β-Blockers and Cardiovascular Events in Patients With and Without Myocardial Infarction
Post Hoc Analysis From the CHARISMA Trial

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Background—The long-term efficacy of β-blockers in patients with and without myocardial infarction (MI) is controversial. Methods and Results—This is post hoc analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial of 4772 patients with prior MI, 7804 patients with known atherothrombosis, and 2101 patients with risk factors alone but without heart failure. Primary outcome was a composite of nonfatal MI, stroke, or cardiovascular mortality. The cohorts were divided into 2 groups based on baseline β-blocker use. In the propensity score–matched prior MI cohort, after 28 months of follow-up, β-blocker use was associated with a 31% lower risk of the primary outcome (70 [7.1%] versus 100 [10.2%]; hazards ratio, 0.69; 95% confidence interval, 0.50–0.94; P=0.021), driven by a lower risk of recurrent MI (33 [3.4%] versus 48 [4.9%]; hazards ratio, 0.62; 95% confidence interval, 0.39–1.00; P=0.049) with no difference in mortality (52 [5.3%] versus 66 [6.7%]; P=0.20). In the known atherothrombotic disease and the risk factors alone cohorts, β-blocker use was not associated with lower ischemic outcomes, whereas a trend toward a higher risk of stroke (3.5% versus 1.5%; hazards ratio, 2.13; 95% confidence interval, 0.92–4.92; P=0.079) was observed in the risk factors alone cohort. This higher stroke risk was significant in the regression model adjusted to the propensity score (hazards ratio, 2.69; 95% confidence interval, 1.33–5.44; P=0.006) and in the multivariable models. Conclusions—β-blocker use in patients with prior MI but no heart failure was associated with a lower composite cardiovascular outcome driven by lower risk of recurrent MI with no difference in mortality. However, β-blocker use was not associated with lower cardiovascular events in those without MI, with a suggestion of inferior outcome with regard to stroke risk.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00050817.

Key Words: coronary artery disease ■ myocardial infarction ■ outcome measures
WHAT IS KNOWN

• β-blockers are efficacious in preventing long-term adverse cardiovascular outcomes based on data from post–myocardial infarction (MI) trials.
• However, the trials predate modern reperfusion and medical therapy and have been widely extrapolated to cohorts without MI or heart failure

WHAT THE STUDY ADDS

• Data from this post hoc analysis from the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial support that β-blocker use in patients with prior MI but no heart failure is associated with a lower composite cardiovascular outcome, driven mainly by lower risk of recurrent MI with no difference in mortality.
• However, β-blocker use is not associated with lower cardiovascular events in those without MI, with a suggestion of inferior outcome with regard to stroke risk.

the present study was to validate the above findings using data from a randomized trial where the outcomes were adjudicated. Our hypothesis was that the β-blockers are efficacious at preventing long-term cardiovascular events in patients with a prior MI, but not in patients with coronary artery disease without MI or in those with risk factors alone.

Methods

Study Population

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was a prospective, randomized trial to evaluate the efficacy and safety of clopidogrel plus aspirin as compared with aspirin alone at high risk for cardiovascular events. The design and the main results of the trial have been published previously. This is a nonprespecified post hoc analysis of the trial data from a randomized trial where the outcomes were adjudicated by the clinical events committee, blinded to patient treatment assignment.

Statistical Analyses

Propensity Score Matching

Cox proportional hazard models were used to assess the effect of prior β-blocker usage and the primary outcome. Given differences in baseline characteristics between participants in the 2 groups (Tables 1–3) for each of the 3 cohorts, the primary analysis alone may not adequately control for confounding and bias. Hence, we analyzed the data further using propensity score analysis. The propensity score provides a conditional probability of having a particular exposure (β-blocker use) given a set of baseline measured covariates and was estimated using a nonparsimonious multivariable logistic regression model using β-blocker use as the dependent variable and all the baseline characteristics (regardless of statistical significance) displayed in Figure 1A–1C as covariates. Matching was performed separately for each cohort using a 1:1 matching without replacement (Greedy matching protocol) with a caliper width equal to 0.2 of the SD of the logit of the propensity score. C-statistics for the 3 populations were 0.80 (prior MI), 0.81 (known atherothrombotic disease), and 0.78 (risk factors alone). Absolute standardized differences were estimated for all the covariates before and after matching to assess prematch imbalance and postmatch balance. Absolute standardized differences <10% for a given covariate indicate a relatively small imbalance. For the matched cohort, paired comparisons were performed using McNemar test for binary variables and paired t test or paired sample Wilcoxon signed-rank test for continuous variables, depending on the normality of the variable. Cox proportional regression model on the matched cohort was performed after stratifying on the matched pair.

Sensitivity Analyses

Sensitivity analysis was performed to assess the robustness of the results. A regression adjustment to the propensity score was performed, where the analyses for the primary and secondary outcomes were performed after adjusting to the propensity score. The advantage of this model is the use of all patient population rather than a reduced population resulting from a propensity score matching, resulting in greater power and precision. In addition, an inverse probability of treatment weight (IPTW)–adjusted analyses and stabilized IPTW–adjusted analyses were performed.

Multivariable Analyses

Multivariable models were constructed for the propensity score–matched, propensity score–adjusted, and IPTW models. All baseline characteristics were considered for inclusion into the models, and a stepwise elimination procedure was used. A Bootstrapping technique was used to draw 500 samples from the original data and rerun the stepwise modeling process to confirm the model. A 2-sided P value of <0.05 was considered statistically significant. All statistical analysis were performed using SAS version 9.2 (SAS institute, Cary, NC).

Falsification Hypothesis

We used a falsification hypothesis, a claim that is distinct from the one being tested that is highly unlikely to be causally related to the intervention in question. Our falsification hypothesis was that β-blockers are associated with increased risk of bleeding. Three types of bleeding were tested in the propensity-matched cohort: severe bleeding, moderate bleeding, and severe/moderate bleeding.

Results

The CHARISMA trial enrolled 15,603 patients from 32 countries between October 2002 and November 2003. Of these
patients, 4772 were in the prior MI cohort, 7804 patients in the known atherothrombotic cohort, and 2101 patients in the risk factors alone cohort. Patients (n=926) with a history of heart failure were excluded.

Prior MI Cohort

Of the 4772 patients in the cohort, 3451 (72%) were on a β-blocker. Propensity score matching matched 1962 patients with similar propensity scores (Table 1). After match the
absolute standardized differences were <10% for all the variables indicating an adequate match (Figure 1A).

In the propensity score–matched cohort, β-blocker use was associated with a 31% lower risk of primary outcome (70 [7.1%] versus 100 [10.2%]; HR, 0.69; 95% CI, 0.50–0.94; \( P = 0.021 \)), driven mainly by a lower risk of recurrent MI (33 [3.4%] versus 48 [4.9%]; HR, 0.62; 95% CI, 0.39–1.00; \( P = 0.049 \)) when compared with no β-blocker use with no difference for other
outcomes (Figure 2A and 2B). There was no difference in mortality (52 [5.3%] versus 66 [6.7%]; \(P=0.20\)), cardiovascular mortality (31 [3.2%] versus 39 [4.0%]; \(P=0.53\)), stroke (23 [2.3%] versus 28 [2.9%]; \(P=0.47\)), or hospitalization (138 [14.1%] versus 126 [12.8%; \(P=0.29\) between the 2 groups.

Known Atherothrombotic Cohort
Of the 7804 patients in the cohort, 2581 (33%) were on a \(\beta\)-blocker. Propensity score matching matched 3758 patients with similar propensity scores (Table 2). After match the absolute standardized differences were <10% for all the variables indicating an adequate match (Figure 1B).

\(\beta\)-blocker use was not associated with any lower risk of primary outcome (126 [6.7%] versus 117 [6.2%]; \(P=0.64\); Figure 3A and 3B), all-cause death (74 [3.9%] versus 76 [4.0%; \(P=0.67\)], cardiovascular death (42 [2.2%] versus 48 [2.6%; \(P=0.39\)], MI (31 [1.6%] versus 30 [1.6%; \(P=0.69\)], stroke (70 [3.7%] versus 60 [3.2%; \(P=0.52\)], or hospitalization (244 [13%] versus 217 [11.5%; \(P=0.58\) when compared with no \(\beta\)-blocker use (Figure 3A).

Risk Factors Alone Cohort
Of the 2101 patients in the cohort, 562 (27%) were on a \(\beta\)-blocker. Propensity score matching matched 1036 patients with similar propensity scores (Table 3). After match the absolute standardized differences were <10% for all the variables indicating an adequate match (Figure 1C).

\(\beta\)-blocker use was not associated with any lower risk of primary outcome (126 [6.7%] versus 117 [6.2%; \(P=0.64\); Figure 4A and 4B), all-cause death (21 [4.1%] versus 20 [3.9%; \(P=0.87\)], cardiovascular death (15 [2.9%] versus 15 [2.9%; \(P=0.84\), MI (6 [1.2%] versus 5 [1.0%; \(P=0.53\), or hospitalization (39 [7.5%] versus 29 [5.6%; \(P=0.19\) when compared with no \(\beta\)-blocker use with a higher risk of stroke (18 [3.5%] versus 8 [1.5%; \(P=0.07\); Figure 4A) in the matched cohort. In a regression model adjusted to the propensity score \(\beta\)-blocker use was associated with a higher stroke risk (HR, 2.69; 95% CI, 1.33–5.44; \(P=0.006\).

Sensitivity Analysis
Sensitivity analysis based on various statistical models (for \(\beta\)-blocker use versus no \(\beta\)-blocker use) yielded largely similar
results for the primary outcome. For the prior MI cohort both the regression adjustment to propensity score (HR, 0.74; 95% CI, 0.56–0.96; \(P=0.02\)) and the IPTW-adjusted analysis (HR, 0.72; 95% CI, 0.58–0.88; \(P=0.001\)) showed a lower risk with \(\beta\)-blocker use. For the known atherothrombotic cohort the regression adjustment to propensity score showed no lower risk (HR, 1.13; 95% CI, 0.96–1.31; \(P=0.16\)).

Figure 1. A, Absolute standardized differences before and after matching in the (A) prior myocardial infarction cohort, (B) known coronary artery disease cohort, and (C) risk factors alone cohort. ACE indicates angiotensin-converting enzyme; ASA, aspirin; BMI, body mass index; CAGB, coronary bypass graft surgery; CCB, calcium channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; GP, glycoprotein; HTN, hypertension; Hx, history of; PAD, peripheral arterial disease; LMWH, low molecular weight heparin; NSAIDS, nonsteroidal anti-inflammatory agents; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SC, subcutaneous; and TIA, transient ischemic attack.

Figure 2. A, Outcomes in propensity-matched patients on and not on \(\beta\)-blockers in the prior myocardial infarction (MI) cohort (\(P\) values from Cox proportional hazards model). B, Survival free of primary outcome based on \(\beta\)-blocker use status in the prior MI cohort (\(P\) values from log-rank test). CI indicates confidence interval; CV, cardiovascular; and HR, hazards ratio.
95% CI, 0.91–1.41; \( P = 0.28 \)), whereas the IPTW-adjusted analysis, if anything, indicated higher risk (HR, 1.25; 95% CI, 1.05–1.48; \( P = 0.01 \)) with \( \beta \)-blocker use. Similarly, for the risk factors alone cohort the regression adjustment to propensity score model showed no lower risk (HR, 1.48; 95% CI, 0.92–2.37; \( P = 0.10 \)) with the IPTW analysis, if anything, showed higher risk (HR, 1.71; 95% CI, 1.18–2.48; \( P = 0.004 \)) with \( \beta \)-blocker use. Results were similar when the stabilized IPTW models or adjusting to quintiles of propensity were performed (data not shown).

### Multivariable Analysis

The various multivariable models yielded largely similar results for the primary outcome. For the prior MI cohort, multivariable propensity score–matched model (HR, 0.65; 95% CI, 0.45–0.93; \( P = 0.02 \)), multivariable propensity score–adjusted model (HR, 0.76; 95% CI, 0.58–0.98; \( P = 0.04 \)), and the multivariable IPTW model (HR, 0.71; 95% CI, 0.58–0.88; \( P = 0.001 \)) showed a lower risk with \( \beta \)-blocker use. For the known atherothrombotic cohort, the multivariable propensity score–matched model (HR, 1.13; 95% CI, 0.83–1.54; \( P = 0.42 \)) and multivariable propensity score–adjusted model (HR, 1.11; 95% CI, 0.90–1.38; \( P = 0.34 \)) showed no lower risk, with the IPTW model, if anything, showed higher risk with \( \beta \)-blocker use (HR, 1.22; 95% CI, 1.03–1.44; \( P = 0.02 \)). Similarly, for the risk factor alone cohort, the multivariable propensity score–matched model (HR, 1.30; 95% CI, 0.68–2.46; \( P = 0.42 \)) and the multivariable propensity score–adjusted model (HR, 1.46; 95% CI, 0.92–2.32; \( P = 0.11 \)) showed no lower risk with the IPTW model, if anything, showed higher risk (HR, 1.62; 95% CI, 1.12–2.34; \( P = 0.01 \)) with \( \beta \)-blocker use.

### Falsification Hypothesis

There was no difference between \( \beta \)-blocker use versus no \( \beta \)-blocker use for any of the bleeding outcomes tested. The risk of severe, moderate, and severe/moderate bleeding was similar in the prior MI cohort (\( P \) values of 0.27, 0.33, and 1.00 respectively), known atherothrombosis cohort (\( P \) values of 0.61, 0.90, and 0.46 respectively), or the risk factor alone cohort (\( P \) values of 0.82, 0.11, and 0.22, respectively) thus disproving the falsification hypothesis.

### Discussion

The principal findings from this post hoc analysis of 14,677 patients without heart failure was that \( \beta \)-blocker use was...
associated with lower primary outcome, driven largely by a lower rate of recurrent MI in the prior MI cohort, but with no significant lower mortality. Of note, β-blocker use was not associated with lower outcomes in patients with established atherothrombotic disease or in those with risk factors alone, and in some models showed an association with higher primary outcomes, including higher stroke. The results are largely similar to those of the prior REACH registry β-blocker analysis.2

Prior MI Cohort

The evidence for β-blocker use after MI dates back to the First International Study of Infarct Survival (ISIS-1) trial where atenolol was associated with significant reduction in vascular death at 7 days (3.87% versus 4.57%; P<0.04) when compared with controls.15 This was in the era before modern medical therapy or reperfusion was routine. In fact, in the ISIS-1 trial only 5% of patients were on antplatelet agent at discharge, with no reference to lipid-lowering agents. However, in the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) published in 2005 of 45 852 patients with acute MI, metoprolol was not superior to placebo for either the coprimary end points of 30-day death and 30-day death/MI or cardiac arrest, despite almost 3× the sample size as that of the ISIS-1 trial.16,17 In COMMIT, 54% of patients received a fibrinolytic agent, all patients received aspirin, and 50% of patients were treated with dual antiplatelet therapy of aspirin and clopidogrel. Therefore, the mortality benefit of β-blocker use in post-MI patients without out heart failure in the modern era of revascularization/medical therapy is unclear. In the REACH registry, β-blocker use in patients with prior MI was not associated with lower mortality (HR, 0.93; 95% CI, 0.80–1.08; P=0.34).2 Similarly, in the French registries of Acute ST-elevation and non-ST-elevation Myocardial Infarction (FAST) MI registry, 5-year survival was not different (HR, 0.90; 95% CI, 0.38–2.10) for patients taking or not taking β-blocker at 1 year after MI.18 Moreover, in the Coronary REvascularization Demonstrating Outcome Study in Kyoto (CREDO-Kyoto) Acute Myocardial Infarction registry β-blocker use was not associated with lower 3-year cardiac death or MI in the 3692 patients who underwent percutaneous coronary intervention within 24 hours from onset of ST-segment–elevation MI (HR, 1.43; 95% CI, 1.06–1.94; P=0.01).19

Even in the ISIS-1 trial, the vascular death rate after day 7 was similar during the long term (8.6% versus 8.8%; P=NS), suggesting perhaps that the mortality benefit of β-blockade, if any, likely occurs early. However, in the CARvedilol Post InfaRction SurvIval COntRol in Left Ventricular DysfunctioN (CAPRICORN) trial of post-MI left ventricular (LV) systolic dysfunction, β-blockers were associated with similar rate of primary end point (death or hospital admission for cardiovascular problem) but a significant decrease in death, cardiovascular death, nonfatal MI, and death/MI when compared with placebo.20 The results of the present study, in which we excluded patients with heart failure, are not applicable to patients such as those enrolled in CAPRICORN.

Our results are concordant with the above-noted studies showing no overall difference in mortality whether patients were on a β-blocker at the time of entry into the CHARISMA trial. However, β-blocker use was associated with a lower risk of recurrent MI in the prior MI cohort, although no adjustment was performed for multiple testing. Similarly, in the REACH registry analysis, although there was no significant difference in overall mortality, β-blocker use was associated with a significant reduction in secondary outcomes driven by a reduction in hospitalization for cardiovascular causes in the subgroup of patients who had experienced an MI within 1 year.2 It may, therefore, be appropriate to use β-blocker over short- to intermediate-term after MI in all patients,21 with more extended use in subjects with MI with concomitant heart failure or LV dysfunction.20 In patients with intolerance to β-blockers, a prior study supports verapamil–trandolapril strategy that provides similar outcomes with better subjective well-being and angina relief compared with β-blocker use.22

Known Atherothrombotic Disease Cohort

In patients with stable angina, there is a general perception that β-blocker use is associated with better outcomes, including better angina relief and possible decrease in cardiovascular outcomes. In a meta-analysis of 89 randomized trials enrolling 21 674 patients with stable angina, β-blockers were not associated with a mortality benefit when compared with placebo (odds ratio, 0.42; 95% CI, 0.15–1.21) or with other agents (odds ratio, 0.98; 95% CI, 0.86–1.10).23 Similarly, in the CREDO-Kyoto registry of 5288 patients with coronary artery disease but without MI or heart failure undergoing percutaneous coronary intervention, β-blocker use was associated with worse 3-year cardiac death or MI in an adjusted analysis (HR, 1.48; 95% CI, 1.48–2.10; P=0.02).24 In the analysis from the REACH registry, there was no difference in event rates between patients in the β-blocker group when compared with the no β-blocker group for death, MI, or stroke.2 The results of the present study add to the mounting scientific evidence that show no reduction in the risk of ischemic outcomes with β-blocker therapy. Thus, data from both randomized trials and observational studies show largely consistent findings.

Nevertheless, one can argue that the main reason to use β-blockers in stable angina is angina relief and not necessarily reduction of hard clinical outcomes. However, data from 26 randomized trials of patients with stable angina show that β-blocker use was no better than placebo for reducing the number of angina attacks per week (–4.30; 95% CI, –12.03 to 3.43) and was associated with an increase in the incidence of unstable angina (odds ratio, 3.32; 95% CI, 1.50–7.36).25

Risk Factors Alone Cohort

In a meta-analysis of 13 randomized trials with 105 951 patients with hypertension, β-blocker use was associated with no benefit for death or MI when compared with other agents, but was associated with a 16% increase in the risk of stroke (relative risk, 1.16; 95% CI, 1.04–1.30).26 Similarly, we have shown in a meta-analysis of randomized trials that β-blockers when compared with other agents are associated with a 19% increase in stroke in the elderly.2 Interestingly, this higher stroke risk with β-blocker use was also seen in our prior analysis from the REACH registry (HR, 1.22; 95% CI, 0.99–1.52; P=0.06) as well as in the current analysis from the CHARISMA trial (P=0.07). In addition, this association of higher stroke was significant in the regression model adjusted to the propensity score (HR, 2.69; 95% CI, 1.33–5.44; P=0.006). Thus, the results of randomized trials and
observational studies are largely concordant, pointing to perhaps worse outcomes with \( \beta \)-blockers than with other antihypertensive drug classes in patients with risk factors alone. The increased risk of stroke has been shown to be the result of inefficient reduction in central aortic pressures with \( \beta \)-blockers.27 Heart rate lowering has also been implicated as one of the reasons for less effective central aortic pressure reduction with \( \beta \)-blocker use.28,29 The differential effect of \( \beta \)-blockers in patients with and without MI is likely because of the variable risk benefit profile in these cohorts. In patients with prior MI the benefits of reducing arrhythmias, reducing heart rate and rate pressure product, and thereby increasing the threshold for ischemia likely outweigh the risk of adverse metabolic effects. However, in patients without MI, the risk benefit profile does not seem to be favorable.

**Newer Vasodilating \( \beta \)-Blockers**

One explanation for the lack of efficacy of \( \beta \)-blockers is that older agents such as atenolol or metoprolol were used. The newer vasodilating \( \beta \)-blockers have less adverse metabolic effects, including less weight gain, lesser increase in central aortic pressure, and lower probability of causing new onset diabetes mellitus—all potentially favorable properties.30 Ironically, no such concerns existed when trials using the same older agents had positive results such as atenolol in the ISIS-1 trial and metoprolol in the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Moreover, there are no robust randomized trial data to support long-term cardiovascular benefits of newer vasodilating \( \beta \)-blockers in patients without heart failure or LV dysfunction. In the Carvedilol Acute Myocardial Infarction trial (CAMIS), carvedilol was not associated with better cardiovascular outcomes when compared with atenolol (relative risk, 1.00; 95% CI, 0.6–1.5; \( P=0.99 \)) among patients with acute coronary syndromes and largely preserved LV ejection fraction.31 In addition, the PASSAT trial showed that carvedilol was not superior to metoprolol with respect to myocardial injury and improvement of global and regional LV function when administered before reperfusion in patients with ST-segment–elevation MI undergoing percutaneous coronary intervention.32 There were no differences in any cardiac events, including cardiac death (2.0% versus 0.0%; \( P=0.99 \)), reinfarction (0.0% versus 2.0%; \( P=0.99 \)), or shock (2.0% versus 4.0%; \( P=0.99 \)) between carvedilol versus metoprolol groups.32

**Study Limitations**

This is a nonprespecified post hoc analysis of a randomized trial in which \( \beta \)-blocker use was not randomly assigned and hence selection bias cannot be ruled out, despite rigorous propensity score matching. Data on the type of \( \beta \)-blocker used, the dosage of \( \beta \)-blocker, or the indication for therapy were not available. Although propensity score matching adjusts for many known confounders, other unmeasured confounders cannot be fully accounted for and are best evaluated in a randomized controlled trial. However, the results were consistent in several different models. In addition, the falsification hypothesis further points to a potential spurious association of \( \beta \)-blocker use with the results seen in this study. Nevertheless, the results from this CHARISMA post hoc analysis are largely similar to that of the REACH registry \( \beta \)-blocker analysis and are largely parallel with the findings from randomized controlled trials.

**Conclusions**

In this post hoc analysis from the CHARISMA trial, \( \beta \)-blocker use in patients with prior MI but no heart failure was associated with better clinical outcomes driven mainly by a reduction in recurrent MI but with no mortality benefit. \( \beta \)-blocker use was not associated with lower cardiovascular events in those without MI, with even a suggestion of worse outcomes. In patients without previous events but with multiple cardiovascular risk factors, there is a concern that these agents might increase the risk of stroke. Randomized controlled trials are needed to evaluate the efficacy of newer \( \beta \)-blockers with vasodilating properties in patients without heart failure or LV systolic dysfunction.

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**Disclosures**

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