Long-Term Mortality Associated With Use of Carvedilol Versus Metoprolol in Heart Failure Patients With and Without Type 2 Diabetes: A Danish Nationwide Cohort Study

Brian Schwartz, MD, MPH; Colin Pierce, MD; Christian Madelaire, MD, PhD; Morten Schou, MD, PhD; Søren Lund Kristensen, MD; Gunnar H. Gislason, MD, PhD; Lars Kober, MD, DSc; Christian Torp-Pedersen, MD, DSc; Charlotte Andersson, MD, PhD

BACKGROUND: Carvedilol may have favorable glycemic properties compared with metoprolol, but it is unknown if carvedilol has mortality benefit over metoprolol in patients with type 2 diabetes (T2D) and heart failure with reduced ejection fraction (HFrEF).

METHODS AND RESULTS: Using Danish nationwide databases between 2010 and 2018, we followed patients with new-onset HFrEF treated with either carvedilol or metoprolol for all-cause mortality until the end of 2018. Follow-up started 120 days after initial HFrEF diagnosis to allow initiation of guideline-directed medical therapy. There were 39,260 patients on carvedilol or metoprolol at baseline (mean age 70.8 years, 35% women), of which 9,355 (24%) had T2D. Carvedilol was used in 2,989 (32%) patients with T2D and 10,411 (35%) of patients without T2D. Users of carvedilol had a lower prevalence of atrial fibrillation (20% versus 35%), but other characteristics appeared well-balanced between the groups. Totally 11,306 (29%) were deceased by the end of follow-up. We observed no mortality differences between carvedilol and metoprolol, multivariable-adjusted hazard ratio (HR) 0.97 (0.90–1.05) in patients with T2D versus 1.00 (0.95–1.05) for those without T2D, \( P \) for difference = 0.99. Rates of new-onset T2D were lower in users of carvedilol versus metoprolol; age, sex, and calendar year adjusted HR 0.83 (0.75–0.91), \( P < 0.0001 \).

CONCLUSIONS: In a contemporary clinical cohort of HFrEF patients with and without T2D, carvedilol was not associated with a reduction in long-term mortality compared with metoprolol. However, carvedilol was associated with lowered risk of new-onset T2D supporting the assertion that carvedilol has a more favorable metabolic profile than metoprolol.

Key Words: carvedilol ■ metoprolol ■ mortality ■ type 2 diabetes

The use of \( \beta \)-blockers have been shown to significantly reduce the mortality risk in patients with heart failure with reduced ejection fraction (HFrEF).1 Specifically, the use of bisoprolol, carvedilol, and metoprolol have proven mortality benefit (versus placebo) in several large clinical trials over the years.2–5 Furthermore, while these 3 agents have generally been shown to be equivalent in observational studies,6–9 a randomized clinical trial (COMET [Carvedilol Or Metoprolol European Trial]) comparing metoprolol tartrate 50 mg BID to carvedilol 25 mg BID suggested superiority of carvedilol.10 However, target dosages have been criticized for not being equipotent and differ from normal clinical practice (where metoprolol succinate is used at a target dose of 200 mg daily).

Carvedilol has been shown to have a better glycemic profile than metoprolol in patients with type 2 diabetes (T2D) and hypertension, but it is not known...
CLINICAL PERSPECTIVE

What Is New?
- β-Blockers improve mortality in patients with heart failure reduced ejection fraction and there is some evidence that carvedilol has improved glycemic properties compared with metoprolol, but it is unknown if this translates into a relative mortality benefit in heart failure patients with and without type 2 diabetes or lower incidence of type 2 diabetes in heart failure patients without type 2 diabetes.
- While there is no mortality benefit associated with use of carvedilol versus metoprolol, a lower incidence of type 2 diabetes in patients with heart failure reduced ejection fraction started on carvedilol compared with metoprolol was observed in our study.

What Are the Clinical Implications?
- This study supports current guidelines recommending either carvedilol or metoprolol in patients with heart failure reduced ejection fraction, but does suggest that the pharmacologic properties of carvedilol may offer a more favorable metabolic profile than metoprolol overall.

Nonstandard Abbreviations and Acronyms

| ATC | anatomical therapeutic classification |
|-----|---------------------------------------|
| HFrEF | heart failure reduced ejection fraction |
| T2D  | type 2 diabetes                         |

β-blockers in HF treatment,9 and to investigate potential differences in treatment effects associated with carvedilol between patients with and without T2D in a real-world cohort of patients with new-onset HFrEF. Additionally, we analyzed the risk of developing new-onset T2D during follow-up according to carvedilol versus metoprolol use in the sample free from T2D at baseline to investigate if carvedilol may have clinically beneficial effects on glucose-metabolism in real life.

METHODS

Due to the secure nature of the Danish nationwide registries, the data used in this manuscript can only be accessed through collaboration via a Danish authorized institution. Per Danish law, registry-based studies using de-identified data are exempted from institutional review board approval. We used the Danish national registries to identify a cohort of patients with newly diagnosed HFrEF with and without T2D stratified by β-blocker use (carvedilol versus metoprolol). In brief, all Danish citizens and residents are given a social security number at birth that is used to anonymously track both inpatient and outpatient medical encounters. Starting in 1978, the Danish patient registry has collected data on all in- and outpatient visits at Danish hospitals.17 Each patient is given a diagnosis (s) based on International Classification of Disease (ICD) coding that is used for reimbursement, which allows exposures and outcomes to be linked across institutions. The majority of cardiovascular disease diagnoses have been validated with good to excellent positive predictive values.18 All Danish pharmacies are mandated to register prescription claims based on dates and anatomical therapeutic classification (ATC) codes since 1995 and these data can be linked with the ICD data and mortality on an individual level.19 Full diagnostic codes for comorbidities and medications are available in Table S1. To meet inclusion criteria for this study, patients needed a first HF diagnosis (ICD-10 code I50 in the absence of prior ICD-8 codes 427.09–427.11, 427.19, and 424.49) between January 1, 2010 and December 31, 2018. We identified those with reduced ejection fraction based on a validated algorithm consisting initiating treatment with both an angiotensin converting enzyme inhibitor or an angiotensin II blocker plus a β-blocker within 120 days after the HF diagnosis. This definition has been shown to capture the majority of new-onset HFrEF in our registries (defined as a left ventricular ejection fraction ≤40%), with a sensitivity of 85% and a positive predictive value of 95%.20 We stratified data by T2D status, defined as a diagnosis of diabetes (ICD E11, E14), excluding type 1 diabetes (ICD E10), or a claimed prescription of at least one hypoglycemic agent within 120 days of HF diagnosis. Incident T2D was defined by the same criteria. We calculated...
mortality rates for each subgroup starting on day 120 after HF diagnosis and censoring on December 31, 2018 or emigration if it occurred before death. Full flowchart of the selection process is available in Figure S1.

Statistical Analysis
Baseline characteristics stratified by T2D status and carvedilol versus metoprolol use are presented as the total number of patients (%) or means (SD). Comparison of characteristics between metoprolol and carvedilol users were done by the Chi-squared test and the t test for categorical and continuous variables, respectively. Mortality rates (per 100 person years) were calculated over the entire follow up period for all subgroups, and hazard ratios (HRs) associated with carvedilol were estimated by Cox proportional hazards regression models using metoprolol as a referent. All values were given alongside 95% CIs. Models were adjusted for age, sex, and year, plus use of angiotensin receptor blocker (versus angiotensin converting enzyme inhibitor use), ischemic heart disease, atrial fibrillation, and insulin use. Multivariable models included all variables in the baseline table; Table 1. We tested for statistically significant differences in mortality risk associated with carvedilol (versus metoprolol) for patients with and without T2D by inclusion of an interaction term in the models. As sensitivity, we used inverse probability weighted Cox regression models to adjust for some of the potential unmeasured confounders. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A 2-sided P<0.05 was considered statistically significant.

RESULTS
Baseline Characteristics
Overall 39 260 patients (65% men) with new-onset HF were either on metoprolol or carvedilol between January 1, 2010 and December 31, 2018. Of these, 11 306 (29%) were deceased by the end of the follow up period. A total of 9355 (24%) had a diagnosis of T2D at the start of the study. Between the 2 agents, 13 400 (33%) were taking carvedilol and 26 860 (66%) were taking metoprolol, similar distributions between T2D and non-diabetic patients, Table 1. Overall, patients with T2D had increased comorbidity and were slightly older than patients without T2D, Table S2. Among patients with and without T2D the prevalence of patients with prior stroke, peripheral vascular disease and liver disease were similar between carvedilol and metoprolol users, while there were more patients with atrial fibrillation and hypertension on metoprolol than carvedilol for both groups. There was similar use of most medications (metformin, insulin, sulfonylurea, thiazolidinedione, GLP 1 agonist, DPP4, SGLT 2, loop diuretic, angiotensin receptor blocker, thiazide, clopidogrel, aspirin, and statin) among patients taking carvedilol and metoprolol in both T2D and no T2D subgroups. However, the prevalence of anticoagulants (warfarin and novel oral anticoagulants) were higher among patients taking metoprolol in both patients with and without T2D.

Mortality Rates
Among patients with T2D, our data showed a 5 year mortality of 39% (37%-41%) for carvedilol and 43% (42%-45%) for metoprolol. Among patients without T2D, 5-year mortality was 28% (27%-29%) for carvedilol and 34% (33%-34%) for metoprolol; Figure. The mortality rate for the entire population of HF patients was 8.2 (95% CI, 8.1–8.4) per 100 person-years. Among patients with T2D on carvedilol, the crude mortality rate was 9.9 (9.3–10.6) versus 11.5 (11.0–11.9) per 100 person-years for metoprolol users, with a HR associated with carvedilol of 1.00 (95% CI, 0.93–1.08) adjusted for age, sex, and calendar year. The mortality rates for patients without T2D were significantly lower than for those with T2D (6.7 [6.5–7.0] for carvedilol and 8.2 [8.0–8.5] for metoprolol per 100 person-years), but the HR associated with carvedilol (versus metoprolol) was similar (1.03 [0.98–1.08]). HRs remained unchanged after adjustment for comorbidities and medication use; Table 2. The test for difference in HRs associated with carvedilol versus metoprolol between patients with and without T2D was insignificant (P=0.99).

Incidence Rates of New Onset T2D
Among individuals without T2D, users of carvedilol had a lower incidence rate of new-onset T2D, compared with metoprolol users (n=658 versus 1387 individuals developed diabetes; 1.87 [1.73–2.02] versus 2.18 [2.07–2.30] cases per 100 person-years); age, sex, and calendar year adjusted HR for carvedilol 0.83 (0.75–0.91), P<0.0001. The average time to T2D onset was 2.4 years (SD 2.0 years) for patients taking carvedilol and 2.3 (SD 1.9 years) years for patients taking metoprolol.

Sensitivity Analyses
Applying inverse probability weighted Cox regression models (propensity for receiving calculated using all variables from Table 1, c statistic 0.66), similar results to the main models were observed, multivariable adjusted HR associated with carvedilol 1.00 (95% CI, 0.97–1.02, P=0.87), compared with metoprolol. Results were similar in patients with T2D (HR associated with carvedilol 0.99 [0.94–1.04, P=0.57]) and without T2D (1.00 [0.97–1.03, P=0.92] for carvedilol versus metoprolol, P for interaction =0.60.)
Restricting the analysis to cardiovascular mortality (n=8135), similar results were observed overall, HR associated with carvedilol 0.99 (0.94–1.04, P=0.61) versus metoprolol, with no differential association observed for use in patients with and without diabetes (P for interaction 0.86).

**DISCUSSION**

We examined the long-term mortality associated with use of carvedilol versus metoprolol in a contemporary cohort of patients with HFpEF, with and without T2D. We observed that patients with T2D had greater mortality than patients without T2D, but found no differences in outcomes associated with use of carvedilol versus metoprolol. There have been very few investigations examining both mortality differences for patients with HF and T2D on carvedilol versus metoprolol and how these findings may differ to individuals without T2D. Overall, β-blockers have been shown to be less efficacious for mortality-reduction in T2D compared with patients without T2D (16% versus 28% relative risk reduction, P for difference 0.023 in a large meta analysis). Therefore, studies investigating if carvedilol is superior to metoprolol in T2D is of particular interest and was outlined as an unanswered question in the recent consensus document on heart failure and T2D by the American Heart Association.

The pharmacologic mechanism behind a theorized difference in outcome between carvedilol and metoprolol in the T2D population partly relates to impaired distribution of glucose to peripheral muscles and increased insulin resistance associated with the HF state. By blockage of the alpha receptors, carvedilol is thought to improve glucose distribution to peripheral tissue, theoretically thereby having the potential to improve glycemic control and possibly outcomes in patients with T2D and HF. Consistent with this proposed pharmacologic mechanism, there was a lower rate of incident T2D in patients free from T2D at the start of follow up for carvedilol versus metoprolol users in both COMET and our study (HR, 0.78 [95% CI 0.61–0.997] in the COMET study versus 0.83 [0.75–0.91] in our study). Further, to our knowledge, a subgroup analysis of COMET is the one study to date that examined mortality differences in carvedilol versus metoprolol in patients with T2D and HF. Ultimately, COMET suggested a small but insignificant reduction in mortality for carvedilol over metoprolol in patients with T2D (HR, 0.85 [0.69–1.06], P=0.147), but with the limitation that the target dose of carvedilol (25 mg BID) was relatively higher than the target dose of metoprolol (50 mg BID, respectively). While there was no marginal mortality benefit for carvedilol in our study, our findings are overall consistent with other observational studies in the general HF population to date. Further, our study was based on a real-world Danish sample where titration to maximally tolerated dosing of carvedilol (50 mg BID) and metoprolol (200 mg daily) was recommended, consistent with HF guidelines. A second possible explanation for the difference between our study and the COMET trial was that the patients included in the COMET study used only metoprolol.
tartrate, while metoprolol succinate is the standard practice in the long-term HF treatment in Denmark.

As T2D is a significant predictor of overall mortality and hospitalization in patients with HF, the finding that there is no difference in mortality between carvedilol and metoprolol for patients with T2D, despite a plausible pharmacologic mechanism is important. It is, however, unknown if carvedilol may have beneficial effects on other endpoints (not investigated in this study), such as renal failure. In this context, a higher rate of progression to microalbuminuria was documented for patients with T2D and hypertension who used metoprolol (versus carvedilol) in the GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol in Hypertensives) trial. Carvedilol use was also associated with a smaller increase in triglyceride levels and relative improvements in high density lipoproteins compared with metoprolol. It is possible that HF patients with T2D have such a high baseline risk of mortality that a minor theoretical difference would be of little relative importance to the risk. It is also likely that modern HF treatment (including appropriate reduction of afterload and downregulation of the neurohumoral axis) is sufficient to secure circulation and insulin/glucose distribution to peripheral muscles.

Finally, in both the COMET subgroup analysis and in this study, there was no interaction between carvedilol and metoprolol in patients with and without T2D (P for interaction in COMET subgroup 0.77 compared with 0.99 for our study). Thus, in real-life data, the postulated favorable glycemic properties of carvedilol over metoprolol do not appear to be of major importance.

### Table 1. Baseline Table

|                  | T2D (N=9355) | No T2D (N=29 905) | P for difference | T2D (N=10 411) | No T2D (N=19 494) | P for interaction |
|------------------|--------------|------------------|------------------|----------------|------------------|------------------|
| **Sex (men)**    | 2137 (71.5%) | 4161 (65.4%)     | <0.0001          | 7044 (67.7%)   | 12 291 (63.1%)   | <0.0001          |
| **Age, y (SD)**  | 69.0 (11.2)  | 72.1 (10.6)      | <0.0001          | 68.2 (12.8)    | 72.1 (12.2)      | <0.0001          |
| **Comorbidity**  |              |                  |                  |                |                  |                  |
| Stroke           | 343 (11.5%)  | 810 (12.7%)      | 0.09             | 809 (7.8%)     | 1872 (9.6%)      | <0.0001          |
| Peripheral vascular disease | 335 (11.2%)  | 684 (10.7%)      | 0.50             | 551 (5.3%)     | 1076 (5.6%)      | 0.41             |
| Liver disease    | 13 (0.4%)    | 26 (0.4%)        | 0.85             | 49 (0.5%)      | 72 (0.4%)        | 0.19             |
| Renal disease    | 257 (8.6%)   | 652 (10.2%)      | 0.012            | 440 (4.2%)     | 981 (5.0%)       | 0.002            |
| COPD             | 338 (11.3%)  | 818 (12.9%)      | 0.035            | 982 (9.4%)     | 2015 (10.3%)     | 0.013            |
| Cancer           | 379 (12.7%)  | 919 (14.4%)      | 0.022            | 1449 (13.9%)   | 2719 (14.0%)     | 0.94             |
| Atrial fibrillation | 602 (20.1%) | 2187 (34.4%)     | <0.0001          | 2086 (20.0%)   | 6990 (35.9%)     | <0.0001          |
| Hypertension     | 1537 (51.4%) | 3757 (59.0%)     | <0.0001          | 3543 (34.0%)   | 8271 (42.4%)     | <0.0001          |
| Ischemic heart disease | 1818 (61.5%) | 4261 (65.4%)     | 0.0001           | 5054 (47.9%)   | 11 415 (55.9%)   | <0.0001          |
| **Medication**   |              |                  |                  |                |                  |                  |
| Metformin        | 1770 (59.2%) | 3768 (59.2%)     | 0.98             | 0.00           | 0.00             |                  |
| Insulin          | 1070 (35.8%) | 2137 (33.6%)     | 0.034            | 0.00           | 0.00             | 0.00             |
| Sulfonylurea     | 466 (15.6%)  | 924 (14.5%)      | 0.17             | 0.00           | 0.00             |                  |
| Thiazolidinedione| <3 (NA)      | 8 (0.13%)        | 0.44             | 0.00           | 0.00             |                  |
| GLP-1 agonist    | 206 (6.9%)   | 413 (6.5%)       | 0.46             | 0.00           | 0.00             | 0.00             |
| DPP4 inhibitor   | 243 (8.1%)   | 461 (7.2%)       | 0.13             | 0.00           | 0.00             | 0.00             |
| SGLT-2 inhibitor | 92 (3.1%)    | 132 (2.1%)       | 0.003            | 0.00           | 0.00             |                  |
| Mineralocorticoid receptor antagonist | 1185 (39.7%) | 2021 (31.8%)     | <0.0001          | 4097 (39.4%)   | 5981 (30.7%)     | <0.0001          |
| Loop diuretic    | 2305 (77.1%) | 4691 (73.7%)     | 0.0004           | 6937 (66.6%)   | 12 251 (62.8%)   | <0.0001          |
| Angiotensin II receptor blocker | 850 (28.8%) | 2145 (32.9%)     | 0.0004           | 2444 (23.2%)   | 5396 (26.4%)     | <0.0001          |
| Thiazide         | 334 (11.2%)  | 829 (13.0%)      | 0.012            | 544 (5.2%)     | 1482 (7.6%)      | <0.0001          |
| Warfarin         | 529 (17.7%)  | 1620 (25.5%)     | <0.0001          | 1899 (18.2%)   | 5126 (26.3%)     | <0.0001          |
| Direct oral anticoagulants | 91 (3.0%) | 389 (6.1%)       | <0.0001          | 397 (3.8%)     | 1453 (7.5%)      | <0.0001          |
| Clopidogrel      | 637 (21.3%)  | 1328 (20.9%)     | 0.62             | 1798 (17.3%)   | 3601 (18.5%)     | 0.01             |
| Aspirin          | 1870 (62.6%) | 3736 (58.7%)     | 0.0004           | 5376 (51.6%)   | 9996 (51.3%)     | 0.55             |
| Statin           | 2213 (74.0%) | 4837 (76.0%)     | 0.042            | 5492 (92.0%)   | 11 044 (56.7%)   | <0.0001          |
for clinical outcomes in patients with T2D, although carvedilol may lower the risk of developing new-onset T2D among HFrEF patients free from T2D at HF onset, compared with metoprolol.

**Strengths and Limitations**

There were several important strengths of this study. First, this was one of the largest cohort studies (39,260 patients) to examine the differences between β-blockers in HF patients. It was also one of few studies to date to examine this question in patients with both HF and T2D, and to compare the difference in effect to patients without T2D. Furthermore, to our knowledge, it is the only study to date in patients with both HF and T2D to compare metoprolol succinate formulation (XL/CR) to carvedilol. Finally, we were able to adjust for a significant number of comorbidities and as well as medication differences between groups that could have potentially changed results. There were also some weaknesses that should be addressed. First, the Danish registries comprise a relatively racially homogenous population, and this study should be replicated in a more diverse population. Second, the algorithm underlying the selection process to identify patients with HFrEF in our study was based on validated work from 2 clinics out of approximately 40 specialized HF clinics in Denmark. However, all clinics are run based on the same model and Danish guidelines with excellent quality control data.26 Third, we were not able to account for different doses for each agent. However, as it is standard practice to titrate doses of β-blockers to the maximally tolerated in HFrEF patients, this weakness is somewhat minimized.24,25 Fourth, we were not able to adjust for NYHA classification, though we did adjust for use of mineralocorticoid receptor antagonists and use of loop diuretics, both of which are potential markers of HF severity.27 Fifth, there was a significant difference in prevalence of atrial fibrillation in the metoprolol versus carvedilol groups and although we adjusted, residual confounding cannot be excluded (since atrial fibrillation has been associated with increased risk of mortality in patients with heart failure).28 Finally, as this is an observational study, results should ideally be replicated in a randomized control trial.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

In a contemporary clinical cohort of patients with HFrEF, carvedilol was not associated with a reduction in long-term mortality compared with metoprolol. While carvedilol was not superior to metoprolol among patients with established T2D, it was associated with lowered risk of new-onset T2D, supporting the assertion that carvedilol may have a more favorable metabolic profile than metoprolol overall. Our data support current clinical guidelines that recommend both metoprolol and carvedilol as first-line treatment of HFrEF.

**ARTICLE INFORMATION**

Received June 3, 2021; accepted August 9, 2021.

**Affiliations**

Section of Internal Medicine, Department of Medicine, Boston Medical Center, Boston University School of Medicine, Boston, MA (B.S., C.P.); Department of Cardiology, Odense University Hospital, Odense, Denmark (C.M.); Department of Cardiology, Herlev and Gentofte Hospital, Copenhagen University Hospital, Hørsholm, Denmark (M.S., S.L.K., G.H.G., C.A.); Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark (L.K.); Departments of Cardiology and Clinical Investigations, Hillerød Hospital, Hillerød, Denmark (C.T.); Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark (C.T.); and Department of Medicine, Section of Cardiovascular Medicine, Boston Medical Center, Boston University School of Medicine, Boston, MA (C.A.).

**Sources of Funding**

This work was supported by the National Institutes of Health (grant number 1R38HL143584, Multi-Disciplinary Training for Promoting Research In Medical Residency) to Brian Schwartz, MD, MPH.
SUPPLEMENTAL MATERIAL
Table S1. Diagnoses and medication classification.

| Disease                     | ICD 10 and 8 codes                                                                 |
|-----------------------------|------------------------------------------------------------------------------------|
| Atrial Fibrillation         | 148, 4274                                                                          |
| Hypertension                | I10-I15, 400-404, or defined as taking at least two antihypertensive agents, according to a previously validated algorithm. |
| Ischemic Heart Disease      | I20-25, 410-413                                                                    |
| Stroke                      | I63-64                                                                             |
| Peripheral Vascular Disease | I70, I74                                                                           |
| Liver disease               | K704, K711, K766, B150, B160, B190                                                 |
| Renal disease               | N03, N04, N17, N18, N19, R34, I12, I13, T858-59, Z992                              |
| COPD                        | J42, J44, 490-92                                                                   |
| Cancer                      | DC00-DC97, 140-195, 200-209                                                        |
| Medications                 | ATC codes                                                                          |
| Insulin use                 | A10A                                                                               |
| Thiazide diuretics          | C03AA                                                                              |
| ACE inhibitor               | C09AA                                                                              |
| Angiotensin II receptor blocker | C09CA                                                  |
| Spironolactone              | C03DA01                                                                            |
| Eplerenone                  | C03DA04                                                                            |
| Loop diuretics              | C03C                                                                               |
| Carvedilol                  | C07AG02                                                                            |
| Metoprolol                  | C07AB02                                                                            |
| Clopidogrel                 | B01AC04                                                                            |
| Aspirin                     | B01AC06                                                                            |
| Statin                      | C10AA                                                                              |
| Metformin                   | A10BA02                                                                            |
| Sulfonylurea                | A10BB                                                                              |
| Thiazolidinedione           | A10BG                                                                              |
| GLP 1 Agonist               | A10BJ                                                                              |
| DPP4                        | A10BH                                                                              |
| SGLT2 Inhibitor             | A10BK                                                                              |
| Warfarin                    | B01AA                                                                              |
| Direct oral anticoagulants  | B01AA, B01AE07                                                                     |
|                          | Diabetes (N=9,355) | No diabetes (N=29,905) | P for difference |
|--------------------------|---------------------|------------------------|-----------------|
| **Sex (men)**            | 6298 (67%)          | 19,335 (65%)           | <0.0001         |
| **Age, years (st.d)**    | 71.1 (10.9)         | 70.7 (12.6)            | 0.012           |
| **Comorbidity**          |                     |                        |                 |
| **Stroke**               | 1,153 (12.3%)       | 2,681 (9.0%)           | <0.0001         |
| **Peripheral vascular disease** | 1,019 (10.9%)       | 1,627 (5.4%)           | <0.0001         |
| **Liver disease**        | 39 (0.4%)           | 121 (0.4%)             | 0.87            |
| **Renal Disease**        | 909 (9.7%)          | 1,421 (4.8%)           | <0.0001         |
| **COPD**                 | 1,156 (12.4%)       | 2,997 (10.0%)          | <0.0001         |
| **Cancer**               | 1,289 (13.9%)       | 4,168 (13.9%)          | 0.88            |
| **Atrial fibrillation**  | 2,789 (29.8%)       | 9,076 (30.4%)          | 0.32            |
| **Hypertension**         | 5,294 (56.6%)       | 11,814 (39.5%)         | <0.0001         |
| **Ischemic Heart Disease** | 6,040 (64.6%)       | 16,120 (53.9%)         | <0.0001         |
| **Medication**           |                     |                        |                 |
| **Metformin**            | 5,538 (59.2%)       |                        |                 |
| **Insulin**              | 3,207 (34.3%)       |                        |                 |
| **Sulfonylurea**         | 1,390 (14.9%)       |                        |                 |
| **Thiazolidinedione**    | 10 (0.1%)           |                        |                 |
| Drug Class                      | N (%)       | N (%)       | p-value |
|--------------------------------|-------------|-------------|---------|
| GLP-1 agonist                  | 619 (6.6%)  |             |         |
| DPP4 inhibitor                 | 704 (7.5%)  |             |         |
| SGLT-2 inhibitor               | 224 (2.4%)  |             |         |
| Mineralocorticoid receptor     | 3,206 (34.3%) | 10,078 (33.7%) | 0.31   |
| Loop diuretic                  | 6,996 (74.8%) | 19,188 (64.2%) | <0.0001 |
| Angiotensin II receptor blocker| 2,959 (31.6%) | 7,491 (25.1%) | <0.0001 |
| Thiazide                       | 1,163 (12.4%) | 2,026 (6.8%) | <0.0001 |
| Warfarin                       | 2,149 (23.0%) | 7,025 (23.5%) | 0.30   |
| Direct oral anticoagulants     | 480 (5.1%)  | 1,850 (6.2%) | 0.0002 |
| Clopidogrel                    | 1,965 (21.0%) | 5,399 (18.1%) | <0.0001 |
| Aspirin                        | 5,606 (59.9%) | 15,372 (51.4%) | <0.0001 |
| Statin                         | 7,050 (75.4%) | 16,536 (55.3%) | <0.0001 |
Figure S1. Flowchart of study population.

91,107 patients with first-diagnosed HF aged 30 years or above

| 17,364 excluded with shorter follow-up than 4 months |
|-----------------------------------------------------|
| 73,743 with at least 4 months of follow-up |
| 33,075 not treated with both a RAS-inhibitor or ARB and carvedilol or metoprolol |
| 40,668 were in treatment with both a RAS-inhibitor or ARB and carvedilol or metoprolol |
| 1,408 patients with type 1 diabetes excluded |
| 39,260 patients included |