Differential Effects of β-Blockers on Albuminuria in Patients With Type 2 Diabetes


Abstract—Increases in the cardiovascular risk marker microalbuminuria are attenuated by blood pressure reduction using blockers of the renin-angiotensin system. Such changes in microalbuminuria have not been observed when β-blockers are used. A prespecified secondary end point of the Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was to examine the effects of different β-blockers on changes in albuminuria in the presence of renin-angiotensin system blockade. Participants with hypertension and type 2 diabetes were randomized to either metoprolol tartrate (n=737) or carvedilol (n=498) in blinded fashion after a washout period of all antihypertensive agents except for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Blinded medication was titrated to achieve target blood pressure, with a 5-month follow-up period. The current analysis examined microalbuminuria, using spot urine albumin:creatinine, in participants who had values at screening and trial end. A greater reduction in microalbuminuria was observed for those randomized to carvedilol (−16.2%; 95% confidence interval, −25.3, −5.9; P=0.003). Of those with normoalbuminuria at baseline, fewer progressed to microalbuminuria on carvedilol versus metoprolol (20 of 302 [6.6%] versus 48 of 431 [11.1%], respectively; P=0.03). Microalbuminuria development was not related to differences in blood pressure or achievement of blood pressure goal (68% carvedilol versus 67%, metoprolol). Presence of metabolic syndrome at baseline was the only independent predictor of worsening albuminuria throughout the study (P=0.004). β-Blockers have differential effects on microalbuminuria in the presence of renin-angiotensin system blockade. These differences cannot be explained by effects on blood pressure or α1-antagonism but may relate to antioxidant properties of carvedilol. (Hypertension. 2005; 46:1309-1315.)

Key Words: diabetes mellitus ■ metoprolol ■ hypertension, arterial ■ morbidity

Microalbuminuria, defined as a urine albumin:creatinine of 30 to 300 mg/g, is an accepted marker of cardiovascular risk.1,2 Microalbuminuria is associated with abnormal vascular responsiveness and increased membrane permeability in people with hypertension or diabetes.2,3 Many of the causes of microalbuminuria relate to increased inflammation of the vasculature and subsequent increased vascular permeability in conditions such as fever and diabetes. Thus, agents associated with reduction in inflammation result, in most cases, in reductions of microalbuminuria.

Microalbuminuria is present in anywhere from 19% to 40% of patients with type 2 diabetes4–6 and is associated with an increase in cardiovascular morbidity and mortality.7–9 Increases in pre-existing microalbuminuria to macroalbuminuria (proteinuria), >300 mg/d, is associated with increased risk of progression to renal failure and peripheral neuropathy in those with diabetes.1,10 Recent post hoc analyses of large outcome trials suggest that agents that lower blood pressure and albuminuria in people with hypertension with or without diabetes may yield better cardiovascular and renal outcomes than agents that only lower pressure.11,12 β-Blockers, although well known to decrease cardiac-related mortality, have not shown the same benefit on renal or stroke outcomes when compared with agents that lower blood pressure and albuminuria. This divergent effect may relate to their effects on albuminuria, which is not well studied. Studies in diabetic and nondiabetic nephropathy with short- or long-acting β-blockers fail to show a substantive reduction in microalbuminuria when compared with angiotensin-converting enzyme (ACE) inhibition.13–15 However, to date, β-blockers have not been examined with regard to their effects on albuminuria in the presence of agents already known to affect blood pressure

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and albuminuria (ie, ACE inhibitors or angiotensin receptor blockers [ARBs]).

The Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was a double-blind parallel multicenter trial that examined the effects of 2 different β-blockers on glycemic and metabolic control in patients with hypertension and type 2 diabetes. A prespecified end point of GEMINI was to examine the effects of these agents on changes in albuminuria in the presence of renin-angiotensin system (RAS) blockade.

This article details prespecified and other post hoc analyses of the main trial to assess the following: (1) the proportion of patients with normoalbuminuria (urine albumin:creatinine <30 mg/g) at baseline who progressed to microalbuminuria; (2) changes in urine albumin:creatinine from baseline among those with microalbuminuria in the context of blood pressure lowering; (3) impact of blood pressure reduction on change in microalbuminuria between groups; (4) blood pressure control based on baseline presence of microalbuminuria; and finally (5), predictors of microalbuminuria development.

Methods
A detailed description of the rationale and study design of the GEMINI trial was presented previously. Briefly, study participants included both males and females between 30 and 80 years of age with documented type 2 diabetes and stage 1 or 2 hypertension. Diabetes control had to be stable for 3 months and blood pressure treatment stable for 1 month before enrollment. At enrollment, an ACE inhibitor or ARB had to be part of the antihypertensive regimen. People with significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, unstable angina, congestive heart failure, a myocardial infarction or stroke within the previous 3 months, kidney disease serum creatinine >2.5 mg/dL, or urine albumin:creatinine >300 mg/g among other factors were excluded. All participants gave written informed consent, and the protocol and procedures were approved by the institutional review board of each participating center.

Participants remained on their ACE inhibitor or ARB after the screening visit. All other antihypertensive medications were discontinued for a 2- to 4-week period. Participants were eligible for randomization if systolic blood pressure after washout was >130 and ≤179 mm Hg, diastolic blood pressure was >80 to ≤109 mm Hg, and fasting hemoglobin A1c (HbA1c) 6.5% to 8.5%, with ≤0.5% increase during the mandatory minimum 4-week period from screening to randomization. Automated randomization (randomization and medication ordering system, Glaxo Smith Kline) used a randomly permuted block of 5 in a 2:3 carvedilol:metoprolol distribution and incorporated stratification to equalize ARB and thiazolidinedione (TZD) medications in the treatment groups. Participants were titrated progressively with approved doses of carvedilol (6.25 mg, 12.5 mg, and 25.0 mg BID) and metoprolol tartrate (50 mg, 100 mg, and 200 mg BID) at 1- to 2-week intervals toward target blood pressure levels defined by the protocol. Hydrochlorothiazide (12.5 mg) and a dihydropyridine calcium antagonist were added sequentially, as necessary, to achieve target blood pressure. On reaching target blood pressure or the highest dose level of blinded medication, participants were then followed for an additional 5 months, with the maximum length being 35 weeks.

Urine samples for urine albumin:creatinine determination used the first morning void and were assessed at the screening and maintenance visits at months 3 and 5. Efficiency measures such as HbA1c, fasting glucose, blood pressure, and pulse were assessed monthly. All laboratory samples were obtained after a minimum 9-hour fast and analyzed by a central laboratory (Quest Diagnostics). Urine albumin was determined using nephelometry (immunodetection/turbidometric assay analyzed via Behring BNII), and creatinine via spectrophotometry (Olympus AU640).

Statistical Methods
The target sample size for the GEMINI study was 1210 participants (484 carvedilol and 726 for metoprolol) using a 2:3 randomization ratio.12 The population of subjects investigated in the analyses presented here consists of those subjects that were randomized, had a valid on-therapy HbA1c value, and had valid baseline and on-therapy urine albumin:creatinine measurements. For the purpose of evaluation of urine albumin:creatinine, baseline is defined conservatively as the screening visit value to minimize the confounding effects of intersubject variations in washout of antihypertensive medications and blood pressure changes secondary to washout.

The treatment difference in the urine albumin:creatinine change from baseline was assessed by an analysis of covariance adjusting for baseline urine albumin:creatinine, treatment group, and the following design characteristics: ARB use and TZD use (per the model used for analysis of the primary end point [HbA1c] in the GEMINI trial) and the study itself. The study was included as a covariate because the GEMINI trial consisted of 2 simultaneous identical studies (1 including sites from the eastern United States and the other from the western United States). Baseline and month 5 urine albumin:creatinine data were log-transformed before analysis, the results of which were exponentiated and expressed as percent treatment difference. The mean change from baseline values within treatment groups were exponentiated to obtain the ratio of post-treatment to pretreatment urine albumin:creatinine and then expressed as mean percentage change from baseline.

A multivariate analysis was also performed to examine the interactions of a variety of covariates with changes in albuminuria. This analysis only contained patients with no missing values for all covariates and a systolic blood pressure >130 mm Hg at baseline (332 carvedilol and 453 metoprolol subjects). An additional ad hoc analysis was performed to assess the change in urine albumin:creatinine adjusting for the following covariates: age, gender, race (white, black, other), baseline LDL, baseline HDL, and baseline HbA1c because they have been shown in other studies to affect changes in microalbuminuria. However, it should be noted that all covariates in the main effects model must be considered when interpreting the results of this later analysis. The significance level used for the test of each covariate effect is 0.05. The treatment-by-covariate interactions were investigated individually at a significance level of 0.10. No adjustments were made for multiple comparisons.

Additionally, an exploratory ad hoc analysis was performed via logistic regression and Wald χ² statistic to investigate the following covariates as predictors of worsening of albuminuria: treatment, baseline homeostasis model assessment index, insulin resistance, baseline systolic blood pressure, and presence of the metabolic syndrome (as defined by the World Health Organization criteria). In addition, the following “study design” covariates were included in the analysis: the study itself, baseline TZD use, and baseline ARB use. For this analysis, baseline urine albumin:creatinine was defined as the measurement taken at the screening visit. A total of 803 participants (334 carvedilol and 469 metoprolol) were included in this analysis. A backward elimination analysis was used with conservative entry criteria of 0.10 and removal criteria of 0.15. The conservative criteria were chosen to allow for the detection of possibly meaningful covariates despite the limitations arising from the small numbers associated with the analysis.

The proportion of subjects progressing from normoalbuminuria to microalbuminuria was assessed via logistic regression adjusting for baseline urine albumin:creatinine, treatment group, and the design characteristics described above. The treatment odds ratio (OR) with corresponding 95% confidence interval (CI) and P value are presented. All analyses were performed using SAS version 8 (SAS Institute Inc). Missing month 5 values were imputed using the last observation carried forward. P values and 2-sided 95% CIs are reported, with treatment comparisons tested at a 0.05 significance level.
Results

Patient Characteristics

A total of 1235 participants were randomized (498 carvedilol and 737 metoprolol) in GEMINI. Of these, 388 (78%) and 542 (74%) comprised the evaluable efficacy population for each group are shown in Figure 2.

Table 2. Albumin:Creatinine Values (mg albumin:g creatinine) at Baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total Population</th>
<th>All Patients in Analysis</th>
<th>0–&lt;30 mg/g</th>
<th>30–300 mg/g</th>
<th>&gt;300 mg/g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60.7 (9.4)</td>
<td>61.1 (9.7)</td>
<td>60.8 (9.2)</td>
<td>61.3 (9.6)</td>
<td>60.6 (8.1)</td>
</tr>
<tr>
<td>% Female</td>
<td>39.8</td>
<td>48.0</td>
<td>37.9</td>
<td>45.6</td>
<td>42.1</td>
</tr>
<tr>
<td>% White/black/other ethnicity</td>
<td>77/12/11</td>
<td>74/14/11</td>
<td>76/12/12</td>
<td>75/14/11</td>
<td>76/13/12</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>33.5 (5.8)</td>
<td>33.7 (6.2)</td>
<td>33.6 (5.9)</td>
<td>33.7 (6.0)</td>
<td>33.7 (5.9)</td>
</tr>
<tr>
<td>C-peptide, fasting (nmol/l)</td>
<td>1.1 (0.5)</td>
<td>1.1 (0.5)</td>
<td>1.1 (0.5)</td>
<td>1.2 (0.5)</td>
<td>1.2 (0.5)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.2 (0.6)</td>
<td>7.2 (0.5)</td>
<td>7.2 (0.5)</td>
<td>7.3 (0.5)</td>
<td>7.3 (0.5)</td>
</tr>
<tr>
<td>BP (mm Hg)</td>
<td>149/88 (12/8)</td>
<td>149/87 (12/8)</td>
<td>149/87 (11/8)</td>
<td>148/87 (11/8)</td>
<td>148/87 (10/8)</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>74 (9)</td>
<td>74 (9)</td>
<td>74 (9)</td>
<td>73 (9)</td>
<td>76 (7)</td>
</tr>
</tbody>
</table>

At screening assessment; SD in parentheses. Note that 8 of 11 (73%) randomized patients (5 carvedilol and 6 metoprolol) with a positive smoking history in the main trial were included in this analyses; 6 of the 8 (75%) were normoalbuminuric at screening, and 2 had microalbuminuria.

Urinary Albumin:Creatinine

Baseline urine albumin:creatinine values are presented in Table 2. The baseline distribution of albuminuria using the definition of normal as <30 mg/g, microalbuminuria between 30 and 300 mg/g, and macroalbuminuria of >300 mg/g, respectively, is shown in Figure 1. Approximately one fourth of the participants had some level of albuminuria defined as >30 mg albumin/gram creatinine on a spot urine. An evaluation of the entire cohort demonstrated a 16% (95% CI, 6%, 25%; P=0.003) relative reduction in albuminuria by carvedilol at the end of trial. The absolute changes in albuminuria for each group are shown in Figure 2.

Among patients with normoalbuminuria at screening, significantly fewer progressed to microalbuminuria on carvedilol (6.6%) compared with metoprolol (11.1%). Thus, the odds of progressing to microalbuminuria were 47% less for subjects receiving carvedilol compared with those receiving metoprolol tartrate (OR, 0.53; 95% CI, 0.30 to 0.93; P=0.03). This observation was further confirmed by the fact that within the group that remained normoalbuminuric throughout the study, there was a further reduction in albuminuria within the normal range (Figure 3). Among patients who had microalbuminuria at baseline, a similar change in urine albumin:creatinine was observed in both groups: carvedilol (n=77; −42.6%Δ; 95% CI, −57.3%, −22.9%; P=0.0003) and metoprolol tartrate (n=98; −29.5%Δ; 95% CI, −45.2%, −9.3%; P=0.007). Correlation coefficients generated for the observed change in urine albumin:creatinine and systolic blood pressure reduction suggest no relationship between these parameters (r=0.2 for both carvedilol and metoprolol tartrate).

Blood Pressure

No differences were noted in baseline blood pressure values of the subgroup of participants with microalbuminuria (149±10/87±8 [carvedilol] versus 150±10/86±8 [metoprolol tartrate]) or those with normoalbuminuria (149±11/87±8 [carvedilol] versus 148±11/86±8 [metoprolol tartrate]). Moreover, blood pressure values at study termination were

Figure 1. Distribution of urinary albumin:creatinine at baseline by treatment group.
also not different regardless of microalbuminuria presence at screening. However, the magnitude of blood pressure lowering was less in those with microalbuminuria at screening compared with those with normoalbuminuria (Figure 4).

The dose of randomized drug required to achieve target blood pressure in those with albuminuria (ie, 15.6 mg carvedilol twice daily and 104.7 mg metoprolol twice daily) was similar to those for the entire study cohort. It should be noted that in the cohort with microalbuminuria, similar numbers of patients required a calcium antagonist to achieve blood pressure goal, whereas relatively more participants in the carvedilol group required the use of low-dose hydrochlorothiazide, an observation also true in those without microalbuminuria (Figure 5). Despite the higher rate of diuretic use in this group, better glycemic control was noted.16

**Multivariate Analysis in Albuminuria Change**

The ad hoc analysis performed to assess the change in urine albumin:creatinine adjusting for age, gender, race (white, black, or other), baseline LDL, baseline HDL, and baseline HbA1c demonstrated that only treatment and baseline urine albumin:creatinine were significant (P<0.05). Race (P=0.08) and age (P=0.05) approached but failed to achieve statistical significance. Moreover, there were no significant treatment-by-covariate interactions (Table 3). Under the revised main effects model, the percent treatment difference was −13.9%, with a 95% CI of −24.2%, −2.2%.

In a separate analysis, the presence of metabolic syndrome at baseline corresponded to a 168% increase in the odds of experiencing a worsening in albuminuria over the 5-month follow-up of this study (OR, 2.68; 95% CI, 1.358, 5.297; P=0.004). The only other covariate that approached but failed to reach significance was assignment to treatment group favoring carvedilol with a 36% reduction in the odds of worsening albuminuria (OR, 0.64; 95% CI, 0.405, 1.038; P=0.071).

**Discussion**

Persistent presence of microalbuminuria is a well-accepted cardiovascular risk factor.18 A recent analysis of the Losartan Intervention For Endpoint reduction in hypertension study...
Although it has been argued that blood pressure lowering is the primary reason for prevention or decline in microalbuminuria, only studies with agents that block the RAS system have successfully prevented its development.\textsuperscript{19–22} The present post hoc analysis of the GEMINI trial demonstrates that despite similar levels of blood pressure in the presence of an RAS blocker, carvedilol retarded development of new-onset microalbuminuria in participants with type 2 diabetes and hypertension to a greater extent than metoprolol tartrate. However, if microalbuminuria was present, blood pressure reduction with either β-blocker reduced microalbuminuria. This confirms the results of 2 previous small open-label clinical studies, in which carvedilol was shown to reduce microalbuminuria in hypertensive patients without diabetes.\textsuperscript{23,24} However, in 1 of these studies, the decrease in the percentage of patients with microalbuminuria was not correlated with the magnitude of blood pressure reduction,\textsuperscript{23} a finding observed in our analysis. These results together support the notion that carvedilol attenuated development of microalbuminuria, an effect that cannot be solely attributed to its α-blocking blood pressure–lowering properties because most studies of α-blockade in people with diabetes fail to show a substantive sustained effect on albuminuria reduction.\textsuperscript{25–27}

Our analysis also noted that presence of metabolic syndrome at baseline was a predictor of worsening albuminuria over the duration of the study, independent of other factors. It also shows that those with albuminuria had a lower magnitude of blood pressure reduction over a given period compared with those with normal levels of albuminuria at baseline. This analysis illustrates that the presence of the metabolic syndrome clearly predicts worsening of albuminuria, independent of blood pressure. Hence, selecting antihypertensive agents that increase insulin resistance and worsen glycemic control would not be ideal in such patients, especially given the results of our analysis that demonstrate that presence of a RAS blocker only partially reduces the risk of microalbuminuria development in the presence of some β-blockers.\textsuperscript{16}

One possible explanation for the differential effect of carvedilol on prevention of microalbuminuria might relate to alterations in increased vascular permeability caused by increased oxidant stress.\textsuperscript{28,29} Although not measured in this trial but observed in other studies, carvedilol has antioxidant effects that may reduce vascular injury and hence permeability and thus retard development of microalbuminuria by inhibiting inflammatory processes in addition to lowering blood pressure.\textsuperscript{30–32} This hypothesis is being explored in an ongoing randomized trial.

Another possible association between the benefit of a reduced development of microalbuminuria may relate to glycemic control because those randomized to carvedilol maintained glycemic control, whereas those on metoprolol tartrate had worsened control. It is clear from the Diabetes Control and Complication trial that those randomized to the group with higher HbA1c values had a greater incidence of microalbuminuria after an 8-year follow-up of participants.\textsuperscript{33} This relationship between glycemic control and albuminuria is also evident in patients with type 2 diabetes.\textsuperscript{34} In contrast, data from the GEMINI trial suggest that no association exists between changes in glycemic control or blood pressure with changes in albuminuria; however, the study duration may have been too short to appreciate fully the impact of these variables on albuminuria.

Progression of microalbuminuria to macroalbuminuria or proteinuria indicates progression of vascular disease now involving the renal parenchyma. We did not examine patients with kidney disease; however, 1 long-term trial examined the effects of the β-blocker metoprolol succinate on progression of kidney disease. The AASK trial studied patients with nondiabetic kidney disease with albuminuria.\textsuperscript{15} This trial confirms the observations of the GEMINI trial in that the β-blocker used reduced pre-existing albuminuria, but unlike

| TABLE 3. Covariate Analysis of Change From Baseline to Maintenance Month 5 in Albuminuria |
|-----------------|-------|-------|-------|
| Covariate       | df * | F Value | P Value |
| Main effects    |       | F Value |       |
| Baseline albuminuria | 1    | 84.65  | <0.0001 |
| Study           | 1    | 0.30   | 0.5862  |
| TZD use at baseline | 1    | 0.40   | 0.5248  |
| ARB use at baseline | 1    | 0.71   | 0.4005  |
| Treatment       | 1    | 5.29   | 0.0217  |
| Race            | 2    | 2.52   | 0.0809  |
| Gender          | 1    | 1.42   | 0.2343  |
| Age             | 1    | 3.84   | 0.0505  |
| Baseline LDL    | 1    | 1.08   | 0.2998  |
| Baseline HDL    | 1    | 0.75   | 0.3876  |
| Baseline HbA1c  | 1    | 0.07   | 0.7981  |
| Interaction effects† |       | F Value |       |
| Treatment×baseline UAC | 1    | 0.84   | 0.3595  |
| Treatment×study | 1    | 0.50   | 0.4785  |
| Treatment×TZD use at baseline | 1    | 2.29   | 0.1309  |
| Treatment×ARB use at baseline | 1    | 1.72   | 0.1905  |
| Treatment×race  | 2    | 0.27   | 0.7665  |
| Treatment×gender | 1    | 0.13   | 0.7213  |
| Treatment×age   | 1    | 1.00   | 0.3183  |
| Treatment×baseline LDL | 1    | 1.86   | 0.1736  |
| Treatment×baseline HDL | 1    | 0.34   | 0.5621  |
| Treatment×baseline HbA1c | 1    | 0.50   | 0.4808  |

\textsuperscript{†}Each treatment-by-covariate interaction term was added 1 at a time to the main effects model and tested at the 0.10 significance level.
the GEMINI trial, it was not paired to an ACE inhibitor or ARB. Moreover, in experimental studies, carvedilol has been shown to preserve kidney structure and function.30,35,36 This renoprotective effect is thought to be, at least in part, attributable to the antioxidant activity of carvedilol.

These observations, if confirmed in properly powered prospective studies, hold the promise that some β-blockers may further reduce the risk of adverse metabolic effects and may further reduce cardiovascular risk to greater extent than commonly used β-blocker agents. The data demonstrate prevention of microalbuminuria development by a β-blocker that cannot be explained by differences in traditional markers known to predispose to its development (ie, elevated blood pressure or high blood glucose). Although this effect may relate to antioxidant effects of this agent, further studies need to confirm this hypothesis.

Perspective
Urinary albumin excretion beyond the upper limits of normal (ie, >30 mg per day) is linearly associated with increased risk of cardiovascular events. Once levels of albuminuria exceed 300 mg per day, kidney disease is now present, and the risk for progression to kidney failure is increased. Increased albumin excretion has been linked with increased inflammatory markers such as C-reactive protein, suggesting that increased albumin in the urine signifies an inflammation of the vasculature.

Blood pressure reduction toward the guideline recommended goal helps prevent development of albuminuria, especially when antihypertensive agents that block the renin-angiotensin-aldosterone system such as ACE inhibitors and ARBs are used. This post hoc analysis of a prospective clinical trial, the primary purpose of which was to assess the effects of 2 different β-blockers on blood sugar control, evaluated data on development and changes in albuminuria. The primary study was positive and showed that in the presence of an ACE inhibitor or ARB, carvedilol, an αβ-blocker, preserved glycomic control in those with diabetes, whereas metoprolol did not. Additionally, this analysis shows that carvedilol reduces the risk of development of or increases in another cardiovascular risk marker: albuminuria. The mechanism by which this drug has this effect probably relates to its antioxidant activity rather than its α-blocking effects because α-blockers do not substantially affect albuminuria. These data suggest that not all β-blockers are the same with regard to their effects on cardiovascular risk factors. A prospective study is needed to assess whether this effect on albuminuria will translate to lower cardiovascular events.

References


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for the GEMINI Investigators

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