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Prophylactic treatment with coenzyme Q10 in patients undergoing cardiac surgery: could an antioxidant reduce complications? A systematic review and meta-analysis

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Abstract

Coenzyme Q10 (CoQ10) is a lipid-soluble antioxidant that could have beneficial effects in patients undergoing cardiac surgery with cardiopulmonary bypass. There is no clear evidence about its clinical effects or a systematic review published yet. We aimed to conduct a systematic review and meta-analysis of the literature to elucidate the role of coenzyme Q10 in preventing complications in patients undergoing cardiac surgery with cardiopulmonary bypass. We searched the PubMed Database using the following keywords: Coenzyme Q10, ubiquinone, ubiquinol, CoQ10, Heart Surgery, Cardiac surgery. Articles were systematically retrieved, selected, assessed and summarized for this review. We performed separate meta-analyses for different outcomes (inotropic drug requirements after surgery, incidence of ventricular arrhythmias and atrial fibrillation, cardiac index 24 h after surgery and hospital stay), estimating pooled odds ratios (ORs) or mean differences of the association of CoQ10 administration with the risk of these outcomes. Eight clinical trials met our inclusion criteria. Patients with CoQ10 treatment were significantly less likely to require inotropic drugs after surgery {OR [95% confidence interval (CI) 0.47 (0.27–0.81)]}, and to develop ventricular arrhythmias after surgery [OR (95% CI) 0.05 (0.01–0.31)]. However, CoQ10 treatment was not associated with Cardiac index 24 h after surgery [mean difference (95% CI) 0.06 (−0.30 to 0.43)], hospital stay (days) [mean difference (95% CI) −0.61 (−4.61 to 3.39)] and incidence of atrial fibrillation [OR (95% CI) 1.06 (0.19–6.04)]. Since none of the clinical trials included in this review report any adverse effects associated to CoQ10 administration, and coenzyme Q10 has been demonstrated to be safe even at much higher doses in other studies, we conclude that CoQ10 should be considered as a prophylactic treatment for preventing complications in patients undergoing cardiac surgery with cardiopulmonary bypass. However, better quality randomized, controlled trials are needed to clarify the role of CoQ10 in patients undergoing cardiac surgery with cardiopulmonary bypass.

Keywords: Coenzyme Q10 • Ubiquinone • Ubiquinol • Cardiac surgery • Cardiopulmonary bypass • Meta-analysis

INTRODUCTION

Coenzyme Q10 (CoQ10), also known as ubiquinone (in its oxidized form) or ubiquinol (in its reduced form), is a lipid-soluble molecule that consists of an aromatic ring and a 10-unit isoprenoid chain. It is embedded into the mitochondrial electron transport chain. The presence of this molecule in our bodies is due to dietary intake and endogenous synthesis of ubiquinone from its molecular precursors.

Average dietary intake in the population is 3–6 mg/day. The main sources of this antioxidant are meat, fish, nuts and olive oil. It is also found in fruits and vegetables, in smaller amount [1].

Endogenous synthesis is due to the combination of two metabolic pathways: the quinone pathway, which synthesizes the electron carrier ring, and the mevalonate pathway, which synthesizes the lipid-soluble isoprenoid chain. HMG-CoA reductase is required to produce isoprenoid chains, and this enzyme is also required to produce endogenous cholesterol and, therefore, it is a target of statins [2].

The main function of CoQ10 is to transfer high-energy electrons from Complex I and II (NADH dehydrogenase and succinate dehydrogenase, respectively) to Complex III (Cytochrome bc_1-complex), in the oxidative phosphorylation reaction at the inner mitochondrial membrane.

In the beginning of this reaction, NADH and $FADH_2$ donate high-energy electrons to Complex I and II, respectively, which donate them to ubiquinone, transforming it into ubiquinol (oxidized form). These electrons are then transferred through the mitochondrial membrane to complex III, and ubiquinol transforms into ubiquinone again.

This redox reactions at the inner mitochondrial membrane establishes an H^+ transmembrane gradient that allows cell production of ATP (the basic source of energy for the organism) [3]. CoQ10 is a molecule especially important in tissues with high metabolic requirements, like the liver, brain and heart.

A clear association between low plasma levels of CoQ10 and heart failure has been established [4], and it has also been established as an independent predictor of greater mortality among patients with heart failure [5]. In addition, many cases of inherited

CoQ10 deficiency have been described, caused by autosomal recessive mutations of genes involved in its synthesis. CoQ10 deficiency has been associated with five major clinical phenotypes: encephalomyopathy, severe infantile multisystemic disease, cerebellar ataxia, nephrotic syndrome and isolated myopathy. CoQ10 supplementation was successful in treating patients with myopathy according to several clinical trials [6].

Cardiopulmonary bypass (CPB) during cardiac surgery may cause an important myocardial injury due to ischaemia–reperfusion states and blood exposure to non-biological surfaces with subsequent inflammatory activation.

Administration of cardioplegia during ischaemia and myocardial hibernation (tricarboxylic acid cycle and mitochondrial electron transport chain downgrade their activity) help to protect myocardium from this shortage of oxygen. However, housekeeping processes, like ion homeostasis, require ATP that is then obtained from anaerobic glycolysis. Non-mitochondrial ATP turnover during ischaemia, combined with the accumulation of lactic acid from glycolysis at low oxygen tension, results in ischaemic intracellular acidosis. Production of reactive oxygen species (ROS) is a self-limiting process during ischaemia due to tricarboxylic acid cycle and cytochrome c inhibition. In addition, the concentration of buffer molecules like glutathione, and superoxide dismutase activity diminish. All these changes yield a sensitive environment for molecular damage.

In the 1970s, the occurrence of cellular damage due to myocardial reperfusion after a long period of ischaemia was described, and it was correlated with increased cardiac enzyme blood levels, which is explained by an increase in oxidative stress in injured tissue. $O_2^{\cdot -}$ sources during reperfusion are cytochrome p450, xanthine oxidase and especially mitochondrial electron transport damage. O_2 restoration to preischaemic levels would reactivate the tricarboxylic acid cycle that would feed the mitochondrial electron transport chain in its first steps, but a temporary inactivation of cytochrome c would make the final donation of electrons to O_2 and its conversion to H_2O impossible. Conversely, $O_2^{\cdot -}$ would be produced in intermediate locations of the chain (Complex III).

$O_2^{\cdot -}$ serves as a precursor to the formation of H_2O_2, $^{\cdot}OH$ and $NO^{\cdot}$. All of them share the capability to take electrons from other molecules (oxidizing), thereby modifying its structure and function. Membrane lipid peroxidation in addition to protein oxidation and nitrification are both well-described processes that occur during surgery coupled with cardiopulmonary bypass triggering increased incidence of arrhythmias, myocardial dysfunction and hospital stay after the procedure [7].

There are different strategies to prevent or reduce CPB damage after surgery. One of them is using antioxidants prior to surgery in order to compensate for the high production of ROS. In the last decades, several clinical trials using these compounds have been published that include *N*-acetylcysteine, α-tocopherol or vitamin E, propofol and CoQ10.

Although CoQ10 as a prophylactic treatment of complications in patients undergoing cardiac surgery could have beneficial effects, there is no clear evidence about its clinical effects, or a systematic review published yet. In this context, we aimed to systematically review the literature and to conduct a meta-analysis of the results to quantitatively summarize the existing evidence on this topic. Results from this review combined with the discussion may help clinicians to elucidate if CoQ10 should be recommended to prevent complications in patients undergoing cardiac surgery.

MATERIALS AND METHODS

Inclusion criteria

We included all clinical trials that assessed the effect of CoQ10 supplementation in patients undergoing cardiac surgery. We placed no restrictions on language. We excluded observational studies.

Participants. We established no restrictions and included all patients, regardless of age, who underwent cardiac surgery requiring CBP, including coronary artery bypass graft, valve repair or valve replacement.

Intervention. We included studies with an administration of any dose of CoQ10 prior to surgery. We excluded those studies that combined CoQ10 with other antioxidants in order to ensure the specificity of CoQ10.

Outcomes. Any possible postoperative complications including mortality, arrhythmias, low cardiac output, inotropic drug use or requirements, and hospital stay.

Search methods

We searched the PubMed Database on the 10 January 2014 using the following algorithm: (coenzyme Q10 OR ubiquinone OR ubiquinol OR CoQ10) AND (Heart Surgery OR Cardiac surgery). Two authors (Fernando de Frutos and Alfredo Gea) independently carried out the search.

Data collection and analysis

Studies were independently assessed by two of the authors (Fernando de Frutos and Alfredo Gea) identifying their fulfilment of the inclusion criteria. Disagreements were resolved by discussion.

Statistical analysis

We chose the inverse variance method and conducted random-effects meta-analysis for each of the identified outcomes. We estimated pooled odds ratios (OR) (when the outcome was dichotomous), or mean differences (when the outcome was continuous) and their 95% confidence intervals (95% CI) of the association of CoQ10 administration with the risk of the different outcomes. We used Review Manager 5.2 to conduct the statistical analyses [8].

RESULTS

We summarized the flow of papers through the search and selection process using a flow chart. Out of 120 papers identified in the search, 60 articles were excluded early in the selection process because the title was irrelevant to our main area of interest. The 60 remaining articles were assessed and 44 papers were excluded as they did not meet some of the inclusion criteria. Five articles were excluded as they did not include an abstract, nor a link to the full text, and they vanished after limiting articles to 'Clinical trial' with the database tools. Of the 11 clinical trials that use CoQ10 prior to cardiac surgery, 2 were excluded as they combined

CoQ10 with other antioxidants. Two articles portrayed the information of the same clinical trial, so it was included only once. Eight clinical trials were finally included in our review.

In addition, we searched the ClinicalTrials.gov database on the 10 January 2014 using 'coenzyme Q10' as a keyword in order to find clinical trials that were being performed.

Of 81 results, only 1 was a clinical trial using CoQ10 prior to cardiac surgery. Its status was completed and it matched with a clinical trial published in 2010 [9] that had been already excluded as it combined CoQ10 with other antioxidants.

We checked the bibliographic references of identified clinical trials to find any paper not previously identified by the electronic

Table 1: Characteristics of all studies selected in the systematic review

	Population/surgery	Intervention (CoQ10)	Control	Results (CoQ10 vs Control)
Makhija *et al.* [10]	*n* = 30 Elective coronary artery bypass graft	150–180 mg/day orally, divided in three doses for 7–10 days before surgery	None	Reperfusion arrhythmias (0 vs 10) Ventricular fibrillation (0 vs 1) Ventricular ectopics (0 vs 2) Ventricular arrhythmias (0 vs 3) Atrial fibrillation (0 vs 0) Dopamine requirement [3.2 (±1.2) vs 8.6 (±2.3) μg/kg/min, *P* <0.001] Hospital stay [7.1 (±1.1) vs 10.3 (±7.8) days, *P* = 0.020]
Rosenfeldt *et al.* [11]	*n* = 121 Elective coronary artery bypass graft ± valve repair	300 mg/day orally (mean = 2 weeks before surgery)	Placebo	MDA in mitochondrial membranes [0.9 (±0.04) vs 1.6 (±0.12) nmol/mg protein, *P* = 0.002] Post-bypass Cardiac index [3.1 (±0.01) vs 3.2 (±0.1) l/m^2/min, *P* = 0.75] Troponin Ia at 24 h [14.1 (±1.2) vs 13.6 (±1.2) μg/l, *P* = 0.64] Inotropic drug use (24 vs 33%, *P* = 0.39) Hospital stay (7 vs 6 days, *P* = 0.58)
Zhou *et al.* [12]	*n* = 24 Cardiac valve replacement	100 mg/day intravenously for 10 days (7/3) + 100 μg/ml (120 μM) with cardioplegia + 10 mg/kg in continuous intravenous drip during surgery	None	Plasma MDA: lower Serum CK-MB: lower Erythrocyte SOD activity after CPB: higher Cardiac index at 8 h [2.84 (±0.37) vs 2.35 (±0.25) l/m^2/min, *P* <0.01] Cardiac index at 12 h [3.09 (±0.45) vs 2.57 (±0.34) l/m^2/min, *P* <0.05] Cardiac index at 24 h [2.95 (±0.39) vs 2.67 (±0.33) l/m^2/min, *P* = NS] Dopamine requirements after surgery (16.67 vs 41.67%, *P* = 0.15)
Taggart *et al.* [13]	*n* = 20 Elective coronary artery bypass graft	600 mg oral in divided doses 12 h before surgery	Placebo	Myoglobin: no differences CK-MB: no differences Troponin T: no differences Inotropic drug requirements: none Atrial fibrillation (3 vs 2)
Chello *et al.* [14]	*n* = 40 Elective coronary artery bypass graft	150 mg/day orally, divided in three doses for 7 days before surgery	None	Plasma MDA after the aortic cross-clamp release: lower (*P* <0.01) CK-MB after the aortic cross-clamp release: lower (*P* <0.01) Cardiac index at 24 h [3.0 (±0.2) vs 3.1 (±0.1) l/m^2/min, *P* = NS] Inotropic drug requirements (25 vs 30%, *P* = NS) Dopamine requirement [3.2 (±0.4) vs 5.0 (±0.6) μg/kg/min, *P* <0.01] Atrial premature beats (7 vs 9 patients, *P* = NS) Atrial fibrillation (0 vs 1) Ventricular arrhythmias (1 vs 12)
Chen *et al.* [15]	*n* = 22 Cardiac surgery with CPB	150–200 mg/day orally for 5–7 days before surgery, until a total dose 1000 mg	None	Inotropic drug requirements (18.2 vs 45.5%, *P* = NS) Ventricular myocardial ultrastructure: better preserved Atrial tissue: no differences
Judy *et al.* [16]	*n* = 20 Elective coronary artery bypass graft ± valve repair	100 mg/day orally for 14 days before surgery and 30 days after surgery	Placebo	Cardiac index after surgery [3.0 (±0.4) vs 2.5 (±0.28) l/m^2/min, *P* <0.01] Ejection fraction at initial surgical recovery [42 (±4.4) vs 21 (±5) %, *P* <0.01] Inotropic drug requirements: all patients in the control group (two died of pump failure)
Tanaka *et al.* [17]	*n* = 50 Cardiac valve replacement	30–60 mg/day orally for 6 days before surgery	None	Inotropic drug requirements (40 vs 72%, *P* <0.05)

MDA: malondialdehyde; CPB: cardiopulmonary bypass; CK-MB: creatine kinase MB; SOD: superoxide dismutase.

searches. We also approached three authors of papers included in our review by email and made inquiries as to any other clinical trials they might know of. We did not receive any answer.

Main characteristics of the studies included are presented in Table 1.

Risk of bias

We assessed the risk of bias in clinical trials following the Cochrane Collaboration handbook for systemic reviews of interventions [18]. We used the 'Risk of bias summary' figure to illustrate the judgement ('Low risk', 'High risk', 'Unclear risk' of bias) for each trial. (Fig. 1)

Random sequence generation was described in two articles (Rosenfeldt *et al.* [11], Taggart *et al.* [13]) while four articles (Makhija *et al.* [10], Zhou *et al.* [12], Chen *et al.* [15], Judy *et al.* [16]) did not include this information. Two articles used hospital history number to allocate patients to intervention groups. (Chello *et al.* [14], Tanaka *et al.* [17]).

Allocation concealment was described in two articles (Rosenfeldt *et al.* [11], Makhija *et al.* [10]) and only three trials used placebos to compare CoQ10 effects in the control group (Rosenfeldt *et al.* [11], Taggart *et al.* [13], Judy *et al.* [16]).

Selective reporting was noted in three trials (Zhou *et al.* [12], Taggart *et al.* [13], Judy *et al.* [16]) as they did not report information about some haemodynamic outcome information.

Source of funding was not declared by five clinical trials (Makhija *et al.* [10], Zhou *et al.* [12], Chello *et al.* [14], Chen *et al.* [15], Tanaka *et al.* [17]), while two clinical trials were funded by the pharmaceutical industry (Taggart *et al.* [13] and Judy *et al.* [16]). Rosenfeldt *et al.* [11] was allegedly funded by the National Heart Foundation of Australia and Blackmores Australia Pty Ltd but they did not declare the absence of conflicts of interest.

Only three trials compared CoQ10 administration with placebos (Rosenfeldt *et al.* [11], Taggart *et al.* [13], Judy *et al.* [16]), while the rest compared CoQ10 with a control group that did not receive any placebo (Makhija *et al.* [10], Zhou *et al.* [12], Chello *et al.* [14], Chen *et al.* [15], Tanaka *et al.* [17]).

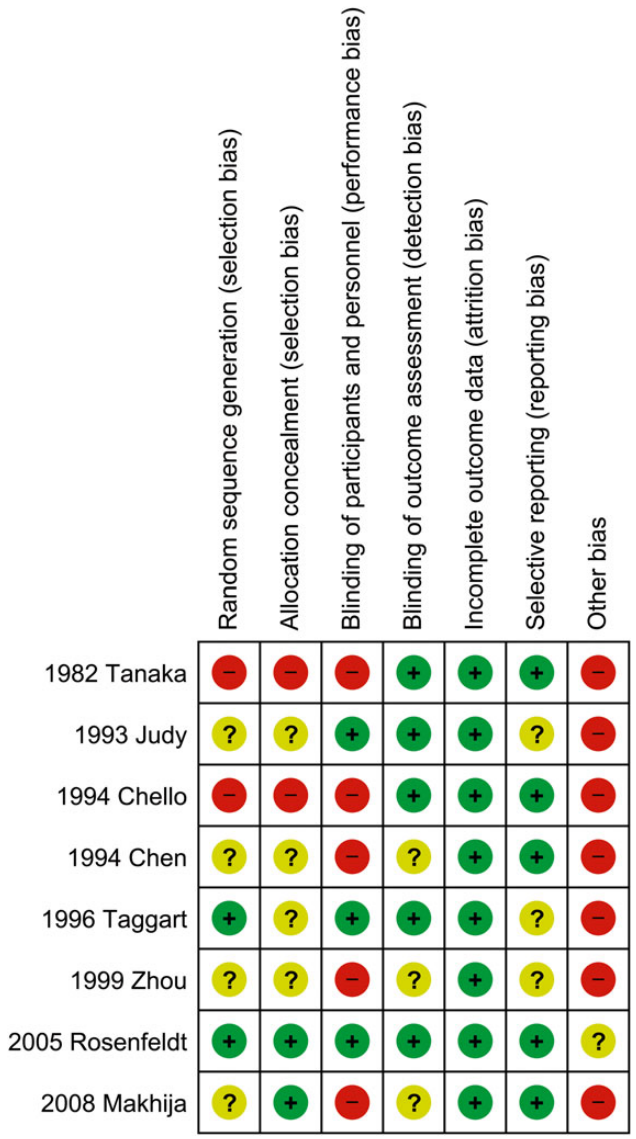

Figure 1: Red: high risk; yellow: unclear risk; green: low risk.

Meta-analysis results

Firstly, we analysed inotropic drug use after surgery as an outcome. Results are presented in Fig. 2. Six out of the eight studies evaluated presented data on inotropic drug requirements. The results from the meta-analysis show that CoQ10 administration before surgery in patients undergoing cardiac surgery with cardiopulmonary bypass significantly reduces the risk of requiring inotropic drugs after surgery in 53% [pooled OR (95% CI) 0.47 (0.27–0.81); $P = 0.006$].

Then, we analysed the Cardiac Index, measured in l/m^2/min, 24 h after surgery (figure available on request). Only two studies presented cardiac index as an outcome. Results were not conclusive about the role of CoQ10 in the management of the cardiac index [pooled mean difference (95% CI) 0.06 (−0.30 to 0.43); $P = 0.73$].

Regarding hospital stay (days) (figure available on request). Combining the results from the two studies that offered this information, we obtained no significant reduction in hospital stay [mean difference (95% CI) −0.61 (−4.61 to 3.39); $P = 0.76$].

With respect to the incidence of ventricular arrhythmias (Fig. 3), we found a significant reduction in the group treated with CoQ10 [pooled OR (95% CI) 0.05 (0.01–0.31); $P = 0.001$].

However, the incidence of atrial fibrillation did not significantly differ between intervention and control groups [pooled OR (95% CI) 1.06 (0.19–6.04); $P = 0.95$] (figure available on request).

DISCUSSION

The evidence collected in this review shows that there are a few and heterogeneous randomized controlled trials that investigate the role of CoQ10 administration before surgery in patients undergoing cardiac surgery. However, results from the meta-analyses suggest that CoQ10 may reduce the requirements of inotropic drugs after surgery, and the incidence of ventricular arrhythmias.

The first important result of this systematic review is that retrieved clinical trials are substantially heterogeneous. The dose of CoQ10 administered and the treatment regimen widely varies among studies. Taggart *et al.* [13] used high CoQ10 doses (600 mg)

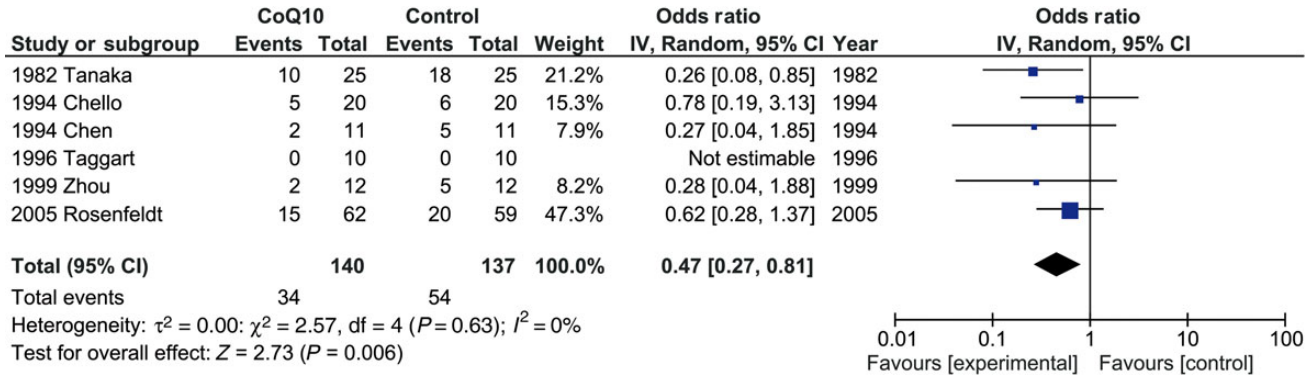

Figure 2: Inotropic drug use after surgery. CoQ10: Coenzyme Q10; 95% CI: 95% confidence interval.

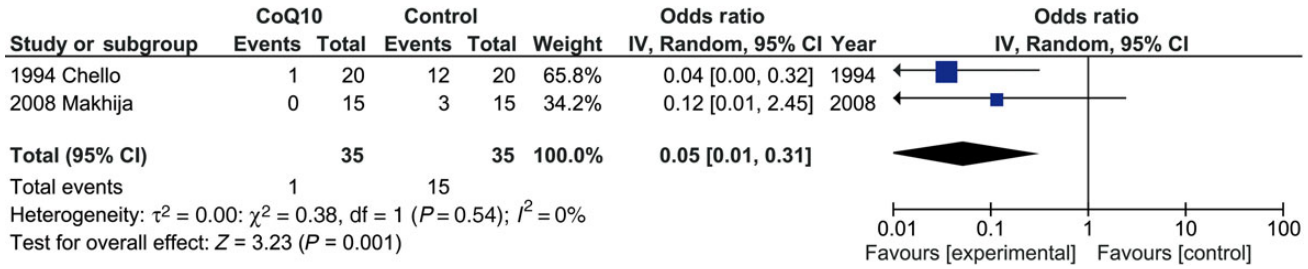

Figure 3: Ventricular arrhythmias.

just 12 h before surgery, avoiding its administration on the days before surgery. Zhou *et al.* [12] included CoQ10 administration for 7 days before surgery combined with addition of CoQ10 to cardioplegia and continuous intravenous drip during surgery and oral administration for 3 days after surgery. The rest of the trials described the administration of CoQ10 orally the days before surgery from 5 to 7 days (Chen *et al.* [15]) to 14 days before plus 30 days after surgery (Judy *et al.* [16]).

CoQ10 doses varied from the first published clinical trial (Tanaka *et al.* [17]) which used 30–60 mg/day to the following trial, which progressively increased the dose to 300 mg/day (Rosenfeldt *et al.* [11]), although the last published trial (Makhija *et al.* [10]) reduced the dose to 150–180 mg/day.

Outcomes that are reported in clinical trials are very diverse, which represents a big limitation when pooling outcomes in a meta-analysis. The proportion of patients that require inotropic drugs after surgery is the only outcome that is reported by the majority of studies. Most of the outcomes that are reported in included clinical trials are not clinical outcomes (mortality, arrhythmias, low cardiac output) but intermediate disease markers (serum CK-MB or plasma MDA).

Most clinical trials were performed on small samples, from 20 [13,16] to 121 patients [11]. Randomized, controlled trials with small sample size have a higher risk of generating non-homogeneous groups in terms of potential confounding factors, which is the main strength of these kinds of studies.

Moreover, none of the clinical trials included in this review report any adverse effects associated with CoQ10 administration and that CoQ10 has been demonstrated to be safe even at much higher doses (1200 mg/day) by other studies [19].

Trials assessing the effect of other antioxidant molecules, like *N*-acetylcysteine, α-tocopherol or vitamin E, or propofol, appear to reduce surrogate biochemical measures of injury, but these results do not consistently manifest themselves in clinical outcome benefits [7].

CONCLUSIONS

CoQ10 administration before surgery in patients undergoing cardiac surgery with cardiopulmonary bypass significantly reduces the proportion of patients who require inotropic drugs after surgery and significantly reduces the incidence of ventricular arrhythmias after surgery. However, there is no evidence to conclude that CoQ10 improves the cardiac index 24 h after surgery, or reduces hospital stay or the incidence of atrial fibrillation. None of the clinical trials reported any adverse effects. We conclude that CoQ10 should be considered as a prophylactic treatment for preventing complications in patients undergoing cardiac surgery with cardiopulmonary bypass. However, we would like to call for adequately powered, better quality and long-term randomized clinical trials to clarify the preventive role of CoQ10 on myocardial damage due to CPB.

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