CLINICAL TRIAL

A Randomized, Double-Blind, Placebo-Controlled Crossover Study of Coenzyme Q_{10} Therapy in Hypertensive Patients With the Metabolic Syndrome

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BACKGROUND

Our aim was to examine the effects of adjunctive coenzyme Q_{10} therapy on 24-h ambulatory blood pressure (BP) in subjects with the metabolic syndrome and inadequate BP control.

METHODS

In a randomized, double-blind, placebo-controlled 12-week crossover trial, coenzyme Q_{10} (100 mg twice daily) or placebo was administrated to 30 subjects with the metabolic syndrome, and inadequate BP control (an average clinic BP of ≥140 systolic mm Hg or ≥130 mm Hg for patients with type 2 diabetes) while taking an unchanged, conventional antihypertensive regimen. Clinic and 24-h ambulatory BP were assessed pre- and post-treatment phases. The primary outcomes were the changes in 24-h systolic and diastolic BP during adjunctive therapy with coenzyme Q_{10} vs. placebo and prespecified secondary outcomes included changes in BP loads.

RESULTS

Compared with placebo, treatment with coenzyme Q_{10} was not associated with statistically significant reductions in systolic ($P = 0.60$) or diastolic 24-h ambulatory BP ($P = 0.12$) or heart rate ($P = 0.10$), although daytime diastolic BP loads, were significantly lower during coenzyme Q_{10} administration with thresholds set at >90 mm Hg ($P = 0.007$) and ≥85 mm Hg ($P = 0.03$). Coenzyme Q_{10} was well tolerated and was not associated with any clinically relevant changes in safety parameters.

CONCLUSIONS

Although it is possible that coenzyme Q_{10} may improve BP control under some circumstances, any effects are likely to be smaller than reported in previous meta-analyses. Furthermore, our data suggest that coenzyme Q_{10} is not currently indicated as adjunctive antihypertensive treatment for patients with the metabolic syndrome whose BP control is inadequate, despite regular antihypertensive therapy.

Keywords: *ambulatory blood pressure monitoring; arterial pressure; blood pressure; clinical trial; coenzyme Q10; hypertension; metabolic syndrome*

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Control of blood pressure (BP) in hypertensive patients often requires multiple drug therapy but poor adherence is frequently due, in part, to undesirable side effects. Accordingly, adjunctive therapy with agents such as coenzyme Q_{10} supposedly with few side effects, have become increasingly popular. Coenzyme Q_{10} is an antioxidant and integral component of the mitochondrial electron transport chain.[1] There is evidence that plasma coenzyme Q_{10} concentrations are reduced in patients with essential hypertension.[2] Furthermore, increased oxidative stress has been observed in hypertensive states.[3] It has been proposed that coenzyme Q_{10} supplementation has an antihypertensive action resulting from vasodilatation via a direct effect on the endothelium and underlying vascular smooth muscle.[4–6]

A number of clinical studies have described the potential of coenzyme Q_{10} to lower BP in hypertensive patients.[2,7–17] Rosenfeldt *et al.* conducted a meta-analysis, comprising three randomized trials,[7–9] one randomized crossover study,[10] and eight open-label studies[2,11–17] in 362 hypertensive patients, most of whom had essential hypertension or isolated systolic hypertension.[4] They reported that coenzyme Q_{10} therapy had the potential to reduce BP by up to 17/10 mm Hg.[4] The meta-analysis was however, limited by the inclusion of studies which were open-labeled and not placebo-controlled. Furthermore, there were considerable differences in patient populations with respect to age, underlying disease and comorbidities, coenzyme Q_{10} dose and duration, and use of concomitant antihypertensive therapy between the trials. Finally, the meta-analysis did not make use of individual patient data from the component studies, which would have provided a more robust assessment of any effect of coenzyme Q_{10} on arterial pressure.

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More recently, a Cochrane review addressed the evidence for coenzyme Q_{10} efficacy in the treatment of essential hypertension.[18] This review was of three double-blind randomized, placebo-controlled studies with a total of 96 participants,[18] including the crossover study,[10] and two of the randomized controlled studies[7,8] in the Rosenfeldt *et al.* meta-analysis.[4] Whilst this review found that coenzyme Q_{10} lowered the BP by 11/7 mm Hg after 4–12 weeks of therapy in comparison to placebo,[18] the authors cautioned that "Due to possible unreliability of some of the included studies, it is uncertain whether or not coenzyme Q_{10} reduces BP in the long-term management of primary hypertension." The reviewers concluded that larger properly conducted randomized controlled trials are warranted.[18]

Since type 2 diabetes and the metabolic syndrome are associated with elevated oxidative stress,[6] we investigated the effect of coenzyme Q_{10} treatment on arterial pressure in subjects with the metabolic syndrome and inadequate BP control despite standard antihypertensive therapies in a double-blind, placebo-controlled 12-week crossover trial that assessed both 24-h ambulatory BP parameters and clinic BP. Additionally, we investigated the role of the presence of type 2 diabetes or cardiovascular disease, baseline ambulatory BP levels, nocturnal dippers, treatment with statins, metformin, angiotensin-converting enzyme inhibition and β blockade and coenzyme Q_{10} levels achieved on the potential effects of coenzyme Q_{10} on BP.

METHODS

This was a randomized, double-blind, placebo-controlled 12-week crossover study, with a four week washout between treatment phases. The study took place in clinic rooms at the Lipid and Diabetes Research Group, Diabetes Research Institute, Christchurch Hospital Campus, Christchurch, New Zealand. The recruitment of patients was conducted by a Research Nurse at the Lipid and Diabetes Research Group. Patients were recruited from general practitioners and research databases, and through advertisements in Christchurch. The study protocol was approved by the Upper South B Regional Ethics Committee (New Zealand), and written informed consent was obtained from all participants.

Patients. We enrolled 31 patients, aged 25–75 years, with hypertension defined as an average clinic systolic BP of ≥140 mm Hg, or ≥130 mm Hg for patients with type 2 diabetes mellitus, and receiving conventional antihypertensive medication which had been unchanged for at least one month. All patients had the metabolic syndrome as defined by the International Diabetes Federation 2005 guidelines;[19] a waist circumference ≥94 cm (males) or ≥80 cm (females), and at least one of the following in addition to treated hypertension: triglycerides ≥1.7 mmol/l or specific therapy for elevated triglycerides, high-density lipoprotein <1.0 mmol/l (males) <1.3 mmol/l (females) or specific therapy for a low high-density lipoprotein, or fasting plasma glucose >5.6 mmol/l. Patients were predominantly Caucasian (90%) with 10% of Maori descent. We excluded patients if they had uncontrolled hypertension (office BP >160/100 mm Hg), a history of coronary angioplasty, coronary stent placement, coronary bypass surgery, or myocardial infarction within the 6 months before screening, or a history of cerebrovascular accident within the 12 months before screening. Further exclusions were unstable angina, symptomatic chronic heart failure requiring treatment, atrial fibrillation, type 1 diabetes mellitus, type 2 diabetes mellitus requiring insulin, hemoglobin A_{1c} >9%, significantly deranged liver function tests (alanine aminotransferase ≥3 times the upper level of normal), significant renal impairment (plasma creatinine >150 μmmol/l), autonomic neuropathy, body mass index >40 kg/m^2 or an upper arm circumference >42 cm, other significant comorbidities, current smoking, warfarin treatment, or antioxidant vitamin supplementation, including coenzyme Q_{10}. Patients maintained their standard antihypertensive therapies and any lipid lowering treatment unchanged for the duration of the study period. Patients were asked to maintain their usual diets and physical activity and not to alter their lifestyle during the interventional period.

Randomization. After a 2-week screening period, eligible patients were randomized in a balanced fashion to treatment with either coenzyme Q_{10} 100 mg twice daily or placebo for 12 weeks, followed by a 4-week washout period, and then received the alternative "treatment" for a further 12 weeks. Both Q-Gel and placebo were supplied by Tishcon (Salisbury, MD), and were identical in appearance and taste. We selected Q-Gel as it has previously been shown to have superior bioavailability in comparison to other coenzyme Q_{10} formulations.[20] Randomization was performed in permutation blocks of six from a computer-generated randomization list by a statistician with no clinical involvement in the study. The study treatments were dispensed by an independent pharmacist in identical numbered bottles with the lowest available number allocated to each sequential participant. Compliance with treatment was assessed at the end of each intervention through capsule count. Participants and investigators administering the treatment and assessing outcomes were blinded to treatment assignment and to plasma coenzyme Q_{10} levels.

Outcome measures. The primary outcomes were 12-week changes in mean 24-h ambulatory systolic and diastolic BP. Secondary outcomes were 12-week changes in 24-h mean arterial pressure, pulse pressure and heart rate, and the changes in mean daytime and nighttime BP and heart rate, minimum and maximum BP and heart rate levels, morning surge and nocturnal fall in systolic and diastolic BP, 24-h and daytime and nighttime BP loads, BP and heart rate variability, clinic BP and heart rate, and plasma coenzyme Q_{10} levels. Safety data, including electrolytes, renal and liver function and a full blood count were assessed at the end of each 24-h monitoring period, and adverse events were documented. The effect of *post-hoc* subgroups including the presence of type 2 diabetes, cardiovascular disease, baseline ambulatory systolic and diasto-

lic BP levels, nocturnal BP dippers, treatment with statins, metformin, and angiotensin-converting enzyme inhibition, β-blockade, and coenzyme Q_{10} levels achieved were examined for all primary and secondary outcomes.

BP measurements. Clinic and 24-h ambulatory BP measurements were taken at baseline and at the end of both treatment periods, in the clinic rooms of the Lipid and Diabetes Research Group. Clinic BP was recorded using standard sphygmomanometry between 0700 and 1100 h according to current guideline recommendations.[21,22] BP was assessed after 5 min of rest in the sitting position using appropriately sized cuffs. Three BP measurements were obtained at 2-min intervals and the mean of these recordings were calculated as the final clinic BP values. Serial BP measurements were performed by the same trained operator using the same calibrated sphygmomanometer throughout the study. Twenty-four hours ambulatory BP monitoring was performed with the validated TM-2430 device, A&D, Saitama, Japan (accuracy ± 3 mm Hg for BP, ± 5% for pulse) and suitably sized cuffs. Patients were asked to refrain from drinking alcoholic or caffeinated beverages within 8 h before the visit and to withhold short acting nitrates within 4 h of the visit. The monitoring started between 0700 and 1100 h after clinic BP measurements had been recorded, with ambulatory BP readings obtained at 20-min intervals over the 24-h period. Participants were instructed to engage in their usual physical activity levels, but to avoid strenuous exercise during the monitoring period and to record bed and rise times. Datasets with <80% valid readings were excluded from analysis. Data were analyzed using Doctory Pro Ambulatory BP monitor data analysis software (TM-2430-13; A&D). Daytime and nighttime were defined by the established method of narrow fixed time intervals, described in the European Society of Hypertension Guidelines 2005 (ESH) (daytime 0900–2059 h, nighttime 0100–0559 h).[22] Thresholds for normal ambulatory BP levels were defined according to the European Society of Cardiology Task Force Guidelines for the Management of Arterial Hypertension (ESH/ESC),[23] the ESH Guidelines, 2005 (ESH),[22] the American Heart Association Recommendations for Blood Pressure Measurement, 2005 (AHA),[21] and the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes (IDACO) study data.[24]

Biochemical parameters. Total plasma coenzyme Q_{10} was measured by reverse phase high-performance liquid chromatography with electrochemical detection.[25] Plasma total cholesterol, triglycerides, and high-density lipoprotein-cholesterol were determined by an enzymatic colorimetric method (Architect c8000 analyzer; Abbott Laboratories, Abbott Park, IL). Low-density lipoprotein-cholesterol was calculated from the Friedewald equation. High-sensitivity C-reactive protein levels were determined by rate nephelometry. Safety markers, including electrolytes, plasma glucose, renal and liver function (Architect c8000 analyzer), hemoglobin A_{1c} (Biorad Variant HPLC), and a full blood count (Coulter Electronics, Luton, UK) were measured. Urine concentrations of creatinine and sodium were also determined (Architect c8000 analyzer).

Sample size. The sample size was based on published estimated treatment effects from studies included in meta-analyses examining the BP-lowering efficacy of coenzyme Q_{10} in patients with hypertension.[4,18] A total of 30 patients in a crossover design was calculated to provide sufficient power (>80%) to detect a statistically significant (two-tailed $\alpha = 0.05$) difference in the change from baseline between placebo and coenzyme Q_{10} of 8 mm Hg for systolic BP and 4 mm Hg for diastolic BP, assuming SDs of 13 and 7 mm Hg, respectively, allowing for a 10% attrition rate.

Statistical analysis. All statistical analyses were performed using SPSS Base version 17.0 (SPSS, Chicago, IL). Comparison of changes from baseline for each primary and secondary variable, between the placebo and treatment phases was tested using analysis of variance with repeated measures. For *post-hoc* subgroup analyses, the influence of potential mitigating factors including presence of type 2 diabetes or cardiovascular disease, baseline ambulatory systolic and diastolic BP levels, nocturnal BP dippers, treatment with statins, metformin, and angiotensin-converting enzyme inhibition, β-blockade, and coenzyme Q_{10} levels achieved on changes primary and secondary outcomes were analyzed using these variables as between subject factors in analysis of variance with repeated measures. The treatment effect size was calculated as the absolute value of the difference between the changes in variables following coenzyme Q_{10} and placebo treatment divided by the s.d. of the change. Variables are summarized as mean ± s.e.m. and categorical data are presented as percentages. Statistical significance was inferred when $P < 0.05$.

RESULTS

Patient characteristics

Recruitment started in December 2008 and was completed in January 2010, with follow-up completed in August 2010. Of 60 potential participants screened, 31 entered and 30 completed the study and were included in the analysis (**Figure 1**). Demographic characteristics are shown in **Table 1**. Overall compliance rates based on capsule counts were 96% during coenzyme Q_{10} therapy and 95% during placebo. There was no difference in baseline plasma coenzyme Q_{10} levels before placebo and coenzyme Q_{10} treatment phases ($P = 0.18$). Plasma coenzyme Q_{10} increased 3.7-fold after 12 weeks on coenzyme Q_{10} therapy compared with placebo administration ($P < 0.0001$).

BP and heart rate

There were no significant reductions in mean 24-h systolic or diastolic BP, 24-h pulse pressure, mean arterial pressure or heart rate following coenzyme Q_{10} therapy compared with placebo (**Table 2**). Likewise there were no changes in mean clinic systolic or diastolic BP after coenzyme Q_{10} therapy com-

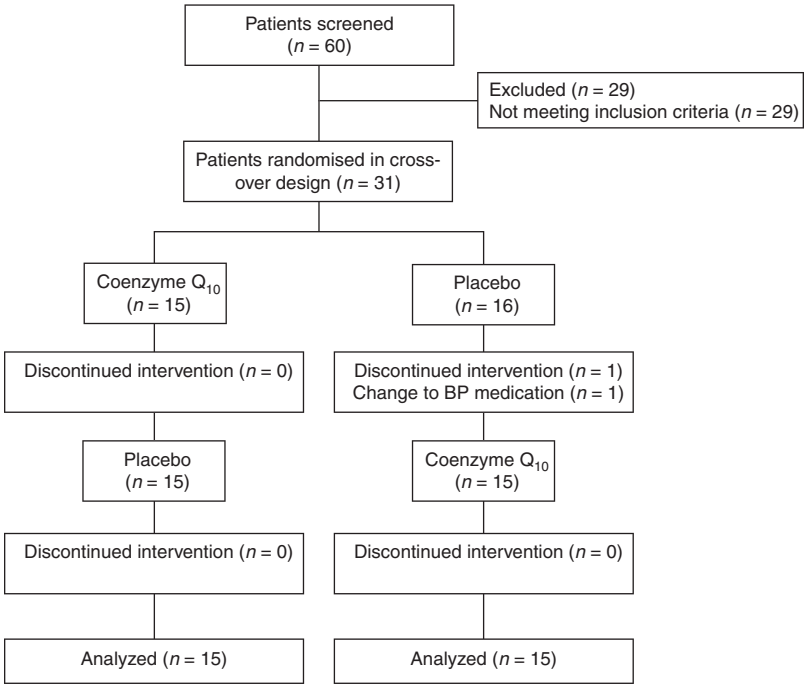

Figure 1 | Flow of patients through the trial. BP, blood pressure.

pared with placebo, however there was a significant increase in clinic heart rate during the placebo phase compared with the coenzyme Q_{10} phase ($P = 0.04$) (Table 2).

There were no significant effects of coenzyme Q_{10} on mean daytime or nighttime BP in comparison to placebo treatment, although there was a small increase in daytime diastolic BP during placebo administration ($P = 0.14$) (Table 2). Daytime and nighttime heart rates were not altered with coenzyme Q_{10} therapy, whereas nighttime heart rate increased significantly on placebo treatment compared with coenzyme Q_{10} treatment ($P = 0.006$). Furthermore, there were no changes in the mean daytime/nighttime BP ratios or nighttime/daytime BP ratios with coenzyme Q_{10} vs. placebo therapy (data not shown). Minimum and maximum daytime and nighttime BP readings were not significantly different following coenzyme Q_{10} and placebo supplementation (data not shown). Minimum and maximum daytime heart rate levels were also unchanged, but there was an increase in minimum nighttime heart rate during the placebo phase compared with the coenzyme Q_{10} phase (2.7 vs. −0.4 beats/min, $P < 0.05$).

Ambulatory BP load, morning surge, and nocturnal fall

There were no significant differences in 24-h systolic or diastolic BP loads with coenzyme Q_{10} compared with placebo administration (Table 3). Similarly, there was no effect of coenzyme Q_{10} therapy on daytime systolic BP loads; however there was a significant reduction in daytime diastolic BP loads, with thresholds set at >90 mm Hg ($P = 0.007$) and ≥85 mm Hg ($P = 0.03$) during coenzyme Q_{10} treatment compared with placebo (Figure 2). Nighttime BP loads were similar during the two treatment phases and there were no differences in the preawakening morning surge or sleep through morning surge in systolic or diastolic BP between coenzyme Q_{10} and placebo phases (Table 3). Similarly, there were no effects of coenzyme Q_{10} on the nocturnal fall and percentage nocturnal fall in systolic and diastolic BP in comparison with placebo (Table 3).

Ambulatory BP and heart rate variability

There were no significant differences in the 24-h average real variability (ARV_{24}) for systolic or diastolic BP or heart rate during coenzyme Q_{10} vs. placebo treatment (Table 4). The s.d. of the mean 24-h BP and heart rate were also unchanged by coenzyme Q_{10} vs. placebo administration. There was no effect of coenzyme Q_{10} therapy on the s.d. of mean daytime or nighttime BP or heart rate compared with placebo administration (Table 4).

Day and nighttime parameters were also assessed as the participants reported bed and arise times, and arbitrarily (daytime 0600–2059 h, nighttime 2100–0559 h). There were no consistently statistically significant differences in results for any of the parameters described above when these different definitions were used (data not shown).

Subgroup analysis

In *post-hoc* subgroup analyses, that included the sequence of study treatment, baseline systolic and diastolic BP levels, presence of type 2 diabetes, presence of cardiovascular disease, concentration of coenzyme Q_{10} achieved on therapy (>2.5 μg/ml and >3.5 μg/ml), nocturnal fall in systolic BP >10% and diastolic BP >10%, or treatment with statins, metformin, angiotensin-converting enzyme inhibitors, or β-blockers, there was no evidence of any treatment effect of coenzyme Q_{10} on

Table 1 | Baseline characteristics of completing patients ($n = 30$).

Patient characteristics	
Age, years	64 ± 1
Male/female	15/15
Clinic SBP, mm Hg	147.8 ± 2.1
Clinic DBP, mm Hg	77.4 ± 2.2
Heart rate, beats per minute	71.3 ± 2.8
Waist, cm	110.2 ± 2.1
Weight, kg	94.1 ± 2.9
Body mass index, kg/m^2	32.1 ± 0.9
Cardiovascular disease, *n* (%)	9 (30.0)
Type 2 diabetes, *n* (%)	16 (53.3)
Plasma glucose, mmol/l	6.1 ± 0.2
Plasma creatinine, μmol/l	87 ± 3
Total cholesterol, mmol/l	5.0 ± 0.2
Triglycerides, mmol/l	2.1 ± 0.3
HDL-cholesterol, mmol/l	1.18 ± 0.06
Antihypertensive medication, n (%)	
ACE inhibitor	21 (70)
β-Blocker	16 (53.3)
Diuretic	13 (43.3)
Calcium-channel blocker	11 (36.7)
Angiotension II receptor blocker	5 (16.7)
α-Blocker	4 (13.3)
Number of antihypertensives, n (%)	
1	8 (26.7)
2	10 (33.3)
3	7 (23.3)
4	4 (13.3)
5	1 (3.3)
Concomitant medications, n (%)	
Aspirin	14 (46.7)
Metformin	13 (43.3)
Sulfonylurea	7 (23.3)
Statins	16 (53.3)
Fibrates	2 (6.7)

Data are expressed as mean ± s.e.m. or number (percentage).
ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; HDL, high-density lipoprotein; SBP, systolic blood pressure.

24-h ambulatory BP parameters or heart rate compared with placebo (data not shown).

Tolerability and adverse events

Coenzyme Q_{10} was well tolerated and there were no reported serious adverse events following either coenzyme Q_{10} or placebo treatment. There were no clinically or statistically significant changes in biochemistry and hematology safety parameters including assessment of electrolytes, liver, and renal function, and complete blood count (data not shown).

DISCUSSION

There is considerable enthusiasm for the use of coenzyme Q_{10} as an antihypertensive agent. The concept has attraction since patients with essential hypertension and/or diabetes mellitus reportedly have evidence of oxidative stress,[3] and low-circulating levels of coenzyme Q_{10},[2] a number of clinical studies have documented an antihypertensive action of coenzyme Q_{10} supplementation,[2,7–17,26,27] and coenzyme Q_{10} has been demonstrated experimentally to induce vasodilatation through effects on the endothelium and vascular smooth muscle.[5,6] Support for the concept comes from the meta-analysis of Rosenfeldt *et al.*,[4] which concluded that until the results of further trials are available, "it would seem acceptable to add coenzyme Q_{10} to conventional antihypertensive therapy…" and that it "…may have a particular therapeutic role in hypertensive patients with consistently increased levels of oxidative stress as in diabetes or renal failure." As mentioned in the Introduction section, however, this meta-analysis is open to a number of questions and criticisms. Furthermore, a subsequent, more selective analysis by the Cochrane Hypertension Group,[18] concluded that "…it is uncertain whether or not coenzyme Q_{10} reduces BP in the long-term management of primary hypertension." In view of this uncertainty, we carried out the present study to determine whether coenzyme Q_{10}, when added to conventional antihypertensive therapy, reduces arterial pressure in patients with the metabolic syndrome and inadequately controlled hypertension. This was a double-blind, placebo-controlled, crossover study using both 24-h and clinical BP recordings.

We observed that, compared to placebo, 12 weeks of coenzyme Q_{10} supplementation was not associated with clinically significant reductions in clinic or 24-h ambulatory BP in patients with the metabolic syndrome and inadequately treated hypertension. Furthermore, there were no changes in mean daytime and nighttime ambulatory BP with coenzyme Q_{10} compared with placebo treatment. Although there were trends for a small reduction in 24-h systolic and diastolic BP and mean arterial pressure in favor of coenzyme Q_{10}, these effects were not statistically significant. In view of evidence that a blunted decrease in nocturnal BP is associated with target organ damage,[28] and is a strong independent risk factor for cardiovascular mortality,[29] it is pertinent to note that 50% of our patients were "nondippers" and this remained unchanged with coenzyme Q_{10} in comparison to placebo treatment, indicating no improvement in the nondipper status of our patients.

BP loads can be defined as the proportion of 24-h, daytime or nighttime BP readings that are increased relative to predetermined thresholds as described by White *et al.*[30] Since there is no standardized definition of what represents "normal" ambulatory BP,[31] we used thresholds defined from current guidelines to assess 24 h, daytime and nighttime BP loads.[21–24] In hypertensive patients, BP loads have been reported to be

Table 2 | Effect of coenzyme Q_{10} on ambulatory and clinic blood pressure and heart rate ($n = 30$)

	Coenzyme Q_{10}		Placebo		Advantage to coenzyme Q_{10}[a]	*P* value[b]
	Baseline	12 weeks	Baseline	12 weeks		
24-h Blood pressure and heart rate						
Systolic blood pressure, mm Hg	144.3 ± 2.7	143.2 ± 2.5	143.9 ± 2.7	143.6 ± 2.4	0.9 (−2.4, 4.1)	0.60
Diastolic blood pressure, mm Hg	79.0 ± 1.7	78.7 ± 1.7	78.1 ± 1.7	79.2 ± 1.7	1.3 (−0.3, 2.9)	0.12
Pulse pressure, mm Hg	65.3 ± 1.8	64.5 ± 1.7	65.7 ± 1.9	64.5 ± 1.7	−0.4 (−3.0, 2.1)	0.73
Mean arterial pressure, mm Hg	100.8 ± 1.9	100.2 ± 1.8	100.1 ± 1.9	100.6 ± 1.8	1.2 (−0.8, 3.1)	0.25
Heart rate, bpm	69.5 ± 1.8	69.2 ± 1.6	69.2 ± 1.9	70.9 ± 2.0	2.1 (−0.5, 4.6)	0.10
Clinic blood pressure and heart rate						
Systolic blood pressure, mm Hg	142.8 ± 2.0	141.8 ± 3.1	140.1 ± 2.1	142.2 ± 2.5	3.0 (−2.7, 8.7)	0.30
Diastolic blood pressure, mm Hg	74.2 ± 2.1	73.3 ± 2.3	72.2 ± 2.0	73.4 ± 1.9	2.0 (−1.1, 5.1)	0.21
Heart rate, bpm	72.0 ± 2.8	72.6 ± 1.8	70.1 ± 2.5	75.7 ± 2.4	4.8 (0.2, 9.4)	0.04
Daytime[c]						
Systolic blood pressure, mm Hg	148.6 ± 2.8	148.4 ± 2.5	148.6 ± 2.8	150.0 ± 2.3	1.6 (−3.1, 6.3)	0.50
Diastolic blood pressure, mm Hg	82.6 ± 1.7	82.6 ± 1.8	81.1 ± 1.7	83.3 ± 1.7	2.2 (−0.7, 5.1)	0.14
Pulse pressure, mm Hg	66.1 ± 2.1	65.9 ± 1.8	67.5 ± 2.0	66.6 ± 1.7	−0.6 (−4.3, 3.1)	0.73
Mean arterial pressure, mm Hg	104.6 ± 1.8	104.5 ± 1.9	103.6 ± 1.9	105.5 ± 1.7	2.0 (−1.2, 5.2)	0.21
Heart rate, bpm	73.3 ± 2.0	73.0 ± 1.9	73.2 ± 2.3	74.7 ± 2.3	1.8 (−1.3, 4.8)	0.25
Nighttime[c]						
Systolic blood pressure, mm Hg	133.6 ± 3.6	132.1 ± 3.6	132.7 ± 3.4	130.7 ± 3.5	−0.5 (−5.2, 4.2)	0.84
Diastolic blood pressure, mm Hg	72.1 ± 2.2	71.6 ± 2.1	71.1 ± 2.2	70.4 ± 2.1	−0.2 (−3.7, 3.2)	0.90
Pulse pressure, mm Hg	61.5 ± 2.1	60.6 ± 2.1	61.6 ± 2.2	60.4 ± 2.2	−0.3 (−2.5, 2.0)	0.81
Mean arterial pressure, mm Hg	92.6 ± 2.6	91.7 ± 2.5	91.6 ± 2.5	90.5 ± 2.5	−0.3 (−4.1, 3.5)	0.87
Heart rate, bpm	62.5 ± 1.7	62.2 ± 1.8	60.8 ± 1.7	64.1 ± 2.1	3.7 (1.2, 6.2)	0.006

Data are expressed as mean ± s.e.m.
bpm, beats/min.
[a]Difference between mean change after placebo and coenzyme Q_{10} (95% CI). [b]ANOVA with repeated measures for comparison of between group changes. [c]Daytime and nighttime defined by the narrow fixed time interval method described in the European Society of Hypertension Guidelines 2005. Statistical significance was defined as $P < 0.05$.

more closely related to cardiac function and left ventricular hypertrophy than mean BP.[30,32–34] The key study by White *et al.*[30] established that there was a marked increase in the prevalence of left ventricular hypertrophy in untreated hypertensive patients, with systolic BP loads >50% and diastolic BP loads exceeding 40%. Recently, Andrade *et al.*[35] demonstrated that a daytime systolic load of 24.5% or greater (>135 mm Hg) independently predicted cardiovascular events in elderly hypertensive patients. To our awareness this is the first study to examine the effect of coenzyme Q_{10} on BP loads in treated hypertensive patients. Compared with placebo, coenzyme Q_{10} treatment had favorable effects on daytime diastolic BP loads >90 mm Hg and ≥85 mm Hg but no effect on 24-h or nighttime loads. The mechanisms underlying this effect of coenzyme Q_{10} may involve changes in cardiac and/or vascular (large or small vessel) function but our study was not designed to assess these possibilities. Whatever the underlying mechanisms, our data raise the possibility that although coenzyme Q_{10} supplementation did not lead to reductions in absolute BP levels, patients may nevertheless benefit through a decrease in daytime arterial load. We cannot rule out the possibility, however, that these statistically significant and rather small effects on BP load may reflect a type 1 error, given the large number of variables examined in this study.

Our observations in hypertensive patients with the metabolic syndrome may not necessarily apply to other patient groups. For example, some studies reporting an antihypertensive effect of coenzyme Q_{10}, enrolled patients with considerably higher baseline levels of BP (systolic BP >160 mm Hg) than in the present study. A more obvious treatment effect might be expected in subjects with higher baseline BP levels. Consistent with this, less pronounced BP-lowering effects of coenzyme Q_{10} have been reported in modestly hypertensive patients with type 2 diabetes.[26,27] However, a recent meta-analysis found no evidence that the efficacy of BP-lowering treatment depends substantively upon baseline BP levels.[36] It is possible also that there are significant interactions of coenzyme Q_{10} with other therapies. For example, Chew *et al.* demonstrated a more pronounced antihypertensive effect of coenzyme Q_{10} when administered in combination with fenofibrate to patients with type 2 diabetes.[27] Only two of our patients were on fibrate therapy. Although our study was sufficiently powered to detect an 8/4 mm Hg change in BP, we cannot rule out the possibility of smaller antihypertensive effects of coenzyme Q_{10} treat-

Table 3 | Effect of coenzyme Q_{10} on ambulatory blood pressure load, morning surge and nocturnal fall in blood pressure ($n = 30$)

	Coenzyme Q_{10}		Placebo		Advantage to coenzyme Q_{10}[a]	*P* value[b]
	Baseline	12 weeks	Baseline	12 weeks		
24-h BP loads						
% SBP >135 mm Hg	65.8 ± 4.8	64.2 ± 4.3	64.5 ± 4.1	65.4 ± 4.1	2.5 (−4.3, 9.3)	0.46
% SBP ≥125 mm Hg	81.0 ± 3.2	79.0 ± 3.4	79.2 ± 3.3	80.3 ± 3.2	3.1 (−2.1, 8.4)	0.23
% DBP >85 mm Hg	35.4 ± 4.7	33.5 ± 4.6	32.8 ± 4.3	34.5 ± 4.5	3.7 (−1.9, 9.2)	0.19
% DBP ≥ 80 mm Hg	47.7 ± 5.4	46.7 ± 4.8	45.5 ± 4.9	46.9 ± 4.8	2.4 (−2.9, 7.7)	0.37
Daytime BP loads[c]						
% SBP >140 mm Hg	62.8 ± 5.3	65.2 ± 4.5	63.9 ± 4.6	68.1 ± 4.5	1.8 (−9.0, 12.6)	0.74
% SBP ≥130 mm Hg	81.6 ± 3.5	82.5 ± 3.5	81.2 ± 3.1	85.0 ± 3.1	2.8 (−6.5, 12.1)	0.55
% DBP >90 mm Hg	30.6 ± 4.8	26.3 ± 4.5	24.7 ± 4.3	30.2 ± 4.8	9.7 (2.8, 16.6)	0.007
% DBP ≥ 85 mm Hg	42.3 ± 5.4	40.1 ± 5.1	38.3 ± 4.9	44.5 ± 5.2	8.3 (0.8, 15.8)	0.03
Nighttime BP loads[c]						
% SBP >125 mm Hg	63.8 ± 6.9	60.5 ± 5.9	61.2 ± 6.5	58.7 ± 6.5	0.8 (−10.8, 12.3)	0.90
% SBP ≥120 mm Hg	69.8 ± 6.1	69.8 ± 5.9	70.0 ± 6.0	67.2 ± 6.1	−2.7 (−12.7, 7.2)	0.58
% DBP >75 mm Hg	43.4 ± 7.4	40.8 ± 6.4	41.0 ± 6.6	35.6 ± 6.5	−2.9 (−14.6, 8.8)	0.62
% DBP ≥ 70 mm Hg	55.1 ± 7.0	51.6 ± 6.7	54.3 ± 6.6	48.6 ± 7.0	−2.3 (−14.0, 9.5)	0.70
Preawakening morning surge						
SBP (mm Hg)	14.3 ± 3.7	15.3 ± 2.8	16.9 ± 2.7	17.5 ± 3.0	−0.4 (−8.3, 7.5)	0.91
DBP (mm Hg)	10.8 ± 2.1	13.0 ± 1.8	12.1 ± 1.7	12.6 ± 1.9	−1.8 (−6.3, 2.8)	0.44
Sleep through morning surge						
SBP (mm Hg)	28.2 ± 3.4	26.0 ± 2.8	30.4 ± 2.6	31.2 ± 3.5	3.0 (−5.6, 11.5)	0.48
DBP (mm Hg)	18.0 ± 1.5	19.4 ± 1.6	19.2 ± 1.8	21.2 ± 1.9	0.6 (−5.0, 6.1)	0.84
Nocturnal fall[b]						
SBP (mm Hg)	15.1 ± 3.0	16.3 ± 3.1	15.9 ± 3.0	19.2 ± 3.1	2.1 (−4.9, 9.0)	0.55
DBP (mm Hg)	10.5 ± 1.5	11.0 ± 1.9	10.0 ± 1.6	13.0 ± 1.6	2.4 (−2.9, 7.8)	0.36
% Nocturnal fall[c]						
SBP (%)	10.0 ± 2.0	10.9 ± 2.1	10.5 ± 1.9	12.8 ± 2.0	1.4 (−3.0, 5.7)	0.53
DBP (%)	12.8 ± 1.8	13.0 ± 2.2	12.4 ± 2.0	15.6 ± 1.8	3.1 (−2.9, 9.0)	0.30

Data are expressed as mean ± s.e.m.
BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.
[a]Difference between mean change after placebo and coenzyme Q_{10} (95% CI). [b]ANOVA with repeated measures for comparison of between group changes. [c]Daytime and nighttime defined by the narrow fixed time interval method described in the European Society of Hypertension Guidelines 2005. Statistical significance was defined as $P < 0.05$.

ment in our patient group. Less significant BP reductions with coenzyme Q_{10} may be relevant at a population level but further trials would require larger numbers.

Our findings concur with one other double-blind, placebo-controlled intervention trial by Mori *et al.*,[37] who found 8 weeks of coenzyme Q_{10} administration had no effect on 24-h ambulatory BP in patients with chronic kidney disease. In that study, treated BP levels were 125/73 mm Hg before randomization. As noted above, however, any antihypertensive action of coenzyme Q_{10} is likely to be less obvious the lower the baseline level of BP. In this regard, it has been shown that coenzyme Q_{10} does not have vasodilatory effects in normotensive animals or humans.[4]

In a recent meta-analysis of over 8,000 people from 11 trials, BP variability assessed by SD_{dn} and ARV_{24}, was shown to be a significant and independent predictor of mortality and cardiovascular events, after adjustment for 24-h BP levels and other covariables.[38] Although, the proportion of the risk explained by the variability was low, the BP variability did add to risk stratification.[38] This prompted us to examine whether coenzyme Q_{10} may have an effect on BP variability. We observed no changes in SD or ARV_{24} with 12 weeks supplementation, suggesting that coenzyme Q_{10} does not influence BP variability in this treated hypertensive population.

We found no change in clinic heart rate with coenzyme Q_{10}, but a significant increase with placebo after 12 weeks ($P < 0.05$). We also observed an increase in the adjusted nighttime heart rate of 3.6 beats/min with placebo compared with coenzyme Q_{10} ($P < 0.006$). Conversely, in the double-blind, placebo controlled study of Singh *et al.*, coenzyme Q_{10} (120 mg daily) reduced heart rate in 58 patients receiving antihypertensive medication and presenting with coronary artery disease.[8]

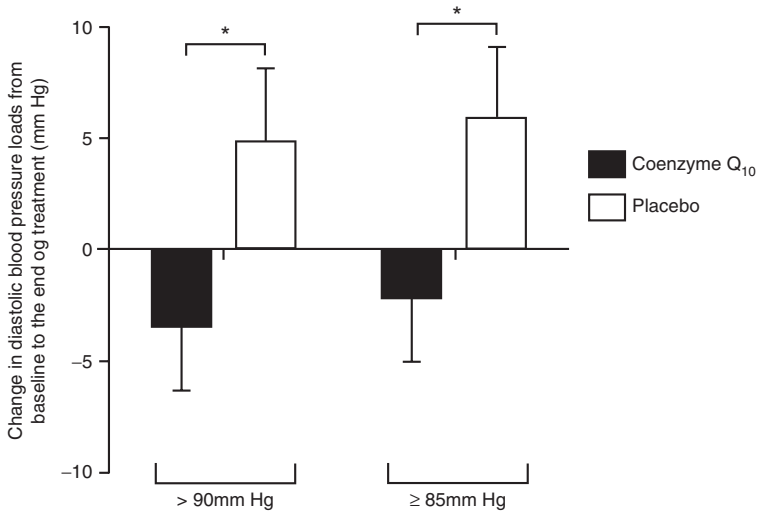

Figure 2 | Changes in daytime diastolic blood pressure loads from baseline following 12 weeks of treatment with coenzyme Q_{10} or placebo. *$P < 0.05$ for comparison of between group changes.

Table 4 | Effect of coenzyme Q_{10} on ambulatory blood pressure and heart rate variability ($n = 30$)

	Coenzyme Q_{10}		Placebo		Advantage to coenzyme Q_{10}[a]	*P* value[b]
	Baseline	12 weeks	Baseline	12 weeks		
24-h ARV_{24}						
SBP	13.6 ± 0.5	13.9 ± 0.6	14.5 ± 0.5	13.9 ± 0.6	−0.9 (−2.6, 0.8)	0.28
DBP	10.2 ± 0.6	10.3 ± 0.7	10.7 ± 0.6	10.4 ± 0.7	−0.4 (−2.0, 1.2)	0.59
HR	7.1 ± 0.6	6.8 ± 0.6	6.5 ± 0.5	6.0 ± 0.4	−0.2 (−1.8, 1.4)	0.79
24-h SD						
SBP	18.7 ± 0.7	18.9 ± 0.9	19.6 ± 0.7	19.7 ± 0.8	−0.2 (−2.5, 2.1)	0.87
DBP	13.3 ± 0.6	14.1 ± 0.8	13.3 ± 0.6	14.3 ± 0.8	0.2 (−1.8, 2.2)	0.81
HR	11.7 ± 0.8	10.6 ± 0.7	11.0 ± 0.8	10.3 ± 0.8	0.3 (−1.7, 2.3)	0.75
Daytime SD[c]						
SBP	16.2 ± 0.6	16.6 ± 0.9	17.0 ± 0.7	17.0 ± 0.8	−0.5 (−3.2, 2.2)	0.72
DBP	13.3 ± 0.9	13.0 ± 0.9	12.5 ± 0.8	13.3 ± 0.9	1.0 (−1.8, 3.8)	0.47
HR	12.1 ± 1.0	9.9 ± 0.8	9.7 ± 0.8	9.7 ± 0.9	2.1 (−1.4, 5.6)	0.24
Nighttime SD[c]						
SBP	13.0 ± 0.8	13.3 ± 1.1	14.3 ± 0.7	13.3 ± 0.8	−1.3 (−5.2, 2.7)	0.52
DBP	9.1 ± 0.7	10.2 ± 1.3	9.0 ± 0.6	8.0 ± 0.5	−2.1 (−5.5, 1.3)	0.22
HR	4.8 ± 0.4	4.9 ± 0.6	4.4 ± 0.4	4.6 ± 0.3	0.0 (−1.2, 1.2)	0.99

Data are expressed as mean ± s.e.m.
ARV_{24}, 24 h average real variability; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.
[a]Difference between mean change after placebo and coenzyme Q_{10} (95% CI). [b]ANOVA with repeated measures for comparison of between group changes. [c]Daytime and nighttime defined by the narrow fixed time interval method described in the European Society of Hypertension Guidelines 2005. Statistical significance was defined as $P < 0.05$.

After 8 weeks of follow-up, a significant reduction in heart rate of 12 (95% CI 9, 15) beats/min was observed in the coenzyme Q_{10} group compared with the control group.[8] By contrast, in a controlled intervention trial of 74 patients with chronic kidney disease, 8 weeks of coenzyme Q_{10} treatment (200 mg daily) was associated with a small but significant increase in 24-h heart rate ($P < 0.03$).[37]

Post-hoc analyses of subgroups in our study showed no consistently significant differences in the response to adjunctive coenzyme Q_{10} therapy. As has previously been reported,[4,39–46] coenzyme Q_{10} treatment was well tolerated and was not associated with clinically relevant changes in safety parameters.

Although our study was sufficiently powered to detect an 8/4 mm Hg change in BP, we cannot rule out the possibility of smaller antihypertensive effects of coenzyme Q_{10} treatment in our patient group. Further trials would require larger numbers in order to confirm whether supplementation with coenzyme Q_{10} confers a less significant BP-lowering effect in similar populations. For example, on the basis of the observed effect

sizes in the present study (0.10 and 0.30 for 24-h systolic and diastolic BP, respectively), a sample size of ~190 in a crossover design would be required to detect a differential reduction from coenzyme Q_{10} of 2 mm Hg in systolic and diastolic BP as statistically significant. There is a strong likelihood of type 1 errors, given the multiple BP parameters examined in our trial. We had limited statistical power for the *post-hoc* subgroup analyses, and can therefore not exclude the possibility of significant effects of coenzyme Q_{10} treatment within the subgroups we examined.

In conclusion, this adequately powered, randomized controlled study demonstrated that compared with placebo, coenzyme Q_{10} does not result in clinically significant reductions in systolic or diastolic 24-h ambulatory BP or heart rate in patients with the metabolic syndrome and inadequately treated hypertension, although there was a significant reduction in daytime diastolic BP loads. Coenzyme Q_{10} was well tolerated and was not associated with any clinically relevant changes in safety parameters. Whereas we cannot rule out the possibility that coenzyme Q_{10} may have clinically useful antihypertensive effects in selected populations, our data does not support a role in the routine management of patients with the metabolic syndrome. We cannot however, exclude a small hypotensive effect, which may still have clinical benefits at the population level, in this group. There is a need for further randomized controlled trials to establish whether coenzyme Q_{10} has any role as an adjunct or alternative to conventional therapy in hypertensive patients. Such trials could include patients with borderline hypertension, a direct comparison of coenzyme Q_{10} therapy with other antihypertensive agents, or combination treatment with other agents such as fenofibrate where interactive effects with coenzyme Q_{10} have been observed and further exploration of effects on diastolic BP loads.

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