Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension
A Randomized Controlled Trial

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Context β-blockers have been shown to decrease cardiovascular risk in patients with hypertension and type 2 diabetes mellitus (DM); however, some components of the metabolic syndrome are worsened by some β-blockers.

Objective To compare the effects of β-blockers with different pharmacological profiles on glycemic and metabolic control in participants with DM and hypertension receiving renin-angiotensin system (RAS) blockade, in the context of cardiovascular risk factors.

Design, Setting, and Participants A randomized, double-blind, parallel-group trial (The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives [GEMINI]) conducted between June 1, 2001, and April 6, 2004, at 205 US sites that compared the effects of carvedilol and metoprolol tartrate on glycemic control. The 1235 participants were aged 36 to 85 years with hypertension (>130/80 mm Hg) and type 2 DM (glycosylated hemoglobin [HbA1c], 6.5%-8.5%) and were receiving RAS blockers. Participants were followed up for 35 weeks.

Interventions Participants were randomized to receive a 6.25- to 25-mg dose of carvedilol (n=498) or 50- to 200-mg dose of metoprolol tartrate (n=737), each twice daily. Open-label hydrochlorothiazide and a dihydropyridine calcium antagonist were added, if needed, to achieve blood pressure target.

Main Outcome Measures Difference between groups in mean change from baseline HbA1c following 5 months of maintenance therapy. Additional prespecified comparisons included change from baseline HbA1c in individual treatment groups, treatment effect on insulin sensitivity, and microalbuminuria.

Results The 2 groups differed in mean change in HbA1c from baseline (0.13%; 95% confidence interval [CI], –0.22% to –0.04%; P=.004; modified intention-to-treat analysis). The mean (SD) HbA1c increased with metoprolol (0.15% [0.04%]; P<.001) but not carvedilol (0.02% [0.04%]; P=.65). Insulin sensitivity improved with carvedilol (–9.1%; P=.004) but not metoprolol (–2.0%; P=.48); the between-group difference was –7.2% (95% CI, –13.8% to –0.2%; P=.004). Blood pressure was similar between groups. Progression to microalbuminuria was less frequent with carvedilol than with metoprolol (6.4% vs 10.3%; odds ratio, 0.60; 95% CI, 0.36-0.97; P=.04).

Conclusions Both β-blockers were well tolerated; use of carvedilol in the presence of RAS blockade did not affect glycemic control and improved some components of the metabolic syndrome relative to metoprolol in participants with DM and hypertension. The effects of the 2 β-blockers on clinical outcomes need to be compared in long-term clinical trials.

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glycemic control. In persons with DM, β-blockers have been shown to increase fasting glucose by as much as 28 mg/dL (1.55 mmol/L). and HbA₁c, by up to 1%. To attain the current guideline recommendations for blood pressure (BP) in persons with DM (<130/80 mm Hg), use of several antihypertensive agents is required. All guidelines recommend β-blockers among other classes to achieve this goal. To date, no study has examined the effect of any β-blocker on glycemic control in persons with hypertension and DM who are concomitantly receiving a RAS blocker known to improve glycemic control. 

To test the hypothesis that in the presence of RAS blockers, use of a β-blocker demonstrated to reduce insulin resistance maintains better glycemic control as assessed by HbA₁c than a β-blocker without that effect, we compared the effects of the β-blocker carvedilol with metoprolol. HbA₁c was assessed because it was linearly related to risk of cardiovascular complications of type 2 DM in the UKPDS.

METHODS

Study Design and Participants

The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial is a randomized, double-blind, parallel-group, multicenter design (205 US sites) that compared the effects of carvedilol and metoprolol tartrate on glycemic control. Participants continued to receive their ARB following screening. All other antihypertensive medications were discontinued over a 2- to 4-week period. Participants were eligible for randomization if they had mild to moderate hypertension after washout (systolic BP >130≤179 mm Hg and diastolic BP >80≤109 mm Hg), and fasting HbA₁c was 6.5% to 8.5% with or without DM. A detailed description of the study design and statistical methods has been published elsewhere. Figure 1 summarizes participant screening and study flow. Participants were men and women aged 36 to 85 years with documented type 2 DM and stage 1 or 2 hypertension. Antidiabetic treatment must have been stable for 3 months and antihypertensive treatment stable for 1 month, and include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). Exclusion criteria included significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, unstable angina, sick sinus syndrome, second or third degree heart block without a pacemaker, congestive heart failure, a myocardial infarction or stroke within the previous 3 months, bradycardia), pulmonary disease, stage 3 or higher kidney disease, or use of a nonocular β-blocker within the previous 3 months. All participants gave written informed consent, and the protocol and procedures were approved by the institutional review board of each participating center.

Intervention and Patient Monitoring

Participants continued to receive their ACE inhibitor or ARB following screening. All other antihypertensive medications were discontinued over a 2- to 4-week period. Participants were eligible for randomization if they had mild to moderate hypertension after washout (systolic BP >130≤179 mm Hg and diastolic BP >80≤109 mm Hg), and fasting HbA₁c was 6.5% to 8.5% with or without DM. A detailed description of the study design and statistical methods has been published elsewhere. Figure 1 summarizes participant screening and study flow. Participants were men and women aged 36 to 85 years with documented type 2 DM and stage 1 or 2 hypertension. Antidiabetic treatment must have been stable for 3 months and antihypertensive treatment stable for 1 month, and include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB). Exclusion criteria included significant cardiovascular disease (uncontrolled or symptomatic arrhythmias, unstable angina, sick sinus syndrome, second or third degree heart block without a pacemaker, congestive heart failure, a myocardial infarction or stroke within the previous 3 months, bradycardia), pulmonary disease, stage 3 or higher kidney disease, or use of a nonocular β-blocker within the previous 3 months. All participants gave written informed consent, and the protocol and procedures were approved by the institutional review board of each participating center.

Figure 1. Participant Recruitment and Follow-up Flow Diagram

The modified intention-to-treat analysis included all patients who had baseline and on-treatment glycosylated hemoglobin assessed.
assign treatment by container number. Commercial supplies of metoprolol tartrate and carvedilol were identically over-encapsulated, packaged, and labeled with unique container numbers. All participants and site/spouse personnel involved in conduct of the trial were blinded to treatment group.

Each patient’s dose was titrated progressively from 6.25 mg of carvedilol twice daily and 50 mg of metoprolol twice daily to a maximum dose of 25 mg and 200 mg twice daily, respectively, at 1- to 2-week intervals toward target BP levels for a total of 2 to 7 weeks. Target systolic BP was 135 mm Hg or less for those participants with baseline of 140 to 179 mm Hg and 130 mm Hg or less for those with baseline of 130 to 140 mm Hg. Target diastolic BP was 85 mm Hg or less for those participants with baseline diastolic BP of 90 to 109 mm Hg and 80 mm Hg or less for those participants with baseline diastolic BP of 80 to 90 mm Hg. A dose of 12.5-mg hydrochlorothiazide followed by a dihydropyridine calcium antagonist were added as necessary to achieve target BP. On reaching target BP or the highest dose level, participants began 5 months of maintenance therapy. Maximum study length per participant was 35 weeks, including down-titration as necessary and safety follow-up. No longer term follow-up was planned.

Study Outcomes

The primary outcome was the difference in change from baseline HbA1c between groups following 5 months of maintenance therapy. Secondary outcomes that were prespecified included changes from baseline HbA1c in the individual treatment groups, changes in systolic and diastolic BP, fasting glucose and insulin, insulin resistance using the Homeostasis Model Assessment-Insulin Resistance (HOMA-IR, a validated clinical index of insulin resistance derived from fasting insulin and glucose levels19), cholesterol subfractions (total, low-density lipoprotein, and high-density lipoprotein), triglycerides, urinary albumin/creatinine ratio (mg/g), and withdrawals due to worsening glycemic control (fasting plasma glucose >270 mg/dL [>15.0 mmol/L] confirmed by retest; permanent change to antidiabetic medication, or recurrent or clinically concerning hyperglycemia or hypoglycemia). Patients taking insulin were excluded from analyses of insulin or insulin resistance. Lastly, 3 post hoc analyses performed were new use of statins and increases in HbA1c of more than 0.5% and more than 1%.

Statistical Methods

All data are expressed as mean (SD) unless otherwise noted. The primary outcome of between-group difference of change in HbA1c was assessed using an intention-to-treat analysis. In addition, 2 principal secondary hypotheses were tested: metoprolol worsens glycemic control and carvedilol does not, as measured by change in HbA1c. Sample size calculation was based on detecting a difference for the primary outcome of 0.30% in HbA1c change from baseline between carvedilol and metoprolol. Assuming an SD of 1.2% and using a 2-sided test at a 5% significance level, 338 participants per treatment group would yield 90% power. To evaluate the secondary hypothesis, that metoprolol worsens glycemic control, and to detect a HbA1c change from baseline of +0.15% with 1.2% SD, a 2-sided test at the 5% significance level required 505 participants to achieve 80% power. For the secondary hypothesis that carvedilol does not worsen glycemic control, a limit was set of +0.10% for HbA1c change from baseline between carvedilol and metoprolol. Assuming an SD of 1.2% and using a 2-sided test at a 5% significance level, 338 participants per treatment group would yield 90% power. To evaluate the hypothesis that metoprolol worsens glycemic control, and to detect a HbA1c change from baseline of +0.15% with 1.2% SD, a 1-sided “as good as or better” test with 2.5% significance level required 183 participants to achieve 80% power.

The target sample size was thus finalized at 1210 participants (484 in the carvedilol group and 726 in the metoprolol group) using a 2:3 randomization ratio, and including overages of 10% to account for participants dropping out and of 20% to compensate for a possible treatment-by-thiazolidinedione use interaction. These sample sizes provide 94% power to test the primary hypothesis and 96% and 80% power, respectively, for the secondary hypotheses. Assumptions for mean HbA1c change from baseline and SDs were based on literature review of studies examining the effect of carvedilol20-22 and selective β1-blockers23,24 on HbA1c.

The primary analysis for treatment group difference in HbA1c change from baseline was based on analysis of covariance, adjusting for treatment group, baseline HbA1c, ARB use, and thiazolidinedione use. Because the trial began as 2 simultaneous identical studies (one including sites from eastern United States and the other from western United States) per Food and Drug Administration requirement, an effect for study was also included. When recruitment for one area of the country became very slow, it was decided to combine the 2 studies and forego seeking approval for a new indication so that 1 adequately powered study would address the hypothesis. The treatment-by-study and treatment-by-thiazolidinedione interactions were tested and found to be nonsignificant. Because baseline use of ARBs and thiazolidinediones were stratification factors, they were retained in the model.

A multivariate analysis of covariance was performed to consider effects of factors on HbA1c change from baseline. The covariates of interest included baseline HbA1c, study, and treatment group; baseline use of ARBs and thiazolidinediones, ARBs, statins, hydrochlorothiazide, and calcium antagonist use during the study; race (white, black, or other declared by the participant); sex; and end of study treatment dose level. Race was assessed in the study to determine the distribution of the cohort studied and not to test an a priori hypothesis. Interactions of treatment with hydrochlorothiazide, race, statin, and dose level were also included. Lastly, post hoc analyses to evaluate the percentage of participants who had more than 0.5% and more than 1% increases in HbA1c were
performed. These analyses corrected for baseline HbA1c, treatment randomization, thiazolidinedione, ARB, hydrochlorothiazide, age, sex, and statin use. An additional post hoc analysis evaluated use of statins in the 2 groups.

For secondary outcomes, all continuous variables were analyzed via analysis of covariance using a similar model as specified for the primary efficacy parameter. Due to skewness of the data, a natural log transformation was used for analyzing urinary albumin/creatinine ratio, lipids, and HOMA-IR. Analysis of binary variables was based on logistic regression with a model adjusting for treatment group, study, and baseline HbA1c, and ARB and thiazolidinedione use.

Analyses were based on a modified intention-to-treat efficacy population defined as participants randomized with valid baseline and at least 1 on-therapy assessment. Change from baseline was calculated only for participants with both baseline and at least 1 on-therapy measurement. Results were based on analysis at maintenance month 5 visits for all variables, with missing values imputed using last observation carried forward analysis. (There were 70 [15%] of 454 missing values in the carvedilol group and 111 [16%] of 657 in the metoprolol group at month 5.) In addition, a true intention-to-treat analysis was performed that included all existing data from all participants using last observation carried forward. All analyses were performed using SAS version 8 (SAS Institute Inc, Cary, NC). Two-sided P values and 95% confidence intervals (CIs) are reported. Treatment comparisons were tested at a 5% significance level (P<.05) and tests of interactions were performed using a 10% significance level (P<.10).

Du-1. Characteristics of the Participants Receiving Either Carvedilol or Metoprolol Therapy

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Carvedilol (n = 498)</th>
<th>Metoprolol (n = 737)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>60.7 (9.4)</td>
<td>61.1 (9.7)</td>
</tr>
<tr>
<td>Women</td>
<td>198 (39.8)</td>
<td>354 (48.0)</td>
</tr>
<tr>
<td>Race/ethnicity†</td>
<td>White</td>
<td>382 (76.7)</td>
</tr>
<tr>
<td>Black</td>
<td>62 (12.4)</td>
<td>105 (14.2)</td>
</tr>
<tr>
<td>Asian</td>
<td>20 (4.0)</td>
<td>23 (3.1)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>31 (6.2)</td>
<td>55 (7.5)</td>
</tr>
<tr>
<td>Other/multiracial</td>
<td>3 (0.6)</td>
<td>6 (0.8)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>33.5 (5.8)</td>
<td>37.7 (6.2)</td>
</tr>
<tr>
<td>C-peptide, ng/mL</td>
<td>3.36 (1.59)</td>
<td>3.42 (1.62)</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.2 (0.55)</td>
<td>7.19 (0.54)</td>
</tr>
</tbody>
</table>

Antidiabetic medications

| Sulfonylurea‡ | 91 (18.3) | 117 (15.9) |
| Biguanides‡ | 79 (15.9) | 108 (14.7) |
| Thiazolidinediones‡ | 16 (3.2) | 28 (3.8) |
| Meglitinides‡ | 1 (0.2) | 4 (0.5) |
| Multiple agents | 260 (52.2) | 414 (56.2) |
| Insulin | 40 (8.0) | 60 (8.1) |
| None | 40 (8.0) | 57 (7.7) |

Abbreviations: BMI, body mass index calculated as weight in kilograms divided by the square of height in meters; HbA1c, glycosylated hemoglobin.

*Data are presented as No. (%) unless otherwise specified.†Race was self-described by the participant and was assessed to determine the distribution of the cohort studied and not to test an a priori hypothesis.‡Monotherapy; does not reflect use of these agents as part of multiguent therapy.

RESULTS

Patient Enrollment

A total of 1235 participants were randomized at 205 sites in the United States (n = 498 in the carvedilol group and n = 737 in the metoprolol group) and comprise the primary intention-to-treat analysis. Of these, 454 (91%) and 657 (89%) participants comprised the modified intention-to-treat efficacy population, having both baseline and on-therapy HbA1c measurements. Additionally, the entire 5 months of maintenance treatment were completed by 399 (80%) of 498 participants in the carvedilol group and 547 (74%) of 737 participants in the metoprolol group (Figure 1).

Baseline Characteristics

Patient demographic characteristics at study entry were similar (Table 1). At screening, nearly all participants were receiving an ACE inhibitor or ARB; 718 (58%) of 1235 participants were receiving 2 or more antihypertensive agents and almost half were taking statins (Table 2). Following discontinuation of antihypertensive medications other than ACE inhibitor or ARB, baseline BP remained well above the recommended target of 130/80 mm Hg. Diabetes mellitus was well-controlled (mean baseline HbA1c, 7.2%), with mean body mass index of 34 (calculated as weight in kilograms divided by the square of height in meters). A total of 674 participants were receiving multiple antidiabetic medications and 100 (8%) were taking insulin (Table 1). Less than 10% of the cohort had a history of coronary artery disease.

Treatment Characteristics

Treatment duration was longer in the carvedilol group (mean [SD], 155 [32] days in the carvedilol group vs 147 [60] days in the metoprolol group; P = .01) due to drug discontinuation in the metoprolol group associated with adverse effects. The mean doses required to achieve target BP were 17.5 mg twice daily for carvedilol and 128 mg twice daily for metoprolol, with approximately half of each group requiring the highest dose. No difference in the proportion of each group that required 12.5-mg hydrochlorothiazide or a calcium antagonist was observed (Table 2).
Primary Outcome

The mean difference between carvedilol and metoprolol with respect to the change in HbA1c from baseline was 0.12% (SD, 0.04%; 95% Cl, –0.20% to –0.03%; P = .006) for the intention-to-treat analysis using last observation carried forward and 0.13% (SD, 0.05%; 95% Cl, –0.22% to –0.04%; P = .004) for the modified intention-to-treat analysis.

Prespecified Secondary Outcomes

Carvedilol treatment had no effect on HbA1c (mean [SD] change from baseline to end point, 0.02% [0.04%]; 95% CI, –0.06% to 0.10%; P = .65), while metoprolol increased HbA1c (0.15% [0.04%]; 95% CI, 0.08%–0.22%; P < .001) (Figure 2).

Metabolic. More participants withdrew due to worsening glycemic control in the metoprolol group (16 [2.2%] of 737 participants in the metoprolol group vs 3 (0.6%) of 498 in the carvedilol group, P = .04). Additionally, HOMA-IR was reduced by carvedilol (–9.1%, P = .004) but not metoprolol (–2.0%, P = .48); the between-group difference was –7.2% (95% CI, –13.8% to –0.2%; P = .004). Changes in the HOMA-IR significantly correlated with changes in HbA1c (r = 0.16 for carvedilol, P = .002 vs r = 0.29 for metoprolol, P < .001). Metoprolol in-

Table 3. Cardiovascular and Metabolic Measures in the Modified Intention-to-Treat Populationa

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BP, mean (SE), mm Hg‡</th>
<th>Diastolic</th>
<th>Heart rate/min, mean (SE)‡</th>
<th>Mean ACR, mg/g§</th>
<th>Mean HOMA-IR§</th>
<th>Mean plasma glucose, mg/dL†</th>
<th>Mean serum insulin, µU/mL‡</th>
<th>Mean body weight, kg‡</th>
<th>Mean serum cholesterol levels, mg/dL§</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Participants Baseline</strong></td>
<td>454</td>
<td>454</td>
<td>454</td>
<td>388</td>
<td>371</td>
<td>419</td>
<td>387</td>
<td>456</td>
<td>433</td>
</tr>
<tr>
<td><strong>BP, mean (SE), mm Hg‡</strong></td>
<td>149.4 (0.6)</td>
<td>87.0 (0.4)</td>
<td>73.7 (0.5)</td>
<td>13.3</td>
<td>6.0</td>
<td>147.0</td>
<td>21.6</td>
<td>456</td>
<td>185.6</td>
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<tr>
<td><strong>Mean ACR, mg/g§</strong></td>
<td>11.1</td>
<td>5.8</td>
<td>9.1</td>
<td>–14.0</td>
<td>–9.1</td>
<td>–9.1</td>
<td>–19.4</td>
<td>97.2</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Mean HOMA-IR§</strong></td>
<td>12.0</td>
<td>5.8</td>
<td>5.8</td>
<td>13.3</td>
<td>6.2</td>
<td>154.7</td>
<td>20.2</td>
<td>98.2</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Mean plasma glucose, mg/dL†</strong></td>
<td>147.0</td>
<td>154.7</td>
<td>154.7</td>
<td>13.3</td>
<td>6.2</td>
<td>145.7</td>
<td>20.2</td>
<td>98.2</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Mean serum insulin, µU/mL‡</strong></td>
<td>21.6</td>
<td>19.6</td>
<td>19.6</td>
<td>13.3</td>
<td>12.0</td>
<td>154.7</td>
<td>20.2</td>
<td>98.2</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Mean body weight, kg‡</strong></td>
<td>97.2</td>
<td>97.2</td>
<td>97.2</td>
<td>13.3</td>
<td>12.0</td>
<td>145.7</td>
<td>20.2</td>
<td>98.2</td>
<td>–3.3</td>
</tr>
<tr>
<td><strong>Mean serum cholesterol levels, mg/dL§</strong></td>
<td>185.6</td>
<td>185.6</td>
<td>185.6</td>
<td>13.3</td>
<td>12.0</td>
<td>145.7</td>
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<tr>
<td><strong>Prespecified Secondary Outcomes</strong></td>
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</table>

The change from baseline to maintenance month 5 (primary outcome) was significant (mean difference [SD], 0.13% [0.05%]; 95% confidence interval, –0.22% to –0.04%; P = .004). Error bars indicate SD from mean.
Table 4. Covariate Analysis of Change from Baseline to Month 5 in HbA1c

<table>
<thead>
<tr>
<th>Covariate</th>
<th>df</th>
<th>F Value+</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Baseline HbA1c*</td>
<td></td>
<td>37.0</td>
<td>&lt;.001</td>
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<tr>
<td>Treatment</td>
<td></td>
<td>4.97</td>
<td>.03</td>
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<tr>
<td>Race</td>
<td></td>
<td>5.48</td>
<td>.004</td>
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<tr>
<td>Statin</td>
<td></td>
<td>7.83</td>
<td>.006</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td>1.13</td>
<td>.29</td>
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<tr>
<td>Hydrochlorothiazide</td>
<td></td>
<td>0.25</td>
<td>.62</td>
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<tr>
<td>Baseline thiazolidinedione</td>
<td></td>
<td>0.70</td>
<td>.40</td>
</tr>
<tr>
<td>Baseline ARB</td>
<td></td>
<td>0.59</td>
<td>.44</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td>2.40</td>
<td>.12</td>
</tr>
<tr>
<td>Treatment × race</td>
<td></td>
<td>0.05</td>
<td>.95</td>
</tr>
<tr>
<td>Treatment × statin</td>
<td></td>
<td>0.12</td>
<td>.73</td>
</tr>
<tr>
<td>Treatment × hydrochlorothiazide</td>
<td>1</td>
<td>1.98</td>
<td>.16</td>
</tr>
<tr>
<td>Treatment × dose</td>
<td></td>
<td>0.001</td>
<td>.96</td>
</tr>
</tbody>
</table>

Abbreviations: ARB, angiotensin II receptor blocker; HbA1c, glycosylated hemoglobin.

*The following factors were tested at the 5% level and found not to be significant: study, baseline thiazolidinedione use, baseline ARB use, hydrochlorothiazide use, and study medication dose achieved. Similarly, the interactions of treatment × hydrochlorothiazide, treatment × race, treatment × statin, and treatment × study medication dose achieved were not significant at the 10% level.

[1]The estimated coefficient for the baseline HbA1c was −0.26 (95% confidence interval, −0.34 to −0.17; P < .001), suggesting that there is a change (reduction) of 0.26 in month 5 HbA1c levels for each unit increase in baseline HbA1c, given that all the other terms in the model are held constant.

creased triglycerides (13%, P < .001), whereas carvedilol had no effect; no treatment difference for low-density lipoprotein or high-density lipoprotein cholesterol was noted between groups.

Cardiovascular. Blood pressure and heart rate were similarly controlled in both groups (Table 3). Approximately 44% of each treatment group required hydrochlorothiazide and approximately 25% required a dihydropyridine calcium antagonist, or both, to achieve goal BP. In a post hoc analysis, BP levels of less than 130/80 mm Hg were achieved in most participants (310 [68%] of 454 in the carvedilol group vs 427 [67%] of 636 in the metoprolol group).

Microalbuminuria, defined as a urinary albumin/creatinine excretion rate of approximately 30 to 300 mg/g, was present in 77 (20%) of 388 participants in the carvedilol group and 97 (18%) of 542 participants in the metoprolol group at baseline. At study end, carvedilol reduced the albumin/creatinine ratio compared with metoprolol (16% relative reduction, P = .003) (Table 3). Of those with albuminuria of 30 mg/g or less at baseline, fewer participants progressed to microalbuminuria in the carvedilol group (25 [6.4%] of 388 in the carvedilol group vs 56 [10.3%] of 542 in the metoprolol group; odds ratio [OR] for carvedilol vs metoprolol, 0.60; 95% CI, 0.36-0.97; P = .04).

Post Hoc Analyses

One post hoc analysis adjusted for baseline statin use (taken by 505 [45%] of 1118 participants) and showed similar treatment effects. More participants had a statin initiated or existing statin dose increased in the metoprolol group (32 [4.9%] of 659 participants in the metoprolol group vs 11 [2.4%] of 459 participants in the carvedilol group, P = .04).

In a second post hoc analysis, the proportion of participants with an increase in HbA1c of at least 0.5% was higher in the metoprolol group (199 [30%] of 657 participants in the metoprolol group vs 99 [22%] of 454 participants in the carvedilol group; OR for carvedilol vs metoprolol, 0.64; 95% CI, 0.49-0.85; P = .002). An increase of at least 1% was also more frequent in the metoprolol group (93 [14.2%] of 657 participants in the metoprolol group vs 32 [7.0%] of 454 participants in the carvedilol group; OR for carvedilol vs metoprolol, 0.46; 95% CI, 0.30-0.70; P < .001). After adjustment, the percentage of participants with increases of more than 1% remained significant between groups (OR, 0.46; 95% CI, 0.30-0.70; P < .001). Multivariate analysis tested for an interaction with each of the following covariates: baseline HbA1c, treatment group, race, sex, baseline thiazolidinedione or ARB, and on-treatment hydrochlorothiazide, calcium antagonist, or statin, and found no significant interactions (Table 4).

Adverse Events

No differences were observed between groups in overall safety profile (Table 5). Significant weight gain was observed in the metoprolol group (mean [SD], 1.2 [0.2] kg for metoprolol, P < .001 vs 0.2 [0.2] kg for carvedilol, P = .36). Structured surveillance of hypoglycemic episodes using patient diary recordings revealed that both asymptomatic and symptomatic episodes occurred in similar percentages of participants receiving carvedilol and metoprolol. Three participants (0.4%) withdrew from treatment with metoprolol due to hypoglycemia. Bradycardia was more frequent in the metoprolol group than in the carvedilol group.

A total of 19 participants (3.8%) taking carvedilol and 36 (4.9%) taking metoprolol had nonfatal serious adverse events. In the carvedilol group, 6 participants had 7 cardiac events recorded, of which 2 were acute myocardial infarction; in the metoprolol group, 7 participants had events recorded, of whom 1 had acute myocardial infarction. Metabolic events were recorded for 1 participant in the carvedilol group vs 3 in the metoprolol group. Two participants had 3 nervous system events reported in the carvedilol group vs 6 in the metoprolol group; 1 participant in each group had a stroke. No participant taking carvedilol had a respiratory event in contrast with 7 events in 6 participants taking metoprolol. One report of gangrene was made in the carvedilol group.

Three participants died, 1 taking carvedilol and 2 taking metoprolol; none were taking the study drug at the time of death. The participant taking carvedilol died of gastric cancer 39 days after stopping medications.
participants taking metoprolol who died, 1 died of gastrointestinal hemorrhage 2 days after stopping study medication and 1 died of an unknown cause 38 days after stopping study medication. More detailed information on clinical outcomes is available from the authors on request.

**COMMENT**

The GEMINI trial is the first randomized trial to compare the effects of 2 different β-blockers on glycemic control as well as other cardiovascular risk factors in a cohort with glycemic control similar to the UKPDS. Our trial demonstrates differences in stabilization of glycemic control and improvement of insulin resistance between carvedilol and metoprolol at doses needed to achieve BP goal. Carvedilol stabilized HbA1c, improved insulin resistance, and slowed development of microalbuminuria in the presence of RAS blockade compared with metoprolol. Outcome trials indicate that aggressive management of cardiovascular risk factors, such as BP, lipid abnormalities, and glycemic control, reduce cardiovascular risk in patients with DM.

Given that only 7.3% of participants from the NHANES IV study actually achieve goals recommended by all guidelines (HbA1c <7%, systolic BP <130 mm Hg, and total cholesterol <200 mg/dL [<5.18 mmol/L]), it is important to use antihypertensive therapies that not only reduce cardiovascular risk but also help stabilize or improve components of the metabolic syndrome, assuming similar clinical outcomes.3

In the UKPDS and Norfolk studies, the risk of cardiovascular events directly correlates with the level of glycemic control as assessed by HbA1c.2,20 Thus, hypothetically, worsening of glycemic control may not allow for maximal benefit on cardiovascular risk reduction of β-blockers, although this possibility has not been tested directly. In our study, both β-blockers were well tolerated and the mean increase in HbA1c was modest with metoprolol; however, in a post hoc analysis, increases of more than 1% occurred in more than twice as many participants randomized to metoprolol as carvedilol, and a greater number of participants randomized to metoprolol were withdrawn due to worsening glycemic control. An analysis to define predictors of adverse glycemic response to β-blockade failed to identify any factors.

Our findings were not linked to a primary cardiovascular outcome. However, 4 randomized trials4-7 have evaluated RAS blockers and cardiovascular outcomes; the different effects on metabolic factors found in these studies may provide insights relevant to our study. One trial4 showed a clear benefit of losartan on cardiovascular events and 3 trials showed no difference between RAS blockade and β-blockade6 or conventional therapy.5,7 Cardiovascular outcomes in 3 of these trials were correlated with baseline level of glycemia; those patients with greater degrees of hyperglycemia had more benefit from RAS blockers.4,6 These studies suggest that when treating patients with DM and hypertension, the use of antihypertensive agents that facilitate glycemic control and reduce cardiovascular risk factors may be associated with fewer cardiovascular events.

In UKPDS 39,8 a study with similar HbA1c levels to our cohort, participants allocated to atenolol had a higher mean HbA1c compared with captopril in the first 4 years of follow-up, and required an increase in antidiabetic medication use in 66% of patients vs 53% in those taking captopril. In the last 4 years of the trial, there was no difference in glycemic control and cardiovascular outcomes for the trial did not differ. Conversely, in the Captopril Prevention Project trial,9 in the subgroup of patients with DM at baseline, who had blood glucose values higher than GEMINI (mean glucose approximately 180 mg/dL [10 mmol/L] at baseline or an HbA1c of approximately 8%), captopril significantly reduced fatal cardiovascular events compared with conventional therapy (β-blocker or thiazide).9 Lastly, the Swedish Trial in Old Patients with Hypertension-2 study7 showed no difference between RAS blockers and β-blockers on cardiovascular outcomes and no difference in DM incidence; however, few data are presented on the subset of patients with DM at baseline. Data from the European Prospective Investigation of Cancer and Nutrition cohort study57 suggested that among men with HbA1c less

<table>
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<th>Table 5. Adverse Effects Reported in at Least 4% of Participants</th>
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<td><strong>Adverse Effects</strong></td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Asymptomatic hypoglycemia†</td>
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<td>Dizziness</td>
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<td>Headache</td>
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<td>Diarrhea</td>
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<td>Symptomatic hypoglycemia†</td>
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<td>Cough</td>
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<td>Diabetes mellitus worsened‡</td>
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<td>Bradycardia</td>
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*Assessed by χ² analysis.
†Reports of hypoglycemia were generated from structured surveillance of patient diaries.
‡As reported by investigator.

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than 7%, an increase in HbA1c of 1% was associated with a 28% increase in risk of death. If these data are extrapolated to participants in our study, who had mean HbA1c levels of more than 7%, the change in HbA1c observed in our study would be associated with a 5.2% decrease in cardiac mortality and a 5.7% decrease in cardiac events.

The decrease in the HbA1c, while statistically significant and clinically relevant was less than we predicted based on previous studies. We believe there are 2 reasons for this observation. First, the baseline HbA1c levels were lower than other studies used to derive the power calculations, with 39% of participants having HbA1c levels of less than 7%. Second, this is the first study to our knowledge of glycemic control with β-blockers in participants with type 2 DM in which all participants received RAS blockade that lowers insulin resistance.28 In spite of these optimal circumstances for glycemic control, the HbA1c difference between groups favored carvedilol.

Using the HOMA-IR model, we demonstrated a reduction in insulin resistance with carvedilol compared with metoprolol, an effect that correlated with HbA1c. Treatment with carvedilol was associated with improvement in total cholesterol and a smaller increase in triglyceride levels relative to metoprolol. This finding supports the effect of carvedilol on reducing insulin resistance, which has been previously shown in the more time-intensive insulin clamp studies.21 No treatment differences were observed in low-density lipoprotein or high-density lipoprotein cholesterol levels, which may, in part, be explained by the fact that there were no constraints on lipid medications. Preexisting statin use occurred in almost half of participants; notably, significantly more participants in the metoprolol group had statin therapy initiated or had their statin dose increased during the study. An early outcome trial with a nonselective β-blocker before statin use, however, demonstrated a reduction in cardiovascular outcomes in spite of worsening lipid profile.29

Blood pressure reduction is a cornerstone of therapy for cardiovascular risk reduction in DM.10,11,30 In this study, although BP reduction was comparable in both groups, the dose of metoprolol was limited by its impact on heart rate. An analysis of data show a dosage ratio of 1:2 carvedilol:metoprolol on heart rate reduction.31 Thus, doses of metoprolol needed to achieve BP goals in our participants resulted in a higher incidence of bradycardia.

All participants received an ACE inhibitor or ARB known to affect microalbuminuria.10,32-35 Participants who were normotensive showed a reduction in progression to microalbuminuria with carvedilol as well as a reduction in existing microalbuminuria. Metoprolol failed to decrease microalbuminuria, a finding also observed in the African-American Study of Kidney Disease trial with long-acting metoprolol.36 This result may be related to an improvement in insulin resistance as noted by differences in the HOMA-IR index or an effect on oxidant stress as described in other studies with carvedilol.22,37,38

The major limitation of this short-term treatment trial is the use of surrogate markers in place of definitive outcomes, such as cardiovascular events and mortality; an outcome trial is needed to assess whether the glucose differences noted translate to improved outcomes. The differences in factors included in the cardiovascular risk profile and metabolic effects support earlier mechanistic studies. We conclude that use of β-blockade when combined with RAS blockade in participants with type 2 DM and hypertension was well tolerated and effective in achieving BP targets. However, carvedilol resulted in improved cardiovascular risk factors and stabilized glycemic control relative to metoprolol.

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Author Contributions: Drs Bakris and Bell had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.


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CARVEDIOL VS METOPROLOL FOR DIABETES MELLITUS AND HYPERTENSION

After completion of the study, a complete copy of the database was transferred to Rush University Medical Center. Primary statistical analysis was performed by GlaxoSmithKline but verified independently by the Statistics Section of the Department of Preventive Medicine and Epidemiology. Data were analyzed by the first and corresponding authors and they were further analyzed by the statistician. All authors were involved in the interpretation of results. The final decision on content was exclusively retained by the authors.

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REFERENCES


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