Comparison of the Effects of Doxazosin and Atenolol on Target Organ Damage in Adults with Type 2 Diabetes Mellitus and Hypertension in the CARDHIAC Study: A 9-Month, Prospective, Randomized, Open-Label, Blinded-Evaluation Trial

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ABSTRACT

Objective: The CARDHIAC (CARduran® en pacientes Diabéticos con HIpertensión Arterial no Controlada) trial examined the effects of doxazosin gastrointestinal therapeutic system (GITS) and atenolol on 3 separate measures of target-organ damage—left ventricular mass index (LVMI), carotid intima media thickness (IMT), and urinary albumin excretion (UAE)—in patients with type 2 diabetes mellitus and hypertension.

Methods: This trial had a prospective, open-label, blinded-evaluation design and a duration of 9 months. Patients whose blood pressure (BP) was uncontrolled (systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg) despite at least 1 month of treatment with a renin–angiotensin blocker and a diuretic were randomly allocated to receive doxazosin GITS 4 mg or atenolol 50 mg once daily in addition to their existing treatment. Seated BP was measured at study visits at 1, 3, 6, and 9 months; if the BP goal was not achieved at any visit, the dose of doxazosin or atenolol was titrated upward to 8 or 100 mg, respectively. Treatment compliance (pill count) and adverse reactions were monitored at each visit. Each patient underwent echocardiography and Doppler ultrasonography at baseline and at the end of the study for evaluation of the change in LVMI. The change in carotid IMT was evaluated by carotid ultrasound examination at the same time points. UAE also was measured at baseline and the end of the study.

Results: Sixty patients (100% white; 51% female; mean [SD] age, 63.4 [7.5] years; body mass index, 28.2 [3.4] kg/m^2) were randomized to receive doxazosin GITS (n = 32) or atenolol (n = 28). At baseline, mean BP was 150.2 (10.6)/90.1 (7.3) mm Hg in the doxazosin group and 153.1 (13.8)/92.3 (6.1) mm Hg in the atenolol group (P = NS). At the end of the study, BP had decreased by 10.1 (3.2)/5.2 (1.3) mm Hg in the doxazosin group and 12.2 (4.2)/6.3 (2.1) mm Hg in the atenolol group (both, $P < 0.001$ vs baseline; P = NS between groups). Heart rate at the end of the study was 78 (6) beats/min in the doxazosin group (P = NS vs baseline) and 66 (7) beats/min in the atenolol group ($P < 0.01$ vs baseline and between groups). LVMI decreased by 10.8% in the doxazosin group ($P = 0.001$ vs baseline) and 4.2% in the atenolol group (P = NS vs baseline; $P = 0.03$ between groups). The changes in carotid IMT and UAE were not statistically significant between groups.

Conclusions: In this study in hypertensive patients with type 2 diabetes, LVMI was significantly decreased in doxazosin-treated patients relative to baseline and compared with atenolol-treated patients. The differences in carotid IMT and UAE were not statistically significant between groups. (*Clin Ther*. 2008;30:98–107) © 2008 Excerpta Medica Inc.

Key words: atenolol, diabetes, doxazosin, hypertension, target organ damage.

INTRODUCTION

Diabetes is an important health care problem, with microangiopathic and macroangiopathic consequences

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that markedly increase cardiovascular morbidity and mortality. Because of the increasing prevalence of obesity and a sedentary lifestyle, the frequency of diabetes is likely to grow in the coming years.[1] In Spain, the prevalence of diabetes has been estimated at ~6%.[2]

Although diabetes is a major cardiovascular risk factor in itself, its presence increases the risk for other cardiovascular risk factors, particularly hypertension. The prevalence of hypertension is increased 1.5- to 2-fold in patients with diabetes compared with those without diabetes, and patients with hypertension have a 2.5-fold increased risk of developing diabetes compared with those without hypertension.[3] Patients with both hypertension and diabetes are at a greatly increased risk for macrovascular outcomes (ischemic heart disease, stroke, peripheral vascular disease) and microvascular complications (retinopathy, nephropathy, neuropathy). As many as 75% of macrovascular complications in patients with diabetes are associated with hypertension.[4] Despite the importance of achieving blood pressure (BP) control in patients with hypertension, clinical practice guidelines from the European Society of Hypertension and the European Society of Cardiology also emphasize the importance of preventing target-organ damage.[5]

Only about half of patients respond to antihypertensive monotherapy, approximately one quarter of whom achieve BP control; the response is even poorer (<15%) in those with diabetes and hypertension.[6,7] Therefore, a large proportion of those with diabetes and hypertension may require several drugs to achieve BP goals. Renin–angiotensin system blockade has been recommended as the first-line therapeutic approach to hypertension in patients with diabetes.[6,8]

Doxazosin, a selective α_1-adrenergic–receptor antagonist, has been found to be effective and well tolerated, particularly as part of a combination regimen.[9–11] Treatment with doxazosin has been reported to exert positive metabolic effects. After 12 weeks of doxazosin treatment, the rate of metabolic clearance of glucose increased from 2.35 to 3.37 mL/min · kg and fasting plasma glucose decreased from 11.9 to 10.9 mmol/L (P = NS),[12] suggesting an improvement in insulin sensitivity. Although β-blockers effectively reduce BP, they are associated with negative metabolic effects. In a recent meta-analysis that included 94,492 patients with hypertension, β-blocker therapy was associated with a 22% increased risk for new-onset diabetes compared with nondiuretic antihypertensive agents (relative risk = 1.22; 95% CI, 1.12–1.33).[13]

Several studies have examined the effects of antihypertensive drugs on isolated target-organ damage.[6,8,11,13] This paper presents the results of the CARDHIAC (CARduran® en pacientes Diabéticos con HIpertensión Arterial no Controlada) trial, which compared the effects of third-line antihypertensive therapy with doxazosin gastrointestinal therapeutic system (GITS) or atenolol on left ventricular mass index (LVMI), carotid intima media thickness (IMT), and urinary albumin excretion (UAE) in patients with type 2 diabetes and uncontrolled hypertension.

PATIENTS AND METHODS

The CARDHIAC trial was a single-center, prospective, randomized, open-label, blinded-outcome evaluation that was approved by the local ethics committee and conducted according to good clinical practice guidelines. Eligible patients were aged ≥18 years with type 2 diabetes and hypertension that was uncontrolled (systolic BP ≥130 mm Hg and/or diastolic BP ≥80 mm Hg[5]) despite at least 1 month of treatment with the combination of a renin–angiotensin blocker (angiotensin-converting enzyme [ACE] inhibitor or angiotensin-receptor blocker [ARB]) and a diuretic at maximum doses and no contraindications to the use of atenolol or doxazosin. Written informed consent was obtained from all patients before randomization.

Patients were allocated by simple randomization to receive doxazosin GITS 4 mg or atenolol 50 mg once daily in addition to their existing renin–angiotensin blocker and diuretic treatment. Seated BP was measured at study visits at 1, 3, 6, and 9 months. If the BP goal was not achieved at any visit, doxazosin or atenolol was titrated upward to 8 or 100 mg, respectively. Treatment compliance was determined by pill count at each visit; >80% compliance was considered good. Patients were questioned about the occurrence of adverse events at each visit, and adverse events were recorded by a blinded investigator.

Seated BP readings were obtained using a validated automated device after the patient had rested for 5 minutes.[5] Patients were advised to avoid smoking or drinking coffee within 30 minutes before measurement of BP. The BP recorded for each visit was the mean of 2 separate measurements. When there was a difference of ≥5 mm Hg between readings, a third measurement was obtained. At each visit, resting

heart rate was obtained manually from the radial pulse over 60 seconds.

At baseline and the end of the study, each patient underwent echocardiography with 2-dimensional guided M-mode measurement and Doppler ultrasound examination. LVMI was assessed from the parasternal long-axis view, with normalization for body surface area using the Devereux formula.[14] Left ventricular hypertrophy (LVH) was defined as an LVMI ≥125 g/m^2 (men) or ≥110 g/m^2 (women).[5] The left ventricular ejection fraction and endocardial shortening fraction were calculated using standard formulas.[15] Left ventricular filling flow was recorded using pulsed Doppler ultrasound with an apical approach. The sample volume was placed at the level of the mitral leaflet. The peak velocities of early diastolic filling and atrial filling, their ratio, and the deceleration time of the E wave were determined. The isovolumic relaxation time (IVRT) was measured by pulsed Doppler ultrasound with the sample volume placed between the septal mitral valve and the left ventricle outflow tract. All measurements were performed at end-expiration.

Carotid ultrasound examinations were also performed at baseline and the end of the study. Standardized longitudinal B-mode images were obtained of the near and far walls of 3 segments of the carotid artery. The common carotid artery was assessed in the segment extending from 10 to 20 mm proximal to the tip of the flow divider. The carotid bifurcation was assessed from the tip of the flow divider, extending 10 mm proximal to the tip of the flow divider. The internal carotid artery was assessed in the 10 mm distal to the tip of the flow divider. The image boundaries were marked manually. Both mean and maximum IMT were measured; measurements were made 4 times for each segment. A mean IMT <0.9 mm was considered normal.[16,17] The carotid ultrasound and echocardiographic examinations were performed by a single investigator who was blinded to patients' clinical data and treatment assignment.

UAE was determined at the beginning and end of the study. It was measured in 2 samples of urine collected over 8 hours; a value <30 μg/min was considered normal.[5] Fasting glucose, glycosylated hemoglobin, and the lipid profile were determined using standard procedures according to local regulations.

Statistical Analysis

The calculated sample size (n = 60) was based on a difference of at least 5% between groups for each outcome, an α level of 0.05, a test power of 0.80, and loss to follow-up of 1% to 5%. The outcome variables were the relative changes in LVMI, IMT, and UAE with doxazosin and atenolol. Categorical data are expressed as percentages, and continuous data as mean (SD). The Mann-Whitney *U* test was used to assess treatment effects on continuous variables. Categorical variables were analyzed using the χ^2 test. The Kruskal-Wallis test for repeated or independent measurements was used to evaluate differences in the quantitative variables over time or between groups. Multivariate analysis was performed to assess potential predictive factors for the 3 measures of target-organ damage at baseline. The potential predictive factors were sex, age, body mass index, baseline BP, BP decrease, duration of diabetes, and presence of other target-organ damage. Statistical significance was set at $P < 0.05$ for all tests.[18] The data were analyzed using SPSS for Windows version 11.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Sixty patients (100% white; 51% female; mean [SD] age, 63.4 [7.5] years; body mass index, 28.2 [3.4] kg/m^2) were randomly allocated to receive doxazosin GITS (n = 32) or atenolol (n = 28). Baseline characteristics were comparable between groups (**Table I**). Baseline systolic BP was 150.2 (10.6) mm Hg in the doxazosin group and 153.1 (13.8) mm Hg in the atenolol group; diastolic BP was 90.1 (7.3) and 92.3 (6.1) mm Hg, respectively. Baseline heart rate was 77 (8) beats/min in both groups.

At the end of the study, BP had decreased by a mean (SD) of 10.1 (3.2)/5.2 (1.3) mm Hg in the doxazosin group and by 12.2 (4.2)/6.3 (2.1) mm Hg in the atenolol group (both, $P < 0.001$ vs baseline; P = NS between groups) (**Figure 1**). Heart rate at the end of the study was 78 (6) beats/min in the doxazosin group (P = NS vs baseline) and 66 (7) beats/min in the atenolol group ($P < 0.01$ vs baseline and between groups). There were no significant differences between groups in the lipid profile or fasting serum glucose levels.

At baseline, echocardiographic parameters were comparable in the 2 groups. **Table II** summarizes the quantitative echocardiographic changes from baseline to the end of the study. LVMI was significantly reduced from baseline in the doxazosin group (from a mean [SD] of 129.9 [22.6] to 115.7 [19.3] g/m^2; $P < 0.01$), mainly as

Table I. Baseline characteristics of the study population. Values are mean (SD) unless otherwise specified.

Variable	Doxazosin (n = 32)	Atenolol (n = 28)	*P*
Sex, %			0.50
Female	52	48	
Male	48	52	
Age, y	62.4 (7.5)	64.8 (7.6)	0.18
Body mass index, kg/m^2	28.1 (3.4)	28.3 (3.5)	0.37
Duration of diabetes, y	7.3 (4.6)	7.6 (5.2)	0.90
Blood pressure, mm Hg			
Systolic	150.2 (10.6)	153.1 (13.8)	0.50
Diastolic	90.1 (7.3)	92.3 (6.1)	0.43
Heart rate, beats/min	77 (8.0)	77 (8.0)	0.48
Glycosylated hemoglobin, %	7.2 (0.7)	7.2 (0.9)	0.85
Fasting glucose, mg/dL	134 (14.6)	133 (21.9)	0.78
Total cholesterol, mg/dL	209 (46.5)	203 (23.7)	0.75
Low-density lipoprotein cholesterol, mg/dL	137.4 (43.4)	125.6 (27.0)	0.29
Urinary albumin excretion, µg/min	26.1 (42.3)	22.8 (31.5)	0.91

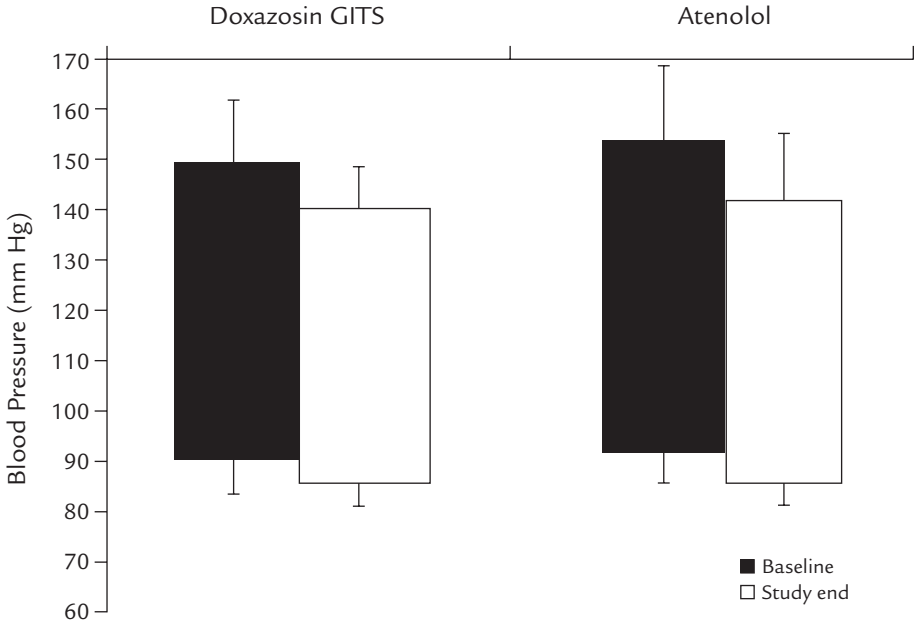

Figure 1. Mean (SD) changes in blood pressure from baseline to the end of the study ($P < 0.001$ vs baseline in both groups; P = NS between groups). GITS = gastrointestinal therapeutic system.

Table II. Changes in echocardiographic parameters from baseline to the end of the study. Values are mean (SD).

	Doxazosin (n = 32)			Atenolol (n = 28)			
Variable	Baseline	Final	*P* Versus Baseline	Baseline	Final	*P* Versus Baseline	*P* Between Groups
LVMI, g/m^2	129.9 (22.6)	115.7 (19.3)	<0.01	129.4 (26.3)	124.3 (22.2)	0.07	0.03
LVMI, by sex							
Male	131.2 (28.3)	116.6 (20.2)	<0.01	132.8 (24.3)	129.2 (22.4)	0.09	0.02
Female	127.5 (24.2)	114.0 (18.6)	<0.01	126.9 (20.2)	120.1 (20.6)	0.06	0.04
LVDD, mm	47.7 (4.4)	45.7 (5.7)	0.36	47.6 (4.5)	48.1 (4.3)	0.38	0.40
LVSD, mm	28.1 (4.4)	28.0 (7.8)	0.50	28.3 (3.3)	27.3 (5.6)	0.18	0.34
PWT, mm	8.6 (2.1)	7.9 (1.0)	<0.01	8.7 (1.5)	8.8 (1.3)	0.22	0.04
IVST, mm	8.9 (1.8)	8.1 (1.3)	<0.01	8.7 (2.0)	8.6 (1.1)	0.33	0.04
EF, %	72 (6.8)	71 (6.3)	0.43	73 (13.0)	71 (6.8)	0.68	0.50
E-wave peak velocity, cm/sec	70.3 (13.6)	66.5 (10.4)	0.08	69.4 (19.5)	72.0 (19.4)	0.42	0.09
A-wave peak velocity, cm/sec	75.4 (20.9)	74.2 (24.7)	0.32	82.9 (27.7)	80.9 (30.6)	0.13	0.24
Deceleration time, milliseconds	238 (57.9)	233 (55.5)	0.04	220 (57.3)	233 (54.9)	0.36	0.21
IVRT, milliseconds	112 (17.8)	127 (28.2)	<0.01	116 (22.6)	112 (31.4)	0.27	0.07

LVMI = left ventricular mass index; LVDD = left ventricular diastolic diameter; LVSD = left ventricular systolic diameter; PWT = posterior wall thickness; IVST = interventricular septum thickness; EF = ejection fraction; IVRT = isovolumic relaxation time.

a result of decreases in posterior-wall and interventricular septum thickness, but not in the atenolol group (from 129.4 [26.3] to 124.3 [22.2] g/m^2; $P = 0.03$ between groups). Only the doxazosin group had significant reductions from baseline in deceleration time (from 238 [57.9] to 233 [55.5] milliseconds; $P = 0.04$) and IVRT (from 112 [17.8] to 127 [28.2] milliseconds; $P < 0.01$). At the end of the study, LVMI was reduced by 10.8% in the doxazosin group ($P = 0.001$ vs baseline) and 4.2% in the atenolol group (P = NS vs baseline; $P = 0.03$ between groups) (**Figure 2**). At baseline, 62.5% of patients in the doxazosin group and 64.2% of patients in the atenolol group had LVH (P = NS). The decreases in LVMI at the end of the study were significantly greater in the subgroup of patients with LVH at baseline (–11.8% doxazosin, –5.3% atenolol; both, $P < 0.01$ vs baseline; $P < 0.01$ between groups).

At baseline, 43.7% of patients in the doxazosin group and 46.4% of patients in the atenolol group had an IMT >0.9 mm (P = NS). After 9 months of treatment, 37.5% and 42.8% of the respective groups had an IMT >0.9 mm (P = NS). The IMT index was normalized in 34.0% of patients treated with doxazosin and 25.0% of patients treated with atenolol (P = NS). Differences in the change in carotid IMT were not statistically significant between groups (–0.006 vs –0.003 mm, respectively) (**Figure 3**).

At baseline, 21.8% of patients in the doxazosin group and 17.8% of patients in the atenolol group had microalbuminuria (P = NS). The difference in change in UAE was not statistically significant between treatments (–0.1 μg/min doxazosin and 0.3 μg/min atenolol) (**Figure 4**).

On multivariate analysis, predictive factors for baseline LVH were age ($P = 0.001$) and microalbuminuria

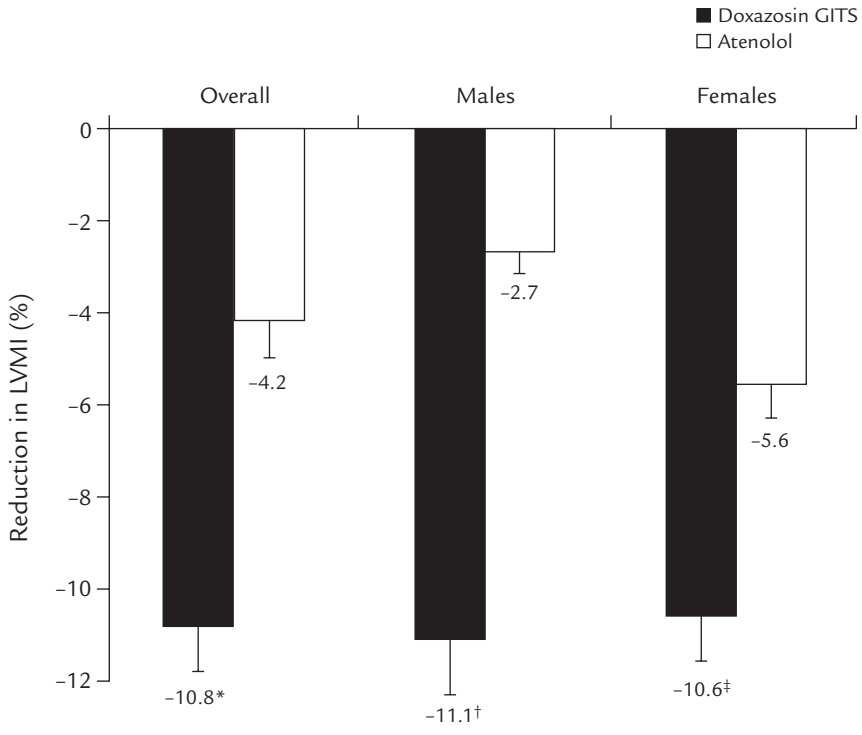

Figure 2. Mean (SD) reductions in left ventricular mass index (LVMI) with doxazosin and atenolol in the overall population, men, and women. *P = 0.03 versus atenolol; †P < 0.001 versus atenolol; ‡P = 0.04 versus atenolol. GITS = gastrointestinal therapeutic system.

(P = 0.03), whereas systolic BP was not a significant predictor. Predictors of increased mean IMT at baseline were systolic BP and duration of diabetes (both, P < 0.05). Predictors of increased maximum IMT at baseline were age (P < 0.001), duration of diabetes (P = 0.029), and antidiabetic treatment (diet alone vs pharmacologic therapy; P = 0.003). No factors were found to be significant predictors of baseline microalbuminuria.

Organ damage was assessed in the overall population based on changes in 3 measures (LVMI, carotid IMT, and UAE). When the evaluation was based on the combination of all 3 measures, target-organ damage was detected in 69.1% of patients. In comparison, the proportion of patients with target-organ damage was 60.3% based on changes in LVMI plus carotid IMT (P = NS vs all 3 criteria), 53.0% based on LVMI plus UAE (P = 0.03), and 41.7% based on carotid IMT plus UAE (P = 0.02).

Adverse events were reported by 5 patients in the doxazosin group (3 orthostatic hypotension, 1 sickness, 1 diarrhea) and 3 patients in the atenolol group (2 bradycardia, 1 sickness). All adverse events were of mild severity. Good compliance was documented in 90.6% of the doxazosin group and 89.3% of the atenolol group (P = NS). One patient withdrew consent and discontinued the study.

DISCUSSION

Prevention of target-organ damage is crucial to improving the cardiovascular prognosis of patients with hypertension, particularly those with diabetes.[3–5] Although all antihypertensive agents are effective in achieving BP control, not all are associated with equivalent protective benefits against target-organ damage.[5] Inhibition of the renin–angiotensin system is effective in the treatment of hypertension in patients with diabetes, but the response to monotherapy is usually insufficient to attain BP control and the addition of other antihypertensive agents may be required.[5]

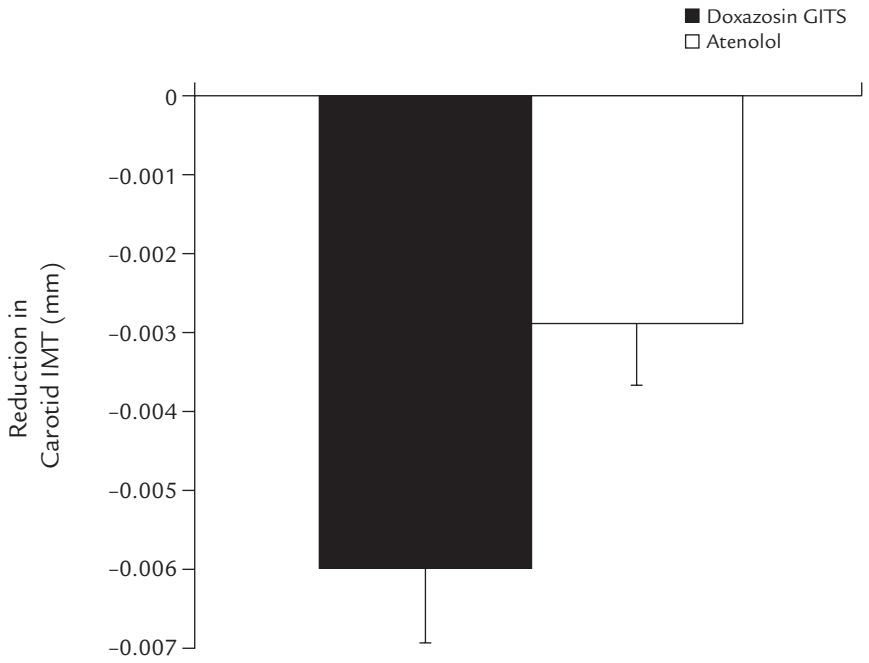

Figure 3. Mean (SD) reductions in carotid intima media thickness (IMT) with doxazosin and atenolol ($P = 0.07$ between groups). GITS = gastrointestinal therapeutic system.

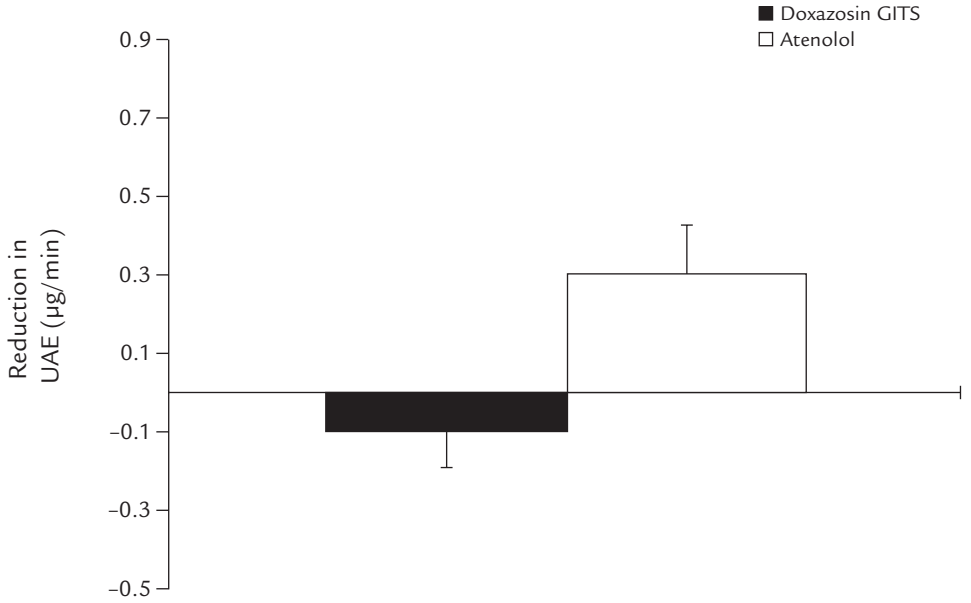

Figure 4. Mean (SD) reductions in urinary albumin excretion (UAE) with doxazosin and atenolol ($P = 0.08$ between groups). GITS = gastrointestinal therapeutic system.

The results of this study suggest that despite achieving similar BP reductions, doxazosin GITS exerted a greater protective effect on LVMI than atenolol in a group of patients with diabetes and hypertension. Doxazosin and atenolol are well-known and effective antihypertensive agents. Although guidelines from the European Society of Hypertension and the European Society of Cardiology recommend β-blockers as first-line therapy for hypertension,[5] the effectiveness of β-blockers in reducing the risk of morbidity and mortality compared with other antihypertensive agents (eg, diuretics, ACE inhibitors, ARBs, calcium channel blockers) has been questioned in recent years.[19] Moreover, there is evidence that atenolol increases the risk of new-onset diabetes.[20]

To our knowledge, this study is the first to assess the effect of antihypertensive drugs on 3 different measures of target-organ damage.[1,5] Reduction in LVH through the use of antihypertensive therapy has been associated with a marked improvement in the cardiovascular prognosis.[21] Patients with diabetes who are treated for hypertension have been reported to have less reduction in LVH than those without diabetes.[22,23] Experimental data in animals have suggested that doxazosin protects against the development of LVH.[24] Because myocardial fibrosis may be a consequence of apoptosis and doxazosin has been reported to have a positive effect on apoptosis compared with no treatment in animals,[24] the foregoing data suggest an added cardiac protective benefit for doxazosin. In the present study, doxazosin GITS, added to an inhibitor of the renin–angiotensin system and a diuretic, was associated with a significant decrease in LVMI ($P = 0.001$ vs baseline; $P = 0.03$ vs atenolol) that was significantly greater in patients with LVH at baseline ($P < 0.01$). Interestingly, the reduction in LVMI was due to a reduction in wall thickness, with no significant change in cavity size. This finding may be associated with a more positive pattern of ventricular geometry.[23] Therefore, the results suggest that doxazosin may provide additional benefits in patients with diabetes and hypertension.

Hypertension increases carotid IMT.[17] A recent meta-analysis of the effect of different antihypertensive drugs on IMT in randomized controlled trials found a reduced rate of IMT with similar decreases in BP in patients with diabetes or coronary heart disease who received antihypertensive treatment (including doxazosin) compared with diuretics or β-blockers.[25] However, in the present study, the difference in change in carotid IMT did not reach the predetermined level of significance between groups.

Microalbuminuria is frequently found in diabetic patients with hypertension and is an independent predictor not only of renal damage, but also of higher cardiovascular risk.[6,8] Control of BP is crucial to reducing the progression of chronic kidney disease.[5,6,8,26] Renin–angiotensin blockade should also be considered in any patient with chronic kidney disease, in particular when albuminuria is present.[26] Animal data suggest that the combination of doxazosin and an inhibitor of the renin–angiotensin system may provide greater renoprotective effects than an inhibitor of the renin–angiotensin system alone.[27] However, the present study found no statistically significant differences in the change in UAE between treatment groups.

Although the relevance of resting heart rate as a prognostic factor is not yet well established, several epidemiologic studies have found heart rate to be an independent risk factor for cardiovascular and all-cause mortality in patients with coronary artery disease.[28,29] Because patients with diabetes are at high risk for coronary artery disease, atenolol may have value in this context relative to other classes of antihypertensive drugs.

Guidelines from the European Society of Hypertension and the European Society of Cardiology recommend the use of echocardiography, carotid ultrasound, and measurement of UAE to detect target-organ damage in patients with hypertension.[5] However, because these techniques are impractical in general clinical practice, it is important to know which of these measures is most efficient.[30] The present data suggest that although detection of microalbuminuria is the easiest procedure to perform in everyday practice, the combination of echocardiography and carotid ultrasound is a useful approach to detecting target-organ damage in patients with diabetes and hypertension.

Some limitations of this study should be mentioned. The PROBE (prospective, randomized, open-label, blinded-evaluation) design may introduce potential bias, although it has been used in multiple trials and is thought to more nearly approximate clinical practice than a randomized controlled design.[31] Although the differences in change in carotid IMT and UAE were not statistically significant in this study, it is possible that small significant differences, if they existed, might have been found in a larger sample or

over a longer period. Because the study duration was 9 months, it is not possible to say with certainty that the benefits observed were related only to the study drugs; in fact, it is possible that the results may have been influenced by participants' previous treatments. Again, because of the 9-month study period, it is not possible to draw any conclusions about whether the observed effects would be maintained over time. The small sample size may explain why no factors were found to influence baseline UAE in the multiple regression model. Finally, the inclusion and exclusion criteria used do not allow extrapolation of the results beyond the studied population.

CONCLUSIONS

In these patients with diabetes and hypertension, LVMI was significantly decreased in doxazosin-treated patients compared with atenolol-treated patients. The differences in change in carotid IMT and UAE were not significant between groups.

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