Role of Coenzyme Q10 (CoQ10) in Cardiac disease, Hypertension and Meniere-like syndrome

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Abstract
Coenzyme Q10 (ubiquinone) is a mitochondrial coenzyme which is essential for the production of ATP. Being at the core of cellular energy processes it assumes importance in cells with high energy requirements like the cardiac cells which are extremely sensitive to CoQ10 deficiency produced by cardiac diseases. CoQ10 has thus a potential role for prevention and treatment of heart ailments by improving cellular bioenergetics. In addition it has an antioxidant, a free radical scavenging and a vasodilator effect which may be helpful in these conditions. It inhibits LDL oxidation and thus the progression of atherosclerosis. It decreases proinflammatory cytokines and decreases blood viscosity which is helpful in patients of heart failure and coronary artery disease. It also improves ischemia and reperfusion injury of coronary revascularisation. Significant improvement has been observed in clinical and hemodynamic parameters and in exercise tolerance in patients given adjunctive CoQ10 in doses from 60-200 mg daily in the various trials conducted in patients of heart failure, hypertension, ischemic heart disease and other cardiac illnesses. Recently it has been found to be an independent predictor of mortality in congestive heart failure. It has also been found to be helpful in vertigo and Meniere like syndrome by improving immune system. Further research is going on to establish firmly its role in the therapy of cardiovascular diseases.

Key words Coenzyme Q10, Bioenergetics, Antioxidant, Heart disease, Hypertension, Meniere’s disease.

Abbreviations CoQ10, coenzyme Q10 CHF Congestive heart failure, DCM, Dilated cardiomyopathy HCM, Hypertrophic cardiomyopathy ecSOD, extracellular superoxide dismutase CAD, Coronary artery disease AMI, Acute myocardial infarction, EF, Ejection fraction NYHA, New York Heart Association

1. Introduction
Advances in molecular medicine have provided novel insights into the pathophysiology of heart disease. Coenzyme Q10 (CoQ10) exerts action at the cellular level and rectifies some of the basic deficiencies leading to aggravation of these diseases. These include correction of the energy depletion and oxidant stress which are inherent in these conditions.

Coenzyme Q10 plays a key role in mitochondrial oxidative phosphorylation and ATP production. It is therefore essential for all energy-dependent processes in the heart, including heart-muscle contraction and functioning of ATP regulated membrane channels. Heart is a metabolically active organ which needs plenty of energy and has a large number of mitochondria. CoQ10 is found in the membranes of many organelles. Since its primary function in cells is in generating energy, the highest concentration is found on the inner membrane of the mitochondrion. Some other organelles that contain CoQ10 include endoplasmic reticulum, peroxisomes, lysosomes and vesicles. It is a membrane stabilizer and preserves myocardial sodium-potassium ATPase activity and stabilises myocardial calcium dependent ion channels.

Heart is highly sensitive to CoQ10 deficiency. Both dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are frequently accompanied by defective levels of specific oxidative phosphorylation/respiratory enzyme activities. (Marin-Garcia et al., 1995 and Rustin et al., 1994). The reduced energy reserve in heart failure may be considered to contribute to the progression of the disease (Vogt et al., 1998).

Exogenous CoQ10 is taken up by CoQ10-deficient cells and can be demonstrated to be incorporated into the mitochondria for maintenance of optimal cellular and mitochondrial function. (Nakamura et al., 1980) Newer P31 NMR spectroscopy studies have documented enhanced cellular high energy phosphate concentrations with CoQ10 supplementation in experimental models (Crestanello et al., 1996). CoQ10 thus has potential for prevention and treatment of cardiovascular disease by improving cellular bioenergetics.

2. Chemistry
Coenzyme Q10 was first isolated in 1957 from beef mitochondria and is known to be highly concentrated in heart muscle cells due to the high energy requirements of this cell type (Crane et al., 1957). It is a naturally occurring fat-soluble vitamin-like quinone commonly known as, CoQ10. It is also called ubiquinone as it is ubiquitous or present in all eukaryotic cells. Chemically CoQ10 is 2, 3 dimethoxy - 5 methyl - 6 decaprenyl benzoquinone. The functional group in CoQ10 is the quinone ring. By reduction of the quinone to quinol (H2
CoQ10) a carrier of protons and electrons is produced.

3. Sources
It is present in foods such as beef, poultry and broccoli (Ellin et al., 1999). Other sources of CoQ10 are soya oil, fish oils, peanuts, sardines and mackerel. Dietary intake of CoQ10 is 2-5 mg per day, which is always inadequate to provide levels in the body required to be beneficial in pathological states.

4. Potential clinical uses for CoQ10
CoQ10 is useful in arteriosclerosis, ischemic heart disease, chronic heart failure (for both systolic and diastolic heart failure), hypertrophic cardiomyopathy, cardiovascular surgery, hypertension, arrhythmias, valvular heart diseases, toxin-induced cardiomyopathy including statin cardiomyopathy and Meniere’s disease.

5. Co Q10 deficiency in cardiac diseases
Studies performed by Folkers et al., in 1970 showed that 70 - 75% of heart patients exhibit low levels of CoQ10. Circulating levels of CoQ10 were significantly lower in patients with ischemic heart disease and in those with dilated cardiomyopathy as compared to healthy controls (Langsjoen et al., 1990). Myocardial deficiencies of CoQ10 were also found in the majority of patients with aortic stenosis or insufficiency, mitral stenosis or insufficiency, diabetic cardiomyopathy, tetralogy of Fallot, atrial septal defects and ventricular septal defects (Folkers et al., 1970). The concentrations of CoQ10 declined progressively in both blood and myocardial tissue with increasing severity of heart disease (Littarru et al., 1972).

Normal blood levels range from 0.7-1.0 μg/mL (Redalieu et al., 1968). Doses of 30-60 mg/day (approximately 1kg of body weight) are generally recommended to prevent CoQ10 deficiency and to maintain normal serum concentrations. However optimum clinical benefit requires above normal CoQ10 blood levels which may be 2 to 4 times higher. High blood levels may be required to attain an elevation of tissue CoQ10 levels or to rescue defective mitochondrial function. Therapeutic doses of 100-200 mg/day are advocated for the treatment of chronic heart diseases. In patients with cardiomyopathy and myocardial deficiency of CoQ10, oral administration of 100 mg/day of CoQ10 for 2-8 months resulted in an increase in myocardial CoQ10 levels ranging from 20-85% (Folkers et al., 1985). These higher doses may achieve serum concentrations of 2.0-3.0 μg/mL, reported by some investigators to have a positive impact on cardiovascular health. Patients with advanced heart failure often fail to achieve adequate blood (plasma) levels, even when high doses of conventional CoQ10 are given. It has recently been shown that significant clinical benefit in heart failure patients requires a plasma CoQ10 level of around 4 micro g/mL (Langsjoen et al., 2007).

In severe heart failure patients, the only way these higher levels can be obtained appears to be with ubiquinol, the reduced form which is much more effective than conventional ubiquinone since it is eight times better absorbed. Most of commercially available CoQ10 supplements comprise ubiquinone. The most advanced CoQ10 formulas now contain ubiquinol (Hosoe et al., 2007). Recommended daily dosages of ubiquinol range from 100 mg to 300 mg. In a dose of 450 mg a day it achieved a plasma level of 4 micro g/mL and was much more successful in reversing the course of a severe heart failure. In the recent study conducted by Dr. Langsjoen, the ejection fraction improved from 24% up to 45% in ubiquinol-treated patients who had follow-up echocardiograms. This represented a recovery of up to 88% in this critical measurement of cardiac output. The higher blood levels of CoQ10 and the improved ejection fractions were accompanied by a remarkable clinical improvement in these heart failure patients. It is believed that supplemental ubiquinol represents a major scientific advance in the fifty year history of CoQ10 research (Langsjoen et al., 2007). CoQ10 dosage guidelines, which appeared to be safe and well tolerated were recently suggested for adults to be upto 1200mg/day (Hathcock et al., 2006). There is a delay in the onset of clinical improvement of one to four weeks after initiation of treatment and a further delay of several months in maximal clinical benefit. Possible reasons for this delay include time to attain adequate tissue levels of CoQ10 or time to synthesize CoQ10 dependent apoenzymes.

6. Mechanism of action
The possible therapeutic mechanisms of action of coenzyme Q10 in cardiovascular diseases are as follows:
- Improvement of cardiac bioenergetics
- Direct free radical scavenger and antioxidant effect
- Correction of coenzyme Q10 deficiency state
- Improved endothelial function and vasodilatory effect
- Direct membrane-stabilizing activity due to phospholipid protein interactions
Preservation of myocardial Na⁺-K⁺ ATPase activity
Stabilization of integrity of Ca2+-dependent slow channels.
Correction of mitochondrial "leak" of electrons during oxidative respiration
Induction of DT diaphorase
Possible effects on prostaglandin metabolism.
Antiviscosity effect
Altering the immune response
(Greenberg et al., 1990)

6.1 Improvement of cardiac bioenergetics
Cardiac contraction occurs after Ca2+ release from sarcoplasmic reticulum (SR) which activates the contractile proteins. During diastole, cytosolic Ca2+ re-sequesters into the SR. The cardiac contraction and the uptake of free cytoplasmic calcium into the sarcoplasmic reticulum is an energy-requiring mechanism (Kayo et al., 2005). Myocardial relaxation which is dependent on active Ca2+ uptake by the sarcoplasmic reticulum is not a passive process. Rather this latter step requires more energy. In cardiac failure, changes in Ca2+ transport and metabolism have also been found (Marin-Garcia et al., 2001). Myocardial failure may be related to decreased energy production by the mitochondria. There is a decrease in energy availability for Ca2+ uptake in SR (diastolic failure) and for delivery to the contractile apparatus impairing cross bridge cycling (systolic failure). Since CoQ10 participates in the transport of electrons from organic substrates to oxygen in the respiratory chain of mitochondria with the production of energy, it has a role in providing energy for the functioning of the failing and energy depleted heart.

6.2 Antioxidant action
Because of its ability to transfer electrons it acts as an antioxidant. The presence of CoQ10 in other membranes besides mitochondria, shows that its antioxidant effect may also be of physiological importance. In most membranes enzymes have been defined which can reduce the quinone and oxidize the quinol (Crane et al., 2001). CoQ10 must be reduced to ubiquinol denoted QH2 to wield its maximum anti-oxidative function. In its reduced form (ubiquinol), the coenzyme Q10 molecule holds electrons loosely and will quite easily give up one or two electrons to neutralize free radicals. It is this form which displays its strongest antioxidant activity (Mellors et al., 1966). Sophisticated biochemical markers of oxidative injury are now demonstrating in-vivo the antioxidant cell protective effects of CoQ10. Its main role as an antioxidant is in the mitochondria where it first participates in the process by which free radicals are generated and then helps to quench the extra free radicals that threaten cellular components such as DNA, RNA, and cell membranes.

Its antioxidant properties contribute to prevention of lipid peroxidation. It has been found to be efficient in preventing LDL oxidation which is an important step in evolution of atherosclerosis (Yokoyama et al., 1996). CoQ10 has a direct anti-atherogenic effect, which has been demonstrated in apolipoprotein E-deficient mice fed with a high-fat diet. In this model, supplementation with CoQ10 at pharmacological doses was capable of decreasing the absolute concentration of lipid hydroperoxides in atherosclerotic lesions and of minimizing the size of atherosclerotic lesions in the whole aorta. Whether these protective effects are only due to the antioxidant properties of coenzyme Q or due to some other mechanisms remains to be established (Littarru et al., 2007).

6.3 Endothelial function
Endothelium-bound extracellular Superoxide Dismutase (ecSOD) activity is a major antioxidant enzyme system of the vessel wall which is reduced in patients with coronary artery disease. A recent study showed improvement in the endothelial relaxation with coenzyme Q10 administration. This might be related to its capability of enhancing endothelial function by counteracting nitric oxide oxidation (Belardinelli et al., 2008 and Tiano et al., 2007). CoQ10 has been recently shown to improve the endothelial relaxation in diabetic patients. Indeed, in vitro study indicates that CoQ10 can efficiently prevent high glucose induced endothelial cell apoptosis and adhesion to monocytes, which are relevant to the pathogenesis of atherosclerosis (Tsuneki et al., 2007).

6.4 Membrane stabilization and fluidity
The membrane stabilizing property of CoQ10 has been postulated to involve the phospholipid-protein interaction that increases prostaglandin (especially prostacyclin) metabolism. It is thought that CoQ10 stabilizes myocardial calcium-dependent ion channels and prevents the depletion of metabolites essential for ATP.
synthesis. CoQ10 also decreases blood viscosity and improves blood flow to cardiac muscle in patients with ischemic heart disease (Kato et al., 1990).

6.5 Reduction in proinflammatory cytokines

It is becoming increasingly apparent that inflammatory mediators play a crucial role in the development of congestive heart failure and acute myocardial infarction and several strategies to counterbalance the different aspects of inflammatory response are considered. The most important proinflammatory cytokines implicated in the progression of congestive heart failure are IL-6 and TNF-alpha. A double blind placebo controlled randomised trial conducted on 31 patients of heart failure of mixed etiology for 12 weeks using 270mg/day of ubiquinol along with oral carnitine showed marked reduction in IL-6 and TNF-alpha in the treated group as compared with the placebo. Thus CoQ10 also acts by altering the immune response (Kumar et al., 2007). In a recent study the administration of CoQ10 significantly attenuated the increase of oxidative and nitrative stress markers and inflammatory markers in a dose-dependent manner. CoQ10 reduced the elevated serum insulin levels, although it did not affect the elevated glucose level and dyslipidemia. It also reduced elevated blood pressure, but did not affect body weight gain in cases of metabolic syndrome. In addition, CoQ10 improved endothelial dysfunction in the mesenteric arteries suggesting that the antioxidant properties of CoQ10 can be effective in ameliorating cardiovascular risk in metabolic syndrome (Masaru et al., 2008).

7. Role of CoQ10 in congestive heart failure (CHF)

Chronic heart failure represents a major public health burden and its prognosis is comparable to that of a malignant disease.

7.1 Deficiency in congestive heart failure

Heart failure is often characterized by an energy depletion status that has been associated with low endogenous CoQ10 levels. Its levels are depleted in both serum and myocardial tissue samples of patients with chronic heart failure (Folkers et al., 1970, 1985). The myocardial tissue levels in CHF patients are on average 33% lower than in control patients. Patients with severe CHF, namely New York Heart Association (NYHA) classes III and IV, tend to have lower levels of endogenous CoQ10 than that of patients with NYHA class I CHF or healthy subjects and may be more likely to attain a favourable clinical response to CoQ10 supplementation (Mortensen et al., 1984). The need for measurement of plasma CoQ10 is based on the relationship between levels and outcomes, as in chronic heart failure, where it may identify individuals most likely to benefit from supplementation therapy. During CoQ10 supplementation plasma CoQ10 levels should be monitored to ensure efficacy, given that there is variable bioavailability between commercial formulations, and known inter-individual variation in CoQ10 absorption (Molyneux et al., 2008).

Its deficiency may well be a primary etiologic factor in some types of heart muscle dysfunction while in others it may be a secondary phenomenon. In both cases it is a treatable factor in this otherwise hopeless condition. The possible usefulness of the CoQ10 in the treatment of CHF may be related to its ability to increase ATP synthesis with enhancement of myocardial contractility (Crane et al., 2001). Recently it has been found to be an independent predictor of mortality in congestive heart failure (Molyneux et al., 2008).

7.2 Oxidative stress

In addition, the myocardium of patients with heart failure demonstrates increased oxidative stress which can be corrected by CoQ10. With CoQ10 there was a significant decline in TBARS and MDA which are indicators of oxidative stress, indicating that scavenging of free radicals may be a possible mechanism for the beneficial effect of CoQ10 in heart failure (Kumar et al., 2002).

7.3 Trials relating to congestive heart failure

Improvement in myocardial function with CoQ10 supplementation has been demonstrated in a variety of animal models. The first patients with heart failure were treated with coenzyme Q10 by Yamamura in 1967. By mid 1980's it became apparent that it was safe and effective in the short-term treatment of patients with heart failure. Several long-term trials were undertaken to evaluate its efficacy and safety using parameters like echocardiography. CoQ10 was added to standard treatments for heart failure such as diuretics, digitalis preparations (Lanoxin), and ACE inhibitors.

In 1994, a study conducted by Langsjoen et al illustrated the usefulness of CoQ10 in clinical cardiology. It tested CoQ10 in different types of myocardial diseases including ischemic cardiomyopathy, dilated cardiomyopathy, primary diastolic dysfunction, hypertensive heart disease and valvular heart disease etc
Patients were treated with an average of 240 mg of CoQ10 per day and followed for up to eight years. Significant improvement in NYHA functional classification was observed. 58 percent of patients improved by one NYHA class, 28 percent by two classes, and 1.2 percent by three NYHA classes. Myocardial function became measurably improved within one month with maximal improvement usually obtained by six months and this improvement was sustained in the majority of patients. The withdrawal of CoQ10 therapy resulted in a measurable decline in myocardial function within one month and a return to pretreatment measurements within three to six months. An average of 50% reduction in the requirement for concomitant cardiovascular drug therapy and a complete lack of toxicity were demonstrated. Since this study, numerous other studies have demonstrated the benefit of CoQ10 supplementation in congestive heart failure related to primary cardiomyopathies or secondary forms of heart failure. It was concluded that supplemental treatment of CHF with CoQ10 is consistent with an improvement of stroke volume, ejection fraction, cardiac output, cardiac index and end diastolic volume index (Soja et al., 1997 and Sander et al., 2006). Out of over a dozen studies conducted during the last two decades (Table 1) only a few trials failed to show any benefit (Khatta et al., 2000 and Watson et al., 1999) corresponding to 10% of the total number of patients treated in double-blind trials. Dosage in these trials ranged from 60 to 200 mg/day with treatment periods ranging from 1 to 6 months. There was a 3.7% net improvement in ejection fraction (Sander et al., 2006). Treating 1000 patients for 1 year with study doses of CoQ10 prevented 200 hospitalisations due to worsening of CHF symptoms (Morisco et al., 1993).

7.4 Larger trials

Two large multicenter, open-label studies evaluated the efficacy and safety of CoQ10 as an adjuvant therapy in CHF. These two studies examined a total of more than 4000 patients with varying severity of CHF who experienced clinical improvement in signs and symptoms such as cyanosis, oedema, pulmonary rales, dyspnoea, and palpitations (Baggio et al., 1994 and Lampertico et al., 1993). Baggio et al. (1994) published the largest open trial in heart failure involving 2,664 patients treated with up to 150 mg of CoQ10 per day, noting significant benefit and lack of toxicity. At the end of the three-month study period, the results indicated improvements in cyanosis (78.1%), edema (78.6%), pulmonary rales (77.8%), hepatomegaly (49.3%), jugular reflux (71.8%), dyspnea (52.7%), palpitations (75.4%), sweating (79.8%), vertigo (73.1%), subjective arrhythmia (63.4%), insomnia (62.8%) and nocturia (53.6%). Fifty-four percent of patients had improvements of at least three symptoms. Moreover, 28.8% of patients entered as NYHA Class III improved in score to Class II and 89.7% of patients entered as NYHA class II improved in score to Class I. The authors concluded that patients receiving CoQ10 improved functionally and that patients in NYHA Class II showed better improvement rates than did patients in NYHA Class III.

7.5 Q-SYMBO study (The planned SYMptoms, BIomarker status (BNP))

The encouraging results with CoQ10 in heart failure and need for further research constitute the background for the Q-SYMBO study (Mortensen, 2003) is an ongoing multinational, double blind, placebo-controlled trial. Approximately 550 patients in NYHA classes III-IV receiving standard therapy for chronic heart failure are being randomized to treatment with CoQ10 300 mg/day or placebo in parallel groups. It should help answer many of the unanswered questions.

7.6 Role in dilated cardiomyopathy (DCM)

Dilated cardiomyopathy is a form of cardiac muscle disease characterized by ventricular dilatation, contractile dysfunction and eventual congestive heart failure. 143 cases of DCM, 98% of whom were in NYHA Classes II and IV, were given 100 mg of coenzyme Q10 orally in addition to their conventional medical programme in an open-label long-term study. Mean ejection fraction of 44% rose to 60% within 6 months and stabilized at that level with 84% of patients showing statistically significant improvement. Eighty five percent of patients improved by one or two NYHA classes. Survival figures were also encouraging (Langsjoen et al., 1990). Other trials confirmed these findings, showing that CoQ10 administration significantly improved the cardiac function in dilated cardiomyopathy and resistant heart failure (Mortensen et al., 1985).

7.7 Use in patients with end stage heart failure targeted for heart transplantation.

In a randomised, double blind, placebo controlled trial, the effects of oral treatment with CoQ10 for 12 weeks was compared with placebo group (21 CoQ10 group A patients and 21 Placebo group B patients). Patients of heart failure were diagnosed by two dimensional /doppler echocardiography. After treatment for 12 weeks with
CoQ10 there was significantly less dyspnoea, palpitation and weakness in the treated group as compared with the placebo. Diene conjugates, thiobarbituric acid reactive substances (TBARS) and malondialdehyde (MDA) which are parameters of oxidative damage also significantly declined in CoQ10 group. There was also a significant reduction in left ventricular wall thickness, left ventricular mass, ejection fraction, end systolic and end diastolic volumes in the CoQ10 treated group as compared to the placebo (Kumar et al., 2002). The administration of CoQ10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life. An important note to be made is that most patients of end stage heart failure are on warfarin oral anticoagulant therapy and concomitant CoQ10 therapy may decrease international normalised ratio (INR) in these cases.

7.8 CoQ10 in diastolic dysfunction

Diastolic dysfunction is one of the earliest identifiable signs of myocardial failure which accounts for 30-49% of heart failure cases. Patients with diastolic dysfunction have an impairment of the filling phase of the cardiac cycle which causes a major limitation in their ability to increase cardiac output. It causes either decreased left ventricular end diastolic volume or a compensatory increased left ventricular end diastolic pressure and leads to pulmonary venous hypertension and the syndrome of ‘diastolic heart failure.’ In the process of relaxation a great deal of ATP is required to re-establish trans-membrane Ca2+ gradients which allow the uncoupling of actin/myocin and relaxation. Alterations in energy metabolism may lead to diastolic dysfunction and subsequently maladaptive cardiac remodelling.

Left ventricular diastolic dysfunction is associated with increased mortality rates in patients of chronic heart failure independent of systolic function. In a study of effect of CoQ10 in diastolic dysfunction in hypertrophic cardiomyopathy (HCM) 200 mg/day of CoQ10 was added to the conventional treatment in 46 patients with HCM diagnosed clinically and by echocardiography (Group I) (Kumar et al., 2007). Cases of long standing hypertension were excluded. A comparable control group of 41 age/sex matched cases of HCM received only conventional therapy. The follow up period ranged from 9.4 months-27.5 months (mean of 14.5 months). There was a significant improvement in the parameters like NYHA class \( \geq 1 \), in quality of life (QOL), on 6 minutes walk test, in diastolic dysfunction by \( \geq 1 \) parameter and in mitral regurgitation \( \geq 1 \) grade. Post treatment echocardiogram showed significant reduction in left ventricular outflow tract gradient \( \geq 15 \) mm Hg in obstructive cases (12 out of 46) in the treatment group. The mean interventricular septal and posterior wall thickness showed a significant reduction. No patient in the treatment group had ventricular tachycardia whereas 4 cases in the control group had this arrhythmia. In both groups 1 patient was lost due to sudden cardiac death. (Fig1) Similar observations have been made by Langsjoen et al.,1997 and 1993). Thus CoQ10 may be recommended as a safe, effective and promising adjuvant complementary therapy for diastolic heart failure in conditions like HCM.

7.9 HMG-CoA reductase inhibitors & CoQ10

Statins which are used to treat elevated blood cholesterol levels by blocking cholesterol biosynthesis also block CoQ10 biosynthesis (Folkers et al, 1990). The resulting lowering of blood CoQ10 level is due to the partially shared biosynthetic mevalonate pathway of CoQ10 and cholesterol. Statins can reduce serum levels of coenzyme Q10 by up to 40% along with reduction in cholesterol / LDL levels by inhibiting HMG CoA reductase. This depletes the CoQ10 in patients with heart failure using statins and produces significant harmful effects which can be negated by oral CoQ10 supplementation (Ghirlanda et al., 1993).Recent studies have shown long term statin therapy to induce diastolic dysfunction in persons with initial normal cardiac function (Silver et al., 2003). From 1990-2004, 13 controlled trials demonstrated significant CoQ10 depletion secondary to statin therapy (Hargreaves et al., 2005). Consequently, supplementing with CoQ10 is highly recommended to prevent the myopathic and other side effects associated with the statin drugs. In a study of 103 patients, statins along with CoQ10 produced beneficial effect in patients of ischemic dilated cardiomyopathy and the combination decreased the side effects of statins (Kumar et al., 2005).

8. Role of CoQ10 in hypertension

8.1 Studies background

In animal models of hypertension, including spontaneously hypertensive rats, uninephrectomized rats treated with saline and deoxycorticosterone and experimentally hypertensive dogs, orally administered CoQ10 significantly lowered blood pressure. In another experimental study of hypertensive rats, a deficiency in the
activity of succinate de-hydrogenase CoQ10 reductase in leucocytes was found. (Iwamoto et al. 1974). Deficient activity of this enzyme can result in decreased levels of CoQ10. Having identified same deficiency in human subjects with chronic hypertension, investigators conducted a pilot study in which they concluded that increased succinate dehydrogenase CoQ10 reductase activity and subsequent increased CoQ10 level leads to decreases in systolic and diastolic blood pressures (Yamagami et al., 1974). Tissue deficiencies have been observed in patients of hypertension. Enzymatic deficiency of CoQ10 has been reported in 39% of hypertensive patients compared with only 6% of healthy controls.

8.2 Mechanism of action in hypertension

**a. Effects on vascular endothelium** Although the mechanism behind CoQ10’s antihypertensive effect is not conclusive, it is likely to be attributed to its ability to induce vasodilation via decreased peripheral resistance in the vasculature (Kamoto et al., 1991).

**b. Antioxidant properties** Another hypothesis is that CoQ10’s antioxidant properties result in quenching of free radicals that cause inactivation of endothelium-derived relaxing factor and/or fibrosis of arteriolar smooth muscle (Ignarro et al., 1989).

**c. Improved diastolic function** With impairment of diastolic function, cardiac output can increase only by rise in catecholamines and increased heart rate. It is postulated that the blood pressure lowering effect of CoQ10 may in part be an indirect effect, whereby improved diastolic function leads to a lessening in the adaptive high catecholamine state of hypertensive disease (Langsjoen et al., 1993).

**d. Decrease in blood viscosity** It is also possible that the blood viscosity lowering effect of CoQ10 may favorably influence hypertension (Kato et al., 1990).

**e. Effect on angiotensin and aldosterone** It is thought that coenzyme Q10 reduces aldosterone secretions and compromises the effect of angiotensin in sodium retention (Louis et al., 1965).

There are several reports concerning the effect of CoQ10 on blood pressure in human studies. In an open-label study, doses of CoQ10 to maintain a serum level >2.0 ug/mL were added to standard antihypertensive drug therapy in 109 symptomatic patients with essential hypertension. The average daily dose of CoQ10 was 225 mg. Gradual improvements in functional and clinical status were observed within the first six months necessitating a decrease in antihypertensive drug therapy. Fifty-one percent of the patients were able to use 1-3 lesser antihypertensive drugs at an average of 4.4 months after starting CoQ10 treatment (Langsjoen et al., 1994).

8.3 Meta-analysis of clinical antihypertensive trials

A recent meta-analysis of clinical trials investigating the use of CoQ10 for treatment of hypertension assessed its overall efficacy, consistency of therapeutic benefit and side effects (Rosenfeldt et al., 2007). It included twelve trials conducted since 1975 which examined a total of 362 hypertensive individuals, for a period of 8-12 weeks, and used daily CoQ10 doses of 100-120 mg. Four were prospective randomised trials and eight were before and after studies (in which the effect of CoQ10 on blood pressure was compared with the previous level). CoQ10 reduced systolic blood pressure by as much as 17 mmHg and diastolic blood pressure by up to 10 mmHg, without significant side effects. In many other trials, statistically significant decreases in systolic and diastolic blood pressure were observed with CoQ10 dosages that ranged from 30-360 mg/day in patients with hypertension. (Table II). It has been shown to be particularly effective in hypertension in diabetics where it not only lowers blood pressure but also improves diabetic control perhaps by improving insulin resistance. It is important to note that in all these clinical trials, CoQ10 was used in addition to traditional antihypertensive medical treatments and not alone.

Kimura et al. (2008) have recently reported a case of 67 year old woman with essential hypertension with a maximum blood pressure of 155/100mm Hg who had been prescribed candesartan cilextil as an outpatient for about 5 years and did not respond to it and she frequently experienced side effects. After administration of CoQ10 her diastolic blood pressure normalised within 1 week and the systolic blood pressure after 1 month and she was later able to discontinue the antihypertensive drug.

It is interesting to note that beta-blocker medication inhibits CoQ10 dependent enzymes and possibly compromise their effect by causing CoQ10 deficiency on long term use. It should be noted that the effect of CoQ10 on blood pressure was usually not seen until after 4-12 weeks of therapy. This observation is consistent with the delayed increase in enzyme activity that results from administration of CoQ10. Thus, CoQ10 is not a typical antihypertensive drug; rather, it seems to correct some metabolic abnormality that is involved in the
pathogenesis of hypertension.

9. Role in ischemic heart disease (IHD)

Controlled trials in IHD did not begin until the mid 1980's with the first publication by Hiasa in 1984 in which 18 patients were randomized to receive either intravenous CoQ10 or placebo. The treated patients showed an increase in exercise tolerance of one stage or greater in modified Bruce protocol as compared to the placebo group, with less ST-segment depression on exercise and experienced less angina with no alteration in heart rate or blood pressure. A year later, Kamikawa et al. studied 12 patients with chronic stable angina in a double-blind placebo controlled randomized crossover protocol using 150 mg a day of oral CoQ10. Exercise time increased significantly from 345 seconds to 406 seconds with CoQ10 treatment and time until 1 mm of ST depression increased significantly from 196 seconds to 284 seconds (P < 0.01). Schardt et al. (1986) studied 15 patients with exercise-induced angina treated with 600 mg per day of CoQ10 with a placebo controlled double-blind crossover design and noted similar results. Since the CoQ10 treatment caused no significant alteration in heart rate or blood pressure, it was concluded that the mechanism of action was related to a direct effect on myocardial metabolism. A trial conducted by Wilson et al. (1991) showed similar benefit including a significant reduction in the number of anginal episodes and nitrate consumption. In a recent study (Kumar et al., 2005) on 106 cases of acute coronary syndrome which included Non -ST elevation myocardial infarction and unstable angina, adjunctive CoQ10 therapy produced symptomatic improvement in anginal scores and resulted in decreased development of significant left ventricular dysfunction by clinical/echocardiographic criteria and a decreased need for revascularization therapy by percutaneous transluminal coronary angioplasty/ coronary artery bypass surgery with a lesser mortality at 6 months follow up. (Fig 2)

The role of free radicals in cell injury and cell death in settings of ischemia and reperfusion is becoming increasingly well established. CoQ10's antioxidant properties and its location within the mitochondria (the centre of free radical production) make it an obvious candidate for a potential therapeutic agent in this situation (Yokoyama et al., 1996). It also improves myocardial ischemia by improving coronary vasodilatation and by improving endothelial function. Reactive oxygen species seem to play an important role in vascular homeostasis. In conditions of high oxidative stress such as coronary artery disease, the rate of inactivation of nitric oxide to peroxynitrite by superoxide anions may be reduced by CoQ10. Patients with lower levels of extracellular superoxide dismutase (ecSOD) demonstrate greater improvements than patients with normal ec-SOD levels, suggesting that higher the oxidative stress greater is the improvement in the endothelium-dependent relaxation after the administration of CoQ10 (Belardinelli et al., 2008).

It may also influence vascular function indirectly via inhibition of oxidative damage to LDL (Stoker et al., 1991) and prevention of atherosclerosis. CoQ10 is crucial for preservation of oxidative phosphorylation and reduction of myocardial damage during conditions of metabolic stress. The mechanism for improved exercise tolerance in patients with stable angina may be due to ischemic myocardial protection by CoQ10, allowing tissue to reach higher levels of energy expenditure (Crane et al., 2001).

CoQ10 also decreases blood viscosity and improves blood flow to cardiac muscle in patients with ischemic heart disease (Kato et al., 1990). It also helps in ischemic heart disease by decreasing the inflammatory cytokines and prevents the hyperglycemia induced endothelial cell damage, monocyte adhesion and evolution of atherosclerotic lesions in diabetic patients (Tsuneki et al., 2007).

In acute myocardial infarction, in recent trials, use of CoQ10 produced significant reduction in postinfarct angina, left ventricular dysfunction and arrhythmias due to prevention of QT prolongation by optimising membrane repolarisation although there was no significant change in the mortality pattern. A study of 144 patients with acute myocardial infarction (AMI) that was published in 1998 demonstrated a halving of total cardiac events in those given CoQ10 compared with placebo. In another randomized double-blind controlled trial involving 71 patients, oral treatment with coenzyme Q10 (120 mg/day) after 1 year showed that total cardiac events were 24.6% vs. 45.0% (p < 0.02) including non-fatal infarction 13.7% vs. 25.3% (p < 0.05) and cardiac deaths were significantly lower in the intervention group compared to control group. The extent of cardiac disease, elevation in cardiac enzymes, left ventricular enlargement and previous coronary artery disease showed no significant differences between the two groups (Singh et al., 1998 and 2003).
10. Role in arrhythmias

There is some anecdotal experimental and clinical evidence of a beneficial effect of coenzyme Q10 in cardiac arrhythmias. This effect could be due to improvement of cellular membrane function and energy production and reduction of the myocardial ischemia that can generate arrhythmias. In heart failure there is Ca2+ overload due to decreased uptake by the sarcoplasmic reticulum associated with depressed diastolic energetics. This results in increased Na+/Ca2+ exchange activity. Calcium efflux is associated with Na+ influx which can prolong depolarization and cause after depolarizations. (Schillingera et al., 2003). CoQ10 has a beneficial effect on arrhythmias possibly due to improved energetics in the above situation.

Twenty-seven patients with ventricular premature beats (VPB’s) and no evidence of organic heart disease received a placebo for 3-4 weeks, followed by 60 mg/day of coenzyme Q10 for 4-5 weeks. The reduction in VPB’s was significantly greater after CoQ10 than after placebo. The beneficial effect of CoQ10 was seen primarily in diabetics, in whom the mean reduction in VPB frequency was 85.7%. A significant reduction in VPB’s also occurred in 1 (11%) of 9 otherwise healthy patients and in 4 (36%) of 11 patients with hypertension (Fujioka et al., 1983). Kuklinski et al. (1994) studied 61 patients with acute myocardial infarction, randomized to obtain either placebo or 100 mg of CoQ10 with 100 mg of selenium for a period of one year. The treatment group showed no prolongation of the corrected QT-interval whereas, in the placebo group, 40% showed prolongation of the corrected QT-interval of greater than 440 milliseconds (P < 0.001). Although there were no significant differences in the acute hospitalization, the one year follow-up revealed six patients (20%) in the control group died from re-infarction, whereas one patient in the treatment group suffered a noncardiac death. The prevention of QT-interval prolongation can be explained by an enhancement in myocardial bioenergetics with an improvement in sodium potassium ATPase function, thereby optimizing membrane repolarization and decreasing occurrence of dangerous arrhythmias like ventricular tachycardia and ventricular fibrillation (Greenberg et al., 1990).

11. Protection during cardiac surgery

Postoperative low cardiac output is a major cause of early death following 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. All but one of these trials have shown a beneficial effects of some kind. The one trial showing an absence of effect (Taggart et al., 1996) used oral CoQ10 for only 12 hours before surgery, an inadequate time frame for sufficient dosing to increase myocardial levels.

Chello et al. (1994) randomized 40 patients to receive either placebo or 150 mg per day of oral CoQ10 one week prior to coronary artery bypass graft surgery. A significant decrease in postoperative markers of oxidative damage was observed in the treatment group with lower concentrations of coronary sinus thiobarbituric acid reactive substances, conjugated dienes and cardiac isoenzymes of creatine kinase. The treatment group also showed a significantly lower incidence of ventricular arrhythmias in the recovery period and the mean dose of dopamine required to maintain stable hemodynamics was significantly lower in the CoQ10 treated group. Prior treatment with CoQ10 two weeks before coronary artery bypass surgery or valve replacement lead to decreased requirement of inotropic drugs, improved left ventricular function indices and shorter recovery time. Another prospective randomised placebo controlled trial of 300 mg per day of oral CoQ10 for two weeks preoperatively in 121 coronary bypass or valve replacement procedures by Rosenfeldt et al.(2005) showed increased mitochondrial CoQ10 content, increased efficiency of mitochondrial energy production and improved contractile function in myocardial trabeculae and better postoperative surgical results.

12. Role in doxorubicin cardiotoxicity

Recent trials with anticancer drug Doxorubicin (Adriamycin) including those in animal models, have noted a reduction in cardiac coenzyme Q10 depletion and cardiotoxicity associated with coadministration of coenzyme Q10 (Judy et al.,1984). Addition of 50mg/day of CoQ10 along with adriamycin significantly reduced cardiotoxicity on long term use.

13. Role in mitral valve prolapse (MVP) syndrome

There are reports of some benefit of CoQ10 in mitral valve prolapse (MVP) syndrome with symptomatic improvement & better handgrip strength in some cases. In a study of 27 cases of MVP syndrome by Langsjoen
et al., (1999) use of CoQ10 resulted in symptomatic improvement with better diastolic function in majority of the cases.

14. Role in Meniere’s like syndrome
As far back as 1988, researchers were aware that CoQ10 was effective in promoting recovery from acute sudden deafness. A Japanese study was conducted on guinea pigs with acute sensorineural hearing loss artificially induced by hypoxia (lack of oxygen) conditions. The results showed that CoQ10 “is effective in promoting recovery from damage to auditory hairs as well as in preventing respiratory metabolic impairment of hair cells due to hypoxia” (Yao et al., 2004).

Oxidative stress causes ischemia due to oxidation of proteins and lipids and could be among the etiological factors in the genesis of hearing disorders. In patients with a low plasma CoQ10 concentration, CoQ10 supplementation may decrease the tinnitus expression. In a preliminary trial, the effects of CoQ10 were studied on patients with tinnitus. The study involved 20 patients with tinnitus and lasted for 16 weeks. CoQ10 levels were recorded before the study began. Tinnitus questionnaire (TQ) was used to evaluate efficacy. Patients were given CoQ10 100 mg three times daily. At the end of the study the mean plasma concentration of CoQ10 significantly increased and was still elevated 4 weeks after the study ended. No statistical differences in tinnitus questionnaire scores were recorded. However, a subgroup of 7 patients had significant reductions in questionnaire scores from 38 to 24. These responders had a reduction in all dimensions of the TQ score compared with their initial values except for the dimension of emotional distress. The patients in this group who responded well had a much lower level of CoQ10 before the study began than non-responders. Moreover, the increase of CoQ10 levels was significantly higher in responders than in non-responders. Supplementation with coenzyme Q10 for 16 weeks significantly improved tinnitus in people who had initially low blood levels of CoQ10 (Khan et al., 2007).

During a large multicenter clinical trial of 2664 patients with congestive heart failure, 73.1 % cases who had experienced vertigo reported a decrease in the symptom after 3 months of treatment with 50 to 150 mg of CoQ10 daily (Baggio E et al., 1994). In another recent case report by Kimura et al. (2008), a hypertensive patient on CoQ10 also experienced considerable relief from his meneire disease like symptoms.

15. Conclusion
Coenzyme Q10 is a critical adjuvant therapy for patients with cardiac diseases due to its beneficial effects on cellular bioenergetics, regulation of cell membrane channels and its antioxidant effect. It may allow for a reduction of other pharmacological therapies, improvement in quality of life and a decrease in the incidence of complications. However, dosing, clinical application, bioavailability and dissolution of CoQ10 deserve careful scrutiny whenever employing this nutrient. The assessment of blood levels in ‘therapeutic failures’ appears warranted. It produces maximum improvement in heart failure cases with diastolic & systolic dysfunction where its beneficial role is well established especially on the ‘quality of life’ and reduction in number of hospitalisations although mortality benefits are not clearly seen. Favourable effects have been observed in patients of hypertension allowing decrease in other antihypertensive medication. The available trials also show improvement in exercise tolerance and generally beneficial effects in cases of ischemic heart disease, arrhythmias and cardiac surgery and also in meneire’s like hearing disturbances. The smaller number of patients and shorter duration of most of the trials underline the need for further research in this regard. Coenzyme Q10 may be ushering in a new era of cellular/biochemical treatment, complementing the existing approach of treating cardiovascular diseases.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>No. of Patients</th>
<th>NYHA Class on Entry</th>
<th>CoQ10 Oral Dosage (mg)</th>
<th>Treatment Duration (months)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson PS et al. (1999)</td>
<td>Crossover</td>
<td>30</td>
<td>Unknown</td>
<td>33 t.i.d.</td>
<td>2 x 3</td>
<td>EF and SVR unaltered, left ventricular systolic and diastolic volume ↓</td>
</tr>
<tr>
<td>Khatta M et al. (2000)</td>
<td>Two parallel groups</td>
<td>35</td>
<td>III-IV</td>
<td>200 q.d.</td>
<td>6</td>
<td>Exercise duration↑, EF unaltered, oxygen consumption ↑</td>
</tr>
<tr>
<td>Keogh MC et al. (2003)</td>
<td>Randomised double-blind, placebo-controlled</td>
<td>39</td>
<td>II-III</td>
<td>150 mg/day</td>
<td>3</td>
<td>NYHA class in the CoQ10 group: significant improvement of 0.5 class compared with the placebo (n = 18) (P = 0.01). Specific Activities Scale class showed a significant (P = 0.004) improvement in the CoQ10 group, but no change in the placebo group. 6-min walk-test distance (P = 0.047) increase in the CoQ10 group with no change in the placebo group.</td>
</tr>
<tr>
<td>Belardinelli R. et al. (2006)</td>
<td>Double-blind, placebo-controlled cross-over design</td>
<td>23</td>
<td>NYHA class II and III with stable CHF secondary to ischemic heart disease [ejection fraction 37±7%]</td>
<td>100 mg bid with exercise training</td>
<td>2</td>
<td>As compared to exercise training (ET) plus placebo, CoQ10 plus ET showed significant improvement. CoQ10’s main effect was: peak VO2+9%, endothelium-dependent dilation of the brachial artery (EDDBA) +38%, systolic wall thickening score index (SWTI) –12%; The combination of CoQ(10) and ET resulted in higher plasma CoQ(10) levels and more pronounced effects on all the abovementioned parameters. However, significant synergistic effect of CoQ(10) with ET was observed only for peak SWTI suggesting that ET amplifies the effect of CoQ(10) on contractility of dysfunctional myocardium.</td>
</tr>
<tr>
<td>Munkholm H. et al. (2008)</td>
<td>Randomized double-blind placebo controlled</td>
<td>22</td>
<td>NYHA class II-III with mean left ventricular (LV) ejection fraction 26%, mean LV internal diameter 71 mm</td>
<td>100 mg twice daily</td>
<td>3</td>
<td>A right heart catheterisation was done including a 3 minute exercise test. The stroke index at rest and work improved significantly, the pulmonary artery pressure at rest and work decreased (significantly at rest), and the pulmonary capillary wedge pressure at rest and work decreased (significantly at 1 min work).</td>
</tr>
<tr>
<td>Hosseini et al. (2008)</td>
<td>Randomized placebo controlled</td>
<td>50</td>
<td>NYHA class II-III</td>
<td>100mg daily</td>
<td>12</td>
<td>Significant increase in ejection fraction and improvement in symptoms</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; EF = ejection fraction; SI = stroke index; CI = cardiac index; EDVI = end-diastolic volume index; W = watts; SV = stroke volume; CO = cardiac output; EDV = end-diastolic volume; SVR = systemic vascular resistance; PEP:LVET = preejection period:left ventricular ejection time ratio; QOL = quality of life.
<table>
<thead>
<tr>
<th>Study Design</th>
<th>Author</th>
<th>No. of Patients</th>
<th>CoQ10 Dosage (mg)</th>
<th>Treatment Duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo controlled</td>
<td>Yamagami et al. (1986)</td>
<td>20</td>
<td>33.3 t.i.d.</td>
<td>12 wks</td>
<td>SBP ↓ (mm Hg): 167 vs 148 (p&lt;0.001 vs baseline)</td>
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<tr>
<td>Cohort</td>
<td>Digiesi et al. (1994)</td>
<td>26</td>
<td>50 b.i.d.</td>
<td>10 wks</td>
<td>SBP ↓ (mm Hg): 164.5 vs 146.7 (p&lt;0.001 vs baseline)</td>
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<td>DBP ↓ (mm Hg): 98.1 vs 86.1 (p&lt;0.001 vs baseline)</td>
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<td>Serum TC ↓ (mg/dl): 222.9 vs 213 (p&lt;0.005 vs baseline)</td>
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<td></td>
<td>Langsjoen et al. (1994)</td>
<td>109</td>
<td>75-360 q.d. (mean 225 q.d.)</td>
<td>Mean 13 months</td>
<td>SBP ↓ (mm Hg): 159 vs 147 (p&lt;0.001 vs baseline)</td>
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<td>DBP ↓ (mm Hg): 94 vs 85 (p&lt;0.001 vs baseline)</td>
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<td>NYHA class improved: 2.40 vs 1.36 (p&lt;0.001 vs baseline)</td>
</tr>
<tr>
<td>Placebo controlled</td>
<td>Singh R et al. (1999)</td>
<td>59</td>
<td>60 b.i.d.</td>
<td>8 wks</td>
<td>SBP ↓ (mm Hg): 164 vs 152 (p&lt;0.05 vs placebo)</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Burke et al. (2001)</td>
<td>46 men and 37 women with isolated systolic hypertension.</td>
<td>60mg b.i.d.</td>
<td>12 weeks</td>
<td>The mean reduction in systolic blood pressure of the CoQ10-treated group was 17.8 ± 7.3 mm Hg (mean ± SEM).</td>
</tr>
<tr>
<td>Randomised double-blind placebo-controlled</td>
<td>Hodgson et al. (2002)</td>
<td>It was performed in 80 subjects with uncomplicated type 2 diabetes and dyslipidaemia</td>
<td>100 mg b.i.d.</td>
<td>12 weeks</td>
<td>The main effect of CoQ 10 was to significantly decrease systolic (-6.1±2.6 mmHg, P=0.021) and diastolic (-2.9±1.4 mmHg, P=0.048) blood pressure and Hba1c (-0.37±0.17%, P=0.032).</td>
</tr>
</tbody>
</table>
Effect of coenzyme Q10 on patients of hypertrophic cardiomyopathy after a mean treatment period of 1.4 months Group I (On adjunctive coenzyme Q10 therapy), Group II (Not receiving CoQ10). Improvement in New York Heart Association (NYHA) class ≥ 1, improvement in quality of life (QOL) on detailed questionnaire, improvement in diastolic dysfunction by ≥ 1 parameter, improvement in mitral regurgitation (MR) ≥ 1 grade, significant reduction in left ventricular outflow tract (LVOT) gradient ≥ 15 mm Hg in obstructive cases, no of deaths (A): Significant reduction in interventricular thickness (IVS) and posterior wall thickness in post treatment period (9.4 – 27.5 months) (B)

FIG 1.
Comparison of end point parameters after adjunctive coenzyme Q10 therapy in 106 cases of acute coronary syndrome. Parameter 1 – Symptomatic improvement of anginal scoring system. 2 – Development of significant left ventricular dysfunction. 3 – Need for revascularisation by percutaneous transluminal angioplasty or coronary artery bypass. 4 – End point mortality.

Fig 2.
References:


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