2DM or patients without T2DM having no recorded diagnosis of CVD, CKD, or HF at baseline

Outcome	Patients with T2DM (N = 426,186)		Patients without T2DM (N = 1,018,609)		Crude HR (95% CI)	Adjusted HR (95% CI)[b]
	Cases[a]	Event rate per 1000 person-years (95% CI)	Cases[a]	Event rate per 1000 person-years (95% CI)		
CKD/HF	34,954	33.5 (33.2–33.9)	37,940	18.0 (17.8–18.1)	1.86 (1.84–1.89)	2.02 (1.99–2.05)
CKD	17,002	15.8 (15.6–16.1)	12,724	5.9 (5.8–6.0)	2.67 (2.60–2.73)	2.84 (2.77–2.90)
HF	22,079	20.7 (20.4–21.0)	28,033	13.2 (13.0–13.3)	1.56 (1.54–1.59)	1.72 (1.69–1.75)
MI	2304	2.1 (2.0–2.2)	2324	1.1 (1.0–1.1)	1.94 (1.83–2.06)	2.11 (1.99–2.24)
Stroke	12,002	11.1 (10.9–11.3)	18,456	8.6 (8.5–8.8)	1.28 (1.25–1.31)	1.42 (1.39–1.45)
PAD	6118	5.6 (5.5–5.7)	6875	3.2 (3.1–3.3)	1.76 (1.70–1.82)	1.87 (1.80–1.93)

T2DM type 2 diabetes mellitus, *CVD* cardiovascular disease, *CKD* chronic kidney disease, *HF* heart failure, *CI* confidence interval, *HR* hazard ratio, *MI* myocardial infarction, *PAD* peripheral artery disease

[a]Cases documented during the follow-up period

[b]Adjusted for age and sex

DISCUSSION

In a previous study, CKD/HF was the most frequent initial complication among patients in early stages of T2DM and the presence of CKD/HF was associated with greater mortality risk compared with the presence of individual ASCVDs [5]. The present study confirmed the burden of HF and CKD in patients in early stages of T2DM using age-/sex-matched patients without T2DM as a reference group. CKD/HF was the most frequent initial manifestation and its incidence was higher in patients with T2DM than in the patients without T2DM. Furthermore, a history of CKD/HF was associated with greater mortality risk compared with ASCVD, regardless of the presence of T2DM. Therefore, we may assume that the high incidence of CKD/HF contributes to the greater overall mortality risk in patients in early stages of T2DM than in patients without T2DM (Fig. 1c). Considering the burden of HF and CKD revealed in this study, comprehensive management, which includes early diagnosis, prevention, and treatment of cardiorenal diseases, in addition to glycemic control, is necessary from the early stages of T2DM in order to improve its prognosis.

Although CKD was more common than HF in the Japanese T2DM population in the previous study (event rates for CKD and HF 17.1 and 13.6/1000 patient-years) [5], HF was more frequent than CKD in the present study (Fig. 1; event rates CKD and HF 15.8 and 20.7/1000 patient-years). One explanation may involve differences in patient selection. The previous study only examined patients with T2DM, whereas we included patients with or without T2DM who were matched by age and sex. This may result in differences in the baseline characteristics of the cohorts between the two studies. Despite the differences, both studies revealed that HF and CKD were more frequent initial manifestations than MI, PAD, or stroke in patients with T2DM. It is widely accepted that CKD is a common complication of T2DM, and diabetes is the most common cause of CKD and end-stage renal disease [9]. Furthermore, CKD often develops in the early stages of T2DM [10–13]. Our data provide further evidence that CKD is a common, early comorbidity in patients with T2DM, and was more frequent in this

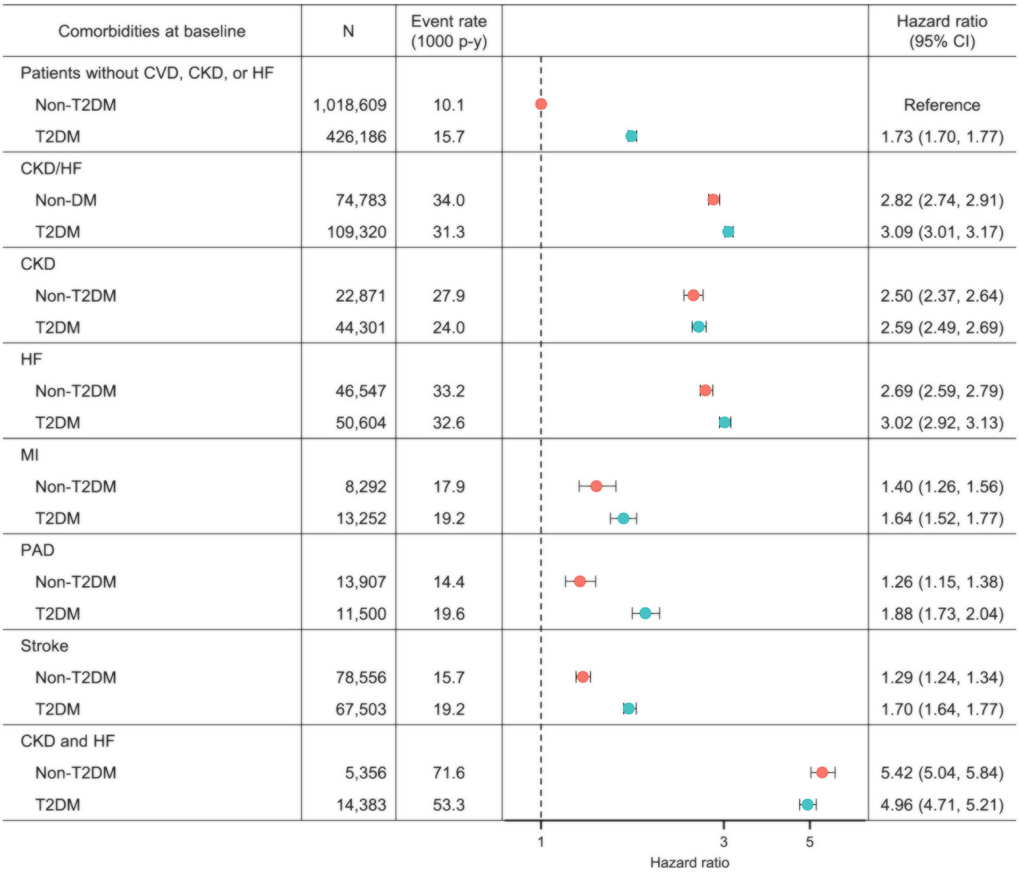

Fig. 2 Risk of all-cause mortality associated with a history of CKD/HF, CKD, HF, CKD & HF, MI, PAD, or stroke in patients with T2DM and patients without T2DM. *CI* confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *HF* heart failure, *MI* myocardial infarction, *PAD* peripheral artery disease, *p-y* patient-years, *T2DM* type 2 diabetes

population than in age-/sex-matched patients without T2DM.

An epidemiological link between diabetes and development of HF is evident even in the absence of ASCVD. Diabetes itself was reported to be an important risk factor for the development of HF with a relative risk of 2.14 (95% CI 1.96–2.34) for new-onset HF [14]. Additionally, an association between glycemic control and HF was demonstrated in a previous study, in which each 1% increase in HbA1c increased the risk of HF by 8% [15]. In addition, the UKPDS study revealed that a 1% reduction in HbA1c was associated with a 16% decrease in the risk of developing HF [16]. It was also suggested that left ventricular diastolic dysfunction is associated with the extent of insulin resistance and often precedes the onset of T2DM [17]. Consistently, we found a high cumulative incidence of HF compared with that of other comorbidities in this cohort of patients in early stages of T2DM. Furthermore, the cumulative incidence of HF was greater in patients with T2DM than in patients without T2DM, supporting an association between T2DM and HF development. The coexistence of diabetes and HF in the early stage of T2DM suggests we should reconsider the preventive measures and diagnose HF promptly in patients with T2DM.

ASCVDs are well-recognized macrovascular complications that nearly double the mortality risk in patients with T2DM [18–20]. The present study showed higher incidence rates of ASCVDs among patients in early stages of T2DM

compared with patients without T2DM, coupled with numerically greater mortality risks. Considering the evidence that intensified multifactorial interventions for blood glucose, blood pressure, and serum lipid have beneficial effects on reducing the risk of vascular complications in Japanese patients with T2DM [21], our data demonstrate the importance of comprehensive management of risk factors for atherosclerosis in patients in early stages of T2DM.

We also revealed that the mortality risks in patients with T2DM with a history of CKD or HF exceeded those of patients with T2DM with a history of ASCVDs, highlighting the impact of CKD and HF on the prognosis of T2DM. From a therapeutic perspective, cardiovascular outcome trials of sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated reduced risk of cardiovascular and renal outcomes, even in the absence of evident CVD or renal dysfunction at baseline [22–24]. More recent trials have demonstrated the effects of SGLT2 inhibitors on secondary prevention of HF and CKD, independent of diabetes [25–27]. Additionally, a recent trial demonstrated that finerenone, a mineralocorticoid receptor antagonist that targets a pathway common to both CVD and renal dysfunction, reduced the risks of CKD progression and CV events in patients with T2DM [28]. Taken together, the results of these studies suggest that therapeutic agents, which effectively target the cardiorenal pathway, will become a key component of the comprehensive care of T2DM, including the primary and secondary prevention of cardiovascular and renal complications.

Our study has also demonstrated the substantial burdens of HF and CKD on the prognosis of patients without T2DM because the HR exceeded that of patients with T2DM (5.42 vs. 4.96). Because patients without T2DM, who were matched to T2DM by age and sex, were selected for this study, the generalizability of this finding needs to be carefully considered. Nevertheless, the development of HF and CKD had a remarkable impact on prognosis regardless of the presence or absence of T2DM. This highlights the importance of screening and early intervention for these diseases, and should help raise awareness of the cardio-renal interaction.

There are several limitations in this study. First, causality cannot be inferred from this observational study. Second, because the MDV database comprises hospital claims data, the validity of the results depends on the quality and completeness of the data recorded, and missing values can be expected. Third, the data were mostly collected from secondary care rather than primary care hospitals, which may introduce selection bias. Fourth, patients cannot be followed up if they are transferred to other healthcare facilities. Fifth, residual confounding may remain, although the patients were matched by age and sex to patients without T2DM to minimize this possibility.

CONCLUSIONS

Among the comorbidities examined in this study, CKD/HF was the most frequent initial manifestation among patients in early stages of T2DM. Notably, the incidence of CKD/HF was considerably higher in patients with T2DM than that in patients without T2DM. A history of HF or CKD imposed a substantial burden on the prognosis of patients with T2DM, and the presence of both HF and CKD further elevated the mortality risk in this population. Our results suggest that HF and CKD contribute to the excess mortality risk in the early stages of T2DM, underscoring the need for additional treatment strategies on top of conventional glycemic and atherosclerotic factor controls. A holistic approach for the management of T2DM that encompasses the prevention and treatment of HF and CKD should be considered in order to further improve the quality of life and prognosis of patients with T2DM.

ACKNOWLEDGEMENTS

Funding. This study and the corresponding analyses were supported and funded by AstraZeneca K.K., Osaka, Japan. The publication fee for this manuscript, including the Rapid Service

Fee, was funded by AstraZeneca K.K. and Ono Pharmaceutical Co., Ltd., Osaka, Japan.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study concept and design. The general content of the manuscript was agreed upon by all authors. The first draft of the manuscript was developed by TK and AH, and all authors contributed to its development. All authors approved the final version of the manuscript before its submission. A team at AstraZeneca reviewed the manuscript during its development and was allowed to make suggestions. However, the final content was determined by the authors.

Disclosures. Naru Morita, Hiroki Akiyama, Yoko Kidani, and Toshitaka Yajima are full-time employees of AstraZeneca K.K. Issei Komuro has received grants from Astellas Pharma Inc., Boehringer Ingelheim Japan, Kowa Pharmaceutical Co. Ltd., Daiichi Sankyo Company Limited., Mitsubishi Tanabe Pharma Corporation, Shionogi & Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Company Limited., Toa Eiyo Ltd., Honorarium: Astellas Pharma Inc., Boehringer Ingelheim Japan, Kowa Pharmaceutical Co. Ltd., Daiichi Sankyo Company Limited., Mitsubishi Tanabe Pharma Corporation, Shionogi & Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Takeda Pharmaceutical Company Limited., and Toa Eiyo Ltd.; and lecture/other fees from AstraZeneca. Takashi Kadowaki has received grants from Asahi Mutual Life Insurance Co., Boehringer Ingelheim Japan, Daiichi Sankyo Company Limited., Kowa Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Corporation, MSD K.K., Novo Nordisk Pharma Ltd., Sanofi K.K., Takeda Pharmaceutical Company Limited; and lecture/other fees from AstraZeneca K.K., Astellas Pharma Inc., Boehringer Ingelheim Japan, Daiichi Sankyo Company Limited., Eli Lilly Japan K.K., Kowa Pharmaceutical Co. Ltd., Kyowa Hakko Kirin Co., Ltd., Mitsubishi Tanabe Pharma Corporation, MSD K.K., Ono Pharmaceutical Company Co., Ltd., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd., Sanwa Kagaku Kenkyusho Co. Ltd., Taisho Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Company Limited.

Medical Writing Assistance. Nicholas D. Smith (EMC K.K.) for medical writing support, which was funded by AstraZeneca K.K. and Ono Pharmaceutical Co., Ltd.

Compliance with Ethics Guidelines. This study was approved by Non-Profit Organization MINS Institutional Review Board (D1690R00061). Because this study was a retrospective observational study with anonymized data collection, informed consent was not required.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to the research contracts.

REFERENCES

1. Ogurtsova K, da Rocha Fernandes JD, Huang Y, et al. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017;128:40–50.

2. Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.

3. Arnold SV, Kosiborod M, Wang J, Fenici P, Gannedahl G, LoCasale RJ. Burden of cardio-renal-metabolic conditions in adults with type 2 diabetes within the diabetes collaborative registry. Diabetes Obes Metab. 2018;20(8):2000–3.

4. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med. 2011;364(9):829–41.

5. Birkeland KI, Bodegard J, Eriksson JW, et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: a large multinational cohort study. Diabetes Obes Metab. 2020;22(9):1607–18.

6. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. J Am Coll Cardiol. 2018;71(23):2628–39.

7. Tanabe M, Nomiyama T, Motonaga R, Murase K, Yanase T. Reduced vascular events in type 2 diabetes by biguanide relative to sulfonylurea: study in a Japanese hospital database. BMC Endocr Disord. 2015;15:49.

8. Tanabe M, Motonaga R, Terawaki Y, Nomiyama T, Yanase T. Prescription of oral hypoglycemic agents for patients with type 2 diabetes mellitus: a retrospective cohort study using a Japanese hospital database. J Diabetes Investig. 2017;8(2):227–34.

9. Shahbazian H, Rezaii I. Diabetic kidney disease; review of the current knowledge. J Ren Inj Prev. 2013;2(2):73–80.

10. Spijkerman AM, Dekker JM, Nijpels G, et al. Microvascular complications at time of diagnosis of type 2 diabetes are similar among diabetic patients detected by targeted screening and patients newly diagnosed in general practice: the hoorn screening study. Diabetes Care. 2003;26(9):2604–8.

11. An J, Nichols GA, Qian L, et al. Prevalence and incidence of microvascular and macrovascular complications over 15 years among patients with incident type 2 diabetes. BMJ Open Diabetes Res Care. 2021;9(1):e001847.

12. Bonora E, Trombetta M, Dauriz M, et al. Chronic complications in patients with newly diagnosed type 2 diabetes: prevalence and related metabolic and clinical features: the Verona Newly Diagnosed Type 2 Diabetes Study (VNDS) 9. BMJ Open Diabetes Res Care. 2020;8(1):e001549.

13. Gedebjerg A, Almdal TP, Berencsi K, et al. Prevalence of micro- and macrovascular diabetes complications at time of type 2 diabetes diagnosis and associated clinical characteristics: a cross-sectional baseline study of 6958 patients in the Danish DD2 cohort. J Diabetes Complicat. 2018;32(1):34–40.

14. Kodama S, Fujihara K, Horikawa C, et al. Diabetes mellitus and risk of new-onset and recurrent heart failure: a systematic review and meta-analysis. ESC Heart Fail. 2020;7(5):2146–74.

15. Iribarren C, Karter AJ, Go AS, et al. Glycemic control and heart failure among adult patients with diabetes. Circulation. 2001;103(22):2668–73.

16. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321(7258):405–12.

17. Fontes-Carvalho R, Ladeiras-Lopes R, Bettencourt P, Leite-Moreira A, Azevedo A. Diastolic dysfunction in the diabetic continuum: association with insulin resistance, metabolic syndrome and type 2 diabetes. Cardiovasc Diabetol. 2015;14:4.

18. Emerging Risk Factors Collaboration, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375(9733):2215–22.

19. Litwak L, Goh SY, Hussein Z, Malek R, Prusty V, Khamseh ME. Prevalence of diabetes complications in people with type 2 diabetes mellitus and its association with baseline characteristics in the multinational A1chieve study. Diabetol Metab Syndr. 2013;5(1):57.

20. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. Lancet Diabetes Endocrinol. 2015;3(2):105–13.

21. Ueki K, Sasako T, Okazaki Y, et al. Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled

trial. Lancet Diabetes Endocrinol. 2017;5(12):951–64.

22. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644–57.

23. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380(4):347–57.

24. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117–28.

25. Heerspink HJL, Stefansson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436–46.

26. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019;381(21):1995–2008.

27. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020;383(15):1413–24.

28. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–29.