The effects of ω3 fatty acids and coenzyme Q_{10} on blood pressure and heart rate in chronic kidney disease: a randomized controlled trial

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Background and objective **Chronic kidney disease (CKD) associates with increased cardiovascular disease (CVD) risk. Hypertension is a major determinant of progression of CKD. Omega-3 fatty acids (ω3FA) protect against CVD via improvements in blood pressure, heart rate, vascular reactivity and serum lipids. Coenzyme Q_{10} (CoQ) may improve blood pressure and vascular function. This study determined whether ω3FA and CoQ have independent or additive effects in improving the cardiovascular profile, particularly blood pressure and heart rate, in nondiabetic patients with CKD stages 3–4.**

Methods **In a double-blind, placebo-controlled intervention, patients were randomized to either ω3FA (4 g), CoQ (200 mg), both supplements or control (4 g), daily for 8 weeks.**

Results **Eighty-five patients aged 56.5 ± 1.4 years; BMI 27.3 ± 0.5 kg/m^2; supine blood pressure 125.0/72.3 mmHg; and glomerular filtration rate 35.8 ± 1.2 ml/min/1.73 m^2, were randomized. Seventy-four completed the study. ω3FA, but not CoQ, reduced 24-h ambulatory heart rate ($P<0.0001$) and blood pressure ($P<0.0001$). Main effects for ω3FA on 24-h measurements were −3.3 ± 0.7/ −2.9 ± 0.5 mmHg and −4.0 ± 0.5 bpm. Postintervention blood pressure showed significant interactions between treatments. ω3FA reduced triglycerides 24% ($P<0.001$). There were no changes in glomerular filtration rate, urinary albumin or total protein excretion, cholesterol, HDL-cholesterol (C), LDL-C, glucose, insulin, or high-sensitivity C-reactive protein.**

Conclusion **This study has shown that ω3FA reduce blood pressure, heart rate and triglycerides in patients with CKD. CoQ had no independent effect on blood pressure but increased heart rate. These results show that ω3FA lower blood pressure and may reduce cardiovascular risk in nondiabetic patients with moderate-to-severe CKD.**
J Hypertens **27:1863–1872**

Journal of Hypertension 2009, **27**:1863–1872

Keywords: blood pressure, chronic kidney disease, coenzyme Q_{10}, heart rate, omega-3 fatty acids

Abbreviations: C, cholesterol; CKD, Chronic kidney disease; CoQ, Coenzyme Q_{10}; CRP, C-reactive protein; DHA, docosahexaenoic acid; GFR, glomerular filtration rate; EPA, eicosapentaenoic acid; ω3FA, ω3 fatty acids

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Received 2 January 2009 **Accepted** 13 May 2009

Introduction

Chronic kidney disease (CKD) is associated with an increased prevalence in all-cause mortality, cardiovascular events and hospitalization, independent of known risk factors and a history of cardiovascular disease (CVD) [1–3]. There is a two- to 50-fold increased risk of CVD in patients with CKD, with about 50% of the mortality of patients with end-stage renal failure on dialysis attributed to CVD [1,4].

Multiple modifiable risk factors contribute to the increased risk of CVD in CKD. These include hypertension, endothelial dysfunction, left ventricular hypertrophy (LVH), arterial stiffness, an atherogenic lipid profile, insulin resistance, hyperoxidative stress, inflammation, anaemia, derangements in calcium–phosphate homeostasis and enhanced coagulability [1,2,5].

Hypertension is both a cause and a consequence of renal disease and, irrespective of cause, hypertension is a major determinant of progression of renal disease and the risk of end-stage renal failure [5,6]. Evidence suggests that blood pressure (BP) control will retard development and/or progression of renal failure [6]. Consequently, the WHO-International Society of Hypertension Guidelines advocate an aggressive BP-lowering strategy should be adopted in patients with CKD [7]. Endothelial dysfunction is one of the main functional arterial abnormalities detected in both the conduit and resistance vessels of patients with CKD in the absence of overt atherosclerotic

0263-6352 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e32832e1bd9

coronary artery disease [8]. Inflammation, insulin resistance and hypertension were independently associated with impaired vascular function in patients with CKD [8].

Abnormalities of lipid metabolism in patients with CKD include hypertriglyceridaemia, particularly when glomerular filtration rate (GFR) is reduced, normal or increased total cholesterol and LDL-C, and reduced HDL-C [9]. Lipid abnormalities may be a consequence of, as well as being a factor that contributes to, the progression of renal disease.

Patients with CKD are often on multiple-drug therapies to achieve control of BP, dyslipidaemia and mineral disorders. Complementing drug treatment of CKD with specific nutritional measures may have the benefit of not only reducing the need for drug therapies and symptoms of CKD, but also ameliorating associated CVD complications. In this regard, there is considerable evidence that omega-3 fatty acids (ω3FA), specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are protective against CVD [10,11]. ω3FA have multiple biological effects, including benefits on BP and vascular reactivity, cardiac function, lipid metabolism, platelet and leukocyte function, cytokine production and oxidative stress [11]. Supplementation with coenzyme Q_{10} (CoQ) has been shown to improve BP [12] and endothelial dysfunction of the brachial artery in type 2 diabetes mellitus [13], as well as enhance the benefit of peroxisome proliferator-activated receptor-α agonists on the vascular wall [14].

To our knowledge, the effectiveness of ω3FA and CoQ on cardiovascular risk factors has not been examined in patients with CKD. The aim of this study was to examine the potential independent and additive effects of ω3FA and CoQ on BP, vascular function and dyslipidaemia in nondiabetic patients with moderate-to-severe CKD. Secondary endpoints included heart rate (HR), glucose–insulin response and proteinuria.

Methods

Study population

Nondiabetic men and women with chronic renal impairment, aged 25–75 years, were recruited from the renal units of Royal Perth, Sir Charles Gairdner and Fremantle Hospitals, in Perth, Western Australia. All participants had estimated (e)GFR [15] greater than 15 and less than 60 ml/min/1.73 m^2 and serum creatinine less than 350 μmol/l.

Patients were nonsmokers and were excluded if they had angina pectoris; major surgery, a cardiovascular event or diagnosis of symptoms within the last 3 months; BP greater than 170/100 mmHg; diabetes; liver disease; nephrotic syndrome (proteinuria >3 g/day or protein/creatinine ratio >300 mg/mmol); or haemoglobin less than 110 g/l. Patients were excluded if they regularly took nonsteroidal anti-inflammatory or immunosuppressive drug therapy, nitrates (including Viagra); ate more than one fish meal per week or regularly took fish oil supplements; or if they consumed an average of more than four standard alcoholic drinks per day. Patients were not excluded if they received antihypertensive or lipid-lowering medication. The study was approved by the ethics committees of the three hospitals. All patients gave informed written consent. The study was registered with the Australian Clinical Trials Register (ACTRN012605000088640).

Dietary education and intervention

During a 3-week familiarization period, participants continued their usual diet and alcohol intake. After collection of baseline measurements, participants were stratified by age and BMI, and randomized by the statistician to one of four study groups: ω3FA (4 g daily), CoQ (200 mg daily), the two treatments combined, or control (4 g daily olive oil) using computer-generated random numbers. The allocation sequence was concealed using numbered containers until interventions were assigned at the time of enrolment by study personnel not involved in the process of randomization. The intervention was double-blind, placebo-controlled and of 8 weeks duration.

Omega-3 fatty acid capsules (Omacor, Solvay Pharmaceuticals, Pymble, NSW, Australia) contained 460 mg EPA, 38 mg docosapentaenoic acid and 380 mg DHA, and 4.1 mg α-tocopherol, per 1000 mg capsule. Control capsules (1000 mg) contained olive oil (Cardinal Health Australia, Braeside, Victoria, Australia). CoQ and placebo capsules (50 mg) were provided by Blackmores Australia (Balgowlah, NSW, Australia). Capsules were taken as 2×1 g ω3FA or control, and 2×50 mg CoQ or placebo, b.i.d. with meals.

Volunteers were asked to maintain their usual diets, medications, alcohol intake and physical activity and not to alter their lifestyle, during the intervention. At baseline, patients completed a lifestyle questionnaire providing information on alcohol and beverage intake, physical activity and use of prescribed or nonprescribed medication. All measurements were performed at baseline and during the last week of intervention. Patients were contacted by telephone on a regular basis. Compliance with the supplements was monitored by capsule count and measurement of plasma fatty acids and plasma CoQ.

Diet, lifestyle assessment and anthropometry

At 2-weekly intervals, a dietician interviewed the volunteers to ensure usual eating habits were maintained; alcohol intake, physical activity and use of medications were monitored using 7-day retrospective diaries; and weight was measured using an electronic scale with the patient without shoes and wearing light clothing and height using a stadiometer.

Ambulatory blood pressure monitoring

Ambulatory blood pressure and HR were monitored over 24 h at baseline and at the end of intervention using the SpaceLabs Monitor (Model 90217, SpaceLabs Medical Inc, Issaquah, Washington, USA) fitted by a trained nurse who instructed the patient in its use. The recorder was preset to record BP and HR every 20 min during waking hours and every 30 min during sleep [16–18].

Biochemical measurements

Overnight fasting venous blood was collected after patients had rested in a recumbent position for 10 min. Full blood counts and haemoglobin were measured using the Technicon H1 Analyser (Bayer Diagnostics, Sydney, Australia). Serum lipids, glucose, insulin and high-sensitivity C-reactive protein (CRP) were measured as previously described [19,20]. Plasma CoQ was measured by reverse-phase high-performance liquid chromatography using electrochemical detection [21]. Serum for insulin, lipid and lipoprotein analyses was stored at −80°C. Platelet phospholipid fatty acids were measured by gas chromatography as previously described [19]. Samples from baseline and end of intervention were measured in a single assay to minimize interassay variation. Aliquots from 24-h urines collected at baseline and end of intervention were frozen at −80°C and thawed immediately prior to analysis.

Vascular function studies and echocardiography

Reactive hyperaemia

Forearm circulation: Forearm blood flow was measured in the left arm by venous occlusion, strain-gauge plethysmography after patients were rested for 10 min in a supine position [22].

Brachial artery: Patients rested supine for 10 min prior to the procedure. The brachial artery was imaged 5–10 cm above the antecubital crease in ultrasound B-mode using a 12 MHz linear array transducer fixed in position by a stereotactic clamp and connected to an Accuson Aspen Ultrasound System [23,24]. Images were stored digitally and arterial diameter was quantitated using a computerized edge-detection algorithm [23] and percentage response calculated.

Arterial compliance

Systemic arterial compliance was measured using an HDI-PulseWave CR-2000 Cardiovascular Profiling System (Hypertension Diagnostics Inc, Eagan, Minnesota, USA) [8]. The radial artery waveform was recorded noninvasively using tonometry and computerized analysis of the diastolic decay curve generated estimates of arterial compliance: C1, a measure of large artery compliance (capacitance) and C2, a measure of small artery compliance (reflectance).

Echocardiography

Transthoracic echocardiography was performed by Echo Services at Hollywood Private Hospital, Perth, using an Acuson Sequoia Ultrasound System (Siemens AG, Munich, Germany) with digital storage (KinetDx; Siemens AG). A combination of standard 2D echo, spectral Doppler, colour M-mode and tissue Doppler measurements was carried out [25]. Diastolic dysfunction employed an age-corrected and modified Garcia protocol when at least three of seven parameters are abnormal. The primary endpoint was continuous measures of diastolic dysfunction, as measured by the E/E', using tissue Doppler imaging and the robust categorical definition based on the measurement of several diastolic parameters.

Statistical analysis

Sample size was based on data from our studies of ω3FA and BP [16–18]; serum lipids [18,19]; and vascular function [26]. Fifteen patients per group (30 per intervention arm) gave an 80% power to detect a 3 mmHg difference in ambulatory systolic blood pressure (SBP), at $\alpha = 0.05$. The study had more than 80% power to detect main effect changes of 20% in HDL_2-C, 20% in triglycerides and more than 20% in flow-mediated dilation. Postintervention data were analysed using SPSS15.0 (SPSS Inc., Chicago, Illinois, USA) or SAS 9.0 (SAS Inc, USA) with general linear models adjusting for baseline values and assessing main and interactive effects of ω3FA and CoQ. Analyses included only participants who completed the trial. Baseline measures were compared by one-way analysis of variance. In the presence of statistically significant interactions, analysis was carried out by treatment group. Significance levels were adjusted for multiple comparisons by the Tukey test. Values are means (SEM) or geometric mean [95% confidence interval (CI)].

Results

Study population

The flow of participants through the study is shown in Fig. 1. At baseline there were 63 men and 22 women of mean age 56.5 ± 1.4 years, BMI 27.3 ± 0.5 kg/m^2 and clinic BP $125.0 \pm 1.7/72.3 \pm 0.9$ mmHg. Mean eGFR was 35.8 ± 1.2 ml/min/1.73 m^2 (range 17.3–58.1 ml/min/1.73 m^2) (stages 3–4 CKD [15]). Baseline characteristics of the patients who completed the trial confirmed the groups were well matched (Tables 1–4).

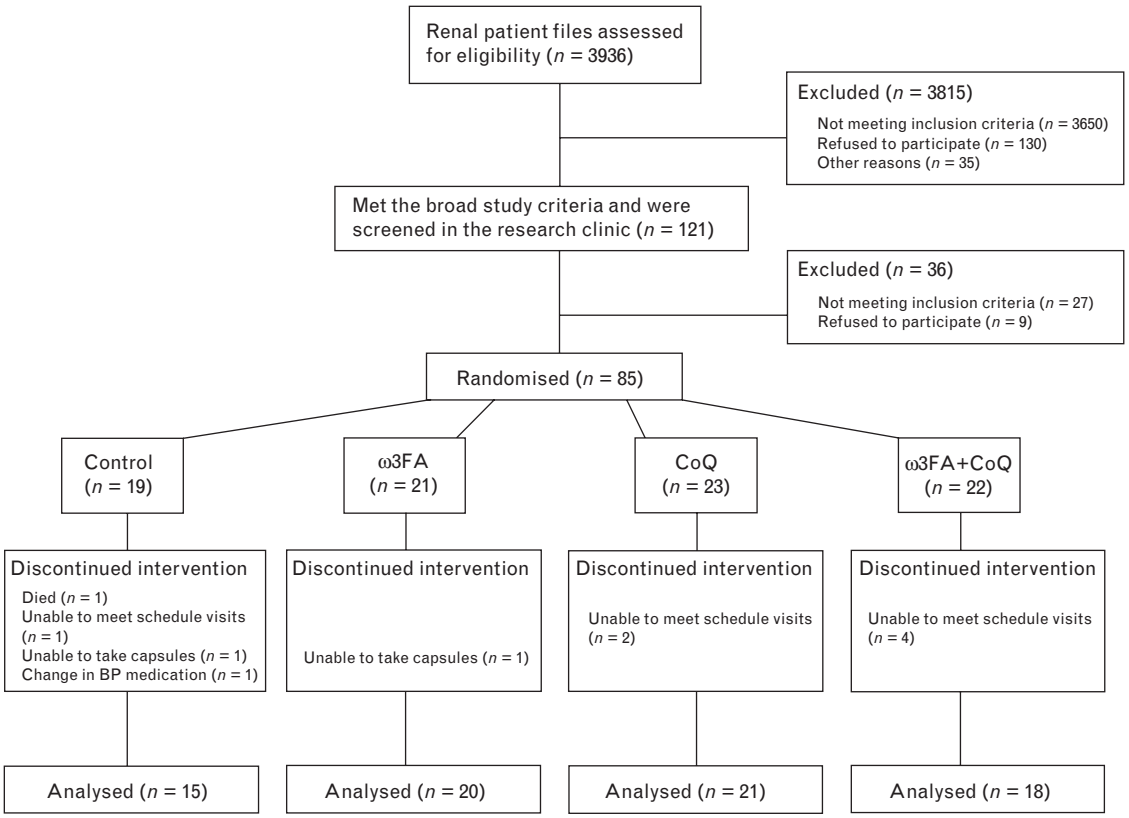
Diet, lifestyle, serum and urinary analytes

Adherence to the interventions was confirmed by capsule counts. There were no changes in medications, energy, macronutrient and micronutrient intake in the four groups during the intervention. There were no significant differences between groups at baseline in bodyweight, eGFR, or serum or urinary analytes, and no significant changes during the intervention (Table 2).

Platelet phospholipid fatty acids

Baseline platelet phospholipid fatty acids were not different between the groups. Changes in long-chain ω6FA and ω3FA confirmed compliance with capsule intake (Fig. 2).

Fig. 1



The flow of participants through the study. BP, blood pressure; CoQ, coenzyme Q_{10}.

Table 1 Baseline characteristics of participants that completed the trial

	Control ($n=15$)	ω3FA ($n=20$)	CoQ ($n=21$)	ω3FA + CoQ ($n=18$)
Men/women (*n*/*n*)	8/7	12/8	17/4	17/1
Age (years)	58.6 ± 2.6	53.3 ± 3.2	55.4 ± 2.7	56.9 ± 3.9
BMI (kg/m^2)	27.6 ± 1.7	26.7 ± 1.2	26.6 ± 0.9	27.9 ± 0.8
Supine SBP (mmHg)[a]	127.7 ± 4.1	126.3 ± 3.4	122.6 ± 3.3	124.5 ± 4.6
Supine DBP (mmHg)[a]	71.9 ± 2.6	75.0 ± 1.6	72.9 ± 1.6	68.7 ± 2.4
Haemoglobin (g/l)	127.4 ± 5.4	134.2 ± 3.7	135.5 ± 2.7	130.3 ± 3.4
Serum γ-glutamyl transferase (U/l)	18.6 ± 1.1	24.5 ± 1.1	24.2 ± 1.2	28.5 ± 1.1
Serum uric acid (mmol/l)	0.44 ± 0.03	0.47 ± 0.03	0.48 ± 0.03	0.49 ± 0.02
Serum urea (mmol/l)	12.7 ± 1.1	14.8 ± 1.6	12.6 ± 1.5	14.7 ± 1.1
Renal diagnosis				
Polycystic kidney disease	4	5	2	0
Glomerulonephritis	5	4	7	4
Hypertensive nephrosclerosis/renovascular	1	0	2	3
Reflux nephropathy	0	1	2	2
Other	5	10	8	9
Antihypertensive medication (*n*)				
ACE inhibitors	11	12	16	16
AII blockers	4	9	11	6
β-Blockers	2	5	4	5
Ca^{2+} channel blocker	7	7	6	6
Diuretics	3	7	6	7
Other	5	2	5	5
Antihypertensive/patient (*n*)				
1	3	4	6	4
2	6	10	7	4
3	4	4	5	6
≥4	2	2	3	4
Lipid-lowering medication (*n*)				
Statins	10	10	11	13

Values are mean ± SEM. [a]Average of 10 readings in the clinic using a Dinamap 1846 SX/P blood pressure monitor. Baseline measures were compared by one-way analysis of variance and were not significantly different.

Table 2 Body weight, GFR, serum and 24-h urinary analytes at baseline and postintervention

	Control ($n=15$)	ω3FA ($n=20$)	CoQ ($n=21$)	ω3FA + CoQ ($n=18$)
Body weight (kg)				
Baseline	79.9 ± 5.0	78.0 ± 4.0	78.9 ± 2.8	83.2 ± 2.3
Postintervention	80.5 ± 5.1	79.0 ± 4.0	79.2 ± 2.7	83.9 ± 2.3
eGFR (ml/min/1.73m^2)[a]				
Baseline	34.6 ± 2.3	36.4 ± 2.8	38.8 ± 2.2	30.5 ± 2.2
Postintervention	33.3 ± 2.1	36.7 ± 2.8	39.4 ± 2.4	30.6 ± 2.5
Serum creatinine (μmol/l)				
Baseline	177.0 ± 13.5	189.8 ± 16.5	174.6 ± 11.7	223.2 ± 14.0
Postintervention	180.6 ± 12.8	190.1 ± 17.4	170.0 ± 11.2	225.4 ± 15.2
Serum calcium/phosphate				
Baseline	2.9 ± 0.1	2.9 ± 0.1	3.1 ± 0.1	2.9 ± 0.1
Postintervention	3.0 ± 0.2	3.0 ± 0.2	2.9 ± 0.1	3.0 ± 0.1
Urinary Na^+ (mmol/24h)				
Baseline	173.7 ± 13.3	165.4 ± 11.6	171.1 ± 13.7	185.1 ± 11.6
Postintervention	164.3 ± 11.7	160.0 ± 14.7	145.7 ± 8.5	184.4 ± 17.5
Urinary K^+ (mmol/24 h)				
Baseline	75.7 ± 5.7	70.7 ± 4.4	74.5 ± 4.4	71.7 ± 5.0
Postintervention	71.9 ± 3.6	64.9 ± 3.8	67.4 ± 3.1	66.2 ± 4.8
Urinary protein (g/24 h)				
Baseline	0.61 ± 0.20	0.52 ± 0.15	0.79 ± 0.24	1.09 ± 0.30
Postintervention	0.73 ± 0.26	0.56 ± 0.19	0.81 ± 0.28	1.12 ± 0.31
Urinary albumin (mg/24 h)				
Baseline	313 ± 129	331 ± 127	576 ± 204	744 ± 228
Postintervention	416 ± 190	367 ± 154	576 ± 212	802 ± 262
Urinary protein/creatinine (mg/mmol)				
Baseline	50.4 ± 15.0	39.5 ± 11.2	53.4 ± 13.3	85.5 ± 21.4
Postintervention	58.5 ± 20.5	45.3 ± 15.4	58.9 ± 18.5	90.7 ± 24.3

Values expressed as mean ± SEM. ω3FA, omega-3 fatty acid; ANOVA, analysis of variance; CoQ, coenzyme Q_{10}; GFR, glomerular filtration rate. [a] Calculated using the Modification of Diet in Renal Disease (MDRD) Study Eq. [15]. Baseline measures were compared by one-way ANOVA and were not significantly different between groups. Using general linear model analysis, there were no significant treatment effects on postintervention values after adjustment for baseline value.

Table 3 Serum lipids, glucose, insulin and C-reactive protein at baseline and postintervention

					Main effects (*P*-value)	
	Control ($n=15$)	ω3FA ($n=20$)	CoQ ($n=21$)	ω3FA + CoQ ($n=18$)	ω3FA	CoQ
Cholesterol (mmol/l)						
Baseline	4.6 (4.3, 5.0)	5.0 (4.6, 5.4)	5.2 (4.7, 5.6)	4.3 (3.8, 4.8)	−0.1 (−0.3, 0.2)	−0.2 (−0.4, 0.1)
Postintervention	4.8 (4.4, 5.1)	5.0 (4.5, 5.5)	4.9 (4.4, 5.5)	4.2 (3.5, 4.8)	($P=0.721$)	($P=0.056$)
HDL-C (mmol/l)						
Baseline	1.34 (1.11, 1.56)	1.27 (1.14, 1.41)	1.27 (1.05, 1.49)	1.08 (0.98, 1.18)	0.03 (−0.06, 0.11)	−0.09 (−0.01, −0.18)
Postintervention	1.41 (1.13, 1.70)	1.32 (1.13, 1.51)	1.23 (1.00, 1.47)	1.08 (0.96, 1.21)	($P=0.547$)	($P=0.043$)
HDL_2-C (mmol/l)						
Baseline	0.80 (0.66, 0.94)	0.77 (0.65, 0.89)	0.72 (0.59, 0.85)	0.74 (0.65, 0.84)	−0.04 (−0.12, 0.04)	−0.02 (−0.10, 0.06)
Postintervention	0.81 (0.67, 0.95)	0.70 (0.60, 0.81)	0.69 (0.50, 0.88)	0.70 (0.61, 0.80)	($P=0.337$)	($P=0.658$)
HDL_3-C (mmol/l)						
Baseline	0.54 (0.35, 0.72)	0.51 (0.39, 0.62)	0.53 (0.33, 0.74)	0.34 (0.20, 0.47)	0.03 (−0.06, 0.13)	−0.08 (−0.18, 0.01)
Postintervention	0.61 (0.36, 0.85)	0.62 (0.48, 0.75)	0.54 (0.36, 0.73)	0.34 (0.24, 0.51)	($P=0.517$)	($P=0.077$)
LDL-C (mmol/l)						
Baseline	2.6 (2.1, 3.0)	2.9 (2.6, 3.3)	3.2 (2.7, 3.6)	2.4 (1.9, 2.8)	0.1 (−0.1, 0.3)	−0.1 (−0.3, 0.1)
Postintervention	2.6 (2.2, 3.0)	3.0 (2.6, 3.5)	3.0 (2.4, 3.5)	2.4 (1.8, 3.0)	($P=0.292$)	($P=0.318$)
Triglycerides (mmol/l)[a]						
Baseline	1.4 (1.2, 1.8)	1.6 (1.3, 2.1)	1.7 (1.3, 2.2)	1.8 (1.4, 2.1)	−0.4 (−0.6, −0.2)	0.1 (−0.1, 0.3)
Postintervention	1.5 (1.2, 1.9)	1.2 (1.0, 1.5)	1.6 (1.3, 2.0)	1.4 (1.1, 1.7)	($P<0.001$)	($P=0.691$)
Glucose (mmol/l)						
Baseline	4.9 (4.6, 5.2)	4.8 (4.4, 5.1)	4.7 (4.3, 5.1)	5.0 (4.7, 5.3)	0.1 (−0.1, 0.3)	0.1 (−0.1, 0.3)
Postintervention	4.9 (4.6, 5.2)	5.0 (4.6, 5.4)	4.9 (4.6, 5.3)	5.1 (4.8, 5.4)	($P=0.462$)	($P=0.518$)
Insulin (mU/l)[a]						
Baseline	9.9 (7.4, 13.3)	10.4 (7.8, 13.8)	10.0 (7.5, 13.3)	13.3 (10.5, 17.0)	0.8 (−1.3, 2.9)	0.6 (−1.6, 2.7)
Postintervention	9.8 (7.3, 13.2)	11.6 (8.6, 15.5)	11.1 (8.3, 14.9)	14.2 (11.0, 18.4)	($P=0.445$)	($P=0.525$)
HOMA-IR						
Baseline	2.2 (1.6, 2.9)	2.2 (1.6, 3.0)	2.1 (1.5, 2.8)	3.0 (2.3, 3.8)	0.6 (−0.1, 1.4)	0.5 (−0.3, 1.2)
Postintervention	2.1 (1.5, 2.9)	2.5 (1.8, 2.9)	2.4 (1.8, 3.3)	3.2 (2.4, 4.2)	($P=0.400$)	($P=0.450$)
C-reactive protein (mg/l)[a]						
Baseline	1.56 (0.87, 2.81)	1.74 (0.99, 3.06)	1.46 (0.99, 2.14)	2.23 (1.51, 3.29)	0.01 (−0.15, 0.16)	−0.03 (−0.19, 0.11)
Postintervention	1.79 (0.87, 3.66)	1.80 (1.02, 3.17)	1.46 (0.99, 2.17)	2.25 (1.38, 3.69)	($P=0.936$)	($P=0.656$)

Values expressed as mean (95% confidence interval). ω3FA, omega-3 fatty acid; ANOVA, analysis of variance; CoQ, coenzyme Q_{10}; HOMA-R, homeostasis model assessment index ratio. [a] Geometric mean (95% confidence interval). Baseline measures were compared by one-way ANOVA and were not significantly different between groups. General linear model analysis tested for main effects and interactions on postintervention values adjusted for baseline value, and for lipids, treatment with lipid-lowering drugs.

Table 4 Mean 24-h, awake and asleep blood pressure at baseline and postintervention

					ANOVA at baseline (*P*-value) Main Effects (*P*-value)		
	Control ($n=15$)	ω3FA ($n=20$)	CoQ ($n=21$)	ω3FA + CoQ ($n=18$)	ω3FA	CoQ	Interaction (*P*-value)
24-h SBP (mmHg)							
Baseline	117.2 ± 1.9	120.4 ± 2.1	119.0 ± 2.3	119.2 ± 2.1	NS		
Postintervention	118.6 ± 0.8	116.9 ± 0.7	120.8 ± 0.7†,††	115.9 ± 0.7*	−3.3 ± 0.7 (<0.0001)	0.6 ± 0.7 (NS)	0.0274
24-h DBP (mmHg)							
Baseline	72.2 ± 2.0	74.8 ± 1.7	73.7 ± 1.5	69.5 ± 2.0	NS		
Postintervention	72.8 ± 0.6	71.7 ± 0.5	74.2 ± 0.5†,††	69.4 ± 0.5***	−2.9 ± 0.5 (<0.0001)	−0.5 ± 0.5 (NS)	0.0002
Awake SBP (mmHg)							
Baseline	122.1 ± 2.1	126.5 ± 2.2	123.7 ± 2.2	122.3 ± 1.8	NS		
Postintervention	122.8 ± 1.0	121.1 ± 0.9	124.9 ± 0.8†,††	121.3 ± 0.9	−2.6 ± 0.9 (0.003)	1.1 ± 0.9 (NS)	NS
Awake DBP (mmHg)							
Baseline	76.6 ± 2.2	80.2 ± 1.8	78.0 ± 1.6	72.7 ± 2.1	NS		
Postintervention	76.7 ± 0.7	75.8 ± 0.6	77.7 ± 0.6††	73.7 ± 0.6**	−2.4 ± 0.6 (0.0001)	−0.5 ± 0.6 (NS)	0.0139
Asleep SBP (mmHg)							
Baseline	108.7 ± 2.3	108.8 ± 2.3	111.0 ± 3.4	112.9 ± 3.2	NS		
Postintervention	110.1 ± 1.3	109.5 ± 1.2	113.2 ± 1.1†,††	105.2 ± 1.2*	−4.3 ± 1.2 (0.0003)	−0.6 ± 1.2 (NS)	0.0018
Asleep DBP (mmHg)							
Baseline	64.4 ± 2.0	64.5 ± 1.7	66.4 ± 1.6	63.3 ± 2.2	NS		
Postintervention	65.3 ± 0.9	64.1 ± 0.8	67.9 ± 0.8†,††	60.6 ± 0.8***	−4.3 ± 0.8 (<0.0001)	−0.5 ± 0.8 (NS)	0.0003

Values expressed as mean ± SEM. Postintervention data are adjusted for baseline values. Baseline measures were compared by one-way ANOVA. General linear model analysis tested for main effects and interactions on postintervention values adjusted for baseline value. Significance levels were adjusted for multiple comparisons by the Tukey test. ω3FA, omega-3 fatty acid; ANOVA, analysis of variance; CoQ, coenzyme Q_{10}; NS, not significant. $^{*}P<0.05$. $^{**}P<0.01$. $^{***}P<0.001$ denotes a significance vs. control. $^{\dagger}P<0.05$ denotes a significance vs. ω3FA group. $^{\dagger\dagger}P<0.001$ denotes a significance vs. ω3FA + CoQ group.

EPA and DHA were increased ($P<0.0001$) in the ω3FA and ω3FA ± CoQ groups, relative to the two other groups. 22:5ω3 was increased in the ω3FA group ($P<0.05$) relative to the control group. 20:4ω6 decreased, albeit nonsignificantly, in the two groups taking ω3FA. There were no significant changes in other fatty acids or in fatty acids in the control group.

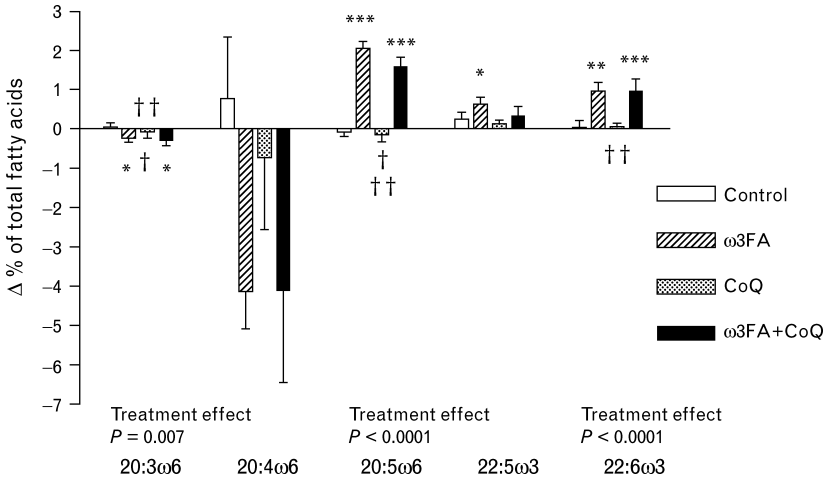
Plasma coenzyme Q_{10}

Coenzyme Q_{10} supplementation increased plasma CoQ concentration in the CoQ ($P<0.0001$) and ω3FA ± CoQ ($P<0.0001$) groups, relative to the two other groups (Fig. 3). The increase in plasma CoQ in the ω3FA ± CoQ CoQ group was attenuated ($P=0.005$) relative to the CoQ group.

Serum lipids and C-reactive protein

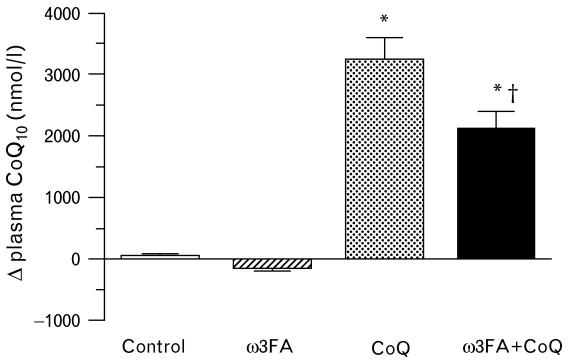
Baseline serum lipids and lipoproteins were not significantly different between groups (Table 3). There were no significant changes in total cholesterol, LDL-C, HDL-C or HDL subfractions following ω3FA. Triglycerides were reduced by 24% in the ω3FA and ω3FA ± CoQ

Fig. 2



Changes in percentage platelet phospholipid fatty acids. General linear model analysis tested for treatment effects on postintervention values adjusted for baseline value. Post-hoc comparisons used the Tukey test. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$ denotes a significance vs. control; $^{\dagger}P<0.05$ denotes a significance vs. ω3FA group; $^{\dagger\dagger}P<0.05$ denotes a significance vs. ω3FA ± CoQ group. ω3FA, omega-3 fatty acid; CoQ, coenzyme Q_{10}.

Fig. 3



Changes in plasma CoQ_{10}. General linear model analysis tested for treatment effects on postintervention values adjusted for baseline value. Treatment effect $P < 0.0001$. Post-hoc comparisons used the Tukey test. $^{*}P < 0.0001$ denotes a significance vs. control and ω3FA groups; $^{\dagger}P = 0.005$ denotes a significance vs. CoQ. ω3FA, omega-3 fatty acid; CoQ, coenzyme Q_{10}.

($P < 0.001$ for main effect) groups. CoQ did not affect lipids other than for a small reduction in HDL-C ($P = 0.043$). CRP was not different between groups at baseline or postintervention (Table 3).

Serum glucose and insulin

At baseline there were no differences between groups in fasting blood glucose, insulin or insulin sensitivity homeostasis model assessment (HOMA) [HOMA equation] (Table 3). Neither ω3FA nor CoQ significantly altered these variables.

Microalbuminuria/proteinuria

At baseline, mean urinary albumin excretion was 497 mg/24 h. The mean urine albumin/creatinine ratio was 36.9 mg/mmol. All patients had a urine albumin/creatinine ratio at least 2.5 mg/mmol for men and 3.5 mg/mmol for women, consistent with microalbuminuria as defined by the UK Renal Association 2005 Chronic Kidney Disease guidelines [27]. In addition, patients had a mean urinary protein/creatinine ratio of 56.6 mg/mmol indicative of the presence of proteinuria (i.e. urine protein/creatinine ratio ≥45 mg/mmol) [27]. There were no significant differences at baseline between groups in 24-h albuminuria or total protein and these were unchanged after intervention (Table 2).

Ambulatory blood pressure and heart rate

There were no significant differences in mean BP or HR between the groups at baseline (Tables 4 and 5). In main effects analysis, ω3FA, but not CoQ, significantly reduced 24-h SBP ($P < 0.0001$) and diastolic blood pressure (DBP) ($P < 0.0001$). Awake BP was reduced (SBP, $P < 0.003$; DBP, $P = 0.0001$), but the greatest fall occurred in asleep BP (SBP, $P = 0.0003$; DBP, $P < 0.0001$).

Blood pressure changes showed significant treatment interactions. Analyses on baseline-adjusted postintervention BP showed significant treatment effects. Relative to the control group, there were reductions in postintervention 24-h ($-1.7 \pm 1.1/-1.0 \pm 0.7$ mmHg), awake ($-1.7 \pm 1.3/-0.8 \pm 0.9$ mmHg) and asleep ($-0.6 \pm 1.7/-1.2 \pm 1.2$ mmHg) SBP and DBP in the ω3FA group. In contrast, CoQ supplementation alone resulted in a small nonsignificant increase in 24-h, awake and asleep SBP and DBP relative to the control group. In the ω3FA ± CoQ group, 24-h ($-2.7 \pm 1.1/-3.4 \pm 0.7$ mmHg, $P < 0.05$), awake ($-1.5 \pm 1.3/-2.9 \pm 0.9$ mmHg, $P < 0.05$), and asleep ($-4.9 \pm 1.7/-4.8 \pm 1.2$ mmHg, $P < 0.05$) SBP and DBP were significantly reduced. The significant fall in 24-h SBP in the ω3FA ± CoQ group was due to a greater reduction in asleep BP, a finding that is similar to that observed in main effects analysis. However, the fall in 24-h DBP in the ω3FA ± CoQ group was attributable to reductions in both awake and asleep DBP. SBP and DBP in the CoQ group were significantly higher than in the ω3FA or ω3FA ± CoQ groups.

In main effects analysis, ω3FA, but not CoQ, significantly reduced HR during 24-h ($P < 0.0001$), awake ($P < 0.0001$)

Table 5 Mean 24-h, awake and asleep heart rate at baseline and postintervention

					ANOVA at baseline (*P*-value) Main Effects (*P*-value)		
	Control ($n = 15$)	ω3FA ($n = 20$)	CoQ ($n = 21$)	ω3FA ± CoQ ($n = 18$)	ω3FA	CoQ	Interaction (*P*-value)
24-h HR (bpm)							
Baseline	73.0 ± 2.1	66.9 ± 1.5	66.6 ± 2.1	69.3 ± 2.2	NS		
Postintervention	70.5 ± 0.6	65.6 ± 0.5***	70.8 ± 0.5†,††	67.6 ± 0.5***	−4.0 ± 0.5 (<0.0001)	1.1 ± 0.5 (0.030)	0.0978
Awake HR (bpm)							
Baseline	77.1 ± 2.4	70.2 ± 1.9	70.1 ± 2.5	72.7 ± 2.7	NS		
Postintervention	74.3 ± 0.8	68.5 ± 0.7***	74.1 ± 0.6†,††	71.0 ± 0.7***	−4.4 ± 0.7 (<0.0001)	1.2 ± 0.7 (NS)	0.0551
Asleep HR (bpm)							
Baseline	65.4 ± 2.1	60.7 ± 1.8	60.3 ± 1.5	62.9 ± 1.6	NS		
Postintervention	63.9 ± 0.8	59.9 ± 0.7**	64.3 ± 0.7†,††	61.3 ± 0.7*	−3.5 ± 0.7 (<0.0001)	0.8 ± 0.7 (NS)	NS

Values expressed as mean ± SEM. Postintervention data are adjusted for baseline values. Baseline measures were compared by one-way ANOVA. General linear model analysis tested for main effects and interactions on postintervention values adjusted for baseline value. Significance levels were adjusted for multiple comparisons by the Tukey test. ω3FA, omega-3 fatty acid; ANOVA, analysis of variance; CoQ, coenzyme Q_{10}; HR, heart rate; NS, not significant. $^{*}P < 0.05$. $^{**}P < 0.01$. $^{***}P < 0.001$ denotes a significance vs. control. $^{\dagger}P < 0.0001$ denotes a significance vs. ω3FA group. $^{\dagger\dagger}P < 0.001$ denotes a significance vs. ω3FA ± CoQ group.

and asleep ($P < 0.0001$) periods (Table 5). In contrast, CoQ increased 24-h HR ($P = 0.03$). Relative to the control group, HR was reduced in the ω3FA (24 h: -4.9 ± 0.8 bpm, $P < 0.0001$; Awake: -5.8 ± 1.0 bpm, $P < 0.0001$; Asleep: -4.0 ± 1.1 bpm, $P = 0.002$) and ω3FA ± CoQ (24 h: -2.9 ± 0.8 bpm, $P = 0.001$; Awake: -3.2 ± 1.0 bpm, $P = 0.001$; Asleep: -2.6 ± 1.1 bpm, $P = 0.05$) groups. There were no treatment interactions for HR.

At least 50% of patients in each group were taking angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin II receptor blockers (AII blockers) for BP control. Analyses that adjusted for these confounders showed similar effects as above of ω3FA or CoQ on BP.

Vascular function studies and echocardiography

There were no differences between groups at baseline or after intervention in hyperaemic responses of the forearm or brachial artery. Large (C1) and small (C2) artery compliance at baseline were not significantly different between groups. Postintervention, C1 was improved ($P = 0.05$) in the ω3FA group (19.10 ml/mmHg, 95% CI = 17.48–20.73) relative to the control group (16.32 ml/mmHg, 95% CI = 14.45–18.18) after adjustment for baseline value, age, sex and BMI. Indices of diastolic function employing an age-corrected and modified Garcia protocol were not different between groups at baseline and were not altered by the supplements.

Discussion

The rationale for supplementing ω3FA and CoQ in nondiabetic patients with CKD was related to their potential independent benefits to improve the cardiovascular risk profile, particularly BP and vascular function. Daily 4 g ω3FA reduced BP and HR. However, the effects on BP were more pronounced when ω3FA were taken in conjunction with CoQ, although CoQ had no significant independent effect on BP. Furthermore, the greatest effects were seen on asleep BP. The finding of an interaction between ω3FA and CoQ on BP is difficult to explain in view of the lack of effect of CoQ alone on BP and needs confirmation. CoQ alone increased 24-h HR. There were no effects of ω3FA or CoQ on renal function, proteinuria, total cholesterol, HDL-C, LDL-C, glucose, insulin, or CRP. However, ω3FA significantly reduced triglycerides by 24%. Neither supplements altered vascular or diastolic function.

Morbidity and mortality from CVD in patients with CKD can be a consequence of atherosclerotic coronary artery disease, coronary spasm with angiographically normal coronary arteries, arrhythmias or sudden cardiac death, and cardiac failure [3]. Population studies show the risk of CVD significantly increases with declining GFR [1,2]. Thus, our patients with a mean eGFR of 35.8 ml/min/1.73 m^2 (stages 3–4 CKD [15]) would be expected to have a five-fold, 11-fold and 45-fold increased age-standardized risk of death from any cause, cardiovascular events and hospitalization, respectively [1,2].

The cause of the increased risk of CVD in patients with CKD is multifactorial and is likely attributable, in part, to the presence of hypertension, diabetes, obesity, dyslipidaemia and smoking [5]. Patients with CKD have a significantly higher prevalence of hypertension and hypertension treatment, but are less likely to achieve optimal BP control compared with healthy controls [5].

Data from a long-term follow-up of the MDRD Study showed a benefit in tight BP control among patients with primarily nondiabetic kidney disease [28]. The effect of hypertension and hypertension treatment in CKD on CVD outcomes has not been extensively studied. However, a subgroup analysis of the Systolic Hypertension in Elderly Program showed a 30–40% reduction in CVD events as a result of SBP reduction among persons with mild renal impairment [29]. In our study, although patients had well controlled BP, we demonstrated reductions in BP with ω3FA. The reduction in nocturnal BP may be of particular benefit because of the association between nocturnal hypertension and LVH and CVD risk [30,31]. Despite a fall in BP, 24-h albumin and total protein excretion did not change, due possibly to the magnitude of the fall in BP, insufficient power to detect a change or the relatively short intervention.

There is considerable evidence that ω3FA reduce all-cause mortality, sudden cardiac death and possibly stroke [10,11]. ω3FA supplementation has been suggested as a therapeutic approach to improving kidney function or slowing the progression of CKD [32]. In high-risk patients with IgA nephropathy, ω3FA markedly reduced progression of renal disease with benefits persisting after 6.4 years of follow-up [33].

The reduction in BP reported in CKD patients agrees with previously documented antihypertensive effects of ω3FA [34]. In a meta-analysis, Geleijnse *et al.* [35] showed a reduction in BP of $-2.1/-1.6$ mmHg, with the greatest effect in older ($-3.5/-2.4$) and hypertensive ($-4.0/-2.5$) individuals. In contrast, Svensson *et al.* [36] did not demonstrate any change on 24-h BP in patients with CKD after 8 weeks of 2.4 g daily ω3FA. The variation in response may reflect differences in the dose of ω3FA or other factors that might impact upon BP, such as sodium restriction [37], although, in our study, patients did not alter sodium intake and 24-h sodium excretion did not change throughout the intervention.

We previously showed that ω3FA had independent and additive effects to weight control on BP in overweight treated hypertensive patients [16]. Additionally, DHA, but not EPA, significantly reduced 24-h and awake BP [17], and improved endothelial and smooth muscle function in

the forearm microcirculation [26], in overweight, hypercholesterolaemic patients. The benefits of ω3FA on BP are likely due to changes in vascular, cardiac and/or autonomic function [34]. Mechanisms by which ω3FA influence BP and vascular function include suppression of vasoconstrictor prostanoids, enhanced production/or release of nitric oxide, reduced plasma noradrenaline, changes in calcium flux and increased membrane fluidity [34].

Despite the reduction in BP, we were unable to show changes in vascular function measured as hyperaemic responses in the forearm or brachial artery, although measurement of arterial compliance showed large artery elasticity was improved following ω3FA. These findings may not be surprising, as not all studies have shown changes in vascular function following ω3FA [34]. Potential reasons include methodology, dose and duration of therapy. However, we showed improved blood flow in the forearm microcirculation of overweight, dyslipidaemic patients, using the 'gold standard' for assessment of vascular function employing intra-arterial administration of vasoactive drugs [26].

The reduction in HR in CKD patients receiving ω3FA is in accordance with the literature on people with normal renal function [16–18,38] and suggests that there is a significant cardiac component associated with the antihypertensive effects.

The lipid profile in patients with CKD is amenable to favourable modification by ω3FA [39]. CKD associates with hypertriglyceridaemia, with normal or slightly increased total cholesterol and LDL-C, and reduced HDL-C [9]. ω3FA reduce triglycerides [39], and increase HDL-C, due primarily to an increase in HDL_2-C [18,19]. In CKD patients, we showed no significant changes in total cholesterol, LDL-C, HDL-C or the HDL subfractions following ω3FA, but triglycerides were significantly reduced by 24%, a finding that might be beneficial in ameliorating renal as well as systemic consequences of dyslipidaemias. Svensson *et al.* [36] similarly showed a 21% reduction in triglycerides after ω3FA in patients with CKD.

Coenzyme Q_{10} plays a critical role in electron transport during oxidative phosphorylation in mitochondria. It is a potent antioxidant and membrane stabilizer, and has antiatherosclerotic properties [40]. CoQ supplementation is free of side effects in dosages up to 600 mg/day. In our patients, 200 mg daily increased plasma CoQ by three- to four-fold, similar to studies in other populations [12–14].

Coenzyme Q_{10} deficiency occurs in disorders with high-energy requirement such as CKD. Moreover, the unique bio-energetic properties of CoQ are especially pertinent to the high metabolic demands of cardiomyocytes such as may occur in patients with CKD. There is also evidence that CoQ may benefit ventricular dysfunction and heart failure [41]. We were, however, unable to shown any significant benefits of CoQ on HR or indices of diastolic function, which may not be surprising in view of the relatively short period of intervention.

Clinical trials have shown 200 mg daily oral CoQ reduced BP and improved glycaemic control [12], and improved endothelial dysfunction of the brachial artery [13], in patients with type 2 diabetes. We anticipated similar benefits of CoQ in patients with CKD. In contrast, there was no effect of CoQ to lower BP, or on fasting serum glucose, insulin, or HOMA. The lack of effect of CoQ on BP was accompanied by no significant effects on indices of vascular function. An unexpected result was that CoQ associated with a small, albeit borderline significant, reduction in HDL-C. This finding remains unexplained and needs confirmation in future studies.

In conclusion, the present study has shown that ω3FA significantly benefited BP and HR, and reduced serum triglycerides. The fall in BP was independent of effects on renal function (proteinuria and eGFR), which may not be surprising given the magnitude of the BP change and the relatively short intervention. Future studies should include long-term supplementation in order to determine effects of ω3FA on renal function in patients with CKD. These results show that ω3FA lower BP and may reduce cardiovascular risk in nondiabetic patients with moderate-to-severe CKD.

Acknowledgements

We thank Jackie Mansour and Noeline Atkins for nursing assistance and diet counselling, and Lynette McCahon and Lisa Rich for technical assistance. Dr Philip Currie at Echo Services carried out the echocardiographic studies. We thank the renal physicians from Royal Perth Hospital (Dr Mark Thomas, Dr Barry Saker, Dr Kevin Warr), Fremantle Hospital (Dr Paolo Farrari, Dr Helen Rhodes, Dr Hemant Kulkarni) and Sir Charles Gairdner Hospital (Dr Brian Hutchison, Dr Neil Boudville, Dr Grant Luxton, Dr Harry Moody, Dr Steven Richards) for their assistance in the recruitment of patients.

Supported by a grant from the National Health and Medical Research Council of Australia and the Hollywood Private Hospital Research Foundation. Omacor capsules were donated by Solvay Pharmaceuticals, Pymble, NSW, Australia. Coenzyme Q_{10} and placebo capsules were donated by Blackmores Australia, Balgowlah, NSW, Australia.

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