Hemodynamic Effects of Fenofibrate and Coenzyme Q_{10} in Type 2 Diabetic Subjects With Left Ventricular Diastolic Dysfunction

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OBJECTIVE — To investigate the effects of fenofibrate and coenzyme Q_{10} (CoQ) on diastolic function, ambulatory blood pressure (ABP), and heart rate (HR) in type 2 diabetic subjects with left ventricular diastolic dysfunction (LVDD).

RESEARCH DESIGN AND METHODS — We randomized, double-blind, 74 subjects to fenofibrate 160 mg daily, CoQ 200 mg daily, fenofibrate 160 mg plus CoQ 200 mg daily, or matching placebo for 6 months. Echocardiography (including tissue Doppler imaging) and 24-h ABP and HR monitoring were performed pre- and postintervention.

RESULTS — Neither fenofibrate nor CoQ, alone or in combination, altered early diastolic mitral annular myocardial relaxation velocity (E′), early-to-late mitral inflow velocity ratio (E/A), deceleration time, isovolumic relaxation time, or the ratio of early mitral flow velocity to early diastolic mitral annular myocardial relaxation velocity (E/E′) compared with placebo ($P > 0.05$). Fenofibrate and CoQ interactively ($P = 0.001$) lowered 24-h systolic blood pressure (-3.4 ± 0.09 mmHg, $P = 0.010$), with a prominent nocturnal effect (-5.7 ± 1.5 mmHg, $P = 0.006$). Fenofibrate (-1.3 ± 0.5 mmHg, $P = 0.013$) and CoQ (-2.2 ± 0.5 mmHg, $P < 0.001$) independently lowered 24-h diastolic blood pressure. Fenofibrate reduced 24-h HR (-3.3 ± 0.5 beats/min, $P < 0.001$), but CoQ had no effect on HR.

CONCLUSIONS — In type 2 diabetic subjects with LVDD, neither fenofibrate nor CoQ, alone or in combination, improved diastolic function significantly. However, fenofibrate and CoQ independently and interactively lowered 24-h blood pressure, and fenofibrate alone reduced 24-h HR.

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The increased risk of cardiac failure in diabetes reflects not only coexistent coronary artery disease and hypertension, but also a specific diabetic cardiomyopathy (DCM) (1). Multiple mechanisms underlie DCM, including altered substrate utilization and energetics, oxidative stress, endothelial dysfunction, myocardial fibrosis, and myocyte apoptosis. DCM can manifest as impaired relaxation and increased stiffness of the myocardium (2), detectable preclinically by echocardiography as left ventricular diastolic dysfunction (LVDD). Therapies targeting hypertension, dyslipidemia, and hyperglycemia, as well as the specific mechanisms underlying DCM, may prevent progression of LVDD to overt cardiac failure.

Fenofibrate, a peroxisome proliferator–activated receptor (PPAR)-α agonist, lowers triglycerides and raises HDL cholesterol. It could improve LVDD in diabetes by reducing myocardial free fatty acid and triglyceride delivery, thereby decreasing formation of lipid intermediates and oxidant species that promote myocyte apoptosis and fibrosis (1). However, in experimental animal models, PPAR-α overstimulation can promote fatty acid oxidation, leading to inefficient myocardial bioenergetics and pathologic remodeling (3). Importantly, there is no evidence for this in humans treated with fibrates (4), and in clinical trials in type 2 diabetes, fenofibrate reduced angiographic progression of coronary atherosclerosis (5) and microangiopathy (6), improved endothelial dysfunction (7), and modestly lowered blood pressure (BP) (6). Despite these effects, fenofibrate did not significantly decrease coronary events, the primary end point, in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (6), but it did reduce total cardiovascular events.

Coenzyme Q_{10} (CoQ), a key intermediary in mitochondrial electron transport, has potent antioxidant properties. CoQ supplementation could improve LVDD by increasing myocardial energy production and decreasing oxidative stress, actions complementary to fenofibrate. CoQ improves endothelial function in type 2 diabetes (8), with modest beneficial effects on BP (9) and left ventricular (LV) systolic function (10).

We previously showed that fenofibrate and CoQ synergistically improve microcirculatory function in type 2 diabetes (11). By targeting several mechanisms underlying LVDD in type 2 diabetes, we hypothesized that these treatments would improve cardiac function. Although fenofibrate and CoQ may lower clinic blood pressure (CBP), their effect on diurnal BP has not been investigated. Our secondary hypothesis was that these treatments would independently and interactively lower ambulatory blood pressure (ABP) and, by improving cardiac function, also lower heart rate (HR).

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RESEARCH DESIGN AND METHODS

Subjects

We studied 74 type 2 diabetic subjects, aged 40 to 79 years, who had LVDD on echocardiography. All were recruited from clinical databases at teaching hospitals in Perth, Western Australia. Type 2 diabetes was defined by American Diabetes Association criteria. Exclusions included daytime insulin use, GHb ≥9.0%, resting BP >150/90 mmHg, fasting cholesterol ≥7.0 mmol/l, triglycerides ≥4.0 mmol/l, creatinine >130 μmol/l, treatment with fibrates or CoQ >30 mg/day, and any cardiovascular event within the preceding 6 months. The study was approved by the ethics committees of Royal Perth, Fremantle, and Sir Charles Gairdner Hospitals. All participants gave informed written consent.

Study design

Subjects were randomized, double-blind, to fenofibrate 160 mg daily (Laboratoires Fournier, Chenove, France), CoQ 200 mg daily (RP Scherer, Braeside, Australia), fenofibrate 160 mg plus CoQ 200 mg daily, or matching placebo for 6 months. These doses and this duration of therapy were equivalent to those employed in previous clinical studies of these compounds (7,8,11). Participants underwent two echocardiograms at baseline and two at treatment end, with pre- and postintervention data taken as the mean value at each time point. The primary echocardiographic end point was early diastolic septal mitral annular myocardial relaxation velocity (E′), a tissue Doppler index of diastolic function. In this factorial design, a sample size of 15 subjects per treatment group was required to detect main treatment effects of 10% change in E′ compared with placebo at $\alpha = 0.05$ and 80% power. Secondary end points included other diastolic and systolic function indexes, left atrial volume (LAV), and LV mass (LVM). ABP and HR were monitored over 24 h at baseline and treatment end. Fasting venous samples were drawn at baseline and treatment end to measure lipids, apolipoproteins, glucose, GHb, and CoQ. Creatinine, hepatic transaminases, and creatine kinase were monitored periodically throughout the study.

Echocardiography

Transthoracic echocardiography was performed at rest. Mitral annular tissue Doppler, transmitral and pulmonary venous (PV) flow, and color M-mode flow propagation (Vp) were measured in the apical four-chamber view. LV end-diastolic and end-systolic volumes were estimated in the apical two-chamber view (Simpson's biplane method) to calculate LV ejection fraction (LVEF). Data were taken as the mean of three measurements on different cardiac cycles. Exclusions included LVEF <50%, wall motion abnormalities, valvular disease, atrial fibrillation, frequent ectopy, paced rhythm, and early-to-late mitral inflow velocity ratio (E/A) wave fusion. One echocardiographer, blinded to treatment allocation, performed all studies.

LVDD classification

LVDD was classified using age-specific modifications of the Canadian Consensus (12) and Garcia (13) criteria. Participants were classified as having mild LVDD if three or more of the following criteria were met, including at least one of the first two: reduced E/A (age 40–49 years: <1.3; 50–59 years: <1.2; 60–69 years: <1.1; 70–79 years: <0.8), increased deceleration time (DT) (40–59 years: >200 ms; 60–69 years: >220 ms; 70–79 years: >250 ms), isovolumic relaxation time (IVRT) >100 ms, reduced E′ (40–59 years: <10.0 cm/s; 60–79 years: <8.0 cm/s), and Vp <45.0 cm/s. Participants were classified as having moderate LVDD if the ratio of early mitral flow velocity to early diastolic mitral annular myocardial relaxation velocity (E/E′) >8.0 and three or more of the following were met: >40% decrease in E/A with Valsalva maneuver, E/Vp >1.50, systolic-to-diastolic PV flow velocity ratio (PV S/D) <1.00, atrial systolic PV reversal flow velocity (PV 'a' rev) ≥0.35 m/s, normal E/A, and normal DT.

Ambulatory monitoring

ABP and HR were measured every 20 min during daytime (0900–2100) and every 30 min at night (2100–0900) using an Ultralite 90217 Monitor (Spacelabs Medical, Issaquah, WA). Participants recorded sleeping and waking times during monitoring. Datasets with <80% valid readings were excluded from analysis.

Laboratory analyses

Cholesterol, triglycerides, and HDL cholesterol were measured by enzymatic methods (Hitachi, Tokyo, Japan; Roche Diagnostics, Mannheim, Germany), and LDL cholesterol was calculated. Apolipoproteins (apos) A-I, A-II, and B-100 were measured by immunonephelometry (Dade-Behring BNII, Marburg, Germany) and C-III by immunoturbimetry (Wako Pure Chemical Industries, Osaka, Japan). Nonesterified fatty acids (NEFAs) were measured by enzymatic methods (Wako Pure Chemical Industries), plasma CoQ by reverse-phase high-performance liquid chromatography using electrochemical detection, and cellular CoQ by high-performance liquid chromatography using isolated peripheral blood mononuclear cells with correction for protein content.

Statistical analyses

Data were analyzed using SPSS 12.0 (Chicago, IL) and SAS 9.1 (Cary, NC). Values are presented as means ± SEM unless otherwise indicated. Skewed data were logarithmically transformed. Only subjects who completed the study were included in efficacy analyses. Main treatment effects on echocardiographic and biochemical indexes were assessed using general linear modeling with adjustment for baseline and study site. For ABP and HR, main treatment effects were assessed using mixed models (study subject as random effect) adjusted for baseline, study site, hour, weight change, and antihypertensive use. Where significant treatment interaction was found, analyses by treatment group were undertaken with Scheffe adjustment for multiple comparisons. *P* values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics

We randomized 74 eligible subjects to placebo ($n = 20$), fenofibrate ($n = 19$), CoQ ($n = 16$), or fenofibrate + CoQ ($n = 19$). Clinical characteristics were comparable across treatment groups (Table 1). Participants were typically overweight with satisfactory control of BP, lipids, and glycemia. Median diabetes duration was 4 years; one-third of cases were diet treated. Nearly one-half of subjects were taking antihypertensive medication, most commonly ACE inhibitors; over one-half were taking statins. On echocardiography, 12 participants (16.2%) had LV hypertrophy (LVM/height ≥143 g/m for men; ≥102 g/m for women). Most subjects (86.5%) had mild LVDD.

Clinical and biochemical responses

A total of 69 subjects completed the trial. Reasons for withdrawal were new-onset atrial fibrillation ($n = 1$), transaminase el-

Table 1—*Baseline characteristics of randomized subjects*

	Placebo	Fenofibrate	CoQ	Combination
n	20	19	16	19
Age (years)	62.4 ± 8.8	64.8 ± 7.3	61.3 ± 4.1	63.0 ± 9.4
Male/female (*n*)	14/6	13/6	13/3	13/6
BMI (kg/m^2)	30.7 ± 5.0	29.9 ± 5.6	30.1 ± 4.6	28.7 ± 3.4
Fasting glucose (mmol/l)	7.2 ± 1.8	7.0 ± 1.1	7.6 ± 1.6	7.6 ± 2.2
GHb (%)	6.5 ± 1.0	6.5 ± 0.9	6.6 ± 0.9	6.6 ± 0.8
Duration of type 2 diabetes (years)	5.5 (4.1–7.5)	4.5 (2.7–7.5)	3.1 (1.8–5.4)	3.0 (2.0–4.9)
Resting SBP (mmHg)	130.5 ± 15.7	131.0 ± 17.8	136.8 ± 14.7	132.8 ± 17.3
Resting DBP (mmHg)	73.0 ± 11.8	73.3 ± 10.4	76.9 ± 10.0	74.1 ± 9.2
Total cholesterol (mmol/l)	4.4 ± 1.2	4.6 ± 0.9	4.6 ± 0.9	4.6 ± 0.8
Triglycerides (mmol/l)	1.6 ± 0.7	1.6 ± 1.0	1.7 ± 0.7	1.7 ± 0.8
HDL cholesterol (mmol/l)	1.22 ± 0.27	1.29 ± 0.36	1.25 ± 0.25	1.35 ± 0.38
LDL cholesterol (mmol/l)	2.5 ± 1.1	2.6 ± 0.7	2.6 ± 0.8	2.5 ± 0.7
Serum creatinine (umol/l)	82 ± 16	74 ± 10	79 ± 15	75 ± 15
History of ischemic heart disease	15.0	15.8	12.5	10.5
LV hypertrophy	20.0	26.3	6.3	10.5
LVDD: mild/moderate (*n*)	16/4	17/2	15/1	16/3
Medications				
No antihyperglycemic medication	25.0	42.1	43.8	26.3
Metformin	60.0	47.4	50.0	68.4
Sulphonylurea	50.0	42.1	37.5	21.1
Nocturnal basal insulin	5.0	10.5	6.3	0.0
No antihypertensive medication	35.0	63.2	50.0	63.2
ACE inhibitor	45.0	26.3	37.5	15.8
Angiotensin receptor blocker	15.0	10.5	6.3	5.3
β-Adrenergic receptor blocker	5.0	5.3	25.0	10.5
Calcium channel blocker	25.0	15.8	18.8	10.5
Diuretic	30.0	10.5	18.8	10.5
Statin	75.0	36.8	68.8	52.6

Data are means ± SD, percent, or geometric means (95% CI).

evation more than three times the upper limit of normal ($n = 1$), and personal choice ($n = 3$). The subjects with adverse events were on fenofibrate alone.

Compared with placebo, neither body weight (data not shown) nor glycemia changed with any of the treatments (Table 2). Total, HDL, and LDL cholesterol and NEFAs were similarly unaltered, but fenofibrate lowered triglycerides, apoB-100, and apoC-III and increased apoA-I and apoA-II ($P < 0.05$). CoQ supplementation increased both plasma and cellular CoQ levels ($P < 0.01$).

Echocardiographic indexes

Compared with placebo, none of the treatments significantly altered the primary end point (E′) or any of the following diastolic function indexes: E/A, DT, IVRT, PV S/D, or E/E′ (Table 3). However, fenofibrate increased Vp (2.4 ± 1.0 cm/s, P = 0.020), and CoQ increased E/Vp (0.12 ± 0.05, $P = 0.007$) and PV 'a' rev (0.02 ± 0.01m/s, $P = 0.009$). In most subjects (82.6%), LVDD classification was unchanged by treatment: one subject each in the fenofibrate and fenofibrate + CoQ groups progressed from mild to moderate LVDD, whereas LVDD improved in four subjects taking placebo, three taking fenofibrate, two taking CoQ, and one taking fenofibrate + CoQ. None of the treatments significantly altered systolic function (systolic myocardial contraction velocity [S′ and LVEF) or cardiac structure (LAV and LVM). Adjustment for statin use did not alter these findings.

ABP and HR

Of those who completed the study, eight subjects declined ambulatory monitoring and seven had insufficient readings. Fenofibrate and CoQ synergistically ($P = 0.001$) lowered 24-h systolic BP (SBP) (fenofibrate + CoQ: −3.4 ± 0.9 mmHg, $P = 0.010$; fenofibrate: 1.8 ± 1.0 mmHg, $P = 0.341$; CoQ: −0.3 ± 1.1 mmHg, $P = 0.992$; all P vs. placebo), particularly during sleep (fenofibrate + CoQ: −5.7 ± 1.5 mmHg, $P = 0.006$; fenofibrate: −0.2 ± 1.5 mmHg, $P = 0.999$; CoQ: 2.2 ± 1.7 mmHg, $P = 0.647$; all P vs. placebo) (Table 4). Fenofibrate (−1.3 ± 0.5 mmHg, $P = 0.013$) and CoQ (−2.2 ± 0.5 mmHg, $P < 0.001$) had independent effects in lowering 24-h diastolic BP (DBP): fenofibrate lowered asleep DBP (−2.6 ± 0.9, $P = 0.005$), whereas CoQ lowered awake DBP (−2.7 ± 0.6, $P < 0.001$). Fenofibrate also decreased 24-h HR (−3.3 ± 0.5 beats/min, $P < 0.001$), observed during both waking and sleeping ($P < 0.001$). CoQ supplementation did not alter HR. Adjustment for statin use did not alter these findings.

CONCLUSIONS— In type 2 diabetic subjects with LVDD, fenofibrate and CoQ, alone or in combination, did not significantly alter LV function. However, we provide new evidence that these treatments have independent and interactive effects in lowering ABP, with fenofibrate alone also decreasing HR.

Table 2—*Effect of interventions on biochemical variables*

	Placebo	Fenofibrate	CoQ	Combination	*P* for interaction	Fenofibrate main effect	*P*	CoQ main effect	*P*
n	20	16	16	17					
Fasting glucose (mmol/l)									
Baseline	7.2 ± 0.4	6.8 ± 0.3	7.6 ± 0.4	7.7 ± 0.5					
End	7.4 ± 0.3	7.1 ± 0.3	7.7 ± 0.4	7.2 ± 0.4	0.404	−0.3 ± 0.3	0.294	−0.1 ± 0.3	0.659
GHb (%)									
Baseline	6.5 ± 0.2	6.2 ± 0.1	6.6 ± 0.2	6.6 ± 0.2					
End	6.4 ± 0.2	5.9 ± 0.2	6.5 ± 0.2	6.5 ± 0.2	0.184	−0.2 ± 0.1	0.136	0.1 ± 0.1	0.483
Total cholesterol (mmol/l)									
Baseline	4.4 ± 0.3	4.7 ± 0.2	4.6 ± 0.2	4.5 ± 0.2					
End	4.3 ± 0.2	4.5 ± 0.2	4.7 ± 0.2	4.1 ± 0.2	0.086	−0.3 ± 0.2	0.069	0.0 ± 0.2	0.966
Triglycerides (mmol/l)									
Baseline	1.6 ± 0.2	1.6 ± 0.2	1.7 ± 0.2	1.7 ± 0.2					
End	1.8 ± 0.2	1.2 ± 0.1	1.6 ± 0.1	1.1 ± 0.1	0.615	−0.6 ± 0.1	<0.001	−0.2 ± 0.1	0.070
HDL cholesterol (mmol/l)									
Baseline	1.22 ± 0.06	1.28 ± 0.10	1.25 ± 0.06	1.36 ± 0.10					
End	1.20 ± 0.06	1.38 ± 0.10	1.24 ± 0.07	1.33 ± 0.09	0.068	0.05 ± 0.04	0.150	−0.06 ± 0.04	0.107
LDL cholesterol (mmol/l)									
Baseline	2.5 ± 0.2	2.7 ± 0.2	2.6 ± 0.2	2.4 ± 0.2					
End	2.3 ± 0.2	2.6 ± 0.2	2.7 ± 0.2	2.3 ± 0.2	0.081	−0.1 ± 0.1	0.442	0.2 ± 0.1	0.286
ApoA-I (g/l)									
Baseline	1.35 ± 0.05	1.42 ± 0.07	1.40 ± 0.05	1.51 ± 0.07					
End	1.39 ± 0.05	1.57 ± 0.08	1.42 ± 0.05	1.56 ± 0.08	0.397	0.09 ± 0.04	0.028	−0.06 ± 0.04	0.134
ApoA-II (g/l)									
Baseline	0.32 ± 0.01	0.32 ± 0.01	0.33 ± 0.01	0.32 ± 0.01					
End	0.32 ± 0.01	0.39 ± 0.02	0.33 ± 0.01	0.39 ± 0.02	0.871	0.08 ± 0.01	<0.001	0.00 ± 0.01	0.706
ApoB-100 (g/l)									
Baseline	0.90 ± 0.06	0.96 ± 0.04	0.98 ± 0.05	0.91 ± 0.04					
End	0.88 ± 0.05	0.88 ± 0.05	0.98 ± 0.05	0.77 ± 0.04	0.113	−0.10 ± 0.04	0.008	−0.01 ± 0.04	0.793
ApoC-III (mg/l)									
Baseline	125.8 ± 8.2	125.8 ± 10.0	130.9 ± 6.8	126.1 ± 8.9					
End	129.8 ± 8.6	103.0 ± 8.3	130.7 ± 5.6	95.8 ± 5.8	0.588	−29.1 ± 4.4	<0.001	−5.1 ± 4.4	0.250
NEFAs (mmol/l)									
Baseline	0.40 (0.30–0.52)	0.34 (0.27–0.43)	0.37 (0.26–0.54)	0.32 (0.23–0.44)					
End	0.38 (0.28–0.51)	0.29 (0.20–0.40)	0.37 (0.29–0.48)	0.27 (0.19–0.37)	0.836	−0.08	0.057	0.01	0.866
Plasma CoQ (μmol/l)									
Baseline	1.5 (1.2–1.8)	1.8 (1.5–2.3)	1.7 (1.4–2.2)	1.5 (1.2–1.8)					
End	1.4 (1.2–1.8)	1.8 (1.5–2.2)	5.3 (3.9–7.2)	4.1 (3.1–5.4)	0.090	0.2	0.250	3.2	<0.001
Cellular CoQ (nmol/g protein)									
Baseline	108 (94–125)	107 (95–120)	123 (105–145)	118 (105–132)					
End	116 (97–39)	101 (91–112)	147 (119–183)	139 (125–153)	0.582	−12	0.203	33	0.001

Data are means ± SEM or geometric means (95% CI). Main effect vs. placebo, adjusted for baseline and study site (general linear model).

Table 3—*Effect of interventions on echocardiographic indices*

	Placebo	Fenofibrate	CoQ	Combination	*P* for interaction	Fenofibrate main effect	*P*	CoQ main effect	*P*
n	20	16	16	17					
E′ (cm/s)									
Baseline	8.4 ± 0.3	8.5 ± 0.3	9.2 ± 0.4	8.6 ± 0.4					
End	8.6 ± 0.3	8.1 ± 0.3	8.9 ± 0.4	8.7 ± 0.4	0.094	−0.1 ± 0.2	0.539	0.1 ± 0.2	0.698
E/A									
Baseline	0.82 ± 0.03	0.83 ± 0.03	0.90 ± 0.04	0.91 ± 0.10					
End	0.83 ± 0.03	0.85 ± 0.03	0.92 ± 0.04	0.99 ± 0.11	0.262	0.04 ± 0.02	0.112	0.04 ± 0.02	0.129
DT (ms)									
Baseline	218 ± 6	233 ± 7	215 ± 8	215 ± 7					
End	215 ± 6	220 ± 9	206 ± 7	212 ± 6	0.376	2 ± 6	0.779	−2 ± 6	0.737
IVRT (ms)									
Baseline	106 ± 3	108 ± 1	108 ± 2	109 ± 2					
End	108 ± 2	112 ± 3	109 ± 3	111 ± 2	0.655	2 ± 2	0.338	−1 ± 2	0.530
Vp (cm/s)									
Baseline	41.5 ± 1.4	42.0 ± 1.3	44.1 ± 2.0	41.9 ± 1.7					
End	40.9 ± 1.2	44.4 ± 1.8	42.9 ± 1.7	42.9 ± 1.9	0.531	2.4 ± 1.0	0.020	−0.8 ± 1.0	0.451
E/E′									
Baseline	7.7 ± 0.3	8.0 ± 0.4	7.8 ± 0.5	7.9 ± 0.5					
End	7.6 ± 0.3	8.5 ± 0.3	8.3 ± 0.5	8.6 ± 0.5	0.345	0.5 ± 0.3	0.078	0.4 ± 0.3	0.130
E/Vp									
Baseline	1.56 ± 0.07	1.60 ± 0.06	1.59 ± 0.05	1.60 ± 0.08					
End	1.59 ± 0.06	1.56 ± 0.05	1.70 ± 0.07	1.73 ± 0.07	0.367	0.00 ± 0.05	0.940	0.12 ± 0.05	0.007
PV S/D									
Baseline	1.55 ± 0.06	1.50 ± 0.06	1.41 ± 0.09	1.61 ± 0.13					
End	1.60 ± 0.06	1.52 ± 0.07	1.43 ± 0.09	1.43 ± 0.08	0.933	−0.06 ± 0.07	0.390	−0.12 ± 0.07	0.081
PV 'a' rev (m/s)									
Baseline	0.33 ± 0.01	0.33 ± 0.01	0.31 ± 0.01	0.33 ± 0.01					
End	0.32 ± 0.01	0.32 ± 0.01	0.33 ± 0.01	0.34 ± 0.01	0.785	0.00 ± 0.01	0.457	0.02 ± 0.01	0.009
LVEF (%)									
Baseline	63.2 ± 0.9	61.6 ± 1.0	64.6 ± 0.9	63.3 ± 1.2					
End	64.1 ± 0.8	62.6 ± 1.2	64.6 ± 1.1	62.4 ± 0.8	0.615	0.0 ± 0.8	0.961	1.3 ± 0.8	0.102
S′ (cm/s)									
Baseline	8.8 ± 0.2	9.4 ± 0.3	9.4 ± 0.3	8.7 ± 0.3					
End	9.1 ± 0.2	9.3 ± 0.4	9.8 ± 0.4	8.6 ± 0.3	0.417	−0.5 ± 0.3	0.071	0.0 ± 0.3	0.914
LAV/BSA (ml/m^2)									
Baseline	30.4 ± 1.3	32.4 ± 1.8	31.3 ± 1.8	35.9 ± 2.5					
End	32.4 ± 1.5	33.9 ± 1.8	31.7 ± 1.5	36.4 ± 2.6	0.649	0.4 ± 1.0	0.693	−1.0 ± 1.0	0.335
LVM/BSA (g/m^2)									
Baseline	92.5 ± 3.8	101.5 ± 4.2	94.8 ± 3.5	90.1 ± 3.8					
End	95.0 ± 4.0	106.3 ± 4.5	95.1 ± 3.1	91.2 ± 4.2	0.533	2.4 ± 1.8	0.195	−3.5 ± 1.8	0.059

Data are means ± SEM. Main effect vs. placebo, adjusted for baseline and study site (general linear model). BSA, body surface area.

Cardiac function

LVDD is common in diabetes and is associated with increased mortality (14). However, few studies have investigated potential therapies. In type 2 diabetic subjects with LVDD, 6 months' treatment with candesartan improved one index of diastolic filling (E/A), but not another (DT) (15). In hypertensive patients with LVDD, 12% of whom had diabetes, BP reduction over 38 weeks improved myocardial relaxation (E′) irrespective of the agent used, but the independent effect of diabetes was not assessed (16). No trials have previously examined fenofibrate's effect on cardiac failure or LVDD. Small trials in heart failure patients collectively suggest a modest benefit of CoQ on systolic function (10), but no studies have investigated its effect on LVDD.

In type 2 diabetes, LVDD is associated with abnormal high-energy phosphate metabolism (17), and we anticipated that fenofibrate and CoQ would improve LVDD in type 2 diabetes by reducing lipotoxicity and oxidative stress and improving endothelial function and myocellular energetics. However, we did not demonstrate treatment effects on myocardial relaxation (E′) or several other diastolic function indexes, suggesting that possible favorable effects of fenofibrate could have been offset by adverse consequences of PPAR-α stimulation on myocardial fatty acid oxidation and energetics (3). Our study was powered to detect clinically relevant main treatment effects of ≥10% change in E′ compared with placebo. We observed statistically significant mixed treatment effects on several secondary diastolic indexes, such as increase in Vp (potentially beneficial),

Table 4—*Effect of interventions on ABP and HR*

	Placebo	Fenofibrate	CoQ	Combination	*P* for interaction	Fenofibrate main effect	*P*	CoQ main effect	*P*
n	15	15	10	14					
24-h									
SBP (mmHg)									
Baseline	125.4 ± 1.5	130.3 ± 2.8	126.2 ± 3.6	125.7 ± 3.1					
End	126.0 ± 2.5	130.2 ± 3.2	125.9 ± 4.7	123.0 ± 2.6	0.001	—	—	—	—
DBP (mmHg)									
Baseline	73.8 ± 2.3	73.1 ± 1.9	73.5 ± 2.0	72.3 ± 1.9					
End	74.3 ± 2.9	72.1 ± 1.9	72.3 ± 2.7	70.1 ± 1.6	0.732	−1.3 ± 0.5	0.013	−2.2 ± 0.5	< 0.001
HR (bpm)									
Baseline	73.9 ± 2.8	72.3 ± 2.7	70.4 ± 2.5	73.3 ± 2.8					
End	74.5 ± 2.5	70.2 ± 2.9	72.7 ± 2.3	70.9 ± 2.4	0.859	−3.3 ± 0.5	< 0.001	0.2 ± 0.5	0.716
Awake									
SBP (mmHg)	130.3 ± 1.6	134.5 ± 2.8	130.8 ± 2.9	130.1 ± 3.3					
Baseline	130.5 ± 2.9	134.3 ± 3.0	130.4 ± 4.6	129.0 ± 2.7	0.035	—	—	—	—
End									
DBP (mmHg)	77.9 ± 2.5	76.2 ± 1.7	77.3 ± 1.8	76.2 ± 2.1					
Baseline	78.5 ± 3.0	75.3 ± 1.9	76.1 ± 3.0	74.3 ± 1.6	0.275	−0.6 ± 0.6	0.319	−2.7 ± 0.6	< 0.001
End									
HR (bpm)									
Baseline	77.0 ± 3.1	75.8 ± 3.1	73.2 ± 2.9	76.2 ± 3.2					
End	77.5 ± 2.6	72.6 ± 3.3	75.8 ± 2.6	74.9 ± 2.7	0.285	−3.0 ± 0.7	< 0.001	0.6 ± 0.6	0.305
Asleep									
SBP (mmHg)									
Baseline	114.6 ± 2.0	120.6 ± 3.4	116.4 ± 6.3	117.0 ± 3.3					
End	116.5 ± 2.6	120.0 ± 3.7	117.9 ± 5.5	111.4 ± 2.9	0.002	—	—	—	—
DBP (mmHg)									
Baseline	65.1 ± 2.2	65.8 ± 2.2	64.9 ± 3.2	64.6 ± 1.8					
End	65.8 ± 2.6	64.9 ± 2.0	66.7 ± 3.1	61.4 ± 1.8	0.392	−2.6 ± 0.9	0.005	−1.3 ± 0.9	0.139
HR (bpm)									
Baseline	67.4 ± 2.3	65.1 ± 2.3	64.8 ± 2.3	67.3 ± 2.2					
End	68.5 ± 2.5	64.0 ± 2.6	67.2 ± 2.2	63.2 ± 2.1	0.381	−3.5 ± 0.7	< 0.001	−0.1 ± 0.6	0.858

Data are means ± SEM. Main effect vs. placebo, adjusted for baseline, study site, hour, change in weight, and antihypertensive medication use (mixed models).

E/Vp, and PV 'a' rev (potentially adverse), but these were small (<10%) and unlikely to be clinically important.

Significant treatment effects may have been masked by our selection of subjects with predominantly mild LVDD and satisfactory control of BP, lipids, and glycemia. Many were taking medications that could have affected cardiac function, such as ACE inhibitors, angiotensin receptor blockers, and statins. Fenofibrate and CoQ might have greater impact in patients with more advanced LVDD and worse BP and metabolic control. Ischemic heart disease was not formally excluded, but no subjects had wall motion abnormalities on echocardiography.

Despite favorable effects on triglycerides and apolipoproteins, fenofibrate did not raise HDL cholesterol or lower NEFAs significantly. However, most subjects had mild dyslipidemia. Greater treatment effects and clinical benefit might be expected in patients with lower HDL cholesterol (6). Whether higher-dose fenofibrate and CoQ given for longer periods could improve LVDD needs to be established.

The strengths of our study include the use of contemporary techniques (including tissue Doppler imaging) and multiple echocardiographic indexes to assess cardiac function. Traditional diastolic function measures (indirect mitral inflow indexes such as E/A, DT, and IVRT) may be affected by volume loading and have nonlinear associations with LVDD; our primary end point, E′, is less load dependent. Measurement of PV flow and Vp yielded additional diastolic function indexes, and we carefully selected subjects for having LVDD using a comprehensive classification system. We did not observe any treatment effect on this categorical LVDD definition, but our study had insufficient power to test this.

Blood pressure

Clinical trials of fenofibrate in type 2 diabetes have yielded inconsistent BP findings. In the FIELD study, there was a placebo-adjusted 2 mmHg systolic and 1 mmHg diastolic reduction in median CBP (6), but in the smaller Diabetes Atherosclerosis Intervention Study (DAIS), there was no significant change (5). By contrast, an uncontrolled short-term study in healthy adults showed that fenofibrate increased ambulatory SBP by 3 mmHg (18). Animal experiments suggest a role for PPAR-α in mediating hypertension and atherosclerosis (19), but their relevance to human disease is uncertain. Meta-analyses suggest that CoQ supplementation in hypertensive patients reduces CBP by up to 10 mmHg SBP and 8 mmHg DBP (9), but its effect on ABP has not been previously examined.

Our finding that fenofibrate and CoQ independently and interactively lowered

ABP is consistent with their beneficial effects on endothelial dysfunction. Fenofibrate's hypotensive effect may reflect increased endothelial NO bioavailability and reduced endothelin-1 production. CoQ could improve NO bioavailability by reducing oxidative stress and recoupling NO synthase activity. However, fenofibrate and CoQ's interactive effects may be mediated by non-NO mechanisms (11).

We previously showed that CoQ, but not fenofibrate, reduced CBP (11). In the present study, we were able to demonstrate independent and interactive effects of both treatments on ABP, possibly because multiple measurements over 24 h provide greater statistical power, even with limited sample sizes. Fenofibrate, alone or combined with CoQ, had greater effects at night perhaps because BP is subject to less variation during sleep. This does not, however, explain CoQ's greater effect on daytime BP, which might be due to interaction with factors such as concomitant morning medications.

In hypertensive type 2 diabetic patients, lowering CBP reduces macro- and microvascular complications. However, ABP, in particular nocturnal BP, predicts cardiovascular risk better than CBP (20). By lowering ABP, especially at night, fenofibrate and CoQ may potentially improve clinical outcomes in diabetes, where concomitant hypertension augments risk. In the FIELD study, modest lowering of CBP was not paralleled by reduction in coronary events, although secondary vascular outcomes were reduced (6). Longer treatment may be required for BP reduction to improve LVDD (16), as processes such as LV remodelling occur over an extended period.

HR

HR may be an important therapeutic target because it independently predicts cardiovascular risk (21). In hypertriglyceridemic subjects, short-term bezafibrate treatment reduced clinic HR by 3 bpm, (22), but no controlled studies have examined fibrate effects on ambulatory HR. In our study, fenofibrate lowered HR throughout the 24-h period by >3 bpm, which may translate to a 10–15% reduction in cardiovascular risk (21). The underlying mechanism is unclear. HR reduction may reflect increased myocardial efficiency and decreased oxygen demand related to decreased lipid substrate supply (1). Other possibilities include PPAR-α–mediated effects on baroreceptor and cardiac pacemaker sensitivity or sympathovagal outflow. Indeed, PPAR-α affects orphan nuclear receptor Rev-erb-α expression (23), which regulates clock genes mediating circadian hemodynamic and sympathoadrenal responses. NO also regulates cardiac autonomic function, but whether fenofibrate alters sympathovagal tone through this mechanism merits investigation.

Although fenofibrate and CoQ did not improve diastolic function in type 2 diabetic patients with mild LVDD and satisfactory BP and metabolic control, we observed beneficial hemodynamic effects with no significant adverse cardiac sequelae. Further studies are required to explore the benefits and risks of fenofibrate and CoQ in diabetic patients with more severe LVDD and metabolic abnormalities treated for longer periods. Combining these treatments with agents such as renin-angiotensin system inhibitors and advanced glycation end-product cross-link breakers should be investigated. Ultimately, larger long-term trials are required to determine whether combining fenofibrate with CoQ reduces clinical cardiovascular outcomes, such as heart failure, in type 2 diabetes.

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