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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

Brian Schwartz, MD, MPH; Colin Pierce, MD; Ramachandran S. Vasan, MD; Morten Schou, MD, PhD; Michel Ibrahim, MD; Kevin Monahan, MD; Asya Lyass, PhD; Morten Malmberg, MD; Gunnar H. Gislason, MD, PhD; Lars Køber, MD, DSc; Christian Torp-Pedersen, MD, DSc; Charlotte Andersson, MD, PhD

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...
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

| Acronym | Definition                  |
|---------|-----------------------------|
| IHD     | ischemic heart disease      |
| T2D     | type 2 diabetes             |

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. 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.

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. 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 I22, I23, 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), 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 (1995–1999) | Period 2 (2000–2004) | Period 3 (2005–2009) | Period 4 (2010–2014) | Period 5 (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 (std.)    | 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%)       | 48.945 (22.5%)       | 71.051 (26.2%)       | 72.274 (24.2%)       |
| ACE Inhibitor    | 31.384 (27.4%)       | 80.168 (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 (8.64%)       | 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%)       | 81.980 (40.5%)       | 125.514 (60.2%)      | 197.800 (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 | ...                  | 1616 (1.96%)         | 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%)       |
| SGLT2 inhibitor  | ...                  | ...                 | ...                 | 4057 (1.50%)          | 30.794 (10.3%)       |

ACE indicates angiotensin converting enzyme; DPP4, dipeptidyl peptidase 4; GLP-1, glucagon like peptide-1; and SGLT-2, sodium-glucose transport protein 2 inhibitors.
estimator generalizes the Kaplan Meier curve to account for multiple competing risks.\textsuperscript{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\%
(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. This is significantly higher than...
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

![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.](http://ahajournals.org)
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37}

**ARTICLE INFORMATION**

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**Supplementary Material**

Tables S1–S8

Figure S1
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**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.

| Age Group       | Period 1          | Period 2          | Period 3          | Period 4          | Period 5          |
|-----------------|-------------------|-------------------|-------------------|-------------------|-------------------|
|                 | (1995-1999)       | (2000-2004)       | (2005-2009)       | (2010-2014)       | (2015-2018)       |
| Age ≤50 years   |                   |                   |                   |                   |                   |
| 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  | 763 (3.8%)        | 2,536 (9.9%)      | 4,032 (11.0%)     | 4,992 (11.1%)     | 5,745 (11.6%)     |
| antagonists     |                   |                   |                   |                   |                   |
| 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  | 4,653 (8.2%)      | 18,582 (22.5%)    | 35,991 (31.1%)    | 52,089 (34.4%)    | 59,716 (36.5%)    |
| antagonists     |                   |                   |                   |                   |                   |
| 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  | 1,587 (4.3%)      | 7,188 (15.9%)     | 15,893 (28.3%)    | 26,356 (35.4%)    | 33,649 (39.5%)    |
| antagonists     |                   |                   |                   |                   |                   |
| 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  | Period 4  | 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                      | 0.080   | REF                   | 0.79 (0.73-0.86) | <0.0001 |
| 1996 | 0.62(0.36-1.06)          | 0.0001  | 0.73(0.67-0.80)       | 0.473   |
| 1997 | 0.57 (0.32-1.00)         | 1.16(0.07-1.26) | 0.554 | 1.12 (1.03-1.21) | 0.009   |
| 1998 | 0.86 (0.51-1.43)         | 1.20 (1.11-1.30) | 0.163 | 0.99 (0.92-1.07) | 0.117   |
| 1999 | 1.08 (0.67-1.75)         | 1.26 (0.66-0.77) | 0.261 | 0.54 (0.54-0.69) | <0.0001 |
| 2000 | 1.38 (0.88-2.18)         | 1.26 (0.66-0.77) | 0.261 | 0.54 (0.54-0.69) | <0.0001 |
| 2001 | 1.05 (0.65-1.67)         | 0.852   | 1.07 (0.98-1.15)      | 0.781   |
| 2002 | 0.88 (0.55-1.40)         | 0.81 (0.75-0.88) | 0.504 | 0.54 (0.49-0.62) | <0.0001 |
| 2003 | 0.92 (0.58-1.46)         | 0.96 (0.43-0.50) | 0.51 (0.46-0.56)      | <0.0001 |
| 2004 | 0.77 (0.48-1.22)         | 0.46 (0.39-0.46) | 0.40 (0.37-0.44)      | <0.0001 |
| 2005 | 0.86 (0.54-1.35)         | 0.39 (0.37-0.44) | 0.40 (0.37-0.44)      | <0.0001 |
| 2006 | 0.76 (0.48-1.19)         | 0.38 (0.34-0.40) | 0.37 (0.34-0.40)      | <0.0001 |
| 2007 | 0.50 (0.31-0.82)         | 0.130   | 0.40 (0.37-0.43)      | <0.0001 |
| 2008 | 0.49 (0.30-0.79)         | 0.150   | 0.39 (0.36-0.42)      | <0.0001 |
| 2009 | 0.72 (0.46-1.13)         | 0.110   | 0.39 (0.36-0.42)      | <0.0001 |
| 2010 | 0.70 (0.45-1.10)         | 0.130   | 0.37 (0.34-0.40)      | <0.0001 |
| 2011 | 0.60 (0.38-0.95)         | 0.130   | 0.37 (0.34-0.40)      | <0.0001 |
| 2012 | 0.71 (0.45-1.11)         | 0.150   | 0.39 (0.36-0.42)      | <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 (0.32-0.41) | <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                   |         |
| 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.