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ORIGINAL RESEARCH

Lifetime Risk of Heart Failure and Trends in Incidence Rates Among Individuals With Type 2 Diabetes Between 1995 and 2018

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BACKGROUND: There are limited data on the lifetime risk of heart failure (HF) in people with type 2 diabetes and how incidence has changed over time. We estimated the cumulative incidence and incidence rates of HF among Danish adults with type 2 diabetes between 1995 and 2018 using nationwide data.

METHODS AND RESULTS: In total, 398 422 patients (49% women) with type 2 diabetes were identified. During follow-up, 36 400 (9%) were diagnosed with HF and 121 459 (30%) were censored due to death. Using the Aalen-Johansen estimators, accounting for the risk of death, the estimated residual lifetime risk of HF at age 50 years was calculated as 24% (95% CI 22%–27%) in women and 27% (25%–28%) in men. During the observational period, the proportion of patients treated with statins, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and metformin increased from <30% to >60%. Similarly, the annual incidence rates of HF decreased significantly, with declines being greater in older versus younger individuals (5% versus 2% in age >50 versus ≤50 years, respectively; $P<0.0001$) and in women versus men (5% versus 4%, $P=0.02$), but similar in patients with and without IHD (4% versus 4%, $P=0.53$).

CONCLUSIONS: The current lifetime risk of HF in type 2 diabetes approximates 1 in 4 for men and women. Paralleled by an increase in use of evidence-based pharmacotherapy over the past decades, the risk of developing HF has declined across several subgroups and regardless of underlying IHD, suggesting that optimal diabetes treatment can mitigate HF risk.

Key Words: cumulative risk ■ heart failure ■ incidence rate ■ temporal trends ■ type 2 diabetes

Type 2 diabetes (T2D) is one of the strongest risk factors for the development of heart failure (HF), with an ≈2-fold increase in risk compared to people without T2D.[1] T2D is also one of the most prominent risk factors for mortality among HF patients, regardless of the underlying HF etiology.[2–4] However, despite the well-recognized increased risks and poor prognosis, little is known about absolute risks, including lifetime risk estimates of HF in patients with T2D, which could inform preventative strategies.

Evidence that T2D is an important risk factor for HF began to emerge more than four decades ago with the Framingham Heart Study, which demonstrated that the incidence of HF was significantly higher among persons with pre-existing T2D compared to individuals without diabetes, even after controlling for possible mediators such as coronary artery disease and shared risk factors including excessive weight, high age, and increased blood pressure.[5] Over the past couple of decades, pharmacological and non-pharmacological

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CLINICAL PERSPECTIVE

What Is New?

- Patients with type 2 diabetes have a high risk of heart failure, but few studies estimating the lifetime risks and how incidence have changed over time are available.
- At age 50 years, the current residual lifetime risk ≈1 in 4 for men and women.
- Over the past decades, treatment with renin-angiotensin-system inhibitors, statins, and metformin has increased substantially, paralleled by a ≈50% decrease in incidence rates of heart failure.

What Are the Clinical Implications?

- Use of modern guideline directed pharmacotherapy and changed population characteristics is likely to translate into reductions in lifetime risk in the near future.

Nonstandard Abbreviations and Acronyms

IHD	ischemic heart disease
T2D	type 2 diabetes

treatment of T2D and its complications (including ischemic heart disease [IHD]) has evolved. In 1998, the first UKPDS (United Kingdom Prospective Diabetes Study) was published and showed reduced mortality with metformin in overweight patients with T2D, a reduction of diabetes-related endpoints with strict blood pressure control, and a beneficial effect of a strict glycemic control on microvascular complications.[6–8] In 2004 Danish guidelines were changed, recommending tight blood pressure control in all patients with T2D (<130/80 mm Hg in the absence of cardiovascular disease, <125/80 mm Hg in patients with albuminuria), an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker to all individuals with T2D unless contraindicated, and metformin in overweight patients.[9] In 2012, HbA1c was introduced for the diagnosis of T2D and subsequently replaced the 2 hour oral glycemic tolerance test and fasting blood glucose levels. So far, sparse data are available to understand on how all these changes have affected the incidence of HF.[10,11] Hence, addressing the temporal trends in the development of HF among patients with T2D is a research priority.[12] In this investigation, we estimated the lifetime risk of HF in people with T2D and temporal trends in incidence between 1995 and 2018 in Denmark both overall and according to age, sex, use of insulin, and prevalent IHD.

METHODS

Due to the secure nature of the Danish Patient Registries, the data used in this manuscript can only be granted access to through collaboration via a Danish authorized institution. Per Danish law, registry-based studies using de-identified data are exempted from institutional review board approval. All Danish residents are assigned a social security number at birth or upon immigration. This number is registered at every health care contact and permits linkage of diagnoses across institutions and time. Health care is made equally accessible to all people using tax revenue and is not paid into through copayments. During hospital and clinic visits, any diagnoses of relevance (main diagnosis and contributing diagnoses) are recorded in the Danish Patient Registry (starting in 1978) which also forms the basis for economic reimbursement to the individual departments and clinics. The validity of most diagnoses, including T2D and HF, are high in this registry.[13–16] Since 1995, data on all claimed prescriptions are available in the Danish Prescription Registry, which is complete and includes date of redemption and type of medication.[17]

We identified all adult individuals (aged >18 years) with T2D, defined as a diagnosis of diabetes (*International Classification of Disease* [*ICD*] E11, E14, excluding type 1 diabetes [*ICD* E10]), or a claimed prescription of at least one hypoglycemic agent between 1995 and 2018. Patients who were under the age of 30 years when claiming the first prescription of insulin, without any other oral agents, were assumed to have type 1 diabetes or gestational diabetes, in accordance with prior work.[18] Full diagnostic codes for comorbidity and pharmacotherapy are available in the Table S1. We identified HF (*ICD-8* codes 427.09-427.11, 427.19, 424.49 and *ICD-10* codes I42, I43, and I50) and calculated incidence rates and cumulative risk of HF over the follow up period, censoring at December 31, 2018, at time of emigration, or death. We stratified data based on age (>50 versus ≤50 years), sex, use of insulin, and underlying IHD (*ICD-10* I20, I21, I22, I23, I24, I25) to compare trends in incidence rates over time. Lifetime risk was defined as the proportion of patients in this cohort that developed heart failure according to accrued age, censored at time of emigration, end of follow up, or death, accounting for competing risk (see Statistical Analysis below). Age was used as the underlying time-scale for these models and separate models were run for different ages. For instance, the residual risk of heart failure at age 50 was calculated using an observation start = max(50th birthday, first calendar year of interest [for main models this was 1995], diabetes date) and observation end = min(last calendar year of interest [2018], heart failure date, death date, emigration date).

In addition, we compared temporal trends of cumulative ten-year risk of HF among patients free from HF at age 50, 60, and 70 years over the time-periods of 1995, 2000, and 2005 to analyze how risk has changed over time. Individuals were removed between time cohorts if they developed HF prior to start of the next calendar period or were otherwise carried over if they were HF free at the start of the next timeframe. In sensitivity models, we analyzed a combined endpoint comprising mortality and HF, cardiovascular mortality and HF, as well as mortality and cardiovascular mortality separately, to ensure that competing risks were not influencing our main analyses.

Statistical Analysis

Population characteristics are presented as means with standard deviation and percentage of the total study population for five study periods between 1995 and 2018 (for Table). People contributed with risk time to the various periods as long as they had prevalent T2D were alive, and were free from HF. Use of medication (within the selected time-period), age, and prevalent comorbidity were updated for each calendar period between the first diagnosis of T2D and the first calendar period of interest and the last of heart failure, death, or end of that specific calendar period. Incidence rates (per 100 person-years) of HF were calculated by calendar year. Trends in incident heart failure were calculated as incidence rate ratios (with corresponding 95% CIs) for years 1995 to 2018, using Poisson regression models (counting only the first HF event, according to the principle outlined elsewhere),[19] with the year 1995 used as the referent year, Figure 2. All patients were followed from the date of T2D (or Jan 1, 1995, if the first T2D diagnosis was made earlier than Jan 1, 1995) until first HF date, emigration, death, or Dec 31, 2018, whichever came first. Models were adjusted for age and sex, presence of IHD, and insulin use and the multivariable models included all variables in the baseline table, Table. Data were also stratified by sex, insulin use, age (>50 versus ≤50 years), and IHD and we tested for statistical interactions in incidence rates between calendar year and these 4 characteristics by inclusion of an interaction term (eg, calendar year × sex) in the overall models.

We estimated the cumulative (lifetime) incidence of HF using the Aalen-Johansen estimator (to account for competing risk of death) and stratified by sex among individuals with T2D free from HF at ages 30, 40, 50, 60, and 70 years, respectively. The Aalen-Johansen

Table. Population Characteristics

	Period 1	Period 2	Period 3	Period 4	Period 5
	(1995–1999)	(2000–2004)	(2005–2009)	(2010–2014)	(2015–2018)
Sex (men)	59 215 (51.7%)	79 721 (52.0%)	106 629 (51.1%)	138 619 (51.2%)	152 243 (51.0%)
Age, y (st.d.)	65.5 (16.2)	65.2 (15.5)	64.6 (15.6)	65.1 (15.4)	65.3 (15.5)
Ischemic heart disease	23 459 (20.5%)	32 263 (21.1%)	41 653 (20.0%)	53 013 (19.6%)	54 474 (18.3%)
Atrial fibrillation	6316 (5.5%)	7964 (5.2%)	13 169 (6.3%)	21 940 (8.1%)	30 505 (10.2%)
Hypertension	22 111 (19.3%)	36 847 (24.1%)	70 489 (33.8%)	111 678 (41.2%)	138 491 (46.4%)
Medical therapy					
Insulin	40 519 (35.4%)	53 799 (35.1%)	67 429 (32.3%)	78 588 (29.0%)	84 066 (28.2%)
Thiazide diuretics	4302 (3.8%)	18 771 (12.3%)	46 945 (22.5%)	71 051 (26.2%)	72 274 (24.2%)
ACE Inhibitor	31 384 (27.4%)	60 168 (39.3%)	100 725 (48.3%)	124 303 (45.9%)	111 855 (37.5%)
Angiotensin II receptor blocker	7009 (6.12%)	28 306 (18.5%)	55 916 (26.8%)	83 437 (30.8%)	99 110 (33.2%)
Beta blocker	19 452 (17.0%)	40 952 (26.7%)	62 737 (30.1%)	84 423 (31.2%)	88 953 (29.8%)
Clopidogrel	148 (0.13%)	4932 (3.22%)	11 160 (5.35%)	23 143 (8.54%)	32 968 (11.1%)
Aspirin	34 342 (30.0%)	66 101 (43.1%)	99 904 (47.9%)	115 807 (42.7%)	102 642 (34.4%)
Statin	7554 (6.60%)	53 205 (34.7%)	127 025 (60.9%)	185 301 (68.4%)	201 916 (67.7%)
Metformin	25 810 (22.6%)	61 980 (40.5%)	125 514 (60.2%)	197 600 (72.9%)	216 757 (72.7%)
Sulfonylurea	64 133 (56.0%)	78 515 (51.3%)	81 174 (38.9%)	65 041 (24.0%)	42 073 (14.1%)
Thiazolidinedione	…	1618 (1.06%)	2633 (1.26%)	1199 (0.44%)	253 (0.08%)
GLP-1 Agonist	…	…	2817 (1.35%)	23 731 (8.76%)	35 381 (11.9%)
DPP4 inhibitor	…	…	7802 (3.74%)	24 865 (9.18%)	35 657 (12.0%)
SGLT 2 inhibitor	…	…	…	4057 (1.50%)	30 794 (10.3%)

ACE indicates angiotensin converting enzyme; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon like peptide-1; and SLGT-2, sodium-glucose transport protein 2 inhibitors.

estimator generalizes the Kaplan Meier curve to account for multiple competing risks.[20,21] Finally, we compared ten-year incidences between calendar periods (1995, 2000, and 2005) and tested for statistically significant differences between strata using Gray's test. All analyses were performed using SAS version 9.4 (SAS institute, Cary, NC, USA). A 2-sided *P*-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 398 422 patients (49% women) had a diagnosis of T2D between Jan 1, 1995 and Dec 31, 2018 and were free from HF at this point. There were slightly more men than women throughout the observational period. The proportion of patients diagnosed with IHD remained stable throughout the observational period. The prevalence of atrial fibrillation, hypertension, and insulin use all increased over the study time frame from 1995 to 2018. Use of ACE inhibitor, angiotensin II receptor blockers, beta blockers, clopidogrel, and metformin also increased over time. SGLT2 inhibitor use was recorded starting in 2013 and increased from 2010 to 2018, and GLP-1 agonist use started in 2005 and likewise increased in use. Sulfonylurea and thiazolidinedione use decreased over the study time period; Table. The relative increase in use of medications (ACE inhibitor, angiotensin II receptor blockers, beta blockers, and statins) was similar across age groups and in those with and without ischemic heart disease, while the absolute increases were greater in older patients and those with ischemic heart disease, Tables S2 and S3.

Lifetime (Cumulative) Risk Estimates

During follow-up, 36 400 (9%) were diagnosed with HF and 121 459 (30%) were censored for death. The estimated residual lifetime risk of developing HF among people with diabetes at age 50 years was 24% (95% CI 22%–27%) in women and 27% (25%–28%) in men. The cumulative risk of HF for people with T2D who were free from HF at age 30, 40, 50, 60, and 70 years are presented in Figure 1A. As shown in Figure 1B, the risk appeared to decrease over time. Among individuals aged 50 years, the ten-year risk of HF decreased from 11.0% (1995–2005) to 8.7% (2005–2015), *P*<0.0001. 10-year risks also decreased for those free from HF at age 60 years, 18.0% in 1995 to 2005 to 12.2% in 2005 to 2015, *P*<0.0001, and from 21.3% to 16.2% between 1995 and 2005 and 2005 to 2015, *P*<0.0001, for people aged 70 years.

Incidence Rates of HF

As shown in Figure 2 upper panel, a significant decrease in incidence rates of HF was seen between 1995 and 2018. Adjusted for age, sex, insulin use, and IHD, similar patterns were observed for incidence rate ratios, Figure 2 lower panel. Modeled per calendar year increase since 1995, this corresponded to an adjusted annual 4% decrease (incidence rate ratio 0.96 [0.95–0.96]).

Rates were higher in men than women and in patients with use of insulin and in the presence of IHD, but declined across all groups, Figure 3. The annual decrease (adjusted for sex, age, insulin, and IHD) was 5% (incidence rate ratio per year 0.95 [0.95–0.96]) in individuals aged >50 years versus 2%

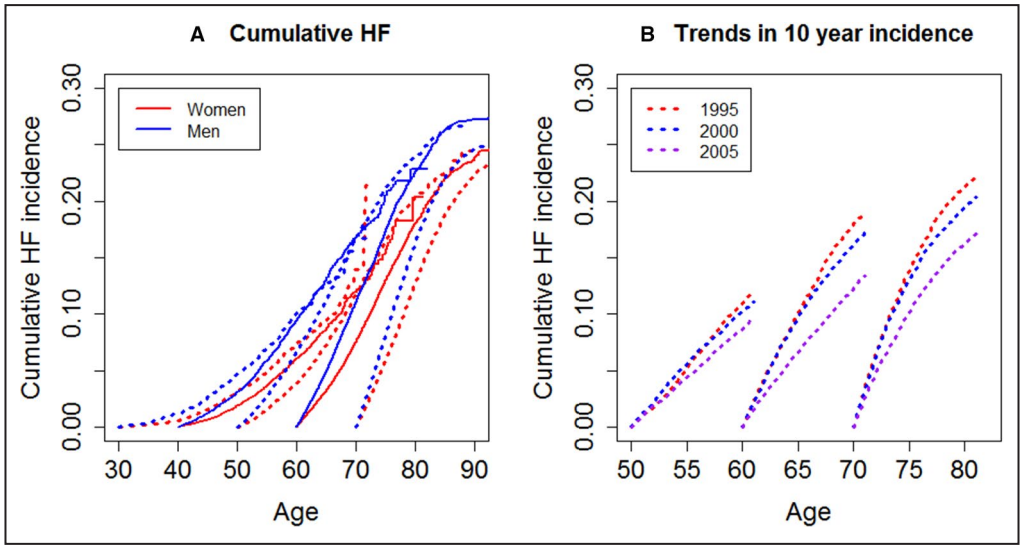

Figure 1. Cumulative incidence of heart failure (Y axis) over the adult life course at different ages (X axis) (A) and development over 10-year risks by calendar time (B).
P for differences between men and women (**A**) and across calendar periods and (**B**) all <0.0001.

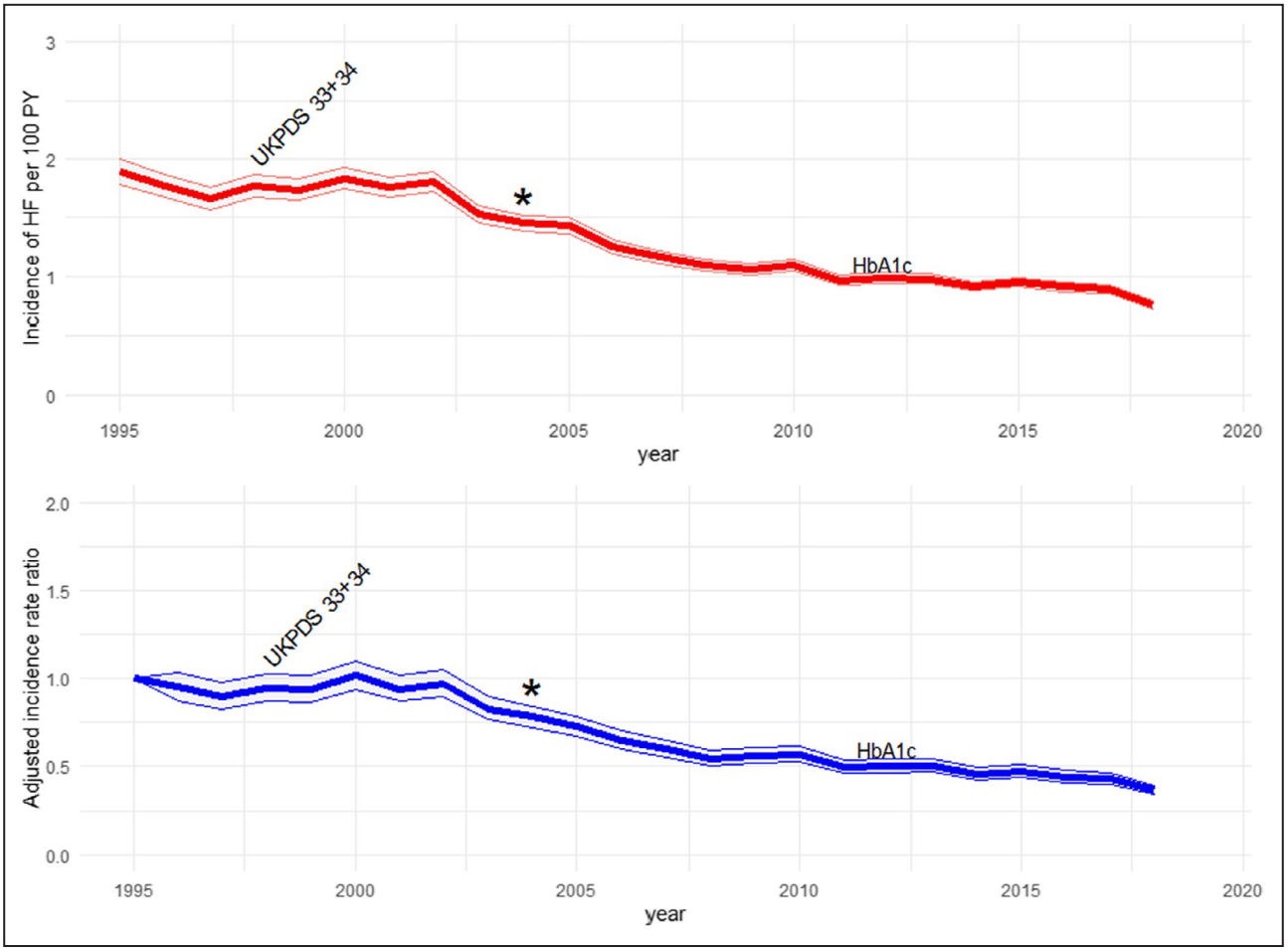

Figure 2. Incidence rates (upper, red panel) and incidence rate ratios adjusted for sex, age, ischemic heart disease, and insulin use (lower, blue panel) by calendar period.
*Indicates that new guidelines for the management of type 2 diabetes were implemented (2004). See text for further explanations. HbA1c indicates that this biomarker was introduced for the diagnosis of type 2 diabetes (2012). Shaded areas represent 95% CI. HF indicates heart failure; PY, person years; UKPDS, United Kingdom Prospective Diabetes study.

(0.98 [0.97–0.99]) in persons ≤50 years, $P<0.0001$; 4% (0.96 [0.96–0.96]) among men versus 5% (0.95 [0.95–0.96]) in women, $P=0.02$; 4% (0.96 [0.95–0.96]) in individuals without IHD versus 4% in persons with IHD (0.96 [0.95–0.96]), $P=0.53$; and 3% (0.97 [0.97–0.97]) in people on insulin versus 5% (0.95 [0.95–0.95]) among people without use of insulin, $P<0.0001$. The declining trends persisted upon further adjustment, Tables S4 through S8. Multivariable adjusted incidence rate ratio was 0.29 (95% CI 0.27–0.32, $P<0.0001$) for 2018 versus 1995 for the overall cohort. Similar declines were observed in HF mortality, CV mortality, and overall mortality after sensitivity analysis, Figure S1.

DISCUSSION

Our study examined the cumulative incidence of HF in individuals with T2D over the follow-up period and temporal trends in HF risks over the past decades. Our data demonstrated that at age 50 years, the cumulative incidence of HF was 27% for men versus 24% for women. Meanwhile HF incidence rates decreased significantly between 1995 and 2018 across all age groups, though at a faster rate for older individuals. Similar declines were seen in both sexes and among patients with and without IHD.

Lifetime (Cumulative) Risks

Despite the increasing prevalence of T2D and the well-known elevated risk of HF associated with T2D, data on absolute (lifetime) risks of HF among patients with T2D are sparse. He et al used the first National Health and Nutrition Examination Survey (NHANES) data set to examine epidemiological trends and risk factors for HF in T2D and showed a cumulative incidence of HF 65% in men and 62% in women at age 85 in people followed from age ≈50 years.[22] This is significantly higher than

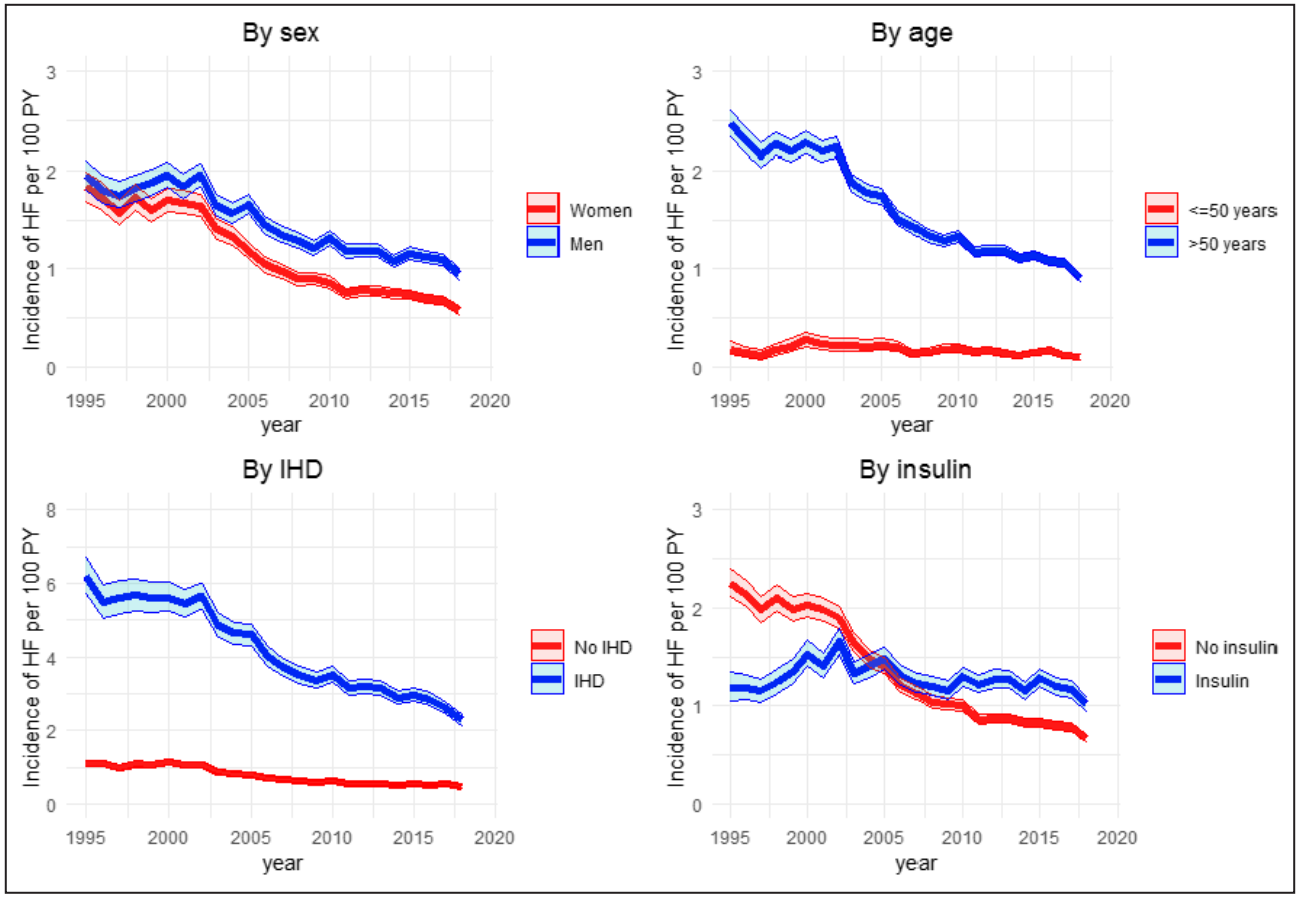

Figure 3. Incidence rates by subgroups (age, sex, insulin, and IHD).
Shaded areas represent 95% CI. HF indicates heart failure; and IHD, ischemic heart disease.

our estimates of residual lifetime risk of 27% and 24% in men and women, respectively. The differences may in part be due to changes in diagnostics and severity of diabetes, but also different methodology. While we accounted for the competing risk of death using the Aalen-Johansen estimators, He et al used the Kaplan-Meier method, which does not adjust for competing risk and, therefore, tends to overestimate cumulative incidence in the presence of a high baseline mortality risk; we did observe in our population that more people were censored for death than developed HF. Improvement in therapeutic management of T2D over time is also likely to have impacted the lifetime risk estimates; He et al followed patients throughout the 1970s and 1980s compared to 1995 to 2018 for our cohort.

Temporal Trends in HF risks

We have previously reported that the incidence rates of HF declined by 31% between 1996 and 2012 in the general Danish population aged >50 years (age and sex-adjusted incidence rate ratio 0.69 [0.67–0.71]).[23] In the comparable segment of people with T2D we herein reported a 56% reduction between 1995 and 2012 (age and sex-adjusted incidence rate ratio 0.44 [0.41–0.47]). For individuals aged ≤50 years of age in the same period, the incidence rates increased by 50% in the entire Danish population, while in the segment of patients with T2D, we reassuringly found that the rates had declined by 2% per year.[23] Thus, people with T2D appear to have experienced greater rates of declines in HF than non-diabetic individuals in the community. It was hypothesized by Christiansen et al that the rising incidence of HF among younger individuals in Denmark may be due to a higher prevalence of comorbidities and adverse risk factors (especially obesity) over time.[23] The impact of rising BMI on increasing HF incidence is likely to be blunted among a cohort of T2D because obesity is highly prevalent among the diabetic population.[24,25]

Improved pharmacological management of T2D has likely had a distinct impact on the population of patients with T2D, although several randomized clinical trials have been unable to demonstrate a clear direct effect of tight glycemic control on macrovascular events, including HF.[6,7,26–28] Over time, it has become evident that the cardiovascular safety profile and mechanisms of action of anti-diabetic drugs may be

more important than their glucose lowering effects. For example, sulfonylurea and thiazolidinedione use have been associated with increased risk of HF events compared to use of either metformin or newer hypoglycemic agents.[12,29–31] As in other populations, the proportion of individuals using these agents declined over time in our cohort, which correlated with and may have contributed to our observed reduction in HF incidence.[32] Finally, the increasing use of SGLT-2 inhibitors (since about 2013 in our sample) and their associated reductions in mortality and HF hospitalizations correlates with and may have contributed to the very recent decreases in HF rates.[33]

Another possible explanation for the rapidly declining HF rates over time in patients with T2D is that the evolving therapeutic preventive strategies (eg, statin use, better blood pressure control) and management of IHD may have contributed to reductions in HF incidence in our investigation. In this context, Ford et al sought to examine the decrease in US deaths from coronary disease from 1980 to 2000 using a statistical model to examine changes in risk factor prevalence and compared the expected mortality reduction to the observed mortality reduction. That study suggested that about half of US deaths from coronary artery disease in this timeframe could be explained by reductions in major risk factor while the other half was likely due to improvements in medical and surgical management of coronary artery disease.[34] While HF incidence was not a primary or secondary outcome, it is possible that incident HF has fallen even after adjustment for cardiovascular risk factors and comorbidities over time.[24] Whereas our cohorts showed similar reductions of HF in both IHD- and non-IHD-stratified data, improved early detection and intervention in IHD patients may still have contributed to a reduction of incident HF among IHD patients over time.

Finally, neurohormonal modulation is a common target in patients T2D and proteinuria, and may have influenced the development of HF in our patient population.[35] For example, it is well known that the renin-angiotensin-aldosterone system is activated as a result of chronic hyperglycemia and insulin resistance. Such renin-angiotensin-aldosterone system activation is a key contributor to the pathophysiology of diabetic cardiomyopathy via its direct impact on left ventricular hypertrophy and systolic function.[12,36] Over time, more than two thirds of all patients with T2D received either an angiotensin-converting enzyme inhibitor or an angiotensin-II receptor blocker, which might directly have led to mitigated risk.

Strengths and Limitations

The strengths of our investigation include its large sample size and the leverage of comprehensive nationwide data. The multivariable adjustment and ability to stratify our data (due to large sample size) allowed us to explore multiple possible explanations for the observed trends in HF that may not have been possible in previous studies examining HF trends. Despite the many strengths, there are also some limitations that need to be acknowledged. First, the Danish registries consist of a relatively homogeneous population, being predominantly of white European ancestry, and all individuals have equal access to health care, irrespectively of insurance and socioeconomic status. Second, due to the methods for recording the diagnosis of HF, the present study is limited by an inability to distinguish between HF with reduced and preserved ejection fraction. There were also other potentially relevant comorbidities and risk factors that we were not able to adjust for in our multivariable model. These included obesity, physical inactivity, and unhealthy diet that may also impact HF incidence trends. We also did not have any way to adjust for diabetes duration. Finally, the diagnostic criteria of T2D changed during the observational period in Denmark (from use of elevated fasting or random blood glucose levels or oral glucose tolerance tests to defining diabetes based on HbA1c levels in later time periods), which may have affected the prevalence of T2D in our study and possibly also contributed to a varying diabetes phenotype over time.[37]

ARTICLE INFORMATION

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Disclosures

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Supplementary Material

Tables S1–S8
Figure S1
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REFERENCES

1. Kenny HC, Abel ED. Heart failure in type 2 diabetes Mellitus. *Circ Res*. 2019;124:121–141. doi: 10.1161/CIRCRESAHA.118.311371
2. Rosengren A, Edqvist J, Rawshani A, Sattar N, Franzén S, Adiels M, Svensson AM, Lind M, Gudbjörnsdottir S. Excess risk of hospitalisation for heart failure among people with type 2 diabetes. *Diabetologia*. 2018;61:2300–2309. doi: 10.1007/s00125-018-4700-5
3. Andersson C, Weeke P, Pecini R, Kjaergaard J, Hassager C, Køber L, Torp-Pedersen C. Long-term impact of diabetes in patients hospitalized with ischemic and non-ischemic heart failure. *Scand Cardiovasc J*. 2010;44:37–44. doi: 10.3109/14017430903312438
4. Dauriz M, Mantovani A, Bonapace S, Verlato G, Zoppini G, Bonora E, Targher G. Prognostic impact of diabetes on long-term survival outcomes in patients with heart failure: a meta-analysis. *Diabetes Care*. 2017;40:1597–1605. doi: 10.2337/dc17-0697
5. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol*. 1974;34:29–34. doi: 10.1016/0002-9149(74)90089-7
6. *Group. Lancet*. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS). 1998;352:854–865.
7. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352:837–853. doi: 10.1016/S0140-6736(98)07019-6
8. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:703–713. doi: 10.1136/bmj.317.7160.703
9. Drivsholm T, Hansen CN, Henderson D, Noriingriis C, Schultz-Larsen P. Type 2-diabetes I almen praksis: En evidensbaseret vejledning. *Dansk Selskab for Almen Medicin-2004*. 2004;6:27–34.
10. Lawson CA, Zaccardi F, McCann GP, Davies MJ, Kadam UT, Khunti K. Trends in cause-specific outcomes among individuals with type 2 diabetes and heart failure in the United Kingdom, 1998–2017. *JAMA Netw Open*. 2019;2:e1916447. doi: 10.1001/jamanetworkopen.2019.16447
11. Khera R, Kondamudi N, Zhong L, Vaduganathan M, Parker J, Das SR, Grodin JL, Halm EA, Berry JD, Pandey A. Temporal trends in heart failure incidence among medicare beneficiaries across risk factor strata, 2011 to 2016. *JAMA Netw Open*. 2020;3:e2022190. doi: 10.1001/jamanetworkopen.2020.22190
12. Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, Deswal A, Dickson VV, Kosiborod MN, Lekavich CL, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. *Circulation*. 2019;140:e294–e324. doi: 10.1161/CIR.0000000000000691
13. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449–490. doi: 10.2147/CLEP.S91125
14. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, Sorensen HT. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol*. 2019;11:563–591. doi: 10.2147/CLEP.S179083
15. Sundboll J, Adelborg K, Munch T, Froslev T, Sorensen HT, Botker HE, Schmidt M. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ Open*. 2016;6:e012832. doi: 10.1136/bmjopen-2016-012832
16. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sorensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. *BMC Med Res Methodol*. 2011;11:83. doi: 10.1186/1471-2288-11-83
17. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish national prescription registry. *Int J Epidemiol*. 2017;46:798–798f. doi: 10.1093/ije/dyw213
18. Schramm TK, Gislason GH, Køber L, Rasmussen S, Rasmussen JN, Abildstrøm SZ, Hansen ML, Folke F, Buch P, Madsen M, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. *Circulation*. 2008;117:1945–1954. doi: 10.1161/CIRCULATIONAHA.107.720847
19. Rostgaard K. Methods for stratification of person-time and events - a prerequisite for Poisson regression and SIR estimation. *Epidemiol Perspect Innov*. 2008;5:7. doi: 10.1186/1742-5573-5-7
20. Allignol A, Beyersmann J, Schmoor C. Statistical issues in the analysis of adverse events in time-to-event data. *Pharm Stat*. 2016;15:297–305. doi: 10.1002/pst.1739
21. Aalen O, Johansen S. An empirical transition matrix for nonhomogeneous Markov chains based on censored observations. *Scand J Stat*. 1978;5:141–150.
22. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med*. 2001;161:996–1002. doi: 10.1001/archinte.161.7.996
23. Christiansen MN, Kober L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, Gislason GH, Torp-Pedersen C, Andersson C. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. *Circulation*. 2017;135:1214–1223. doi: 10.1161/CIRCULATIONAHA.116.025941
24. Christiansen MN, Køber L, Weeke P, Vasan RS, Jeppesen JL, Smith JG, Gislason GH, Torp-Pedersen C, Andersson C. Age-specific trends in incidence, mortality, and comorbidities of heart failure in Denmark, 1995 to 2012. *Circulation*. 2017;135:1214–1223. doi: 10.1161/CIRCULATIONAHA.116.025941
25. Colosia AD, Palencia R, Khan S. Prevalence of hypertension and obesity in patients with type 2 diabetes mellitus in observational studies: a systematic literature review. *Diabetes Metab Syndr Obes*. 2013;6:327–338. doi: 10.2147/DMSO.S51325
26. Castagno D, Baird-Gunning J, Jhund PS, Biondi-Zoccai G, MacDonald MR, Petrie MC, Gaita F, McMurray JJ. Intensive glycemic control has no impact on the risk of heart failure in type 2 diabetic patients: evidence from a 37,229 patient meta-analysis. *Am Heart J*. 2011;162:938–948.e2. doi: 10.1016/j.ahj.2011.07.030
27. Gerstein HC, Miller ME, Byington RP, Goff DC, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358:2545–2559. doi: 10.1056/NEJMoa0802743
28. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358:2560–2572. doi: 10.1056/NEJMoa0802987
29. Wexler DJ. Sulfonylureas and cardiovascular safety: the final verdict? *JAMA*. 2019;322:1147. doi: 10.1001/jama.2019.14533
30. Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289. doi: 10.1016/S0140-6736(05)67528-9
31. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJV and Team RS. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373:2125–2135. doi: 10.1016/S0140-6736(09)60953-3
32. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. *Diabetes Care*. 2018;41:69–78. doi: 10.2337/dc17-1414
33. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
34. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935

35. (KDIGO) KDIGO KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. 2020;98.
36. Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. *Circ Res*. 2018;122:624–638. doi: 10.1161/CIRCRESAHA.117.311586
37. Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K; Register SGotND. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. *Diabetologia*. 2008;51:2187–2196. doi: 10.1007/s00125-008-1156-z
38. Olesen JB, Lip GYH, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, Selmer C, Ahlehoff O, Olsen A-m s, Gislason GH, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ*. 2011;342:d124. doi: 10.1136/bmj.d124

SUPPLEMENTAL MATERIAL

Table S1. Diagnostic codes.

Disease	**ICD 10 and 8 codes**
Type 2 Diabetes	E11, E14, 250
Heart Failure	I42, I43, I50, 427.09-427.11, 427.19, 428.49, 428.99
Atrial Fibrillation	148, 4274
Hypertension	I10-I15, 400-404, or defined as taking at least two antihypertensive agents, according to a previously validated algorithm.[38]
Ischemic Heart Disease	I20-25, 410-413
Medications	**ATC codes**
Insulin use	A10A
Thiazide diuretics	C03AA
ACE inhibitor	C09AA
Angiotensin II receptor blocker	C09CA
Beta blocker	C07
Clopidogrel	B01AC04
Aspirin	B01AC06
Statin	C10AA
Metformin	A10BA02
Sulfonylurea	A10BB
Thiazolidinedione	A10BG
GLP 1 Agonist	A10BJ
DPP4	A10BH
SGLT2 Inhibitor	A10BK

Table S2. Trends in Medical Therapy Stratified by Age Group.

	Period 1	Period 2	Period 3	Period4	Period 5
	(1995-1999)	(2000-2004)	(2005-2009)	(2010-2014)	(2015-2018)
Age ≤50 years	20,264	25,592	36,699	45,190	49,439
Use of					
ACE inhibitor	4,114 (20.3%)	6,098 (23.8%)	9,461 (25.8%)	9,708 (21.5%)	7,512 (15.2%)
Angiotensin II antagonists	763 (3.8%)	2,536 (9.9%)	4,032 (11.0%)	4,992 (11.1 %)	5,745 (11.6%)
Statins	837 (4.1%)	5682 (22.2%)	12,642 (34.5%)	15,269 (33.8%)	14,603 (29.5%)
Beta blockers	1,816 (9.0%)	3,285 (12.8%)	4,367 (11.9%)	4,657 (10.3%)	4,463 (9.0%)
Age >50-75 years	56,917	82,494	115,701	115,469	163,538
Use of					
ACE inhibitor	19,128 (33.6%)	36,997 (44.9%)	63,163 (54.6%)	76,399 (50.4%)	67,030 (41.0%)
Angiotensin II antagonists	4,653 (8.2%)	18,582 (22.5%)	35,991 (31.1%)	52,089 (34.4%)	59,716 (36.5%)
Statins	6,071 (11.7%)	38,109 (46.2%)	83,593 (72.3%)	116,861 (77.2%)	123,079 (75.7%)
Beta blockers	11,448 (20.1%)	24,294 (29.5%)	37,222 (32.2%)	48,501 (32.0%)	48,495 (25.7%)
Age >75 years					
Use of					
ACE inhibitor	8,142 (21.8%)	17,073 (37.8%)	28,101 (50.0%)	38,196 (51.4%)	37,313 (43.8%)
Angiotensin II antagonists	1,587 (4.3%)	7,188 (15.9%)	15,893 (28.3%)	26,356 (35.4%)	33,649 (39.5%)
Statins	646 (1.7%)	9,412 (20.9%)	30,790 (54.8%)	53,171 (71.5%)	64,234 (75.3%)
Beta blockers	6,188 (16.6%)	13,373 (29.6%)	21,148 (37.6%)	31,265 (42.1%)	35,995 (42.2%)

ACE inhibitor, angiotensin converting enzyme inhibitor

Table S3. Trends in Medical Therapy Stratified by Ischemic Heart Disease.

	Period 1	Period 2	Period 3	Period4	Period 5
	(1995-1999)	(2000-2004)	(2005-2009)	(2010-2014)	(2015-2018)
Ischemic heart disease	23,459	32,263	41,651	53,013	54,474
Use of					
ACE inhibitor	8,375 (35.7%)	16,704 (51.8%)	24,603 (59.1%)	29,696 (56.0%)	25,286 (46.4%)
Angiotensin II antagonists	1,476 (6.3%)	6,609 (20.5%)	13,258 (31.8%)	19,649 (37.1%)	21,762 (40.8%)
Statins	3,766 (16.1%)	16,476 (51.2%)	32,733 (78.6%)	45,968 (86.7%)	47,814 (87.8%)
Beta blockers	8,058 (34.4%)	17,724 (54.9%)	25,980 (62.4%)	34,071 (64.3%)	34,029 (62.5%)
No ischemic heart disease	91,008	43,464	76,122	94,607	86,589
Use of					
ACE inhibitor	23,009 (25.3%)	43,464 (35.9%)	76,122 (45.6%)	94,607 (43.4%)	86,569 (35.5%)
Angiotensin II antagonists	5,533 (6.1%)	21,697 (17.9%)	42,658 (25.6%)	63,788 (29.3%)	77,348 (31.7%)
Statins	3,788 (4.2%)	36,729 (30.4%)	94,292 (56.5%)	139,333 (63.9%)	154,102 (63.2%)
Beta blockers	11,394 (12.5%)	23,228 (19.2%)	36,757 (22.0%)	50,352 (23.1%)	54,924 (22.5%)

ACE inhibitor, angiotensin converting enzyme inhibitor

Table S4. Adjusted Incident Rate Ratios for Heart Failure Among Patients with T2DM.

Year	Adjusted * IRR (95% CI)	p-value	Multivariable adjusted †IRR (95% CI)	p-value
1995	REF	REF	REF	REF
1996	0.95 (0.88-1.03)	0.238	0.79 (0.72-0.85)	<0.0001
1997	0.88 (0.81-0.96)	0.003	0.96 (0.88- 1.04)	0.286
1998	0.91 (0.84-0.99)	0.028	1.15 (1.06-1.24)	0.0009
1999	0.90 (0.83-0.97)	0.007	1.11 (1.03-1.20)	0.010
2000	0.97(0.90-1.05)	0.410	1.20 (1.11-1.30)	<0.0001
2001	0.90 (0.83-0.97)	0.006	1.06 (0.98-1.15)	0.124
2002	0.92 (0.86-1.00)	0.043	0.99 (0.91-1.06)	0.714
2003	0.79 (0.73-0.85)	<0.0001	0.81(0.75-0.88)	<0.0001
2004	0.75 (0.69-0.81)	<0.0001	0.72 (0.66-0.77)	<0.0001
2005	0.69(0.64-0.75)	<0.0001	0.64 (0.60-0.70)	<0.0001
2006	0.61 (0.56-0.66)	<0.0001	0.52 (0.48- 0.56)	<0.0001
2007	0.55 (0.51-0.60)	<0.0001	0.46 (0.43-0.50)	<0.0001
2008	0.50 (0.46-0.54)	<0.0001	0.42 (0.39-0.46)	<0.0001
2009	0.50 (0.47-0.54)	<0.0001	0.41 (0.38-0.44)	<0.0001
2010	0.51 (0.47-0.55)	<0.0001	0.41 (0.38-0.44)	<0.0001
2011	0.44 (0.41-0.47)	<0.0001	0.38 (0.35-0.41)	<0.0001
2012	0.44 (0.41-0.47)	<0.0001	0.38 (0.35-0.41)	<0.0001
2013	0.44 (0.41-0.47)	<0.0001	0.40 (0.37-0.43)	<0.0001
2014	0.39 (0.36-0.42)	<0.0001	0.39 (0.36-0.42)	<0.0001
2015	0.40 (0.37-0.43)	<0.0001	0.42 (0.39-0.46)	<0.0001
2016	0.37 (0.34-0.40)	<0.0001	0.42(0.39-0.45)	<0.0001
2017	0.35 (0.33-0.38)	<0.0001	0.42 (0.39-0.45)	<0.0001
2018	0.29 (0.27-0.32)	<0.0001	0.30 (0.27-0.32)	<0.0001

IRR= incidence rate ratio, CI=confidence interval

*adjusted for age, sex, insulin use, atrial fibrillation, hypertension, ischemic heart disease

† adjusted for age, sex, insulin use, atrial fibrillation, hypertension, ischemic heart disease, thiazides, ACEi, ARB, beta blockers, aspirin, clopidogrel, statin, metformin, sulfonylurea, thiazolidinedione, GLP1 agonists, DPP4, SGLT2 inhibitors

Table S5. Adjusted Incidence Rate Ratios Among Patients with T2DM Stratified by Age.

Year	Age < 50 IRR * (95% CI)	p-value	Age >50 IRR * (95% CI)	p-value
1995	REF	REF	REF	REF
1996	0.62(0.36-1.06)	0.080	0.79 (0.73-0.86)	<0.0001
1997	0.57 (0.32-1.00)	0.052	0.97 (0.89-1.05)	0.473
1998	0.86 (0.51-1.43)	0.554	1.16(01.07-1.26)	0.0004
1999	1.08 (0.67-1.75)	0.757	1.12 (1.03-1.21)	0.009
2000	1.38 (0.88-2.18)	0.163	1.20 (1.11-1.30)	<0.0001
2001	1.05(0.65-1.67)	0.852	1.07 (0.98-1.15)	0.117
2002	0.88 (0.55-1.40)	0.581	0.99 (0.92-1.07)	0.781
2003	0.92 (0.58-1.46)	0.721	0.81(0.75-0.88)	<0.0001
2004	0.77 (0.48-1.22)	0.261	0.71 (0.66-0.77)	<0.0001
2005	0.86 (0.54-1.35)	0.504	0.64 (0.54-0.69)	<0.0001
2006	0.76 (0.48-1.19)	0.228	0.51 (0.46-0.56)	<0.0001
2007	0.50 (0.31-0.82)	0.006	0.46 (0.43-0.50)	<0.0001
2008	0.49 (0.30-0.79)	0.003	0.42 (0.39-0.46)	<0.0001
2009	0.72 (0.46-1.13)	0.158	0.40 (0.37-0.44)	<0.0001
2010	0.70(0.45-1.10)	0.122	0.40 (0.37-0.44)	<0.0001
2011	0.60 (0.38-0.95)	0.030	0.38 (0.35-0.41)	<0.0001
2012	0.71 (0.45-1.11)	0.130	0.37 (0.34-0.40)	<0.0001
2013	0.60 (0.38-0.95)	0.028	0.40 (0.37-0.43)	<0.0001
2014	0.52 (0.32-0.84)	0.007	0.39 (0.36-0.42)	<0.0001
2015	0.68 (0.43-1.06)	0.089	0.42 (0.39-0.45)	<0.0001
2016	0.72 (0.46-1.13)	0.152	0.41 (0.38-0.44)	<0.0001
2017	0.57 (0.36-0.91)	0.019	0.42 (0.39-0.45)	<0.0001
2018	0.46 (0.28-0.75)	0.002	0.29 (0.27-0.32)	<0.0001

IRR= incidence rate ratio, CI=confidence interval

* adjusted for sex, insulin use, atrial fibrillation, hypertension, ischemic heart disease, thiazides, ACEi, ARB, beta blockers, aspirin, clopidogrel, statin, metformin, sulfonylurea, thiazolidinedione, GLP1 agonists, DPP4, SGLT2 inhibitors

Table S6. Adjusted Incidence Rate Ratios Among Patients with T2DM Stratified by Sex.

Year	Females IRR *	p-value	Males IRR*	p-value
1995	REF	REF	REF	REF
1996	0.82 (0.79-0.93)	0.002	0.75 (0.67-0.85)	<0.0001
1997	0.98 (0.87-1.11)	0.763	0.93 (0.83-1.05)	0.239
1998	1.18(1.05-1.33)	0.006	1.12 (1.00-1.25)	0.050
1999	1.14 (1.01-1.29)	0.030	1.09 (0.98-1.21)	0.126
2000	1.26 (1.12-1.41)	<0.0001	1.16 (1.04-1.29)	0.005
2001	1.11 (0.99-1.25)	0.066	1.02 (0.92-1.14)	0.678
2002	1.00 (0.90-1.13)	0.883	0.97 (0.87-1.07)	0.527
2003	0.85 (0.75-0.95)	0.005	0.79 (0.71-0.87)	<0.0001
2004	0.74 (0.66-0.84)	<0.0001	0.69 (0.62-0.77)	<0.0001
2005	0.61 (0.54-0.69)	<0.0001	0.67 (0.60-0.74)	<0.0001
2006	0.54 (0.48-0.61)	<0.0001	0.51 (0.46-0.57)	<0.0001
2007	0.46 (0.41-0.52)	<0.0001	0.46 (0.41-0.51)	<0.0001
2008	0.44 (0.39-0.49)	<0.0001	0.41 (0.37-0.46)	<0.0001
2009	0.41 (0.37-0.46)	<0.0001	0.40 (0.37-0.45)	<0.0001
2010	0.40 (0.35-0.45)	<0.0001	0.42 (0.38-0.46)	<0.0001
2011	0.36 (0.32-0.40)	<0.0001	0.40 (0.36-0.44)	<0.0001
2012	0.36 (.32-0.41)	<0.0001	0.39 (0.35-0.43)	<0.0001
2013	0.42 (0.37-0.47)	<0.0001	0.39 (0.35-0.43)	<0.0001
2014	0.41 (0.36-0.46)	<0.0001	0.38 (0.34-0.42)	<0.0001
2015	0.41 (0.36-0.46)	<0.0001	0.43 (0.39-0.48)	<0.0001
2016	0.41 (0.36-0.46)	<0.0001	0.42 (0.38-0.47)	<0.0001
2017	0.41 (0.36-0.46)	<0.0001	0.42 (0.38-0.47)	<0.0001
2018	0.29 (0.26-0.33)	<0.0001	0.30 (0.27-0.33)	<0.0001

IRR= incidence rate ratio, CI=confidence interval

* adjusted for sex, insulin use, atrial fibrillation, hypertension, ischemic heart disease, thiazides, ACEi, ARB, beta blockers, aspirin, clopidogrel, statin, metformin, sulfonylurea, thiazolidinedione, GLP1 agonists, DPP4, SGLT2 inhibitors

Table S7. Adjusted Incidence Rate Ratios Among Patients with T2DM Stratified by IHD.

Year	No IHD IRR * (95% CI)	p-value	IHD IRR * (95% CI)	p-value
1995	REF	REF	REF	REF
1996	0.99 (0.88-1.12)	0.890	0.62(0.55- 0.70)	<0.0001
1997	1.23 (1.09-1.38)	0.0009	0.76(0.68- 0.86)	<0.0001
1998	1.49 (1.33-1.67)	<0.0001	0.91 (0.81-1.02)	0.119
1999	1.41 (1.26-1.59)	<0.0001	0.91 (0.81-1.02)	0.095
2000	1.62 (1.45-1.81)	<0.0001	0.93 (0.84-1.04)	0.205
2001	1.39 (1.24-1.56)	<0.0001	0.85 (0.76-0.94)	0.003
2002	1.35 (1.21-1.51)	<0.0001	0.76 (0.68-0.84)	<0.0001
2003	1.05 (0.93-1.17)	0.447	0.66 (0.59- 0.74)	<0.0001
2004	0.92 (0.82-1.03)	0.167	0.58 (0.52-0.65)	<0.0001
2005	0.79 (0.71-0.89)	<0.0001	0.54 (0.48-0.60)	<0.0001
2006	0.68 (0.61-0.77)	<0.0001	0.43 (0.39-0.48)	<0.0001
2007	0.59 (0.53-0.67)	<0.0001	0.38(0.34-0.43)	<0.0001
2008	0.51 (0.46-0.58)	<0.0001	0.37 (0.33-0.41)	<0.0001
2009	0.52 (0.46-0.58)	<0.0001	0.35 (0.32-0.39)	<0.0001
2010	0.50 (0.44-0.56)	<0.0001	0.36 (0.32-0.40)	<0.0001
2011	0.46 (0.41-0.51)	<0.0001	0.34 (0.31-0.38)	<0.0001
2012	0.47 (0.42-0.53)	<0.0001	0.33 (0.30-0.37)	<0.0001
2013	0.49 (0.44-0.55)	<0.0001	0.35 (0.32-0.39)	<0.0001
2014	0.49 (0.44-0.55)	<0.0001	0.34 (0.30-0.38)	<0.0001
2015	0.52 (0.46-0.58)	<0.0001	0.37 (0.34-0.41)	<0.0001
2016	0.53 (0.47-0.59)	<0.0001	0.36 (0.32-0.40)	<0.0001
2017	0.55 (0.49-0.61)	<0.0001	0.34 (0.31-0.38)	<0.0001
2018	0.37 (0.33-0.42)	<0.0001	0.25 (0.23-0.28)	<0.0001

IRR-Incident rate ratio, CI= confidence interval, IHD=ischemic heart disease

*adjusted for sex, insulin use, atrial fibrillation, hypertension, ACEi, ARB, beta blockers, aspirin, clopidogrel, statin, metformin, sulfonylurea, thiazolidinedione, GLP1 agonists, DPP4, SGLT2 inhibitors

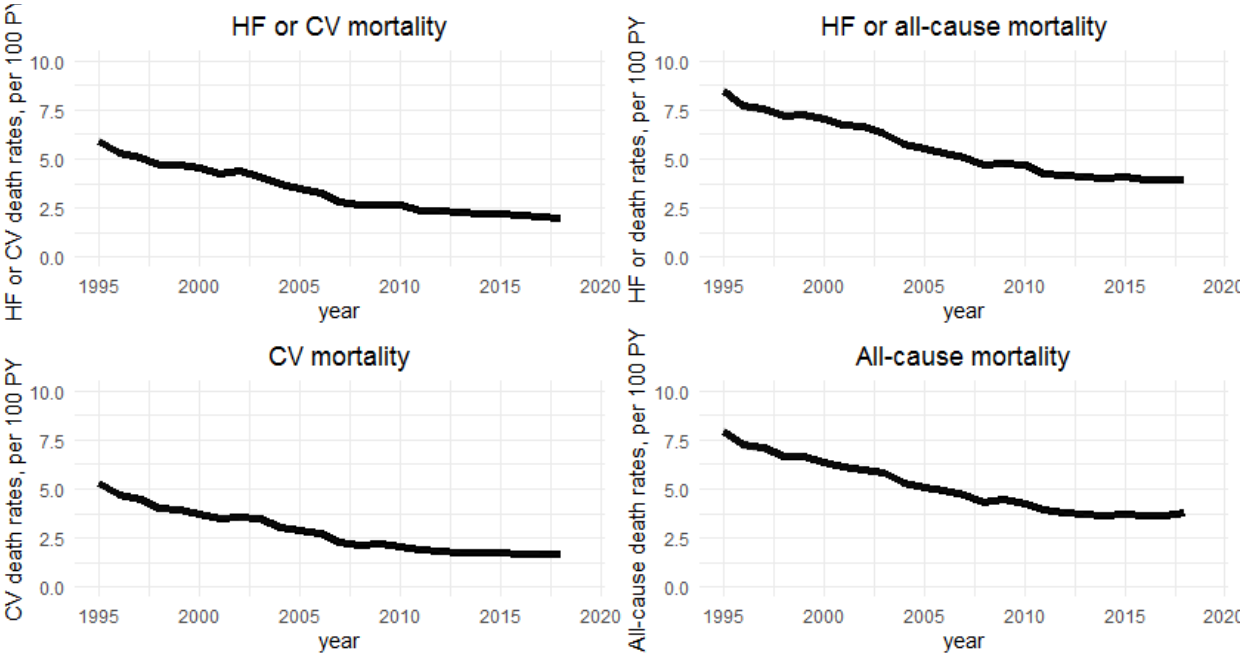
Table S8. Adjusted Incidence Rate Ratios Among Patients with T2DM Stratified by insulin use.

Year	No Insulin IRR* (95% CI)	p-value	Insulin IRR* (95% CI)	p-value
1995	REF	REF	REF	REF
1996	0.75 (0.69-0.83)	<0.0001	0.86 (0.72-1.02)	0.079
1997	1.02 (0.92-1.12)	0.742	0.83 (0.69-0.98)	0.027
1998	1.25 (1.13-1.37)	<0.0001	0.92 (0.87-1.15)	0.711
1999	1.15 (1.05-1.26)	0.003	1.05 (0.89-1.23)	0.566
2000	1.25 (1.14-1.37)	<0.0001	1.14 (0.98-1.33)	0.093
2001	1.14 (1.04-1.24)	0.006	0.97 (0.83-1.13)	0.707
2002	0.99 (0.90-1.08)	0.797	1.03 (0.89-1.20)	0.689
2003	0.87(0.79-0.95)	0.002	0.77 (0.66-0.90)	0.001
2004	0.74 (0.67-0.81)	<0.0001	0.73 (0.62-0.85)	<0.0001
2005	0.63 (0.57-0.69)	<0.0001	0.71 (0.61-0.83)	<0.0001
2006	0.54 (0.49-0.59)	<0.0001	0.53 (0.46-0.62)	<0.0001
2007	0.48 (0.44-0.53)	<0.0001	0.47 (0.40-0.55)	<0.0001
2008	0.43 (0.39-0.48)	<0.0001	0.44 (0.38-0.52)	<0.0001
2009	0.42 (0.39-0.47)	<0.0001	0.42 (0.36-0.49)	<0.0001
2010	0.42(0.38-0.46)	<0.0001	0.43 (0.37-0.50)	<0.0001
2011	0.38 (0.35-0.42)	<0.0001	0.42 (0.36-0.48)	<0.0001
2012	0.38 (0.35-0.42)	<0.0001	0.41 (0.35-0.48)	<0.0001
2013	0.40 (0.37-0.44)	<0.0001	0.42 (0.36-0.49)	<0.0001
2014	0.42 (0.38-0.46)	<0.0001	0.37 (0.32-0.43)	<0.0001
2015	0.44 (0.40-0.48)	<0.0001	0.43(0.37-0.50)	<0.0001
2016	0.44 (0.40-0.48)	<0.0001	0.41 (0.35-0.48)	<0.0001
2017	0.45 (0.41-0.49)	<0.0001	0.39 (0.34-0.46)	<0.0001
2018	0.32 (0.29-0.35)	<0.0001	0.28 (0.24-0.32)	<0.0001

IRR-Incident rate ratio, CI= confidence interval

*adjusted for sex, ischemic heart disease, atrial fibrillation, hypertension, ACEi, ARB, beta blockers, aspirin, clopidogrel, statin, metformin, sulfonylurea, thiazolidinedione, GLP1 agonists, DPP4, SGLT2 inhibitors

Figure S1. Trends in Cardiovascular, Heart Failure and Overall Mortality.



Heart failure (HF) or Cardiovascular (CV) mortality rates (left upper panel), HF or all cause mortality (right upper panel), CV mortality (left lower panel) and all cause mortality (right lower panel) by calendar time