SJIF Impact Factor: 5.464

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

ISSN: 2457-0400
Volume: 6.
Issue: 3.
Page N. 121-131
Year: 2022

Original Article www.wjahr.com

CARVEDILOL COMPARED WITH METOPROLOL SUCCINATE IN THE TREATMENT AND PROGNOSIS OF PATIENTS WITH STABLE CHRONIC HEART FAILURE

Premshanker Singh*[1], Vikram Singh[2], Mridu Singh[3], D. P. Singh[4], PK. Singh[5]

[1]FMR Prof and Head Medicine, [2]Prof and Head Medicine, [3]Assoc Prof Medicine, [4]FMR Senior Resident Medicine, [5]FMR Senior Resident Medicine, Dr. RML Institute of Medical Sciences, Lucknow, India-226010.

Received date: 12 January 2022 **Revised date:** 01 February 2022 **Accepted date:** 21 February 2022

***Corresponding Author: Premshanker Singh**

FMR Prof and Head Medicine, Dr. RML Institute of Medical Sciences, Lucknow, India-226010.

ABSTRACT

β-Blockers exert a prognostic benefit in the treatment of chronic heart failure. Their pharmacological properties vary. The only substantial comparative trial to date—the Carvedilol or Metoprolol European Trial—has compared carvedilol with short-acting metoprolol tartrate at different dose equivalents. We therefore addressed the relative efficacy of equal doses of carvedilol and metoprolol succinate on survival in single center tertiary care hospital of Dr RML Institute of Medical Sciences, Lucknow(DR RML IMS LKO) India. Two thousand and eight hundred patients with stable systolic chronic heart failure who were using either carvedilol or metoprolol succinate were identified in Medical OPD(MOPD) of Dr RML Institute of Medical Sciences, Lucknow(DR RML IMS LKO), India Patients were individually matched on both the dose equivalents and the respective propensity scores for β-blocker treatment. During a follow-up for 17 670 patient-years, it was found that 304 (27.2%) patients died in the carvedilol group and 1066 (36.8%) in the metoprolol group. In a univariable analysis of the general sample, metoprolol therapy was associated with higher mortality compared with carvedilol therapy (hazard ratio, 1.49; 95% confidence interval, 1.31–1.69; $P<0.001$). This difference was not seen after multivariable adjustment (hazard ratio, 0.93; 95% confidence interval, 0.57–1.50; $P=0.75$) and adjustment for propensity score and dose equivalents (hazard ratio, 1.06; 95% confidence interval, 0.94–1.20; $P=0.36$) or in the propensity and dose equivalent–matched sample (hazard ratio, 1.00; 95% confidence interval, 0.82–1.23; $P=0.99$). These results were essentially unchanged for all prespecified subgroups In outpatients with chronic heart failure, no conclusive association between all-cause mortality and treatment with carvedilol or metoprolol succinate was observed after either multivariable adjustment or multilevel propensity score matching. The beneficial effects of β-blockers are well

INTRODUCTION

- 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. 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 year[2,3,4,5] Furthermore, while these 3 agents have generally been shown to be equivalent in observational studies,[6,7,8,9] 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[1] 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 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[10,12] 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.[13,14,15] 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[16,17] 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

Patients recruitment was prospective and continuous for 03 years wef 07 Apr 2017 t0 07 Apr 2020 in Medical OPD(MOPD) of Dr RML Institute of Medical Sciences, Lucknow(DR RML IMS, LKO) All patients gave their written informed consent for data storage and evaluation. All patients were included after stabilization of both clinical status and medication The diagnosis of heart failure was established according to guidelines on the basis of typical symptoms and signs resulting from an objective abnormality of cardiac structure or function on echocardiography, cardiac magnetic resonance imaging, or left heart catheterization[15,16,17] All included patients had a left ventricular ejection fraction (LVEF) <45%.Baseline characteristics included medical history, physical examination, LVEF, laboratory results, and medication. Glomerular filtration rate was estimated using the Modification of Diet in Renal Disease equation. Surviving patients were followed up for a minimum of 6 months. Determination of survival status and follow-up were performed by scheduled visits to the outpatient clinic, by telephone calls either to the patients' homes or to their physicians, or by electronic hospital records. For the purpose of this analysis, patients alive at this point were censored as alive at the date of this last contact. In addition, for the Norwegian Heart Failure Registry, mortality data were obtained at regular intervals from the National Statistics Bureau, Statistics Norway. All-cause mortality was the predefined end point for the purpose of this analysis.

Statistical Analysis

All tests are 2-tailed, and $P<5\%$ was regarded as statistically significant. Variables are presented as mean±SD, median (interquartile range), or number percentages (%) as appropriate. Chi-squared test was performed to compare frequencies. To test the significant differences between groups, the 2-sample Wilcoxon signed-rank test and Student *t* test were used where appropriate. Differences in event-free survival were analyzed using uni- and multivariable Cox proportional hazard models and displayed using the Kaplan–Meier plot for survival. To account for possible confounders, 3 strategies were applied: First, all variables found to be significant in univariable Cox analysis and those different between β-blocker groups were entered in a single multivariable Cox model. Second, a propensity score for the conditional probability of receiving either β-blocker (carvedilol versus metoprolol succinate) was derived as described below and used together with β-blocker equivalent dose for control in a common (trivariable) model. Third, a 2-level matching process was performed as described below, and the original analysis was repeated in the matched cohort. Because our database includes patients from 28 hospitals in 2 European countries, regional differences may affect study results. To account for a possible center-related bias, multivariable analyses included individual center as a forced independent covariate. Analyses were repeated in prespecified subgroups with respect to age (above versus below median), sex, cause of heart failure (ischemic versus nonischemic), LVEF (≤35% versus >35%), NYHA functional class (I/II versus III/IV), renal function (glomerular filtration rate, ≤60 mL/min per 1.73 m^2 versus >60 mL/min per 1.73 m^2), obstructive pulmonary disease (yes versus no), diabetes mellitus (yes versus no), heart rate (≤75 versus >75 per minute), rhythm (sinus rhythm, yes versus no), and blood pressure (above versus below median). In addition, survival was analyzed in patients with sinus rhythm plus LVEF ≤35% because this patient cohort showed the greatest benefit from carvedilol therapy in COMET. Interaction terms were calculated for each of the predefined subgroups in the propensity-matched sample. The propensity score was calculated as the single composite variable from a nonparsimonious multivariate logit-linked binary logistic regression of the baseline characteristics. The β-blocker agent was a dependent variable.[22] The logit of the probability of receiving either carvedilol or metoprolol succinate according to this score formed the basis of our matching procedure. Dose equivalent of the respective β-blocker was not part of the propensity score to separately account for one of the main criticisms of the COMET trial. Patients were individually matched on both the propensity of receiving either β-blocker and their dose equivalents using the Mayo Clinic SAS macro gmatch. The matching procedure was performed in 2 steps. First, caliper matching of the propensity score was applied with caliper size predefined as 0.2 of the SD of the total sample.[23] In a 1-pass procedure starting with a given patient receiving carvedilol, the closest match of a patient receiving metoprolol succinate was identified. Second, dose equivalents for the β-blockers were compared. If doses were equivalent or varied ≤10%, the

pair of patients was retained for analysis and removed from the total sample to allow for the next matching cycle to take place. If doses were varied >10%, the pair was rejected. Then the first step of the matching process was repeated to identify the next closest match to the carvedilol patient of the failed match according to the propensity score. If a further patient on metoprolol succinate was thus identified, the second step was repeated. In case of no match according to the propensity score and dose equivalent could be identified, the carvedilol patient was removed from the total sample and the matching cycle started with the next patient receiving carvedilol.

RESULTS

Patient Characteristics and Follow-Up

We identified a total of 4016 patients who met the inclusion criteria outlined above. Of these, 3311 patients were extracted from the Norwegian Heart Failure Registry, and 705 patients were included into the Heart Failure Registry of the University of Heidelberg. The number of patients included in each participating center is shown in Table I in the Data Supplement. A total of 2898 patients (72.2%) received metoprolol succinate with a median dose of 103 (51–195) mg/d (53 [26–100] % of target dose). Carvedilol was given in 1118 patients (27.8%) with a median dose of 38 (25–50) mg/d (75 [50–100] % of target dose). Baseline characteristics of patients receiving metoprolol succinate differed from those treated with carvedilol in a substantial number of other variables(Table-1). Overall, patients receiving metoprolol succinate were older and more likely to be NYHA functional class III than those on carvedilol. In addition, the proportion of patients with ischemic heart failure was higher in the metoprolol succinate group.

Table 1: Baseline Characteristics for the Complete Cohort and Separate With Respect to Receipt of Carvedilol or Metoprolol Succinate

	All Patients (n=4016)	Carvedilol (n=1118)	*P* Value	Metoprolol Succinate (n=2898)
Age, y, n=4015	67±13	63±14	<0.001*	68±13
Male, n (%), n=4016	2949 (73.4)	852 (76.2)	0.01*	2097 (72.4)
BMI, kg/m², n=3643	27±5	27±5	0.11	27±5
Cause of CHF, n=4016				
CHD, n (%)	2128 (53.0)	498 (44.5)	<0.001*	1630 (56.2)
dCMP, n (%)	871 (21.7)	393 (35.2)		478 (16.5)
Other, n (%)	1017 (25.3)	227 (20.3)		790 (27.3)
NYHA, n (%), n=3947				
I	697 (17.7)	261 (23.8)	<0.001*	436 (15.3)
II	2140 (54.2)	593 (54.2)		1547 (54.2)
III	1093 (27.7)	239 (21.8)		854 (29.9)
IV	17 (0.4)	2 (0.2)		15 (0.5)
LVEF, %, n=3731	32±11	30±10	<0.001*	33±11
BPsys, mm Hg, n=3979	122±20	120±20	<0.001*	123±20
Sinus rhythm, n (%), n=3981	2572 (64.6)	756 (68.5)	<0.01*	1816 (63.1)
HR, 1 per minute, n=3968	67±14	68±19	<0.01*	67±12
NT-proBNP, pg/mL, n=1419	898 (322–2203)	754 (263–1839)	0.001*	991 (356–2330)
Creatinine, µmol/L, n=3874	95 (80–118)	93 (79–117)	0.07	96 (81–119)
eGFR, mL/min per 1.73 m², n=3873	64 (49–81)	67 (51–85)	<0.001*	63 (49–79)
Sodium, mmol/L, n=3852	140±3	140±3	0.13	140±3
Potassium, mmol/L, n=3865	4.4±0.5	4.4±0.5	0.28	4.4±0.4
Hemoglobin, g/dL, n=2697	13.7±1.6	13.6±1.6	<0.01*	13.8±1.5
Comorbidities				
OPD, n (%), n=4016	508 (12.6)	161 (14.4)	0.04*	347 (12.0)
aHT, n (%), n=4016	1501 (37.4)	407 (36.4)	0.42	1094 (37.8)
Hyperlipidemia, n (%), n=4016	2373 (59.1)	600 (53.7)	<0.001*	1773 (61.2)
Smoker, n (%), n=4016	640 (15.9)	166 (14.8)	<0.001*	474 (16.4)
Stroke, n (%), n=4016	358 (8.9)	64 (5.7)	<0.001*	294 (10.1)
PVD, n (%), n=4016	319 (7.9)	90 (8.1)	0.88	229 (7.9)
Diabetes mellitus, n (%), n=4016	744 (18.5)	210 (18.8)	0.80	534 (18.4)
Treatment				
β-blocker dose equivalent, %, n=4016	53 (26–100)	75 (50–100)	0.54	53 (26–100)
β-blocker dose equivalent, n (%), n=4016				
<10%	35 (0.9)	9 (0.8)	<0.001*	26 (0.9)
10%–19%	290 (7.2)	70 (6.3)		220 (7.6)
20%–29%	770 (19.2)	146 (13.1)		624 (21.5)
30%–39%	129 (3.2)	32 (2.9)		97 (3.3)
40%–49%	1 (0.0)	1 (0.0)		0 (0.0)

50%–59%	1156 (28.8)	263 (23.5)		893 (30.8)
60%–69%	35 (0.9)	5 (0.4)		30 (1.0)
70%–79%	272 (6.8)	63 (5.6)		209 (7.2)
80%–89%	2 (0.0)	2 (0.2)		0 (0.0)
≥90%	1326 (33.0)	527 (47.1)		799 (27.6)
ACEi, n (%), n=4016	3252 (81.0)	892 (79.8)	0.21	2360 (81.4)
ACEi dose equivalent, %, n=3246	100 (50–100)	100 (50–100)	0.10	100 (50–100)
ARB, n (%), n=4011	903 (22.5)	293 (26.2)	<0.001*	610 (21.1)
ACEi or ARB, n (%), n=4016	4016 (100)	1118 (100)	1	2898 (100)
ACEi/ARB dose equivalent, %, n=4011	100 (50–100)	100 (50–100)	0.01*	100 (50–100)
Aldosterone antagonist, n (%), n=4016	1264 (31.5)	458 (41.0)	<0.001*	806 (27.8)
Loop diuretic, n (%), n=4016	3040 (75.7)	867 (77.5)	0.09	2173 (75.0)
Loop diuretic dose, mg furosemide, n=3026	40 (40–80)	40 (30–80)	<0.001*	40 (40–80)
Aspirin, n (%), n=4016	1826 (45.5)	416 (37.2)	<0.001*	1410 (48.7)
Statin, n (%), n=4016	1966 (49.0)	587 (52.5)	<0.01	1379 (47.6)
Heart Failure Registry, n=4016				
Norwegian, n (%)	3309 (82.4)	782 (69.9)	<0.001*	2527 (87.2)
Heidelberg, n (%)	707 (17.6)	337 (30.1)		370 (12.8)

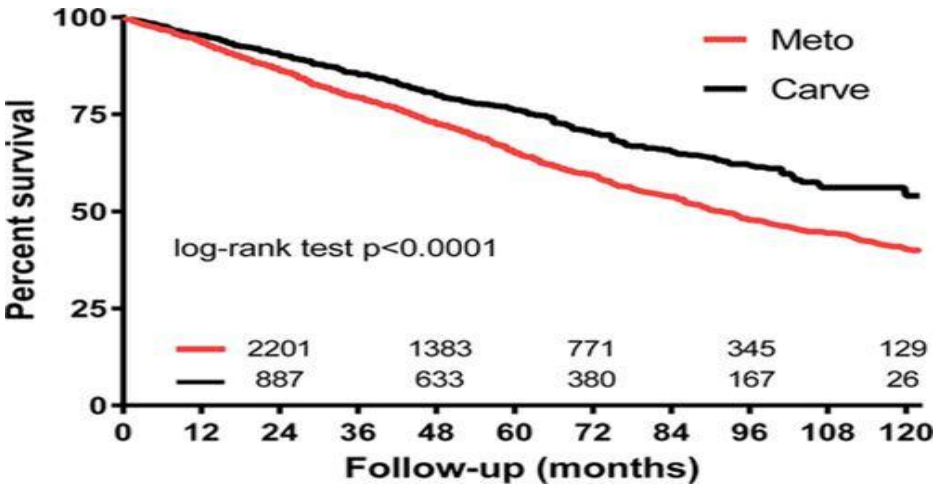
Values shown are mean±SD or median (interquartile range). Dose equivalent represents percentage achieved by the individual drug with respect to the guideline recommended target dose. As some patients were treated with both ACEis and ARBs, number of patients treated with ACEis and ARBs do not add up 100%. ACEi indicates angiotensin-converting enzyme inhibitor; aHT, arterial hypertension; ARB, angiotensin receptor antagonist; BMI, body mass index; BPsys, systolic blood pressure; CHD, coronary heart disease; CHF, chronic heart failure; dCMP, dilated cardiomyopathy; eGFR, estimated glomerular filtration rate calculated using the Modification of Diet in Renal Disease equation; HR, heart rate; LVEF, left ventricular ejection fraction; n, number; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; OPD, obstructive pulmonary disease; and PVD, peripheral vascular disease.

*P<0.05.

Total follow-up was 212 066 patient-months (17 672 patient-years) with a mean follow-up duration of 52.8±33.6 months. During that time, a total of 1370 patients (34.1%) died, 1066 (36.8%) in the metoprolol succinate group and 304 (27.2%) in the carvedilol group.

Prognostic Significance in the General Example

In a univariable analysis of the complete sample (n=4016), receipt of metoprolol succinate was associated with higher all-cause mortality compared with carvedilol (hazard ratio [HR], 1.49; 95% confidence interval [CI], 1.31–1.69; P<0.001; Figure 1). This result did not persist when controlling for the propensity of receiving the individual β-blocker and the β-blocker equivalent dose in a trivariable model using these variables (HR, 1.06; 95% CI, 0.94–1.20; P=0.36). This trivariable model included 3016 patients and 942 deaths during follow-up. Finally, the common multivariable model revealed no difference in survival (HR, 0.93; 95% CI, 0.57–1.50; P=0.75). The multivariable model included 638 patients. Of these, 153 patients died during follow-up.



- Download figure
- Download PowerPoint

Figure 1: Kaplan–Meier curves for 10-year survival for hospital outpatients with heart failure receiving carvedilol and metoprolol succinate.

Subgroups (General Sample)

Subgroup analyses in the general sample with respect to age, sex, cause of heart failure, LVEF, NYHA functional class, renal function, obstructive pulmonary disease, diabetes mellitus, heart rate, rhythm, blood pressure, and sinus rhythm plus LVEF ≤35% for both controlling strategies mainly confirmed nonsuperiority of either β-blocker. The few significant results were inconsistent between adjustment strategies. Although the trivariable (propensity score/β-blocker equivalent dose–adjusted) models found metoprolol succinate to be associated with higher all-cause mortality in younger patients, in nondiabetics, in patients with ischemic cause, in patients with a heart rate ≤75 per minute, in patients with sinus rhythm, and in those with sinus rhythm and LVEF ≤35%, these results could not be reproduced in the common multivariable model. For complete results, see **Table 2.**

Table 2. Cox Regression Analyses for All-Cause Mortality of the Complete Cohort About Receipt of Metoprolol Succinate (Versus Carvedilol) in the Respective Subgroups Listed, Separate for Adjustment Strategy

Subgroup		Trivariate (Propensity Score/equivalent dose Adjusted)			Multivariable Adjusted		
		HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age, y	>63.5	1.07	0.89–1.23	0.47	0.94	0.55–1.61	0.83
	≤63.5	1.47	1.03–2.09	0.04*	1.50	0.29–7.70	0.63
Sex	Male	1.20	0.99–1.44	0.06	0.97	0.56–1.70	0.93
	Female	1.09	0.79–1.48	0.61	0.17	0–366.77	0.65
Cause	Ischemic	1.26	1.02–1.55	0.03*	0.89	0.45–1.76	0.73
	Nonischemic	1.06	0.83–1.37	0.63	0.86	0.34–2.16	0.74
NYHA	III/IV	1.15	0.87–1.51	0.34	0.64	0.30–1.37	0.25
	I/II	1.09	0.89–1.32	0.40	1.98	0.87–4.50	0.10
LVEF, %	≤35	1.13	0.95–1.36	0.18	1.08	0.64–1.82	0.77
	>35	1.29	0.92–1.81	0.15	0.71	0.46–1.11	0.13
eGFR, mL/min per 1.73 m^2	≤60	1.05	0.85–1.29	0.66	0.79	0.40–1.56	0.49
	>60	1.27	0.99–1.64	0.07	0.80	0.34–1.93	0.62
OPD	Yes	1.25	0.79–1.98	0.35	1.61	0.93–2.79	0.09
	No	1.16	0.98–1.38	0.09	0.99	0.57–1.71	0.97
Diabetes mellitus	Yes	1.10	0.78–1.54	0.58	2.12	0.26–17.39	0.48
	No	1.20	1.01–1.44	<0.05*	0.77	0.44–1.37	0.38
Heart rate, per minute	>75	1.03	0.74–1.44	0.86	0.50	0.10–2.61	0.41
	≤75	1.20	1.01–1.45	<0.05*	0.99	0.56–1.73	0.96
Sinus rhythm	Yes	1.32	1.07–1.63	0.01*	1.01	0.57–1.81	0.97
	No	0.99	0.77–1.27	0.92	0.88	0.42–1.87	0.88
BPsys, mm Hg	>120	1.21	0.96–1.54	0.10	1.73	0.91–3.28	0.10
	≤120	1.16	0.93–1.44	0.20	0.83	0.50–1.41	0.50
Sinus rhythm and LVEF ≤35%		1.41	1.10–1.80	0.01*	1.58	0.84–2.97	0.16

The cut offs for age and systolic blood pressure were chosen as they represented the respective cohort median. BPsys indicates systolic blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; HR, hazard ratio; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association; and OPD, obstructive pulmonary disease.

*P <0.05.

Prognostic Significance in the Matched Sample

The propensity score was derived from 29 baseline variables in a subset of 3016 patients with complete data of these variables. The C-statistic of the propensity score was 0.69. The matching procedure identified 740 pairs of patients with equal probability of either carvedilol or metoprolol succinate therapy while receiving it at equivalent doses. The propensity score matching significantly reduced standardized differences <10% in the absolute values for most observed covariates, demonstrating an improvement in the covariate balance across the treatment grou**ps (Figure 2**). The distribution of β-blocker dose equivalents in the matched sample is depicted in **Table 3**.

Table 3. Distribution of β-Blocker Dose Equivalents in the Matched Sample				
β-Blocker Dose Equivalent	**All Patients (n=1480)**	**Carvedilol (n=740)**	***P* Value**	**Metoprolol Succinate (n=740)**
<10%	5 (0.3)	3 (0.4)		2 (0.3)
10% to 19%	87 (5.9)	45 (6.1)		42 (5.7)
20% to 29%	222 (15.0)	108 (14.6)		114 (15.4)
30% to 39%	37 (2.5)	20 (2.7)		17 (2.3)
40% to 49%	0 (0.0)	0 (0.0)	0.99	0 (0.0)
50% to 59%	369 (24.9)	184 (24.9)		185 (25.0)
60% to 69%	2 (0.1)	1 (0.1)		1 (0.1)
70% to 79%	91 (6.1)	46 (6.2)		45 (6.1)
80% to 89%	1 (0.0)	1 (0.1)		0 (0.0)
≥90%	666 (45.0)	332 (44.9)		334 (45.1)

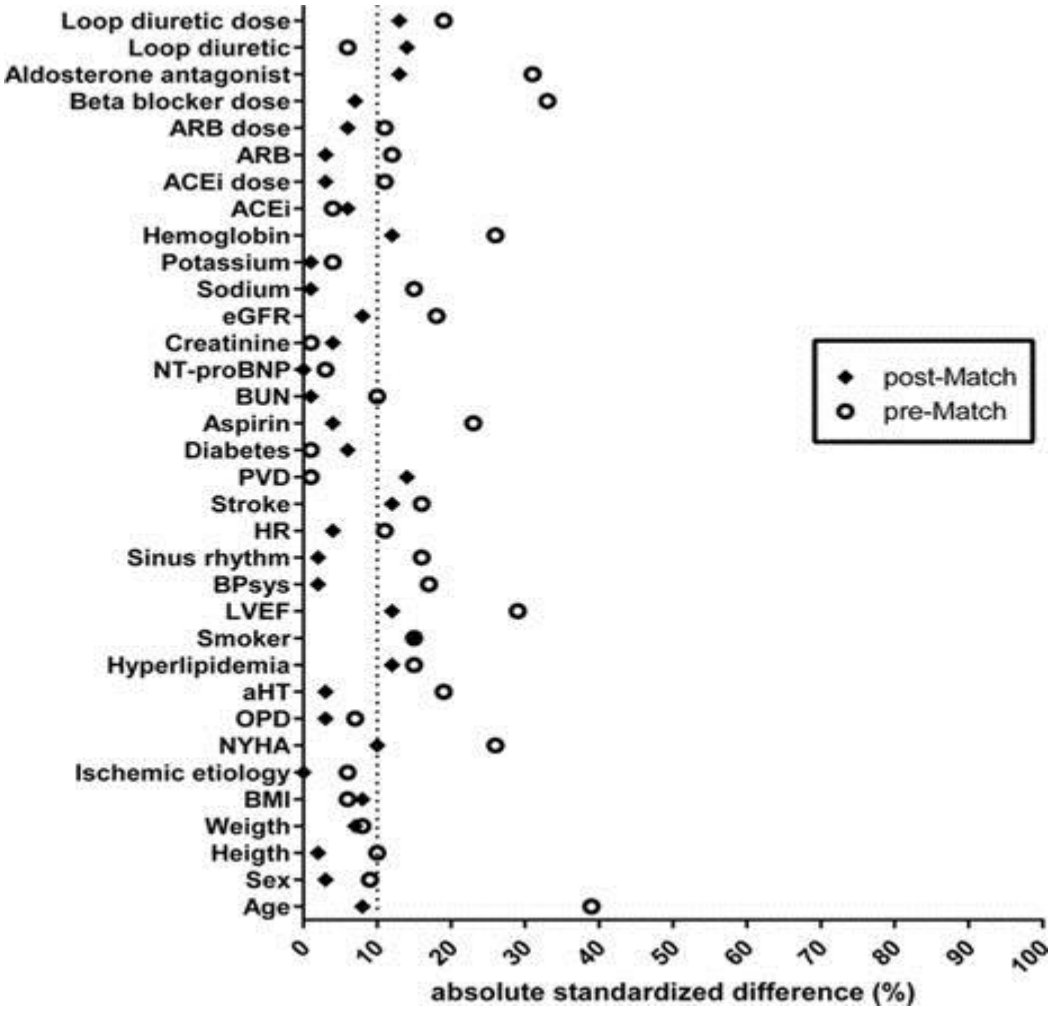


Figure 2: Absolute standardized differences before and after propensity score matching comparing covariate values for hospital outpatients with heart failure receiving carvedilol or metoprolol succinate. ACEi indicates angiotensin-converting enzyme; aHT, arterial hypertension; ARB, angiotensin receptor blocker; BMI, body mass index; BPsys, systolic blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; OPD, obstructive pulmonary disease; and PVD, peripheral vascular disease.

In the matched sample, 365 patients died during follow-up. No significant association between treatment with the 2 β-blockers and all-cause mortality was noted (HR, 1.00; 95% CI, 0.82–1.23; *P*=0.99). The Kaplan–Meier curve for survival is presented in Figure 3.

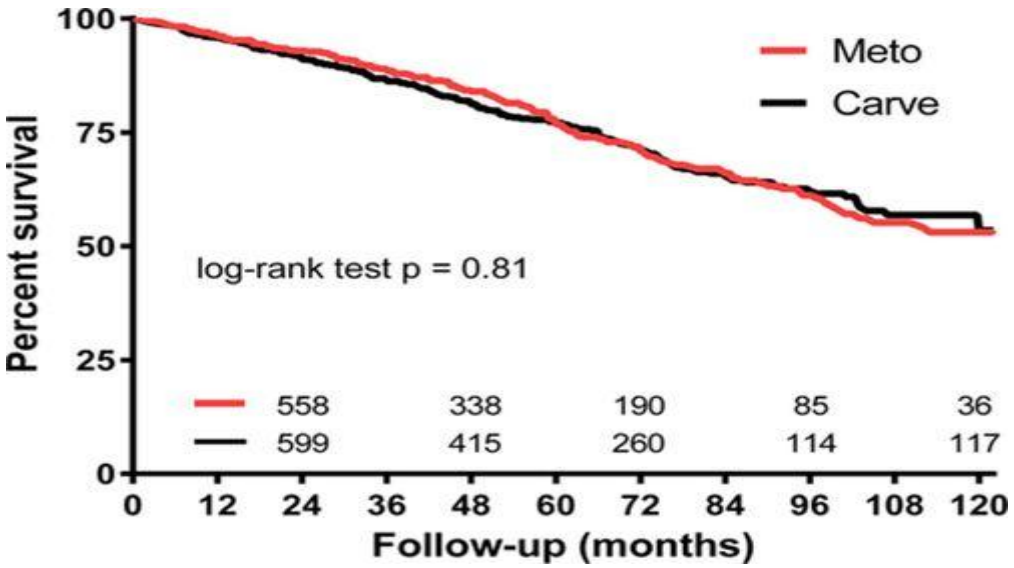


Figure 3: Kaplan–Meier curve for 10-year survival about all-cause mortality in the propensity and dose equivalent–matched cohort for hospital outpatients with heart failure receiving carvedilol and metoprolol succinate.

Subgroups (Matched Sample)

Survival in carvedilol-treated patients was similar to that of patients receiving metoprolol succinate in all prespecified subgroups in the matched sample. The respective interaction terms indicated absence of significant interaction between subgroups and individual β-blocker agents. The relevant plot is shown in Figure 4. In addition, the Kaplan–Meier survival curves for matched patients with sinus rhythm and LVEF ≤35% with respect to β-blocker treatment are shown in Figure I in the Data Supplement.

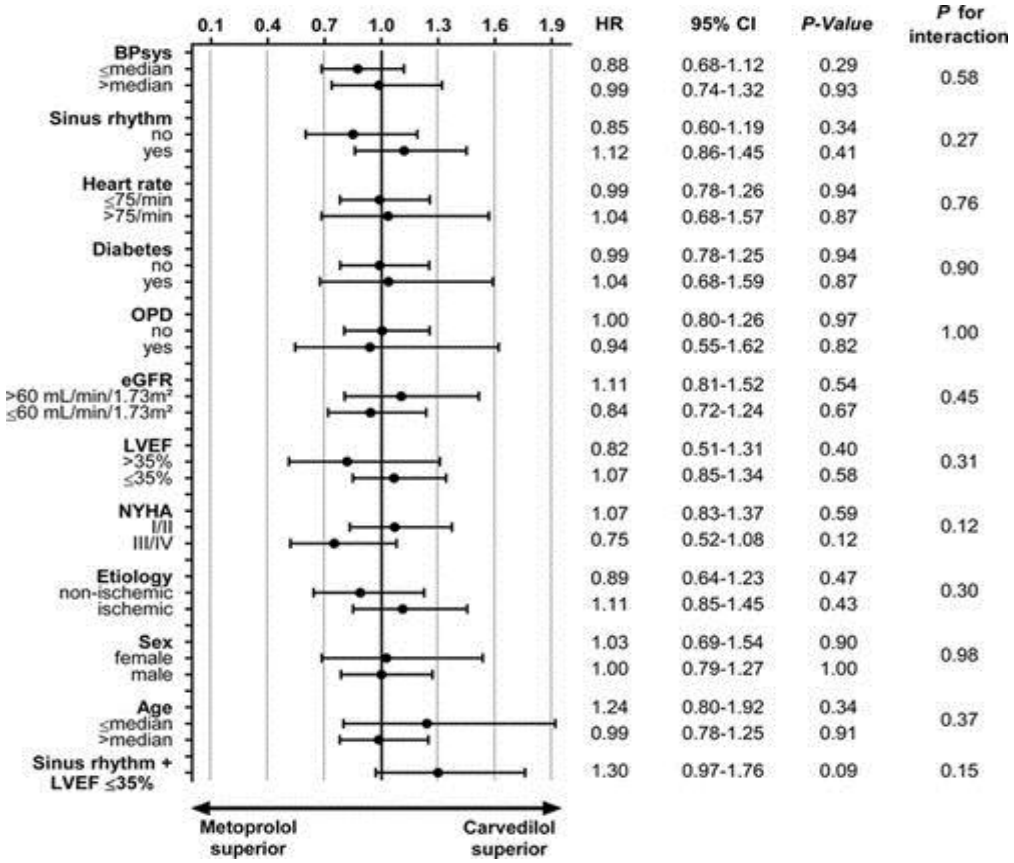


Figure 4: Cox regression analyses for all-cause mortality about the use of metoprolol succinate (compared with carvedilol) in the predefined subgroups for the propensity score-matched cohort.

BPsys indicates systolic blood pressure; eGFR, estimated glomerular filtration rate using the Modification of Diet in Renal Disease equation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; and OPD, obstructive pulmonary disease. Our results were supported by the formal sensitivity analysis. The Γ-value was 0.86, indicating only little residual bias (no residual bias at Γ=1.0). Inversely, this means that to attribute a possible survival benefit to an unobserved covariate rather than the receipt of carvedilol or metoprolol succinate, that unobserved covariate would only need to produce a 14% increase in the odds of receipt of a certain β-blocker while being a moderate-to-weak predictor of all-cause mortality. We identified N-terminal pro-brain natriuretic peptide, hemoglobin, and loop diuretic dose as variables with a significant amount of missing values **(Table 1**). The multivariable available case model, including N-terminal pro-brain natriuretic peptide, hemoglobin, and loop diuretic dose, comprised n=1239 patients. Its HR was 0.88 (95% CI, 0.–1.17; *P*=0.38). The multivariable available case model, excluding N-terminal pro-brain natriuretic peptide, hemoglobin, and loop diuretic dose, comprised n=3197 patients. Its HR was 1.06 (95% CI, 0.92–1.23; *P*=0.42). The multivariable analysis in the multiple imputed data set (n=100 repetitions) yielded an HR of 1.06 (95% CI, 0.94–1.21), which corresponds well to the multivariable available case model, excluding N-terminal pro-brain natriuretic peptide, hemoglobin, and loop diuretic dose.Following the study by Mitra et al[28] the calculation of the propensity score was repeated in each of the multiple imputed data sets (n=100), and the propensity score was averaged for each record across the completed data sets. We computed the C-statistic as 0.71 from the logistic regression model with the averaged linear predictor as predictor of caseness and obtained the identical result after averaging over the n=100 C-statistics, computed from each of the imputed samples. This result corroborates the suitability of using the averaged linear predictor in the full original sample for the matching procedure, as proposed by Mitra et al.**[28]**On the basis of the averaged propensity score of the multiple imputed data sets, the matching procedure identified 939 pairs of patients with equal probability of either carvedilol or metoprolol succinate therapy while receiving it at equivalent doses. Of these, 530 patients died during follow-up. Again, no significant association between β-blocker treatment and mortality was observed in the matched sample (HR, 1.05; 95% CI, 0.89–1.25; *P*=0.55).

DISCUSSION

Our results contrast to the findings of COMET, which is the only sufficiently powered prospective clinical trial ever to compare the efficacy of 2 β-blockers in patients with CHF. COMET, in return, was criticized both for its nonequivalent formulation and the inconsistent dosing. As with COMET, more patients on carvedilol in our general cohort received target doses when compared with patients on metoprolol. In this constellation, use of carvedilol was associated with a significant survival benefit, thus reproducing the main result of COMET. This prognostic difference, however, was no longer significant when applying the controlling strategies to the respective Cox models. After matching for both the propensity score and the dose equivalent, the prognostic difference between carvedilol and metoprolol succinate treatment completely disappeared. It is here that our study significantly adds to the current understanding of guideline-appropriate β-blocker therapy. In real life, target dose may be achieved more frequently when using carvedilol rather than metoprolol, resulting in an indirect survival benefit for patients receiving carvedilol over those receiving metoprolol. An intrinsic prognostic difference between carvedilol and metoprolol succinate, however, seems not to exist when used at equivalent doses.Our results confirm the notion of an equal prognostic benefit from carvedilol and the succinate formulation of metoprolol, which[3031] is the latter reported data from the Danish Heart Failure Registry. Our study extends their findings both in terms of a significantly longer follow-up duration and the fact that we separately accounted for one of the main criticisms of COMET by introducing dose equivalents into our matching strategy. Furthermore, we could not confirm a dependence of the prognostic benefit derived from either β-blocker on the cause of CHF as noted in a retrospective analysis by Shore et al. Besides the succinate formulation, metoprolol tartrate has also been compared with carvedilol in small prospective trials and retrospective analyses of heart failure databases[31-35] The collective findings, however, remained inconclusive[36.37] In addition, it has been questioned whether metoprolol tartrate is comparable with metoprolol succinate in the treatment of patients with CHF because data on the comparative effects of the 2 formulations are scarce and again inconclusive[31,37,38] An ongoing meta-analysis on this issue has not yet been published.**[40]** It seems conceivable, however, that differences in the therapeutic efficiency between carvedilol and metoprolol succinate may exist in certain subgroups of patients. For instance, it has been postulated that carvedilol might induce favorable changes on glycemic control and lipid profiles[41-44] In a post hoc analysis of COMET, however, both diabetic and nondiabetic subjects had a similar reduction in mortality with carvedilol when compared with metoprolol tartrate[40] Also, it was hypothesized that the α-adrenergic properties of carvedilol may offset its nonselective β-blockade–induced bronchoconstriction[45] This, however, was not confirmed by others[46] Furthermore, there is conflicting evidence as to the prognostic benefit of β-blockers in patients with CHF and atrial fibrillation. On the one hand, 2 recently published meta-analyses of placebo-controlled randomized β-blocker trials found a lack of efficacy of β-blocker treatment in this patient sample[47,48] On the other hand, a retrospective analysis of the US Carvedilol Heart Failure Trial demonstrated that carvedilol improves outcomes in CHF patients with atrial fibrillation. Then again, a retrospective analysis of the

MERIT-HF study did not detect an effect of treatment with metoprolol succinate on mortality in the subset of CHF patients with atrial fibrillation[48] Finally, it has been reported that carvedilol may be preferable to metoprolol tartrate to prevent the development of renal failure in patients with CHF[49] These studies, however, included few patients, and in some studies follow-up was short. In contrast, we could not demonstrate any inconsistencies in our main result in any of our predefined subgroups in our large cohort with a substantially longer follow-up.

CONCLUSIONS

In this retrospective study comparing carvedilol and metoprolol succinate therapy of outpatients with CHF from 2 European HF databases, patients treated with carvedilol were younger and more likely to receive target doses, which entailed improved survival. However, after either multivariable adjustment or matching for propensity and dose equivalence, there was no significant benefit of carvedilol compared with metoprolol succinate for survival.

Funding-None.
Conflict of Interest-None.
Ethical Clearance-Taken from EthicalCommittee of Institute.

REFERENCES

1. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol, 1995; *25*: 1225–1231. doi:10.1016/0735-1097(95)00012-S.
2. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U. S. Carvedilol Heart Failure Study Group. N Engl J Med, 1996; *334*: 1349–1355.
3. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med, 2001; *344*: 1651–1658. doi:10.1056/NEJM200105313442201.
4. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, Gottlieb SS, Pearle D, Cody RJ, Gregory JJ, Kantrowitz NE, LeJemtel TH, Young ST, Lukas MA, Shusterman NH. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation, 1996; *94*: 2793–2799.
5. Australia-New Zealand Heart Failure Research Collaborative Group. Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Circulation, 1995; *92*: 212–218
6. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. Circulation, 1996; *94*: 2807–2816.
7. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. Lancet, 2001; *357*: 1385–1390.
8. Joglar JA, Acusta AP, Shusterman NH, Ramaswamy K, Kowal RC, Barbera SJ, Hamdan MH, Page RL. Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: retrospective analysis of the US Carvedilol Heart Failure Trials Program. Am Heart J, 2001; *142*: 498–501. doi:10.1067/mhj. 2001. 117318.
9. Kowey PR. A review of carvedilol arrhythmia data in clinical trials. J Cardiovasc Pharmacol Ther, 2005; *10*(suppl 1): S59–S68.
10. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). MERIT-HF Study Group. JAMA, 2000; *283*: 1295–1302.
11. Brophy JM, Joseph L, Rouleau JL. Beta-blockers in congestive heart failure. A Bayesian meta-analysis. Ann Intern Med, 2001; *134*: 550–560.
12. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, Katz SD, Klapholz M, Moser DK, Rogers JG, Starling RC, Stevenson WG, Tang WH, Teerlink JR, Walsh MN; Heart Failure Society of America. HFSA 2010 comprehensive heart failure practice guideline. J Card Fail, 2010; *16*: e1–194. doi:10.1016/j. cardfail. 2010. 04. 004.
13. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation.

Circulation, 2009; *119*: e391–e479. doi:10.1161/CIRCULATIONAHA.109.192065
14. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J, 2012; *33*: 1787–1847.
15. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. Circulation, 1998; *98*: 1184–1191.
16. Ruffolo RR, Gellai M, Hieble JP, Willette RN, Nichols AJ. The pharmacology of carvedilol. Eur J Clin Pharmacol, 1990; *38*(suppl 2): S82–S88.
17. Tangeman HJ, Patterson JH. Extended-release metoprolol succinate in chronic heart failure. Ann Pharmacother, 2003; *37*: 701–710.
18. Galatius S, Gustafsson F, Atar D, Hildebrandt PR. Tolerability of beta-blocker initiation and titration with bisoprolol and carvedilol in congestive heart failure – a randomized comparison. Cardiology, 2004; *102*: 160–165. doi:10.1159/000080485.
19. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet, 2003; *362*: 7–13. doi:10.1016/S0140-6736(03)13800-7.
20. Torp-Pedersen C, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lutiger B, Metra M, Remme WJ, Scherhag A, Skene A; COMET Investigators. Effects of metoprolol and carvedilol on cause-specific mortality and morbidity in patients with chronic heart failure–COMET. Am Heart J, 2005; *149*: 370–376.
21. Wikstrand J, Wedel H, Castagno D, McMurray JJ. The large-scale placebo-controlled beta-blocker studies in systolic heart failure revisited: results from CIBIS-II, COPERNICUS and SENIORS-SHF compared with stratified subsets from MERIT-HF. J Intern Med, 2014; *275*: 134–143. doi:10.1111/joim. 12141.
22. Rubin DB. On principles for modeling propensity scores in medical research. Pharmacoepidemiol Drug Saf, 2004; *13*: 855–857. doi:10.1002/pds. 968.
23. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J, 2009; *51*: 171–184. doi:10.1002/bimj. 200810488.
24. Ahmed A, Zannad F, Love TE, Tallaj J, Gheorghiade M, Ekundayo OJ, Pitt B. A propensity-matched study of the association of low serum potassium levels and mortality in chronic heart failure. Eur Heart J, 2007; *28*:1334–1343. doi:10.1093/eurheartj/ehm091.
25. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ. Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol, 2001; *54*: 387–398.
26. Rosenbaum PR. Observational Studies. 2 ed. Heidelberg, Berlin: Springer, 2002; 39(5): 165-170.
27. Love TE. Spreadsheet-based sensitivity analysis calculations for match samples.
28. MitraR, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. Stat Methods Med Res, 2012. 10. 1177/0962280212445945.
29. Pasternak B, Svanström H, Melbye M, Hviid A. Association of treatment with carvedilol vs metoprolol succinate and mortality in patients with heart failure. JAMA Intern Med, 2014; *174*: 1597–1604.
30. Shore S, Aggarwal V, Zolty R. Carvedilol or sustained-release metoprolol for congestive heart failure: a comparative effectiveness analysis. J Card Fail, 2012; *18*:919–924. doi:10. 1016/j. cardfail. 2012. 10. 016
31. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: a prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation. 2000; *102*:546–551.
32. Delea TE, Stanford R, Hagiwara M, Edelsberg JS, Oster G. Death and hospitalization in heart failure patients receiving carvedilol vs. metoprolol tartrate. Int J Cardiol, 2005; *99*: 117–124. doi:10.1016/j. ijcard. 2004. 05. 029.
33. Go AS, Yang J, Gurwitz JH, Hsu J, Lane K, Platt R. Comparative effectiveness of beta-adrenergic antagonists (atenolol, metoprolol tartrate, carvedilol) on the risk of rehospitalization in adults with heart failure. Am J Cardiol. 2007; *100*:690–696. doi:10.1016/j. amjcard, 2007. 03. 084.
34. Mrdovic IB, Savic LZ, Perunicic JP, Asanin MR, Lasica RM, Jelena MM, Matic MD, Vasiljevic ZM, Ostojic MC. Randomized active-controlled study comparing effects of treatment with carvedilol versus metoprolol in patients with left ventricular dysfunction after acute myocardial infarction. Am Heart J, 2007; *154*:116–122. doi:10.1016/j. ahj. 2007. 03. 049.

35. Lazarus DL, Jackevicius CA, Behlouli H, Johansen H, Pilote L. Population-based analysis of class effect of β blockers in heart failure. Am J Cardiol, 2011; *107*:1196–1202. doi:10.1016/j. amjcard. 2010. 12. 017.
36. DiNicolantonio JJ, Lavie CJ, Fares H, Menezes AR, O'Keefe JH. Meta-analysis of carvedilol versus beta 1 selective beta-blockers (atenolol, bisoprolol, metoprolol, and nebivolol). Am J Cardiol, 2013; *111*: 765–769. doi:10.1016/j. amjcard. 2012. 11. 031.
37. Chatterjee S, Biondi-Zoccai G, Abbate A, D'Ascenzo F, Castagno D, Van Tassell B, Mukherjee D, Lichstein E. Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ, 2013; *346*:f55.
38. Kukin ML, Mannino MM, Freudenberger RS, Kalman J, Buchholz-Varley C, Ocampo O. Hemodynamic comparison of twice daily metoprolol tartrate with once daily metoprolol succinate in congestive heart failure. J Am Coll Cardiol, 2000; *35*: 45–50.
39. Aquilante CL, Terra SG, Schofield RS, Pauly DF, Hatton PS, Binkley PF, Johnson JA. Sustained restoration of autonomic balance with long- but not short-acting metoprolol in patients with heart failure. J Card Fail, 2006; *12*: 171–176. doi:10.1016/j. cardfail. 2005. 12. 002.
40. Kotecha D, Manzano L, Altman DG, Krum H, Erdem G, Williams N, Flather MD; Beta-Blockers in Heart Failure Collaborative Group. Individual patient data meta-analysis of beta-blockers in heart failure: rationale and design. Syst Rev, 2013; *2*: 7. doi:10.1186/2046-4053-2-7.
41. Bell DS, Bakris GL, McGill JB. Comparison of carvedilol and metoprolol on serum lipid concentration in diabetic hypertensive patients. Diabetes Obes Metab, 2009; *11*: 234–238.
42. Phillips RA, Fonseca V, Katholi RE, McGill JB, Messerli FH, Bell DS, Raskin P, Wright JT, Iyengar M, Anderson KM, Lukas MA, Bakris GL; GEMINI Investigators. Demographic analyses of the effects of carvedilol vs metoprolol on glycemic control and insulin sensitivity in patients with type 2 diabetes and hypertension in the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) study. J Cardiometab Syndr, 2008; *3*: 211–217. doi:10.1111/j. 1559-4572. 2008. 00017.
43. Torp-Pedersen C, Metra M, Charlesworth A, Spark P, Lukas MA, Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Remme WJ, Scherhag A; COMET investigators. Effects of metoprolol and carvedilol on pre-existing and new onset diabetes in patients with chronic heart failure: data from the Carvedilol Or Metoprolol European Trial (COMET). Heart, 2007; *93*: 968–973. doi:10.1136/hrt. 2006. 092379.
44. Fonarow GC, Deedwania P, Fonseca V, Nesto RW, Watson K, Tarka E, Lukas MA, Madan A, Shabbout M. Differential effects of extended-release carvedilol and extended-release metoprolol on lipid profiles in patients with hypertension: results of the Extended-Release Carvedilol Lipid Trial. J Am Soc Hypertens, 2009; *3*: 210–220. doi:10.1016/j. jash. 2009. 01. 004.
45. Sirak TE, Jelic S, Le Jemtel TH. Therapeutic update: non-selective beta- and alpha-adrenergic blockade in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol, 2004; *44*: 497–502.
46. Jabbour A, Macdonald PS, Keogh AM, Kotlyar E, Mellemkjaer S, Coleman CF, Elsik M, Krum H, Hayward CS. Differences between beta-blockers in patients with chronic heart failure and chronic obstructive pulmonary disease: a randomized crossover trial. J Am Coll Cardiol, 2010; *55*: 1780–1787.
47. Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, Lip GY, Coats AJ, Andersson B, Kirchhof P, von Lueder TG, Wedel H, Rosano G, Shibata MC, Rigby A, Flather MD; Beta-Blockers in Heart Failure Collaborative Group. Efficacy of β blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. Lancet, 2014; *384*: 2235–2243. doi:10.1016/S0140-6736(14)61373-8.
48. Rienstra M, Damman K, Mulder BA, Van Gelder IC, McMurray JJ, Van Veldhuisen DJ. Beta-blockers and outcome in heart failure and atrial fibrillation: a meta-analysis. JACC Heart Fail, 2013; *1*: 21–28. doi:10.1016/j. jchf. 2012. 09. 002.
49. Van Veldhuisen DJ, Aass H, El Allaf D, Dunselman PH, Gullestad L, Halinen M, Kjekshus J, Ohlsson L, Wedel H, Wikstrand J; MERIT-HF Study Group. Presence and development of atrial fibrillation in chronic heart failure. Experiences from the MERIT-HF Study. Eur J Heart Fail, 2006; *8*: 539–546.