Meta-Analysis of Carvedilol Versus Beta 1 Selective Beta-Blockers (Atenolol, Bisoprolol, Metoprolol, and Nebivolol)

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Because carvedilol is a unique vasodilating β blocker (BB) exerting antioxidant activity and pleiotropic effects, it was theorized that it may confer more potent beneficial effects on cardiovascular mortality and morbidity in acute myocardial infarction (AMI) and heart failure (HF) settings. A systematic review and meta-analysis was performed of randomized, controlled, direct-comparison trials that included adults receiving atenolol, bisoprolol, metoprolol, nebivolol, or carvedilol to evaluate the effects of carvedilol compared to other BBSs on mortality, cardiovascular events, and hospital readmissions in the setting of AMI or systolic HF. Compared to β\textsubscript{1}-selective BBs used in HF (8 trials, \(n = 4,563\)), carvedilol significantly reduced all-cause mortality (risk ratio 0.85, 95% confidence interval 0.78 to 0.93, \(p = 0.0006\)). In 3 trials of patients with AMI (\(n = 644\)), carvedilol significantly reduced all-cause mortality by 45% (fixed-effects model: risk ratio 0.55, 95% confidence interval 0.32 to 0.94, \(p = 0.03\), random-effects model: risk ratio 0.56, 95% confidence interval 0.26 to 1.12, \(p = 0.10\)), with no reduction in non-fatal MI (risk ratio 0.61, 95% confidence interval 0.31 to 1.22, \(p = 0.16\)). In conclusion, carvedilol, as compared against atenolol, bisoprolol, metoprolol and nebivolol in randomized direct comparison trials, significantly reduced all-cause mortality in systolic HF patients. Additionally, carvedilol significantly reduced all-cause mortality compared with β\textsubscript{1}-selective BBs in AMI patients using the fixed-effects model but not using the random-effects model. © 2013 Elsevier Inc.

Although guidelines for the treatment of patients with acute coronary syndromes, acute myocardial infarctions (AMIs), and heart failure (HF) recommend the use of β blockers (BBs) as first-line therapy, they do not specifically recommend 1 BB over another.\textsuperscript{1,2} However, carvedilol has been shown to significantly reduce all-cause mortality and cardiovascular (CV) events (nonfatal and fatal stroke and myocardial infarction [MI]) compared to metoprolol in patients with HF (in the Carvedilol or Metoprolol European Trial [COMET]).\textsuperscript{3} Thus, we sought to compare carvedilol against the most frequently prescribed β\textsubscript{1}-selective BBs (atenolol, metoprolol, and bisoprolol) and the most recently approved β\textsubscript{1}-selective BB (nebivolol) in patients with AMI or systolic HF.

Methods

A systematic review of the available published research according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for the conduct of systematic reviews of intervention studies was performed.\textsuperscript{4} Studies were identified through searches of the following sources: Ovid M EDTLINE (1977 to 2012), PubMed (1978 to 2011), and Embase (1977 to 2012). To identify further potentially relevant studies missed by the electronic database search, reference lists from identified trials and review reports were manually screened. Searches were restricted to

![Figure 1. Process for selecting included trials.](http://dx.doi.org/10.1016/j.amjcard.2012.11.031)
Studies were selected for inclusion on the basis of the following criteria: (1) study design: randomized controlled trials, (2) type of participants: adults (age ≥ 18 years), (3) intervention: carvedilol, (4) comparator: atenolol, bisoprolol, metoprolol, or nebivolol, and (5) outcomes: all-cause mortality, CV events (fatal and nonfatal strokes, fatal and nonfatal MI), and HF or CV-related hospital readmissions. We excluded studies that did not report mortality or morbidity outcomes. The titles and abstracts of studies identified by the search strategy were independently screened by 2 reviewers (J.J.D. and H.F.), and clearly irrelevant studies were discarded.

The following data elements were extracted from each study: the number of patients per arm, the nature of the intervention, patient inclusion criteria, cause of HF, type of AMI index event (e.g. percentage non-ST-segment elevation MI, percentage ST-segment elevation MI, percentage unstable angina), and baseline and follow-up blood pressure, ejection fraction, and heart rate (supplemental tables are available by request). The following outcomes were also extracted from each trial: all-cause mortality, CV events (nonfatal and fatal stroke, nonfatal and fatal MI), and HF or CV-related hospital readmissions. Quality assessment was judged according to the following criteria: concealment of allocation and blinding of treatment allocation; similarity of the 2 groups at baseline (statistically similar between the comparison groups in each trial, except for 3 trials: Mrdovic et al. had significantly more baseline coronary artery disease or idiopathic dilated cardiomyopathy patients and higher baseline heart rates in the carvedilol group but higher baseline systolic blood pressures and lower ejection fractions in the nebivolol group. Trials enrolled a median of 150 patients (interquartile range 67 to 3,029) with a median follow-up period of 12 months (interquartile range 0.5 to 58).

Four studies scored well on the methodologic quality indicators (supplemental tables with details are available by request). Concealed allocation and blinding of ≥ 1 outcome assessment were stated in 3 and 5 of 11 trials, respectively. Eight trials (n = 4,563) reported on all-cause mortality in patients with systolic HF. There was a significant decrease in mortality for carvedilol compared to β1-selective BBs (RR 0.85, 95% CI 0.78 to 0.93, p = 0.0006, I² = 0%; Figure 2). The number needed to treat over the course of the trials was 22 (95% CI 14 to 52).

Three trials (n = 644) reported on all-cause mortality in patients with AMI. There was a significant 45% reduction in all-cause mortality in patients on carvedilol vs. β1-selective
BBs by using a fixed-effects model (RR 0.55, 95% CI 0.32 to 0.94, p = 0.03, Figure 3) but not by random-effects model (RR 0.56, 95% CI 0.26 to 1.12, p = 0.10), I² = 10%. The number needed to treat over the course of the trials was 21 (95% CI 11 to 227).

Three trials (n = 644) reported on nonfatal MI. For patients taking carvedilol compared to β₁-selective BBs, there was no reduction in nonfatal MI (RR 0.61, 95% CI 0.31 to 1.22, p = 0.16, I² = 0%; Figure 4).

Two trials (n = 3,099) reported on HF readmissions. Compared to β₁-selective BBs, there was no significant benefit on reducing HF readmissions with carvedilol (RR 0.98, 95% CI 0.93 to 1.03, p = 0.45) I² = 0%; (Figure 5).

Only 1 trial (n = 232) compared atenolol to carvedilol in patients with AMI. Compared to atenolol, carvedilol did not reduce all-cause mortality, although the small sample size may have rendered this nonsignificant (RR 0.39, 95% CI 0.08 to 1.95, p = 0.25).

Two trials in patients with HF (n = 957) were performed with bisoprolol versus carvedilol. Compared to bisoprolol, carvedilol did not reduce all-cause mortality (RR 0.54, 95% CI 0.22 to 1.34, p = 0.19, I² = 0%).

Four HF trials compared metoprolol tartrate to carvedilol (n = 3,376). Compared to metoprolol, carvedilol caused a significant reduction in all-cause mortality (RR 0.86, 95% CI 0.78 to 0.94, p = 0.001, I² = 0%). In the AMI setting, 2 direct-comparison trials (n = 390) indicated no significant reduction in all-cause mortality with carvedilol compared to metoprolol tartrate (RR 0.95, 95% CI 0.13 to 7.13, I² = 53%). However, the study by Mrdovic et al. carrying approximately 86% of the weight for AMI mortality end points, indicated that carvedilol was associated with a significant 47% reduction in all-cause mortality (RR 0.53, 95% CI 0.29 to 0.94, p = 0.02).

Two HF trials compared nebivolol to carvedilol (n = 230). Compared to nebivolol, carvedilol was not associated with a reduction in all-cause mortality (RR 0.80, 95% CI 0.22 to 2.91, p = 0.73, I² = 0%).

Discussion

In this systematic review of 11 randomized controlled trials in 5,207 patients, we found that carvedilol significantly reduced all-cause mortality in patients with HF. Additionally, in patients with AMI, carvedilol significantly reduced
all-cause mortality by fixed-effects model (but not by random-effects model) but did not reduce nonfatal MI compared to other commonly prescribed BBs, although carvedilol did demonstrate trends for reducing this end point. The preferential reduction in mortality with carvedilol in HF, however, was not associated with a significant reduction in HF hospital readmission compared to the other BBs, suggesting a discordant relative effect of these agents on mortality versus overall cardiac compensation.

The potential mechanisms responsible for the observed beneficial impact of carvedilol compared to other BBs may in part be established through carvedilol’s pleotropic effects (antioxidant and vasodilating), which are not shared by the commonly prescribed \(\beta_1\)-selective BBs (i.e., atenolol, metoprolol, and bisoprolol). Compared to metoprolol, carvedilol has been shown in 2 randomized, direct-comparison trials to significantly reduce atrial fibrillation after coronary artery bypass graft surgery.\(^{18,19}\) Moreover, in the Carvedilol Post Infarction Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial, carvedilol caused a 76% reduction in arrhythmias (ventricular tachycardia, fibrillation, or flutter; \(p < 0.0001\)), a 52% reduction in supraventricular arrhythmias (\(p = 0.0015\)), and a 26% reduction in sudden cardiac death (\(p = 0.098\)) compared to placebo.\(^{20}\) Thus, carvedilol appears to have significant antiarrhythmic effects, which may not be as prominent in \(\beta_1\)-selective BBs. This would potentially lead to better reductions in sudden cardiac death and all-cause mortality in patients with AMIs and those with HF. In fact, sudden cardiac death was significantly reduced with carvedilol compared to metoprolol in the COMET trial (218 vs 262, hazard ratio 0.81, 95% CI 0.68 to 0.97, \(p = 0.02\)).\(^{21}\) Moreover, in a meta-analysis of >2,000 patients with HF (encompassing 19 randomized trials), carvedilol significantly increased left ventricular systolic function more so than metoprolol.\(^{22}\) In the setting of HF, the \(\beta_2\) receptors in the heart are upregulated,\(^{23}\) and thus the use of a \(\beta_1\)-selective BB may not adequately protect the myocardium from excessive adrenergic tone. Carvedilol is a potent BB that blocks \(\beta_1\), \(\beta_2\), and \(\alpha\) receptors in the heart and thereby confers comprehensive adrenergic blockade, which may be especially advantageous for patients with HF or AMI.

Carvedilol lowers blood pressure mainly through vasodilation, whereas \(\beta_1\)-selective BBs do so by a reduction in cardiac output (an untoward effect in patients with HF).\(^{24}\) Improved versus reduced cardiac output may allow carvedilol to improve insulin sensitivity, whereas atenolol and metoprolol worsen insulin sensitivity.\(^{24}\) In the COMET study, carvedilol, compared to metoprolol, reduced the risk for new diabetes development over the 5-year study by 22% (\(p = 0.048\)).\(^{25}\) In contrast to metoprolol and atenolol, carvedilol has a neutral or favorable effect on levels of triglycerides and high-density lipoprotein cholesterol.\(^{25}\) Additionally, in the Glycemic Effects in Diabetes Mellitus; Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) randomized trial, 40% fewer patients progressed to microalbuminuria in the carvedilol arm than in the metoprolol arm.\(^{25}\)

Moreover, carvedilol has been shown to reduce cardiac adrenergic activity, improve New York Heart Association functional class, improve stroke work, and improve stroke volume compared to atenolol and metoprolol.\(^{22,24}\) Additionally, carvedilol exerts favorable effects on cardiac output compared to the other standard nonvasodilating BBs.\(^{26}\) Furthermore, \(\beta_1\)-selective BBs upregulate \(\beta_1\) receptor density and increase \(\beta_1\) receptor sensitivity to adrenergic stimulation; this has not been seen with carvedilol.\(^{22}\) Missing doses of \(\beta_1\)-selective BBs has been associated with a significant increase in death (due to sudden cardiac death and HF), which may be caused by rebound tachycardia, leading to deterioration in patients with HF.\(^{27}\)

In summary, improvements in ejection fraction, symptomatic functional class, stroke volume, stroke work, cardiac output, insulin sensitivity, and adrenergic activity with carvedilol, along with a potential increase in the risk for death with \(\beta_1\)-selective BBs if strict compliance is not followed, all may contribute to the overall morbidity and mortality benefits noted with carvedilol compared to \(\beta_1\)-selective BBs.

These findings suggest that carvedilol reduces all-cause mortality compared to \(\beta_1\)-selective BBs in systolic HF patients and in patients with AMIs. Although current guidelines for the treatment of patients with HF and acute coronary syndromes or AMIs do not recommend 1 BB over another,\(^{1,2}\) substantial evidence, discussed previously, appears to favor carvedilol in the settings of ischemic heart disease, particularly systolic HF. Although a large, randomized, multicenter trial is required to confirm the results of this meta-analysis in patients with AMI, COMET has confirmed carvedilol’s efficacy over metoprolol in patients with systolic HF.\(^{3}\) Thus, clearly for patients with systolic HF, carvedilol should be considered the BB of first choice. Atenolol has not been shown to improve long-term CV prognosis after AMI, nor has it been shown to be effective for improving outcomes in patients with HF.\(^{28}\) Additionally, when used for hypertension, atenolol does not protect against heart disease or reduce mortality despite lowering elevated blood pressure.\(^{29}\) The fact that atenolol continues to be 1 of most widely prescribed BBs (presumably because of habit) is indefensible from a scientific perspective.

Several important potential study limitations should be considered. First, not all of the trials included in our meta-analysis were double blind (\(n = 3\)), with 4 of the 11 included trials being rated as moderate or good in quality (i.e., Jadad score \(\geq 3\) of 5). Second, most trials included relatively small numbers of patients, with the exception of COMET (\(n = 3,029\)), which contributed approximately 94% of mortality events in the HF trials. In particular, our meta-analysis may have been underpowered in patients with AMIs to differentiate the relative benefits of carvedilol compared to the other \(\beta_1\)-selective BBs. Nevertheless, even in the patients with AMIs (\(n = 644\)), significance in favor of carvedilol therapy was present. Moreover, all “hard outcomes” showed minimal heterogeneity among trials, mortality in HF (\(I^2 = 0\%\)), mortality in AMI (\(I^2 = 10\%)\) and nonfatal MI (\(I^2 = 0\%)\). Finally, as in most such meta-analyses, comparing several therapeutic agents, various dosages of the individual agents were used, which is also typically present in clinical situations, and generally, these different BBs provided similar reductions in rest heart rate, which generally indicates potential clinical efficacy.

Disclosures

Dr. Lavie has served as a consultant and speaker for GlaxoSmithKline, London, United Kingdom (but not regarding \(\beta\) blockers). Dr. O’Keefe is a speaker for...
GlaxoSmithKline and Forest Pharmaceuticals, St. Louis, Missouri.

Supplementary Data

Supplementary data related with this article can be found, in the on-line version, at http://dx.doi.org/10.1016/j.amjcard.2012.11.031


