Overview of Coenzyme Q10 treatment in Cardiovascular Disease

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Multiple treatment options with Coenzyme Q10 in cardiovascular disease

1. Prophylactic in statin therapy
2. Ischemic heart disease and angina pectoris
3. Pretreatment of CABG or valve surgery
4. Adjunctive therapy in arterial hypertension
5. Prophylactic in anthracycline therapy
6. Chronic heart failure - Results from Q-SYMBIO
   on behalf of the study investigators

Frederick Crane, 1957
Isolated orange-colored molecule from beef-heart mitochondria.

Karl Folkers, 1958
Determined the chemical structure of the molecule as a quinone Coenzyme Q

Karl Folkers, 1983
Lecture in Copenhagen
Biochemical rationale and myocardial tissue data on the effective therapy of cardiomyopathy with Coenzyme Q10 (CoQ10)

Dilated cardiomyopathy Biopsy from the left ventricle


<table>
<thead>
<tr>
<th>Blood CoQ10 (µg/ml)</th>
<th>Myocardial CoQ10 (µg/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (N=6)</td>
<td>0.70 ± 0.22</td>
</tr>
<tr>
<td>II (N=18)</td>
<td>0.77 ± 0.17</td>
</tr>
<tr>
<td>III (N=11)</td>
<td>0.60 ± 0.20</td>
</tr>
<tr>
<td>IV (N=8)</td>
<td>0.66 ± 0.18</td>
</tr>
<tr>
<td>I + II vs. III + IV</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

Mean ± SD

<table>
<thead>
<tr>
<th>NYHA Class</th>
<th>Blood CoQ10 (µg/ml)</th>
<th>Myocardial CoQ10 (µg/mg)</th>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>III</td>
<td>0.64</td>
<td>1.57</td>
</tr>
<tr>
<td>IV</td>
<td>0.73</td>
<td>1.47</td>
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<tr>
<td>III</td>
<td>0.40</td>
<td>0.71</td>
</tr>
<tr>
<td>IV</td>
<td>0.95</td>
<td>2.59</td>
</tr>
<tr>
<td>IV</td>
<td>0.57</td>
<td>0.80</td>
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<tr>
<td>Mean ± SD</td>
<td>0.66 ± 0.20</td>
<td>1.50 ± 0.78</td>
</tr>
</tbody>
</table>

Coenzyme Q10 (ubiquinone)

Biological actions:
- Biosynthesis of ATP (vital role in bioenergetics)
- Free radical scavenger (our body’s antioxidant)
- Enhancing membrane stability
- Regulating genes
Coenzyme Q10 Body Content

<table>
<thead>
<tr>
<th>Sample</th>
<th>Weight of CoQ10 (mg)</th>
<th>Content (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Interstitial Volume</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Heart</td>
<td>84</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory muscle</td>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>1000</td>
<td>20</td>
</tr>
<tr>
<td>Liver</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Fat</td>
<td>200</td>
<td>50</td>
</tr>
<tr>
<td>Total</td>
<td>1423</td>
<td></td>
</tr>
</tbody>
</table>


Age-related distribution of Coenzyme Q10 in human organs

Kalen A et al. Lipids 1989;24(7):579
Bioavailability of Oral CoQ10 in Healthy Volunteers

Weis M, Mortensen SA et al. 1994

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AUC of Q10
Mean and SEM

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Average serum Q₁₀ₐ concentrations expected in people taking "standard Q₁₀ₐ preparation, 30 mg" or "standard Q₁₀ₐ preparation, 100 mg" at various dosages, based on data for 133 participants in controlled trials

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Increase of CoQ10 in blood vs. age

$r = 0.48; p = 0.01$


Coenzyme Q10 and Selenium reduces cardiovascular mortality in elderly people

Cardiovascular mortality and N-terminal-proBNP reduced after combined selenium and coenzyme Q10 supplementation: A 5-year prospective randomized double-blind placebo-controlled trial among elderly Swedish citizens

Clinical trial sponsored by Coenzyme Q10 and Selenium

KiSel-10 study, 2012

Coenzyme Q10 and Selenium reduces cardiovascular mortality in elderly people

Cohort of Swedish elderly persons (N = 443)
Monitored with
• clinical examinations
• Echocardiography
• cardiac biomarker NT-proBNP

Results
50% reduction in cardiovascular mortality (p=0.015)
Lower NT-proBNP in active group (p=0.014)
Better cardiac function in active group (p=0.03)

Alehagen U et al. Int J Cardiol 2012

KiSel-10 study, 2012

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Mevalonate chain


Coenzyme Q10, mol/l

Weeks

Mortensen SA et al. Molec Aspects Med 1997;18:s137-44

Effects of statins in hypercholesterolemic patients

Mortensen SA et al. Molec Aspects Med 1997;18:s137-44
Rosuvastatin 10 mg/day reduced serum CoQ10 significantly by 39%. Patients with lower CoQ10 levels were older, in more advanced CHF, with higher NT-proBNP, higher mortality (univariate analysis: P=0.03), (multivariable analysis: n.s.)

More patients in the rosuvastatin group compared to placebo experienced primary endpoints, greater all-cause mortality and coronary endpoints (n.s.). Depletion of myocardial CoQ10 might explain the neutral outcome of the study.

Low Coenzyme Q10 levels and the outcome of statin treatment in heart failure (CORONA)

Controlled Rosuvastatin Multinational Study in Heart failure (substudy)
Rosuvastatin 10 mg/day reduced serum CoQ10 significantly by 39%.

Patients with lower CoQ10 levels were older, in more advanced CHF, with higher NT-proBNP, higher mortality (univariate analysis: P=0.03), (multivariable analysis: n.s.)

More patients in the rosuvastatin group compared to placebo experienced primary endpoints, greater all-cause mortality and coronary endpoints (n.s.). Depletion of myocardial CoQ10 might explain the neutral outcome of the study.

McMurray JJV et al., JACC 2010;56:1196 Mortensen SA, JACC 2011;57:1569 (letter)

CoQ10 lessens myopathic symptoms in patients on statins

32 patients randomized in a double-blind study to either:
CoQ10 (N=18) 100 mg daily or Vitamin E (N=14) 400 IU daily for 30 days.

• Pain remained unchanged in Vitamin E group.
• Pain severity decreased by 40% (p <0.001) in CoQ10 group.
• Pain interference with daily activities decreased by 38% (p=0.02) in CoQ10 group.

Conclusion:
Encouraging evidence for the use of CoQ10 in alleviating myopathic pain in patients taking statins.

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CoQ10 in ischemic heart disease

Double-blind placebo-controlled trials with CoQ10 in angina pectoris

<table>
<thead>
<tr>
<th>1st. author</th>
<th>Pt. no.</th>
<th>Design</th>
<th>CoQ10 dose</th>
<th>Treatment length</th>
<th>Exercise tolerance</th>
<th>Time to ischemia</th>
<th>Angina/NTG*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiasa</td>
<td>18</td>
<td>Parallel groups</td>
<td>1.5 mg/kg/day</td>
<td>7 days</td>
<td>↑</td>
<td>↑ n.a.</td>
<td>n.a</td>
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<tr>
<td>Schardt</td>
<td>15</td>
<td>Cross over</td>
<td>600 mg/day</td>
<td>4 days</td>
<td>n.a.</td>
<td>↑ n.a.</td>
<td>n.a</td>
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<tr>
<td>Kamikawa</td>
<td>12</td>
<td>Cross over</td>
<td>150 mg/day</td>
<td>4 weeks</td>
<td>↑</td>
<td>↑ n.a.</td>
<td>n.a</td>
</tr>
<tr>
<td>Mazzola</td>
<td>20</td>
<td>Cross over</td>
<td>60 mg/day</td>
<td>4 weeks</td>
<td>↑ n.a.</td>
<td>↑ n.a.</td>
<td>n.a</td>
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<tr>
<td>Wilson</td>
<td>58</td>
<td>Parallel groups</td>
<td>300 mg/day</td>
<td>4 weeks</td>
<td>↑ n.a.</td>
<td>↑ n.a.</td>
<td>n.a</td>
</tr>
</tbody>
</table>

* Nitroglycerin consumption
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Controlled trials with CoQ10 in cardiac and vascular surgery

| 1st Author Year | Pt. no. | Operation | CoQ10 mg/day | Treatment length days | Low CD | Tissue damage | Lipid peroxida-
|-----------------|---------|------------|--------------|----------------------|--------|---------------|tion |
| Tanaka, 1982    | 50      | Valve      | 50-60        | 6                    | ↓      | n.a           | n.a  |
| Sunamoto 1991   | 78      | CABG       | 5 mg/kg i.v. | Periop.              | ↓      | ↓             | n.a  |
| Buly 1993       | 20      | Valve/CABG | 100          | 14                   | ↓      | n.a           | n.a  |
| Chen 1994       | 22      | Valve      | 150-200      | 5-7                  | ↓      | ↓             | n.a  |
| Chello 1994     | 40      | CABG       | 150          | 7                    | ↓      | ↓             | ↓    |
| Chello 1996     | 50      | Peripheral Vascular | 150 | 7 | ↓ | ↓ | ↓ |
| Rosenfeldt 2005 | 121     | CABG       | 300          | 14                   | -      | -             | -    |
| Taggart 1998    | 20      | CABG       | 2x 300       | 1                    | -      | -             | -    |

Coenzyme Q10 protection in cardiac surgery

Patients randomized in a double-blind design to CoQ10 300 mg/day (N=62) vs. placebo (N=59) before elective cardiac surgery.

Myocardial trabeculae from right atrial appendage excised.
Mitochondria isolated and studied.
Contractile recovery of trabeculae subjected to hypoxia studied.
Postoperative cardiac function assessed.

Coenzyme Q10 protection in cardiac surgery

In vitro results from CoQ10 treated patients:
1) Significantly increased CoQ10 content in serum, trabeculae and mitochondriae
2) Mitochondrial respiration more efficient
3) Greater recovery of developed force after hypoxia

Clinical results:
Use of inotropic drugs: CoQ10 (24%), placebo (33%), p=0.39
Improved quality of life at follow-up in the CoQ10 group (+13%) vs. placebo (p=0.046)


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CoQ10 in the treatment of hypertension
A meta-analysis of clinical trials

Randomized trials: (patients no. 120)
CoQ10-groups:
SBP decrease from mean 167 to mean 151 mm Hg mean decrease of 17 (13 – 20, with 95% CI), p < 0.001
DBP decrease from mean 101 to mean 95 mm Hg mean decrease of 8 (6 – 10, with 95% CI), p < 0.001
Placebo groups: no significant change

CoQ10 in the treatment of hypertension
A meta-analysis of clinical trials

**Cross-over** (patients no. 18)
SBP/DBP mean decrease of 11/8 mm Hg, respectively (p < 0.001)

**Open label** (patients no. 214)
SBP/DBP mean decrease of 13/10 mm Hg, respectively (p < 0.001)
No change with placebo in these trials.


CoQ10 in the treatment of arterial hypertension
CoQ10 appears to be effective as an antihypertensive agent without side-effects commonly seen with conventional therapy

First line therapy in patients with borderline/mild hypertension where non-pharmacological strategy - lifestyle changes are contemplated

Adjuvant therapy to conventional antihypertensives:
in patients with intolerable side-effects to drugs,
in labile arterial hypertension,
in patients with increased oxidative stress, e.g. diabetes mellitus; renal failure

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CoQ10 for prevention of anthracycline-induced cardiotoxicity

- Several preclinical and clinical studies suggest that cardiotoxicity can be prevented by CoQ10 administration during cancer therapy.
- CoQ10 prevents mitochondrial damage due to oxidative stress from anthracyclines.
- Escalation of anthracycline dose is possible via simultaneous CoQ10 supplementation thus enhancing the anticancer effect of anthracyclines.
- Larger randomized trials are needed.


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Oxidative stress in heart failure
- Catecholamine excess may activate cytokines
- Generation of reactive oxygen species
- Depletion of enzymatic antioxidants
- Vicious metabolic cycle
- Energy starvation of the myocardium

Possible reasons for Coenzyme Q10 deficiency in heart failure
- "Steal-phenomenon" regarding ATP-synthesis when CoQ10 is used in excess as antioxidant due to the oxidative stress in the failing heart.
- Increased demand on the respiratory chain elicited from the neuro-hormonal response.
- Low tissue levels of CoQ10 due to decreased synthesis and low intake from foods during the progression of heart failure.
- CoQ10 synthesis-inhibition (statin therapy)

Treatment of chronic heart failure up to the late eighties
- Bed rest
- Fluid and salt restriction
- Diuretics
- Fox-glove plant extract
- In 1987 new treatment principle using ACE-inhibitors
Pharmacological ways to reduce left ventricular dysfunction

- Beta-blockers
- ACE-I / ARB
- Spironolactone
- Neurohormonal Activation
- LV remodelling
- Metabolic Abnormality
- Carnitine
- CoQ10
- Impaired LV Hemodynamics
- Mortality

Adapted from Jay N. Cohn

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Diagnosis</th>
<th>NYHA class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Longeron</td>
<td>Cross-over</td>
<td>DCM</td>
<td>III-IV</td>
</tr>
<tr>
<td>Joyly</td>
<td>Cross-over</td>
<td>DCM</td>
<td>IV</td>
</tr>
<tr>
<td>Evans</td>
<td>Parallel groups</td>
<td>DCM + BH2</td>
<td>III-IV</td>
</tr>
<tr>
<td>Biais</td>
<td>Cross-over</td>
<td>DCM + BH2</td>
<td>III-IV</td>
</tr>
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<td>Hoffmann-Hang</td>
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<td>DCM + BH2</td>
<td>III-IV</td>
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<td>Paggiol</td>
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<td>Morano</td>
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<td>DCM + BH2</td>
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<td>Watson</td>
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<td>DCM</td>
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<td>III-IV</td>
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<tr>
<td>Strauss</td>
<td>Parallel groups</td>
<td>Mixed etiology</td>
<td>III-IV</td>
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Double-blind trials with Coenzyme Q10 in heart failure

<table>
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<tr>
<th>Study</th>
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<tbody>
<tr>
<td>CoQ10 dose (mg/day)</td>
<td>CoQ10 concentration (mg/mL)</td>
<td>CoQ10 absorption (%)</td>
<td>Side effects related to CoQ10</td>
</tr>
<tr>
<td>100</td>
<td>Yes</td>
<td>100%</td>
<td>No reported</td>
</tr>
<tr>
<td>300</td>
<td>Yes</td>
<td>100%</td>
<td>No reported</td>
</tr>
<tr>
<td>400</td>
<td>Yes (slow release)</td>
<td>50%</td>
<td>No reported</td>
</tr>
<tr>
<td>1000</td>
<td>No</td>
<td>0%</td>
<td>No reported</td>
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<tr>
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<td>No</td>
<td>0%</td>
<td>No reported</td>
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</table>
Results of meta-analyses of Coenzyme Q10 heart failure trials

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal / Year</th>
<th>Randomized trials no.</th>
<th>Significance of parameters</th>
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</thead>
<tbody>
<tr>
<td>Soya, Mortensen</td>
<td>Molec Aspects Med 1997</td>
<td>8</td>
<td>SV, CO, EF, EDVI</td>
</tr>
<tr>
<td>Rosenfeldt et al.</td>
<td>BioFactors 2003</td>
<td>9</td>
<td>(EF)</td>
</tr>
<tr>
<td>Sander et al.</td>
<td>J Cardiac Failure 2006</td>
<td>11</td>
<td>EF, CO</td>
</tr>
</tbody>
</table>

- From 1985 - 2011 available data from a total of 1198 patients randomized in 16 double-blind placebo-controlled trials.
- The trials have been underpowered or not designed to address major clinical endpoints as survival.

Coenzyme Q10: An independent predictor of mortality in chronic heart failure (CHF)

Plasma samples from a cohort of 236 patients admitted with heart failure were assayed for LDL and total cholesterol and total CoQ10.

**Results:**
Independent association between low CoQ10 and increased risk of mortality in CHF (multivariable analysis).

The strength of association between CoQ10 and mortality (HR: 1.99) was greater than that observed for NT-proBNP (HR: 1.82).

Molyneux SL, Florkowski CM et al. JACC 2008;52:1435-41
LVAD implantations at Rigshospitalet
Support with medical treatment before explantation of HeartMate2 (as a bridge to recovery)

24-year old woman
Peripartum Cardiomyopathy
- Carvedilol 12.5 mgx2
- Furosemide 20 mgx1
- Spironolactone 25 mgx1
- Ramipril 5 mgx2
- Coenzyme Q10 100 mgx2

21-year old man
Anthracycline Cardiomyopathy
- Metoprolol 100 mgx2
- Furosemide 20 mgx2
- Spironolactone 25 mgx1
- Candesartan 16 mgx1
- Coenzyme Q10 100 mgx2
Coenzyme Q10: An important advance in the therapy of chronic heart failure

Results from the Q-SYMBIO study on behalf of the study investigators from European, Asian and Australian centers.

Q-SYMBIO

Coenzyme Q10 as adjunctive treatment of chronic heart failure.

A randomized double-blind multicenter trial with focus on changes in symptoms, Biomarker status (BNP) and long-term Outcome.

UBIQUINONE COENZYME Q10

POTENTIAL THERAPEUTIC USES:

CARDIOVASCULAR:
1) CONGESTIVE HEART FAILURE
2) ISCHEMIC HEART DISEASE
3) ANTHRACYCLINE THERAPY
4) PROHLYACTIC IN HEART SURGERY

NON-CARDIOVASCULAR:
1) MUSCULAR DYSTROPHIES
2) MITOCHONDRIAL MYOPATHIES
3) PERIODONTAL DISEASE