Coenzyme Q10 and cardiovascular disease: an overview

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Coenzyme Q10 (CoQ10) is a naturally occurring vitamin-like substance that has three functions of relevance to cardiovascular function: (i) its key role in the biochemical process supplying cardiac cells with energy; (ii) its role as a cell membrane protecting antioxidant; (iii) its direct effect on genes involved in inflammation and lipid metabolism. Although some CoQ10 is obtained from the diet, most is manufactured within the liver, the capacity for which declines with age. These data therefore provide a rationale for the importance of CoQ10 in cardiovascular function, and its dietary supplementation. The objective of this article is therefore to provide a brief overview of the pharmacology of CoQ10, and its role in the prevention and treatment of cardiovascular disease.

Introduction

Coenzyme Q10 (CoQ10) is a naturally occurring vitamin-like substance, first characterised in 1957 by Professor Fred Crane at the University of Wisconsin. CoQ10 is also known as ubiquinone, because of its ubiquitous distribution in all body tissues. Coenzyme quinones occur in several chemical forms, with CoQ10 being the only form found in human tissues (**figure 1**). CoQ10 plays a vital role in the biochemical mechanism supplying cells with energy, acting in conjunction with enzymes (hence the name CoQ10) to convert sugars and fat into energy. The action of CoQ10 is of particular importance in tissues with a high energy requirement, such as cardiac muscle. CoQ10 is also important as an antioxidant within the body. The objective of this article is, therefore, to provide an overview of the pharmacology of CoQ10, and its role in the prevention and treatment of cardiovascular disease.

Functions of CoQ10

CoQ10 is an essential cofactor of enzymes involved in the process that supplies all cells with energy (cellular respiration). Specifically, CoQ10 is an intermediate in the electron transport system that generates energy in the chemical form of adenosine triphosphate (ATP), shuttling electrons from complexes I and II to complex III of the mitochondrial respiratory chain (**figure 2**). Tissues with a high energy requirement, especially the heart and skeletal muscles, contain higher numbers of mitochondria within their cells, and are particularly reliant on maintaining adequate tissue CoQ10 levels for normal functioning.

CoQ10 occurs in cells in two closely related forms, oxidised (ubiquinone) and reduced (ubiquinol) (**figure 1**). The interconversion between these two forms is essential for the normal functioning of CoQ10 (**figure 2**). CoQ10 is important within the body as a major fat-soluble antioxidant, protecting cell membranes (particularly those of mitochondria) from the damaging effects of free radicals. CoQ10 is the only lipid soluble antioxidant produced within the body, and for which there is enzymatic ability for its continual regeneration. When ubiquinone acts as a coenzyme for mitochondrial ATP production, it is reduced to ubiquinol; this, in

Figure 1. Structure of coenzyme Q10

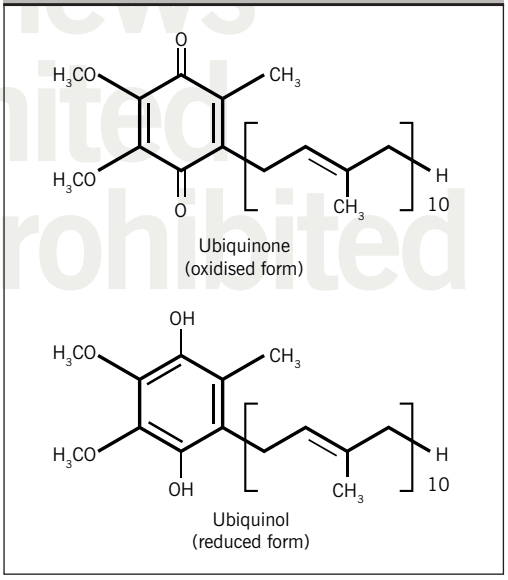
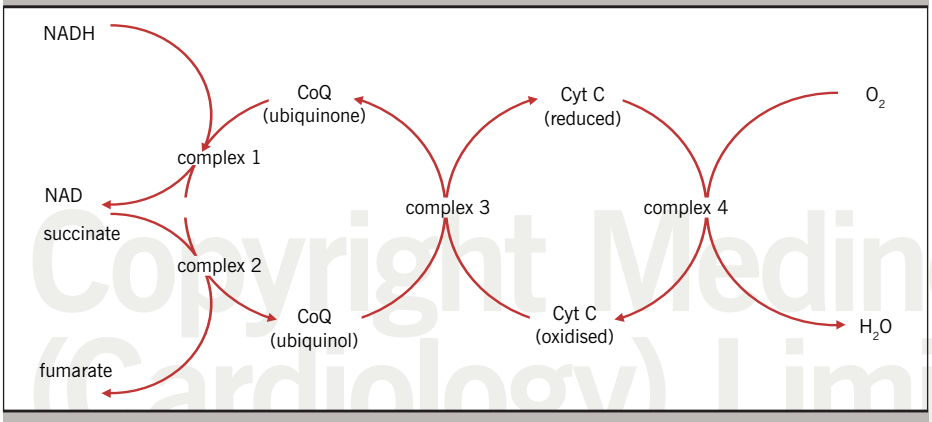
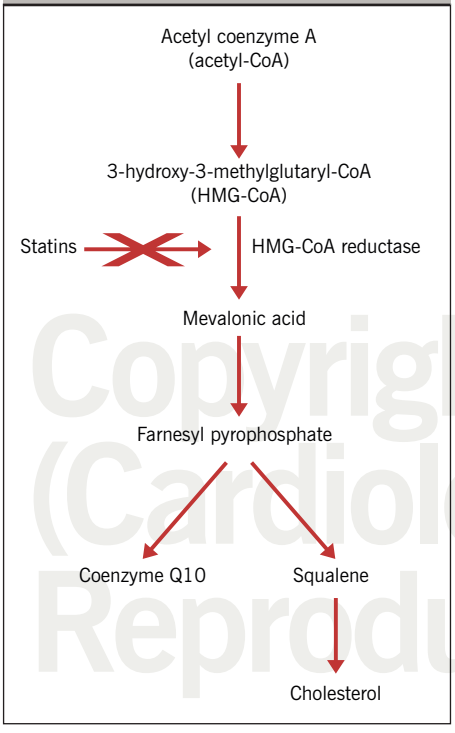


Figure 2. Role of coenzyme Q10 in mitochondrial electron transfer



Key: NADH = nicotinamide adenine dinucleotide hydride; NAD = nicotinamide adenine dinucleotide; CoQ = coenzyme Q10; Cyt C = cytochrome C

Figure 3. Synthetic pathway for coenzyme Q10



turn, is readily oxidised back to ubiquinone via its interaction with free radicals continually generated as by-products of oxidative phosphorylation (**figure 2**).

Most recently, gene expression profiling has shown that CoQ10 influences the expression of several hundred genes. In particular, studies in cell culture, animal models and human subjects have shown that CoQ10 can directly regulate gene expression relevant to inflammation and fat metabolism.[1,2] In addition, CoQ10 supplementation has been reported to decrease levels of inflammatory markers in patients with coronary artery disease.[3]

Synthesis and deficiency of CoQ10

Although some CoQ10 (approx. 25% of requirement) is obtained from the diet, most is manufactured within the body, particularly by the liver. It has been estimated that the population of Denmark, for example, obtain only 3–5 mg of CoQ10 per day from their normal dietary sources.[4] The synthesis of CoQ10 is a complex process requiring a number of amino acid, vitamin and trace element precursors and cofactors; a deficiency in any of these can adversely affect the normal production of CoQ10. It is of note that CoQ10 shares a common synthetic pathway with cholesterol (**figure 3**).

As people age, the capacity of the body to produce CoQ10 decreases; optimal production occurs around the mid-twenties, with a continual decrease thereafter (**figure 4**). CoQ10 levels can also be depleted by intense exercise, certain types of prescription medicines, and by illness. Dietary supplementation with CoQ10, therefore, provides a mechanism to maintain adequate levels within the body. However, it is important to note that the pharmaceutical quality and bioavailability of CoQ10 supplements from different manufacturers may vary widely (see following section).

Most cases of deficiency result from factors such as ageing or the effects of drugs such as statins (secondary deficiency). Primary deficiency results from defects in the genes responsible for the various steps in the body's synthesis of CoQ10; these are rare and can be successfully treated by supplementation if identified in infancy.[5]

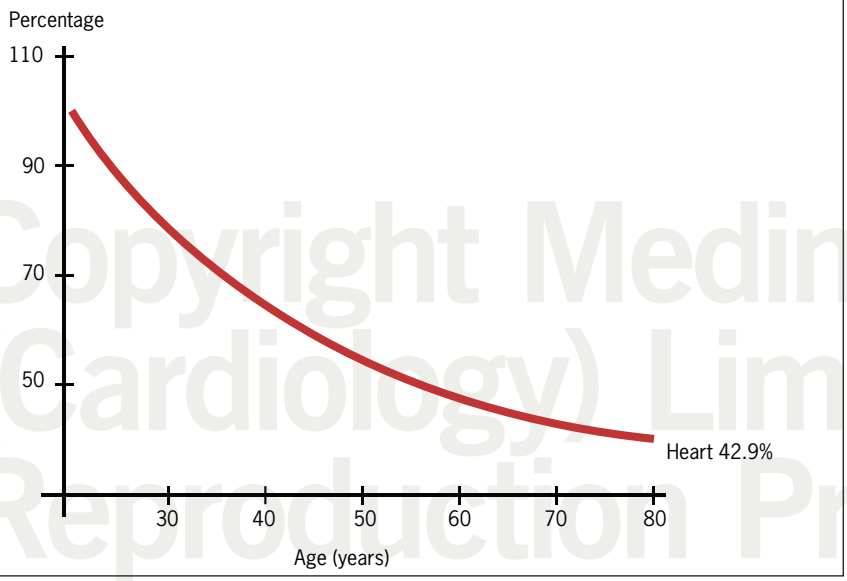
Bioavailability of supplemental CoQ10

Bioavailability is defined as the proportion of an orally administered substance that reaches the systemic circulation. CoQ10 is a fat-soluble substance. Following emulsification and micelle formation, CoQ10 is absorbed by mucosal cells of the small intestine, as for any other dietary fat. CoQ10 is then transported via chylomicrons by the lymphatic system to the liver, where it is released into the blood in association with lipoproteins (very-low-density lipoprotein [VLDL], low-density lipoprotein [LDL], high-density lipoprotein [HDL]). Because of its hydrophobicity and large molecular weight, intestinal absorption of CoQ10 is in general slow and somewhat limited; as much as 50% of a typical oral dose may be excreted in the faeces.

For dietary supplements, oil-based formulations show enhanced bioavailability.[6] There is a correlation between supplemental CoQ10 intake and plasma level, up to approximately 300 mg/day. Absorption of CoQ10 is non-linear, with increasing doses absorbed to a decreasing degree. Higher daily doses of CoQ10 are, therefore, best taken in 100 mg split doses. When first manufactured, CoQ10 is produced in a crystalline form that cannot be absorbed from the digestive tract. In CoQ10 supplements, this crystalline form must be further treated to break it down into individual molecules to enable absorption (**figure 5**), and most importantly, the crystals should not re-form within the capsule. Supplement manufacturers vary in their ability to fulfil these requirements.

For ubiquinone, maximum plasma concentration is reached after approximately six hours, and the half-life is approximately 33 hours, resulting in the time to pharmacological

Figure 4. Age-related decrease in coenzyme Q10 in cardiac tissue



steady state being rather prolonged (1–2 weeks). Normal plasma levels are in the range 0.5 to 1.5 μg/ml. Supplementation with 100 mg CoQ10 twice daily has been reported to raise blood levels from 0.90 to 3.25 μg/ml.[6]

Cardiovascular disease and CoQ10

Early studies on cardiovascular disease were hampered by a shortage of supply of CoQ10, poor absorption of CoQ10 in its original crystalline form, and insufficient daily dosage (30–60 mg). However, subsequent studies demonstrated supplementation with CoQ10 had significant benefits in cardiovascular disease, particularly heart failure, as detailed in the following sections. Langsjoen and Langsjoen[7] state that optimum improvement in heart function requires a plasma CoQ10 level of at least 3 μg/ml. CoQ10 is available as a licensed medicine within the EU as Myoqinon®; however, in the UK, Myoqinon is classified as an unlicensed medicine.

Congestive heart failure (CHF)

Work on CoQ10 and CHF was pioneered in the 1970s by Per Langsjoen, Karl Folkers and Gian Paolo Littarru. They established that patients with CHF had reduced levels of CoQ10 in blood and cardiac tissue, with the degree of deficiency correlating with the severity of heart failure. They further carried out the first clinical trial of CoQ10 in CHF, establishing long-term efficacy and safety in more than 100 patients over a period of six years.[8]

Most subsequent clinical studies (of whichever type) have described significant clinical benefit following supplementation with CoQ10. For example, 24 out of 28 randomised-controlled studies of CoQ10 supplementation in heart failure over a 40-year period (to 2010) reported positive outcomes. Some of these studies have been criticised as being underpowered; however, such criticism cannot be applied, for example, to the study by Morisco *et al.*[9] Their long-term randomised-controlled study of some 600 New York Heart Association (NYHA) class III and IV patients reported adjuvant use of supplemental CoQ10 significantly reduced the incidence of hospitalisation or serious complications in CHF. Some studies, such as that by Watson *et al.*,[10] failed to show any significant benefit following CoQ10 supplementation in CHF, although it has been argued that the dose regimen used in such studies was insufficient.[11]

To date there have been three meta-analyses relating to CoQ10 supplementation and CHF,[12-14] all of which identified significant improvement in parameters such as ejection fraction.

Most clinical trial studies to determine the efficacy and safety of CoQ10 have used the ubiquinone form. Patients with severe CHF are least able to benefit from oral supplementation with conventional ubiquinone CoQ10 supplements (possibly up to 900 mg/day), because of their difficulty in adequately assimilating the latter due to intestinal and hepatic oedema. In the first reported clinical study of CoQ10 in the reduced (ubiquinol) form in such patients,[15] critically ill individuals orally supplemented with an average dose of 450 mg/day ubiquinol for three months showed a three-fold increase in plasma CoQ10 level, and a 25–50% improvement in heart function (quantified via echocardiography ejection fraction).

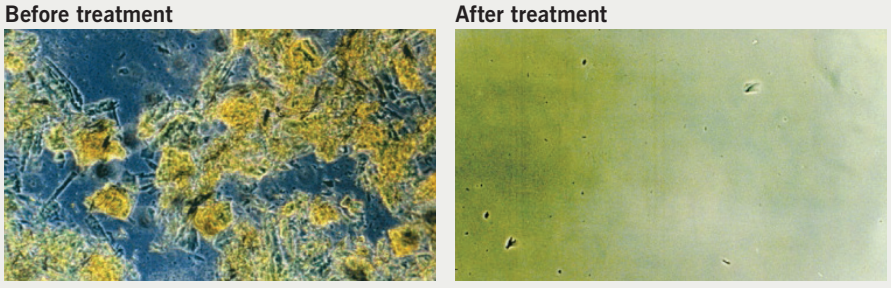
The Q-SYMBIO study

The Q-SYMBIO study is the first randomised-controlled trial adequately powered and of sufficient duration to determine the efficacy of CoQ10 supplementation on morbidity and mortality risk in heart failure patients.[16]

Q-SYMBIO was a long-term (two-year), randomised, double-blind, placebo-controlled, multi-centre trial in 420 patients with chronic heart failure (NYHA class III or IV). Patients were assigned three times 100 mg CoQ10 (Bio-Quinone Q10) daily (or placebo) as adjuvant to conventional medication (ACE inhibitors/beta blockers). Assessment included clinical examination, echocardiography and pro-brain natriuretic peptide (pro-BNP) biochemical marker status. The primary long-term end point was time to first major adverse cardiovascular event (MACE), which included unplanned hospitalisation due to worsening heart failure and cardiovascular death.

Baseline characteristics of the CoQ10 supplemented and placebo groups were similar with regard to mean disease duration (three years), NYHA class (mainly class III), ejection fraction (31%) and standard medication (90% ACE inhibitors/angiotensin receptor blockers, 75% beta blockers). Supplementation with CoQ10 significantly reduced the risk of MACE by 42%, cardiac-related and all-cause mortality were reduced by 44% and 42%, respectively. There was no significant difference in adverse events between the CoQ10 treated and placebo groups over the duration of the study. It should be noted that in short-term assessment (at 16 weeks), there was no significant improvement in patient symptoms

Figure 5. Dissolution of coenzyme Q10 crystals



or functional status following CoQ10 supplementation compared with placebo.

It is of relevance to compare the outcome of the Q-SYMBIO study with that of the recently published PARADIGM (Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial) study.[17] In the PARADIGM study, the drug LCZ696 (a combined angiotensin receptor/neprilysin inhibitor) was compared against the ACE inhibitor enalapril in 8,400 patients with NYHA class II–IV heart failure. Over a period of approximately two years, there was a significant reduction in hospitalisation/cardiovascular death of approximately 18%.

Atherosclerosis

CoQ10 may protect against atherosclerosis by inhibiting the oxidation of LDL-cholesterol. Despite a relatively low level of CoQ10 (0.5–0.8 mol/LDL particle) in LDL-cholesterol compared with alpha tocopherol (8–15 mol/LDL particle), CoQ10 has been shown to be the first line of defence against oxidative stress.[18] Although not widely publicised, there is evidence that the ratio of CoQ10 to LDL-cholesterol may be more important in the prevention of atherosclerosis than is the HDL:LDL cholesterol ratio.[19] The role of CoQ10 in protecting LDL-cholesterol from oxidative damage has been described.[19,20]

In addition to protecting LDL-cholesterol from oxidation, CoQ10 may also inhibit its synthesis. Supplementation with CoQ10 induces characteristic gene expression patterns, which are translated into reduced LDL-cholesterol levels. Thus, 50 healthy men (average age 30 years, average body mass index [BMI] of 24 kg/m^2) supplemented with 150 mg CoQ10 daily for two weeks, showed a reduction in LDL-cholesterol of approximately 13%.[21]

In a double-blind, randomised-controlled trial, Singh *et al.*[22] found supplementation with CoQ10 (120 mg/day for one year) reduced the risk of atherosclerosis in patients following recent myocardial infarction. This was an additional benefit to optimal lipid-lowering therapy provided by lovastatin administration. Similarly, Lee *et al.*[23] reported supplementation with CoQ10 (300 mg/day for three months) significantly increased antioxidant enzyme levels and reduced inflammation in patients with atherosclerosis receiving statin therapy.

A meta-analysis carried out by Gao *et al.*[24] reported supplementation with CoQ10 resulted in significant improvement in arterial endothelial function in patients with and without cardiovascular disease.

Hypertension

The primary action of CoQ10 in hypertension is vasodilation, via direct effects on the endothelium and vascular smooth muscle. Hypertension is associated with an increase in oxidative stress, manifest by increased production of superoxide radicals within blood vessels; these in turn react with endothelial nitric oxide to reduce the availability of this chemical messenger, thereby reducing the ability of the endothelium to induce nitric oxide-mediated relaxation of vascular smooth muscle, and hence vasoconstriction and increased blood pressure.

Several clinical studies have reported that supplementation with CoQ10 can significantly reduce blood pressure in hypertensive patients, without adverse effects. Thus, a randomised-controlled, double-blind trial of 60 patients receiving conventional antihypertensive medication was carried out by Singh *et al.*;[25] supplementation with 60 mg CoQ10 twice daily for eight weeks reduced systolic blood pressure (BP) by 16 mmHg and diastolic BP by 9 mmHg. A randomised-controlled, double-blind trial of 100 patients with isolated systolic hypertension was reported by Burke *et al.*;[26] supplementation with 60 mg CoQ10 twice daily for 12 weeks reduced systolic BP by approximately 18 mmHg. A meta-analysis by Rosenfeldt *et al.*[27] concluded that CoQ10 could lower systolic BP by up to 17 mmHg, and diastolic BP by 10 mmHg, without significant adverse effects in hypertensive patients. CoQ10 appeared effective as an antihypertensive agent either alone, or in combination with conventional antihypertensive drugs.

Prevention of cardiovascular disease

The KiSel-10 study was carried out on the elderly population of the Kinda region of Stockholm, who were given supplemental selenium and CoQ10 (hence KiSel-10). A five-year, prospective, randomised, double-blind, placebo-controlled trial in 440 individuals aged 70–88 years. Participants were assigned 200 μg selenium (SelenoPrecise) and 200 mg CoQ10 (Bio-Quinone Q10) daily, or placebo. Assessment included clinical examination, echocardiography and the biochemical marker of heart tissue stress, N-terminal pro-BNP (NT-proBNP). There was a greater than 50% reduction in cardiovascular mortality in the treatment group versus placebo group (5.9% *vs.* 12.6%). In addition, cardiac function assessed by electrocardiogram (ECG) and NT-proBNP levels were significantly improved in the treatment group compared with placebo.[28] Selenium is a cofactor of the enzyme thioredoxin reductase 1, which plays a key role in the interconversion of ubiquinone and ubiquinol forms of CoQ10.[29]

Statins and CoQ10

Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis. Adverse effects, particularly skeletal muscle pain and weakness, may occur in a significant number of patients; variation from mild myalgia to rhabdomyolysis has been rationalised in terms of genetic susceptibility.[30]

The inhibitory effect of statins on cholesterol biosynthesis is not selective, resulting in the inhibition of several non-sterol isoprenoid end products, including CoQ10. Statins also inhibit the synthesis of vitamin K2, a cofactor for matrix Gla-protein activation, which, in turn, protects arteries from calcification. Statins inhibit the synthesis of several selenoproteins, including thioreductase redoxin 1, which plays a key role in the interconversion of oxidised and reduced forms of CoQ10.[29] The statin-induced reduction in CoQ10 levels has been well documented in both animal model and clinical studies.[31] Many of the adverse effects resulting from statin use can be rationalised in terms of concomitant CoQ10 depletion.

In this regard, a randomised-controlled trial by Caso *et al.*[32] reported supplementation with CoQ10 (100 mg for 30 days) significantly reduced muscle pain associated with statin treatment. More recently, a number of randomised-controlled trials, each comprising approximately 50–60 patients receiving statin therapy, have similarly reported significant benefits following CoQ10 supplementation. Thus Fedacko *et al.*[33] found CoQ10 supplementation (200 mg/day for three months) significantly improved muscle pain and muscle weakness. Pourmoghaddas *et al.*[34] reported supplementation with 10 mg atorvastatin and 200 mg CoQ10/day for four months in heart failure patients (NYHA II–IV) resulted in a significant improvement in ejection fraction, compared with atorvastatin alone. Skarlovnik *et al.*[35] found supplementation with CoQ10 (100 mg/day for 30 days) significantly reduced symptoms in approx 75% of patients with muscle pain receiving statins. Supplementation with higher dose CoQ10 (300 mg/day for 12 weeks) significantly reduced inflammation in patients with coronary artery disease during statin therapy.[23]

However, not all studies have found significant symptomatic benefit following CoQ10 supplementation. In contrast to the above studies, Bookstaver *et al.*[36] found supplementation with CoQ10 (120 mg/day for 1 month) had no significant effect on myalgia in patients receiving statins. Similarly, Bogsrud *et al.*[37] found no significant benefit for statin-induced myopathy following CoQ10 supplementation (400 mg/day for three months). This disparity in outcomes between different studies has been ascribed to differences in supplement bioavailability, and methodological differences in pain assessment. The supply of CoQ10 via National Health Service (NHS) prescription for statin-related myalgia is currently not recommended.[38]

In Canada, the packaging of statin drugs is required to include a so-called black box warning, recommending the drugs be taken in conjunction with CoQ10.

Safety of CoQ10

The safety of CoQ10 has been assessed by Hidaka *et al.*[39] and Hosoe *et al.*[40] CoQ10 is generally well tolerated, with no serious adverse effects reported in long-term use. Very rarely, individuals may experience mild gastrointestinal disturbance. There are no known toxic effects, and CoQ10 cannot be overdosed. CoQ10 is well tolerated in healthy adults at an intake of 900 mg/day, and in rats at a dose of up to 1,200 mg/kg/day. In addition, Yamaguchi *et al.*[41] reported that CoQ10 had no genotoxic activity. CoQ10 is not recommended for pregnant or lactating women, in whom the effects of CoQ10 have not been extensively studied. The safety of CoQ10 has been confirmed in more than 200 randomised-controlled trials, on a wide range of disorders.[42-44]

Several case studies have suggested that CoQ10 may interfere with the action of warfarin; however, a randomised-controlled clinical trial showed CoQ10 supplementation at 100 mg/day had no effect on the clinical action of warfarin.[45]

The product Myoqinon (100 mg CoQ10 capsules) has a marketing authorisation within the EU for the adjuvant treatment of CHF. As part of the licensing procedure, periodic safety update reports (PSURs) have to be submitted every three years. In a sample PSUR, over a three-year period the supply of 1.4 million daily doses, equivalent to 3,900 person-years usage, did not result in any reported serious adverse events ascribable to CoQ10.

Conclusion

CoQ10 has at least three functions of relevance to the cardiovascular system, namely its role in cellular energy production, its role as an antioxidant, and its role in gene expression. These functions, in turn, provide the basis for the plausibility of action of CoQ10 in the management of CHF, atherosclerosis and hypertension, as outlined above.

Because CoQ10 is classed as a nutritional supplement, there is a common misconception that there is little or no evidence to support its use in the management of cardiovascular disease. To date there are more than 600 articles published in the peer-reviewed medical literature listed on the Medline database, including more than 60 double-blind, randomised, placebo-controlled clinical trials. Of course, not all of these articles have reported positive findings with regard to CoQ10 and cardiovascular disease, but the balance of published evidence supports a

Key messages

- Plausibility of mechanism of action. The biochemical functions of coenzyme Q10 (CoQ10) within the cell provide a theoretical basis for its supplementation in cardiovascular disorders
- Evidence of efficacy. Although studies on CoQ10 supplementation in cardiovascular disease have not been without criticism, randomised-controlled, clinical studies (particularly the recent Q-SYMBIO study) have in general reported significant benefit
- Evidence of safety. A large number of randomised-controlled, clinical trials have been carried out in a wide range of disorders; none of these studies have reported serious adverse effects resulting from CoQ10 supplementation
- Bioavailability. Disparities in outcomes between previous studies can be explained in terms of differences in the types of supplements used, the bioavailability of which can vary widely

beneficial role for CoQ10 in the management of cardiovascular disease, as detailed in this review.

There are presently more than 200 randomised-controlled, clinical trials listed on Medline, in which CoQ10 has been investigated in a wide range of disorders. None of these studies have reported significant adverse effects arising from CoQ10 supplementation.

To be effective, CoQ10 needs to be given in sufficient dosage and for sufficient duration. In particular, the role of bioavailability cannot be over-emphasised; a CoQ10 supplement should be used where there is documentary evidence of the capability to raise blood levels to at least 3 μg/ml in human subjects ●

Conflict of interest

The author acts as a medical adviser to Pharma Nord (UK) Ltd.

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