Metabolic Effects of Carvedilol vs Metoprolol in Patients With Type 2 Diabetes Mellitus and Hypertension

A Randomized Controlled Trial

George L. Bakris, MD
Vivian Fonseca, MD
Richard E. Katholi, MD
Janet B. McGill, MD
Franz H. Messerli, MD
Robert A. Phillips, MD, PhD
Philip Raskin, MD
Jackson T. Wright, Jr, MD, PhD
Rosemary Oakes, MS
Mary Ann Lukas, MD
Karen M. Anderson, PhD
David S. H. Bell, MD
for the GEMINI Investigators

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 [HbA_{1c}], 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 HbA_{1c} following 5 months of maintenance therapy. Additional prespecified comparisons included change from baseline HbA_{1c} in individual treatment groups, treatment effect on insulin sensitivity, and microalbuminuria.

Results The 2 groups differed in mean change in HbA_{1c} from baseline (0.13%; 95% confidence interval [CI], –0.22% to –0.04%; $P=.004$; modified intention-to-treat analysis). The mean (SD) HbA_{1c} 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.

JAMA. 2004;292:2227-2236 www.jama.com

DATA FROM LARGE OUTCOME trials indicate that the level of glycemic control predicts cardiovascular events.[1,2] In the UK Prospective Diabetes Study (UKPDS),[2] 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 (HbA_{1c}), 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

Author Affiliations, Financial Disclosures, and the list of GEMINI Investigators are listed at the end of this article.
Corresponding Author: David S. H. Bell, MD, University of Alabama, Room 702, Faculty Office Tower 510, 20th St S, Birmingham, AL 35294 (dshbell@uab.edu).

glycemic control.[4-7] In persons with DM, β-blockers have been shown to increase fasting glucose by as much as 28 mg/dL (1.55 mmol/L),[8] and HbA_{1c}, by up to 1%.[9] 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.[10] All guidelines recommend β-blockers among other classes to achieve this goal.[10-12] 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.[4,13-15]

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 HbA_{1c} than a β-blocker without that effect, we compared the effects of the β-blocker carvedilol with metoprolol. HbA_{1c} was assessed because it was linearly related to risk of cardiovascular complications of type 2 DM in the UKPDS.[16]

METHODS

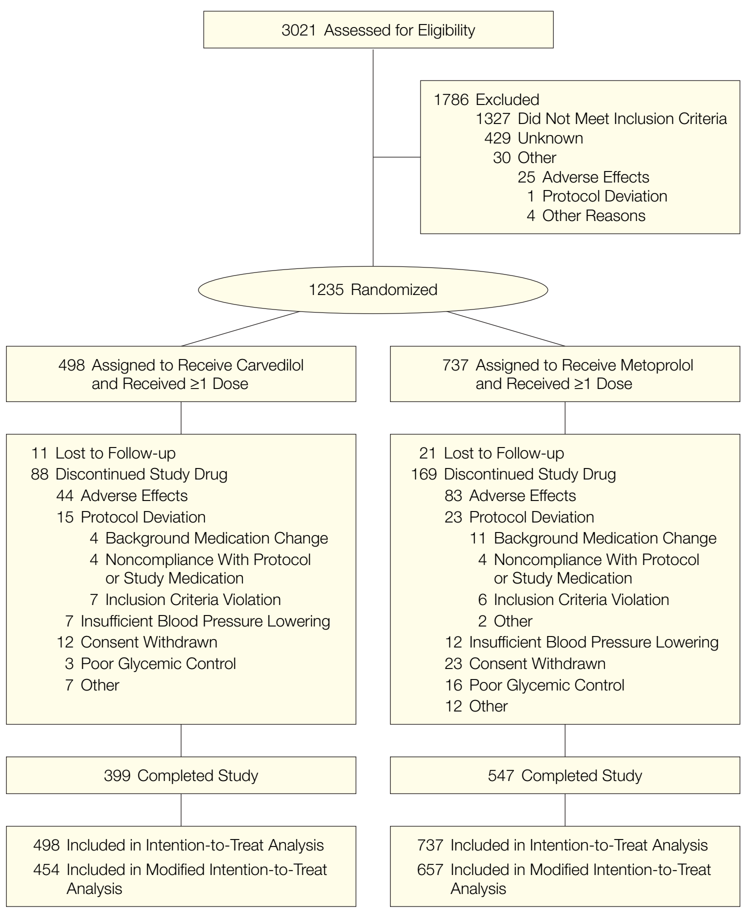
Study Design and Participants

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.[17] 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 HbA_{1c} 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

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/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.[10,18] 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 HbA_{1c} between groups following 5 months of maintenance therapy. Secondary outcomes that were prespecified included changes from baseline HbA_{1c} 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 levels[19]), 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}.

Sample size calculation was based on detecting a difference for the primary outcome of 0.30% in HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} change from baseline, beyond which glycemic control would be said to have worsened. Assuming a HbA_{1c} 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 HbA_{1c} change from baseline and SDs were based on literature review of studies examining the effect of carvedilol[20-22] and selective β_1-blockers[23,24] on HbA_{1c}.

The primary analysis for treatment group difference in HbA_{1c} change from baseline was based on analysis of covariance, adjusting for treatment group, baseline HbA_{1c}, 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 HbA_{1c} change from baseline. The covariates of interest included baseline HbA_{1c}, 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 HbA_{1c} were performed. These analyses corrected for baseline HbA_{1c}, 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 HbA_{1c}, 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 ($P<.10$). Because there was only 1 specified primary parameter, no adjustments were made for multiple comparisons. Summaries of safety data included all randomized participants.

Table 1. Characteristics of the Participants Receiving Either Carvedilol or Metoprolol Therapy*

	Carvedilol (n = 498)	Metoprolol (n = 737)
Demographics		
Age, mean (SD), y	60.7 (9.4)	61.1 (9.7)
Women	198 (39.8)	354 (48.0)
Race/ethnicity†		
White	382 (76.7)	548 (74.4)
Black	62 (12.4)	105 (14.2)
Asian	20 (4.0)	23 (3.1)
Hispanic	31 (6.2)	55 (7.5)
Other/multiracial	3 (0.6)	6 (0.8)
BMI, mean (SD)	33.5 (5.8)	33.7 (6.2)
Biochemistry, mean (SD)		
C-peptide, ng/mL	3.36 (1.59)	3.42 (1.62)
HbA_{1c}, %	7.21 (0.55)	7.19 (0.54)
Antidiabetic medications		
Sulfonylureas‡	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; HbA_{1c}, glycosylated hemoglobin.
SI conversion: To convert C-peptide to nmol/L, multiply by 0.333.
*Data are presented as No. (%) unless otherwise specified. Because of rounding, percentages may not all total 100.
†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 multiagent 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 HbA_{1c} 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 BPs remained well above the recommended target of 130/80 mm Hg. Diabetes mellitus was well-controlled (mean baseline HbA_{1c}, 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 discontinuance 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).

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

	Carvedilol (n = 498)		Metoprolol (n = 737)	
Medication	Baseline	End of Treatment	Baseline	End of Treatment
ACE/ARB	487 (97.8)	483 (97.0)	734 (99.6)	734 (99.6)
Hydrochlorothiazide†	33 (6.6)	216 (43.4)	45 (6.1)	325 (44.1)
Calcium antagonist†	21 (4.2)	123 (24.7)	31 (4.2)	189 (25.6)
α-Blocker†	13 (2.6)	13 (2.6)	14 (1.9)	14 (1.9)
Statins	219 (44.0)	224 (45.0)	334 (45.3)	348 (47.2)

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

Primary Outcome

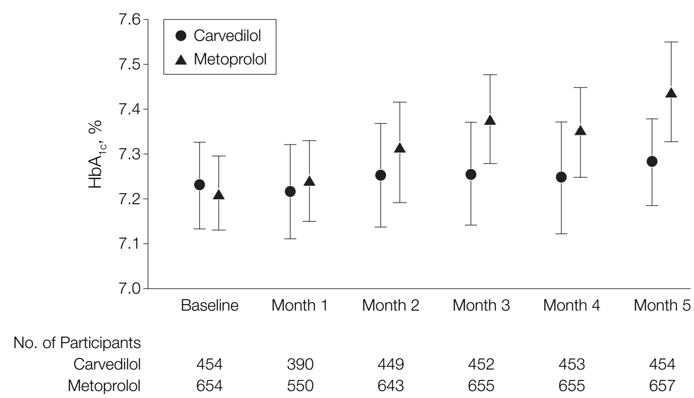
The mean difference between carvedilol and metoprolol with respect to the change in HbA_{1c} from baseline was 0.12% (SD, 0.04%; 95% CI, –0.20% to –0.03%; $P=.006$) for the intention-to-treat analysis using last observation carried forward and 0.13% (SD, 0.05%; 95% CI, –0.22% to –0.04%; $P=.004$) for the modified intention-to-treat analysis.

Prespecified Secondary Outcomes

Carvedilol treatment had no effect on HbA_{1c} (mean [SD] change from baseline to end point, 0.02% [0.04%]; 95% CI, –0.06% to 0.10%; $P=.65$), while metoprolol increased HbA_{1c} (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 and increased with metoprolol (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 HbA_{1c} ($r=0.16$ for carvedilol, $P=.002$ vs $r=0.29$ for metoprolol, $P<.001$). Metoprolol in-

Figure 2. Glycosylated Hemoglobin (HbA_{1c}) 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.

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

	Carvedilol (n = 454)				Metoprolol (n = 657)				Treatment Difference	
Parameter	No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	No. of Participants	Baseline	Maintenance Month 5 or Last Observation Carried Forward	% Change	% Change (95% CI)†	P Value
BP, mean (SE), mm Hg‡										
Systolic	454	149.4 (0.6)	131.3 (0.7)	–17.9 (0.7)	636	149.2 (0.5)	132.3 (0.6)	–16.9 (0.6)	–1.0 (–2.60 to 0.58)	.21
Diastolic	454	87.0 (0.4)	77.1 (0.4)	–10.0 (0.4)	636	86.3 (0.4)	76.8 (0.3)	–10.3 (0.3)	0.29 (–0.61 to 1.20)	.53
Heart rate/min, mean (SE)‡	454	73.7 (0.5)	67.6 (0.4)	–6.7 (0.4)	636	74.5 (0.4)	66.0 (0.4)	–8.3 (0.4)	1.6 (0.70 to 2.58)	<.001
Mean ACR, mg/g§	388	13.3	11.1	–14.0	542	12.0	13.3	2.5	–16.2 (–25.31 to –5.87)	.003
Mean HOMA-IR§	371	6.0	5.8	–9.1	540	5.8	6.2	–2.0	–7.2 (–13.8 to –0.2)	.004
Mean plasma glucose, mg/dL‡	419	147.0	154.7	6.6	607	147.4	158.6	10.6	–4.0 (–8.73 to 0.78)	.10
Mean serum insulin, μIU/mL‡	387	21.6	19.6	–19.4	561	21.2	20.2	–15.1	–4.2 (–16.7 to 8.24)	.51
Mean body weight, kg‡	456	98.2	97.2	0.17	650	97.0	98.2	1.2	–1.0 (–1.43 to –0.60)	<.001
Mean serum cholesterol levels, mg/dL§										
Total	433	185.6	181.7	–3.3	625	185.6	185.6	–0.4	–2.9 (–4.60 to –1.15)	.001
LDL	411	186.6	96.7	–4.0	572	100.5	96.7	–2.7	–1.3 (–4.31 to 1.78)	.40
HDL	432	46.4	42.5	–5.5	625	46.4	42.5	–5.7	0.2 (–1.68 to 2.12)	.83
Mean triglycerides, mg/dL§	433	159.4	168.3	2.2	625	168.3	186.0	13.2	–9.8 (–13.68 to –5.75)	<.001

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)[19]; 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.

*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, the only substantiative difference was that systolic BP changed –16.0 mm Hg in the metoprolol group and the treatment difference between groups was –1.9 (95% 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 treatment difference from metoprolol.

‡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.

Table 4. Covariate Analysis of Change from Baseline to Month 5 in HbA_{1c}*

Covariate	*df*	F Value+	*P* Value
Baseline HbA_{1c}†	1	37.0	<.001
Treatment	1	4.97	.03
Race	2	5.48	.004
Statin	1	7.63	.006
Study	1	1.13	.29
Hydrochlorothiazide	1	0.25	.62
Baseline thiazolidinedione	1	0.70	.40
Baseline ARB	1	0.59	.44
Dose	1	2.40	.12
Treatment × race	2	0.05	.95
Treatment × statin	1	0.12	.73
Treatment × hydrochlorothiazide	1	1.98	.16
Treatment × dose	1	0.001	.96

Abbreviations: ARB, angiotensin II receptor blocker; HbA_{1c}, 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.
†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.

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 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 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 HbA_{1c}, 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 (HbA_{1c} <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 HbA_{1c}.[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 HbA_{1c} 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.

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

	No. of Participants (%)		
Adverse Effects	Carvedilol (n = 498)	Metoprolol (n = 737)	*P* Value*
Fatigue	59 (11.8)	112 (15.2)	.09
Asymptomatic hypoglycemia†	58 (11.6)	76 (10.3)	.46
Dizziness	47 (9.4)	57 (7.7)	.29
Headache	42 (8.4)	58 (7.9)	.72
Diarrhea	39 (7.8)	69 (9.4)	.35
Symptomatic hypoglycemia†	42 (8.4)	65 (8.8)	.81
Edema, peripheral	38 (7.6)	56 (7.6)	.98
Nasopharyngitis	32 (6.4)	44 (6.0)	.74
Nausea	30 (6.0)	36 (4.9)	.38
Hyperglycemia	27 (5.4)	32 (4.3)	.38
Upper respiratory tract infection	27 (5.4)	56 (7.6)	.13
Arthralgia	21 (4.2)	19 (2.6)	.11
Dyspnea	21 (4.2)	42 (5.7)	.25
Cough	20 (4.0)	35 (4.7)	.54
Diabetes mellitus worsened‡	12 (2.4)	32 (4.3)	.07
Bradycardia	7 (1.4)	30 (4.1)	.007

*Assessed by χ^2 analysis.
†Reports of hypoglycemia were generated from structured surveillance of patient diaries.
‡As reported by investigator.

Our findings were not linked to a primary cardiovascular outcome. However, 4 randomized trials[4-7] 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 trial[4] showed a clear benefit of losartan on cardiovascular events and 3 trials showed no difference between RAS blockade and β-blockade[6] 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,[6] a study with similar HbA_{1c} levels to our cohort, participants allocated to atenolol had a higher mean HbA_{1c} 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 HbA_{1c} 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 study[7] 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 study[27] suggested that among men with HbA_{1c} less than 7%, an increase in HbA_{1c} 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 HbA_{1c} levels of more than 7%, the change in HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels were lower than other studies used to derive the power calculations, with 39% of participants having HbA_{1c} 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 HbA_{1c} 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 HbA_{1c}. 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.

Author Affiliations: Department of Preventive Medicine, Rush University Medical Center, Chicago, Ill (Dr Bakris); Department of Medicine, Tulane University, New Orleans, La (Dr Fonseca); Department of Medicine, St John's Hospital, Springfield, Ill (Dr Katholi); Department of Medicine, Washington University School of Medicine, St Louis, Mo (Dr McGill); Department of Medicine, St Luke's-Roosevelt, New York, NY (Dr Messerli); Department of Medicine, Mt Sinai School of Medicine, New York, NY (Dr Phillips); Department of Medicine, University of Texas Southwestern Medical Center, Dallas (Dr Raskin); Departments of Medicine, University Hospitals of Cleveland and the Louis Stokes Cleveland Department of Veterans Affairs Medical Center, Cleveland, Ohio (Dr Wright); GlaxoSmithKline, Philadelphia, Pa (Drs Lukas and Anderson, and Ms Oakes); and Department of Medicine, University of Alabama, Birmingham (Dr Bell).

Financial Disclosures: Dr Bakris has no stock ownership but has received research grants and is a speaker and consultant for Astra-Zeneca, Abbott, Alteon, Boehringer Ingelheim, Forest, GlaxoSmithKline, Merck, Novartis, and Eli Lilly; has received research grants from the National Institutes of Health (NIDDK/NHLBI); and is a speaker and consultant for AusAm, Biovail, Bristol-Myers Squibb/Sanofi, Takeda, and Wyeth. Dr Fonseca has received research grants and is a speaker and consultant for GlaxoSmithKline. Dr Katholi is a speaker for GlaxoSmithKline. Dr McGill has received honoraria and grant support from GlaxoSmithKline and honoraria from Astra-Zeneca. Dr Messerli receives grant/research support from Novartis, Abbott, Pfizer, GlaxoSmithKline, and Procter and Gamble, and is a speaker for Pfizer, Novartis, Abbott, Astra-Zeneca, Bristol-Myers Squibb, Solvay, Forest, GlaxoSmithKline, Boehringer Ingelheim, and Merck. Dr Phillips has received research support from GlaxoSmithKline for GEMINI study. Dr Raskin has received a research grant from GlaxoSmithKline. Dr Wright has no stock ownership but receives research grants, honoraria, and consult fees from Astra, Aventis Pharmaceuticals, Bayer, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis Pharma AG, Pfizer, Phoenix Pharmaceuticals, Searle, GlaxoSmithKline, and Solvay/Unimed. Ms Oakes is an employee of GlaxoSmithKline. Drs Lukas and Anderson are employees of GlaxoSmithKline with stock options, ownership, and patent for method of treatment. Dr Bell is a consultant and speaker for GlaxoSmithKline.

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, Alain Bouchard, MD, David A. Calhoun, MD (Birmingham);Thomas M. Nolen, MD (Columbiana); Robert Israel, MD (Mobile); *Arizona:* Robert Siegel, MD (Gilbert), Richard Albery, MD, Royal B. Anspach, MD, Marshall Block, MD, James V. Felicetta, MD, Richard Heuser, MD, Rajul I. Patel, MD, Ernie Riffer, MD, Edward Tokatlian, MD, Kris Vijay, MD (Phoenix), Paul Fenster, MD, Mark Goldberg, MD, David Johnson, MD, Gregory Koshkarian, MD (Tucson); *California:* Dennis Riff, MD (Anaheim), William Zigrang, MD (Burlingame), Jonathan Hemphill, MD (Carmichael), Georges Argoud, MD (Chula Vista), Roy Kaplan, MD (Concord), George Dennish, MD, James Quigley, DO (Encinitas), Malcolm Sperling, MD (Fountain Valley), Betty Grant-Anderson, MD (Hemet), Sidney Rosenblatt, MD (Irvine), Deanna Cheung, MD (Long Beach), Ken Chiu, MD, Andrew Lewin, MD (Los Angeles), David Price, MD (Milpitis), Henry Sideropoulos, MD (Pasadena), Chiayu Chen, MD (Riverside), Robert J. Doria, MD (San Luis Obispo), Robert Lipetz, DO (Spring Valley), Stanley Rockson, MD (Stanford), Joel Neutel, MD (Tustin), Richard Weinstein, MD (Walnut Creek); *Colorado:* Jennifer Hone, MD (Arvada), Diana Dills, MD (Aurora), Jane Reusch, MD, Nampalli Vijay, MD (Denver), Kenneth Cohen, MD, Debra Friesen, MD (Golden), Peter Smith, MD (Loveland); *Connecticut:* Andrew Rashkow, MD (Derby), William White, MD (Farmington), Arthur DeGraff, MD, Neil Grey, MD (Hartford), James Bernene, MD (New Britain); *Delaware:* Walter R. Powell, MD (Newark); *District of Columbia:* Judith Hsia, MD, Vasilios Papademetriou, MD; *Florida:* Ester Levin, MD, Jeffrey B. Rosen, MD (Coral Gables), John Rozanski, MD, Martin Shansky, MD, Alan Graff, MD, Alan Niederman, MD (Ft. Lauderdale), Marvin Heuer, MD (Gainesville), Michael Galinsky, MD, Sam Lerman, MD, Gregory Serfer, MD (Hollywood), Peter Rossi, MD (Hudson), Rafik Abadier, MD (Inverness), Michael Koren, MD, Mark Stich, MD (Jacksonville), Rajiv Chandra, MD, Gregory Waser, MD (Melbourne), Alvaro Gomez, MD, Luigi Meneghini, MD, Julio Pita, MD, Richard Preston, MD, Paul Seigel, MD, John Sokolowicz, MD (Miami), Robert McGhee, DO, Larry R. Popeil, MD (Ocala), Misal Khan, MD (Panama City), Larry I. Gilderman, MD (Pembroke Pines), Mahfouz El Shahawy, MD (Sarasota), Michael McIvor, MD, Gregg Schuyler, MD (St. Petersburg), Ricky Schneider, MD (Tamarac), Edward Braun, MD, Jesus Navarro, MD (Tampa); *Georgia:* Stephen Broadwater, MD (Augusta), Frank Cole, MD (Fayetteville), Sreeni Gangasani, MD (Lawrenceville), Paul Bradley, MD (Savannah); *Hawaii:* Richard Arakaki, MD (Ewa Beach), Patricia Blanchette, MD, David Fitzpatrick, MD (Honolulu); Idaho: Terry Riske, MD (Hayden Lake), John Liljenquist, MD, Herbert Moskow, MD (Idaho Falls); *Illinois:* Steven Harnack, MD (Aurora), George L. Bakris, MD, Peter Lee, MD, John Sobolski, MD, Danny Sugimoto, MD (Chicago), Dennis Abella, MD (Elk Grove Village), Jeffrey G. Shanes, MD (Melrose Park), Bradley Sakran, MD (O'Fallon), Richard E. Katholi, MD (Springfield), Shahriar Dadkhah, MD, (West Evanston); *Indiana:* George Mark, MD (Elkhart), Andrew Thieneman, MD (Evansville), Phillip Toth, MD (Indianapolis), Gary Erdy, MD (Newburgh), James McCann, MD (Wabash); *Iowa:* Nancy Kane-Johnson, MD, Gregory Peterson, MD (Des Moines), Helmut Schrott, MD (Iowa City); *Kentucky:* Tadarro Richardson, MD (Lexington); *Louisiana:* Peter Abel, MD (Morgan City), Vivian Fonseca, MD, Franz Messerli, MD (New Orleans); *Maine:* Robert J. Weiss, MD (Auburn), Mark Henderson, MD (Bangor); *Maryland:* James Mersey, MD (Baltimore), Boris Kerzner, MD (Pikesville); *Massachusetts:* Terrance Hack, MD (Ayer), Paul Conlin, MD (Boston), Michael J. McCartney, MD (Salisbury), Adnan Dahdul, MD (Springfield), Edward Busick, MD (Waltham), Jayashri Aragam, MD (West Boylston), Charles Birbara, MD (Worcester); *Michigan:* Mohammad Nadeemullah, MD, Amy Rothberg, MD, Martin Stevens, MD (Ann Arbor), Marcus J. Zervos, MD (Birmingham), Gary Ruoff, MD (Kalamazoo), Pramod Raval, MD (Oak Park), Irvin Gastman, MD (Waterford); *Minnesota:* Norman Lunde, MD (Arden Hills), Bonita L. Hill, MD (Chaska), C. Rowen DeBold, MD, Jordan L. Holtzman, MD (Minneapolis), Alan Bank, MD (St. Paul); *Mississippi:* Stanford Owen, MD (Gulfport); *Missouri:* Thomas Crouch, MD, William L. Isley, MD, Sandra Willsie, DO (Kansas City), Mark Entrup, DO (Springfield), Michael Fedak, MD, Janet B. McGill, MD, Arshag Mooradian, MD, Solomon Noguera, MD, Harry Wadsworth, MD (St. Louis), James Farrell, MD (St. Peters); *Nebraska:* Anne Morse, MD (Grand Island), Timothy O. Wahl, MD (Omaha); *Nevada:* Ivan Goldsmith, MD, James Snyder, MD (Las Vegas); *New Hampshire:* Nathaniel Niles, MD (Lebanon); *New Jersey:* Michael Denker, MD (Hackensack), Ronald C. Gove, MD (Linwood), Arnaud Bastien, MD (Magnolia), Zia Salam, MD (Margate), Michael Disciglio, MD (Sea Girt), Ralph Costa, MD (Voorhees); *New Mexico:* Mark Burge, MD, Paul Sandall, MD (Albuquerque); *New York:* Mario Henriquz, MD, Ulrich Schubart, MD (Bronx), Paresh Dandona, MD (Buffalo), Daniel Lorber, MD (Flushing), Zaeem Ansari, MD (Fulton), Amin Elashker, MD (Kingston), Mitchell Patt, MD (Liverpool), Harvey Katzeff, MD (New Hyde Park), Daniel Donovan, MD, Bassem El-Masri, MD, Robert A. Phillips, MD (New York), Mervyn Weershinge, MD (Rochester), Anthony Mercando, MD (Scarsdale), Stephen Nash, MD (Syracuse), Richard Castaldo, MD (Tonawanda), Brian Snyder, MD (West Seneca), Marc Kozinn, MD (Williamsville); *North Carolina:* Mark Feinglos, MD (Durham), John K. Earl, MD (Hickory), John A. Lang, MD (Raleigh), James M. Rhyne, MD (Statesville), Robert H. Hutchins, MD (Wilmington), Thomas Littlejohn, MD Robert Rosen, MD (Winston-Salem); *North Dakota:* Donald Kosiak, MD (Wishek); *Ohio:* Dale Murphy, MD (Akron), David Whittier, MD (Canton), Eli Roth, MD (Cincinnati), Jackson T. Wright, Jr., MD (Cleveland), Douglas Schumacher, MD (Columbus), Stephen Ulrich, MD (Zanesville); *Oklahoma:* Donald Denmark, MD (Oklahoma City), Richard Marple, MD (Tulsa); *Oregon:* M.A. Backus, MD (Bend), Edward Conrad, MD (Oregon City), David G. Van Sickle, MD (Portland); *Pennsylvania:* Robert McInroy, MD (Camp Hill), James Oppy, MD (Connellsville), Lawrence Alwine, MD (Downingtown), Jack Yakish, MD (Erie), Robert K. Hippert, DO (Fleetwood), David Miller, DO (Morrisville), Seth Braunstein, MD, Barry Goldstein, MD (Philadelphia), Larry Adams, MD (Philipsburg), Mark Blatter, MD, Alan Steckel, MD (Pittsburgh), Deepak Santram, MD (West Grove); *South Carolina:* Brent Egan, MD (Charleston), James Allison, MD (Columbia), W. John Henry, III, MD (Greer), Colby Grossman, MD (Summerville); *Tennessee:* David Morin, MD (Bristol), Henry K. Lui, MD (Jackson), Suzanne Satterfield, MD (Memphis), Stephen Davis, MD (Nashville); *Texas:* Bruce Henry, MD (Arlington), Teresa Coats, MD, Paul W. Dlabal, MD, William Gamel, MD, Paul Moore, MD (Austin), Douglas J. Pappas, MD (Corpus Christi), Stephen L. Aronoff, MD, Waymon Drummond, MD, Philip Raskin, MD, Julio Rosenstock, MD (Dallas), Frood Ealani, MD (Fort Worth), Jamal Islam, MD (Galveston), Salah Eddid El Hafi, MD, Alan Garber, MD (Houston), G.M. Gollapudi, MD (Midland), John Gabriel, MD (North Richland Hills), Gregory D. McCarroll, MD, Hugo Rojas, MD, Sherwyn Schwartz, MD, Alexander Shepherd, MD (San Antonio), Scott Yates, MD (The Colony); Utah: Jack Wahlen, MD (Ogden), Thomas Knecht, MD (Salt Lake City); Vermont: Daniel O'Rourke, MD (White River Junction); *Virginia:* Mark Ringold, MD (Christianburg), William Mroczek, MD (Falls Church), Omar Abdullah, MD (Fredricksburg), Ruth Nurnberg, MD, Stephen Richard, MD, Neshan Vranian, MD (Richmond), Nabil Jarmuki, MD (Salem), Puneet Narayan, MD (Springfield); *Washington:* Daniel Gottlieb, MD (Burien), Buckley Eckert, MD (Kirkland), Wayne Larson, MD (Lakewood), Eric Klein, MD (Olympia), Leslie Klaff, MD (Renton), Carol Wysham, MD (Spokane); *Wisconsin:* Melissa Meredith, MD (Madison), Kumar Jain, MD, Dinesh Pubbi, MD (Milwaukee), Zorba R. Paster, MD (Oregon).

Funding/Support: This study was funded by GlaxoSmithKline Pharmaceuticals. Dr Fonseca is supported in part by a National Institutes of Health grant 5M01RR05096 from the Division of Research Resources.
Role of the Sponsor: GlaxoSmithKline participated in discussions regarding study design and protocol development and provided logistical support during the trial. Monitoring of the study was performed by a contract research organization, under contract with GlaxoSmithKline, who maintained the trial database. 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 suggest changes but the final decision on content was exclusively retained by the authors.
Acknowledgment: We thank the GEMINI investigators for their time and commitment to the trial. We acknowledge the contributions made by Sanjib Basu, PhD, visiting Associate Professor, Rush University, and Associate Professor, Northern Illinois University, who performed an independent statistical analysis that confirmed the main results.

REFERENCES

1. Song SH, Brown PM. Coronary heart disease risk assessment in diabetes mellitus: comparison of UKPDS risk engine with Framingham risk assessment function and its clinical implications. *Diabet Med*. 2004;21:238-245.
2. Colagiuri S, Cull CA, Holman RR. Are lower fasting plasma glucose levels at diagnosis of type 2 diabetes associated with improved outcomes? UK Prospective Diabetes Study 61. *Diabetes Care*. 2002;25:1410-1417.
3. Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA*. 2004;291:335-342.
4. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995-1003.
5. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP) randomised trial. *Lancet*. 1999;353:611-616.
6. UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ*. 1998;317:713-720.
7. Hansson L, Lindholm LH, Ekbom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet*. 1999;354:1751-1756.
8. Dornhorst A, Powell SH, Pensky J. Aggravation by propranolol of hyperglycaemic effect of hydrochlorothiazide in type II diabetics without alteration of insulin secretion. *Lancet*. 1985;1:123-126.
9. Holzgreve H, Nakov R, Beck K, Janka HU. Antihypertensive therapy with verapamil SR plus trandolapril versus atenolol plus chlorthalidone on glycemic control. *Am J Hypertens*. 2003;16:381-386.
10. Chobanian AV, Bakris GL, Black HR, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206-1252.
11. Summary of Revisions for the 2004 Clinical Practice Recommendations. *Diabetes Care*. 2004;27(suppl 1):S1-S3.
12. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens*. 2003;21:1011-1053.
13. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.

14. Pollare T, Lithell H, Berne C. A comparison of the effects of hydrochlorothiazide and captopril on glucose and lipid metabolism in patients with hypertension. *N Engl J Med*. 1989;321:868-873.

15. Giordano M, Matsuda M, Sanders L, Canessa ML, DeFronzo RA. Effects of angiotensin-converting enzyme inhibitors, Ca_2+ channel antagonists, and alpha-adrenergic blockers on glucose and lipid metabolism in NIDDM patients with hypertension. *Diabetes*. 1995;44:665-671.

16. Manley S. Haemoglobin A1c–a marker for complications of type 2 diabetes: the experience from the UK Prospective Diabetes Study (UKPDS). *Clin Chem Lab Med*. 2003;41:1182-1190.

17. Bakris G, Bell D, Fonseca V, et al; GEMINI Investigators. The rationale and design of the Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial. *J Diab Compl*. In press.

18. Arauz-Pacheco C, Parrott MA, Raskin P. The treatment of hypertension in adult patients with diabetes. *Diabetes Care*. 2002;25:134-147.

19. Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model: the Mexico City Diabetes Study. *Diabetes Care*. 1996;19:1138-1141.

20. Ehmer B, van der DR, Rudorf J. Influence of carvedilol on blood glucose and glycohaemoglobin A1 in non-insulin-dependent diabetics. *Drugs*. 1988;36(suppl 6):136-140.

21. Giugliano D, Acampora R, Marfella R, et al. Metabolic and cardiovascular effects of carvedilol and atenolol in non-insulin-dependent diabetes mellitus and hypertension: a randomized, controlled trial. *Ann Intern Med*. 1997;126:955-959.

22. Giugliano D, Marfella R, Acampora R, Giunta R, Coppola L, D'Onofrio F. Effects of perindopril and carvedilol on endothelium-dependent vascular functions in patients with diabetes and hypertension. *Diabetes Care*. 1998;21:631-636.

23. Feher M. Antihypertensive drugs and the hypertensive diabetic patient. *J Hum Hypertens*. 1990;4(suppl 3):7-9.

24. Ostman J, Asplund K, Bystedt T, et al. Comparison of effects of quinapril and metoprolol on glycaemic control, serum lipids, blood pressure, albuminuria and quality of life in non-insulin-dependent diabetes mellitus patients with hypertension: Swedish Quinapril Group. *J Intern Med*. 1998;244:95-107.

25. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348:383-393.

26. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European Prospective Investigation into Cancer in Norfolk. *Ann Intern Med*. 2004;141:413-420.

27. Khaw KT, Wareham N, Luben R, et al. Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *BMJ*. 2001;322:15-18.

28. Galletti F, Strazzullo P, Capaldo B, et al. Controlled study of the effect of angiotensin converting enzyme inhibition versus calcium-entry blockade on insulin sensitivity in overweight hypertensive patients: Trandolapril Italian Study (TRIS). *J Hypertens*. 1999;17:439-445.

29. Hawkins CM, Richardson DW, Vokonas PS. Effect of propranolol in reducing mortality in older myocardial infarction patients: the Beta-Blocker Heart Attack Trial experience. *Circulation*. 1983;67:I94-I97.

30. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care*. 1993;16:434-444.

31. Packer M. Do beta-blockers prolong survival in heart failure only by inhibiting the beta1-receptor? a perspective on the results of the COMET trial. *J Card Fail*. 2003;9:429-443.

32. Garg JP, Bakris GL. Microalbuminuria: marker of vascular dysfunction, risk factor for cardiovascular disease. *Vasc Med*. 2002;7:35-43.

33. Pedrinelli R, Dell'Omo G, Di Bello V, Pontremoli R, Mariani M. Microalbuminuria, an integrated marker of cardiovascular risk in essential hypertension. *J Hum Hypertens*. 2002;16:79-89.

34. Stuveling EM, Bakker SJ, Hillege HL, et al. C-reactive protein modifies the relationship between blood pressure and microalbuminuria. *Hypertension*. 2004;43:791-796.

35. Yuyun MF, Khaw KT, Luben R, et al. Microalbuminuria independently predicts all-cause and cardiovascular mortality in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. *Int J Epidemiol*. 2004;33:189-198.

36. Wright JT Jr, Bakris G, Greene T, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA*. 2002;288:2421-2431.

37. Yasunari K, Maeda K, Nakamura M, Watanabe T, Yoshikawa J, Asada A. Effects of carvedilol on oxidative stress in polymorphonuclear and mononuclear cells in patients with essential hypertension. *Am J Med*. 2004;116:460-465.

38. Yasunari K, Maeda K, Nakamura M, Yoshikawa J. Carvedilol inhibits pressure-induced increase in oxidative stress in coronary smooth muscle cells. *Hypertens Res*. 2002;25:419-425.

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.

Michael Rothberg, MD, MPH
michael.rothberg@bhs.org
Division of General Medicine and Geriatrics
Department of Medicine
Baystate Medical Center
Springfield, Mass

1. US Centers for Disease Control and Prevention. Interim Estimates of Populations Targeted for Influenza Vaccination from 2002 National Health Interview Survey Data and Estimates for 2004 Based on Influenza Vaccine Shortage Priority Groups. Available at: http://www.cdc.gov/flu/professionals/vaccination/pdf/targetpopchart.pdf. Accessed October 26, 2004.
2. US Centers for Disease Control and Prevention. Interim Influenza Vaccination Recommendations—2004-05 Influenza Season. Available at: http://www.cdc.gov/flu/protect/whoshouldget.htm. Accessed October 26, 2004.
3. Hak E, Wei F, Nordin J, Mullooly J, Poblete S, Nichol KL. Development and validation of a clinical prediction rule for hospitalization due to pneumonia or influenza or death during influenza epidemics among community-dwelling elderly persons. *J Infect Dis*. 2004;189:450-458.
4. Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348:1322-1332.
5. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med*. 1998;158:1769-1776.

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)."