Cardiovascular Drugs and Therapy 1998;12:347–353
© Kluwer Academic Publishers. Boston. Printed in U.S.A.

Randomized, Double-Blind Placebo-Controlled Trial of Coenzyme Q10 in Patients with Acute Myocardial Infarction

Ram B. Singh, Gurpreet S. Wander, Amit Rastogi, Pradeep K. Shukla, Adarsh Mittal, Jagdish P. Sharma, Shiv K. Mehrotra, Raj Kapoor, and Raj K. Chopra

Heart Research Laboratory, Centre of Nutrition Medical Hospital and Research Centre, Moradabad, India

Summary. **The effects of oral treatment with coenzyme Q10 (120 mg/d) were compared for 28 days in 73 (intervention group A) and 71 (placebo group B) patients with acute myocardial infarction (AMI). After treatment, angina pectoris (9.5 vs. 28.1), total arrhythmias (9.5% vs. 25.3%), and poor left ventricular function (8.2% vs. 22.5%) were significantly ($P < 0.05$) reduced in the coenzyme Q group than placebo group. Total cardiac events, including cardiac deaths and nonfatal infarction, were also significantly reduced in the coenzyme Q10 group compared with the placebo group (15.0% vs. 30.9%, $P < 0.02$). The extent of cardiac disease, elevation in cardiac enzymes, and oxidative stress at entry to the study were comparable between the two groups. Lipid peroxides, diene conjugates, and malondialdehyde, which are indicators of oxidative stress, showed a greater reduction in the treatment group than in the placebo group. The antioxidants vitamin A, E, and C and beta-carotene, which were lower initially after AMI, increased more in the coenzyme Q10 group than in the placebo group. These findings suggest that coenzyme Q10 can provide rapid protective effects in patients with AMI if administered within 3 days of the onset of symptoms. More studies in a larger number of patients and long-term follow-up are needed to confirm our results.**

Cardiovasc Drugs Ther **1998:12**

Key Words. **ubiquinone, ischemia, oxidative stress, antioxidant vitamins, infarction**

Acute myocardial infarction (AMI) may be associated with reperfusion-induced free radical stress, lipid, peroxidation, and antioxidant vitamin and coenzyme Q deficiency [1–4]. These situations are predisposing factors for cardiac necrosis, resulting in arrhythmias, ischemia, myocardial dysfunction, and coronary thrombosis, which continue as a chain reaction for several weeks after infarction [1–5]. Coenzyme Q has been demonstrated to enhance cell membrane stabilization in vitro and to exert bioenergetic and antioxidant effects by acting as a free radical scavenger [6].

Coenzyme Q is a rate-limiting factor in mitochondrial respiratory activity, and a deficiency of coenzyme Q may result in a decrease in intracellular adenosine triphosphate [7].

In one experiment [8] in a swine model, improved myocardial contractility after coenzyme Q supplementation during ischemia-reperfusion injury was observed. Recent studies [9] indicate that coenzyme Q can inhibit platelet aggregation and human vitronectin receptor expression [10], which are important predisposing mechanisms of coronary thrombosis after AMI. Coenzyme Q is a naturally occurring vitamin-like agent that is normally present in cardiac cells and functions as an electron carrier in oxidative phosphorylation [11]. In general, it has no adverse effects. There is much clinical experience, with coenzyme Q therapy in angina pectoris, heart failure, arrhythmias, and myocardial ischemia [12–16]. However, no large-scale, randomized, and controlled trials have been published to date that proof its efficacy in coronary artery disease. In this Indian Experiment of Infarct Survival, we report, possibly for the first time, the effect of coenzyme Q (Hydrosoluble, Q-gel, Tishcon Corporation, USA) in patients with AMI.

Methods

Patient selection

Patients admitted with the suspicion of AMI (n = 174) to the coronary care units of hospitals in the cities of Moradabad and Ludhiana during a period of 6 months were considered for entry into this study. Patients were screened for the following selection criteria [17]. AMI was diagnosed in the presence of symmetric ST-segment elevation of 1 mm from baseline in limb leads

Address for correspondence: Dr R.B. Singh, Hon. Prof. Preventive Cardiology, Heart Research Lab. MHRC, Civil Lines, Moradabad-10 (UP) 244001, India

Received 24 October 1997; receipt/review 40 days; accepted 23 January 1998

or of 2 mm from baseline in chest leads, or T-wave inversions with or without Q waves in a 12-lead electrocardiogram in association with an increase in creatine phosphokinase of at least twice the upper limit of normal values on serial examination (n = 113). Possible AMI was diagnosed by the presence of a convincing history of cardiac chest pain accompanied by an increase of less than twice the upper limit of normal values of cardiac enzymes and electrocardiographic abnormalities that were not diagnostic but were suggestive of AMI (n = 18). Unstable angina was diagnosed by cardiac chest pain lasting for >30 minutes without a significant increase in enzymes, absence of diagnostic electrocardiographic changes, or a combination (n = 13).

Exclusion criteria

Patients were excluded if they had none of the above characteristics and noncardiac chest pain (n = 8); angina pectoris with cardiac chest pain <30 minutes (n = 5); death before randomization (n = 7); blood urea >40 mg/dL (n = 2); cancer (n = 1); diarrhea, dysentery, or persistent vomiting (n = 3); and cardiogenic shock (n = 4). All patients presented within 72 hours of the onset of symptoms of AMI.

Treatment

We supplied identical capsules for placebo treatment from our laboratory. The placebo capsules contained those B-complex vitamins that are less likely to provide any benefit and unlikely to cause any adverse effects to AMI patients during a 4-week trial. Placebo capsules were administered to group B patients. The test drug, coenzyme Q10, is marketed under the trade name Q-Gel, which is a hydrosoluble coenzyme Q10 softsule manufactured by the Tishcon Corporation of the United States, where it is sold as a food supplement. This brand has been proven to achieve the highest serum coenzyme Q10 levels of all brands available as supplements in the United States. Each capsule contains 30 mg coenzyme Q10. All patients in the treatment group (group A) were administered two capsules of Q-Gel two times daily (120 mg of coenzyme Q10/d). The placebo capsules, containing thiamine mononitrate IP 3 mg, riboflavine IP 3 mg, pyridoxine hydrochloride IP 1 mg, and nicotinamide IP 25 mg (two capsules twice daily), were administered to all patients in placebo group B. The active and placebo capsules were not truly identical. Hence, both groups of patients were instructed not to show and compare their capsules with those of other patients and not to show them to their doctor, and both groups met separately. The test substances were provided to patients in containers that were identical in all respects. Compliance was monitored by counting the number of capsules returned by the patients on follow-up visits or each day during hospitalization. All other advices regarding treatment was similar in the two groups.

Study design

All patients with a clinical diagnosis of AMI or unstable angina, after written, informed consent was provided (approved by the review board of human studies in our center), were randomized by pharmacists to receive either coenzyme Q capsules or placebo capsules by the Heart Research Laboratory. The study was blinded for physicians and technicians examining the blood. All patients were stratified into anterior or posterior/inferior wall infarction, with or without complications such as hypotension, arrhythmia, and heart failure. All patients were asked to blindly select one of the cards, each enclosed in a sealed envelope and marked either group A or B, from a pile in which an equal number of each type was included. The intervention group A (n = 73) received coenzyme Q and the placebo group B (n = 71) received B-complex vitamins for a period of 28 days. All other treatments, such as nitrates, aspirin, streptokinase, etc., were administered to both groups of patients. All patients remained in the hospital for 5–15 days.

Study procedures

Clinical, electrocardiographic, radiologic, and laboratory data were recorded during hospitalization on a form designed for this study. Blood pressures were measured after 5 minutes rest, with the patient resting comfortably in the supine position. Phase V Korotkoff sounds were recorded for diastolic blood pressure. Hypertension was defined as blood pressure >140/90 mmHg and hypotension as systolic blood pressure <90 mmHg Smoking was defined as smoking one or more cigarettes or beedies per day. All patients admitted to the unit were monitored on ECG lead II for 24–72 hours after admission. A 12-lead ECG was recorded daily for 4–5 days and then on alternate days, and as indicated with suspicion of reinfarction or arrhythmias in both groups. Heart rate and arrhythmias were recorded from the resting ECG and after 48-hour monitoring. Arrhythmias were treated with drugs in the presence of ventricular ectopic beats, with a minimum of 8 beats/min, which were either unifocal or multifocal, or 3 beats consecutively. Angina was recorded on a questionnaire [17], was treated when chest pain persisted for greater than >1 minute, and was relieved or diminished by taking sublingual nitroglycerin. Heart failure was recorded using the New York Heart Association criteria for a dilated heart as seen on radiologic and ECG dilatation of the left ventricle. Heart enlargement was defined as a dilated heart on radiologic and ECG examination. When there was a change in ventricular enlargement between baseline and 28 days, the same method was used to determine ventricular enlargement in individual patients. Echocardiography was performed after 28 days in some patients. Clinical data, complications, drug intake, and smoking were recorded for 28 days by an interviewer who was unaware of the treatment groups.

Laboratory data

A fasting-state venous blood sample was drawn at entry and on subsequent occasion in the morning and was analyzed for blood counts; hemoglobin; urea; glucose; cardiac enzymes; vitamins A, E, and C; beta-carotene and lipid peroxides (thiobarbituric acid reactive substances [TBARS]); malondialdehyde; and diene conjugates [18–22]. The cardiac enzyme lactate dehydrogenase was estimated on the fifth or sixth day of infarction and as indicated after AMI. Laboratory personnel analyzing the blood were blind to the treatment groups.

The ascorbic acid assay [18] was performed using an ultra violet-visible spectrophotometer in plasma obtained from heparinized blood within 1 hour of collection. Plasma was stored in a refrigerator after centrifugation. Lipid peroxides [21] were measured by a new simple method based on a reaction between thiobarbituric acid and malondialdehyde, which are produced from lipoperoxides during heating. Diene conjugates [22] were measured by optical density. This method measures mainly the 9,11-linoleic acid isomer, which has been identified as the major diene conjugate in human sera. Malondialdehyde [20] is a breakdown product of unsaturated fatty acids. An increase in plasma levels of lipid peroxides, malondialdehyde, and diene conjugates indicates free radical stress and cell damage due to acute myocardial infarction. The coefficients of variation for vitamins A, E, and beta-carotene were 4.7%, 4.3%, and 2.3%, respectively.

Statistical analysis

Sample size calculations for the primary outcome variable, time to development of any cardiovascular endpoint, were based on two-sided tests, with a significance level of 5% and a power of 80%. It was calculated that 144 patients, with 72 in each group, would be necessary to demonstrate a 20% difference between the groups. A P value <0.05 and a two-tailed t-test were considered significant. The two-sample t-test using one-way analysis of variance and the Z score for proportions were used to measure the statistical significance between the two groups. In both groups, data were analyzed on the basis of intention to treat, and in all outcome analyses during follow-up the last available clinical or laboratory data were used for patients who died or we lost to follow-up.

Results

We randomized 144 patients with AMI or unstable angina to intervention group A (n = 73) or placebo group B (n = 71), as shown in Table 1. On entry into the study, the mean age (mean ± SD) was 48.0 ± 8.6 versus 47.6 ± 8.2 years; body weight, body mass index, and male sex did not differ significantly between the two groups (see Table 1). Approximately 20% of the subjects were females in both groups A and B. The clinical and biochemical data and results showed no significant difference in the males. Four women in group A and five in B were tobacco chewers, and all were nonsmokers. Delay from onset of symptoms of AMI to the beginning of treatment was also comparable in the two groups.

The proportions of patients with previous myocardial infarction and angina pectoris were not significantly different between the two groups. However, there were significantly more current smokers and subjects taking nifedipine and fewer exsmokers in the coenzyme Q group than in the placebo group. All remaining characteristics, such as final diagnosis, extent of myocardial disease, complications, and drug therapy administered on admission, showed no significant difference between the two groups (see Table 1).

Baseline concentrations of the antioxidant vitamins A, E, and C and of beta-carotene were markedly lower than usually observed in healthy adults and were comparable in the AMI groups. However, lipid peroxides, malondialdehyde, and diene conjugates, indicators of oxidative bursts, were high in the two experimental groups compared with levels in healthy adults in our laboratory (Table 2). Treatment with coenzyme Q10 and placebo for 28 days was associated with a significant increase in the plasma levels of the antioxidant vitamins A, E, and C and beta-carotene, and a reduction in lipid peroxides, malondialdehyde, and diene conjugates in the coenzyme Q group than in the placebo group.

Angina pectoris, poor left ventricular function, and total cases with arrhythmias were significantly lower in the coenzyme Q group than in the placebo group at 28 days of follow-up. Total cardiac events, which included cardiac deaths and nonfatal infarction, were significantly fewer in the intervention group than in the control group (Table 3). Adverse effects of coenzyme Q, such as nausea, vomiting, epigastric discomfort, and headache, were more common in the coenzyme group than in the placebo group (Table 4).

Discussion

This indian experiment shows that treatment with coenzyme Q10 (120 mg/d) was associated with a significant reduction in angina pectoris, poor left ventricular function, and cardiac arrhythmias in the coenzyme Q group compared with the placebo group. Total cardiac events (cardiac deaths and nonfatal infarction) at 28 days of follow-up were also significantly lower in the intervention group than in the placebo group (15.0 vs. 30.9, $P < 0.02$). These beneficial effects indicate that in patients at relatively high risk for recurrent coronary events, treatment with coenzyme Q10 reduces risk due to its rapid protective effects against acute complications related to myocardial dysfunction and possibly coronary artery thrombosis (see Table 3). In this experiment treatment with oral coenzyme Q10 was administered within a mean of 42 hours after the onset of

Table 1. *Characteristics of randomized subjects at entry to study*

	Coenzyme Q (n = 73)	Placebo (n = 71)
Men	58 (79.4)	57 (80.3)
Body weight (kg)	65.0 ± 6	64.7 ± 6
Body mass index (kg/m^2)	23.8 ± 1.6	23.6 ± 1.5
Previous myocardial infarction	5 (6.8)	8 (11.2)
Previous angina pectoris	9 (12.3)	10 (14.1)
Known hypertension (>140/90 mmHg)	30 (41.0)	29 (40.8)
Current smokers (>1 cigarette/d)	28 (38.3)[a]	18 (25.3)
Exsmoker	8 (10.9)	12 (16.9)
Medication		
Diltiazem (20–160 mg/d)	16 (21.9)	18 (25.3)
Nifedipine (10–30 mg/d)	20 (27.4)	10 (14.1)
Aspirin (75–150 mg/day)	11 (15.4)	9 (12.6)
Enalapril maleate (5–15 mg/d)	4 (5.4)	8 (11.2)
Nitrate (20–40 mg/d)	13 (17.8)	15 (21.1)
Final diagnosis		
Acute myocardial infarction	57 (78.0)	56 (78.8)
Possible acute myocardial infarction	10 (13.7)	8 (11.2)
Unstable angina	6 (8.2)	7 (9.8)
Extent of disease		
Anterior or universal	47 (64.4)	47 (66.2)
Posterior/inferior	20 (27.4)	17 (23.9)
Ventricular ectopics (>8/min)	14 (19.2)	7 (9.8)
Left ventricular enlargement	10 (13.7)	7 (9.8)
Peak creatine phosphokinase (IV)	696 ± 108	668 ± 95
Elapsed time from symptom onset to intervention (h)	42 ± 4.6	46 ± 4.8
Drug therapy given on admission		
Streptokinase (0.75–1.5 million IU; n = 6 vs. 6)	1.32 ± 0.3	1.36 ± 0.3
Nitrates (20–60 mg/d)	70 ± 6	75 ± 7
Aspirin (75–150 mg/d)	105 ± 8	108 ± 9
Diltiazem (60–120 mg/d)	110 ± 11	116 ± 12
Metaprolol (40–120 mg/d)	85 ± 6	90 ± 8

[a]$P < 0.05$.
Values are expressed as number (%) or mean ± SD

Table 2. *Plasma levels of antioxidant vitamins and oxidative stress at entry and changes after treatment*

	Coenzyme Q (n = 73)		Placebo (n = 71)		Difference (95% C.I.)
	At entry	Changes	At entry	Changes	
Vitamin A (μmol/L)	1.98 ± 0.15	+ 0.44	1.95 ± 0.13	+ 0.14	0.3[a] (0.11–0.62)
Vitamin E (μmol/L)	16.3 ± 2.7	+ 10.9	17.1 ± 2.8	+ 2.5	8.4[b] (5.2–16.2)
Vitamin E/cholesterol	3.01 ± 0.54	+ 1.82	3.11 ± 0.55	+ 0.33	1.5[a] (0.44–3.1)
Vitamin C (μmol/L)	4.9 ± 1.2	+ 16.6	5.1 ± 1.3	+ 4.5	12.1[b] (6.6–22.1)
Beta-carotene (μmol/L)	0.18 ± 0.04	+ 0.32	0.19 ± 0.05	+ 0.07	0.25[a] (0.08–0.52)
TBARS (ρmol/L)	1.86 ± 0.42	− 1.02	1.78 ± 0.38	− 0.18	0.84[a] (0.41–1.15)
Malondialdehyde (ρmol/L)	1.75 ± 0.36	− 0.88	1.68 ± 0.35	− 0.21	0.67[a] (0.34–1.1)
Diene conjugate (O D units)	28.8 ± 4.3	− 5.0	29.6 ± 4.4	− 1.5	3.5[a] (1.2–4.8)

[a]$P < 0.05$; [b]$P < 0.01$.
At 28 days laboratory data were available for 68 intervention and 65 placebo group patients and at entry for all patients. Values are expressed as mean ± SD.
CI = confidence interval; TBARS = thiobarbituric acid reactive substances.

Table 3. *Complications and cardiac events in intervention and placbo groups*

	Coenzyme Q (n = 73)	Placebo (n = 71)	Relative risk (95% CI)
Complications			
Angina pectoris	7 (9.5%)	20 (28.1)	0.33 (0.16–0.50)
NYHA class III and IV heart failure	2 (2.7)	8 (11.2)	0.24 (0.11–0.88)
Left ventricular enlargement	4 (5.4)	8 (11.2)	0.48 (0.13–1.51)
Total cases with poor left ventricular function	6 (8.2)[a]	16 (22.5)	0.36 (0.23–0.62)
Ventricular ectopics (>8/min)	5 (6.8)	14 (19.7)	0.34 (0.11–0.88)
Ventricular ectopics (>3 consecutively)	2 (2.7)	4 (5.6)	0.48 (0.12–1.14)
Total arrhythmias	7 (9.5)[a]	18 (25.3)	0.37 (0.22–0.66)
Hypotension (systolic <90 mmHg)	5 (6.8)	3 (4.2)	1.6 (0.6–3.7)
Cardiac events			
Sudden cardiac death	3 (4.1)	4 (5.6)	0.73 (0.32–0.98)
Fatal myocardial infarction	3 (4.1)	5 (7.0)	0.58 (0.32–0.99)
Nonfatal myocardial infarction	5 (6.8)	13 (18.3)	0.37 (0.28–0.77)
Total cardiac deaths	6 (8.2)	9 (12.6)	0.65 (0.32–0.99)
Total cardiac events	11 (15.0)[b]	22 (30.9)	0.48 (0.28–0.80)

P value obtained by comparison of intervention and placebo groups by Z score test for proportions.
[a]$P < 0.05$; [b]$P < 0.02$.
Data are reported as number (%). CI = confidence interval.

symptoms of AMI, which indicates that coenzyme Q10 must have provided rapid protective effects against ischemia-induced cardiac damage due to its beneficial effects on platelet size and diminished vitronection-receptor expression [10]. There were significantly more current smokers in the coenzyme Q group. Because current smokers have a better in-hospital prognosis after AMI, a part of the benefit in the intervention group may be due to cessation of smoking.

Table 4. *Adverse manifestations of coenzyme Q and placebo group*

	Coenzyme Q (n = 73)	Placebo (n = 71)
Nausea	28 (38.3)	11 (15.4)
Vomiting	16 (21.9)	7 (9.8)
Epigastric discomfort	9 (12.3)	7 (9.8)
Headache	9 (12.3)	—
Bodyache	5 (6.8)	—
Hypotension during first week	12 (16.4)	5 (7.0)

There is evidence that coenzyme Q10 can protect against angina pectoris, arrhythmias, and heart failure due to various causes [12–16]. A few double-blind, placebo-controlled trials [13,14] have also been published to demonstrate the role of coenzyme Q10 in coronary artery disease [23–25]. In postinfarction patients [24], treatment with coenzyme Q10 caused a significant beneficial effect on work capacity and a reduction in malondialdehyde levels in the treatment group compared with placebo. In a multicenter study [25], the effect of coenzyme Q10 (150 or 300 mg/d), on exercise duration in stable angina was compared with placebo in 37 patients during a 4-week follow-up. Coenzyme Q10 monotherapy was associated with an increase in exercise duration to onset of angina of 70 seconds in the 300-mg group and 65 seconds in the 150-mg group after 1 week and of 140 and 127 seconds, respectively, at 4 weeks. All these trials were conducted in a small number of patients and had only a short duration of follow-up. In a previous preliminary study by Kuklinski et al. [26], in a smaller series of 61 patients, coenzyme Q10 seemed to improve the course up to 1 year after myocardial infarction. However, in this study the

intervention involved both coenzyme Q10 (100 mg/d) and selenium (100 ug/d).

Apart from clinical beneficial effects, treatment with coenzyme Q10 was associated with a significant reduction in lipid peroxides, malondialdehyde, and diene conjugates, which are indicators of free radical–induced damage during myocardial ischemia (see Table 2) [1–4]. A reduction in malondialdehyde on coenzyme Q10 therapy in patients with myocardial infarction has also been described in other studies [24]. There is evidence that ischemia-induced free radical stress may be associated with accumulation of lipid peroxides and hydroperoxides, which work as oxidants and are damaging to cells during the first few weeks after AMI [1–4]. Therefore, free radical stress, which is maximum during reperfusion injury, continues and treatment with antioxidants may be protective. Treatment with coenzyme Q10 may increase its concentration in the mitochondria and improve mitochondrial respiration [27], producing improved postischemic ventricular recovery [28]. Treatment with coenzyme Q10 may also improve the hyperlipidemia [29] and ischemia induced decrease in coenzyme levels, which may protect against the oxidation of cholesterol and improve coronary endothelial function [30].

We also observed an increase in plasma levels of the antioxidant vitamins A, E, and C and beta-carotene in the coenzyme Q10 group than in the placebo group, although these levels were markedly lower initially in both groups (see Table 2). Regeneration of vitamin E from the alpha-tocopheroxyl radical on coenzyme Q10 administration [31] has been observed in several studies without any influence on other antioxidants. The improvement in plasma levels of antioxidant vitamins and beta-carotene in the intervention group may be due to protection of myocardium by coenzyme Q10 and their decreased intracellular shift and consumption by the myocardial cell. It is possible that coenzyme Q10 provides protection via its antioxidant membrane-stabilizing property and its free radical scavenging activity [6]. Coenzyme Q10 has been demonstrated to protect calcium-dependent and Na, K–dependent ATPase activity [6–8]. The adverse effects of coenzyme Q10 were mainly nausea, vomiting, and headache, which have also been noted in other recent studies [32–35].

In brief, the Indian experiment has shown that treatment with coenzyme Q10 may be protective against angina, arrhythmias, and heart failure as well as against cardiac events in patients with AMI. Coenzyme Q10, with its improved bioavailability [35], should be administered as soon as possible before any other treatment in AMI patients to provide antioxidant protection against reperfusion-induced free radical damage.

References

1. Grech ED, Jackson M, Ramsdale DR. Reperfusion injury after acute myocardial infarction. *Br Med J* 1995;310:477–478.
2. Bernier M, Hearse DJ, Manning AS. Reperfusion induced arrhythmias and oxygen derived free radicals. *Circ Res* 1986;58:331–340.
3. Ceremuzynski L. Hormonal and metabolic reactions evoked by acute myocardial infarction. *Circ Res* 1981;48:765–776.
4. Singh RB, Niaz MA, Rastogi S, Sharma JP, Kumar R, Bishnoi I, Beegom R. Plasma levels of antioxidant vitamins and oxidative stress in patients with suspected acute myocardial infarction. *Acta Cardiol* 1994;49:441–452.
5. Wilkinson P, Sayer J, Laji K, Grundy C, Marchant B, Kopelman P, Timmis AD. Comparison of case fatality in South Asian and white patients after acute myocardial infarction: Observational study. *Br Med J* 1996;312:1330–1333.
6. Beyer RE, The participation of coenzyme Q10 in free radical production and antioxidation. *Free Radic Biol Med* 1990;8: 545–565.
7. Lenaz G, Battino M. Studies on the role of ubiquinone in the control of the mitochondrial respiratory chain. *Free Radic Res Commun*, 1990;8:317–327.
8. Atar D, Mortensen SA, Flachs H, Herzog WR. Coenzyme Q10 protects ischemic myocardium in an open-chest swine model. *Clin Investig* 1993;71:S 103–111.
9. Herzog WR, Schlossberg ML, Mortensen SA, Serebruany VL. Dietary supplementation with coenzyme Q10 reduces platelet aggregability in swine Coenzyme Q. *Res Biol Med* 1995;3:5–8.
10. Serebruany VL, Ordonez JV, Herzog WR, Morten R, Mortensen SA, Folkers K, Gurbel PA. Dietary coenzyme Q10 supplementation alters platelet size and inhibits human Vitronectin (CDSI/CD61) receptor expression. *J Cardiovasc Pharmacol* 1997;29:16–22.
11. Battino M, Fato R, Lenaz G. Coenzyme Q10 can control the efficiency of oxidative phosphorylation. *Int J Tissue React* 1990;12:137–144.
12. Singh RB, Niaz MA, Rastogi V, Rastogi SS. Coenzyme Q in cardiovascular disease. *J Assoc Physiol India* 1998;46: 299–306.
13. Kamikawa T, Kobayashi A, Yamashita T, Hayashi H, Yamasaki N. Effects of coenzyme Q10 on exercise tolerance in chronic stable angina pectoris. *Am J Cardiol* 1985;56:247–257.
14. Mazzola C, Guffanti EE, Vaccarella A, Meregalli M, Colmago R, Ferrario N, Cantoni V, Marcherri G. Noninvasive assessment of coenzyme Q10 in patients with chronic stable effort angina and moderate heart failure. *Curr Ther Res* 1987;41: 923–930.
15. Hofman-Bang C, Rehnqvist N, Swedberg K, Astrom H. Coenzyme Q10 as an adjunctive in treatment of congestive heart failure. *J Am Coll Cardiol* 1992;19(Suppl.):774–776.
16. Takasawa K, Fuse K, Konishi T, Watanabe Y. Prevention of premature ventricular contractions with coenzyme Q10 after coronary artery bypass grafting. In: Folkers K, Littami GP, Yamagami T, eds. *Biomedical and Clinical Aspects of Coenzyme Q*. Vol. 6, Amsterdam: Elsevier 1991:357–359.
17. World Health Organization Myocardial Infarction Community Registers Copenhagen. World Health Organization, 1976.
18. Brubacher G, Vuillenmier JP, Incurtis HC, Roth M, eds. *Vitamin C: Clinical Biochemistry, Principles and Methods, Vol. 2*. Berlin: de Gruyter, 1974:989–997.
19. Vuilleumier JP, Keller HE, Gysel D, Hunziker F. Clinical chemical methods for the routine assessment of the vitamin status in human population. Part 1. The fat soluble vitamins A, E and beta-carotene. *Int J Vit Nutr Res* 1983;58:265–272.

20. Esterbauer H, Cheeseman KH. Determination of aldehyde peroxidation products malonyldialdehyde and 4 hydroxynonenal. *Method Enzymol* 1990;186:407–421.
21. Niato C, Kawamura M, Yamamoto Y. Lipid peroxides as the initiating factor of atherosclerosis. *Am NY Acad Sci* 1993; 676:27–45.
22. Lunec J, Hallovan SP, White AG, Dormandy TL. Free radical oxidation (peroxidation) products in serum and synovial fluids in rheumatoid arthritis. *J Rheumatol* 1981:8:233–245.
23. Schardr F, Welzel D, Schess W, Toda K. Effect of coenzyme Q10 on ischemia-induced ST-segment depression: A double blind, placebo controlled crossover study. In: Folkers K, Yamamura Y, eds. *Biomedical and Clinical Aspects of Coenzyme Q10*, Vol. 5. Amsterdam: Elsevier, 1986:385–394.
24. Rosi E, Lombardo A, Testa M, et al. Coenzyme Q10 in ischaemic cardiopathy. In: Folkers K, Littarru GP, Yamagami T, eds. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 6*. Amsterdam: Elsevier, 1991:321–326.
25. Wilson MF, Frishman WH, Giles T, Sethi G, Greenberg SM, Brackett DJ. Coenzyme Q10 therapy and exercise duration in stable angina. In: Folkers K, Littami GP, Yamagami T, eds. *Biomedical and Clinical Aspects of Coenzyme Q, Vol. 6*. Amsterdam: Elsevier, 1991:339–348.
26. Kuklinski B, Weissenbacher E, Fahnrich A. Coenzyme Q10 and antioxidants in acute myocardial infarction. *Mol Aspect Med* 1994:15(Suppl.):143–147.
27. Barbiroli B, Frassineti C, Martinelli P, Iotti S, Lodi R, Cortelli P, Montagna P. Coenzyme Q10 improves mitochondrial respiration in patients with mitrochondrial cytopathies. An in vivo study on brain and skeletal muscle by phosphorous magnetic resonance spectroscopy. *Cell Mol Biol* 1997:43:741–749.
28. Yoshida T, Maulik G, Bagchi D, Dash SK, Engelman RM, Das DK. Increased myocardial tolerance to ischemia-reperfusion injury by feeding pigs with coenzyme Q10. In: Das DK, Engelman R, Cherian KM, eds. *Myocardial Preservation, Preconditioning and Adaptation. Ann NY Acad Sci* 1996:793:414–419.
29. Kontush A, Reich A, Baum K, Spranger T, Finckh B, Kohlschutter A, Beisiegel U. Plasma ubiquinol is decreased in patients with hyperlipidemia. *Atherosclerosis* 1997:129: 119–126.
30. Yokoyama H, Lingle DM, Crestanello JA, et al. Coenzyme Q10 protects coronary endothelial function from ischaemia reperfusion injury via an antioxidant effect. *Surgery* 1996; 120:189–196.
31. Kagan V, Packer L. Electron transport regenerates vitamin E in mitochandria and microsomes via ubiquinone: An antioxidant aduct. In: Corogni F, Banni S, Desai MA, Rice-Evans C, eds. *Free Radicals and Antioxidants and Nutrition.* London: Richelieu Press, 1993:27–36.
32. Baggio G, Gandini R, Plancher AC, Passeri M, Carmosino G. Italian multicenter study on the safety and efficacy of coenzyme Q10 as adjunctive therapy in heart failure. *Mol Aspects Med* 1994;15(Suppl.):287–294.
33. Karlsson J, Lin L, Gunnes S, Sylven C, Astrom H, Jansson E, Semb B. Muscle characteristics in effort angina before and after CABG. *Can J Cardiol* 1997;13:577–582.
34. Soja AM, Mortensen SA. Treatment of congestive heart failure with coenzyme Q10 illuminated by meta-analyses of clinical trials. *Mol Aspects Med* 1997:18(Suppl.):159–168.
35. Chopra RK, Goldman R, Sinatra ST, Bhagvan HN. Relative bioavailability of coenzyme Q10 formulations in human subjects. *Int J Vit Nutr Res* 1998;68:109–113.