Coenzyme Q\textsubscript{10} in cardiovascular disease

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Abstract

In this review we summarise the current state of knowledge of the therapeutic efficacy and mechanisms of action of CoQ\textsubscript{10} in cardiovascular disease. Our conclusions are: 1. There is promising evidence of a beneficial effect of CoQ\textsubscript{10} when given alone or in addition to standard therapies in hypertension and in heart failure, but less extensive evidence in ischemic heart disease. 2. Large scale multi-centre prospective randomised trials are indicated in all these areas but there are difficulties in funding such trials. 3. Presently, due to the notable absence of clinically significant side effects and likely therapeutic benefit, CoQ\textsubscript{10} can be considered a safe adjunct to standard therapies in cardiovascular disease.

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1. Introduction

Coenzyme Q\textsubscript{10} (CoQ\textsubscript{10}) was discovered by Fredrick Crane in 1957. In the early 1980’s Karl Folkers recognised the therapeutic potential of CoQ\textsubscript{10} in cardiovascular disease and used it to treat patients with heart failure (Folkers et al., 1985; Langsjoen et al., 1985). The initial results were encouraging so that further trials of CoQ\textsubscript{10} in ischemic heart disease and hypertension followed (Folkers et al., 1981). CoQ\textsubscript{10} was also used as a preoperative preparation before cardiac surgery (Judy et al., 1993) and heart transplantation (Berman et al., 2004). In subsequent years, numerous small trials of CoQ\textsubscript{10} in cardiovascular disease have reported promising beneficial results but others have reported no apparent effect. However few of these trials have enrolled sufficient numbers of patients to show significant differences in the major cardiac events (MACE) such as death and myocardial infarction. As a result the CoQ\textsubscript{10} literature is replete with multiple small trials showing promising results in terms of relief of symptoms and improvements in cardiac functional and metabolic parameters but underpowered to show improvements in MACE. Several useful meta-analyses have been published and are presented in detail in this review. These analyses have generally indicated a beneficial effect of CoQ\textsubscript{10} in heart failure and in hypertension.

Heart failure research is growing more demanding by the year due to the potent effects of combined therapy including ACE inhibitors, aldosterone antagonists, and beta-blockers. This therapy has decreased the therapeutic window available for adjunct therapies. As CoQ\textsubscript{10} is not considered a pharmaceutical drug covered by government or health insurance rebate items in the USA and most European countries, patients who use CoQ\textsubscript{10} therapy are involved in considerable personal cost. However this is slowly changing with Japan and some European countries (Hungary, Italy, Norway and Denmark) now granting...
licensed prescription of CoQ10 for heart failure and ischemic heart disease. Despite all these obstacles and disincentives there is a large and ever growing demand by the general public for CoQ10 to treat cardiovascular and other diseases, either with or without medical prescription. Most major therapeutic agents have side effects that reduce the quality of life in many patients and decrease compliance with therapy. By contrast CoQ10 is remarkable for its absence of side effects, which is one of the reasons for patient use of it. Unlike pharmaceutical agents CoQ10 has very little industry financial support to drive a crucial increase in research into its therapeutic efficacy, so progress has been slow and limited. The aim of this paper is to summarise the current state of knowledge of the therapeutic efficacy and mechanisms of action of CoQ10 in the major cardiovascular diseases.

2. Effects of coenzyme Q10 in ischemic heart disease

Oxidative stress arising from the imbalance between augmented free radical production and inadequate antioxidant defence has been implicated in ischaemia-reperfusion injury. In cardiomyocytes mitochondria are abundant, (as much as 60% of cell volume), and in order to fulfil the cell’s predominant dependence on mitochondrial ATP production to support contractile function and cardiac output, mitochondria are densely localised in linear formation adjacent to the myofilament contractile apparatus. In addition, mitochondria are the major source of superoxide in cardiomyocytes, particularly in response to reduced oxygen availability (Hool et al., 2005). This has lead to the development of treatments against ischaemia-reperfusion injury using agents such as CoQ10, which serves multiple molecular roles in the mitochondria and beyond (Ebadi, 2001).

Improved preservation of mitochondrial ATP-generating capacity after ischaemia and reperfusion has been reported for rabbit hearts pre-treated with CoQ10. These results correspond to the improved post-ischaemic preservation of myocardial contractile function and reduced creatine phosphokinase release in CoQ10 pre-treated hearts (Nayler, 1980). Hano et al. (1994) showed that CoQ10 pre-treatment improved post-ischaemic recovery of high-energy phosphates and contractile function in isolated rat hearts, while preventing calcium overload and preserving diastolic function. A more recent study, also using an isolated rat heart model, demonstrated that CoQ10 pre-treatment improved diastolic function during reperfusion, maintained higher ATP levels, preserved coronary vasodilatation by sodium nitroprusside and increased coronary flow (Whitman et al., 1997). In a study in pigs, feeding with CoQ10 for 30 days rendered their hearts more resistant than controls to a combination of regional and global myocardial ischemia. Treated animals demonstrated improved contractile function accompanied by reduced release of creatine kinase and malondialdehyde in the cardiac effluent (Maulik et al., 2000).

We demonstrated the cardioprotective action of CoQ10 in aged (≥70 years) and younger (<70 years) human atrial trabeculae discarded at cardiac surgery (Rosenfeldt et al., 2002). After 30 min of immersion in either CoQ10 (400 μM) or vehicle solution, trabeculae were subjected to 30 min of simulated ischemia. In younger trabeculae CoQ10 produced a small but non-significant increase in post-ischemic contractile recovery (63.4 ± 3.4% to 71.5 ± 3.3%). However in aged trabeculae CoQ10 treatment produced a large increase in recovery from (53.0 ± 2.9%) to a similar level to that seen in the younger trabeculae (74.6 ± 3.5%, P < 0.05). That is CoQ10 exhibited an age-specific cardioprotective effect. CoQ10 is crucial for preservation of oxidative phosphorylation in the myocardium during conditions of metabolic stress with resultant reduction of myocardial damage and improvement of post-stress contractile function.

CoQ10 also specifically binds to a site in the inner mitochondrial membrane that inhibits the mitochondrial permeability transition pore (MPTP) (Fontaine et al., 1998; Walter et al., 2000; Papucci et al., 2003). The MPTP is a large conductance channel, which when opened can trigger the collapse of mitochondrial proton-motive force and membrane potential. In cell death signalling pathways this leads to the disruption of ionic homeostasis and oxidative phosphorylation particularly after ischemia and reperfusion (Di Lisa et al., 2003). CoQ10 protects creatine kinase and other key proteins from oxidative inactivation during reperfusion, a function crucial in preserving energy metabolism and cardiac performance (Crestanello et al., 1996; Chello et al., 1994; Chen et al., 1994; Taggart et al., 1996; Zhou et al., 1999; Choksi et al., 2004).

It has been reported that dietary consumption of oxidised CoQ10 (ubiquinone) in humans and rats leads to a marked rise in plasma of the reduced form of CoQ10, ubiquinol (Mohr et al., 1992, 1999; Kaikkonen et al., 2002). Although the specific mechanism(s) of this conversion of CoQ10 to reduced form upon intestinal absorption are not fully elucidated, the mucosal GSH peroxidase/oxidized glutathione (GSSG) reductase system which catalyses the reduction of lipid hydroperoxides has been implicated (Aw et al., 1992). CoQ10 is carried mainly by lipoproteins in the circulation, predominantly in its reduced form, ubiquinol. Ubiquinol acts as an antioxidant in plasma lipoproteins, lowering the oxidation rate of dietary fatty acids transported in the lipoproteins (Alleva et al., 1995; Tomono et al., 1986; Frei et al., 1990; Stocker et al., 1991). During its anti-oxidative action ubiquinol is oxidised to ubiquinone.

CoQ10 has an important role in preventing the initiation and/or propagation of lipid peroxidation in plasma lipoproteins and membrane proteins. Ferrara et al. (1995) demonstrated that chronic treatment with CoQ10 in rats protected against cardiac injury due to oxidative stress created by hydrogen peroxide (H2O2) in the heart. CoQ10 can inhibit lipid peroxidation in mitochondria (Glinn et al., 1997), protein oxidation (Ernst et al., 2004) and DNA
oxidation (Tomasetti et al., 1999). After its antioxidative action, ubiquinone can be recycled to the antioxidant, active, reduced ubiquinol form via the mitochondrial Q cycle. CoQ_{10} importantly is also responsible for transforming Vitamin E radicals to regenerate the reduced (active) \(\alpha\)-tocopherol form of Vitamin E (Constantinescu et al., 1994).

As well as playing a crucial role in the mitochondrial respiratory chain for ATP production, CoQ_{10} also plays a crucial role in extra-mitochondrial electron transfer such as in the regulation of NADH oxido-reductase activity in the plasma membrane (Lawen et al., 1994; Villalba et al., 1997), and also has potential redox activity in both Golgi apparatus and lysosomes (Crane et al., 1984).

There is another potential molecular action of CoQ_{10} that to date has had little investigation. This relates to the capacity of CoQ_{10} to regulate and alter genomic expression. CoQ_{10} has been shown to target the expression of multiple genes, particularly those involved in cell signalling and intermediary metabolism (Groneberg et al., 2005). Linnane and colleagues (2002), have reported that 25–30 days oral intake of CoQ_{10} (300 mg/day) by patients waiting for hip surgery resulted in a significant change in the expression of 115 genes, 47 up-regulated and 68 down-regulated, as measured by differential gene array chip methodology in vastus lateralis muscle biopsy. Many of these genes included those governing nuclear and other enzymes, transcription factors, muscle fibre components, growth factors, receptors and receptor-activated signal transduction transcription factors, muscle fibre components, growth factors, receptors and receptor-activated signal transduction and other metabolic pathways. This work thus opens an entire new avenue of investigation to tease out other specific mechanisms of CoQ_{10}'s pleotropic actions. Thus gene regulation and control of metabolic flux may explain many of the cardiovascular and other actions of CoQ_{10} whereby it may act in a beneficial way at multiple sites in the pathophysiological cascade.

At a clinical level, protection against myocardial ischemia has been demonstrated in two double blind placebo-controlled crossover trials of CoQ_{10} in patients with ischaemic heart disease by a reduction in angina, improved exercise tolerance and a reduction in ischaemic changes on ECG (Kamikawa et al., 1985; Schardt et al., 1985). These beneficial effects may be related to increased efficiency in myocardial mitochondrial energy production as we have demonstrated in patients with ischaemic heart disease following the treatment with CoQ_{10} (Rosenfeldt et al., 2005).

3. Coenzyme Q_{10} in heart failure

3.1. Loss of efficient respiratory chain function, augmented ROS and diminished ATP

Central to the loss of contractile function in heart failure is the inability of mitochondria to adequately supply the myocardium with ATP, resulting in energy deprivation in the cell and potentially necrotic/apoptotic cell death. It is estimated that the majority of mitochondrial ATP-derived energy supports myocardial contraction; and the maintenance of ion homeostasis; these activities account, respectively for 75% and 25% of cardiomyocyte energy consumption (Giordano, 2005). However, the underlying molecular causal events leading to metabolic dysfunction are poorly understood. The production of reactive oxygen species (ROS) has been shown to increase in the failing heart, and, mitochondrial proteins and lipids may be targets of oxidative damage in the failing heart due to their close proximity to sites of superoxide production. (Fig. 1).

Reduced ATP synthesis, as measured by a lowering of state III (ADP-coupled) respiration has been demonstrated in isolated cardiac mitochondria from failing animal (Sharov et al., 1998) and human (Sharov et al., 2000) hearts, relative to non-failing controls. In an attempt to identify possible causes for this decline, many studies have focused on the measurement of the electron transport chain enzymes in a number of human cardiomyopathies. Most notably, complex I (Scheubel et al., 2002), complex III (Jarreta et al., 2000), and complex IV (Arbustini et al., 1998), have been identified as dysfunctional in end-stage human heart failure. A direct causal relationship, however, has proven elusive over the years, with a poor correlation between reduced complex activities and the severity of disease (Arbustini et al., 1998). This may be partly explained by a large reserve capacity for activity of each respiratory protein complex. For example, up to 50% inhibition of complex I, or IV activity, is required before a significant decline in state III respiration is apparent (Lucas and Szwedea, 1999).

In contrast, Krebs cycle enzymes involved in the regulation of substrate metabolism appear to exert a more direct control over energy output, with a close correlation between the loss of \(\alpha\)-ketoglutarate dehydrogenase (KGDH) activity and decreased state III respiration (Humphries et al., 1998). Due to their close interaction with Complex I, a major site of mitochondrial superoxide formation, NADH-linked enzymes such as KGDH and isocitrate dehydrogenase (ICDH) may be susceptible to ROS-dependent perturbation. Reduced ICDH activity (~30%) has been demonstrated as an early marker of hypertrophy before the onset of ventricular dysfunction, in transgenic hypertrophic cardiomyopathic mice (Lucas et al., 2003) and spontaneously hypertensive rats (SHR) (Benderdour et al., 2004). The decline in \(\alpha\)-KGDH, pyruvate dehydrogenase (PDH) and ICDH activity coincides with the formation of protein thiol adducts with 4-hydroxy-2-nonenal (HNE), a lipid peroxidation aldehyde formed via reaction between arachidonic acid and superoxide (Esterbauer et al., 1991; Humphries and Szwedea, 1998; Humphries et al., 1998; Benderdour et al., 2003). Reduced \(\alpha\)-KGDH activity together with increased HNE-adduct formation has also been described in aged rats (Humphries and Szwedea, 1998; Lucas and Szwedea, 1999). However, the specific role that perturbation of these enzymes play in contributing to an energy deficit in the failing heart awaits detailed examination.
Nevertheless it is apparent that diminished mitochondrial energy metabolism in the failing heart involves dysfunction in Krebs cycle regulation, NADH supply and activity of electron transport chain proteins. Thus CoQ10 may act in a beneficial way at multiple sites in the pathological cascade of advancing heart failure (Fig. 1).

Increased myocardial levels of oxidative stress markers have been demonstrated in animal models of heart failure produced by coronary ligation (Hill and Singal, 1996), pressure overload (Dhalla and Singal, 1994) and rapid cardiac pacing (Ide et al., 2000). ROS are key pathophysiological mediators in myocardial remodelling in heart failure (Singal et al., 1993). In human heart failure, there is also evidence of increased levels of oxidative stress markers such as malondialdehyde (MDA) in serum (Belch et al., 1991), and isoprostanes in urine (Cracowski et al., 2000). Furthermore the levels of these markers correlate with the severity of heart failure.

Elevated MDA concentration has been measured in the plasma of patients with symptoms of moderate congestive heart failure (NYHA III, left ventricular ejection fraction less than 40%), compared to age-matched non-failing controls (ejection fraction greater than 40%), which increased with the duration (years) of congestive heart failure (Diaz-Velez et al., 1996). A significantly high concentration of plasma MDA and reduced thiol has also been reported in heart failure patients with underlying coronary artery disease (McMurray et al., 1990). Mak and co-workers, (2000) demonstrated that total aldehydes are elevated in the plasma of heart failure patients, with a strong negative correlation between total aldehydes and contractility ($-dP/dt$). Keith et al. (1998) also reported a correlation between severity of heart failure and elevated lipid peroxides and MDA in both ischemic heart disease and dilated cardiomyopathy patients with end-stage heart failure. Another indirect marker of oxidative stress, 8-iso-prostaglandin $F_{2}$α, derived from the oxidation of arachidonic acid, is increased in the pericardial fluid of patients in proportion to the severity of heart failure of ischemic and/or valvular disease origin (Mallat et al., 1998).

Direct evidence of augmented myocardial superoxide production in the failing heart has been established in studies using electroparamagnetic spin resonance (EPR) spectroscopy (“spin-trapping”). Increased superoxide production has been demonstrated in the myocardium of explanted human heart failure tissue compared to non-failing donor heart muscle (Sam et al., 2005), confirming the results obtained in a pacing-induced animal model of heart failure (Ide et al., 1999). However, in vivo, real time demonstration of increased cardiac superoxide metabolism in human heart failure is yet to be reported.

A significant contribution of oxygen radical generation in the cardiomyocyte originates within mitochondria during oxidative phosphorylation. It is estimated that during normal metabolism 1–2% of oxygen is incompletely converted to H$_2$O during electron transfer, resulting in the formation of ROS such as the superoxide ($O_{2}^{-}$) and hydroxyl (OH$^-$) anions and H$_2$O$_2$ (Turrens, 1997). The reactivity of oxygen derives from its incomplete pairing of electrons in the outer electron shell, and thus single electron transfer forms the superoxide anion, $O_{2}^{-}$ (Giordano, 2005). The proposed sites of mitochondrial superoxide formation are at Complex I (NADH dehydrogenase) (Turrens and...
Boveris, 1980), and the ubisemiquinone site of Complex III (Turrens et al., 1985), as demonstrated using targeted inhibitors. Due to the location of sites of oxygen radical formation, complex I is expected to release superoxide towards the mitochondrial matrix, whereas superoxide generated at complex III may be directed towards both the matrix and intermembrane space (Turrens et al., 1985; Lesnefsky et al., 2001). Through the use of mass spectroscopy, protein subunits protruding into the mitochondrial matrix have been shown to be most at risk from oxidative damage as targets of HNE binding, or carbonyl and nitrosyl modification under basal conditions. Increased superoxide formation by Complex I has been directly measured in the sub-mitochondrial fraction from failing cardiomyocytes, together with a significant loss of complex I activity (Ide et al., 1999), implicating the mitochondrial electron transport chain as a significant contributor to the pathogenesis of heart failure.

It has been proposed that the amount of superoxide formed is increased under state IV as opposed to state III respiration, due to lower ADP availability and increased molecular oxygen, whereas uncoupling conditions lower the production of ROS. Basal respiration has been shown to increase in patients with congestive heart failure (Poehlman et al., 1994) by increased resting oxygen consumption, indicating an underlying increase in basal ROS production in the diseased state. Under conditions of inefficient mitochondrial respiration due to reduced complex I activity, ROS production may also be increased (Pitkanen and Robinson, 1996; Luo et al., 1997).

3.2. Antioxidant therapy

Li et al. (1995), demonstrated, in a superoxide dismutase ‘knock-out’ genetic mutant mouse model, a rapid onset of severe cardiomyopathy causing death in neonates that implicated inadequate endogenous regulation of superoxide metabolism. Experimental animal studies have reported beneficial effects of antioxidant therapy during the development of heart failure. Vitamin E in guinea pigs with pressure overload can prevent the transition from compensated hypertrophy to heart failure (Dhalla et al., 1996). Similarly probucol, a lipid-lowering agent with antioxidant actions, can protect against heart failure induced by adriamycin (Singal et al., 1995) and diabetes (Kaul et al., 1995) – see Kukin and Fuster (2003) for a detailed review. There are multiple molecular, cellular and neurohormonal mechanisms that contribute to the syndrome of heart failure and it is likely that oxidative stress is involved in some or all of these processes. There is no doubt that antioxidant therapy can attenuate oxidative stress. However, many of the early clinical trials of antioxidant therapy for heart failure were negative. This may be explained by the use of ineffective, incorrectly dosed agents (Cohn, 2003). However the results of using more potent antioxidants such as CoQ10 that have other beneficial actions have been more encouraging (Langsjoen et al., 1985; Poggesi et al., 1991; Peremanetter et al., 1992; Munkholm et al., 1999; Watson et al., 1999). A recent small (n = 23) trial in patients with NYHA Class II and III heart failure using a cross-over design, showed that four weeks of CoQ10 (100 mg tid) therapy improved exercise capacity (VO2), cardiac ejection fraction and endothelium-dependent brachial artery dilation (Belardinelli et al., 2006). Similar effects were achieved by physical exercise training and these effects were in general additive to those of CoQ10 therapy. However most trials have been open label and in some, only 50% of patients took angiotensin converting enzyme (ACE) inhibitors that are now standard therapy for heart failure. Differences in etiology, the stage of heart failure progression and therapeutic treatment history complicate any comparisons between studies and patient groups. Although CoQ10 treatment for heart failure has been claimed to ameliorate symptoms, improve quality of life and reduce rates of hospitalisation, various limitations of such studies and the reported lack of beneficial effects by others (Khatta et al., 2000), indicate the need for large multi-centre, closely monitored double-blind placebo controlled trials in heart failure.

3.3. Meta-analyses of randomised trials of coenzyme Q10 in heart failure

A meta-analysis showing a beneficial effect of CoQ10 in heart failure was published in 1997 (Soja and Mortensen, 1997). We updated their findings by performing a meta-analysis of randomised trials of CoQ10 in heart failure published up to 2003 (Rosenfeldt et al., 2003). Only prospective, randomised, double-blinded and placebo-controlled trials were included in that analysis. The only three parameters with adequate numbers of subjects for meaningful analysis were CoQ10 levels (five trials), ejection fraction at rest (seven trials) and mortality (five trials). Other parameters were measured in only two trials each. For CoQ10 levels (279 patients) the weighted mean difference was 1.4 µg/mL, representing an increase of 161%. For ejection fraction at rest (384 patients) the weighted mean difference showed a trend in favour of CoQ10 of 1.9% (95% confidence limits –0.13 to 3.9%).

An updated meta-analysis has been recently published (Sander et al., 2006). This meta-analysis included eleven randomised trials of coenzyme Q10 in heart failure, including both cross-over and parallel trial designs (Table 1). The main endpoint of resting ejection fraction showed a 3.7% net improvement (1.59–5.77; P < 0.0006; Fig. 2). Stroke index also increased by 5.8 ml (P = 0.02). Subgroup analyses showed that the ejection fraction improvement was more pronounced when studies of NYHA class IV were excluded, when only idiopathic cardiomyopathy was evaluated and among patients not receiving angiotensin converting enzyme (ACE) inhibitors. When the results were re-analysed using a less conservative statistical test (fixed effects modelling) than was used in the initial analysis...
Table 1
Prospective randomised clinical trials of CoQ₁₀ for heart failure

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age</th>
<th>Dose used</th>
<th>Treatment duration</th>
<th>Etiology of HF</th>
<th>NYHA class</th>
<th>Other HF medications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crossover trials</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hoffman-Bang et al., 1995</td>
<td>61</td>
<td>100 mg QD</td>
<td>3 mo (no washout)</td>
<td>Ischemic and nonischemic (idiopathic, hypertensive, valvular, and other)</td>
<td>II–IV (76% Class II)</td>
<td>75% digoxin, 96% diuretics 60% ACE inhibitor, no BB</td>
</tr>
<tr>
<td>(n = 69)</td>
<td>(10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Langsjoen et al., 1985</td>
<td>63</td>
<td>33.3 mg</td>
<td>3 mo (no washout)</td>
<td>Idiopathic</td>
<td>III–IV</td>
<td>100% digoxin, 94% diuretics-No ACE inhibitor or BB</td>
</tr>
<tr>
<td>(n = 19)</td>
<td>(6.7)</td>
<td></td>
<td></td>
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<tr>
<td>Morisco, 1994</td>
<td>50</td>
<td>50 mg TID</td>
<td>1 mo (no washout)</td>
<td>4 CAD and 2 idiopathic</td>
<td>II–IV</td>
<td>Nitro derivatives No ACE inhibitor or BB</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Poggesi et al., 1991</td>
<td>67</td>
<td>50 mg BID</td>
<td>2 mo</td>
<td>13 idiopathic, 7 ischemic (only 18 completed the study)</td>
<td>II–III</td>
<td>Digoxin, diuretics, ACE inhibitor</td>
</tr>
<tr>
<td>(n = 18)</td>
<td>(2.3)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Serra, 1991</td>
<td>59</td>
<td>60 mg QD</td>
<td>1 mo (no washout)</td>
<td>13 CAD, 7 hypertensive</td>
<td>II–III</td>
<td>Digoxin, diuretics, nitrates</td>
</tr>
<tr>
<td>(n = 20)</td>
<td>(6.6)</td>
<td></td>
<td></td>
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<tr>
<td>Watson et al., 1999</td>
<td>55</td>
<td>33 mg TID</td>
<td>3 mo</td>
<td>77% idiopathic, 23% ischemic</td>
<td>Mean 41 mo</td>
<td>80% digoxin, 93% diuretics 83% nitrates or hydralazine, 100% ACE inhibitor, no BB</td>
</tr>
<tr>
<td>(n = 27)</td>
<td>(11)</td>
<td></td>
<td></td>
<td></td>
<td>duration and EF</td>
<td></td>
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<tr>
<td>Parallel trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;35%</td>
<td></td>
</tr>
<tr>
<td>Keogh et al., 2003</td>
<td>62</td>
<td>50 mg TID</td>
<td>3 mo</td>
<td>Ischemic, valvular; idiopathic</td>
<td>II–III EF &lt; 40%</td>
<td>71% digoxin, 91% diuretics, 22% nitrates or hydralazine 100% ACE inhibitor, no BB</td>
</tr>
<tr>
<td>(n = 35)</td>
<td>(8)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Khatta et al., 2000</td>
<td>64</td>
<td>200 mg/d</td>
<td>6 mo</td>
<td>59% ischemic</td>
<td>III–IV EF &lt; 40%</td>
<td>96% diuretics, 100% digoxin, 100% ACE inhibitor or other vasodilators, 78% BB</td>
</tr>
<tr>
<td>(n = 46)</td>
<td>(13)</td>
<td></td>
<td></td>
<td></td>
<td>Class III EF</td>
<td></td>
</tr>
<tr>
<td>Munkholni 1995</td>
<td>57</td>
<td>100 mg BID</td>
<td>3 mo</td>
<td>Ischemic or dilated</td>
<td>II–III EF &lt; 45%</td>
<td>55% digoxin, 86% diuretics, 95% ACE inhibitor, no BB</td>
</tr>
<tr>
<td>(n = 22)</td>
<td>(15)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Judy, 1993</td>
<td>66</td>
<td>100 mg/d</td>
<td>6 mo</td>
<td>Various etiologies</td>
<td>IV</td>
<td>Unknown</td>
</tr>
<tr>
<td>(n = 10)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Permanetter et al., 1992</td>
<td>52</td>
<td>100 mg/d</td>
<td>3 mo</td>
<td>Idiopathic</td>
<td>I–III (60% Class III)</td>
<td>92% digoxin, 64% diuretics, 44% nitrates or nifedipine</td>
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<tr>
<td>(n = 25)</td>
<td></td>
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From Sander et al., 2006, with permission.

ACE, angiotensin-converting enzyme; BB, beta-blockers; BID, twice daily; EF, ejection fraction; HF, heart failure; NYHA, New York Heart Association; QD, once daily, TID, three times daily.

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Fig. 2. Forrest plot of the effect of CoQ₁₀ on cardiac ejection fraction. From Sander et al., 2006, with permission.
(random effects modelling), increases in cardiac output, cardiac index and stroke volume all became significant.

Unfortunately most of the published trials to date have been underpowered to detect significant differences, particularly in major endpoints such as mortality. Trials to detect a mortality difference would need to be prohibitively large, requiring 2000 or more patients per group. For the future, a reasonable expectation would be to conduct a multinational prospective, randomised trial containing 300–400 patients per group to make a more definitive conclusion as to the effects of CoQ10 on cardiac function and symptoms in cardiac failure. Such a trial, the “Q-symbio” trial is currently in progress (Mortensen, 2003).

In light of the encouraging findings of the above mentioned meta-analyses, it is not unreasonable to recommend to patients with symptomatic heart failure despite conventional therapy or those who are experiencing side effects of conventional therapy (especially ACE inhibitors), to take 150–300 mg of CoQ10 daily and to monitor CoQ10 blood levels and the clinical response.

3.4. Statin sensitivity and coenzyme Q10 deficiency

The 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase inhibitors or “statins” are at present one of the most widely prescribed drugs in the Western World. Although the effect of statins on CoQ10 levels will be covered in detail by others in this journal issue, it is important to highlight here apparent complications related to their use in cardiovascular disease. From 1990 to 2003, 15 studies in humans have been published evaluating the effects of statins on CoQ10 metabolism (Langsjoen and Langsjoen, 2003). Nine of these were randomised controlled trials, and eight of these demonstrated significant depletion of plasma CoQ10 due to statin therapy. De Pinieux et al. (1996) reported raised lactate to pyruvate ratios in statin-treated patients, in association with CoQ10 depletion and mitochondrial dysfunction.

Thus some statins, mainly lipid soluble types, may decrease body CoQ10 levels below the threshold that is required for numerous redox-dependent processes. This depletion could be particularly important in the elderly where CoQ10 levels are generally low. Adverse effects of statin-induced CoQ10 reduction have been reported at a mitochondrial level but infrequently at a clinical level. When they do occur these adverse effects may be correctible by concurrent administration of CoQ10. By contrast in a large study of patients with heart failure statin use was associated with lower risks of death or hospitalisation among patients with or without coronary artery disease (Go et al., 2006). This result concurs with the findings of several cohort studies of heart failure patients treated with statins (Udell and Ray, 2006).

Beneficial effects of statins in heart failure may relate to their pleotrophic effects which include improved endothelial function and stimulation of cellular antioxidant and anti-inflammatory processes. In most heart failure patients these beneficial effects may outweigh the detrimental effects of CoQ10 depletion, particularly if such depletion is only partial. Further studies examining the specific mechanisms of cardiovascular-specific local synthesis of CoQ10 and molecular mechanisms of statin action on cellular metabolism are needed.

3.5. Prevention of anthracycline-induced cardiotoxicity

Doxorubicin and other anthracyclines are among the most potent chemotherapeutic agents for the treatment of a wide variety of tumours. However their usefulness is limited by dose-related cardiotoxicity (Tokarska-Schlattner et al., 2006) that leads to arrhythmias and myocardial depression during therapy and to cardiomyopathy that can present years after treatment (Abu-Khalaf et al., 2006). There is increasing evidence (summarised in three reviews: van Dalen et al., 2005; Conklin, 2005; Wouters et al., 2005), that CoQ10 administration can prevent or reduce these undesirable side effects.

The dose-related cardiomyopathy induced by anthracyclines may be explained largely by the induction of irreversible oxidative damage to cardiac mitochondria. These organelles are highly susceptible to the effects of anthracyclines due to the presence of a unique enzyme (a NADH dehydrogenase) in their inner mitochondrial membrane (Conklin, 2005). This enzyme reduces anthracyclines to their semiquinones ultimately resulting in severe oxidative damage to mitochondrial DNA leading to apoptosis of cardiomyocytes. CoQ10 by its antioxidant action and high concentration in the inner mitochondrial membrane can reduce this oxidative damage.

CoQ10 has been shown to protect against anthracycline-induced lipid peroxidation in beef heart mitochondria isolated rat hearts and intact mice, rats and rabbits (Conklin, 2005). These protective effects are not normally seen with other antioxidants such as vitamin E. Three non-randomised clinical trials have shown that the simultaneous treatment of patients with CoQ10 and anthracyclines decreases cardiotoxicity without reducing the anti-tumour effect. However one randomised trial showed no significant difference in effect between CoQ10 treated patients and controls (Wouters et al., 2005).

We conclude that the use of CoQ10 for the prevention and treatment of anthracycline-induced cardiotoxicity is promising on the basis of numerous animal studies and a small number of clinical trials. As with many of the other clinical applications of CoQ10 therapy, larger randomised clinical trials are needed to confirm or deny the preliminary findings, to determine the optimum dose of CoQ10 and whether CoQ10 treatment preserves (or even enhances) anti-tumour effects. In the meantime a case can be made for combining CoQ10 with anthracycline therapy and carefully monitoring the results in terms of cardiotoxicity and anti-neoplastic effects.
4. Coenzyme Q₁₀ in hypertension

4.1. Antihypertensive effects and clinical efficacy

Hypertension is currently managed by a variety of medications. These are effective in reducing blood pressure, but many have undesirable side effects such as renal or cardiac dysfunction, cough and mental depression. CoQ₁₀ has been shown in laboratory and clinical studies to have a hypotensive effect (Yamagami et al., 1975; Singh et al., 1999; Burke et al., 2001; Hodgson et al., 2002). Since 1975, many studies have described the potential of CoQ₁₀ to lower blood pressure in hypertensive patients. Negligible side effects have been reported even with high doses of CoQ₁₀. A study of subjects with type 2-diabetes showed that CoQ₁₀ therapy lowered blood pressure and improved glycemic control (Hodgson et al., 2002). However, despite these reports the current role of CoQ₁₀, if any, in the treatment of hypertension is unclear. We recently reviewed the published clinical trials of CoQ₁₀ in the management of hypertension in terms of its therapeutic effect and side effect profile and conducted a meta-analysis of the pooled results using STATA v.8.2 software with the Cohen method of meta-analysis for weighted mean difference with respect to continuous variables (Rosenfeldt et al., 2007). We identified 12 studies that reported a total of 362 patients in which CoQ₁₀ had been used in the therapy of hypertension (Table 2).

These comprised three randomized controlled clinical trials (Yamagami et al., 1986; Singh et al., 1999; Burke et al., 2001), one cross-over study (Digiesi et al., 1990) and eight open label observational studies without a control group (Yamagami et al., 1975, 1976, 1977; Folkers et al., 1981; Montaldo et al., 1991; Digiesi et al., 1992, 1994; Langsjoen et al., 1994). When trial results were pooled, CoQ₁₀ produced a reduction of up to 17 mmHg in systolic and 10 mmHg in diastolic blood pressure, (Rosenfeldt et al., 2007).

4.2. Mechanism of antihypertensive action

An increase in oxidative stress is well documented in hypertensive states (Koska et al., 1999). In blood vessels, oxidative stress increases the production of superoxide radicals that rapidly react with endothelial nitric oxide (NO) to form peroxynitrite, thus reducing NO availability (Grunfeld et al., 1995). This reduction impairs the ability of endothelium to induce NO-mediated relaxation of underlying smooth muscle with resultant vasoconstriction and increased blood pressure. The primary action of CoQ₁₀ in clinical hypertension is vasodilatation, via a direct effect on the endothelium and vascular smooth muscle resulting in decreased peripheral resistance accompanying lowered blood pressure and unchanged cardiac output (Folkers et al., 1981; Digiesi et al., 1992, 1994). In patients with diabetes or dyslipidemia CoQ₁₀ improves endothelial function and lowers blood pressure (Watts et al., 2002). Thus the benefit of CoQ₁₀ is as a potent lipid-soluble antioxidant that preserves NO availability and reduces vasoconstriction and augmented blood pressure. It should be noted however that in normal animals or humans, CoQ₁₀ has no direct vasodilatory or hypotensive effect. This confirms that the hypotensive effect of CoQ₁₀ is specific to the state of enhanced oxidative stress occurring in hypertensive patients.

4.3. Clinical implications

Being devoid of significant side effects, CoQ₁₀ may thus have a useful clinical role as an adjunct or alternative anti-hypertensive to conventional agents such as diuretics and ACE inhibitors in the treatment of hypertension. In support of this, in one study 50% of subjects treated with CoQ₁₀ were able to cease at least one of their other hypertensive medications (Langsjoen et al., 1994). As CoQ₁₀ has the potential in hypertensive patients to lower systolic blood pressure by up to 17 mmHg and diastolic pressure by up to 10 mmHg

Table 2

<table>
<thead>
<tr>
<th>Trials of CoQ₁₀ in hypertension</th>
<th>Patients (n)</th>
<th>Systolic blood pressure (mmHg)</th>
<th>Diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised trials</strong></td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Treatment group 3</td>
<td>63</td>
<td>167.7</td>
<td>151.1</td>
</tr>
<tr>
<td>(163.7–171.1)</td>
<td>(147.1–155.1)</td>
<td>(−20.6 to −12.6)</td>
<td>(101.0–105.0)</td>
</tr>
<tr>
<td>Control group 57</td>
<td>57</td>
<td>166</td>
<td>163.9</td>
</tr>
<tr>
<td>(162.1–170.0)</td>
<td>(159.9–167.9)</td>
<td>(−6.1 to 1.9)</td>
<td>(100.2–104.7)</td>
</tr>
<tr>
<td>Crossover study</td>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Treatment phase 1</td>
<td>18</td>
<td>167 ± 2.6</td>
<td>156 ± 2.3</td>
</tr>
<tr>
<td>Control phase</td>
<td></td>
<td>166 ± 2.4</td>
<td>166 ± 2.4</td>
</tr>
<tr>
<td>Open label studies</td>
<td>8</td>
<td>214</td>
<td>162</td>
</tr>
<tr>
<td>(158.4–165.7)</td>
<td>(145.0–152.2)</td>
<td>(−17.1 to −9.8)</td>
<td>(95.2–99.1)</td>
</tr>
</tbody>
</table>

From Rosenfeldt et al. (2007), with permission.
without significant side effects, there is now a convincing case for conducting a high quality prospective randomised trial of CoQ10 in order to validate the results of this meta-analysis. In the current era of improved management of hypertension it would be unethical to conduct a placebo-controlled trial in hypertensive patients.

The ideal trial would be one comparing CoQ10 with an ACE inhibitor or diuretic as in the ANBP2 trial (Wing et al., 1996) to demonstrate non-inferiority of CoQ10. Two types of trials would be useful. The more conventional type would be one with the primary endpoint of death and major cardiac events such as stroke. Such a trial would need to include several thousand patients for adequate statistical power. The second type of trial would be one with end points such as adequacy of blood pressure control, improvement in cardiac function, improvement in exercise tolerance and quality of life, as well as prevalence of adverse effects. Until the results of such trials are available it would seem acceptable to add CoQ10 to conventional anti-hypertensive therapy, particularly in patients who are experiencing intolerable side effects of conventional anti-hypertensive therapy. CoQ10 may also have a particular therapeutic role in hypertensive patients with consistently increased levels of oxidative stress as in diabetes or renal failure.

5. Coenzyme Q10 in cardiac surgery

Coenzyme Q10 has been used in the cardiothoracic surgical setting in order to offset reperfusion-related increases in free radical formation and oxidative stress. From 1982 to 2004 at least eight controlled trials of CoQ10 in cardiac surgery have been published (Tanaka et al., 1982; Shiguma et al., 1983; Sunamori et al., 1991; Judy et al., 1993; Chello et al., 1994; Taggart et al., 1996; Zhou et al., 1999; Rosenfeldt et al., 2005). All but one of these have shown a beneficial effect of some kind. The one trial showing an absence of effect (Taggart et al., 1996) used oral CoQ10 for only 12 h before surgery, an inadequate time frame for sufficient dosing to increase myocardial levels. A prospective randomised placebo controlled trial from our unit of 300 mg per day of oral CoQ10 for two weeks preoperatively in 121 coronary bypass or valve replacement procedures showed increased mitochondrial CoQ10 content, increased efficiency of mitochondrial energy production and improved contractile function in myocardial trabeculae (Rosenfeldt et al., 2005).

6. Treating cardiac complications in Friedreich’s ataxia with coenzyme Q10

Friedreich’s ataxia (FRDA) is an autosomal recessive degenerative disease (1 in 30,000 live births) characterized by loss of large sensory neurones in the dorsal root ganglia and degeneration of the dorsal columns of the spinal cord, progressive limb and gait ataxia, loss of deep tendon reflexes, loss of the sense of position and vibration in the lower limbs, dysarthria and hypertrophic cardiomyopathy. The genetic abnormality has been mapped to chromosome 9q13 which encodes the protein frataxin. The genetic abnormality accounting for 98% of cases is the expansion of a GAA triplet repeat in intron 1 of the FRDA gene. This results in decreased frataxin mRNA levels which leads to lower levels of frataxin protein detected in muscle and brain of these patients.

The exact function of frataxin in humans is still unknown although evidence from yeast and mice indicate it has a key role in mitochondrial iron homeostasis. Endomyocardial biopsies in FRDA patients show deficient activity of the iron-sulphur (Fe–S) cluster containing proteins, namely complexes I, II and III of the mitochondrial respiratory chain. It appears that mitochondrial iron accumulation in FRDA is a consequence of deregulation of a mitochondrial iron import system triggered by the decreased amount of frataxin, normally acting as a regulator of the mitochondrial iron homeostasis. Studies of skeletal muscle from these patients have demonstrated a profound deficit of mitochondrial ATP production. Current evidence suggests that this frataxin deficiency results in impaired mitochondrial respiratory chain function due to the mechanisms outlined above. In addition, increased oxidative damage is seen in these patients and is likely to be a secondary consequence of impaired respiratory chain function and increased free radical generation related to Fenton reactions due to excess intracellular iron accumulation.

CoQ10 therapy in conjunction with vitamin E has been assessed in a small study of FRDA patients showing significant improvements in heart and skeletal muscle energetics after 6 months therapy (Cooper and Schapira, 2003). Idibenone, a short chain analogue of CoQ10, is a potent free radical scavenger that crosses the blood brain barrier, and has been recommended in the treatment of FRDA. However a one-year study of idibenone in 29 Friedreich ataxia patients showed a reduction in left ventricular hypertrophy but no improvement in neurological condition (Mariotti et al., 2003).

7. Getting coenzyme Q10 into the heart-dietary and endogenous synthesis

CoQ10 is poorly absorbed from food in the gut: only 10% of CoQ10 contained in a meal is absorbed (Weber et al., 1997). Bioavailability from a standard oral dose is low, being only 2–4% (Zhang et al., 1995), however, it is improved when CoQ10 is in an oily suspension (Bhagavan et al., 2001). Water soluble gel formulations have been developed for improved CoQ10 absorption (Chopra et al., 1998a,b).

Oral supplementation of CoQ10 leads to an elevation of plasma levels, with peak plasma CoQ10 levels occurring between 5 and 10 h after ingestion (Tomono et al., 1986). CoQ10 is absorbed slowly from the gastrointestinal tract, probably due to its high molecular weight and low water solubility. Following absorption from the gastrointestinal
tract, CoQ$_{10}$ is taken up by chylomicrons and transported to the liver for packaging into very low density lipoproteins (VLDL). From there it is transported to various tissues according to their requirement. Orally administered CoQ$_{10}$ appears to have a low clearance rate from the plasma, and therefore has a relatively long plasma half-life of 34 ± 5 h, with excretion predominantly through the biliary tract. Approximately 90 per cent of the steady state serum concentration can be achieved after 4 days of dosing.

Analysis of the distribution of CoQ$_{10}$ in the circulation shows that about 60% of CoQ$_{10}$ is transported by LDL, and less than 30% by HDL (Alleva et al., 1995). However, in the absence of significant exogenous supply of CoQ$_{10}$, individual tissues must rely on their own production as endogenously produced CoQ$_{10}$ is not transported within the body or redistributed to any great degree. Although CoQ$_{10}$ is present in a normal diet, with red meat and poultry being the richest sources, endogenous production appears to be the main source in humans (Weber et al., 1994). Whether it is in the diet or pharmaceutical supplementation, it is the oxidised form of CoQ$_{10}$ that is ingested and absorbed. The CoQ$_{10}$ is then reduced in the circulation, most likely in the red blood cells (Stocker and Suarna, 1993). Thus most CoQ$_{10}$ in the blood is present as the reduced form ubiquinol, consistent with its activity as an antioxidant in the circulation.

In humans, the fate of exogenously administered CoQ$_{10}$ once it reaches the circulation has not been completely elucidated. Work in rat hearts has shown that exogenously administered labelled CoQ$_{10}$ is incorporated into subcellular organelles, especially in the inner membranes and matrix of mitochondria, within 72 h of administration (Nakamura et al., 1980). It has also been demonstrated that incubation of beef heart submitochondrial particles in a CoQ$_{10}$ solution leads to incorporation of CoQ$_{10}$ in their membranes (Lenaz et al., 1994). The same authors found that kinetic saturation with CoQ$_{10}$ could not be achieved because of the intrinsic insolubility of the molecule, thus concluding that the upper limit of electron transfer from NADH is a function of CoQ$_{10}$ solubility in the membrane phospholipids. The bioavailability of different CoQ$_{10}$ preparations varies markedly, with a hydrophilic gel being superior to oil based preparations, with dry powder and tableted preparations being the least bioavailable (Molyneux et al., 2004).

Our own investigations into the use of CoQ$_{10}$ in cardiac surgery patients receiving 300 mg/day orally of CoQ$_{10}$ dispensed in soy bean oil demonstrated a four-fold increase in serum concentration of CoQ$_{10}$, and a 2.5-fold increase in of CoQ$_{10}$ in atrial myocardium which included a 2.4-fold increase of CoQ$_{10}$ in atrial mitochondria (Rosenfeldt et al., 2005).

It has recently been reported that three important genes are crucial to synthesis of CoQ$_{10}$. The CoQ$_2$ gene encodes for p-hydroxybenzoate:polyprenyl transferase, an enzyme which catalyses the prenylation of p-hydroxybenzoate with an all-trans polyprenyl group thus forming the polyisoprenoid side chain (Ashby et al., 1992; Forsgren et al., 2004). Relative expression and function of these genes remain to be determined in humans and specifically in the heart. Although the full molecular nature and sites responsible for de novo synthesis of CoQ$_{10}$ are yet to be fully delineated, there is evidence that CoQ$_{10}$ is synthesised in the endoplasmic reticulum and Golgi system (Kalen et al., 1989). Whether chronic heart disease and/or ageing impact the capacity to conduct endogenous synthesis or metabolise and distribute dietary sourced CoQ$_{10}$ is yet to be elucidated. The capacity to augment myocardial CoQ$_{10}$ in the disease state is crucial to successful therapeutic interventions.

8. Summary and conclusions

There is robust and increasing evidence that oxidative stress is an important contributor to the pathophysiology of cardiovascular diseases including heart failure, hypertension and ischaemic heart disease.

Despite conclusive data of the efficacy of CoQ$_{10}$ therapy in animal models of many human diseases, the previous results of prospective randomised clinical trials while being encouraging have not been uniformly convincing. However recent meta-analyses of trials of the effect of CoQ$_{10}$ therapy for heart failure and for hypertension are more persuasive.

Further research is indicated on the role of CoQ$_{10}$ and other antioxidants in the treatment of the major cardiovascular diseases.

Crucial to therapeutic intervention is the further development of optimal CoQ$_{10}$ formulations designed for maximum and rapid intracellular incorporation of CoQ$_{10}$. Of equal importance, but perhaps more realistic in the longer term, is the expansion of our knowledge regarding the genes and post-transcriptional mechanisms responsible for the endogenous intracellular synthesis of CoQ$_{10}$, particularly during the progression of disease and/or senescence. Such understanding will be crucial to the design of therapeutic agents that will intrinsically augment endogenous synthesis of CoQ$_{10}$.

Conclusive demonstration of the therapeutic potential of CoQ$_{10}$ in heart disease requires the capacity to conduct well designed, multi-centre international trials. Such a task has been a major hurdle due to a relative dearth of funds from governments and industry for the support of a non-proprietary natural agent. However, despite this, in progress is a multi-national prospective randomised clinical trial of CoQ$_{10}$ in advanced cardiac failure, the Q-symbio trial (Mortensen, 2003). This trial is an adequately powered trial to finally prove or disprove the clinical efficacy of CoQ$_{10}$ in heart failure. The next few years should see major advances in our knowledge of the effect of CoQ$_{10}$ in the treatment of diseases where oxidative stress is a major factor.
References


