Cardiac Abnormalities in Diabetic Patients With Neuropathy

Effects of aldose reductase inhibitor administration

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OBJECTIVE — The goal of this study was to determine whether treatment with an aldose reductase inhibitor (ARI) has beneficial effects on asymptomatic cardiac abnormalities in diabetic patients with neuropathy.

RESEARCH DESIGN AND METHODS — Diabetic subjects with neuropathy ($n = 81$) with either a low diastolic peak filling rate or impaired augmentation of left ventricular (LV) ejection fraction (LVEF) during maximal bicycle exercise were identified by gated radionuclide ventriculography. Coronary artery disease, left ventricular hypertrophy, and valvular heart disease were excluded by clinical evaluation, myocardial perfusion imaging, and echocardiography. Subjects were randomized to receive blinded treatment with either the placebo or the ARI zopolrestat 500 or 1,000 mg daily for 1 year.

RESULTS — After 1 year of ARI treatment, there were increases in resting LVEF ($P < 0.02$), cardiac output ($P < 0.03$), LV stroke volume ($P < 0.004$), and exercise LVEF ($P < 0.001$). In placebo-treated subjects, there were decreases in exercise cardiac output ($P < 0.03$), stroke volume ($P < 0.02$), and end diastolic volume ($P < 0.04$). Exercise LVEF increased with ARI treatment independent of blood pressure, insulin use, or the presence of baseline abnormal heart rate variability. There was no change in resting diastolic filling rates in either group.

CONCLUSIONS — Diabetic patients with neuropathy have LV abnormalities that can be stabilized and partially reversed by ARI treatment.

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Heart failure (HF) is a significant cause of morbidity and mortality in patients with diabetes (1). The incidence of HF is increased 2.4-fold in diabetic men and 5.1-fold in diabetic women (2). Although, many of these patients have coexistent hypertension or coronary artery disease (CAD), diabetes further predisposes them to the development of HF (2,3). Diabetic patients also are more prone to develop HF in the setting of acute myocardial infarction (4,5).

Patients with diabetes have abnormalities in left ventricular (LV) function, including parameters of diastolic filling (6,7), LV systolic strain (8), and augmentation of LV ejection fraction (LVEF) with exercise (9–11). Cardiac dysfunction may result from abnormalities in intracellular calcium regulation, heart metabolism, contractile proteins, or remodeling of the extracellular matrix (1,12,13). Both LV systolic and diastolic function are also modulated by autonomic influences. Cardiac autonomic dysfunction is common in diabetes (14) and has been associated with low diastolic peak filling rates (PFR) (6,15) and impaired augmentation of LVEF during exercise (10,16,17). Patients with type 1 diabetes with abnormal LVEF responses during exercise have intact inotropic responses to dobutamine (16) and postextrasystolic potentiation (17), indicating the importance of extrinsic factors, including autonomic function, in determining the cardiac response to exercise.

Aldose reductase inhibitor (ARI) drugs block the entry of glucose into the sorbitol pathway and have been developed for the treatment of diabetic peripheral (18,19) and autonomic neuropathy (20,21). They appear to increase cardiac output during exercise in patients with type 2 diabetes (22). However, it is unclear whether these drugs have beneficial effects on LV performance in diabetic patients with abnormalities in cardiac function. Thus, the purpose of this study was to determine whether ARI treatment would improve cardiac function in asymptomatic diabetic subjects with evidence of decreased LV function but without overt CAD or hypertensive heart disease. Type 1 and type 2 diabetic subjects with abnormalities in either diastolic filling or exercise LVEF were identified and randomized to treatment with either the ARI zopolrestat or placebo, and their cardiac function was then re-evaluated over the course of 1 year.

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Abbreviations: ARI, aldose reductase inhibitor; CAD, coronary artery disease; EDV, end diastolic volume; HF, heart failure; LV, left ventricular; LVEF, left ventricular ejection fraction; PFR, peak filling rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

RESEARCH DESIGN AND METHODS

Subject selection

This was a multicenter randomized, placebo-controlled, double-blind study of subjects with diabetes in whom the effects of treatment with either zopolrestat or placebo on LV function were compared. Subjects with type 1 or type 2 diabetes, who were free from known cardiac disease and able to exercise, were recruited from diabetes clinics at the participating sites and via advertisement. The protocol was approved by the local institutional review board at each site, and informed consent was obtained from subjects.

Subjects were first screened for diabetic complications and considered for inclusion in the study if peripheral neuropathy was present (see below). Subjects were included only if they had an HbA_{1c} between 6 and 10%; this selection was based on the premise that those with excellent control were less likely to have cardiac abnormalities, and those with very poor control required major intensification of diabetes treatment, which might influence cardiac autonomic function (23). Subjects were excluded if they had a systemic disease other than diabetes, creatinine clearance <70 ml/min, liver function abnormalities, severe obesity (more than twice ideal body weight), age >70 years, or treatment with β-blockers, digoxin, nitrates, or calcium channel antagonists.

All subjects underwent evaluation to exclude underlying ischemia, uncontrolled hypertension (sitting blood pressure ≥150/95 mmHg), LV hypertrophy, atrial fibrillation, or valvular heart disease. This included clinical examination, resting electrocardiogram, echocardiogram, and exercise stress testing with single photon emission tomography myocardial perfusion imaging. Subjects with exercise-induced ST-segment depression (≥1 mm) or perfusion defects, or LV hypertrophy (average of septal and posterior wall thickness ≥1.2 cm) were excluded from the study.

Radionuclide ventriculography

After this initial evaluation, potentially eligible subjects were assessed to identify those with either impaired augmentation of LVEF during exercise or low resting diastolic PFR. LV function was assessed using the multigated acquisition methodology at rest and during exercise on a semisupine bicycle (24). Patients exercised with 25-W increments in workload every 3 min until exhaustion or marked dyspnea. All study centers conducted the procedure in a standard manner with avoidance of food, alcohol, caffeine, and smoking for at least 3 h before testing. The studies were processed by the Core Nuclear Cardiology Laboratory at Yale University School of Medicine. LVEF, PFR, and LV stroke volume were calculated using standard methods (25,26).

Subjects were included in the study if they had: *1*) a resting diastolic PFR <3 end diastolic volumes (EDVs) per second (1 SD below the normal mean) (27), *2*) a resting LVEF <50%, or *3*) an increase in LVEF on near-maximal exertion <5% (absolute) unless the LVEF was >70%, in which case a rise of <1% (absolute) above resting was considered abnormal.

Peripheral nerve testing

Signs and symptoms of peripheral neuropathy were assessed using standardized testing and were present in all subjects. Peripheral vibration testing was performed during the initial screening to document eligibility for the study. Although not a primary study outcome, this testing was repeated after 1 year. Vibration threshold was measured in the big toe using the Physitemp Vibraton-2 Vibrometer (Physitemp, Clifton, NJ). Staircase, forced-choice trials were conducted with stimulus intensities lowered after two consecutive correctly identified stimuli and again raised after a single incorrect response. The threshold was defined as the mean of stimulus intensities at all observed changes in the staircase direction, and values >2.6 units in both toes were defined as abnormal (28).

Cardiac autonomic function

Cardiac autonomic function was assessed during the screening to examine subjects for baseline cardiac autonomic neuropathy. Abnormal cardiac autonomic testing was not an inclusion criteria but was examined as a covariate in the analysis of the treatment effects on LV function parameters. Autonomic function was assessed by measuring heart rate variability during a 6-min period of controlled respiration, using an electrocardiogram monitor and respiration pacer (D.E. Hokanson, Bellevue, WA). Information was analyzed by a central reading center at the Southern Illinois University School of Medicine. Cardiac autonomic dysfunction was defined as a circular mean resultant value <15 (29). The Valsalva ratio and coefficient of variation of the R-R interval were also assessed but were not primary study outcomes. Autonomic testing was repeated after 12 months to assess any change following treatment but was not a primary study outcome.

Treatment

Qualifying subjects were randomly assigned to 12 months of treatment with placebo, zopolrestat 500 mg daily, or zopolrestat 1,000 mg daily. These doses were selected based on their ability to inhibit aldose reductase; in a phase 3 clinical study, zopolrestat at doses of 250 or 500 mg daily produced significant decreases in sural nerve sorbitol after 18 months of treatment in subjects with diabetic neuropathy (Pfizer Global Research and Development, unpublished data). Exercise radionuclide ventriculography was repeated at 1, 4, and 12 months, whereas vibration perception threshold, echocardiographic measures, and cardiac autonomic function were again determined at 12 months after initiation of treatment.

Statistical evaluation

Parameters of resting LV function (LVEF, LV stroke volume, PFR, cardiac output, and heart rate) and exercise LV function (LVEF, LV stroke volume, cardiac output, and heart rate) were the principal outcome measures and were analyzed for all subjects at baseline, and then 1, 4, and 12 months after randomization. Groups were compared at baseline using χ^2 and ANOVA. Differences during the follow-up were assessed by ANOCOVA, which included terms for treatment and baseline values as the covariates. Testing for parallelism was performed in relation to each outcome and treatment. Age, sex, type and duration of diabetes, and study site were also considered in the model-fitting process, but none had a significant effect. Treatment comparisons were performed by means of contrasts that were estimated using least square means from a type III analysis of PROC GLM of SAS. Measurements of autonomic activity were performed in the same way but after log transformation to meet distributional assumptions for the models. For all tests, a two-tailed *P* value of 0.05 was used for

Table 1—*Demographics of subjects completing 1 year of treatment*

	Placebo	Zopolrestat
n	21	45
Age (years)	51.8 ± 2.4	52.6 ± 1.1
Sex		
Male	18 (86)	31 (69)
Female	3 (14)	14 (31)
Diabetes		
Type 1	7 (33)	12 (27)
Type 2	14 (67)	33 (73)
Duration of diabetes (years)	14.0 ± 2.0	14.2 ± 1.5
Use of insulin	14 (67)	31 (69)
Cardiac autonomic neuropathy (circular mean resultant <15)	7 (33)	14 (31)
History of hypertension	3 (14)	11 (24)
Use of ACE inhibitors	6 (29)	8 (18)

Data are means ± SD and *n* (%).

significance. An initial analysis demonstrated no trends or significant differences between the effects of the 500- and 1,000-mg doses of zopolrestat on the parameters of LV function studied, and therefore the results of the two dose levels were pooled for analysis. Data are presented as means ± SD.

RESULTS — After the initial screening history, physical examination, and laboratory assessment, 148 subjects were identified who were potentially eligible and underwent full cardiac evaluation. Twelve subjects were excluded due to LV hypertrophy, and 17 were excluded due to ischemia found during stress myocardial perfusion imaging. Of the remaining 119 subjects, 88 (74%) had abnormalities in either diastolic dysfunction or LVEF augmentation during exercise, and 81 patients agreed to be randomized in the study. Of these subjects, 47 (58%) had an isolated low PFR, 12 (15%) had an isolated impaired augmentation of LVEF, and 22 (27%) had both. The demographics of the 66 subjects who completed 1 year of treatment are indicated in Table 1.

Treatment course

Treatment was generally well tolerated, although 15 subjects did not complete the intensive year-long protocol. There were five dropouts in the placebo group and a total of nine in the two active treatment groups. Reasons for dropout included new symptoms or laboratory abnormality (6), request to withdraw (4), disqualification because of noncompliance (3), and one death of a patient in the placebo group. One subject taking 500 mg of zopolrestat developed a threefold elevation in liver transaminases, which returned to normal after discontinuation of therapy, but led to termination from the protocol. Control of diabetes declined equally in both groups during the year of study (HbA_{1c} increased from 7.0 to 8.4% on placebo and from 7.1 to 8.4% on zopolrestat, $P < 0.05$ for each). There were no significant changes in vibration sensation threshold or cardiac autonomic function during the year of treatment.

Radionuclide ventriculography

Baseline resting LVEF, LV stroke volume, and cardiac output values were normal, but PFR values were low normal at the initial evaluation (Table 2). Mean baseline LVEF and PFR were similar in the placebo group and zopolrestat groups (P = NS between groups). After 12 months of treatment with zopolrestat (but not placebo), there were small but statistically significant increments in resting LVEF, cardiac output, and LV stroke volume. There was no evidence of a treatment effect on PFR, although there was a trend for EDV to increase after zopolrestat treatment and to decline with placebo. There were no changes in resting heart rate or blood pressure over time during the study.

The cardiac response to exercise was significantly different in the treatment groups after 1 year (Table 3). Exercise LV stroke volume ($P < 0.02$) and cardiac output ($P < 0.03$) declined over 1 year of placebo treatment, and exercise LVEF also tended to decrease. In contrast, patients treated with zopolrestat showed a significant increase in exercise LVEF ($P < 0.001$) and a trend toward higher LV stroke volume and cardiac output. The differences in exercise LVEF between the two treatment groups over the year of treatment were highly significant ($P < 0.003$) (Fig. 1*A*). The increase in exercise LVEF in the zopolrestat-treated subjects appeared early and was sustained. Similar trends for exercise LV stroke volumes (Fig. 1*B*) and cardiac output to increase were observed in the zopolrestat-treated patients. The increases in exercise LVEF

Table 2—*Radionuclide ventriculography measures at rest*

	Baseline	Week 52	Change	*P* value
Ejection fraction (%)				
Placebo	56.7 ± 1.8	57.9 ± 1.7	1.60 ± 1.52	NS
Zopolrestat	59.7 ± 1.2	61.4 ± 1.2	1.69 ± 0.68	<0.02
Cardiac output (l/min)				
Placebo	7.0 ± 0.6	6.5 ± 0.4	−0.54 ± 0.68	NS
Zopolrestat	5.8 ± 0.3	6.2 ± 0.3	0.46 ± 0.20	<0.03
Stroke volume (ml)				
Placebo	87 ± 8	86 ± 6	−3.6 ± 7.7	NS
Zopolrestat	76 ± 3	84 ± 3	8.5 ± 2.7	<0.004
Heart rate (bpm)				
Placebo	82 ± 4	77 ± 3	−4.5 ± 2.1	NS
Zopolrestat	77 ± 2	75 ± 2	−2.2 ± 1.8	NS
End diastolic volume (ml)				
Placebo	153 ± 14	150 ± 12	−7.3 ± 15.1	NS
Zopolrestat	127 ± 5	136 ± 5	8.3 ± 4.9	NS
PFR (EDV/s)				
Placebo	2.36 ± 0.11	2.56 ± 0.18	0.27 ± 0.18	NS
Zopolrestat	2.61 ± 0.10	2.66 ± 0.09	0.05 ± 0.09	NS

Data are means ± SD unless otherwise indicated. NS, not significant.

Table 3—*Radionuclide ventriculography measures at exercise*

Variable treatment	Baseline	Week 52	Change	*P* value
Ejection fraction (%)				
Placebo	67.0 ± 1.7	64.6 ± 2.1	−2.65 ± 2.02	NS
Zopolrestat	65.6 ± 1.2	69.2 ± 1.1	3.70 ± 0.83	<0.001
Cardiac output (l/min)				
Placebo	13.1 ± 0.9	11.2 ± 0.8	−2.29 ± 0.95	<0.03
Zopolrestat	11.3 ± 0.5	12.0 ± 0.6	0.85 ± 0.59	NS
Stroke volume (ml)				
Placebo	108 ± 9	89 ± 6	−18.8 ± 7.3	<0.02
Zopolrestat	89 ± 3	96 ± 5	8.1 ± 4.9	NS
Heart rate (bpm)				
Placebo	138 ± 5	135 ± 4	−1.7 ± 4.2	NS
Zopolrestat	136 ± 3	125 ± 3	−10.4 ± 2.6	<0.001
EDV (ml)				
Placebo	157 ± 11	136 ± 8	−19.5 ± 8.7	<0.04
Zopolrestat	136 ± 4	140 ± 7	6.4 ± 6.5	NS

Data are means ± SD unless otherwise indicated. NS, not significant.

were consistent when analyzed in relation to the presence or absence of hypertension, cardiac autonomic dysfunction, or insulin treatment. There was a trend noted toward early improvement in these parameters after 4 and 16 weeks of treatment, but these values were not statistically different from baseline (Fig. 1).

PFR was not analyzed during exercise due to the lack of precision of this measurement during exercise. However, exercise LV end diastolic volume significantly decreased in the placebo group over a period of 1 year ($P < 0.04$), with an opposite trend in the zopolrestat treatment group. Over time, there was a significant reduction ($P < 0.001$) in the heart rate achieved during near-maximal exertion in the zopolrestat group. However, there was no correlation between increments in exercise LVEF and decreases in exercise heart rate observed after 1 year of treatment.

CONCLUSIONS — This multicenter double-blind, placebo-controlled, randomized study provides the first longitudinal assessment of LV function in high-risk patients with diabetes complicated by neuropathy. The study subjects did not have heart failure symptoms, LV hypertrophy, or stress-induced myocardial ischemia, but they were found to have mild abnormalities in LV function by stress radionuclide ventriculography. Such patients might be considered to have stage B heart failure, according to the current American College of Cardiology/American Heart Association guidelines (30). The study results suggest that placebo-treated patients tended to develop further impairment in their indexes of LV function over the 1-year follow-up period, whereas those treated with an ARI showed evidence of improvement. Although the changes in function were relatively small, this is the first study to suggest that early abnormalities in LV performance in diabetic subjects might be stabilized and in some cases improved by intervention.

A large fraction (almost three-quarters) of the potentially eligible diabetic subjects with long-standing diabetes and peripheral neuropathy were found to have baseline cardiac functional abnormalities. This observation highlights the prevalence of cardiac abnormalities in high-risk diabetic subjects without clinically evident cardiac disease. In those subjects with abnormalities, 85% had a low diastolic PFR, 42% had impaired exercise LVEF augmentation, and 27% had both. The criterion for diastolic dysfunction (PFR <3.0 EDV/s) identified subjects with PFR values >1 SD below the mean value for healthy subjects (27,31). Thus, the study included those subjects with both low normal (2.5–3.0 EDV/s) and frankly abnormal (<2.5 EDV/s) values, which in part explains the higher incidence of diastolic abnormalities in the subjects. Nonetheless, the findings are still striking in a population that excluded patients with overt LV hypertrophy. The results are also consistent with prior evidence that suggested that diastolic abnormalities precede abnormalities in exercise LVEF in diabetic patients (32,33).

The most pronounced effects of treatment were on cardiac systolic function during exercise. Although less than one-half of the patients had a reduced capacity to increase LVEF during exercise at baseline, zopolrestat increased exercise LVEF in most patients on active treatment for 1 year. This change was evident as a significant increase in exercise LVEF in comparison with baseline pretreatment levels and also by comparison with the control group of patients on placebo. Similar trends were noted for improvements over the year in LV stroke volume and in cardiac output during exercise. The increase in LVEF and stroke volume led to an increase in exercise cardiac output. Improved systolic function in the zopolrestat group may also have prevented exaggerated sympathetic activation during exercise and blunted the excessive heart rate rise, which occurred in the placebo group, as it does in poorly conditioned individuals during exercise.

The study results do not elucidate the mechanism through which zopolrestat increased exercise LVEF in these patients, because there was no evident improvement in the measured indexes of autonomic or peripheral neuropathy after 1 year of treatment. The increase in LVEF during exercise is determined by a number of factors, including neurocardiac sympathetic activation, catecholamine release, intrinsic myocardial contractile reserve, coronary blood flow reserve, myocardial energetics, and cardiac preload and afterload (1). There was no effect of treatment on the blood pressure observed during exercise in these subjects to suggest that zopolrestat treatment decreased afterload. There was also no change in autonomic function as assessed through the measurement of the circular mean resultant of heart rate variability (29), Valsalva ratio, or coefficient of variation of the R-R interval. However, heart rate variability measures are not good indicators of sympathetic autonomic dysfunction (34,35), and it is possible that ARI treatment improved cardiac sympathetic function as it does in diabetic animals (36).

Alternatively, metabolic effects of aldose reductase inhibition directly in the heart might have contributed to improved exercise LV function in these subjects. Aldose reductase mediates flux of

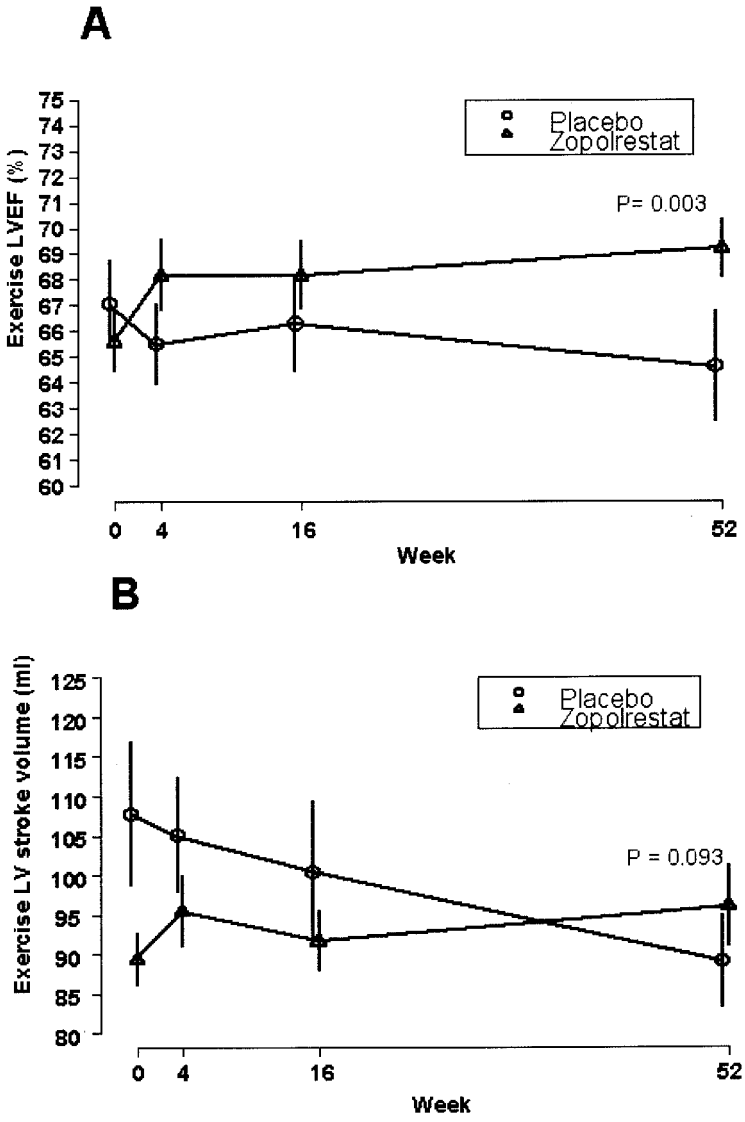

Figure 1—*Exercise LVEF (*A*) and stroke volume (*B*) at baseline and over the course of treatment for 1 year with either placebo or zopolrestat (results from the two zopolrestat groups were pooled as described in the* RESEARCH DESIGN AND METHODS *section). The differences between groups (*P *values in figures) were assessed as the changes over time, using least squares estimates derived from a linear model with adjustment for baseline and site effects. Values are means ± SD.*

glucose into the sorbitol pathway leading to the excessive production of fructose, which is accompanied by reduction in the cytoplasmic ratio of NAD to NADH (37). Alterations in the cytosolic redox state may lead to decreased cardiac energy generation from glucose in the heart (37). Excess polyol pathway flux may also reduce the sensitivity of contractile proteins to calcium, which might impact cardiac function during exercise.

The abnormalities in LV function identified in these asymptomatic diabetic subjects were relatively modest. During the follow-up period, the placebo-treated subjects demonstrated worsening of LV parameters, including small decreases in stroke volume, cardiac output, and LVEF during exercise. This deterioration may in part reflect worsening of glycemic control, which tends to occur in longitudinal studies such as this when diabetes therapy is not intensified (38). Diabetes treatment was provided by the subject's primary physician and did not change over the course of the year. Nonetheless, more long-term studies will be required to address whether abnormalities in LV function identified in this and other studies (6,10,15–17) respond to diabetes treatment and/or ultimately lead to clinical HF in subjects with diabetes. Furthermore, long-term clinical trials would be of interest to establish whether ARIs in combination with other pharmacologic interventions might be effective in preventing or treating symptomatic HF.

Although resting LV systolic function was normal (LVEF ≥50%) in almost all of the subjects at baseline, small but significant improvements in resting LVEF, stroke volume, and cardiac output were also detected after 1 year of treatment with zopolrestat. These increases were consistently seen in subgroups of subjects with hypertension, cardiac autonomic neuropathy, and insulin or ACE inhibitor treatment. On the other hand, there was no change in the PFR to indicate an improvement in resting diastolic function. It is not clear why ARI treatment did not improve diastolic parameters, although it is possible that these agents might not affect remodeling of the extracellular matrix, which leads to diastolic dysfunction in the diabetic heart (39,40).

Only a small number of subjects (~20%) were taking ACE inhibitors throughout the study, and they were equally distributed in the treatment groups. ACE inhibitors have an important role in the treatment of symptomatic diabetic patients with low resting LVEF (41) and also prevent HF in asymptomatic patients with diabetes (42). Although the current trial was not designed to test whether the use of ACE inhibitors influenced the abnormalities in LV function, we observed the most consistent improvements in exercise LVEF in those subjects treated with both an ACE inhibitor and zopolrestat. Of interest, combination treatment with ARIs and ACE inhibitors has synergistic effects in the treatment of diabetic neuropathy in experimental animals (43). Given the importance of both ACE inhibitors and angiotensin receptor blockers, further studies will be required to determine whether ARI treatment in combination with these agents leads to further improvement in LV function or prevents HF in patients with diabetes.

Abnormalities in both resting PFR (31) and LVEF augmentation during exercise (44) can also result from myocardial ischemia. Because this study was intended to address the benefit of ARI treatment in patients without overt CAD, we excluded subjects with evidence of

ischemia based on myocardial perfusion imaging, as has been done in prior studies (6,10,15–17). Although myocardial perfusion imaging detects significant CAD and has prognostic importance (45), it does not entirely exclude the presence of mild CAD, microvascular ischemia, or endothelial dysfunction (46). Experimental studies suggest that the aldose reductase pathway has adverse effects in the ischemic heart (47). We cannot fully exclude the possibility that ischemia occurred during exercise or that ARI treatment effects might have been mediated through an anti-ischemic mechanism.

Diastolic dysfunction is commonly observed in patients with hypertension and LV hypertrophy (31). A hypertensive blood pressure response during exercise can also lead to impaired augmentation of LV systolic function (44). The study entry criteria excluded subjects with poorly controlled hypertension (≥150/95) or LV hypertrophy, who might be expected to have LV functional abnormalities attributable primarily to their hypertension rather than to their diabetes. Fourteen of the 66 subjects who completed the trial did have controlled hypertension, but there was no difference in the response to ARI treatment in those with or without hypertension. This finding is also of clinical importance, because hypertension is extremely common and is an important predictor of HF in patients with type 2 diabetes (38).

In conclusion, these results indicate that abnormalities in LV function observed in patients with diabetes may be stabilized or partially improved with treatment with an ARI. Future studies may be warranted to determine whether these agents have a role in preventing or treating HF in patients with diabetes.

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References

1. Young LH, Russell RR, Chyun DA, Ramahi T: Heart failure in diabetic patients. In *Diabetes and Cardiovascular Disease*. Johnstone M, Veves A, Eds. Totowa, NJ, Humana Press, 2001, p. 281–298
2. Kannel WB, Hjortland M, Castelli WP: Role of diabetes in congestive heart failure: the Framingham Study. *Am J Cardiol* 34:29–34, 1974
3. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK: The progression from hypertension to congestive heart failure. *JAMA* 275:1557–1562, 1996
4. Jaffe AS, Spadaro JJ, Schechtman K, Roberts R, Geltman EM, Sobel BE: Increased congestive heart failure after myocardial infarction of modest extent in patients with diabetes mellitus. *Am Heart J* 108: 31–37, 1984
5. Nesto RW, Zarich S: Acute myocardial infarction in diabetes mellitus. *Circulation* 97:12–15, 1998
6. Kahn JK, Zola B, Juni JE, Vinik AI: Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 7:1303–1309, 1986
7. Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW: Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. *J Am Coll Cardiol* 12:114–120, 1988
8. Fang ZY, Yuda S, Anderson V, Short L, Case C, Marwick TH: Echocardiographic detection of early diabetic myocardial disease. *J Am Coll Cardiol* 41:611–617, 2003
9. Mildenberger RR, Bar-Shlomo B, Druck MN: Clinically unrecognized ventricular dysfunction in young diabetic patients. *J Am Coll Cardiol* 4:234–238, 1984
10. Zola B, Kahn J, Juni J, Vinik AI: Abnormal cardiac function in diabetics with autonomic neuropathy in the absence of ischemic heart disease. *J Clin Endocrinol Metab* 63:208–214, 1986
11. Mustonen JN, Uusitupa MIJ, Tahvanainen K, Talwar S, Laakso M, Lansimies E, Kuikka JT, Pyorala K: Impaired left ventricular systolic function during exercise in middle-aged insulin-dependent and noninsulin-dependent diabetic subjects without clinically evident cardiovascular disease. *Am J Cardiol* 62:1273–1279, 1988
12. Taegtmeyer H, McNulty P, Young ME: Adaptation and maladaptation of the heart in diabetes: Part I. General concepts. *Circulation* 105:1727–1733, 2002
13. Young ME, McNulty P, Taegtmeyer H: Adaptation and maladaptation of the heart in diabetes: Part II. Potential mechanisms. *Circulation* 105:1861–1870, 2002
14. Ziegler D: Cardiovascular autonomic neuropathy: clinical manifestations and measurememt. *Diabetes Rev* 7:342–357, 1999
15. Didangelos TP, Arsos GA, Karamitsos DT, Athyros VG, Karatzas ND: Left ventricular systolic and diastolic function in normotensive type 1 diabetic patients with or without autonomic neuropathy: a radionuclide ventriculography study. *Diabetes Care* 26:1955–1960, 2003
16. Borow KM, Jaspan JB, Williams KA, Neumann A, Wolinski-Walley P, Lang RM: Myocardial mechanics in young adult patients with diabetes mellitus: effects of altered load, inotropic state and dynamic exercise. *J Am Coll Cardiol* 15:1508–1517, 1990
17. Scognamiglio R, Avogaro A, Casara D, Crepaldi C, Marin M, Palisi M, Mingardi R, Erle G, Fasoli G, Dalla Volta S: Myocardial dysfunction and adrenergic cardiac innervation in patients with insulin-dependent diabetes mellitus. *J Am Coll Cardiol* 31:404–412, 1998
18. Greene DA, Arezzo JC, Brown MB: Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy: Zenarestat Study Group. *Neurology* 53:580–591, 1999
19. Vinik AI: Diabetic neuropathy: pathogenesis and therapy. *Am J Med* 107:17S–26S, 1999
20. Didangelos TP, Karamitsos DT, Athyros VG, Kourtoglou GI: Effect of aldose reductase inhibition on cardiovascular reflex tests in patients with definite diabetic autonomic neuropathy over a period of 2 years. *J Diabetes Complications* 12:201–207, 1998
21. Ikeda T, Iwata K, Tanaka Y: Long-term effect of epalrestat on cardiac autonomic neuropathy in subjects with non-insulin dependent diabetes mellitus. *Diabetes Res Clin Pract* 43:193–198, 1999
22. Roy TM, Broadstone VL, Peterson HR, Snider HL, Cyrus J, Fell R, Rothchild AH, Samols E, Pfeifer MA: The effect of an aldose reductase inhibitor on cardiovascular performance in patients with diabetes mellitus. *Diabetes Res Clin Pract* 10:91–97, 1990
23. DCCT Research Group: The effect of intensive therapy on measures of autonomic nervous system function in the Diabetes Control and Complications Trial (DCCT). *Diabetologia* 41:416–423, 1998
24. Borer JS, Bacharach SL, Green MV, Kent KM, Epstein SE, Johnston GS: Real-time radionuclide cineangiography in the noninvasive evaluation of global and regional left ventricular function at rest and during exercise in patients with coronary-artery disease. *N Engl J Med* 296:839–844, 1977
25. Lee F, Fetterman R, Zaret B, Wackers F: Rapid radionucleide derived systolic and diastolic cardiac function using cycle-dependent background correction and Fourier analysis. In *Proceedings of Computers in Cardiology, Institute of Electrical and Electronics Engineers, 1985*. 8–11 September 1985, p. 443–446
26. Massardo T, Gal RA, Grenier RP, Schmidt DH, Port SC: Left ventricular volume calculation using a count-based ratio method applied to multigated radionuclide angiography [published erratum appears in *J Nucl Med* 31:1449, 1990]. *J Nucl*

Med 31:450–456, 1990
27. Spirito P, Maron BJ, Bonow RO: Noninvasive assessment of left ventricular diastolic function: comparative analysis of Doppler echocardiographic and radionuclide angiographic techniques. *J Am Coll Cardiol* 7:518–526, 1986
28. Vinik AI, Suwanwalaikorn S, Stansberry KB, Holland MT, McNitt PM, Colen LE: Quantitative measurement of cutaneous perception in diabetic neuropathy. *Muscle Nerve* 18:574–584, 1995
29. Gelber DA, Pfeifer M, Dawson B, Schumer M: Cardiovascular autonomic nervous system tests: determination of normative values and effect of confounding variables. *J Auton Nerv Syst* 62:40–44, 1997
30. Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldmanmd AM, Francis GS, Ganiats TG, Goldstein S, Gregoratos G, Jessup ML, Noble RJ, Packer M, Silver MA, Stevenson LW, Gibbons RJ, Antman EM, Alpert JS, Faxon DP, Fuster V, Jacobs AK, Hiratzka LF, Russell RO, Smith SC Jr: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary A: report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (committee to revise the 1995 guidelines for the evaluation and management of heart failure). *Circulation* 104:2996–3007, 2001
31. Arrighi JA, Soufer R: Left ventricular diastolic function: physiology, methods of assessment, and clinical significance. *J Nucl Cardiol* 2:525–543, 1995
32. Shapiro LM, Leatherdale BA, Coyne ME, Fletcher RF, Mackinnon J: Prospective study of heart disease in untreated maturity onset diabetics. *Br Heart J* 44:342–348, 1980
33. Raev DC: Which left ventricular function is impaired earlier in the evolution of diabetic cardiomyopathy? *Diabetes Care* 17:633–639, 1994
34. Schnell O, Kirsch CM, Stemplinger J, Haslbeck M, Standl E: Scintigraphic evidence for cardiac sympathetic dysinnervation in long-term IDDM patients with and without ECG-based autonomic neuropathy. *Diabetologia* 38:1345–1352, 1995
35. Stevens MJ, Raffel DM, Allman KC, Dayanikil F, Ficaro E, Sandford T, Wieland DM, Pfeifer MA, Schwaiger M: Cardiac sympathetic denervation in diabetes: implications for enhanced cardiovascular risk. *Circulation* 98:961–968, 1998
36. Kurata C, Okayama K, Wakabayashi Y, Shouda S, Mikami T, Tawarahara K, Sugiyama T: Cardiac sympathetic neuropathy and effects of aldose reductase inhibitor in streptozotocin-induced diabetic rats. *J Nucl Med* 38:1677–1680, 1997
37. Trueblood N, Ramasamy R: Aldose reductase inhibition improves altered glucose metabolism of isolated diabetic rat hearts. *Am J Physiol* 275:H75–83, 1998
38. United Kingdom Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *Br Med J* 317:703–713, 1998
39. Regan TJ, Ettinger PO, Khan MI: Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs. *Circ Res* 35:222–237, 1974
40. Norton GR, Candy G, Woodiwiss AJ: Aminoguanidine prevents the decreased myocardial compliance produced by streptozotocin-induced diabetes mellitus in rats. *Circulation* 93:1905–1912, 1996
41. Shindler DM, Kostis JB, Yusuf S, Quinones MA, Pitt B, Stewart D, Pinkett T, Ghali JK, Wilson AC: Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol* 77:1017–1020, 1996
42. Heart Outcomes Prevention Evaluation Study Investigators: Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE study. *Lancet* 355:253–259, 2000
43. Cotter MA, Mirrlees DJ, Cameron NE: Neurovascular interactions between aldose reductase and angiotensin-converting enzyme inhibition in diabetic rats. *Eur J Pharmacol* 417:223–230, 2001
44. Borer JS, Kent KM, Bacharach SL, Green MV, Rosing DR, Seides SF, Epstein SE, Johnston GS: Sensitivity, specificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease: comparison with exercise electrocardiography. *Circulation* 60:572–580, 1979
45. Hachamovitch R, Berman DS, Shaw LS, Kiat H, Cohen I, Cabico A, Friedman J, Diamond GA: Incremental prognostic value of myocardial perfusion single-photon emission computed tomography for the prediction of cardiac death. *Circulation* 97:535–543, 1998
46. Johnstone M, Creager S, Scales K, Cusco J, Lee B, Creager M: Impaired endothelium-dependent vasodilation in patients with insulin-dependent diabetes mellitus. *Circulation* 88:2510–2516, 1993
47. Hwang YC, Sato S, Tsai JY, Yan S, Bakr S, Zhang H, Oates PJ, Ramasamy R: Aldose reductase activation is a key component of myocardial response to ischemia. *FASEB J* 16:243–245, 2002