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ORIGINAL ARTICLE

Type 2 Diabetes Mellitus and Impact of Heart Failure on Prognosis Compared to Other Cardiovascular Diseases

A Nationwide Study

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BACKGROUND: Heart failure (HF) in patients with type 2 diabetes mellitus (T2D) has received growing attention. We examined the effect of HF development on prognosis compared with other cardiovascular or renal diagnoses in patients with T2D.

METHODS AND RESULTS: Patients with new T2D diagnosis patients were identified between 1998 and 2015 through Danish nationwide registers. At yearly landmark timepoints after T2D diagnosis, we estimated the 5-year risks of death, 5-year risk ratios, and decrease in lifespan within 5 years associated with the development of HF, ischemic heart disease, stroke, peripheral artery disease, and chronic kidney disease. A total of 153 403 patients with newly diagnosed T2D were followed for a median of 9.7 years (interquartile range, 5.8–13.9) during which 48 087 patients died. The 5-year risk ratio of death associated with HF development 5 years after T2D diagnosis was 3 times higher (CI, 2.9–3.1) than patients free of diagnoses (CI, 2.9–3.1). Five-year risk ratios were lower for ischemic heart disease (1.3 [1.3–1.4]), stroke (2.2 [2.1–2.2]), chronic kidney disease (1.7 [1.7–1.8]), and peripheral artery disease (2.3 [2.3–2.4]). The corresponding decrease in lifespan within 5 years when compared with patients free of diagnoses (in months) was HF 11.7 (11.6–11.8), ischemic heart disease 1.6 (1.5–1.7), stroke 6.4 (6.3–6.5), chronic kidney disease 4.4 (4.3–4.6), and peripheral artery disease 6.9 (6.8–7.0). HF in combination with any other diagnosis imposed the greatest risk of death and decrease in life span compared with other combinations. Supplemental analysis led to similar results when stratified according to age, sex, and comorbidity status, and inclusion period.

CONCLUSIONS: HF development, at any year since T2D diagnosis, was associated with the highest 5-year absolute and relative risk of death, and decrease in lifespan within 5 years, when compared with development of other cardiovascular or renal diagnoses.

Key Words: chronic kidney disease ■ epidemiology ■ heart failure ■ mortality ■ myocardial infarction

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WHAT IS KNOWN

- Patients with type 2 diabetes mellitus have a higher risk of developing cardiovascular disease and chronic renal disease.
- Patients with type 2 diabetes mellitus enrolled in trials have higher rates of death following cardiovascular or renal events.

WHAT THE STUDY ADDS

- We describe the absolute risk of survival among real-life patients with type 2 diabetes mellitus who develop cardiovascular and renal disease.
- While heart failure is not the most frequent comorbid disease, it is the most fatal condition in a real-world cohort of patients with type 2 diabetes mellitus.
- This association is present regardless of when the patients develop the cardiovascular or renal disease after diagnosis of type 2 diabetes mellitus.

Heart failure (HF) has in recent years been recognized as an important clinical end point in randomized clinical trials of patients with type 2 diabetes mellitus (T2D), in particular, after the results from randomized controlled trials of sodium-glucose-2-transporter (SGLT2) inhibitors showed benefit on cardiovascular death and HF hospitalisation.[1–3] Several observational studies have highlighted increased mortality following myocardial infarction,[4–7] stroke,[8] chronic kidney disease (CKD),[9,10] and HF[11–14] in patients with T2D. Interestingly, a post hoc analysis from the ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal End Points) suggested considerable mortality following a cardiovascular (including HF) or renal event in patients with T2D.[7] But, trial patients are often enrolled with a long duration of diabetes mellitus and considered high-risk subjects, the risk profile following a cardiovascular or renal diagnosis in real-life patients with newly diagnosed T2D remains unknown.[1,15] In addition, little is known about the prognostic importance in terms of mortality risk of different cardiovascular and renal diagnoses in patients with T2D. Our objective was to estimate, at every year since T2D diagnosis, the absolute risk of death, the risk ratio (RR) of death, and the decrease in lifespan within 5 years following the development of HF, ischemic heart disease (IHD), stroke, CKD, and peripheral artery disease (PAD).

METHODS

Data

The data upon which this analysis is done will not be made publicly available due to the sensitive nature of the data.

Data Sources

In Denmark, every citizen is provided with a unique personal identification number given at birth or immigration and used throughout the Civil Registration System, which allows for cross-linkage of health and administrative databases at the individual level and enables near-complete follow-up. In Denmark, equal access to the health care system is granted to every citizen, including primary and hospital care. Data were collected from 4 nationwide registers made available through Statistics Denmark, a government-based institution responsible for maintenance of multiple registers after anonymization and encryption of the personal identification number. The Danish National Patient Registry entails information on all hospital admissions from 1977 onwards. Each hospital contact is coded with a primary diagnosis and one or more secondary diagnoses according to The *International Classification of Disease, Eighth Revision* (*ICD-8*) until 1993, and *ICD-10* from 1994 onwards. Surgical procedures are coded using the Nordic Medico-Statistical Committee Classification of Surgical Procedures. The Danish National Prescription Registry holds information (dosage, dates, and Anatomic Therapeutic Chemical codes) on all prescriptions dispensed from a pharmacy since 1995. The Danish Cause of Death Registry entails information on date, cause, and place of death from 1970 onwards. The Danish Civil registry holds information on age, gender, and date of birth. The type of registry and data extracted from each registry is described in Table I in the Data Supplement.

Study Population

We defined patients with incident T2D in patients above 18 years according to the following criterion: a first-time redeemed prescription of a noninsulin antidiabetic drug. Patients were eligible for inclusion in the period between January 1, 1998, and December 31, 2015. We excluded patients with a prior diagnosis of HF, IHD, stroke, CKD, PAD, and gestational diabetes mellitus (Figure 1 and Table II in the Data Supplement). Comorbidities were identified from prior hospitalizations and ambulatory contacts up to 10 years before the date of inclusion and continuously throughout the follow-up for the landmark analyses. Information on concomitant medical therapy was obtained from dispensed prescriptions as listed in the Danish National Prescription Registry and defined by at least one redeemed prescription 6 months before the inclusion date. The following drugs were recorded at inclusion: ACE (angiotensin-converting enzyme) inhibitors, ARB (angiotensin II receptor blockers), calcium channel blockers, loop diuretics, thiazides, acetylsalicylic acid, mineralocorticoid receptor antagonists, statins, and β-blockers (Table II in the Data Supplement).

Definitions of Cardiovascular and Renal Diagnoses

Cardiovascular and renal diagnoses in patients with T2D were identified from hospital discharge records and ambulatory contacts in the Danish National Patient Registry. A cardiovascular or renal disease was defined as a diagnosis of HF, IHD, stroke, PAD, or CKD. The diagnoses used are listed in Table II in the Data Supplement.

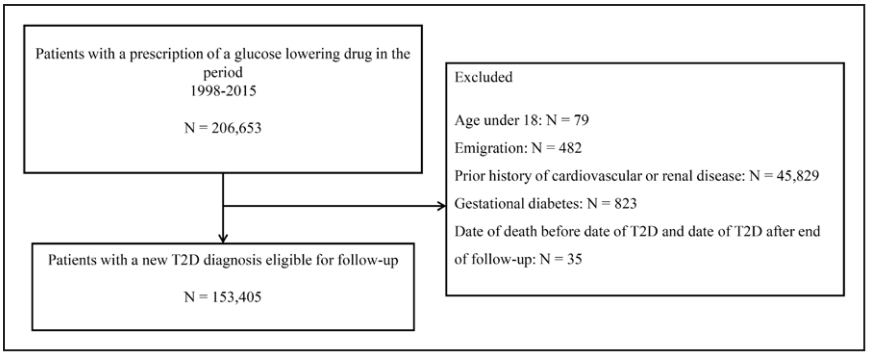

Figure 1. Flowchart of the study cohort showing exclusion and inclusion of patients.
T2D indicates type 2 diabetes mellitus.

Outcome

The main outcome was all-cause death. Patients were followed until emigration, death, or end of the study period (December 31, 2015).

Statistical Analysis

Baseline characteristics were described by use of proportions for categorical variables and means and SD or medians and interquartile ranges for continuous variables. To avoid immortality bias and to supply absolute risk estimates, we used a landmark approach to assess the risk of death associated with the development of cardiovascular or renal disease.[16] For every *t* years of follow-up since T2D diagnosis (*t* years meaning any year during follow-up, 0 to 10 years), we grouped patients still alive at landmark year *t* according to the cardiovascular or renal diagnosis(s) they had received so far. For further information the landmark method, please see Figure I in the Data Supplement. RR and restricted mean time loss were computed as the ratio of Kaplan-Meier risk estimates and as the restricted area under the Kaplan-Meier curve, respectively.[17] The landmark approach provides a method for assessing development of cardiovascular or renal disease according to time since T2D diagnosis. We choose to apply the nonparametric due to the assumption free nature of the analysis, and the inherent ability to provide absolute risk estimates, which are easily interpreted in a real-world clinical setting. In a first analysis, we focused on groups of patients who had received only one type of cardiovascular or renal diagnosis before each landmark year *t*. In a second analysis, we focused on groups of patients who had received 2 diagnoses before each landmark year *t*. Due to a small number of patients at each landmark year for some of the diagnoses, we chose to focus on results from the most common patient groups. RR and restricted mean survival time differences were computed using the group of patients with T2D not diagnosed with any cardiovascular or renal disease as reference. Prespecified subgroup analyses were also performed to assess whether the risk of death differed by age, sex, and comorbidity status. We also performed an additional analysis in which we included only patients who received their diagnoses within 1 year before the landmark year *t*. The purpose was to minimize the effect of longer duration of T2D complications on the results and to ensure comparability of groups across landmark years.

To investigate differences in prognosis and use of pharmacotherapy over time, we stratified the inclusion period in 2 separate time periods: from 1998 to 2008 and 2009 to 2015. For each time period, we recorded demographic details, medication, and present comorbidities at inclusion and calculated the 1-year risk of death following 1 or 2 cardiovascular or renal diagnoses according to each landmark year.

Analyses were performed using SAS (version 9.4 for Windows, SAS Institute, NC) and R, especially the R packages survRM2 and prodlim.[18–20]

Ethics

The study was approved by the Danish Data Protection Agency Danish Data Protection Agency (j-nr. 2007-58-0015 / local.j.nr. GEH-2014-015 I-Suite nr: 02733). In Denmark, ethical approval is not required for register-based studies.

RESULTS

A total of 153 405 patients with newly diagnosed T2D were included between 1998 and 2015 with no prior cardiovascular or renal diagnoses (Figure 1). Patient characteristics at time of inclusion are presented in the Table. Included patients were more likely to be diagnosed with hypertension, while atrial fibrillation, cancer, and chronic obstructive pulmonary disease were diagnosed in <5% of the cohort at time of inclusion (Table). During a median follow-up of 9.7 years (interquartile range, 5.8–13.9) 69 201 patients (45.1%) received a cardiovascular or renal diagnosis. Analyzing these 43 155 (62.3%) received one diagnosis, 17 309 (25.0%) received 2 diagnoses, and 8737 (12.6%) patients received 3 or more. The average number of diagnoses per patient was 0.7.

Prevalence and Duration of Cardiovascular or Renal Disease

Within 10 years of T2D diagnosis, IHD (0.6%–8.0% of all patients) and HF (0.4%–4.5% of all patients) were the most common combination. Stroke, CKD, and PAD were present among 0.1% to 3.1% of all patients within 10 years of T2D diagnosis (Table III in the Data Supplement). At all landmark years, IHD was the most frequent disease, while HF was the least frequent (Table III in the Data Supplement). The age and comorbidity distribution among these groups were similar except for stroke patients, who were more likely

Table. Patient Characteristics of Patients With T2D Free of Diagnoses at Inclusion

	T2D Population
N	153 405
Age, median (IQR)	64.0 (55–72)
Sex (male), n (%)	82 204 (53.6)
Comorbidities at inclusion, n (%)	
Atrial fibrillation	4972 (3.2)
Cancer	5909 (3.9)
COPD	3748 (2.4)
Hypertension	16 662 (10.9)
Medication at inclusion, n (%)	
Statins	52 787 (34.4)
ACE inhibitor/ARBs	64 031 (41.7)
β-blockers	32 921 (21.5)
ASA	36 381 (23.7)
Loop diuretics	20 548 (13.4)
MRA	5621 (3.7)
Thiazide	31 033 (20.2)
Calcium channel blockers	34 234 (22.3)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ASA, acetylsalicylic acid; COPD, chronic obstructive pulmonary disorder; IQR, interquartile range; MRA, mineralocorticoid receptor antagonists; and T2D, type 2 diabetes mellitus.

to have concomitant atrial fibrillation (Figures II and III in the Data Supplement). The median duration of cardiovascular or renal disease in the landmark cohorts was similar among groups at early landmarks and increased at later landmarks, especially among patients with IHD (Table V in the Data Supplement). In patients having 2 diagnoses, the most frequent combination at all landmark years was IHD and HF. Other combinations did not reach above 2 percent of the landmark population each year (Table IV in the Data Supplement). Patients with HF in combination with stroke, CKD, or PAD had similar age distribution and were more likely to suffer from cancer, atrial fibrillation, and chronic obstructive pulmonary disease compared with patients with IHD in combination with stroke, CKD, or PAD (Figures IV and V in the Data Supplement). The median duration of the diagnoses before the landmark year was similar between groups (Table V in the Data Supplement).

Prognosis After Developing 1 Cardiovascular or Renal Disease

The highest 5-year risk of death among patients alive 5 years after T2D diagnosis was found among those who had developed HF (47.6% [95% CI, 44.8–50.3]). By comparison, the risk was <35% for patients who developed IHD, stroke, CKD, and PAD (Figure 2 and Table VI in the Data Supplement). The 5-year RR of death of patients who developed HF within the 5 years following onset of T2D was 3 times higher (CI, 2.9–3.1) than that of patients without cardiovascular and renal disease. Corresponding RR estimates were lower for patients who developed IHD (RR, 1.3 [95% CI, 1.3–1.4]), stroke (RR, 2.2 [95% CI, 2.1–2.2]), CKD (RR, 1.7 [95% CI, 1.7–1.8]), and PAD (RR, 2.3 [95% CI, 2.3–2.4]; Figure 2 and Table VII in the Data Supplement). Patients who developed HF within the 5 years after diagnosis of T2D lived on average 11.7 months less than patients free of cardiovascular and renal disease (95% CI, 11.6–11.8). By comparison, we estimated smaller decreases in lifespan for other diagnoses: IHD (1.6 months [95% CI, 1.5–1.7]), stroke (6.4 months [95% CI, 6.3–6.5]), CKD (4.4 months [95% CI, 4.3–4.6]), and PAD (6.9 months [95% CI, 6.8–7.0]; Figure 2 and Table VIII in the Data Supplement).

Prognosis After Developing a Combination of 2 Cardiovascular or Renal Diseases

The highest risks of death 5 years after T2D diagnosis were found in the patients who had HF in combination with stroke (54.1% [95% CI, 44.7–63.5]) or CKD (63.7% [95% CI, 53.7–73.7]) while the risk was somewhat lower in patients with HF in combination with PAD (48.4% [95% CI, 36.4–60.5]) and IHD (45.5% [95 CI, 42.3–48.7]; Figure 3 and Table VI in the Data Supplement). Patients who developed a combination of IHD and stroke, CKD, or PAD 5 years after T2D diagnosis had a 5-year risk of death below 40%. The 5-year RR of death, with patients with T2D free of cardiovascular or renal disease as reference, was highest among patients with HF in combination with stroke (3.4 [95% CI, 3.3–3.5]), CKD (4.0 [95% CI, 3.9–4.1]), or PAD (3.1 [95% CI, 3.0–3.1]) while other combinations did not exceed a RR estimate above 3.0 (Figure 3 and Table VII in the Data Supplement). The number of months lost in a 5-year span for patients with T2D developing HF in combination with stroke, CKD, PAD, or IHD was 16.2 (95% CI, 16.1–16.4), 18.2 (95% CI, 18.1–18.3), 14.3 (95% CI, 14.2–14.4), and 11 (95% CI, 10.9–11.2) months, respectively. Corresponding estimates among patients developing IHD in combination with stroke, CKD, or PAD was 8 to 9 months (Figure 3 and Table VIII in the Data Supplement).

Prognosis According to Early Versus Late Inclusion Period

A total of 92 837 patients were included between 1998 and 2008 and 60 568 patients were included between 2009 and 2015. Most patients were males in both cohorts (54.1% compared with 52.8%). Patients included in 2009 to 2015 were more likely to be in active treat-

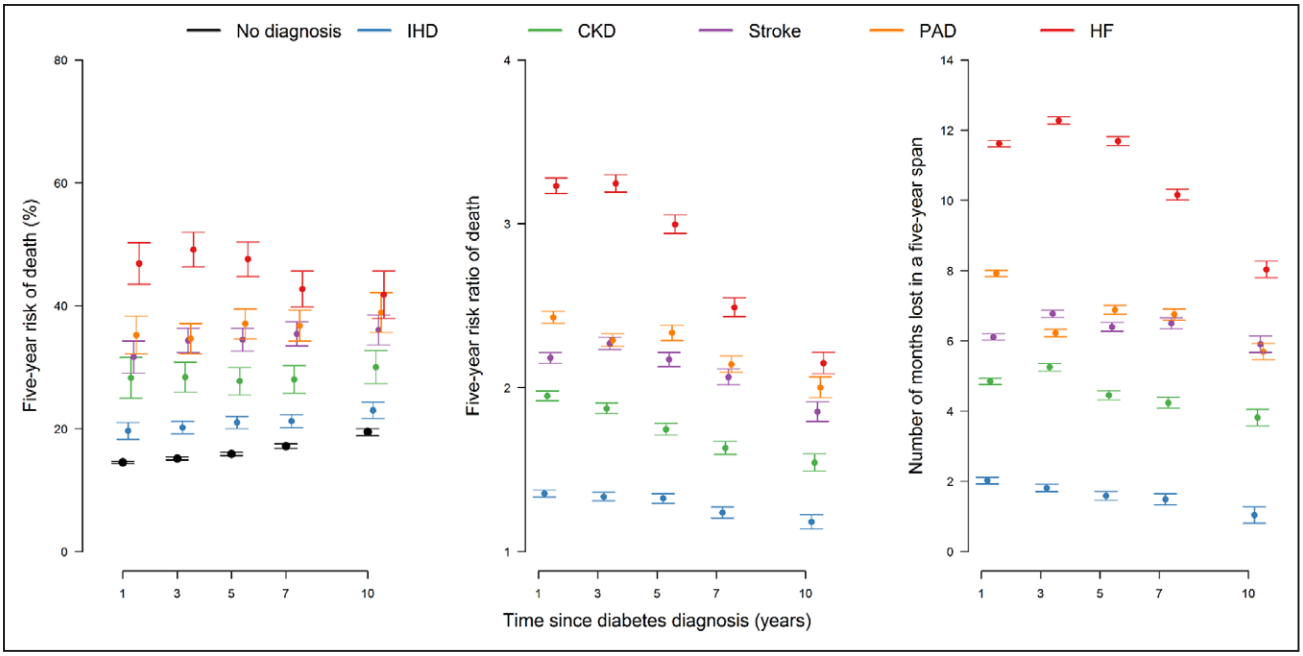

Figure 2. The 5-y risk of death, the 5-y risk ratio of death when compared with patients with type 2 diabetes mellitus (T2D) free of cardiovascular or renal disease, and the expected decrease in lifespan in relation to development of 1 cardiovascular or renal diagnosis.
Vertical bars represent 95% CIs. CKD indicates chronic kidney disease; HF, heart failure; IHD, ischemic heart disease; and PAD, peripheral artery disease.

ment with statins (50.3% versus 24.1%), ACE inhibitors/ARBs (52.8% versus 34.5%), β-blockers (25.4% versus 18.9%), acetylsalicylic acid (25.5% versus 22.6%), and Ca channel blockers (27.7% versus 18.8%; Table IX in the Data Supplement). When examining the 1-year risk of death following a cardiovascular or renal diagnosis in the 2 time periods, the findings were similar to the main analysis. HF alone or in combination with other cardiovascular or renal disease conferred the highest 1-year risk of death (Tables X and XI in the Data Supplement).

Subgroup Analysis

To ensure comparability in the duration of cardiovascular or renal disease up to each landmark year, we per-

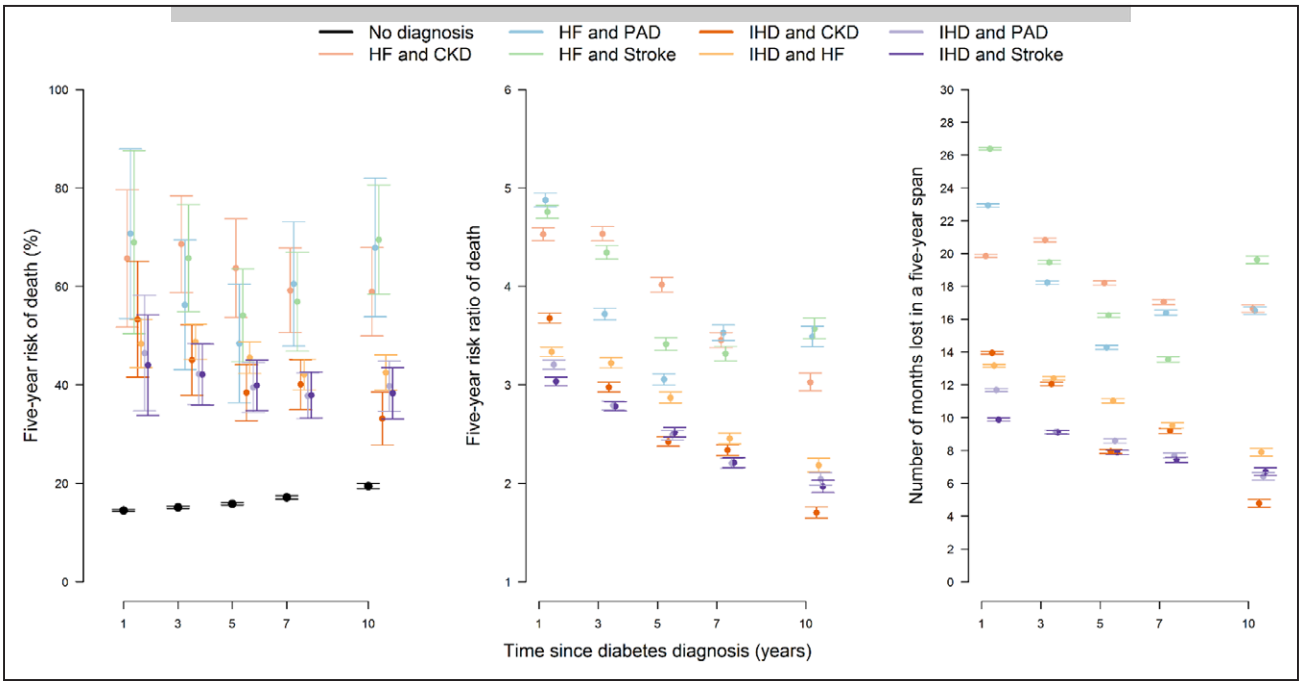

Figure 3. The 5-y risk of death, the 5-y risk ratio of death when compared with patients with type 2 diabetes mellitus (T2D) free of cardiovascular or renal disease, and the expected decrease in lifespan in relation to development of 2 cardiovascular or renal diagnoses.
Vertical bars represent 95% CI. CKD indicates chronic kidney disease; HF, heart failure; IHD, ischemic heart disease; and PAD, peripheral artery disease.

formed an additional analysis, where we only included patients, who received a diagnosis 1 year before the landmark year. The risk of death associated with the receiving of 1 or 2 diagnoses did not differ from our main results (Figures VI and VII in the Data Supplement).

We stratified patients at each landmark year according to gender, age (above and below 65 years), and presence of comorbidities. HF alone or in combination with CKD, stroke, or PAD was associated with the highest absolute 5-year risk of death in all subgroups (Figure 4A and 4B).

DISCUSSION

In a nationwide real-life cohort of >150 000 patients with newly diagnosed T2D, we found that HF development alone or in combination with stroke, CKD, or PAD conferred the highest 5-year risk of death. This translated into an average reduction of 12 to 25 months lived within the next 5 years and a 3- to 5-fold increased 5-year risk of death compared with patients with T2D free of cardiovascular disease. While IHD was the most prevalent disease in the landmark population, risk of death associated with IHD development alone or in combination with stroke, CKD, or PAD was lower than any disease combination that included HF or HF alone. This association was present, when we stratified the cohort according to age, gender, comorbidities at inclusion, and year of inclusion.

Excess risk of death in individuals with T2D has been well documented and has been attributed to an increased risk of cardiovascular disease.[21] Indeed, life expectancy in patients with T2D has been estimated as 5 to 12 years lower than the general population.[22] Additionally, several studies report that patients with T2D have a poorer prognosis following cardiovascular and renal complications than the general population. Most studies focus on a single complication only, hence, information on the impact of more than one diabetic complication or the relative magnitude of each complication is lacking.[8,9,23–25]

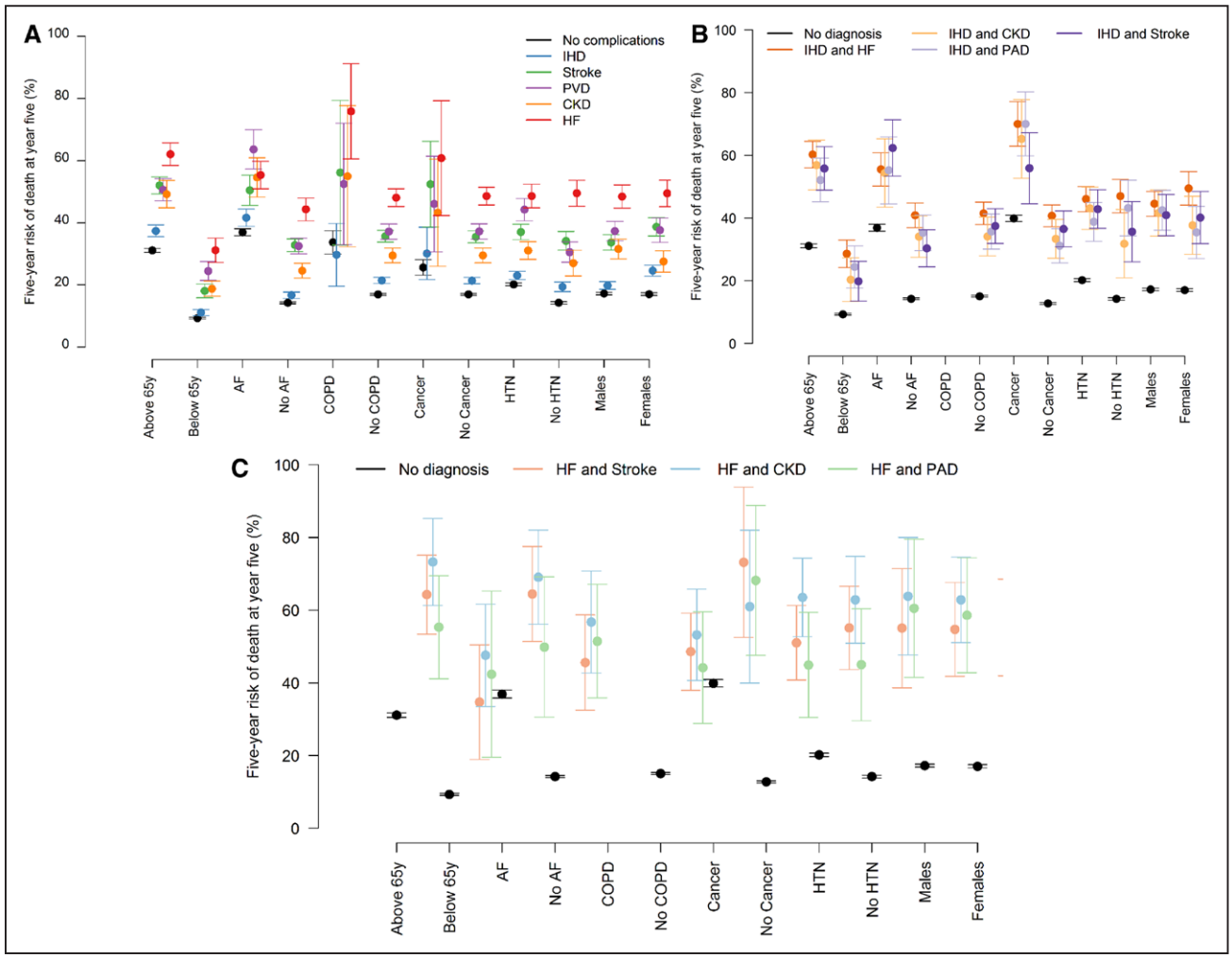

Figure 4. The 5-y risk associated with development of a cardiovascular or renal diagnosis 5 y after type 2 diabetes mellitus (T2D) diagnosis according to sex and comorbidities at inclusion in different subgroups of T2D and cardiovascular or renal diagnoses.
(**A**) in patients developing one diagnosis, (**B**) in patients developing IHD in combination with other diagnoses and (**C**) in patients developing HF in combinations with other diagnoses. Vertical bars represent 95% CI. AF indicates atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HF, heart failure; HTN, hypertension; IHD, ischemic heart disease; and PAD, peripheral vascular disease.

We included HF and assessed the risk of all-cause death according to time since T2D diagnosis, a novel way of addressing prognosis in an incident T2D population and the registries ensures lifelong follow-up of real-world patients. We defined T2D as the first-time redeemed prescription of a noninsulin antidiabetic drug. We wanted to select a homogenous low-risk population primarily diagnosed in the primary sector. Our findings were consistent with Swedish data, showing the hazard ratio estimates of death in patients with T2D, when compared with patients with myocardial infarction, was highest among patients developing HF, followed by CKD, stroke, and amputation.[26] In another study, the risk of death within 1 month after a T2D complication was highest among patients with myocardial infarction, followed by stroke, CKD, HF, and amputation.[27] We included unstable and stable angina pectoris in the definition of IHD, arguably ending with a broader low-risk population not comparable with acute myocardial infarction. A similar argument extends to patients with CKD in contrast to using patients with end-stage renal disease or renal replacement therapy. Additionally, we did not find major differences in 5-year risks of death among patients with HF and IHD (45.5%, at landmark year 5) and HF alone (47.6%, at landmark year 5). This is in contrast to existing literature, where ischemic HF is associated with a higher risk of death compared with nonischemic HF among patients with T2D.[28–30] However, the findings of the present study must be interpreted with caution since we did not have access to echocardiographic measurements and cannot be fully certain of the HF etiology. To ensure comparability across groups, we performed an additional analysis only including patients diagnosed in the year before the landmark. With similar duration of cardiovascular or renal disease, the results did not differ from our primary analysis.

Across the landmark years, we observed continuously smaller differences in 5-year risks of death for all complications, especially for HF (Figure 3). There are several potential explanations: First, increasing age of the study population during follow-up together with only inclusion of patients alive at each landmark will result in a healthy survivor effect in the later landmark years. Second, patients diagnosed at early landmark years cannot reflect true exposure of T2D and other cardiovascular risk factors due to undiagnosed diabetes mellitus for a longer period. Third, differences in duration of complications could result in different prognoses for each complication. However, we did not find major variation in median duration of complications at each landmark (Table V in the Data Supplement).

Inconsistencies of improved or worsened cardiovascular risk profile with different antidiabetic drugs from clinical trials and observational studies have been debated.[31] Contemporary trials with an intervention with SGLT-2 inhibitors or glucagon-like peptide-1 receptor agonists have shown promising results in patients with T2D.[1,15] Treatment effects of different antidiabetic drugs are not covered in the present study as focus was on comparison of different diagnoses. Future studies could potentially separate different antidiabetic drugs effect on certain patient's risk profile for a more personalized approach in diabetes mellitus management.

Limitations

Several limitations of the present study should be acknowledged. First, lack of information on clinical factors reflecting HF and T2D severity including clinical assessment of functional class and smoking status, vital parameters, for example, heart rate and blood pressure, biochemical parameters such as N-terminal prob-type natriuretic peptide, glucose levels, and hemoglobin A1c. Second, we did not have any information on the presence of other microvascular complications, which serve as to highlight the progression and severity of diabetes mellitus illness in patients.

Clinical Implications

Although not the most frequent complication, HF was clearly associated with the most unfavorable prognosis in patients with T2D. When providing care for patients with T2D, we hope that our findings contribute to assessing risk profiles and prognosis, especially concerning the importance of evaluating patients with T2D regularly for HF.

Conclusions

In this nationwide cohort of newly diagnosed patients with T2D, we found that HF development alone or in combination with stroke, CKD, or PAD imposed the highest absolute and relative risk of death along with the greatest decrease in lifespan compared with other combinations of cardiovascular and renal disease.

ARTICLE INFORMATION

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Disclosures

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