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Effects of Beta-Blocker Titration on Glucose Homeostasis in Heart Failure

Orly Vardeny, Pharm.D.¹, James Zebrack, M.D.², Edward M. Gilbert, M.D.², and Kai I. Cheang, Pharm.D., M.S., BCPS³

¹ Assistant Professor, University of Wisconsin School of Pharmacy, Madison, WI

² Department of Internal Medicine, University of Utah, Salt Lake City, Utah

Abstract

Background—Abnormal glucose metabolism and insulin resistance have been associated with heart failure incidence, severity, and mortality. Metabolic parameters such as hepatic glucose production may be altered by β -adrenoceptor antagonists in patients with heart failure.

Objective—This study evaluated the effects of metoprolol or carvedilol up-titration on fasting glucose, insulin resistance and β_2 -mediated glucose production in patients with chronic heart failure.

Methods—This was a prospective, randomized, active comparator study in 15 patients with AHA/ACC Stage C systolic dysfunction HF stable on medical therapy. Participants were randomized to metoprolol 25mg daily or carvedilol 3.125mg twice daily. Metoprolol was titrated to a target of 200mg daily, and carvedilol was titrated to 25mg twice daily over 8 weeks. Insulin resistance as assessed by the homeostatic model, and terbutaline-induced glucose production (AUC_{0-180}), were assessed at baseline and at 4 subsequent β -blocker titration visits over 8 weeks.

Results—In all 15 patients, terbutaline-induced glucose AUC_{0-180} decreased ($p=0.0006$) as β -blocker doses increased. A significant reduction in glucose AUC_{0-180} compared to baseline was only noted in patients taking metoprolol at 100mg daily (-2424.6 [95% CI -372.6 to -4478.4] mg/dL*min) and 200mg daily (-2437.2 [95% CI -15.1 to -4604.4] mg/dL*min), and not observed in those taking carvedilol. After β -blocker titration, fasting glucose concentrations for the metoprolol and carvedilol groups were 86.9 (95% CI 89.8–101.6) mg/dL and 95.7 (95% CI 89.8–101.6) mg/dL, respectively ($p=0.0273$), adjusted for baseline values. There was no significant difference between metoprolol and carvedilol on insulin resistance.

Conclusion—Increasing doses of β -blockers are associated with decreased in β_2 -mediated glucose production in heart failure. Metoprolol, but not carvedilol, decreases hepatic glucose production at commonly used heart failure doses.

Keywords

Heart failure; glucose homeostasis; carvedilol; metoprolol; β_2 -adrenergic receptor

³Corresponding author: Kai I. Cheang, Pharm.D., M.S., BCPS, Virginia Commonwealth University, PO BOX 980533, Richmond, VA 23298-0533, kicheang@vcu.edu, Phone: (804) 828-9698, Fax: (804) 828-8359.

Conflict of Interest Statement:

OV, JZ, and KIC have nothing to declare. EMG is a consultant for Glaxo SmithKline.

BACKGROUND

The human heart failure state leads to alterations in metabolic pathways including worsened glucose metabolism and hyperinsulinemia. Diabetes mellitus is present in 20–25% of patients with chronic heart failure in large clinical trials.^{1–6} Furthermore, abnormal glucose metabolism and insulin resistance have been shown to be independent predictors of incident heart failure,^{7–9} heart failure severity,¹⁰ as well as heart failure mortality.¹ Both fasting and post-load hyperinsulinemia are present in heart failure, suggesting that heart failure may represent an insulin resistant state.^{1, 5, 6} While the exact mechanism whereby altered glucose homeostasis occurs in heart failure is unknown, several pathways have been proposed. Perhaps the most important of these pathways is the neurohormonal compensatory mechanism in heart failure which leads to elevated norepinephrine and epinephrine concentrations. Increased norepinephrine and epinephrine concentrations in turn stimulate hepatic glucose production via β_2 adrenergic receptors (β_2 -AR).^{11, 12}

The degree of β_2 -AR-mediated glucose production in heart failure may be altered furthermore by β -AR antagonists. The use of metoprolol and carvedilol, both β -AR antagonists, is standard management of heart failure. Previous studies indicate that some β -blockers may lead to worsening glycemic control, while other β -blockers may be metabolically neutral or may even improve insulin sensitivity.^{13, 14} Differential metabolic effects of metoprolol (a β_1 selective antagonist) and carvedilol (a non-selective β antagonist) have been demonstrated in hypertensive patients with diabetes mellitus.¹⁴ Moreover, a post-hoc analysis of the COMET study suggested that new onset diabetes was more common in heart failure patients taking metoprolol as compared to carvedilol.¹⁵ It is possible that the differential metabolic effects between metoprolol and carvedilol may be related to their ability to block β_2 -mediated hepatic glucose production, although this remains to be investigated.

In this study, we compared β_2 -mediated glucose production, fasting glucose and insulin resistance between metoprolol and carvedilol during up-titration in patients with AHA/ACC Stage C heart failure.

METHODS

Patients

We studied 15 patients with AHA/ACC Stage C, NYHA FC II–III heart failure, who were derived from a previous study in which heart failure patients were randomized to metoprolol succinate (n=13) or carvedilol (n=12).¹⁶ In this report, we described the effect of β -blocker up-titration in *non-diabetic* participants (n=9 for metoprolol succinate, and n=6 for carvedilol). All participants were recruited from the University of Utah Advanced Therapies Heart Failure Clinic. Eligibility criteria included evidence of systolic dysfunction (ejection fraction 40%) with ACC/AHA Stage C, NYHA Functional Class II–III heart failure. Participants were on stable optimal medical therapy for heart failure (angiotensin converting enzyme inhibitors or angiotensin receptor blockers, digoxin, diuretics) and were not on β -blockers. Exclusion criteria included contraindications to β -blockers (active bronchospastic disease, resting heart rate <55 bpm, systolic blood pressure < 90 mmHg, second or third degree heart block), concomitant use of scheduled inhaled β -agonists, use of β -antagonists, prescription or ingestion of diabetes medications within the past 3 months, or concomitant antiarrhythmics. In addition, patients with unstable angina or myocardial infarction or bypass surgery within the past 3 months, diagnosis of diabetes, significant renal insufficiency (creatinine >2.5 mg/dL), liver disease (transaminase levels 3 times the upper limit of normal), anemia, active myocarditis, hemodynamically significant valvular heart disease, hypertrophic or restrictive cardiomyopathy, were also excluded. The protocol was approved by the University of Utah

and University of Wisconsin institutional review boards, respectively. Informed consent was obtained in accordance with established guidelines for the protection of human subjects.

Study Protocol

We evaluated fasting glucose, insulin resistance and β_2 -mediated glucose production prior to initiation of β -blocker therapy, and at each titration visit until completion of carvedilol and metoprolol titration. The study methods followed those previously described for studying β_2 -AR mediated glucose production.¹⁷ Heart failure participants were admitted to the University of Utah General Clinical Research Center for overnight observation to determine the baseline glucose response to the β_2 agonist, terbutaline. All began fasting at midnight. At 0900, terbutaline was infused at 6 mg/kg (maximum 600 mg) for one hour. Blood samples for insulin and glucose were taken at 15 minutes and 5 minutes prior to infusion, every 10 minutes during terbutaline infusion, every 15 minutes during the first hour post infusion, and every 30 minutes during the second hour post infusion (14 samples total). Seated blood pressures and heart rates were obtained at each blood draw. After the morning procedures, participants were randomized to open-label therapy with either carvedilol (3.125 mg twice daily) or metoprolol succinate (25 mg daily). The starting β -blocker dose was continued for 2 weeks, after which participants returned for a second overnight observation. The assigned β -blocker was administered at 0700, followed by blood sampling and terbutaline infusion at 0900 as performed at the baseline visit. After completion of the infusion and blood draws as described above, the β -blocker dose was doubled for clinically stable patients. Patients were considered clinically stable if they did not have symptomatic dyspnea, hypotension or bradycardia. After two weeks at the higher dose, participants returned to the clinical research center for a third overnight observation and terbutaline study. This two-week cycle continued until each patient reached a target dose of 25 mg twice daily for carvedilol and 200 mg daily for metoprolol succinate. For patients that could not be titrated to the target dose due to symptomatic dyspnea, hypotension or bradycardia, they were titrated to their maximal tolerated dose of the assigned β -blocker. At the fifth visit (week 8), patients returned for their final terbutaline infusion and blood sampling. Fasting insulin levels were also obtained at baseline and final visits. Concomitant heart failure medication doses were to remain constant during β -blocker up-titration. Clinically necessary loop diuretic dose adjustments were allowed.

Sample Size Calculation

Our primary outcome was the area under the glucose-concentration-time curve during and for 120 minutes after the 1-hour terbutaline infusion (AUC_{glucose}), compared between the metoprolol and carvedilol groups. Because no comparative data for AUC_{glucose} between carvedilol and metoprolol has previously been reported in the literature, we based our sample size on the results of a previous report that showed a significant difference between metoprolol and carvedilol in hemoglobin A1c.¹⁴ In this previous study, the end-of-study hemoglobin A1c was 7.42% vs. 7.28% for metoprolol and carvedilol, respectively. Assuming that the standard deviation is 0.09%, which was more conservative than values reported in this previous study, 8 individuals in each β -blocker group were necessary to detect a difference, for a 2-sided test, with $\alpha=0.05$ and a power of 80%.

Statistical Analyses

We analyzed β_2 -mediated glucose production by calculating the area under the glucose-concentration-time curve during and for 120 minutes after the 1-hour terbutaline infusion (AUC_{glucose}) using the trapezoidal rule. Insulin resistance was calculated using the homeostatic model assessment of insulin resistance (HOMA-IR): fasting values of glucose (mmol/L) $\times$ insulin ($\mu\text{IU/mL}$)/22.5.¹⁸ Results that were not normally distributed were log-transformed for statistical analyses, and following back-transformation, were reported in their original units.

Differences between groups at baseline were determined with the Student's two-tailed *t* test, and equalities of variances were assessed with the Brown-Forsythe test. For comparisons with unequal variances, *p*-values of Welch ANOVA tests are reported, as indicated. Due to the small sample size, we also analyzed the data by the nonparametric Wilcoxon test, in addition to using log-transformed variables, to confirm that nonparametric tests yielded the same conclusions. The effects of β -blocker assignment on glucose parameters after drug titration were analyzed by ANCOVA, adjusting for baseline values. The significance of the time trends across the 5 β -blocker titration visits was analyzed using repeated measures ANOVA. The effect of β -blocker on time trends was analyzed using two-way repeated measures ANOVA. If interactions exist between time and drug assignment, post-hoc tests were performed using Tukey HSD. All results were reported as means, or geometric means for log-transformed variables, with 95% confidence intervals (CIs). *P*-values of <0.05 were considered significant. All analyses were performed using JMP 7.0 software (SAS Institute, Cary, NC).

RESULTS

Participants

The sample consisted of 15 participants (5 females, 10 males) with a mean age of 58.9 years (range 38–80 years) (Table 1). Mean ejection fraction was 24.5%. No statistically significant differences in demographics, heart failure severity, medication use and glucose homeostasis were observed at baseline between the carvedilol and metoprolol groups (Table 1).

All participants were able to achieve the maximum β -blocker dose, except for two individuals in the metoprolol group who were titrated to 50 mg daily, and one individual in the carvedilol group who was titrated to 6.25 mg twice daily. Information collected for these 3 individuals were used in the analyses. In addition, 2 individuals in the carvedilol group, and 2 individuals in the metoprolol group, required an increase in their diuretic doses during the study. No significant differences in heart rate ($p=0.0867$), systolic ($p=0.79620$) and diastolic blood pressure ($p=0.1923$) time trends were noted between the metoprolol and carvedilol groups during the dose titration visits (Figure 1).

Effect of β -blocker titration on fasting glucose

Fasting glucose concentrations at baseline were 92.3 (95% CI 86.1–98.9) mg/dL in those taking metoprolol, and 91.5 (95% CI 84.9–98.6) mg/dL for the carvedilol group ($p=0.85$). After completion of β -blocker titration, fasting glucose concentrations for the metoprolol and carvedilol groups were 86.9 (95% CI 89.8–101.6) mg/dL and 95.7 (95% CI 89.8–101.6) mg/dL, respectively ($p=0.0273$, ANCOVA). Fasting glucose profiles during the β -blocker titration visits are shown in Figure 2.

Effect of β -blockers on fasting insulin and insulin resistance

Baseline fasting insulin concentration and HOMA-IR were not different between patients receiving carvedilol vs. metoprolol (Table 1). After β -blocker titration, there was no difference in fasting insulin levels (2.38 [95% CI 2.06–2.71] vs. 2.27 [95% CI 1.94–2.59] μ IU/mL, $p=0.59$, ANCOVA) and HOMA-IR (3.89 [95% CI 3.50–4.27] vs. 3.69 [95% CI 3.34–4.03], $p=0.43$, ANCOVA) between the carvedilol and metoprolol groups, respectively.

Effect of β -blocker titration on terbutaline-induced glucose production

Terbutaline-induced glucose production (glucose AUC₀₋₁₈₀) at baseline was 18108.0 (95% CI 16299.0–19917.0) mg/dL·min in those taking metoprolol, and 18936.0 (95% CI 16720.2–21151.8) mg/dL·min for the carvedilol group ($p=0.54$). When all participants were evaluated together, there was a significant reduction in glucose AUC₀₋₁₈₀ across time as dosages of β -

blockers increased ($p=0.0006$). Terbutaline-induced glucose production by dose titration is shown in Figure 3. After completion of β -blocker titration, glucose AUC_{0-180} was 15546.6 (95% CI 14882.4–16212.6) mg/dL·min for the patients taking metoprolol, and 16351.2 (95% CI 15539.4–16839.0) mmol/L·min for those taking carvedilol ($p=0.12$, ANCOVA), suggesting a divergence between metoprolol and carvedilol at higher doses that is shy of statistical significance (Figure 3). In fact, a significant reduction in glucose AUC_{0-180} compared to baseline was seen only in patients taking metoprolol at 100mg daily (-2424.6 [95% CI -372.6 to -4478.4] mg/dL·min) and 200mg daily (-2437.2 [95% CI -15.1 to -4604.4] mg/dL·min). This reduction in glucose AUC_{0-180} from baseline was not observed in patients assigned to carvedilol ($p=NS$).

DISCUSSION

We sought to determine the effects of β -blockers on glucose dynamics and β_2 -AR-mediated glucose production in patients taking metoprolol succinate or carvedilol at commonly targeted doses. We observed that increased doses of β -blockers resulted in decreased terbutaline-induced glucose production. This occurred in a dose related fashion for metoprolol, where we noted that increased doses led to significantly reduced terbutaline-induced glucose production. For carvedilol, the reduction in terbutaline-induced glucose production was not significant at any of the time points.

Hepatic glucose production is mediated in part by the actions of the catecholamines norepinephrine and epinephrine on β_2 -AR. Terbutaline is a β_2 – selective agent with weak activity at α receptors. Therefore, changes in glucose concentrations in response to terbutaline are likely due to β_2 -AR – mediated glucose production. Terbutaline infusions offer an opportunity to explore hepatic glucose production in an experimental fashion. Similar to our findings, previous investigations have also reported a dose-related reduction in glucose concentrations with terbutaline stimulation and concomitant β -blocker administration.^{17, 19} Carvedilol is non-selective, and metoprolol is β_1 selective at lower doses. Previous studies reported that metoprolol is less β_1 selective at higher doses.¹⁷ According to their adrenergic receptor blocking pharmacology, one would anticipate more pronounced reduction of glucose AUC by carvedilol due to its non-selectivity and affinity to β_2 receptors.²⁰ This expected enhanced reduction of AUC_{glucose} by carvedilol during terbutaline infusion was not seen in our study. It is possible that carvedilol blocks β_2 receptors to a similar extent throughout its dosing range. As such, it may lead to decreased glucose production initially at lower doses, but the effect may remain constant (as seen in Figure 3) if the degree of β_2 blockade is constant as well. Additionally, it is possible that carvedilol treatment leads to β_2 -AR upregulation, as was shown in a murine model of asthma.²¹ Moreover, carvedilol serves as a partial inverse agonist at the β_2 -AR, which may lead to upregulated spontaneous active conformation of β_2 -AR, promoting improved receptor coupling.²² This could explain the reduction of β_2 mediated glucose production that was evident early, which stabilized through up-regulation of the β_2 -AR as patients continued carvedilol administration. In contrast, metoprolol became less β_1 selective at higher doses as titration continued.¹⁷ Metoprolol's blockade of β_2 receptors at higher doses may explain the significant reduction in glucose AUC upon terbutaline infusion at doses of 100 mg daily or above, as compared to baseline.

Reductions in systolic and diastolic blood pressures and heart rates were not significantly different between the β -blocker groups. This suggests that differences in terbutaline-mediated glucose production between the two agents are not attributable to hemodynamic differences or varying levels of adherence.

Our finding that metoprolol's loss of β_1 selectivity at doses above 100 mg daily confirm previous reports¹⁷ and would be clinically relevant in the selection of β -blockers in specific

patient populations. For example, in asthmatic patients, metoprolol may be prescribed due to its β_1 selectivity, but clinicians should be aware that metoprolol loses its β_1 selectivity at high doses. In addition, our finding that metoprolol, but not carvedilol, is associated with reduced β_2 -mediated glucose production, contribute to the current knowledge of the effects of β -blockers on glucose homeostasis in heart failure. The findings of this study suggest that β_2 -mediated glucose production does not explain the decreased risk of incident diabetes associated with carvedilol reported by COMET investigators.¹⁵ Hence, other aspects of glucose handling may be important in mediating a reduction of incident diabetes associated with carvedilol. Future research should concentrate on differences in peripheral insulin sensitivity and glucose utilization between the two β -blockers.

In our study, fasting glucose was higher in patients assigned to carvedilol compared to metoprolol at the conclusion of β -blocker titration. In the COMET study, carvedilol showed a 22% decrease in new-onset diabetes compared with metoprolol tartrate.¹⁵ The GEMINI study, which compared carvedilol and metoprolol in patients with diabetes and hypertension, found similar mean blood glucose concentrations between the two agents over a course of 5 months, yet higher hemoglobin A1c values in the metoprolol group.¹⁴ These previous reports of increased incident diabetes and A1c values with metoprolol contrast with our current findings of lower fasting glucose in heart failure patients assigned to metoprolol. This discrepancy may be due to the acute or short-term effects on fasting glucose during β -blocker up-titration observed in this 8-week study, as compared to chronic blood glucose changes after titration is completed, as studied in COMET and GEMINI. Additionally, differences in study designs, participant characteristics, and sample size may account for differing study results. In our current study, we focused on differences in β_2 -mediated glucose production between metoprolol and carvedilol. Although we expected that carvedilol would have enhanced reduction in β_2 -mediated glucose production compared with metoprolol, in our study, metoprolol but not carvedilol was actually associated with a reduction in β_2 -mediated glucose production. Hence, β_2 -mediated glucose production as evaluated in this study does not seem to explain the decreased risk of incident diabetes associated with carvedilol. Future research should concentrate on differences in peripheral insulin sensitivity and glucose utilization between the two β -blockers.

We did not observe differences in insulin resistance (HOMA-IR) between β -blocker groups during and following dose titrations. These data contrast with previous studies in which increased insulin resistance were found for metoprolol tartrate compared to carvedilol.^{13, 14} Similar to our discrepancies with fasting glucose results in the GEMINI study as mentioned earlier, it is possible that changes in insulin resistance between metoprolol and carvedilol manifest after chronic dosing as examined in prior studies, which we did not measure in our study.

Several limitations should be considered when interpreting the results of this study. Despite the small sample size, we observed significant results regarding β_2 -mediated glucose production in this study. Nonetheless, results observed in this study should be confirmed in a larger cohort of patients. Due to the small sample size of this study, significant clinical differences in gender, race, and hemodynamic measures between groups may be present that were not detected statistically. However, of note, baseline ejection fractions and metabolic variables (glucose, insulin, HOMA-IR) were very similar between the two β -blocker groups. Hence we are confident that there were not baseline differences in heart failure severity and metabolic status that would have biased the comparison between the two β -blocker groups. Secondly, we were primarily interested in the effect of carvedilol vs. metoprolol titration in heart failure patients. Hence, we did not include individuals without heart failure. Future studies should address effects of β -blockers in heart failure compared to healthy individuals. Diuretic dose changes may also affect glucose handling. Adjusting for diuretic dose changes at each

visit in a repeated measures analysis poses unique challenges, and hence we were not able to adjust for the effect of diuretic dose changes on glucose handling. However, the number of individuals requiring an increase in diuretic dose was similar in both β -blocker groups ($n=2$ for carvedilol and $n=2$ for metoprolol). Finally, this was a randomized, but unblinded study. Although it is unlikely that the lack of blinding would affect glucose and insulin values, a blinding procedure would be desirable, especially in any future trials involving more participants. The results of this exploratory study should be considered hypothesis generating in support of future studies evaluating the effects of specific β -blocker pharmacology on glucose handling in patients with heart failure.

CONCLUSIONS

We conclude that as β -blockade increases, β_2 -AR-mediated glucose production is discordantly reduced between metoprolol succinate and carvedilol. These results should provide an impetus for larger-scale studies. As diabetes and heart failure co-exist at accelerating rates, further research should confirm the effects of β -blocker selection and target doses on glucose handling in patients with heart failure.

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Figure 1. Systolic blood pressure (panel A), diastolic blood pressure (panel B), and heart rate (panel C) by β -blocker assignment at baseline and across dose-titration visits

Carvedilol doses are: C6.25 = 3.125mg twice daily, C12.5 = 6.25mg twice daily, C25 = 12.5mg twice daily, and C50 = 25mg twice daily. Metoprolol doses are: M25 = metoprolol succinate 25mg daily, M50 = metoprolol succinate 50mg daily, M100 = metoprolol succinate 100mg daily, and M200 = metoprolol succinate 200mg daily. Values are mean $\pm$ SE.

Figure 2. Fasting plasma glucose by β -blocker assignment at baseline and across dose-titration visits

Carvedilol doses are: C6.25 = 3.125mg twice daily, C12.5 = 6.25mg twice daily, C25 = 12.5mg twice daily, and C50 = 25mg twice daily. Metoprolol doses are: M25 = metoprolol succinate 25mg daily, M50 = metoprolol succinate 50mg daily, M100 = metoprolol succinate 100mg daily, and M200 = metoprolol succinate 200mg daily. Values are mean $\pm$ SE.

* P=0.0273 for comparison between groups at end of titration (ANCOVA).

Figure 3. Glucose AUC (mg/dL *min) upon terbutaline infusion by β -blocker assignment at baseline and across dose-titration visits

Carvedilol doses are: C6.25 = 3.125mg twice daily, C12.5 = 6.25mg twice daily, C25 = 12.5mg twice daily, and C50 = 25mg twice daily. Metoprolol doses are: M25 = metoprolol succinate 25mg daily, M50 = metoprolol succinate 50mg daily, M100 = metoprolol succinate 100mg daily, and M200 = metoprolol succinate 200mg daily. Values are mean $\pm$ SE.

P=0.0006 for trend in all participants across time.

P=0.12 for comparison of trend between carvedilol and metoprolol.

*Reduction in glucose AUC significant compared to baseline: -2424.6 (95% CI -372.6 to -4478.4) mg/dL·min for M100, and -2437.2 (95% CI -15.1 to -4604.4) mg/dL·min for M200.

Table 1

Baseline Clinical Characteristics of Heart Failure Patients assigned to Carvedilol and Metoprolol Succinate

	Carvedilol (n=6)	Metoprolol (n=9)	P-value
Age (yrs) [‡]	57.0 (38.3–84.9)	60.8 (45.9–80.6)	0.78
Race (% of patients)			
Caucasian	83.3	100	0.2
Hispanic	16.7	0	
Gender (% of patients)			
Male	100	55.6	0.06
Female	0	44.4	
NYHA Functional Class (% of patients)			
II	50.0	44.5	0.39
III	50.0	55.5	
Ejection fraction (%) [‡]	26.0 (19.7–34.3)	23.0 (19.1–27.6)	0.42
Systolic blood pressure (mmHg) [‡]	111.9 (97.2–128.8)	115.4 (102.9–129.5)	0.72
Diastolic blood pressure (mmHg) [‡]	66.3 (58.9–74.5)	72.2 (65.6–79.4)	0.25
Heart rate (bpm) [‡]	70.7 (59.4–84.2)	75.3 (65.3–86.7)	0.56
Ischemic Heart disease (% of patients)	33.3	44.4	0.55
Medications (% of patients)			
Diuretics	83.3	77.7	0.79
ACE Inhibitor/Angiotensin Receptor Blocker	66.7	88.9	0.29
Aldosterone Antagonist	66.7	33.3	0.21
Digoxin	50.0	66.7	0.52
Aspirin	66.7	66.7	1.0
Insulin (μ units/mL) [‡]	9.8 (5.2–18.8)	10.0 (6.0–16.6)	0.97
Fasting glucose (mg/dL) [‡]	91.5 (84.9–98.6)	92.3 (86.1–98.9)	0.85
HOMA-IR [‡]	2.71 (1.31–5.62)	2.12 (1.26–3.54)	0.55

HOMA-IR= Homeostatic assessment of insulin resistance

Data are means (95% CI).

[‡]p-value obtained using geometric means.