



CLINICAL RESEARCH STUDY

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Body Weight Changes with β -Blocker Use: Results from GEMINI

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ABSTRACT

PURPOSE: Patients with type 2 diabetes are commonly overweight, which can contribute to poor cardiovascular outcomes. β -blockers may promote weight gain, or hamper weight loss, and are a concern in high-risk patients. The current analysis of the Glycemic Effect in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial evaluates the effects of carvedilol and metoprolol tartrate on weight gain in patients with type 2 diabetes and hypertension.

METHODS: This prespecified secondary analysis of the GEMINI study (n=1106) evaluated change in body weight after 5 months.

RESULTS: Mean (\pm SE) baseline weights were 97.5 (\pm 20.1) kg for carvedilol and 96.6 (\pm 20.1) kg for metoprolol tartrate. Treatment difference (c vs m) in mean (\pm SE) weight change from baseline was -1.02 (± 0.21) kg (95% confidence interval [CI], -1.43 to -0.60 ; $P < .001$). Patients taking metoprolol had a significant mean (\pm SE) weight gain of 1.19 (± 0.16) kg ($P < .001$); patients taking carvedilol did not (0.17 [± 0.19] kg; $P = .36$). Metoprolol tartrate-treated patients with body mass index (BMI) >30 kg/m² had a statistically significant greater weight gain than comparable carvedilol-treated patients. Treatment differences (c vs m) in the obese (BMI >30 kg/m²) and morbidly obese groups (BMI >40 kg/m²) were -0.90 kg (95% CI, -1.5 to -0.3 ; $P = .002$) and -1.84 kg (95% CI, -2.9 to -0.8 ; $P = .001$), respectively. Pairwise correlation analyses revealed no significant associations between weight change and change in HbA_{1c}, HOMA-IR, or blood pressure.

CONCLUSIONS: Metoprolol tartrate was associated with increased weight gain compared to carvedilol; weight gain was most pronounced in subjects with hypertension and diabetes who were not taking insulin therapy. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: β -blockers; Body Mass Index (BMI); Carvedilol; Diabetes; Hypertension; Metoprolol; Weight

Increases in body weight have been documented with long-term therapy of traditional β -blockers.¹ In the United Kingdom Prospective Diabetes Study (UKPDS), 9 years of therapy with atenolol resulted in a weight gain of 3.4 kg, a more

than 2-fold greater increase in body weight than seen with similar therapy with captopril (weight gain 1.6 kg).² Any weight gain is of concern in patients with type 2 diabetes because of the rise in insulin resistance associated with excess weight and obesity.³

The β -blocker carvedilol has not been associated with adverse effects on insulin sensitivity or carbohydrate metabolism when used in the treatment of hypertension in small studies of both diabetic⁴ and nondiabetic⁵ patients.

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The prospective, randomized clinical trial Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI), involving 1235 patients with type 2 diabetes, showed that hemoglobin (HbA_{1c}) levels remained stable in the carvedilol-treated group but increased by 0.15% in patients receiving metoprolol tartrate ($P = .006$ for the difference between agents). Insulin resistance was reduced by carvedilol but increased by metoprolol tartrate, with an overall difference of 7.2% ($P = .004$).⁶ In the study, body weight was measured at baseline and 5-month follow-up for the majority of randomized GEMINI patients (456/498 [90%] carvedilol and 650/737 [88%] metoprolol tartrate patients). In this report, we present the results of the analysis of weight change from the GEMINI trial.

METHODS

GEMINI compared the effects of antihypertensive therapy with carvedilol and metoprolol tartrate on glycemic control in patients with established diagnoses of diabetes and hypertension already taking angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). Detailed descriptions of the study design, methods, and primary results have been presented elsewhere.^{6,7} GEMINI was a prospective, randomized, double-blind, parallel-group, multicenter study including men and women aged 36 to 85 years with documented type 2 diabetes (HbA_{1c} levels 6.5% to 8.5%, C-peptide ≥ 0.6 ng/mL) and stage 1 or 2 hypertension (systolic blood pressure >130 and ≤ 179 mm Hg, and diastolic blood pressure >80 and ≤ 109 mm Hg). Antidiabetic medication must have been stable for at least 3 months, and antihypertensive medication, including an ACE inhibitor or ARB, must have been stable for at least 1 month.

After enrollment, patients discontinued all antihypertensive medications except ACE inhibitors and ARBs, which were continued at their regular dose for 2 to 4 weeks. The remaining qualifying patients were randomized in a 2:3 ratio to receive double-blind carvedilol starting at 6.25 mg bid or metoprolol tartrate starting at 50 mg bid. The rationale for the unequal randomization has been previously described.⁷ Doses were increased stepwise every 1 to 2 weeks to a maximum of 25 mg bid of carvedilol or 200 mg bid of metoprolol tartrate over 2 to 7 weeks in order to achieve target blood pressure. If necessary, adjunctive therapy with hydrochlorothiazide 12.5 mg followed by a dihydropyridine calcium antagonist (amlodipine) and α -blocker was allowed if needed to achieve target blood pressures.

Once target blood pressure or maximum dosage was reached, the study drug was maintained for 5 months.

The primary endpoint of GEMINI was the difference between the carvedilol- and metoprolol tartrate-treated groups in change in HbA_{1c} levels from baseline to maintenance month 5. Change from baseline in body weight was a pre-specified secondary endpoint.⁷ Body mass index (BMI) was determined at baseline and after completion of the 5-month maintenance period as the patient's weight in kilograms divided by the square of the patient's height in meters (kg/m²). Insulin resistance was determined using the Homeostasis Model Assessment–Insulin Resistance (HOMA-IR) index. Correlation analyses were defined post-hoc.^{6,8}

Details of statistical methods used in the overall GEMINI study are described elsewhere.⁶ For these analyses, only subjects with both baseline and at least 1 maintenance assessment of body weight were included. The last observation carried forward was used to impute missing endpoint values. Analysis of covariance (ANCOVA) was performed for change from baseline in weight comparing carvedilol with metoprolol tartrate, adjusting for baseline weight, study, baseline thiazolidinedione use, and baseline ARB use. To assess weight changes between the treatment groups across baseline weight quartiles, a similar exploratory ANCOVA was performed with baseline weight replaced by baseline weight quartiles in the analysis model. Similar exploratory analyses were performed to assess weight changes across baseline BMI categories, which were based on the National Institutes of Health BMI classifications: normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese (30–39.9 kg/m²), and extremely (morbidly) obese (>40 kg/m²). To explore whether or not the use of insulin at baseline had an effect on the weight change, ANCOVA was performed with a model adjusting for baseline weight, study, baseline thiazolidinedione use, baseline ARB use, and baseline insulin use. Statistical interaction between treatment and insulin use was examined. Adjusted (least squares) means, treatment difference, P values, and 95% confidence intervals (CIs) were provided for these analyses. Logistic regression was performed to compare the proportion of weight responders between the treatment groups for each of the following 4 binary responses: any weight loss (ie, a weight change <0 kg), weight loss $\geq 5\%$, weight gain $\geq 5\%$, and weight gain $\geq 7\%$. Each logistic regression analysis model was adjusted for baseline weight, study, baseline thiazolidinedione, and ARB use. Odds ratios, P values, and 95% CIs for carvedilol versus metoprolol tartrate were provided. Exploratory pairwise correlation analyses were performed to assess linear

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- In high-risk patients, attention should be paid to therapy that has associated weight gain; for instance, β -blocker use has been linked to increased body weight.
- Unlike metoprolol tartrate, carvedilol was not associated with significant weight gain in patients with diabetes and hypertension.

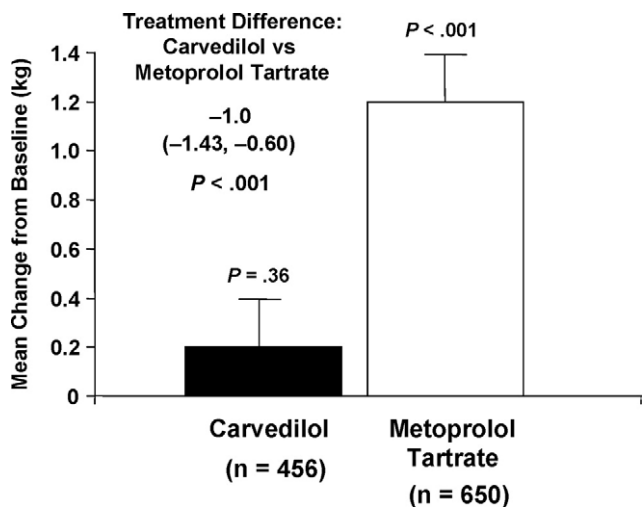


Figure 1 Carvedilol vs metoprolol tartrate: difference in mean weight change from baseline. Carvedilol therapy did not cause a significant weight increase (0.2 kg; $P = .36$), while metoprolol tartrate did significantly increase weight from baseline (1.2 kg; $P < .001$). The difference between the mean weight changes was significant ($P < .001$). From Bakris et al.⁶

association between weight change and changes in HbA_{1c}, HOMA-IR, systolic blood pressure, and diastolic blood pressure for each treatment group. The HOMA-IR values at baseline and at maintenance month 5 were log-transformed, and the change in the log-transformed value was used in the analysis. For all analyses, treatment comparisons were tested at a 0.05 significance level and tests of interaction were performed at a significance level of 0.10. This manuscript is based on retrospective analyses on a secondary variable and therefore no adjustments were made for multiplicity in secondary variable analyses, as originally planned for in the GEMINI study.

RESULTS

A total of 1235 patients were randomized to receive either carvedilol ($n = 498$) or metoprolol tartrate ($n = 737$). Their mean age was 61 years; 55% were male, and approximately 75% were white. Most of the participants were overweight or obese, with a mean baseline BMI of 34 ± 6 kg/m². The diabetic status of the enrollees was well controlled: mean entrance HbA_{1c} was 7.2%. After discontinuation of all blood pressure-lowering medications except ACE inhibitors or ARBs, the mean baseline blood pressure was 149/86 mm Hg. The mean doses required to achieve target blood pressure 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. Of the overall population in GEMINI, 456 carvedilol- and 650 metoprolol tartrate-treated patients had weight measurements at both baseline and at the 5-month endpoint (with last observation carried forward data); these patients form the basis for the remainder of this report.

In the patients analyzed for weight change in this study, the mean (\pm SD) baseline weight was $97.5 (\pm 20.1)$ kg in the

Weight Change (kg)	Carvedilol (N = 456)		Metoprolol Tartrate (N = 650)		Odds Ratio†	P Value	95% CI
	n	(%)	n	(%)			
Change <0	199	(43.6)	225	(34.6)	1.43	.005	1.12-1.83
Loss $\geq 5\%$	23	(5.0)	19	(2.9)	1.82	.059	0.98-3.41
Gain 5%-7%	26	(5.7)	59	(9.1)	0.65	.086	0.40-1.06
Gain $\geq 7\%$	5	(1.1)	29	(4.5)	0.26	.006	0.10-0.67

*All weight change scenarios are not represented, therefore the number of patients does not add to 456/650.
†For carvedilol vs metoprolol comparison.

carvedilol group and $96.6 (\pm 20.1)$ kg in the metoprolol tartrate group. After 5 months of therapy, patients receiving metoprolol tartrate experienced a significant mean (\pm SE) weight gain from baseline of $1.19 (\pm 0.16)$ kg (95% CI, 0.87-1.50; $P < .001$). In contrast, carvedilol-treated patients had no significant mean change from baseline ($0.17 [\pm 0.19]$ kg; 95% CI, -0.20 to 0.53 ; $P = .36$). The difference in mean weight change from baseline between the carvedilol- and metoprolol tartrate-treated groups is shown in [Figure 1](#).

The percentage of responders within each of the 4 specified weight change groups, along with their odds ratios (ORs) and 95% CIs during the 5-month treatment period, are shown in [Table 1](#). Although the numbers of patients in these groups were small, significantly more patients randomized to metoprolol tartrate (4.5%) experienced significant ($\geq 7\%$ body weight) weight gain as compared to carvedilol (1.1%) (carvedilol vs metoprolol OR = 0.26, 95% CI, 0.10-0.67; $P = .006$), and carvedilol was more likely than metoprolol to reduce weight as opposed to causing an increase in weight (carvedilol vs metoprolol OR = 1.43, 95% CI, 1.12-1.83; $P = .005$).

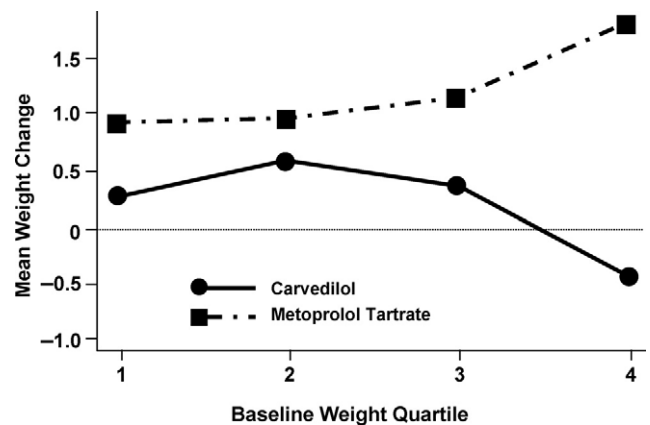


Figure 2 Carvedilol vs metoprolol tartrate: treatment-by-quartile interaction. The difference in weight change between carvedilol and metoprolol tartrate treatment was greatest in the 2 highest baseline weight quartiles. (P values for difference in weight by quartiles: Quartile 1: $P = .13$, Quartile 2: $P = .37$, Quartile 3: $P = .06$, Quartile 4: $P < .0001$) The difference in weight change was greatest between carvedilol and metoprolol tartrate treatment in patients in the fourth quartile ($P < .0001$).

Table 2 Weight Change Analysis Using Baseline Weight Quartiles as Covariate

	Quartile (n)	Adjusted Mean* Baseline Weight (kg)	Adjusted Mean* Month 5 Weight (kg)	Change from Baseline	Carvedilol vs Metoprolol Treatment Difference (P Value)
Carvedilol	1 (108)	74.6	75	0.3	−0.6 ($P = .13$)
Metoprolol	1 (170)	73.4	74.3	0.9	
Carvedilol	2 (120)	88.4	89.1	0.6	−0.4 ($P = .37$)
Metoprolol	2 (154)	89.1	90.0	1.0	
Carvedilol	3 (108)	102.2	102.5	0.3	−0.9 ($P = .06$)
Metoprolol	3 (168)	102.0	103.2	1.2	
Carvedilol	4 (119)	124.0	123.5	−0.4	−2.2 ($P < .0001$)
Metoprolol	4 (157)	124.1	126	1.8	

*Adjusted mean (or least squares mean).

Most of the weight gain observed in the metoprolol tartrate group occurred in patients with the greatest baseline body weight (Figure 2). Patients in the metoprolol tartrate group showed progressive weight gains in the first through the third quartiles (baseline weight 49.7–109.3 kg). Fourth-quartile metoprolol tartrate-treated patients (baseline weight >109.3–173.3 kg) showed a statistically significant difference in weight gain from comparable carvedilol-treated patients. When weight quartile at baseline was controlled for as a covariate, the treatment difference in weight gain was significant in the fourth quartile (Figure 2; Table 2).

Similar results were obtained by analyzing weight change in terms of baseline National Institutes of Health BMI categories: normal (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), obese (30–39.9 kg/m²), and extremely (morbidly) obese (>40 kg/m²) (Table 3).⁹ Metoprolol tartrate-treated patients with BMI >30 kg/m² had a statistically significant greater body weight gain than comparable carvedilol-treated patients. The difference in weight change between carvedilol and metoprolol tartrate became greater with increasing BMI category, with patients in the overweight, obese, and morbidly obese categories having a treatment difference (carvedilol vs metoprolol) of 0.82 (95% CI, −1.16 to 0.00, $P = .04$), −0.90 (95% CI, −1.5 to −0.3; P

=.002), and −1.84 (95% CI, −2.9 to −0.8, $P = .001$), respectively. The analysis of mean weight change from baseline using BMI as a covariate was performed and the findings were consistent with the findings of the original analysis.

Pairwise correlation analyses showed no statistically significant associations between change from baseline in body weight and change from baseline in HbA_{1c}, HOMA-IR, systolic blood pressure, or diastolic blood pressure.

The use of insulin at baseline had an effect on weight change. The treatment-by-insulin interaction was significant ($P = .03$), suggesting a different treatment effect across the 2 subgroups (with and without baseline insulin use) with respect to weight change. For the subjects on insulin therapy at baseline (8% in each group), there was no significant difference in weight gain between the treatment groups (carvedilol vs metoprolol tartrate, $P = .24$). However, for the majority of patients who were not on insulin therapy at baseline, there was a significant difference in weight change from baseline (carvedilol vs metoprolol) (−1.15 [± 0.22] kg, 95% CI, −1.59 to −0.72; $P < .0001$).

To determine if weight gain was due to fluid retention, we investigated BMI at baseline and end of therapy and diuretic use. Mean BMI at baseline was 33.5 kg/m² in the

Table 3 Weight Change Using Baseline BMI Category as Covariate*

	Baseline BMI Class (n)	Mean* Baseline Weight (kg)	Mean* Month-5 Weight (kg)	Change from Baseline	Carvedilol vs Metoprolol Treatment Difference (95% CI, P Value)
Carvedilol	Normal (24)	66.8	69.1	0.27	−0.90 (−2.8 to 1.0, $P = .358$)
Metoprolol	Normal (26)	63.3	64.5	1.17	
Carvedilol	Overweight (120)	82.6	82.6	−0.04	−0.83 (−1.6 to 0.0, $P = .044$)
Metoprolol	Overweight (179)	82.0	82.8	0.78	
Carvedilol	Obese (245)	100.7	100.8	0.15	−0.90 (−1.5 to −0.3, $P = .002$)
Metoprolol	Obese (344)	99.2	100.3	1.05	
Carvedilol	Morbidly obese (66)	123.0	123.5	0.51	−1.84 (−2.9 to −0.8, $P = .001$)
Metoprolol	Morbidly obese (100)	121.5	123.9	2.35	

BMI = body mass index.

BMI was not calculated for 2 patients as either height or weight was not recorded at baseline.

*Adjusted mean (or least squares mean).

carvedilol group and 33.7 kg/m² in the metoprolol group. BMI at the end of the study was 33.5 kg/m² in the carvedilol group and 34 kg/m² in the metoprolol group. Change from baseline was -0.01 in the carvedilol group and $+0.33$ in the metoprolol group. We did not test this treatment difference for significance since it was not part of the original analysis plan. While the difference is not large, the BMI numbers trend in the same direction as the weight numbers. The BMI comparison in addition to a similar percentage of patients requiring a diuretic during the study (due to edema) assures that the weight gain was not due to fluid retention. It is possible that the doses of the medications used would impact exercise tolerance, however the doses were titrated to blood pressure and therefore, we believe, are ones that would commonly be used in practice.

DISCUSSION

In this analysis of the GEMINI trial, we determined the impact of carvedilol and metoprolol tartrate therapy on weight change in a population of patients with diabetes and hypertension. These data suggest favorable effects on weight associated with carvedilol in comparison to metoprolol tartrate. Patients randomized to metoprolol tartrate had significantly greater weight gain than those receiving carvedilol, and significantly more patients on metoprolol had a clinically significant weight gain ($\geq 7\%$ of their body weight). The difference in weight change between carvedilol and metoprolol became greater with increasing baseline weight or BMI category. That is, metoprolol tartrate tended to exacerbate weight gain in patients who were already overweight or obese, while carvedilol had no significant effect. It is important to note that most patients randomized in GEMINI (mean BMI of 34 kg/m²) would be considered overweight or obese at the time of enrollment according to the criteria of the National Institutes of Health.⁹ Eighty percent were overweight or obese, 15% were extremely (morbidly) obese, and only 5% were normal.

Increased body weight is a clinical problem in the vast majority of patients with hypertension and in almost all patients with type 2 diabetes and hypertension. Drugs that either promote weight gain or make it difficult for patients to lose weight are, therefore, of concern in this population. β -blocker use has been linked to body fat accumulation and increased body weight. A systematic analysis was performed on 8 randomized controlled hypertension trials involving 7048 patients (3205 receiving β -blocker therapy), who were followed over a period ranging from 6 months to 10 years.¹ Both first- and second-generation β -blockers were included (propranolol, metoprolol, and atenolol). The analysis reported a greater average weight gain of 1.2 kg in β -blocker-treated patients compared to control subjects, with most of the weight gain occurring within the first few months of starting therapy.

We found no significant linear associations between body weight gain and changes from baseline levels in sys-

tolic blood pressure, diastolic blood pressure, glycemic control (HbA_{1c}), or insulin resistance (HOMA-IR). This lack of association between insulin sensitivity and body weight appears to be at variance with the well-established connection between insulin resistance and obesity,^{10,11} as well as with the generally recognized link between obesity and type 2 diabetes.^{12,13} For example, the San Antonio Heart Study reported waist/hip ratios of insulin-resistant persons to be 15% greater than control subjects.¹⁴ Although most individuals with a BMI ≥ 30 kg/m² have some degree of insulin resistance and postprandial hyperinsulinemia, our failure to observe this association may have been due to the broad range of insulin sensitivities that exist at any given level of body weight and the variations that occur in insulin sensitivity within the obese population.¹⁵ We also should consider that a study duration of only 5 months may not be long enough to allow the changes in insulin resistance to translate into weight changes.

The pathophysiologic mechanism underlying the difference in weight gain with the 2 β -blockers is unclear. It is possible that carvedilol may have an effect on leptin release through its α -blocking effect that is not shared by other β -blockers. α_1 -Blockade with doxazosin has been demonstrated to decrease leptin levels as well as insulin resistance in obese hypertensive patients.¹⁶ Although leptin levels were not measured in our study, elevated leptin levels are known to be associated with obesity.¹⁷ Additionally, although the exact benefit of the antioxidant properties of carvedilol have yet to be elucidated, it has been shown that oxidative stress is increased in obesity and correlates with serum leptin levels and BMI.¹⁸ Studies have shown that obesity is highly associated with states of oxidative stress and low-grade inflammation, suggesting that oxidative stress may play a role in obesity and lowering oxidative stress may decrease obesity.¹⁹

Regardless of the mechanism of weight change associated with these β -blockers, the importance of weight maintenance should not be underemphasized. Obesity is an independent risk factor for cardiovascular disease, and patients with diabetes are often overweight.²⁰ A recent editorial by Drs. Festa and Haffner noted that intensive insulin therapy aimed at decreasing HbA_{1c} levels is likely to improve cardiovascular disease, but attention needs to be paid to limiting weight gain. Limiting weight gain is not an easy goal from the clinical standpoint. From an individual patient's point of view, as well as from a public health care perspective, any intensive treatment regimen aiming at strict glycometabolic control needs to be balanced and measured against any potential adverse effect on weight. Drs. Festa and Haffner conclude, "It is likely that patients with diabetes, both type 1 and type 2, will benefit most from intensive [antiglycemic] treatment, if at the same time they can avoid weight gain or even lose weight as a result of the treatment."²¹ The results of this analysis of GEMINI suggest that in patients who are not on insulin therapy, there appears

to be more risk of weight gain associated with metoprolol tartrate.

There are limitations to this analysis. Although these analyses of the data from GEMINI suggest favorable effects on weight associated with carvedilol in comparison to metoprolol, they are exploratory. The GEMINI trial was not designed and powered to detect differences in weight changes or in weight gain. The weight change analysis involving baseline quartiles, baseline BMI categories, and the weight gain analyses were all defined post-hoc, and the study was not stratified by these characteristics. In addition, there was no adjustment for multiplicity in the analyses (that is, no adjustment of the alpha level to account for all the multiple analyses performed in this report). These are all ad hoc analyses of a secondary efficacy variable. The results reported in this paper are indicative and not conclusive of the effect of carvedilol and metoprolol on weight loss. Other suitably designed studies are needed for confirmation.

CONCLUSIONS

The GEMINI study found that carvedilol produced no significant change in HbA_{1c} and significantly reduced HOMA-IR in hypertensive patients with type 2 diabetes compared with metoprolol tartrate. Metoprolol tartrate led to a significant increase in body weight over 5 months compared with carvedilol. The greatest difference in weight gain between the 2 β -blockers occurred in the most overweight patients and in those not treated with insulin.

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References

- Sharma AM, Pischon T, Hardt S, et al. Hypothesis: Beta-adrenergic receptor blockers and weight gain: A systematic analysis. *Hypertension*. 2001;37:250-254.
- UKPD Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ*. 1998;317:713-720.
- Kaplan NM. Obesity in hypertension: effects on prognosis and treatment. *J Hypertens Suppl*. 1998;16:S35-S37.
- 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.
- Jacob S, Rett K, Wicklmayr M, et al. Differential effect of chronic treatment with two beta-blocking agents on insulin sensitivity: the carvedilol-metoprolol study. *J Hypertens*. 1996;14:489-494.
- Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA*. 2004;292:2227-2236.
- Bakris GL, Bell DS, Fonseca V, et al. The rationale and design of the Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial. *J Diabetes Complications*. 2005;19:74-79.
- Haffner SM, Kennedy E, Gonzalez C, et al. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care*. 1996;19:1138-1141.
- Executive summary of the clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. *Arch Intern Med*. 1998;158:1855-1867.
- Bogardus C, Lillioja S, Mott DM, et al. Relationship between degree of obesity and in vivo insulin action in man. *Am J Physiol*. 1985;248:E286-E291.
- Abbasi F, Brown BW Jr, Lamendola C, et al. Relationship between obesity, insulin resistance, and coronary heart disease risk. *J Am Coll Cardiol*. 2002;40:937-943.
- Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest*. 2000;106:473-481.
- Sullivan PW, Morimoto EH, Ghushchyan V, et al. Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000-2002. *Diabetes Care*. 2005;28:1599-1603.
- Ferrannini E, Haffner SM, Mitchell BD, Stern MP. Hyperinsulinemia: the key feature of a cardiovascular and metabolic syndrome. *Diabetologia*. 1991;34:416-422.
- Grundy SM, Brewer HB Jr, Cleeman II, et al. Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation*. 2004;109:433-438.
- Ueshiba H, Miyachi Y. Effect of doxazosin on insulin resistance in hypertensive patients with obesity. *Horm Metab Res*. 2003;35:532-536.
- Friedman JM. The function of leptin in nutrition, weight, and physiology. *Nutr Rev*. 2002;60:S1-14.
- Ustundag B, Gungor S, Aygun AD, et al. Oxidative status and serum leptin levels in obese prepubertal children. *Cell Biochem Funct*. 2006; [Epub ahead of print].
- Suzuki K, Ito Y, Ochiai J, et al. Relationship between obesity and serum markers of oxidative stress and inflammation in Japanese. *Asian Pac J Cancer Prev*. 2003;4:259-266.
- Klein S, Burke LE, Bray GA, et al. Clinical implications of obesity with specific focus on cardiovascular disease: a statement for professionals from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism: endorsed by the American College of Cardiology Foundation. *Circulation*. 2004;110:2952-2967.
- Festa A, Haffner SM. Inflammation and cardiovascular disease in patients with diabetes: lessons from the Diabetes Control and Complications Trial. *Circulation*. 2005;111:2414-2415.