Comparison of Metoprolol Versus Carvedilol After Acute Myocardial Infarction

Ghaith Zaatari, MD[a], Dan J. Fintel, MD[b], Haris Subacius, MA[c], Joseph J Germano, DO[d], Jacob Shani, MD[e], and Jeffrey J. Goldberger, MD, MBA[a,*], on behalf of the Outcomes of Beta-blocker Therapy After myocardial INfarction (OBTAIN) Investigators

Beta-blockers are typically prescribed following myocardial infarction (MI), but no specific beta-blocker is recommended. Of 7,057 patients enrolled in the OBTAIN multi-center registry of patients with acute MI, 4142 were discharged on metoprolol and 1487 on carvedilol. Beta-blocker dose was indexed to the target daily dose used in randomized clinical trials (metoprolol-200 mg; carvedilol-50 mg), reported as %. Beta-blocker dosage groups were >0% to12.5% (n = 1,428), >12.5% to 25% (n = 2113), >25% to 50% (n = 1,392), and >50% (n = 696). The Kaplan-Meier method was used to calculate 3-year survival. Correction for baseline differences was achieved by multivariable adjustment. Patients treated with carvedilol were older (64.4 vs 63.3 years) and had more comorbidities: hypertension, diabetes, prior MI, congestive heart failure, reduced left ventricular ejection fraction, and a longer length of stay. Mean doses for metoprolol and carvedilol did not significantly differ (37.2 ± 27.8% and 35.8 ± 31.0%, respectively). The 3-year survival estimates were 88.2% and 83.5% for metoprolol and carvedilol, respectively, with an unadjusted HR = 0.72 (p <0.0001), but after multivariable adjustment HR = 1.073 (p = 0.43). Patients in the >12.5% to 25% dose category had improved survival compared with other dose categories. Subgroup analysis of patients with left ventricular ejection fraction ≤40%, showed worse survival with metoprolol versus carvedilol (adjusted HR = 1.281; 95% CI: 1.024 to 1.602, p = 0.03). In patients with left ventricular ejection fraction >40%, there were no differences in survival with carvedilol versus metoprolol. In conclusion, overall survival after acute MI was similar for patients treated with metoprolol or carvedilol, but may be superior for carvedilol in patients with left ventricular ejection fraction ≤40%.
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Beta-blocker therapy after myocardial infarction (MI) improves survival and is a cornerstone of after-MI management. Multiple randomized clinical trials and observational studies supported the use of beta-blocker therapy after-MI, leading to the recommendation of beta-blocker therapy for the majority of patients following acute non-ST elevation MI and ST-elevation MI without any contraindication. The most prescribed beta-blocker after-MI varies from region to region, but the 2 most prescribed are metoprolol and carvedilol.[1-6] In the OBTAIN (Outcomes of Beta-blocker Therapy After myocardial INfarction) registry,[5] metoprolol and carvedilol were the 2 most common beta-blocker prescribed, accounting for 93% of all beta-blockers. Metoprolol is a primarily 1-adrenergic receptor blocker, while carvedilol is a 1-, 2-, and α1- adrenergic receptor blocker which also has pleiotropic anti-oxidant and vasodilatory effects.[7-9] Both metoprolol[10,11] and carvedilol[12] have been reported to improve survival after-MI but little information is available comparing the relative benefits of these agents following acute myocardial infarction.[8,13] This report from the OBTAIN registry study[5] compares the effect of carvedilol and metoprolol on survival following acute MI.

METHODS

This is a sub-study from the OBTAIN registry. Full details are provided in the original report.[5] There were 25 United States sites and 1 Canadian site which enrolled a total of 7,057 patients with acute MI. Only patients discharged on metoprolol or carvedilol were included in this report. The study was approved by each site's Institutional Review Board with a waiver of consent for registry enrollment. Participating centers and study committees and personnel are listed in the original report.[5]

Acute MI was diagnosed by: (1) either creatine kinase elevation >2 times or troponin elevation >3 times the upper limit of normal established at each site and (2) chest pain (or equivalent symptoms suggestive of MI) or electrocardiographic changes consistent with MI. Important

[a]University of Miami Miller School of Medicine, Department of Medicine, Cardiovascular Division, Miami, Florida; [b]Feinberg School of Medicine, Northwestern University, Department of Medicine, Division of Cardiology, Chicago, Illinois; [c]Division of Research and Optimal Patient Care, American College of Surgeons, Chicago, Illinois; [d]Long Island School of Medicine, New York University, Department of Medicine, Division of Cardiology, New York, New York; and [e]Maimonides Medical Center, Department of Cardiology, Brooklyn, New York. Manuscript received November 25, 2020; revised manuscript received and accepted February 2, 2021.

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*Corresponding author: Tel: (305) 243-8092; fax: (305) 243-1731.

E-mail address: j-goldberger@miami.edu (J.J. Goldberger).

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information concerning type of MI, complications of MI, hospitalization course, reperfusion therapy, length of stay, and discharge medications were recorded in the registry in addition to basic demographics and past medical history. All data were collected at the sites, and de-identified patient information was entered into a web-based electronic data capture system.

The managing physician chose the type and dose of beta-blockers. Beta-blocker dose was indexed (administered/target dose) to the target dose used in the randomized clinical trials that established efficacy, metoprolol 200mg/day[10,11] and carvedilol 50mg/day (carvedilol controlled-release equivalent dose-80 mg/day).[12] Beta-blocker dose was classified into 4 pre-specified groups: >0% to 12.5%, >12.5% to 25%, >25% to 50%, and >50% of the target dose.

The pre-specified end point for this study was time to all-cause mortality with survival censored at 3 years. Follow-up vital status was assessed by either chart review, the Social Security Administration Death Master File, or direct communication with the patient/family, as previously reported(5).

Differences in patient characteristics were compared using t-test or non-parametric Wilcoxon test for continuous variables or chi-square tests for categorical variables. The Kaplan-Meier method was used to calculate 3-year survival for the 2 beta-blocker groups and construct survival curves. Proportional hazards frailty regression with patients nested by hospital was used to calculate hazard ratios and confidence intervals, test for the independent effects on survival, and to test interactions with metoprolol versus carvedilol. Cox proportional hazards regression was used to test for the independent effects of beta-blocker dosing on survival. We also performed an interaction test for the difference in metoprolol and carvedilol effects on survival in patients with left ventricular ejection fraction ≤40% and >40%. Adjustment for baseline differences among groups was achieved by multivariable adjustment with the variables listed in Table 1. All tests were 2-tailed and a conventional 5% significance level was used.

RESULTS

The OBTAIN registry included a total of 7,057 patients. In-hospital mortality was 4.7%, and 6,682 were discharged alive. The majority of patients were discharged on beta-blockers 6,115 (92%), of which 5,629 (92%) included either metoprolol (n = 4,142) or carvedilol (n = 1,487). Only 486 patients (7.3%) were prescribed beta-blockers other than metoprolol or carvedilol, while 567 patients (8.5%) were discharged without any beta-blocker. Beta-blocker was initiated within the first 24 hours in 4,538 (80%) of 5,629 patients discharged on metoprolol or carvedilol (metoprolol: 3363 (81%); carvedilol: 1175 (79%)).

Table 1 displays the baseline characteristics of the predominantly male (69%) 5,629 patients discharged alive on either metoprolol or carvedilol. Patients treated with carvedilol were older than those treated with metoprolol. Patients treated with carvedilol had more comorbidities than those treated with metoprolol: hypertension, diabetes mellitus, implantable cardioverter-defibrillator, coronary artery bypass surgery, history of prior MI, history of congestive heart failure, lower mean left ventricular ejection fraction, admission for ST-elevation MI, higher troponin levels, higher resting heart rate, and a longer length of stay. On the other hand, patients in the metoprolol group had a higher percentage of non-ST elevation MI. Moreover, a higher percentage of patients in the metoprolol group were discharged on aspirin, statins, clopidogrel, and dual antiplatelet therapy.

The Kaplan-Meier survival curves are shown in Figure 1. The 3-year survival estimates were 88.2% and 83.5% for metoprolol versus carvedilol, respectively, with an unadjusted HR = 0.72 (CI: 0.613 to 0.846, p <0.0001). However, this difference was no longer significant after multivariate adjustment: HR=1.073 (CI: 0.902 to 1.275, p = 0.43).

The dosage distributions for metoprolol and carvedilol are shown in Figure 2. Mean doses did not significantly differ (37.2 ± 27.8% and 35.8 ± 31.0%, respectively, p = 0.128). Survival curves stratified by dose are shown in Figure 3. In the metoprolol group, patients in the >12.5% to 25% dose category had superior survival compared with all other dose categories, while patients on >50% of target dose had the lowest survival. Similar results were observed for carvedilol. These results are consistent with what was reported in the OBTAIN study.[5]

We further stratified the population according to left ventricular ejection fraction ≤40% or >40%. In patients with left ventricular ejection fraction ≤40%, the distribution of doses by drug type was similar to that of the full sample, with patients on carvedilol receiving somewhat lower doses of the drug (p <0.0001; Figure 2). Mean carvedilol dose was lower (33.4±29.4%) than metoprolol dose (36.9 ± 27.6%, p <0.01). In patients with left ventricular ejection fraction >40%, mean carvedilol and metoprolol dose did not differ (38.4 ± 32.7% and 37.0 ± 27.7%, respectively). The interaction test for the difference between metoprolol and carvedilol effects in the left ventricular ejection fraction ≤40% and >40% subgroups was borderline significant, p = 0.056. After multivariate adjustment, the interaction between beta-blocker type and left ventricular ejection fraction ≤40% was significant, p = 0.021. Among patients with low left ventricular ejection fraction, those treated with metoprolol had worse survival compared with those treated with carvedilol (Table 2); unadjusted HR was 1.051 (CI: 0.847 to 1.303, p = 0.65). After multivariable adjustment, the difference was significant with HR = 1.281 (CI: 1.024 to 1.602, p = 0.03). After multivariable adjustment, the effect of beta-blocker type in patients with left ventricular ejection fraction >40% was not significant; HR=0.850 (CI: 0.653 to 1.106, p = 0.23).

DISCUSSION

In this post hoc analysis of the OBTAIN study, we evaluated the effect of carvedilol versus metoprolol on survival following acute MI. Overall, both drugs individually demonstrated the same pattern of dose-response as was noted in the whole cohort, suggesting that the OBTAIN results are not specifically related to the most commonly prescribed beta-blocker in that study, metoprolol. There was no detectable difference in effect between the 2 beta-blockers. However, in subgroup analysis, patients with depressed left

Table 1
Patient characteristics by discharge metoprolol versus carvedilol

Variable	Beta-Blocker at Discharge		p-value
	Carvedilol (n= 1,487)	Metoprolol (n=4,142)	
Age (years)	64.4±13.5	63.3±13.5	0.004
Men	981 (66%)	2889 (70%)	0.007
White	1125 (76%)	3313 (80%)	0.0005
Black	187 (13%)	434 (11%)	0.03
Asian	32 (2.2%)	104 (2.5%)	0.44
Indian	11 (0.7%)	13 (0.3%)	0.03
Pacific	5 (0.3%)	7 (0.2%)	0.32
Unknown	130 (8.7%)	274 (6.6%)	0.006
Mixed	3 (0.2%)	3 (0.1%)	0.19
Hispanic	157 (11%)	259 (6.7%)	<0.0001
Body mass index (kg/m^2)	29.±6.6	29.2±6.5	0.72
Diabetes mellitus	94 (40%)	1233 (30%)	<0.0001
Hypertension	1058 (71%)	2753 (67%)	0.0007
Hyperlipidemia	798 (54%)	2248 (54%)	0.72
Previous myocardial infarction	343 (23%)	818 (20%)	0.006
Congestive heart failure history	274 (19%)	317 (7.7%)	<0.0001
Chronic obstructive pulmonary disease	171 (12%)	392 (10%)	0.02
Coronary artery bypass graft surgery	259 (18%)	474 (11%)	<0.0001
End stage renal disease	61 (4.1%)	126 (3.0%)	0.05
Cerebrovascular accident/Transient ischemic attack	171 (12%)	413 (10%)	0.01
Current smoker	450 (31%)	1406 (34%)	0.008
Implanted cardioverter-defibrillator*	112 (7.5%)	88 (2.1%)	<0.0001
Myocardial infarction characteristics			
ST-segment elevation myocardial infarction	715 (48%)	1792 (43%)	0.001
Non-ST segment elevation myocardial infarction	770 (52%)	2349 (57%)	0.001
Anterior	332 (46%)	515 (29%)	<0.0001
Inferior/Posterior	278 (39%)	985 (55%)	<0.0001
Thrombolytic therapy	98 (6.6%)	315 (7.6%)	0.2
Primary percutaneous coronary intervention	919 (62%)	2485 (60%)	0.21
In-hospital revascularization (nonprimary percutaneous coronary intervention and coronary artery bypass graft surgery)	351 (24%)	1082 (26%)	0.06
Diagnostic angiography	150 (10%)	415 (10%)	0.94
Admission resting systolic blood pressure (mmHg)	139.6±30.1	141.4±29.5	0.04
Admission heart rate (beats/min)	85.9±22.1	82.3±20.9	<0.0001
Left ventricular ejection fraction (%)	39.9±13.7	48.7±11.7	<0.0001
Troponin (ng/ml)	11.7 (3-42.5)	6.9 (1.9-25.6)	<0.0001
Length of stay (days)	6 (4-9)	5 (3-7)	<0.0001
Discharge Medication			
Beta-blocker dose(%)	35.8±31.0	37.2±27.8	0.128
Aspirin	1367 (92%)	3890 (94%)	0.008
Angiotensin converting enzyme inhibitor /Angiotensin receptor blocker	1009 (68%)	2804 (68%)	0.91
Statin	1214 (82%)	3716 (90%)	<0.0001
Clopidogrel	1014 (68%)	3053 (74%)	<0.0001
Dual antiplatelet	956 (64%)	2935 (71%)	<0.0001
Mortality			
1 year (Kaplan-Meier %)	141 (9.5%)	293 (7.1%)	0.003
2 years (Kaplan-Meier %)	219 (15%)	435 (11%)	<0.0001
3 years (Kaplan-Meier %)	245 (17%)	489 (12%)	<0.0001

Values are mean ± SD, n (%), or median (interquartile range).
* Includes patients with pre-admission implanted cardioverter-defibrillator and those discharged with an implanted cardioverter-defibrillator.

ventricular ejection fraction demonstrated superior survival with carvedilol. Further randomized clinical trials are warranted to evaluate whether carvedilol is superior in patients with left ventricular ejection fraction ≤40% following acute MI.

Despite their widespread use for patients following acute MI, there are inconsistent data on the benefits of these agents. Furthermore, there are no data to suggest that one agent is preferred to the other. In theory, the additional properties attributable to carvedilol, a 1, 2, and α1-adrenergic receptor blocker which also has pleiotropic anti-oxidant and vasodilatory effects[7-9], may provide some benefit. Carvedilol strongly binds -receptors with slower dissociation rate in contrast to metoprolol which has fast offset kinetics.[14] The contemporary PLATE-BLOCK trial[15] showed significantly lower platelet aggregation induced by

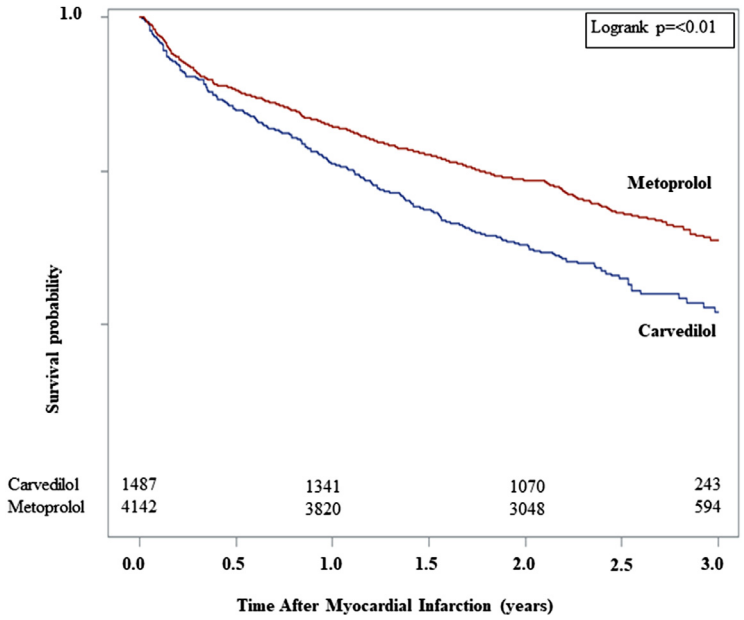

Figure 1. Three-year survival by metoprolol and carvedilol after MI: unadjusted Kaplan- Meier Survival curve.

epinephrine in the carvedilol group than in the metoprolol group at 30 days after-acute coronary syndrome. Additionally, carvedilol's vasodilatory effect may provide potential advantage over metoprolol by simultaneous blocking α1-adrenergic receptors and 1-receptors reducing blood pressure without changing cardiac output.[16] The question remains whether these presumed advantages would translate clinically into improved survival after-MI.

Contemporary guidelines for ST-elevation MI and non-ST elevation MI recommend routine treatment with oral beta-blockers after-MI in all patients without contraindications, but do not advocate for a particular beta-blocker. The evidence supporting beta-blocker benefit has been mostly obtained from randomized clinical trials that were placebo controlled and pre-dated reperfusion therapy.[11,17-20] While the Goteborg trial[11] showed a significant 36% reduction in mortality with metoprolol compared with placebo (at 3 month and 1 year), the MIAMI trial,[10] COMMIT trial,[21] LIT[22] and the Stockholm metoprolol trial[23] did not show significant reduction in all-cause mortality with metoprolol over placebo. Unlike other beta-blockers, carvedilol after-MI trials were conducted in the reperfusion era and often involved patients with reduced ejection fraction.[12,24] The Carvedilol After Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial enrolled patients with acute MI and left ventricular ejection fraction <40%.[12] The study demonstrated a 23% reduction in all-cause mortality with carvedilol versus placebo at 2.5 years. Another randomized trial of 801 patients with MI who underwent PCI and did not have left ventricular dysfunction or heart

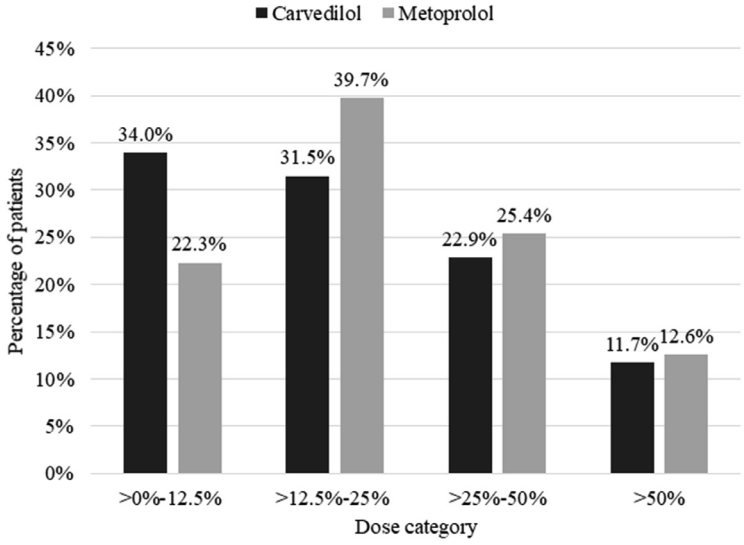

Figure 2. Distribution of Beta-blocker per dose category(p<0.0001).

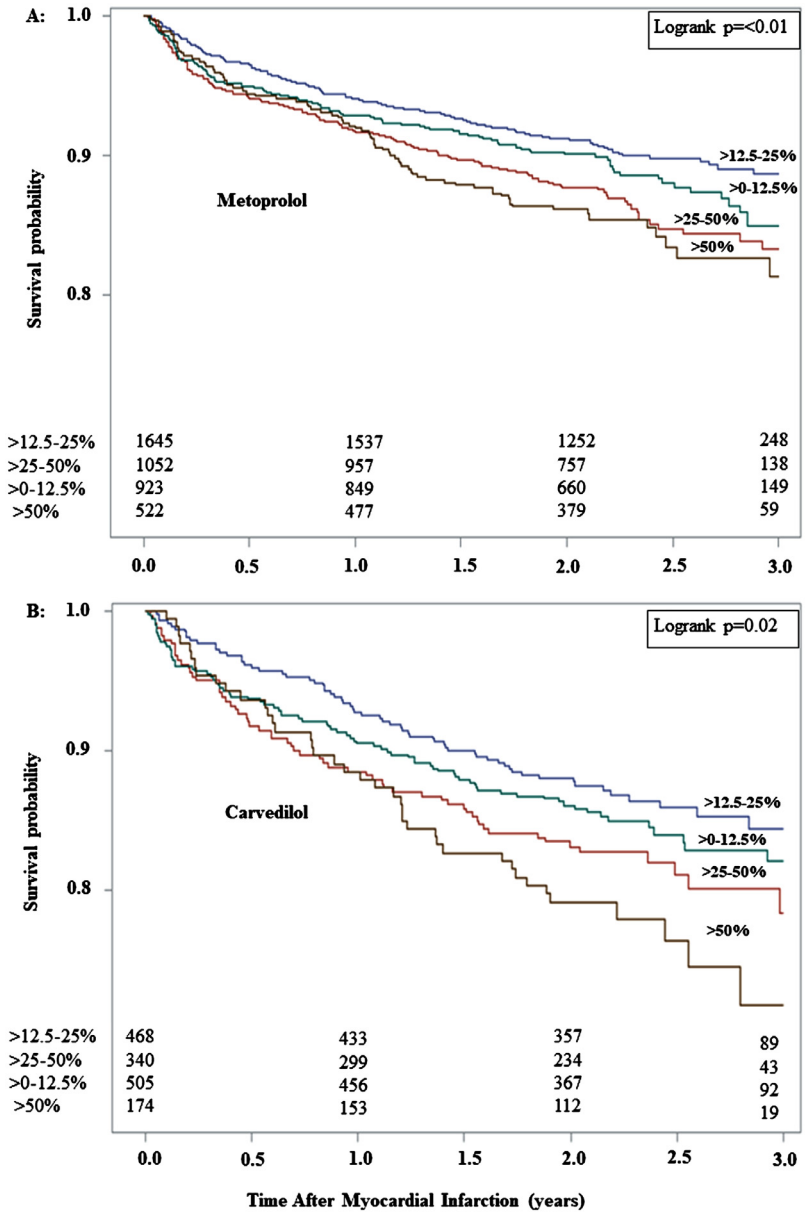

Figure 3. Kaplan-Meier survival curves for (A) the unadjusted analysis comparing 4 metoprolol discharge doses (B) the unadjusted analysis comparing carvedilol 4 discharge doses.

failure[25] showed no significant improvement in survival with carvedilol versus placebo.

Multiple head to head studies have compared metoprolol and carvedilol after-MI.[8,13,26,27] None of the head to head studies done was conclusive enough to recommend one over the other as a guideline for after-MI management, and often, these studies reported conflicting results. Mrdovic et al randomized 313 patients following ST-elevation MI

Table 2
Unadjusted and risk-adjusted HRs for patients on metoprolol versus carvedilol stratified by left ventricular ejection fraction

Unadjusted Hazard Ratios			
Description	HR	95% Wald Confidence Limits	p-value
Left ventricular ejection fraction ≤40%	1.051	0.847- 1.303	0.65
Left ventricular ejection fraction >40%	0.760	0.584- 0.988	0.04
	Risk-Adjusted Hazard Ratios		
Left ventricular ejection fraction ≤40%	1.281	1.024-1.602	0.03
Left ventricular ejection fraction >40%	0.850	0.653- 1.106	0.23

HR= hazard ratio; LVEF= Left ventricular ejection fraction (%).

and left ventricular ejection fraction ≤45% to metoprolol or carvedilol with a mean follow-up duration of 13.4 months.[8] Metoprolol and carvedilol were up-titrated targeting daily doses of 200 mg and 50 mg, respectively. Mean dose achieved after discharge was 149.3 mg and 38.9 mg for metoprolol and carvedilol, respectively. No significant mortality difference was noted. Ozaydin et al showed no difference in survival between the 2 beta-blockers in patients with ST-elevation MI and non-ST elevation MI with left ventricular ejection fraction ≤45%.[13] In this study, 172 patients after-MI with left ventricular ejection fraction ≤45% were randomized to metoprolol (n = 57), carvedilol (n = 60), and nebivolol (n = 55) up-titrating dose as tolerated targeting daily doses of 200 mg, 50 mg, and 10 mg, respectively within 1 month period. The mean daily dose achieved for metoprolol and carvedilol was 57 mg and 20 mg, respectively. Mortality did not differ between carvedilol (1.7%) and metoprolol (1.9%). A recent meta-analysis, including 12 randomized control trials with 61081 patients with acute coronary syndrome showed no difference in survival between metoprolol and carvedilol.[27] Similarly, results in the heart failure subgroup showed no difference. However, in another meta-analysis that compared carvedilol to 1-selective beta-blockers (atenolol, bisoprolol, metoprolol, and nebivolol) in randomized direct comparison trials in patients with MI, carvedilol was found to have significantly lower all-cause mortality.[28] The current guidelines recommend the use of bisoprolol, carvedilol, and extended-release metoprolol succinate in after-MI patients complicated by reduced ejection fraction without favoring one over the other. The present findings support the hypothesis that carvedilol may be preferred in patients with LVEF≤40%, but the inconsistent findings in the literature highlight the need for a large randomized clinical trial to address this question.

The major limitations of this study are that it is not randomized and was a post hoc analysis with significant clinical differences in the 2 groups that were accounted for by multivariable adjustment. It nevertheless represents the largest available comparison of these 2 medications in patients following acute MI. It is notable that the baseline characteristics of patients treated with these medications significantly differed. While the multivariable adjustment seems to have accounted well for these differences, it is possible that there were other unmeasured covariates that were not accounted for. Finally, the analysis is based upon discharge beta-blocker type and dose; it is unknown whether patients were taking metoprolol tartrate or succinate, another factor that could affect outcome.

In conclusion, the overall survival after acute MI was similar for patients treated with metoprolol compared with carvedilol. Our results suggest that outcomes with carvedilol may be superior to metoprolol only in patients with left ventricular ejection fraction ≤ 40%. Further validation of these findings with prospective trials is warranted.

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CREDIT AUTHOR STATEMENT

Ghaith Zaatari: Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization; **Dan J. Fintel:** Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization; **Haris Subacius:** Formal analysis, Data Curation, Writing - Review & Editing; **Joseph J Germano:** Investigation, Writing - Review & Editing; **Jacob Shani:** Investigation, Writing - Review & Editing; **Jeffrey J. Goldberger:** Conceptualization, Methodology, Validation, Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Supervision, Project administration, Funding acquisition

DECLARATION OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

1. Gislason GH, Rasmussen JN, Abildstrøm SZ, Gadsbøll N, Buch P, Friberg J, Rasmussen S, Køber L, Stender S, Madsen M, Torp-Pedersen C. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. *Eur Heart J* 2006;27:1153–1158.
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