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Coenzyme Q_{10}, Rosuvastatin, and Clinical Outcomes in Heart Failure

A Pre-Specified Substudy of CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure)

John J. V. McMurray, MD,* Peter Dunselman, MD, PhD,† Hans Wedel, PhD,‡ John G. F. Cleland,§ Magnus Lindberg, MCs,‖ Åke Hjalmarson, MD, PhD,¶ John Kjekshus, MD, PhD,# Finn Waagstein, MD, PhD,¶ Eduard Apetrei, MD, PhD,** Vivencio Barrios, MD, PhD,†† Michael Böhm, MD, PhD,‡‡ Gabriel Kamenský, MD, PhD,§§ Michel Komajda, MD,‖‖ Vyacheslav Mareev, MD, PhD,¶¶ John Wikstrand, MD, PhD,¶ on behalf of the CORONA Study Group

Glasgow and Yorkshire, United Kingdom; Breda, the Netherlands; Göteborg and Mölndal, Sweden; Oslo, Norway; Bucharest, Romania; Madrid, Spain; Homburg/Saar, Germany; Bratislava, Slovakia; Paris, France; and Moscow, Russia

Objectives The purpose of this study was to determine whether coenzyme Q_{10} is an independent predictor of prognosis in heart failure.

Background Blood and tissue concentrations of the essential cofactor coenzyme Q_{10} are decreased by statins, and this could be harmful in patients with heart failure.

Methods We measured serum coenzyme Q_{10} in 1,191 patients with ischemic systolic heart failure enrolled in CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) and related this to clinical outcomes.

Results Patients with lower coenzyme Q_{10} concentrations were older and had more advanced heart failure. Mortality was significantly higher among patients in the lowest compared to the highest coenzyme Q_{10} tertile in a univariate analysis (hazard ratio: 1.50, 95% confidence interval: 1.04 to 2.6, $p = 0.03$) but not in a multivariable analysis. Coenzyme Q_{10} was not an independent predictor of any other clinical outcome. Rosuvastatin reduced coenzyme Q_{10} but there was no interaction between coenzyme Q_{10} and the effect of rosuvastatin.

Conclusions Coenzyme Q_{10} is not an independent prognostic variable in heart failure. Rosuvastatin reduced coenzyme Q_{10}, but even in patients with a low baseline coenzyme Q_{10}, rosuvastatin treatment was not associated with a significantly worse outcome. (Controlled Rosuvastatin Multinational Study in Heart Failure [CORONA]; NCT00206310)
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Coenzyme Q_{10} (ubiquinone) is a naturally occurring, lipid-soluble, quinone which, by acting as an electron transporter, is an essential cofactor in mitochondrial oxidative phosphorylation and generation of adenosine triphosphate (1,2). In its reduced form, coenzyme Q_{10} is also thought to act as a lipophilic antioxidant protecting cell membranes and lipoproteins in the circulation from oxidation (1–3). About

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*From the BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom; †Amphia Hospital, Breda, the Netherlands; ‡Nordic School of Public Health, Göteborg, Sweden; §Department of Cardiology, University of Hull, Kingston upon Hull, Yorkshire, United Kingdom; ‖AstraZeneca, Mölndal, Sweden; ¶Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden; #Department of Cardiology, Rikshospitalet University Hospital, Oslo, Norway; **Institute of Cardiology, Bucharest, Romania; ††Hospital Ramón y Cajal, Madrid, Spain; ‡‡Universitätsklinikum des Saarlandes, Homburg/Saar, Germany; §§University Hospital Bratislava, Bratislava, Slovakia; ‖‖Department of Cardiology, Pitie Salpetriere Hospital, University Pierre et Marie Curie, Paris, France; and the ¶¶Myasnikov Institute of Cardiology, Moscow, Russia. The CORONA trial was funded by AstraZeneca. Drs. Kjekshus, Dunselman, Cleland, Böhm, Hjalmarson, Hradec, Kamensky, Komajda, McMurray, Waagstein, and Wedel report receiving consulting or advisory board fees from AstraZeneca. Drs. Kjekshus, Grande, Gullestad, Hjalmarson, Apetrei, Barrios, Mareev, Komajda, McMurray and Kamensky report receiving lecture fees from AstraZeneca. Drs. Hjalmarson, McMurray, and Wikstrand report receiving research grants from AstraZeneca. Mr. Lindberg is a current employee of AstraZeneca. Dr. Wikstrand was a former senior medical advisor at AstraZeneca. Dr. McMurray is presently the "Eugene Braunwald Scholar in Cardiovascular Medicine" at the Brigham and Women's Hospital, Boston, Massachusetts.

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one-half of coenzyme Q_{10} is ingested in dietary fat, and the remainder is synthesized endogenously through the mevalonate pathway, which is blocked by statins (1–3).

Coenzyme Q_{10} deficiency has been associated with myopathy, and there has been concern that statins might cause peripheral and cardiac muscle dysfunction by reducing coenzyme Q_{10} production (4,5). In theory, coenzyme Q_{10} depletion could lead to muscle energy starvation (a particular concern in the failing heart [6]) and oxidative damage to myocytes. These theoretical concerns have been coupled with the observation that low cholesterol is associated with a worse prognosis in heart failure (7), forming the basis of articles in the lay press and on the web that have suggested that statins might be dangerous in heart failure. In practice, however, the role of coenzyme Q_{10} in the effect of statins on muscle function (if any) is uncertain, as is the association between plasma coenzyme Q_{10} concentration and clinical outcomes in cardiovascular disease (8–18). In 1 recent study, however, low plasma coenzyme Q_{10} concentration was found to be an independent predictor of mortality in patients hospitalized with heart failure (18).

Because of the concerns alluded to above, the U.S. Food and Drug Administration requested that we measure plasma coenzyme Q_{10} concentration in a subset of the patients with ischemic systolic heart failure enrolled in the CORONA (Controlled Rosuvastatin Multinational Study in Heart Failure) trial. In this pre-specified substudy, we investigated the effect of statin therapy on coenzyme Q_{10} concentration, as well as the relationship between coenzyme Q_{10} and fatal and nonfatal cardiovascular events (19,20).

Methods

Patients. The design and principal findings of the CORONA study have been reported in detail (19,20). Patients ≥60 years of age with chronic New York Heart Association (NYHA) functional class II to IV heart failure of investigator-reported ischemic etiology and a left ventricular ejection fraction (LVEF) of ≤40% (≤0.35 if NYHA functional class II) were eligible, provided that the investigator believed they did not need treatment with a cholesterol-lowering drug.

Exclusion criteria included recent cardiovascular events, procedures, or operations (or planned procedures or operations); acute or chronic liver disease or alanine aminotransferase >2 times the upper limit of normal (ULN); serum creatinine >220 μmol/l (>2.49 mg/dl); chronic muscle disease or unexplained creatine kinase >2.5 times ULN; thyroid-stimulating hormone >2 times ULN; or any other condition substantially reducing life expectancy.

Study procedures. The trial was approved by ethics committees of participating hospitals, and patients provided written informed consent. Patients were allocated, equally, to 10 mg of rosuvastatin or matching placebo, once daily. We measured serum creatinine, creatine kinase, thyroid-stimulating hormone, alanine aminotransferase, high-sensitivity C-reactive protein, and lipid/lipoproteins (total, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein cholesterol, triglycerides, and apolipoprotein [apo] A-1 and B) at baseline in all 5,011 patients.

Abbreviations and Acronyms

apo = apolipoprotein
LDL = low-density lipoprotein
LVEF = left ventricular ejection fraction
NT-proBNP = N-terminal pro–B-type natriuretic peptide
NYHA = New York Heart Association
ULN = upper limit of normal

After the study started, the protocol was amended to include measurement of N-terminal pro–B-type natriuretic peptide (NT-proBNP), which was available in 3,664 (73%) patients. All measurements, except thyroid-stimulating hormone, were repeated at 3 months. In a pre-specified substudy, coenzyme Q_{10} was measured in 1,191 patients using a high-performance liquid chromatography method after extraction of serum into hexane and using vitamin K_1 as an internal standard. The reference range is 0.34 to 2.54 μg/ml (0.39 to 2.94 μmol/l).

All blood samples were nonfasting and were analyzed at a central laboratory (Medical Research Laboratories, Zaventem, Belgium). The LDL was directly measured. Coenzyme Q_{10} was analyzed on fresh samples sent at refrigerated temperature by overnight mail to the central laboratory.

Study outcomes and definitions. The primary outcome was the composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke, analyzed as time to the first event. The secondary outcomes were (in listed order): all-cause mortality, any coronary event (defined as sudden death, fatal or nonfatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, ventricular defibrillation by an implantable cardioverter-defibrillator, resuscitation from cardiac arrest, or hospitalization for unstable angina), cardiovascular mortality (cause-specific cardiovascular death was also analyzed), and number (episodes) of hospitalizations (for cardiovascular causes, unstable angina, and worsening heart failure). The present report focuses on the primary end point, total mortality, the coronary end point, and hospitalizations (all-cause, cardiovascular cause, and worsening heart failure). We also included the additional post-hoc composite outcome of death from any cause or hospitalization for worsening heart failure (analyzed as time to first event) because of previously expressed concerns that coenzyme Q_{10} deficiency might cause worsening heart failure, leading to increased risk of hospital admission and death. We conducted further post-hoc analyses of patients hospitalized for all causes, cardiovascular causes, worsening heart failure, and noncardiovascular causes (analyzed as time to first event). The definition and adjudication of all outcomes have been described in detail previously (19,20). As the result of a protocol amendment adopted 15 months after the start of the trial, patients also completed a questionnaire

about muscle symptoms at each study visit and had a measurement of creatine kinase at 6 and 15 months after randomization, yearly thereafter, and at the last study visit (20). Patients were asked 2 questions: whether they had any muscular pain since the previous visit, and whether they had muscular pain at the present visit.

Analysis plan. We addressed 2 main questions: 1) Was baseline serum coenzyme Q_{10} concentration associated with the range of clinical outcomes described above? 2) Did treatment with rosuvastatin increase the risk of any of the described outcomes in patients with a low serum coenzyme Q_{10} concentration?

To answer the first question, we examined clinical characteristics and outcomes in patients divided according to tertile of baseline coenzyme Q_{10} concentration, and we entered baseline coenzyme Q_{10} (as a continuous variable) in a series of extensive multivariable models previously developed in the CORONA study population (21). These models had been built for the other mortality–morbidity composite outcomes listed in the previous text, in addition to all-cause mortality.

To answer the second question, we examined the effect of rosuvastatin compared with placebo in each of the baseline coenzyme Q_{10} tertiles, looking at both the unadjusted treatment effect and effect of treatment adjusted for age group ($\geq$75/$<$75 years); sex (female/male); baseline LVEF ($\geq$0.25/$<$0.25) and NYHA functional class (III to IV/II); beta-blocker use (yes/no); total cholesterol ($\geq$6.0/$<$6.0 mmol/l); and history of myocardial infarction (yes/no) or hypertension (yes/no), as pre-specified in the main CORONA study analysis plan. Tests for interaction between treatment effect and baseline coenzyme Q_{10} value were carried out as described in the following text.

Statistical analysis. For continuous variables, differences in baseline variables between the patients in each coenzyme Q_{10} tertile were tested with the Student *t* test (NT-proBNP with the Wilcoxon rank-sum test) and for categorical variables with the Fisher exact test. For comparison of tertiles, we used the Jonckheere-Terpstra test (for continuous variables) and the Cochran-Armitage trend test (for categorical variables). The multivariable analyses to which baseline coenzyme Q_{10} concentration was added as a continuous variable have been described in detail previously (21). The 8 most important demographic and clinical variables included age, sex, LVEF, NYHA functional class, heart rate, body mass index, history of diabetes mellitus, and intermittent claudication. The 2 most important biochemical variables were serum creatinine concentration and apoA-1 concentration. The log concentration of the neurohumoral marker NT-proBNP was the single most important predictor of all outcomes (21).

Cox's proportional hazards models (unadjusted and adjusted) were used to calculate hazard ratios and 95% confidence intervals (SAS version 8.2, SAS Institute, Cary, North Carolina) in all patients and in each coenzyme Q_{10} concentration tertile separately. The adjusted Cox regression model incorporated randomized treatment and the variables described earlier. Similar Cox analyses were performed to compare cardiovascular risk between NT-proBNP tertile 1 and tertile 3 in the placebo group.

Total number (episodes) of hospital admissions were analyzed using a permutation test. Tests for interaction between treatment effect and coenzyme Q_{10} tertile, for each outcome, were carried out using a Cox regression analysis with the following covariates, treatment as 0/1, coenzyme Q_{10} tertile as 0/1, and treatment*coenzyme Q_{10} tertile (interaction) as 0/1. We also analyzed interaction by treatment with coenzyme Q_{10} as a continuous variable.

Results

The baseline characteristics of the 1,191 patients with a measurement of coenzyme Q_{10} are shown in Table 1 (all patients and by tertiles of baseline coenzyme Q_{10} concentration).

Baseline characteristics by tertile of coenzyme Q_{10} concentration. Patients in the lowest coenzyme Q_{10} concentration tertile (tertile 1) were, on average, older, in a higher NYHA functional class, had more atrial fibrillation/flutter, had lower plasma lipids, and had a lower LVEF and estimated glomerular filtration rate compared with those in the highest tertile. NT-proBNP concentration was also significantly higher in patients in the lowest coenzyme Q_{10} tertile compared with the highest tertile.

Effect of rosuvastatin on serum LDL and plasma coenzyme Q_{10} concentration (change from baseline to 3-month follow-up visit). In the whole group of patients studied, LDL declined from a mean of 142 mg/dl at baseline to 76 mg/dl at 3 months with rosuvastatin but did not change in the placebo group: 141 mg/dl at baseline and 141 mg/dl at 3 months (48% net difference; $p < 0.0001$). The corresponding net difference in tertiles of coenzyme Q_{10} was 51%, 48%, and 45% (tertiles 1, 2, and 3, respectively).

Overall, coenzyme Q_{10} also declined at 3 months with rosuvastatin but did not change in the placebo group (39% net difference; $p < 0.0001$) (Table 2). Rosuvastatin reduced plasma coenzyme Q_{10} concentration in all 3 tertiles (Table 2).

Clinical outcomes in the placebo group according to baseline coenzyme Q_{10} tertile. In patients treated with placebo, the risk of the pre-defined primary outcome of cardiovascular death, myocardial infarction, or stroke (expressed as patients experiencing an event per 100 person-years of follow-up) was numerically highest in patients in the lowest coenzyme Q_{10} tertile, intermediate in the middle tertile, and lowest in patients in the highest coenzyme Q_{10} tertile (Table 3). The same relationship was seen between coenzyme Q_{10} tertile and mortality, the other composite outcomes, and hospitalizations (Table 4). However, risk was not significantly higher in coenzyme Q_{10} tertile 1, compared with tertile 3, after adjustment for other prognostic variables (Table 5).

Table 1 Characteristics of Patients in Each Tertile According to Baseline Coenzyme Q_{10} Concentration

Variables	All With Coenzyme Q_{10} (n = 1,191)	Tertile 1 (n = 400)	Tertile 2 (n = 387)	Tertile 3 (n = 404)	p Value for Trend Across Tertiles
Demographics					
Age, yrs	73.2 (7.0)	74.7 (7.1)	73.3 (6.9)	71.5 (7.1)	<0.0001
Age ≥75 yrs, n (%)	531 (45)	218 (55)	176 (46)	137 (34)	<0.0001
Female sex, n (%)	239 (20)	78 (20)	82 (21)	79 (20)	>0.2
NYHA functional class, n (%)					0.076
II	559 (47)	169 (42)	194 (50)	196 (49)	
III	621 (52)	228 (57)	190 (49)	203 (50)	
IV	11 (0.9)	3 (0.8)	3 (0.8)	5 (1.2)	
Ejection fraction	0.295 (0.069)	0.287 (0.073)	0.297 (0.067)	0.302 (0.066)	0.0047
BMI, kg/m^2	27.0 (4.2)	26.2 (4.1)	27.1 (4.2)	27.6 (4.2)	<0.0001
Systolic blood pressure, mm Hg	129 (18)	129 (18)	130 (18)	130 (17)	0.19
Diastolic blood pressure, mm Hg	75 (9.3)	74 (9.8)	75 (9.5)	76 (8.6)	0.027
Heart rate, beats/min	71 (11)	71 (11)	71 (11)	71 (12)	>0.20
Medical history, n (%)					
Myocardial infarction	716 (60)	240 (60)	243 (63)	233 (58)	>0.20
Angina pectoris*	868 (73)	277 (69)	285 (74)	306 (76)	0.039
CABG or PTCA/PCI	454 (38)	141 (35)	144 (37)	169 (42)	0.055
Hypertension	593 (50)	193 (48)	190 (49)	210 (52)	>0.20
Diabetes mellitus	329 (28)	112 (28)	104 (27)	113 (28)	>0.20
AF or atrial flutter†	195 (16)	76 (19)	57 (15)	62 (15)	0.030
Stroke	101 (8.5)	37 (9.3)	39 (10)	25 (6.2)	0.12
Intermittent claudication	158 (13)	55 (14)	57 (15)	46 (11)	>0.20
Laboratory measurements					
Total cholesterol, mmol/l‡	5.52 (1.10)	4.95 (0.96)	5.57 (0.88)	6.03 (1.05)	<0.0001
LDL cholesterol, mmol/l‡	3.66 (0.92)	3.26 (0.84)	3.74 (0.82)	3.97 (0.96)	<0.0001
HDL cholesterol, mmol/l‡	1.20 (0.35)	1.17 (0.30)	1.21 (0.34)	1.23 (0.39)	0.14
ApoA-1, g/l	1.49 (0.28)	1.41 (0.25)	1.50 (0.26)	1.57 (0.30)	<0.0001
ApoB, g/l	1.31 (0.30)	1.17 (0.27)	1.33 (0.25)	1.45 (0.29)	<0.0001
Triglycerides, mmol/l§	2.33 (1.50)	1.83 (0.91)	2.16 (1.10)	3.00 (2.10)	<0.0001
Serum creatinine, μmol/l‖	120 (30)	124 (32)	117 (30)	117 (27)	0.0059
Serum creatinine >130 μmol/l, n (%)‖	350 (29)	148 (37)	96 (25)	106 (26)	0.0008
$eGFR_{MDRD}$, ml/min/1.73 m^2 BSA	56 (14)	54 (15)	57 (14)	57 (14)	0.0008
NT-proBNP, pmol/l¶	145 (54–314)	206 (85–416)	125 (52–255)	107 (46–250)	<0.0001
hsCRP, mg/l	3.7 (1.6–7.9)	3.8 (1.6–10.2)	3.6 (1.3–7.9)	3.8 (1.65–7.3)	>0.20
Coenzyme Q_{10}, μg/ml#	0.74 (0.56–0.99)	0.49 (0.39–0.57)	0.74 (0.66–0.82)	1.10 (0.97–1.37)	NA
Medication, n (%)					
Loop diuretic	833 (70)	298 (75)	268 (69)	267 (66)	0.0094
Aldosterone antagonist	363 (31)	133 (33)	118 (31)	112 (28)	0.089
ACE inhibitor or ARB	1,094 (92)	363 (91)	361 (93)	370 (92)	>0.20
Beta-blocker	876 (74)	279 (70)	289 (75)	308 (76)	0.037
Digitalis glycoside	366 (31)	114 (29)	103 (27)	149 (37)	0.0099
Antiarrhythmic therapy	130 (11)	58 (15)	33 (8.5)	39 (9.7)	0.028

Patients are split into 3 equal groups (tertiles) according to baseline coenzyme Q_{10} concentration. Table shows other baseline characteristics in these tertiles. Continuous variables given as mean (SD), coenzyme Q_{10}, NT-proBNP, and hsCRP as median (interquartile range); binary and discrete variables given as n (%). *Past or current. †Current on electrocardiography. ‡To convert to mg/dl, multiply by 38.67. §To convert to mg/dl, multiply by 88.5 μmol/l. ‖To convert to mg/dl, multiply by 0.0113. ¶To convert to pg/ml, multiply by 8.457. In patients with coenzyme Q_{10}, NT-proBNP was measured in 422 placebo- and 415 rosuvastatin-treated patients. #To convert μmol/l, multiply by 1.158.

ACE = angiotensin-converting enzyme; AF = atrial fibrillation; Apo = apolipoprotein; ARB = angiotensin-receptor blocker; BMI = body mass index; BSA = body surface area; CABG = coronary artery bypass graft surgery; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high sensitivity C reactive protein; LDL = low-density lipoprotein; MDRD = modified diet in renal disease; NT-proBNP = N-terminal pro–B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angiography.

Association between coenzyme Q_{10} concentration, mortality, and other clinical outcomes: multivariable analysis. When entered as a continuous variable in our previously described multivariable models, coenzyme Q_{10} was not an independent predictor of all-cause mortality (Table 6), or any of the other mortality–morbidity outcomes examined (data not shown).

Association between rosuvastatin treatment and clinical outcomes according to baseline coenzyme Q_{10} tertile. TOTAL MORTALITY AND COMPOSITE MORTALITY–MORBIDITY END POINTS. The hazard ratio estimating the treatment effect for all 4 time-to-first-event end points was >1.0 in coenzyme Q_{10} tertile 1 and <1.0 in tertiles 2 and 3, although the 95% confidence intervals overlapped 1.0 in all subgroups

Table 2 Baseline and 3-Month Follow-Up Values for Coenzyme Q_{10}

Subgroups	Baseline Median (IQR)	3-Month Follow-Up Median (IQR)	Absolute Median Change	Net Median Change*	% Median Change	p Value*
Tertile 1				−0.25		<0.0001
Placebo (n = 199/181)†	0.48 (0.39–0.56)	0.58 (0.47–0.73)	0.12		+25.4	
Rosuvastatin (n = 201/181)	0.49 (0.39–0.57)	0.35 (0.26–0.45)	−0.13		−27.3	
Tertile 2				−0.27		<0.0001
Placebo (n = 204/187)	0.73 (0.66–0.80)	0.70 (0.55–0.87)	−0.03		−4.8	
Rosuvastatin (n = 183/176)	0.75 (0.68–0.82)	0.46 (0.34–0.59)	−0.30		−40.5	
Tertile 3						<0.0001
Placebo (n = 197/184)	1.11 (0.97–1.31)	0.93 (0.73–1.14)	−0.22	−0.35	−20.3	
Rosuvastatin (n = 207/184)	1.10 (0.97–1.37)	0.53 (0.40–0.70)	−0.57		−53.1	
All patients				−0.29		<0.0001
Placebo (n = 600/552)	0.72 (0.56–0.97)	0.72 (0.54–0.95)	−0.02		−2.7	
Rosuvastatin (n = 591/551)	0.75 (0.56–0.99)	0.44 (0.33–0.59)	−0.31		−41.9	

Baseline and 3-month follow-up values for coenzyme Q_{10} in μg/ml (to convert to μmol/l, multiply by 1.158): median (interquartile range [IQR]), absolute median change, % median change, and p value for % net difference between rosuvastatin and placebo in the 3 tertiles of baseline coenzyme Q_{10} and in all patients with a coenzyme Q_{10} measurement. *Rosuvastatin minus placebo. †Baseline/follow-up numbers.

(Table 3). There was no significant interaction between treatment effect and coenzyme Q_{10} tertile, with p values ranging from 0.14 (primary end point) to 0.26 (coronary end point) for the 4 end points (Table 3). Corresponding p values with coenzyme Q_{10} included as a continuous variable were between 0.49 (coronary end point) and 0.95 (primary end point).

HOSPITALIZATIONS. A similar picture was seen when the post-hoc outcome of number of patients hospitalized (analyzed as time to first hospitalization) was examined, with rosuvastatin:placebo hazard ratios >1 in coenzyme Q_{10} tertile 1 for hospitalizations for any cause, cardiovascular causes, worsening heart failure, and noncardiovascular causes (Table 4). All corresponding hazard ratios in tertiles 2 and 3 were <1. As with all-cause mortality and the composite mortality–morbidity outcomes, there was no statistically significant interaction between treatment and coenzyme Q_{10} tertile, although the p value for cardiovascular hospitalization was 0.052.

By contrast, the total number (episodes) of hospitalizations (a pre-specified secondary end point) for admissions due to any cause, cardiovascular causes, and heart failure

Table 3 Time-to-First Event End Points in All Patients Randomized and in Patients Split Into 3 Equal Groups (Tertiles) According to Baseline Coenzyme Q_{10} Concentration

End Point	Placebo n (Rate)*	Rosuvastatin n (Rate)*	Hazard Ratio†	95% CI†	Subgroup p Value‡	Interaction p Value§
Primary end point‖						0.14
Tertile 1	59 (12.8)	72 (16.8)	1.30 (1.30)	0.92–1.83 (0.92–1.84)	0.13 (0.14)	
Tertile 2	56 (11.4)	41 (8.8)	0.78 (0.81)	0.52–1.17 (0.54–1.21)	>0.20 (>0.20)	
Tertile 3	53 (10.4)	51 (9.7)	0.94 (0.88)	0.64–1.38 (0.60–1.29)	>0.20 (>0.20)	
All randomized	732 (12.3)	692 (11.4)	0.92 (0.92)	0.83–1.02 (0.83–1.02)	0.12 (0.10)	
All-cause mortality						0.24
Tertile 1	67 (14.1)	78 (17.1)	1.21 (1.19)	0.87–1.68 (0.86–1.66)	>0.20 (>0.20)	
Tertile 2	60 (11.8)	44 (9.2)	0.79 (0.82)	0.54–1.17 (0.56–1.22)	>0.20 (>0.20)	
Tertile 3	51 (9.6)	50 (9.2)	0.96 (0.90)	0.65–1.42 (0.61–1.34)	>0.20 (>0.20)	
All randomized	759 (12.2)	728 (11.6)	0.95 (0.95)	0.86–1.05 (0.86–1.05)	>0.20 (>0.20)	
Coronary end point						0.26
Tertile 1	45 (9.9)	54 (12.8)	1.27 (1.28)	0.86–1.89 (0.86–1.90)	>0.20 (>0.20)	
Tertile 2	46 (9.5)	34 (7.4)	0.78 (0.81)	0.50–1.22 (0.52–1.26)	>0.20 (>0.20)	
Tertile 3	45 (9.1)	48 (9.5)	1.06 (1.04)	0.70–1.59 (0.69–1.56)	>0.20 (>0.20)	
All randomized	588 (10.0)	554 (9.3)	0.92 (0.92)	0.82–1.04 (0.82–1.04)	0.18 (0.17)	
All-cause mortality or hospitalization for worsening HF¶						0.17
Tertile 1	86 (19.9)	96 (23.4)	1.17 (1.16)	0.88–1.57 (0.87–1.56)	0.18 (>0.20)	
Tertile 2	79 (17.0)	59 (13.5)	0.81 (0.82)	0.58–1.13 (0.58–1.15)	>0.20 (>0.20)	
Tertile 3	76 (15.6)	66 (13.1)	0.84 (0.80)	0.60–1.17 (0.57–1.11)	>0.20 (0.18)	
All randomized	1,112 (20.5)	1,056 (19.1)	0.93 (0.93)	0.86–1.02 (0.85–1.01)	0.11 (0.09)	

*Events per 100 patient-years of follow-up. †Cox unadjusted (Cox adjusted within parentheses). ‡For unadjusted Cox, p value from log-rank test, for adjusted from Cox. §By treatment comparing the 3 coenzyme Q_{10} subgroups. ‖Cardiovascular death or nonfatal myocardial infarction or nonfatal stroke (time to first event). ¶Post-hoc defined end point.
CI = confidence interval; HF = heart failure.

Table 4 Total Number of Patients Hospitalized and Total Number of Hospitalizations (Episodes) in the 3 Baseline Coenzyme Q_{10} Tertiles

Type of Hospitalization	Type of End Point	Placebo n (Rate)*	Rosuvastatin n (Rate)	Hazard Ratio	95% CI	Subgroup p Value†	Interaction p Value‡
All-cause							0.10
Tertile 1	Patients	119 (37.2)	137 (49.6)	1.32 (1.32)	1.03–1.69 (1.03–1.69)	0.027 (0.030)	
	Hospitalizations	293 (61.8)	296 (65.3)	NA	NA	>0.20	
Tertile 2	Patients	117 (33.2)	103 (30.2)	0.91 (0.90)	0.70–1.19 (0.69–1.18)	>0.20 (>0.20)	
	Hospitalizations	279 (55.0)	215 (45.2)	NA	NA	>0.20	
Tertile 3	Patients	115 (32.5)	117 (32.1)	0.99 (0.98)	0.77–1.29 (0.76–1.27)	>0.20 (>0.20)	
	Hospitalizations	271 (51.1)	295 (54.3)	NA	NA	>0.20	
Cardiovascular							0.052
Tertile 1	Patients	85 (23.2)	98 (28.9)	1.24 (1.23)	0.93–1.66 (0.92–1.64)	0.14 (0.17)	
	Hospitalizations	174 (36.7)	169 (37.3)	NA	NA	>0.20	
Tertile 2	Patients	87 (21.5)	67 (16.9)	0.79 (0.77)	0.58–1.09 (0.56–1.06)	0.15 (0.11)	
	Hospitalizations	165 (32.5)	102 (21.4)	NA	NA	0.032	
Tertile 3	Patients	92 (22.3)	78 (17.5)	0.79 (0.76)	0.58–1.06 (0.56–1.02)	0.12 (0.069)	
	Hospitalizations	166 (31.3)	153 (28.2)	NA	NA	>0.20	
Worsening heart failure							0.51
Tertile 1	Patients	45 (10.4)	44 (10.7)	1.03 (1.02)	0.68–1.56 (0.67–1.55)	>0.20 (>0.20)	
	Hospitalizations	77 (16.2)	69 (15.2)	NA	NA	>0.20	
Tertile 2	Patients	45 (9.7)	30 (6.9)	0.72 (0.69)	0.45–1.14 (0.43–1.10)	0.16 (0.12)	
	Hospitalizations	75 (14.8)	38 (8.0)	NA	NA	0.047	
Tertile 3	Patients	42 (8.6)	36 (7.4)	0.83 (0.78)	0.53–1.29 (0.50–1.22)	>0.20 (>0.20)	
	Hospitalizations	60 (11.3)	58 (10.7)	NA	NA	>0.20	
Noncardiovascular							0.91
Tertile 1	Patients	74 (19.0)	81 (22.7)	1.20 (1.20)	0.97–1.64 (0.87–1.65)	0.26 (0.27)	
	Hospitalizations	119 (25.1)	127 (28.0)	NA	NA	NA	
Tertile 2	Patients	67 (15.8)	68 (17.5)	1.11 (1.14)	0.79–1.55 (0.81–1.61)	0.55 (0.45)	
	Hospitalizations	114 (22.5)	113 (23.7)	NA	NA	NA	
Tertile 3	Patients	62 (14.2)	75 (17.4)	1.23 (1.22)	0.88–1.72 (0.87–1.71)	0.23 (0.25)	
	Hospitalizations	105 (19.8)	142 (26.2)	NA	NA	NA	

*Rate is number of events per 100 patient-years of follow-up. †The p value for number of patients from log-rank, for total number of hospitalizations from permutation test. ‡By treatment comparing the 3 coenzyme Q_{10} subgroups for time to first hospitalization (number of patients variable).
CI = confidence interval; NA = not applicable or not analyzed.

were similar in the 2 treatment groups in tertile 1 and generally numerically fewer in the rosuvastatin group in tertiles 2 and 3 (Table 4).

Outcomes in the lowest coenzyme Q_{10} tertile (tertile 1) by treatment assignment. Although there were no statistically significant differences between the treatment groups in the coenzyme Q_{10} tertile 1, there was an excess of 11 deaths in the rosuvastatin group compared with placebo group (Table 3). There were 5 extra cardiovascular deaths, 3 of which were due to myocardial infarction and 2 of which were sudden. There were 6 extra noncardiovascular deaths. The number of deaths due to

Table 5 Comparison of Risk During Follow-Up of Patients in Coenzyme Q_{10} Tertile 1 Compared to Tertile 3 in the Placebo Group*

End Point	Tertile 1 vs. 3 Hazard Ratio	Tertile 1 vs. 3 95% CI	Tertile 1 vs. 3 p Value
All-cause mortality	1.50 (1.17)	1.04–2.16 (0.79–1.72)	0.030 (0.44)
Hospitalizations			
All-cause	1.13 (1.08)	0.88–1.46 (0.82–1.42)	0.35 (0.58)
Cardiovascular cause	1.04 (0.95)	0.78–1.40 (0.70–1.30)	0.79 (0.76)
Worsening HF	1.20 (0.99)	0.79–1.83 (0.63–1.54)	0.39 (0.94)
Noncardiovascular cause	1.32 (1.34)	0.95–1.86 (0.93–1.93)	0.10 (0.11)
Combined end points			
Primary end point	1.25 (0.93)	0.86–1.82 (0.63–1.38)	0.23 (0.72)
Coronary end point	1.09 (0.89)	0.72–1.65 (0.58–1.39)	0.67 (0.61)
All-cause mortality/HF hospitalization	1.27 (1.05)	0.94–1.74 (0.76–1.46)	0.12 (0.77)

*Cox unadjusted with Cox adjusted within parentheses. For number of end points and rate expressed as number of events per 100 patient-years of follow-up, see Tables 3 and 4.
Abbreviations as in Table 3.

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Table 6 Prognostic Model for Testing Baseline Coenzyme Q_{10} Q as Risk Factor for Total Mortality

Variables	HR	95% CI	Wald	p Value
Step 1				
Placebo group				
Ejection fraction*100	0.96	0.94–0.98	12.0	0.0007
NYHA functional class	1.99	1.33–2.98	11.0	0.0009
Age/10 yrs	1.57	1.17–2.10	9.1	0.0026
BMI, kg/m^2	0.97	0.92–1.02	1.9	0.17
Diabetes mellitus	1.34	0.88–2.04	1.9	0.17
Female sex	0.76	0.46–1.26	1.1	0.29
Intermittent claudication	1.21	0.70–2.10	0.5	0.49
Heart rate/10 beats/min	1.05	0.89–1.24	0.4	0.54
Coenzyme Q_{10}, μg/ml	0.86	0.49–1.50	0.3	0.59
Rosuvastatin group				
Age/10 yrs	1.75	1.30–2.35	14.0	0.0002
Ejection fraction*100	0.96	0.93–0.99	9.2	0.0025
Female sex	0.49	0.28–0.85	6.5	0.011
Coenzyme Q_{10}, μg/ml	0.55	0.31–0.97	4.3	0.039
Diabetes mellitus	1.57	1.02–2.42	4.2	0.040
BMI, kg/m^2	0.95	0.91–1.01	3.2	0.074
NYHA functional class	1.37	0.91–2.07	2.3	0.13
Heart rate/10 beats/min	1.09	0.91–1.31	0.9	0.33
Intermittent claudication	1.10	0.66–1.82	0.1	0.72
Step 2				
Placebo group				
Ejection fraction*100	0.96	0.94–0.99	10.0	0.0015
NYHA functional class	1.87	1.24–2.83	8.8	0.0031
Age/10 yrs	1.49	1.10–2.01	6.6	0.010
BMI, kg/m^2	0.96	0.91–1.01	2.2	0.14
Serum creatinine/10 μmol/l	1.05	0.98–1.11	2.0	0.15
Diabetes mellitus	1.28	0.83–1.98	1.3	0.26
Intermittent claudication	1.22	0.70–2.11	0.5	0.48
Heart rate/10 beats/min	1.06	0.90–1.24	0.4	0.52
ApoA-1, g/l	0.79	0.37–1.72	0.3	0.56
Female sex	0.87	0.51–1.49	0.3	0.61
Coenzyme Q_{10}, μg/ml	0.91	0.52–1.60	0.1	0.74
Rosuvastatin group				
Age/10 yrs	1.60	1.18–2.16	9.0	0.0027
Ejection fraction*100	0.96	0.93–0.99	8.5	0.0035
Serum creatinine/10 μmol/l	1.08	1.02–1.15	6.1	0.013
BMI, kg/m^2	0.94	0.90–1.00	4.6	0.032
Diabetes mellitus	1.55	1.00–2.41	3.9	0.049
ApoA-1, g/l	0.48	0.21–1.08	3.2	0.076
Female sex	0.63	0.35–1.12	2.5	0.12
Coenzyme Q_{10}, μg/ml	0.64	0.36–1.13	2.4	0.13
Heart rate/10 beats/min	112	0.93–1.35	1.5	0.22
NYHA functional class	1.27	0.83–1.93	1.2	0.27
Intermittent claudication	1.06	0.63–1.77	0.05	0.82
Step 3				
Placebo group				
Log NT-proBNP	1.73	1.41–2.11	28.0	<0.0001
NYHA functional class	1.63	1.07–2.48	5.2	0.023
Age/10 yrs	1.40	1.04–1.88	4.8	0.028
Ejection fraction*100	0.98	0.05–1.00	2.7	0.10
Female sex	0.75	0.44–1.30	1.0	0.31
Intermittent claudication	1.21	0.70–2.10	0.5	0.50
ApoA-1, g/l	0.82	0.39–1.75	0.3	0.61
Serum creatinine/10 μmol/l	0.9	0.93–1.05	0.2	0.66
Coenzyme Q_{10}, μg/ml	1.13	0.64–2.01	0.2	0.67
Diabetes mellitus	1.10	0.71–1.70	0.2	0.68
Heart rate/10 beats/min	1.02	0.86–1.20	0.03	0.87
BMI, kg/m^2	1.00	0.95–1.05	0.0	0.92
Rosuvastatin group				
Log NT-proBNP	1.81	1.46–2.24	29	<0.0001
ApoA-1, g/l	0.45	0.20–1.01	3.8	0.053
Age/10 yrs	1.36	0.99–1.87	3.7	0.056
Ejection fraction*100	0.97	0.95–1.00	3.6	0.058
Female sex	0.58	0.33–1.03	3.5	0.063
Diabetes mellitus	1.44	0.93–2.23	2.6	0.10
BMI, kg/m^2	0.96	0.91–1.01	2.4	0.11
Heart rate/10 beats/min	1.10	0.91–1.33	1.0	0.31
Serum creatinine/10 μmol/l	1.03	0.96–1.10	0.8	0.37
Coenzyme Q_{10}, μg/ml	0.82	0.45–1.47	0.5	0.50
NYHA functional class	1.14	0.75–1.74	0.4	0.55
Intermittent claudication	0.96	0.57–1.62	0.0	0.88

Prognostic model for testing baseline coenzyme Q_{10} Q as a risk factor for total mortality in 3 steps according to the CORONA model: step 1 including the 8 most important demographic and clinical variables, step 2 adding the 2 most important biochemical variables, and step 3 adding also the most important predictor of all outcomes, the neurohumoral marker NT-proBNP (see Methods section and Wedel et al. [21]). Placebo group, 114 deaths, 420 patients; rosuvastatin group, 108 deaths, 411 patients. In each step, variables are ranked after Wald value.

HR = hazard ratio; other abbreviations as in Table 1.

worsening heart failure was 21 in each treatment group in coenzyme Q_{10} tertile 1.

Looking at nonfatal events, there were 18 more patients hospitalized at least once for any reason in the rosuvastatin group compared with placebo group; however, only 3 more episodes of hospital admissions. The equivalent numbers for cardiovascular hospitalization were +13 and −5. One fewer patient in the rosuvastatin group than the placebo group was hospitalized for worsening heart failure (and there were 8 fewer admissions for heart failure in the rosuvastatin group). There were 9 more nonfatal myocardial infarctions in the rosuvastatin group in coenzyme Q_{10} tertile 1.

Change in NYHA functional class. The mean change in NYHA functional class from baseline to last study visit in coenzyme Q_{10} tertile 1 was −0.085 in the placebo group and −0.035 in the rosuvastatin group ($p = 0.44$). The equivalent changes in tertile 2 were −0.015 and −0.104 ($p = 0.14$), and in tertile 3, they were −0.122 and −0.145 ($p = 0.75$).

Muscle symptoms and creatine kinase. Similar numbers of patients in each coenzyme Q_{10} tertile reported muscular pain on questioning, and this was also the case for placebo-treated compared with rosuvastatin-treated patients. For the question about muscular pain since the previous visit, the proportions in the placebo group were 7.5%, 10.3%, and 8.1% (tertiles 1, 2, and 3, respectively), and in the rosuvastatin group, they were 8.5%, 9.8%, and 6.3%, respectively. Corresponding figures for the question about muscular pain at the current visit, were 6.0%, 7.4%, and 6.6% (placebo) and 6.0%, 6.0%, and 4.3% (rosuvastatin). Only 1 patient had

a creatine kinase value >10 times ULN during follow-up (randomized to placebo).

Premature discontinuation of study drug. The number of patients in coenzyme Q_{10} tertile 1 who discontinued study drug for any reason was 50 (30 because of an adverse event) in the placebo group and 44 (24 because of an adverse event) in the rosuvastatin group. The equivalent numbers in tertile 2 were 54 (35 because of an adverse event) and 38 (19 because of an adverse event), and in tertile 3, the numbers were 52 (31 because of an adverse event) and 44 (28 because of an adverse event).

Discussion

We found that patients with a lower serum coenzyme Q_{10} concentration at baseline were older and had evidence of more severe heart failure. In particular, several powerful predictors of poor prognosis were more prevalent in patients with a lower coenzyme Q_{10}, including lower LVEF and estimated glomerular filtration rate and higher NYHA functional class and NT-proBNP concentration. Lower coenzyme Q_{10} was also associated with higher age and, as expected, lower lipid levels (lower lipid levels are also a marker of poor prognosis in heart failure). Although lower coenzyme Q_{10} was associated with a higher risk of death in unadjusted analyses, coenzyme Q_{10} concentration was not an independent predictor of mortality in a multivariable analysis (or an independent predictor of any other outcome). This finding differs from that of the 1 other study investigating the relationship between coenzyme Q_{10} and mortality in patients with heart failure (18).

There are several important differences between that report of Molyneux et al. (18) and the present study. Our study was much larger with more patients (1,191 vs. 236) and deaths (350 vs. 76). Indeed, there were twice as many deaths in the lowest coenzyme Q_{10} tertile in our study as in the whole cohort studied by Molyneux et al. (18). That study stored plasma for up to 5.4 years before measurement of coenzyme Q_{10}. Concentration of coenzyme Q_{10} falls with storage, and that may explain the lower levels of coenzyme Q_{10} in the study of Molyneux et al. (12,18). Another important difference was in the multivariable analyses performed. Molyneux et al. (18) adjusted for 5 baseline variables in addition to coenzyme Q_{10}. We adjusted for 14 previously identified independent predictors of outcome (21). Coenzyme Q_{10} may have been an independent predictor of death in the study of Molyneux et al. (18) only because they did not fully adjust for differences in other prognostic variables between patients with a lower or higher coenzyme Q_{10} concentration. For example, when we repeated the limited Cox proportional hazards analysis described by Molyneux et al. (18) using median coenzyme Q_{10} concentration, we found coenzyme Q_{10} to be an independent predictor of mortality ($p = 0.048$; data not shown), although this was not the case after fuller adjustment (Table 6).

We also examined composites of fatal and nonfatal events, including that of death or hospital admission for heart failure, in view of prior concerns that low coenzyme Q_{10} might lead to worsening heart failure. As with mortality, coenzyme Q_{10} concentration was not an independent predictor of any of these other outcomes.

As expected, treatment with rosuvastatin reduced serum coenzyme Q_{10} concentration. In view of prior concerns that statin-induced reductions in coenzyme Q_{10} might be harmful in heart failure, we examined the effect of rosuvastatin on clinical outcomes according to baseline serum coenzyme Q_{10} concentration. Tertile analysis showed a numerically higher event rate in statin-treated compared with placebo-treated patients for all outcomes in patients with the lowest coenzyme Q_{10} concentration. In the other 2 coenzyme Q_{10} tertiles, rosuvastatin treatment was associated with a numerically lower event rate than placebo treatment. None of the tests for interaction between baseline coenzyme Q_{10} concentration tertile and treatment was statistically significant, although this is a test with low power and the p values were borderline, ranging from 0.14 to 0.26.

Although we cannot completely exclude an adverse effect of statin treatment in heart failure patients with a low coenzyme Q_{10} concentration, we believe that several observations make such an effect unlikely. First, we could not demonstrate that low coenzyme Q_{10} concentration, whether "spontaneous" or statin-induced, was independently associated with worse outcome in the multivariable analyses described above. Second, close inspection of outcomes in the lowest coenzyme Q_{10} tertile did not show any evidence of increased risk of the "expected" clinical events, namely, death due to heart failure or heart failure hospitalization in the rosuvastatin group compared with the placebo group. In addition, there was no worsening of NYHA functional class in rosuvastatin-treated patients compared with placebo-treated patients in the lowest coenzyme Q_{10} tertile. Indeed, if there was an excess of any type of event, it was myocardial infarction and noncardiovascular death. Third, we did not find any evidence of the most predicted coenzyme Q_{10}-related effect of statins, namely, muscle symptoms or increased creatine kinase. Furthermore, there were no more discontinuations of rosuvastatin than placebo in the lowest coenzyme Q_{10} tertile.

Conclusions

Although a low serum coenzyme Q_{10} concentration is associated with worse outcomes in heart failure, that is because it is a marker of more advanced disease and is not an independent predictor of prognosis. Statin treatment reduced serum coenzyme Q_{10} concentration, but even in patients with a low starting coenzyme Q_{10}, statin therapy was not associated with a significantly worse outcome, although we had limited statistical power to completely exclude this possibility. Although we cannot completely exclude an interaction between coenzyme Q_{10} concentration

and the effect of statins, no expected or consistent pattern of harm was observed.

Reprint requests and correspondence: Prof. John J. V. McMurray, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, United Kingdom. E-mail: john.mcmurray@glasgow.ac.uk.

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