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

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DATA FROM LARGE OUTCOME trials indicate that the level of glycemic control predicts cardiovascular events.1,2 In the UK Prospective Diabetes Study (UKPDS),3 patients with lower initial glycemia had fewer adverse clinical outcomes despite similar glycemic progression. Taken together with data from the National Health and Nutrition Examination Survey IV (NHANES IV), that only 37% of adults with diabetes mellitus (DM) attain recommended levels of glycosylated hemoglobin (HbA1c), achieving better glycemic control should further reduce the risk of cardiovascular events.3

Randomized trials comparing renin-angiotensin system (RAS) blockers with β-blockers demonstrate that cardiovascular outcomes are improved by RAS blockers, which maintain or improve

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.
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 in participants with hypertension and 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 0.5% or less increase from screening. Randomized treatment assignment was communicated to sites by an automated interactive randomization and medication ordering system (RAMOS, GlaxoSmithKline, Philadelphia, Pa) that used a randomly permuted block of 5 in a 2:3 carvedilol:metoprolol distribution and incorporated stratification to equalize ARBs and thiazolidinedione medications in the treatment groups to
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/sponsor 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, beyond which glycemic control would be said to have worsened. Assuming a HbA1c change from baseline of −0.15% and 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 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 likelihood ratio (\(\chi^2\)) tests of interactions were performed using SAS version 8 (SAS Institute Inc, Cary, NC).

**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 s 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 [52] 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).

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**Table 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 (8.7)</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></td>
<td>Black</td>
<td>62 (12.4)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>20 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>31 (6.2)</td>
</tr>
<tr>
<td></td>
<td>Other/multiracial</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td></td>
<td>BMI, mean (SD)</td>
<td>33.5 (5.8)</td>
</tr>
<tr>
<td></td>
<td>Biochemistry, mean (SD)</td>
<td>C-peptide, ng/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HbA1c, %</td>
</tr>
<tr>
<td></td>
<td>Antidiabetic medications</td>
<td>Sulfonylurea‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biguanides‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thiazolidinediones‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meglitinides‡</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
</tbody>
</table>

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

**Table 2.** Antihypertensive and Statin Use at Baseline and End of Study

<table>
<thead>
<tr>
<th>Medication</th>
<th>Carvedilol (n = 498)</th>
<th>Metoprolol (n = 737)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE/ARB</td>
<td>487 (97.8)</td>
<td>483 (97.0)</td>
</tr>
<tr>
<td>Hydrochlorothiazide†</td>
<td>33 (6.6)</td>
<td>216 (43.4)</td>
</tr>
<tr>
<td>Calcium antagonist†</td>
<td>21 (4.2)</td>
<td>123 (24.7)</td>
</tr>
<tr>
<td>(\beta)-Blocker†</td>
<td>13 (2.6)</td>
<td>13 (2.6)</td>
</tr>
<tr>
<td>Statins</td>
<td>219 (44.0)</td>
<td>224 (45.0)</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
†Data are presented as No. (%) unless otherwise specified.
‡Hydrochlorothiazide, calcium antagonist, and \(\beta\)-blocker use at baseline had to be for nonantihypertensive indication.
**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% CI, –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% CI, –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 = .02). 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 increases

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carvedilol (n = 454)</th>
<th>Metoprolol (n = 657)</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, mean (SE), mm Hg‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>146.4 (0.6)</td>
<td>131.3 (0.7)</td>
<td>19.0 (0.7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>87.0 (0.4)</td>
<td>77.1 (0.4)</td>
<td>10.0 (0.4)</td>
</tr>
<tr>
<td>Heart rate/min, mean (SE)‡</td>
<td>73.7 (0.5)</td>
<td>76.2 (0.4)</td>
<td>–3.0 (0.4)</td>
</tr>
<tr>
<td>Mean ACR, mg/g‡</td>
<td>13.3</td>
<td>11.1</td>
<td>–2.0 (0.4)</td>
</tr>
<tr>
<td>Mean HOMA-IR§</td>
<td>6.0</td>
<td>5.8</td>
<td>–0.2 (0.4)</td>
</tr>
<tr>
<td>Mean plasma glucose, mg/dL‡</td>
<td>147.0</td>
<td>154.7</td>
<td>–7.7 (0.4)</td>
</tr>
<tr>
<td>Mean serum insulin, µU/mL‡</td>
<td>21.6</td>
<td>21.9</td>
<td>–0.3 (0.4)</td>
</tr>
<tr>
<td>Mean body weight, kg‡</td>
<td>84.3</td>
<td>97.0</td>
<td>–2.7 (0.4)</td>
</tr>
<tr>
<td>Mean serum cholesterol levels, mg/dL§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>185.6</td>
<td>181.7</td>
<td>–3.9 (0.4)</td>
</tr>
<tr>
<td>LDL</td>
<td>116.6</td>
<td>106.8</td>
<td>–9.8 (0.4)</td>
</tr>
<tr>
<td>HDL</td>
<td>48.4</td>
<td>42.5</td>
<td>–5.9 (0.4)</td>
</tr>
<tr>
<td>Mean triglycerides, mg/dL‡</td>
<td>159.4</td>
<td>168.3</td>
<td>–8.9 (0.4)</td>
</tr>
</tbody>
</table>

**Figure 2.** Glycosylated Hemoglobin (Hba1c) at Baseline and Each Maintenance Month by Treatment in the Modified Intention-to-Treat Population

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.

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**SI conversions:** To convert total cholesterol, HDL, and LDL to mmol/L, multiply by 0.0259; plasma glucose to mmol/L, multiply by 0.0555; plasma insulin to pmol/L, multiply by 6.945; and triglycerides to mmol/L, multiply by 0.0113.

*All chemistries were performed on samples obtained from fasted participants. Statistical analyses were based on modified intention-to-treat analysis; however, when a true intention-to-treat analysis was performed, only the 617 participants of the 636 randomized to treatment using the full analysis set were included in analyses. The complete Table 3 for the intention-to-treat population is available from the authors on request.

**Abbreviations:** ACR, urinary albumin/creatinine ratio; BP, blood pressure; CI, confidence interval; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance (fasting plasma insulin concentration [µU/mL] × fasting plasma glucose [mmol/L]/22.5); LDL, low-density lipoprotein.

*Data expressed as least squares mean adjusted by the terms in the analysis model.

*Data expressed as geometric means based on exponentiation of the least squares means adjusted by the analysis model of natural log-transformed parameter.
increased 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 HbA\(_{1c}\), of at least 0.5% was higher in the metoprolol group (199 [30%] of 657 participants in the metoprolol group vs 99 [12%] of 654 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 HbA\(_{1c}\), 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. Of the 2 par-
participants taking metoprolol who died, 1 died of gastrointestinal hemorrhage 2 days after stopping study medica-
tion and 1 died of an unknown cause 38 days after stopping study medica-
tion. More detailed information on clinical outcomes is available from the
authors on request.

COMMENT

The GEMINI trial is the first random-
ized trial to compare the effects of 2 dif-
ferent β-blockers on glycemic control as
well as other cardiovascular risk factors
in a cohort with glycemic control simi-
lar to the UKPDS. Our trial demon-
strates differences in stabilization of glyce-
mic control and improvement of insu-
lin resistance between carvedilol and
metoprolol at doses needed to achieve BP
goal. Carvedilol stabilized HbA1c, im-
proved insulin resistance, and slowed de-
development of microalbuminuria in the
presence of RAS blockade compared with
metoprolol. Outcome trials indicate that
aggressive management of cardiovascu-
lar risk factors, such as BP, lipid abnor-
malities, and glycemic control, reduce
cardiovascular risk in patients with DM.25
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 di-
rectly correlates with the level of glyce-
mic control as assessed by HbA1c.2,20
Thus, hypothetically, worsening of glyce-
mic control may not allow for maxi-
mal benefit on cardiovascular risk re-
duction of β-blockers, although this
possibility has not been tested di-
rectly. In our study, both β-blockers
were well tolerated and the mean in-
crease in HbA1c was modest with meta-
prolol; however, in a post hoc analy-
sis, increases of more than 1% occurred
in more than twice as many partici-
pants randomized to metoprolol as
carvedilol, and a greater number of par-
ticipants randomized to metoprolol
were withdrawn due to worsening glyce-
ic control. An analysis to de-
fine predictors of adverse glycemic re-
sponse to β-blockade failed to identify
any factors.

Our findings were not linked to a pri-
mary cardiovascular outcome. How-
ever, 4 randomized trials4-7 have eval-
uated RAS blockers and cardiovascular
outcomes; the different effects on meta-
abolic factors found in these studies may
provide insights relevant to our study.
One trial4 showed a clear benefit of lo-
sartan on cardiovascular events and 3
trials showed no difference between RAS
blockade and β-blockade6 or con-
tventional therapy.5,7 Cardiovascular
outcomes in 3 of these trials were cor-
related with baseline level of glyce-
mia; those patients with greater de-
grees of hyperglycemia had more benefit
from RAS blockers.4,6 These studies suggest that when treating pa-
tients with DM and hypertension, the
use of antihypertensive agents that fa-
cilitate glycemic control and reduce car-
diovascular risk factors may be associ-
ated 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 tak-
ing captopril. In the last 4 years of the
trial, there was no difference in glyce-
ic control and cardiovascular out-
comes for the trial did not differ. Con-
versely, in the Captopril Prevention
Project trial,3 in the subgroup of patients
with DM at baseline, who had blood glu-
cose values higher than GEMINI (mean
glucose approximately 180 mg/dL
[10 mmol/L] at baseline or an HbA1c of
approximately 8%), captopril signifi-
cantly reduced fatal cardiovascular events
compared with conventional therapy
(β-blocker or thiazide).3 Lastly, the Swed-
ish Trial in Old Patients with Hyper-
tension-2 study7 showed no difference
between RAS blockers and β-blockers on
cardiovascular outcomes and no differ-
ence in DM incidence; however, few data
are presented on the subset of patients
with DM at baseline. Data from the Euro-
pean Prospective Investigation of Can-
cer and Nutrition cohort study27 sug-
gested that among men with HbA1c less

Table 5. Adverse Effects Reported in at Least 4% of Participants

<table>
<thead>
<tr>
<th>Adverse Effects</th>
<th>Carvedilol (n = 498)</th>
<th>Metoprolol (n = 737)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>59 (11.8)</td>
<td>112 (15.2)</td>
<td>.09</td>
</tr>
<tr>
<td>Asymptomatic hypoglycemia†</td>
<td>58 (11.6)</td>
<td>76 (10.3)</td>
<td>.46</td>
</tr>
<tr>
<td>Dizziness</td>
<td>47 (9.4)</td>
<td>57 (7.7)</td>
<td>.29</td>
</tr>
<tr>
<td>Headache</td>
<td>42 (8.4)</td>
<td>58 (7.9)</td>
<td>.72</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>39 (7.8)</td>
<td>69 (9.4)</td>
<td>.35</td>
</tr>
<tr>
<td>Symptomatic hypoglycemia†</td>
<td>42 (8.4)</td>
<td>65 (8.8)</td>
<td>.81</td>
</tr>
<tr>
<td>Edema, peripheral</td>
<td>38 (7.6)</td>
<td>56 (7.6)</td>
<td>.98</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>32 (6.4)</td>
<td>44 (6.0)</td>
<td>.74</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (6.0)</td>
<td>36 (4.9)</td>
<td>.38</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>27 (5.4)</td>
<td>32 (4.3)</td>
<td>.38</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>27 (5.4)</td>
<td>56 (7.6)</td>
<td>.13</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21 (4.2)</td>
<td>19 (2.6)</td>
<td>.11</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (4.2)</td>
<td>42 (5.7)</td>
<td>.25</td>
</tr>
<tr>
<td>Cough</td>
<td>20 (4.0)</td>
<td>35 (4.7)</td>
<td>.54</td>
</tr>
<tr>
<td>Diabetes mellitus worsened‡</td>
<td>12 (2.4)</td>
<td>32 (4.3)</td>
<td>.07</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>7 (1.4)</td>
<td>30 (4.1)</td>
<td>.007</td>
</tr>
</tbody>
</table>

*Assessed by χ2 analysis.
†Reports of hypoglycemia were generated from structured surveillance of patient diaries.
‡As reported by investigator.
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 cardiovascular 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 carbidol. The HbA1c difference between groups favored carbidol.

Using the HOMA-IR model, we demonstrated a reduction in insulin resistance with carbidol compared with metoprolol, an effect that correlated with HbA1c. Treatment with carbidol was associated with improvement in total cholesterol and a smaller increase in triglyceride levels relative to metoprolol. This finding supports the effect of carbidol on reducing insulin resistance, which has been previously shown in the more time-intensive insulin clamp studies. 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.

Blood pressure reduction is a cornerstone of therapy for cardiovascular risk reduction in DM. 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 carbidol:metoprolol on heart rate reduction. 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. Participants who were normotensive showed a reduction in progression to microalbuminuria with carbidol 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. 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 carbidol.

The major limitation of this short-term 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, carbidol 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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Acquisition of data: Bakris, Katholi, McGill, Messerli, Phillips, Raskin, Wright, Oakes, Anderson, Bell.

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was validated. Second, there may be barriers to implementing a targeted program. Nevertheless, these results suggest that, while every effort should be made to divert remaining vaccine supplies toward the target groups identified by the CDC, wherever there are insufficient doses for all target-group members, those at highest risk should receive priority. This group includes anyone with a previous hospitalization for pneumonia or influenza, all persons older than 80 years, and patients aged 65 to 80 years with a history of cancer, pulmonary disease, heart disease, dialysis, dementia, or stroke. Encouraging healthy patients younger than 75 years to wait until those at highest risk have had a chance to be vaccinated can help maximize the population outcome this influenza season.

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CORRECTION

Errors in Data Reporting: In the Original Contribution entitled “Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension: A Randomized Controlled Trial” published in the November 10, 2004, issue of THE JOURNAL (2004;292:2227-2236), there were multiple errors in data. On page 2227, in the Results section of the Abstract, “...the between-group difference was –7.2% (95% CI, –13.8% to –0.2%; P = .004).” should have read “…the between-group difference was –7.2% (95% CI, –13.8% to –0.2%; P = .04).” and “…with metoprolol (6.4% vs 10.3%; odds ratio, 0.60; 95% CI, 0.36-0.97; P = .04).” should have read “…with metoprolol (6.6% vs 11.1%; odds ratio, 0.53; 95% CI, 0.30-0.93; P = .03).” On page 2231, in the third column, second line, “P = .004” should have read “P = .04”; and in Table 3 on the same page, the P value for the mean HOMA-IR treatment difference should have been .04 instead of .004; and the baseline mean LDL cholesterol level for carvedilol should have been 96.7 instead of 186.6. On page 2232, in the first column, second paragraph, “…77 (20%) of 388 participants...” should have read “…76 (20%) of 388 participants...” and further down in the same paragraph, “…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).” should have read “…20 (6.6%) of 302 in the carvedilol group vs 48 (11.1%) of 431 in the metoprolol group; odds ratio [OR] for carvedilol vs metoprolol, 0.53; 95% CI, 0.30-0.93; P = .03).”