

**HEMODYNAMIC EFFECTS OF FENOFIBRATE AND COENZYME Q₁₀
IN TYPE 2 DIABETIC SUBJECTS WITH LEFT VENTRICULAR
DIASTOLIC DYSFUNCTION**

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Objective: To investigate the effects of fenofibrate and Coenzyme Q₁₀ (CoQ) on diastolic function, ambulatory blood pressure (BP) and heart rate (HR) in type 2 diabetic (T2DM) subjects with left ventricular diastolic dysfunction (LVDD).

Research Design And Methods: 74 subjects were randomized, double-blind, to fenofibrate 160mg daily, CoQ 200mg daily, fenofibrate 160mg plus CoQ 200mg daily, or matching placebo for six months. Echocardiography (including tissue Doppler imaging) and 24-hour ambulatory BP and HR monitoring were performed pre- and post-intervention.

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 E/E' compared with placebo (p>0.05). Fenofibrate and CoQ interactively (p=0.001) lowered 24-hour systolic BP (-3.4±0.09mmHg, p=0.010), with a prominent nocturnal effect (-5.7±1.5mmHg, p=0.006). Fenofibrate (-1.3±0.5mmHg, p=0.013) and CoQ (-2.2±0.5mmHg, p<0.001) independently lowered 24-hour diastolic BP (DBP). Fenofibrate reduced 24-hour HR (-3.3±0.5 beats/min, p<0.001) but CoQ had no effect on HR.

Conclusions: In T2DM subjects with LVDD, neither fenofibrate nor CoQ, alone or in combination, improved diastolic function significantly. However, fenofibrate and CoQ independently and interactively lowered 24-hour BP, and fenofibrate alone reduced 24-hour HR.

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 remodelling. (3) Importantly, there is no evidence for this in humans treated with fibrates, (4) and in clinical trials in type 2 diabetes (T2DM), 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 endpoint, in the FIELD study (6), but it did reduce total cardiovascular events.

Coenzyme Q₁₀ (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 T2DM, (8) with modest beneficial effects on BP (9) and LV systolic function. (10)

We previously showed that fenofibrate and CoQ synergistically improve microcirculatory function in T2DM. (11) By targeting several mechanisms underlying LVDD in T2DM, we hypothesized that these treatments would improve cardiac function. Although fenofibrate and CoQ may lower clinic BP, their effect on diurnal BP has not been investigated. Our secondary hypothesis was that these treatments would independently and interactively lower ambulatory BP and, by improving cardiac function, also lower HR.

RESEARCH DESIGN AND METHODS

Subjects: We studied 74 T2DM subjects, aged 40 to 79 years, who had LVDD on echocardiography. All were recruited from clinical databases at teaching hospitals in Perth, Western Australia. T2DM was defined by American Diabetes Association criteria. Exclusions included daytime insulin use; GHb \geq 9.0%; resting BP $>$ 150/90mmHg; fasting cholesterol \geq 7.0mmol/L; triglycerides \geq 4.0mmol/L; creatinine $>$ 130 μ mol/L; treatment with fibrates or CoQ $>$ 30mg/day; and any cardiovascular event within the preceding six 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 160mg daily (Laboratoires Fournier, Chenove, France), CoQ 200mg daily (RP Scherer, Victoria, Australia), fenofibrate 160mg plus CoQ 200mg daily, or matching

placebo for six months. These doses and 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 post-intervention data taken as the mean value at each time point. The primary echocardiographic endpoint 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 endpoints included other diastolic and systolic function indices, left atrial volume (LAV) and LV mass (LVM). Ambulatory BP and HR were monitored over 24 hours 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 colour M-mode flow propagation (V_p) 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 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 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 ≥ 3 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 DT (40-59 years: >200ms; 60-69 years: >220ms; 70-79 years: >250ms); isovolumic relaxation time (IVRT) >100ms; reduced E' (40-59 years: <10.0cm/s; 60-79 years: <8.0cm/s); V_p <45.0cm/s. Participants were classified as having moderate LVDD if $E/E' > 8.0$ and ≥ 3 of the following were met: >40% decrease in E/A with Valsalva maneuver; $E/V_p > 1.50$; 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; normal DT.

Ambulatory monitoring: Ambulatory BP and HR were measured every 20 minutes during daytime (0900-2100) and every 30 minutes at night (2100-0900) using an Ultralite 90217 Monitor (Spacelabs Medical, Washington, USA). Participants recorded sleeping/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 Diagnostic GmbH, Mannheim, Germany) and LDL-cholesterol calculated. Apolipoproteins (apo) 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). Non-esterified fatty acids (NEFAs) were measured by enzymatic methods (Wako Pure Chemical Industries), plasma CoQ by reverse-phase high-performance liquid chromatography (HPLC) using electrochemical detection, and cellular CoQ by HPLC using isolated peripheral blood mononuclear cells with correction for protein content.

Statistical analyses: Data were analyzed using SPSS 12.0 (Illinois, USA) and SAS 9.1 (North Carolina, USA). Values are presented as mean \pm 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 indices were assessed using general linear modelling with adjustment for baseline and study site. For ambulatory BP 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, by-treatment-group analyses were undertaken with Scheffe adjustment for multiple comparisons. P values $<$ 0.05 were considered statistically significant.

RESULTS

Baseline characteristics: 74 eligible subjects were randomized 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 were diet-treated. Nearly half were taking antihypertensive medication, most commonly ACE inhibitors; over half were taking statins. On echocardiography, 12 participants (16.2%) had LV hypertrophy (LVM/height \geq 143g/m for men; \geq 102g/m for women). Most subjects (86.5%) had mild LVDD.

Clinical and biochemical responses: 69 subjects completed the trial. Reasons for withdrawal were new-onset atrial fibrillation (n=1), transaminase elevation $>$ 3 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 indices: Compared with placebo, none of the treatments significantly altered the primary endpoint (E'), nor any of the following diastolic function indices: E/A, DT, IVRT, PV S/D or E/E' (Table 3). However, fenofibrate increased Vp (2.4 \pm 1.0cm/s, p=0.020), and CoQ increased E/Vp (0.12 \pm 0.05, p=0.007) and PV 'a' rev (0.02 \pm 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 on fenofibrate, two on CoQ, and one on fenofibrate+CoQ. None of the treatments significantly altered systolic function (systolic myocardial contraction velocity (S'); LVEF) or cardiac structure (LAV; LVM). Adjustment for statin use did not alter these findings.

Ambulatory BP 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-hour systolic BP (SBP) (fenofibrate+CoQ: -3.4 \pm 0.9mmHg, p=0.010; fenofibrate: 1.8 \pm 1.0mmHg, p=0.341; CoQ: -0.3 \pm 1.1mmHg, p=0.992; vs placebo), particularly during sleep (fenofibrate+CoQ: -5.7 \pm 1.5mmHg, p=0.006; fenofibrate: -0.2 \pm 1.5mmHg, p=0.999; CoQ: 2.2 \pm 1.7mmHg, p=0.647; vs placebo) (Table 4). Fenofibrate (-1.3 \pm 0.5mmHg, p=0.013) and CoQ (-2.2 \pm 0.5mmHg, p $<$ 0.001) had

independent effects in lowering 24-hour 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-hour 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 T2DM 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 ambulatory BP, with fenofibrate alone also decreasing HR.

Cardiac function: LVDD is common in diabetes, and is associated with increased mortality. (14) However, few studies have investigated potential therapies. In T2DM subjects with LVDD, six 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 T2DM, LVDD is associated with abnormal high-energy phosphate metabolism, (17) and we anticipated that fenofibrate and CoQ would improve LVDD in T2DM by reducing lipotoxicity and oxidative stress, and improving endothelial function and myocellular energetics. However, we did not demonstrate treatment effects on myocardial relaxation (E') nor on several other diastolic

function indices, 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 $\geq 10\%$ change in E' compared with placebo. We observed statistically significant mixed treatment effects on several secondary diastolic indices, such as increase in Vp (potentially beneficial), 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 nor 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 indices to assess cardiac function. Traditional diastolic function measures (indirect mitral inflow indices such as E/A, DT and IVRT) may be affected by volume loading and have non-linear associations with LVDD; our primary

endpoint, E' , is less load-dependent. Measurement of PV flow and V_p yielded additional diastolic function indices, 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.

BP

Clinical trials of fenofibrate in T2DM have yielded inconsistent BP findings. In FIELD, there was a placebo-adjusted 2mmHg systolic and 1mmHg diastolic reduction in median clinic BP, (6) but in the smaller DAIS study, there was no significant change. (5) By contrast, an uncontrolled short-term study in healthy adults showed that fenofibrate increased ambulatory SBP by 3mmHg. (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 clinic BP by up to 10mmHg systolic and 8mmHg diastolic, (9) but its effect on ambulatory BP has not been previously examined.

Our finding that fenofibrate and CoQ independently and interactively lowered ambulatory BP is consistent with their beneficial effects on endothelial dysfunction. Fenofibrate's hypotensive effect may reflect increased endothelial nitric oxide (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 clinic BP. (11) In the present study, we were able to demonstrate independent and interactive effects of both treatments on ambulatory BP possibly because multiple measurements over 24 hours

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 T2DM patients, lowering clinic BP reduces macro- and microvascular complications. However, ambulatory BP, in particular nocturnal BP, predicts cardiovascular risk better than clinic BP. (20) By lowering ambulatory BP, especially at night, fenofibrate and CoQ may potentially improve clinical outcomes in diabetes, where concomitant hypertension augments risk. In FIELD, modest lowering of clinic BP 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 since it independently predicts cardiovascular risk. (21) In hypertriglyceridemic subjects, short-term bezafibrate treatment reduced clinic HR by 3 beats/min, (22) but no controlled studies have examined fibrate effects on ambulatory HR. In our study, fenofibrate lowered HR throughout the 24-hour period by >3 beats/min, 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/cardiac pacemaker sensitivity or sympathovagal outflow. Indeed, PPAR- α affects 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 T2DM 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 T2DM.

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Table 1. BASELINE CHARACTERISTICS OF RANDOMIZED SUBJECTS

	Placebo (n=20)	Fenofibrate (n=19)	CoQ (n=16)	Combination (n=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 T2DM (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
Beta-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

Mean±SD; *geometric mean (95% CI).

Table 2. EFFECT OF INTERVENTIONS ON BIOCHEMICAL VARIABLES

		Placebo (n=20)	Fenofibrate (n=16)	CoQ (n=16)	Combination (n=17)	<i>p</i> value for interaction	Fenofibrate Main effect	<i>p</i> value	CoQ Main effect	<i>p</i> value
Fasting glucose (mmol/L)	Baseline	7.2±0.4	6.8±0.3	7.6±0.4	7.7±0.5	0.404	-0.3±0.3	0.294	-0.1±0.3	0.659
	End	7.4±0.3	7.1±0.3	7.7±0.4	7.2±0.4					
GHb (%)	Baseline	6.5±0.2	6.2±0.1	6.6±0.2	6.6±0.2	0.184	-0.2±0.1	0.136	0.1±0.1	0.483
	End	6.4±0.2	5.9±0.2	6.5±0.2	6.5±0.2					
Total cholesterol (mmol/L)	Baseline	4.4±0.3	4.7±0.2	4.6±0.2	4.5±0.2	0.086	-0.3±0.2	0.069	0.0±0.2	0.966
	End	4.3±0.2	4.5±0.2	4.7±0.2	4.1±0.2					
Triglycerides (mmol/L)	Baseline	1.6±0.2	1.6±0.2	1.7±0.2	1.7±0.2	0.615	-0.6±0.1	<0.001	-0.2±0.1	0.070
	End	1.8±0.2	1.2±0.1	1.6±0.1	1.1±0.1					
HDL-cholesterol (mmol/L)	Baseline	1.22±0.06	1.28±0.10	1.25±0.06	1.36±0.10	0.068	0.05±0.04	0.150	-0.06±0.04	0.107
	End	1.20±0.06	1.38±0.10	1.24±0.07	1.33±0.09					
LDL-cholesterol (mmol/L)	Baseline	2.5±0.2	2.7±0.2	2.6±0.2	2.4±0.2	0.081	-0.1±0.1	0.442	0.2±0.1	0.286
	End	2.3±0.2	2.6±0.2	2.7±0.2	2.3±0.2					
ApoA-I (g/L)	Baseline	1.35±0.05	1.42±0.07	1.40±0.05	1.51±0.07	0.397	0.09±0.04	0.028	-0.06±0.04	0.134
	End	1.39±0.05	1.57±0.08	1.42±0.05	1.56±0.08					
ApoA-II (g/L)	Baseline	0.32±0.01	0.32±0.01	0.33±0.01	0.32±0.01	0.871	0.08±0.01	<0.001	0.00±0.01	0.706
	End	0.32±0.01	0.39±0.02	0.33±0.01	0.39±0.02					
ApoB-100 (g/L)	Baseline	0.90±0.06	0.96±0.04	0.98±0.05	0.91±0.04	0.113	-0.10±0.04	0.008	-0.01±0.04	0.793
	End	0.88±0.05	0.88±0.05	0.98±0.05	0.77±0.04					
ApoC-III (mg/L)	Baseline	125.8±8.2	125.8±10.0	130.9±6.8	126.1±8.9	0.588	-29.1±4.4	<0.001	-5.1±4.4	0.250
	End	129.8±8.6	103.0±8.3	130.7±5.6	95.8±5.8					
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)	0.836	-0.08	0.057	0.01	0.866
	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)					
Plasma CoQ (umol/L)*	Baseline	6.5 (4.9,8.6)	8.5 (6.2,11.7)	8.1 (6.0,11.0)	6.2 (4.5,8.7)	0.064	-0.5	0.636	21.0	<0.001
	End	5.9 (4.4,8.1)	8.5 (6.4,11.2)	31.8 (22.7,44.5)	23.3 (16.9,32.2)					
Cellular CoQ (nmol/g protein)*	Baseline	108 (94,125)	107 (95,120)	123 (105,145)	118 (105,132)	0.582	-12	0.203	33	0.001
	End	116 (97,39)	101 (91,112)	147 (119,183)	139 (125,153)					

Mean±SEM; *geometric mean (95% CI). Main effect vs placebo, adjusted for baseline and study site (general linear model).

Table 3. EFFECT OF INTERVENTIONS ON ECHOCARDIOGRAPHIC INDICES

		Placebo (n=20)	Fenofibrate (n=16)	CoQ (n=16)	Combination (n=17)	<i>p</i> value for interaction	Fenofibrate Main effect	<i>p</i> value	CoQ Main effect	<i>p</i> value
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

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

Table 4. EFFECT OF INTERVENTIONS ON AMBULATORY BP AND HR

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

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