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. In the UK Prospective Diabetes Study (UKPDS), 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.

Randomized trials comparing renin-angiotensin system (RAS) blockers with β-blockers demonstrate that cardiovascular outcomes are improved by RAS blockers, which maintain or improve glycemic control. 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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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 identi-
cally 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 pro-
gressively 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, respecti-
vely, at 1- to 2-week intervals to-
ward 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 base-
line of 130 to 140 mm Hg. Target dia-
stolic 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 base-
line diastolic BP of 80 to 90 mm Hg. A
dose of 12.5-mg hydrochlorothiazide
followed by a dihydropyridine calcu-
cium antagonist were added as neces-
sary to achieve target BP. On reaching
target BP or the highest dose level, par-
ticipants began 5 months of mainte-
nance therapy. Maximum study length
per participant was 35 weeks, includ-
ing down-titration as necessary and
safety follow-up. No longer term fol-
low-up was planned.

Study Outcomes
The primary outcome was the differ-
ence in change from baseline HbA1c be-
tween groups following 5 months of
maintenance therapy. Secondary out-
comes that were prespecified in-
cluded baseline HbA1c, study, and treat-
ment group; baseline use of ARBs and thia-
zolidinediones, ARBs, statins, hydro-
chlorothiazide, and calcium antago-
nist use during the study; race (white,
black, or other declared by the partici-
pant); sex; and end of study treatment
administration requirement, an effect for
study was also included. When recruit-
ment for one area of the country be-
came very slow, it was decided to com-
bine the 2 studies and forego seeking
approval for a new indication so that 1
adequately powered study would ad-
dress the hypothesis. The treatment-
by-study and treatment-by-thiazoli-
dinedione interactions were tested and
found to be nonsignificant. Because
baseline use of ARBs and thiazolidine-
diones were stratification factors, they
were retained in the model.

A multivariate analysis of covari-
ance was performed to consider ef-
effects of factors on HbA1c change from
baseline. The covariates of interest
included baseline HbA1c, study, and
treatment group; baseline use of thia-
zolidinediones, ARBs, statins, hydro-
chlorothiazide, and calcium antago-
nist use during the study; race (white,
black, or other declared by the partici-
pant); 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 treat-
ment with hydrochlorothiazide, race,
statin, and dose level were also in-
cluded. Lastly, post hoc analyses to
evaluate the percentage of partici-
pants who had more than 0.5% and
more than 1% increases in HbA1c were

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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 last 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 5% significance level (P < .05). 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 ±[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).
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 0.10%; P = .65) while metoprolol increased HbA1c (0.15% [0.04%]; 95% CI, –0.06% to 0.10%; P = .004) for the intention-to-treat analysis using last observation carried forward and 0.13% (SD, 0.04%; 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 < .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 (Table 3), which resulted in a significant improvement from baseline for 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 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></td>
<td>No. of Participants</td>
<td>Maintenance Month 5 or Last Observation Carried Forward</td>
<td>No. of Participants</td>
</tr>
<tr>
<td>BP, mean (SE), mm Hg‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>454</td>
<td>149.4 (0.6)</td>
<td>131.3 (0.7)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>454</td>
<td>87.0 (0.4)</td>
<td>77.1 (0.4)</td>
</tr>
<tr>
<td>Heart rate/min, mean (SE)‡</td>
<td>454</td>
<td>73.7 (0.5)</td>
<td>67.6 (0.4)</td>
</tr>
<tr>
<td>Mean ACR, mg/g§</td>
<td>388</td>
<td>13.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Mean HOMA-IR§</td>
<td>371</td>
<td>6.0</td>
<td>5.8</td>
</tr>
<tr>
<td>Mean plasma glucose, mg/dL‡</td>
<td>419</td>
<td>147.0</td>
<td>154.7</td>
</tr>
<tr>
<td>Mean serum insulin, µIU/mL‡</td>
<td>387</td>
<td>21.6</td>
<td>19.6</td>
</tr>
<tr>
<td>Mean body weight, kg§</td>
<td>456</td>
<td>98.2</td>
<td>97.2</td>
</tr>
<tr>
<td>Mean serum cholesterol levels, mg/dL§</td>
<td>433</td>
<td>185.6</td>
<td>181.7</td>
</tr>
<tr>
<td>LDL</td>
<td>411</td>
<td>186.6</td>
<td>197.6</td>
</tr>
<tr>
<td>HDL</td>
<td>432</td>
<td>46.4</td>
<td>42.5</td>
</tr>
<tr>
<td>Mean triglycerides, mg/dL§</td>
<td>433</td>
<td>159.4</td>
<td>168.3</td>
</tr>
</tbody>
</table>

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 (µIU/mL) × fasting plasma glucose (mmol/L)/22.5; LDL, low-density lipoprotein.

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; serum insulin to pmol/L, multiply by 6.945; and triglycerides to mmol/L, multiply by 0.0113.

*Clinical outcomes 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, the only substantive difference was that systolic BP change –16.0 mm Hg in the metoprolol group and the treatment difference between groups was –1.9 (65% CI, –3.45 to –0.34; P = .02). The complete Table 3 for the intention-to-treat population is available from the authors on request.

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

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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; $P = .04$).

### Table 4. Covariate Analysis of Change from Baseline to Month 5 in HbA$_1c$*

<table>
<thead>
<tr>
<th>Covariate</th>
<th>df</th>
<th>$F$ Value*</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline HbA$_1c$†</td>
<td>1</td>
<td>37.0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment</td>
<td>1</td>
<td>4.97</td>
<td>.03</td>
</tr>
<tr>
<td>Race</td>
<td>2</td>
<td>5.48</td>
<td>.004</td>
</tr>
<tr>
<td>Statin</td>
<td>1</td>
<td>7.68</td>
<td>.006</td>
</tr>
<tr>
<td>Study</td>
<td>1</td>
<td>1.13</td>
<td>.29</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>1</td>
<td>0.25</td>
<td>.62</td>
</tr>
<tr>
<td>Baseline thiazolidinedione</td>
<td>1</td>
<td>0.70</td>
<td>.40</td>
</tr>
<tr>
<td>Baseline ARB</td>
<td>1</td>
<td>0.59</td>
<td>.44</td>
</tr>
<tr>
<td>Dose</td>
<td>1</td>
<td>2.40</td>
<td>.12</td>
</tr>
<tr>
<td>Treatment $\times$ race</td>
<td>2</td>
<td>0.05</td>
<td>.95</td>
</tr>
<tr>
<td>Treatment $\times$ statin</td>
<td>1</td>
<td>0.12</td>
<td>.73</td>
</tr>
<tr>
<td>Treatment $\times$ hydrochlorothiazide</td>
<td>1</td>
<td>1.98</td>
<td>.16</td>
</tr>
<tr>
<td>Treatment $\times$ dose</td>
<td>1</td>
<td>0.001</td>
<td>.96</td>
</tr>
</tbody>
</table>

*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 $\times$ hydrochlorothiazide, treatment $\times$ race, treatment $\times$ statin, and treatment $\times$ study medication dose achieved were not significant at the 10% level.

†The estimated coefficient for the baseline HbA$_1c$ is $-0.26$ (95% confidence interval, $-0.34$ to $-0.17$; $P < .001$), suggesting that there is a change (reduction) of 0.26 in month 5 HbA$_1c$ levels for each unit increase in baseline HbA$_1c$, given that all the other terms in the model are held constant.

### 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 [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 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 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.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 directly correlates with the level of glycemic control as assessed by HbA1c.2,26 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 glycemetic 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-blockade 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,5 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).5 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 study27 suggested that among men with HbA1c less

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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 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 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.29-33 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.10,11,13 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 dose 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.

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. Study concept and design: Bakris, Oakes, Lukas, Anderson, Bell. Acquisition of data: Bakris, Katholi, McGill, Messerli, Phillips, Raskin, Wright, Oakes, Anderson, Bell. Analysis and interpretation of data: Bakris, Fonseca, McGill, Messerli, Wright, Oakes, Lukas, Anderson, Bell. Drafting of the manuscript: Bakris, Fonseca, McGill, Messerli, Wright, Lukas, Anderson, Bell. Critical revision of the manuscript for important intellectual content: Bakris, Fonseca, Katholi, McGill, Messerli, Phillips, Raskin, Wright, Oakes, Anderson, Bell. Statistical analysis: Oakes, Anderson. Obtained funding: Wright, Bell. Administrative, technical, or material support: Fonseca, Katholi, Phillips, Wright, Lukas. Study supervision: Bakris, Wright, Anderson, Bell. The GEMINI Investigators: Alabama: David S. H. Bell, MD, Alan Bouchard, MD, David A. Callhoun, MD (Birmingham), Thomas M. Nolen, MD (ensumbria), Robbert Israel, MD (Mobile); Arizona: Robert Siegel, MD (Gilbert), Richard Albery, MD, Royal B. Ansprech, MD, Marshall Block, MD, James V. Felicetta, MD, Richard Heuser, MD, Rajal J. Patel, MD, Ernie Riffer, MD, Edward Tokatljan, MD, Kris Vijay, MD (Phoenix), Paul Fenster, MD, Mark Goldberg, MD, David Johnson, MD, Gregory Koshkarian, MD (Tucson); California: Dennis Riff, MD (Anaheim), William Zigang, MD (Burlingame), Jonathan Hemphill, MD (Carmichael), Georges Argoud, MD (Chula Vista), Roy Kaplan, MD (Concord), George Dennish, MD, James Quigley, DO (Encinitas), Malcolm Spering, MD, Betty Grant-Anderson, MD (Hemet), Sidney Rosenblatt, MD (Irvine), Deanna Cheung, MD (Long Beach),...
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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 at Rush University. The manuscript was prepared by the first and corresponding authors and they modified the manuscript after consultation with the other authors. GlaxoSmithKline was permitted to review the manuscript and submit to the journal. Final decision on content was exclusively retained by the authors.

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REFERENCES


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).”