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ORIGINAL RESEARCH

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

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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 9355 (24%) had T2D. Carvedilol was used in 2989 (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 β-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

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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

if this difference is clinically important in patients with HFrEF.[11] A secondary analysis of the COMET trial suggested that patients with HFrEF randomized to carvedilol had lower incidence of new-onset diabetes compared with patients randomized to metoprolol.[10,12] However, those with T2D had similar reductions in mortality with carvedilol treatment versus metoprolol treatment as non-diabetic patients, suggesting that the metabolic advantages of carvedilol may not translate into additional mortality benefit in T2D.[12]

Given the high prevalence of T2D among patients with HFrEF, the adverse outcomes associated with T2D in HFrEF, and the potential of carvedilol to mitigate some of the metabolic abnormalities in T2D, studies addressing the mortality associated with carvedilol versus metoprolol in people with T2D and HFrEF are warranted.[13–16] We sought to compare mortality in patients with HFrEF and T2D taking carvedilol with those taking metoprolol (the 2 most commonly used 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.

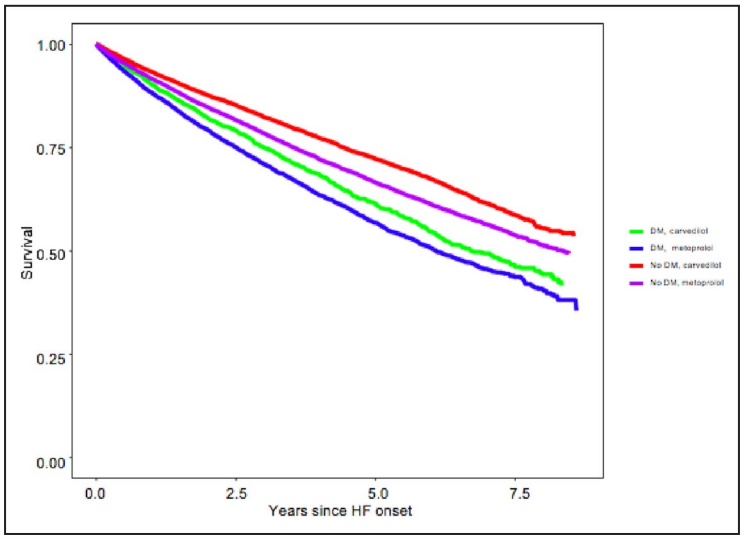

Figure. Proportion of individuals that survive (*Y* axis) in years after heart failure (HF) diagnosis (*X* axis) based on type 2 diabetes (DM) and β-blocker (metoprolol, carvedilol) status.
Green is DM and carvedilol, blue is DM and metoprolol, red is patients without DM and carvedilol and purple is patients without DM and metoprolol.

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 HFrEF, 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).[21] 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.[16]

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.[22,23] 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.[12] 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.[6–8,10] 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.[24,25] 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

Table 1. Baseline Table

	T2D (N=9355)			No T2D (N=29 905)		
	Carvedilol N=2989 (32%)	Metoprolol N=6366 (68%)	*P* for difference	Carvedilol N=10 411 (35%)	Metoprolol N=19 494 (65%)	*P* for difference
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 (5.5%)	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	
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	
DPP4 inhibitor	243 (8.1%)	461 (7.2%)	0.13	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 (52.8%)	11 044 (56.7%)	<0.0001

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[13,15] and hospitalization[14] 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 over metoprolol on other end points (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.[11] Carvedilol use was also associated with a smaller increase in triglyceride levels and relative improvements in high density lipoproteins compared with metoprolol.[11] 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[12] 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 2. Mortality Stratified by β-Blocker and T2D Status

	T2D		No T2D	
	Carvedilol (95% CI)	Metoprolol (95% CI)	Carvedilol (95% CI)	Metoprolol (95% CI)
Mortality rate (per 100 PY)	9.9 (9.3–10.6)	11.5 (11.0–11.9)	6.7 (6.5–7.0)	8.2 (8.0–8.5)
Hazard ratio*	1.00 (0.93–1.08)	Ref	1.03 (0.98–1.08)	Ref
Hazard ratios (multivariable adjusted 1†)	1.01 (0.94–1.09)	Ref	1.05 (1.00–1.11)	Ref
Hazard ratio (multivariable adjusted 2‡)	0.97 (0.90–1.05)	Ref	1.00 (0.95–1.05)	Ref

PY indicates person years.
*Adjusted for age, sex, year.
†Covariables include age, sex, year, angiotensin II receptor blocker, ischemic heart disease, atrial fibrillation, insulin use.
‡Covariable includes age, sex, year, angiotensin II receptor blocker, ischemic heart disease, atrial fibrillation, insulin use, stroke, peripheral vascular disease, liver disease, chronic obstructive lung disease, renal disease, cancer, hypertension, metformin, sulfonylurea, thiazolidinedione, GLP1-agonists, DPP4 inhibitors, SGLT2 inhibitors, mineralocorticoid receptor antagonists, loop diuretic, thiazides, warfarin, novel oral anticoagulant, clopidogrel, aspirin, statin. Antidiabetic medications were only adjusted for in the analyses of patients with diabetes.

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 homogeneous 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

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Supplementary Material

Tables S1–S2
Figure S1
Reference 29

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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.[29]
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

Table S2. Comorbidity and medication use by diabetes status.

	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%)		

GLP-1 agonist	619 (6.6%)		
DPP4 inhibitor	704 (7.5%)		
SGLT- 2 inhibitor	224 (2.4%)		
Mineralocorticoid receptor antagonist	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.