VILNIUS UNIVERSITY
FACULTY OF MEDICINE

Medicine

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INTEGRATED STUDY MASTER'S THESIS

Nutritional Supplements for Heart diseases Systemic literature review

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Vilnius, 2025

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2. ABBREVIATIONS

NT-proBNP = B-type natriuretic peptide;
KiSel-10 = Kisa, Selenium and Coenzyme Q10;
ANOVA = Analysis of variance;
ng/L = Nanogram/liter;
mg/day = Milligram/day;
µg/day = Microgram/day;
NYHA = New York Heart Association;
% = Percent;
HR = Hazard ratio;
CI = Confidence interval;
$\chi 2$ = Chi-Square;
EF = Ejection fraction;
CV = Coefficient of variation;
HT = Hypertension;
IHD = Ischemic heart disease;
mg/d = Milligram/day;
mL/kg/min = Milliliter/kilogram/minute;
mg/mL = Milligram/milliliter;
Q-SYMBIO = Coenzyme Q10 Symptoms, Biomarker status, and long-term Outcome;
MACE = Major adverse cardiovascular events;
beats/min = Beats/minute;
SD = Standard deviation;
mmHg = Millimeter of mercury;
EDD = End-diastolic diameter;
ESD = End-systolic diameter;
mmol = Millimole;
mmol/day = Millimole/day;
bpm = Beats per minute;
DBP = Diastolic blood pressure;
SBP = Systolic blood pressure;
MET = Metabolic equivalent of task;
min = minute;
mm = millimeter;

LVEF = Left ventricular ejection fraction;

mg = milligram;

µg = microgram;

µg/liter = microgram/liter;

SeMet = Selenomethionine;

miRNA = microRNA;

miR = microRNA;

Sec = Selenocysteine;

HSe– = Hydrogen selenide;

SEPHS2 = Selenophosphate synthetase 2;

GPX = Glutathione peroxidase;

TXNRDs = Thioredoxin reductases;

DIO = Iodothyronine deiodinases;

SELENOP = Selenoprotein P;

SELENOT = Selenoprotein T;

SELENOK = Selenoprotein K;

MSRB1 = Methionine sulfoxide reductase B1;

SELENOW = Selenoprotein W;

CoQ10H2 = Ubiquinol;

CoQ10H. = Semiquinone radical;

CoQ10 = Ubiquinone;

ATP = Adenosine triphosphate;

µg/g = microgram/gram;

ROS = Reactive oxygen species;

VLDL = Very-low density lipoprotein;

Mg^{2+} = Magnesium;

Ca^{2+} = Calcium;

mg/dL = Milligram/deciliter;

Tc = Troponin C;

CaM = Calmodulin;

NCX = Na+-Ca2+-exchanger;

SERCA = Sarcoplasmatic/endoplasmic reticulum Ca2+-ATPase;

RYR = Ryanodine receptor;

3. ABSTRACT

Background: Cardiovascular diseases remain the leading cause of morbidity and mortality worldwide. This review focuses on three supplements, selenium, coenzyme Q10 and magnesium, that have been suggested to have beneficial effects in patients with cardiovascular diseases.
Methods: For this systematic literature review, multiple databases (including PubMed and Tripdatabase) were searched for randomized controlled trials that had adult patients with diagnosed cardiovascular diseases in their population. Only studies that had an intervention period of at least six months were included. The intervention was supplementation with either selenium, coenzyme Q10, magnesium, or a combination of those. The outcomes were progression of disease, severity of symptoms, B-type natriuretic peptide, exercise tolerance and cardiovascular mortality. The studies were selected following the Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol. The risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool 2.
Results: Supplementation with selenium and coenzyme Q10 combined might significantly reduce cardiovascular mortality and reduce the increase of B-type natriuretic peptide in elderly patients, especially in those with a moderately increased B-type natriuretic peptide at baseline. Trials with coenzyme Q10 as a monotherapy in congestive heart failure had mixed results. Some studies reported significant improvements in functional status and a reduction in major adverse cardiovascular events, others showed no significant changes in left ventricular ejection fraction or exercise tolerance. In patients with coronary artery disease, magnesium supplementation led to a significant decrease in blood pressure. Also, it led to a significant increase in exercise tolerance, left ventricular ejection fraction and maximal oxygen consumption. For exercise induced arrhythmias and ischemia, the results were mixed.
Conclusion: The results suggest that dietary supplementation may have adjunctive benefits in the management of cardiovascular disease. Combined selenium and coenzyme Q10 supplementation appears promising in reducing cardiac stress and mortality in specific patient populations, while magnesium supplementation may increase myocardial function and exercise tolerance. However, due to several limitations of existing studies, mostly a small and homogenous sample size, more multicentred trials are needed to confirm these benefits and to find an optimal dosage regime.
Keywords: systematic literature review; dietary supplementation; selenium; coenzyme Q10; magnesium; cardiovascular diseases

4. INTRODUCTION

The aim of this systematic literature review is to investigate if and how adult patients with cardiovascular diseases of any kind could benefit from taking dietary supplements for at least six months not considering the dosage.

Investigating this question is important due to the very high impact of cardiovascular diseases on the public health. According to the World Health Organization, cardiovascular diseases were the leading cause of death worldwide in 2021 and still are.

The consummation of dietary supplements grows in popularity among the public (1). However, the effects of dietary supplements on cardiovascular diseases are not fully understood yet. Therefore, it is important to investigate the relationship between cardiovascular diseases and dietary supplements to create evidence-based guidelines and public health strategies.

This review relies on the definition of cardiovascular diseases and dietary supplements. According to Thiriet M. (2019) the term cardiovascular disease includes all diseases that affect the heart, which pumps the blood through the body, and the blood vessels, which carry the blood through the body (2).

According to the United States of America Dietary Supplement Health and Education Act of 1994, "the term dietary supplement means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (A) a vitamin; (B) a mineral; (C) an herb or other botanical; (D) an amino acid; (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)." (3)

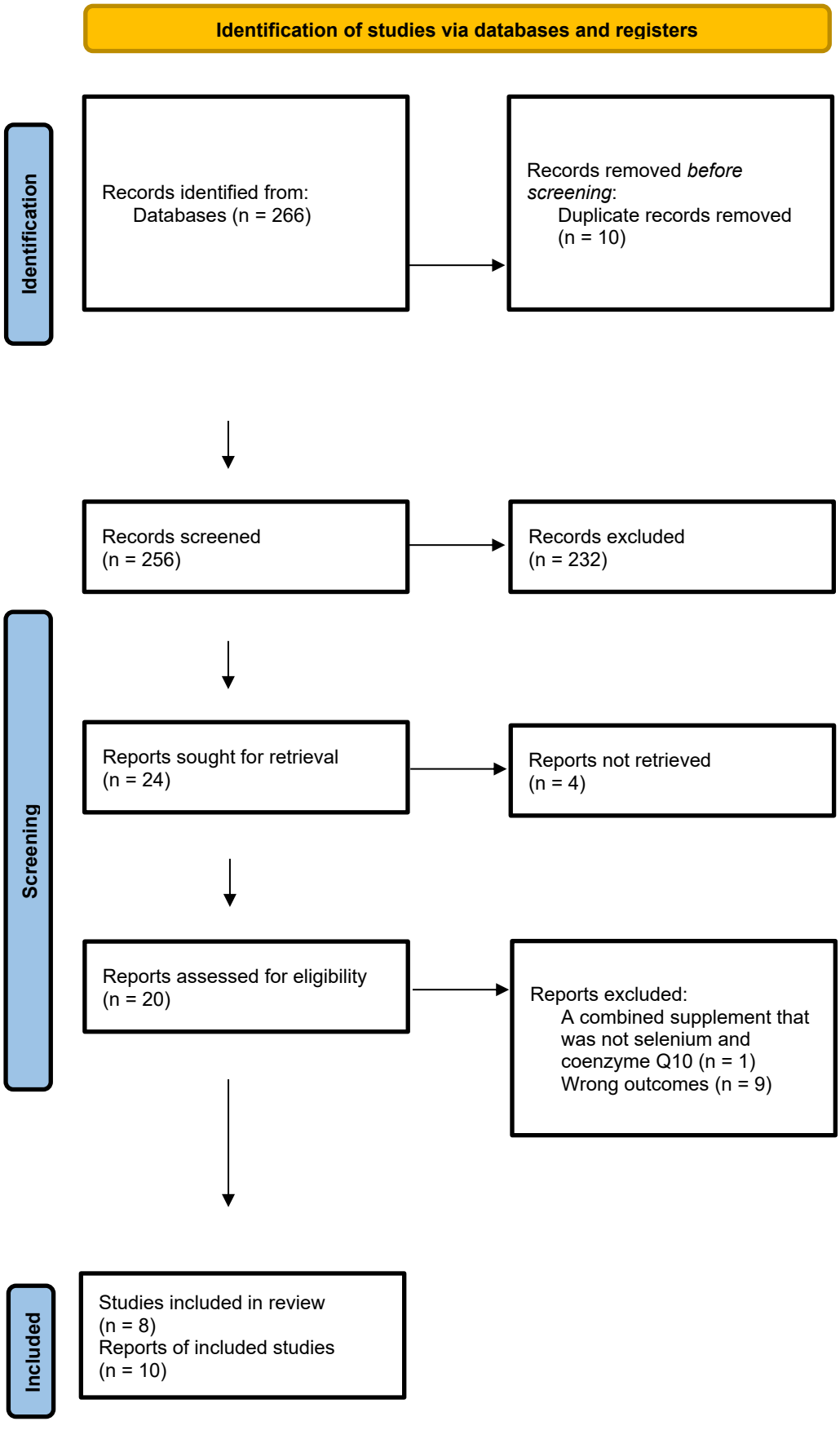
This systematic literature review will investigate the dietary supplements magnesium, selenium, and coenzyme Q10. These specific dietary supplements were chosen because all of them have physiologic properties, which will be discussed later in this review, that could have a positive impact on cardiovascular health.

5. METHODS

For this systematic literature review, existing evidence about the effects of selenium, magnesium and coenzyme Q10 supplementation on cardiovascular health was assessed and analysed to answer the main question this review addresses. Can adults with current cardiovascular disease benefit from taking dietary supplements taken for at least half a year, by slowing heart disease progression, decreasing symptom severity, and preventing complications, compared to those who do not?

Regarding the inclusion criteria, only randomized controlled trials that have a population of adults with diagnosed cardiovascular diseases who take dietary supplements were included. The intervention had to be magnesium, selenium, coenzyme Q10, or their combination, taken regularly for at least six months regardless of dose. The comparative group was humans with cardiovascular diseases who do not take these dietary supplements. Measured outcomes were NT-proBNP levels, cardiovascular mortality, left ventricular ejection fraction, right ventricular ejection fraction, subjective symptom improvement, major adverse cardiovascular events, blood pressure, maximal oxygen consumption, exercise duration and exercise tolerance. PubMed, Tripdabase, references from systematic reviews and references from included articles were searched to identify studies.

6. PREFERRED REPORTING ITEMS FOR SYSTEMATIC REVIEWS AND META-ANALYSES



7. RESULTS

7.1 SELENIUM AND COENZYME Q10

Population	Intervention	Comparison	Outcome	Search Terms
Adults with current cardiovascular disease	Combined selenium and coenzyme Q10 supplementation	Adults with current cardiovascular disease who do not take combined selenium and coenzyme Q10 supplementation	NT-proBNP as a marker of cardiac stress, cardiovascular mortality	("Selenium"[Mesh]) AND "Cardiovascular Diseases"[Mesh]
NT-proBNP = B-type natriuretic peptide				

TABLE 1 – Included reports (selenium and coenzyme Q10)

Authors	Year	Number of Participants	Age of Participants
Johansson et al.	2013	443	70 – 88 years, mean of 78 years
Alehagen et al.	2015	443	70 – 88 years, mean of 78 years
Alehagen et al.	2018	443	70 – 88 years, mean of 78 years

Unfortunately, there were no studies evaluating the effect of selenium alone that met the inclusion criteria. However, there was one study with three reports that analysed a combination of selenium and coenzyme Q10 on elderly Swedish citizens. Kisa, Selenium and Coenzyme Q10 (KiSel-10) is a prospective randomized, double-blinded, placebo controlled study (4). The three reports on the study focused on B-type natriuretic peptide (NT-proBNP) levels (5) and on cardiovascular mortality after 10 (6), and 12 (7) years.

Johansson et al. 2013 found that taking coenzyme Q10 and selenium significantly reduced the increase of NT-proBNP levels. They divided all participants in quintiles, according to their NT-proBNP levels at baseline. Looking at all quintiles together, there was no statistically significant difference in treatment effect between the groups. However, when the authors grouped the subjects into two groups, one in which treatment effect was expected, quintile 2 – 4, and one in which treatment effect was not expected, quintile 1 and 5, there was a statistically significant difference in treatment response between both groups (5). This was demonstrated by a three-way analysis of variance (ANOVA), $F(1, 207) = 5.36$, $p = 0.022$. Due to the statistically significant difference in treatment effect, the authors performed several follow-up two-way ANOVAs, analysing NT-proBNP over time, baseline and 48 months, in treatment and placebo group for quintile 1 – 5 individually, as well as quintile 2 – 4 grouped together. This revealed a statistically significant treatment response in quintile 2 – 4. $F(1, 124) = 7.95$, $p = 0.006$. As well as for quintile 3 alone (5).

TABLE 2 – Analysis of the interaction between group (active substance or placebo) and follow-up (baseline or 48 months) and with B-type natriuretic peptide as outcome measure (logarithmic transformed) according to the quintiles (5)

Quintile	F-Statistic	p value	Significant?
Q1 (15-104 ng/L)	0.210	0.65	No
Q2 (104.01-149.80 ng/L)	2.23	0.14	No
Q3 (149.81-227 ng/L)	4.25	0.045	Yes
Q4 (227.01-395.40 ng/L)	1.60	0.21	No

Johansson et al. 2013 also found that in quintile 2 – 4 active treatment statistically significantly reduced cardiovascular mortality. In the treatment group, 1.8% died of cardiovascular causes in comparison to 10.6% in the placebo group. P value = 0.006. Such an effect was not present in quintile 1 and in quintile 5 (5).

TABLE 3 – The impact of the active substance on cardiovascular mortality according to the different quintiles of B-type natriuretic peptide (5)

	Mortality, %		p value
	Treatment*	Placebo	
Quintile 1 15 – 104 ng/L n = 43	5.1	3.1	0.68
Quintile 2 - 4 104.01–395.40 ng/L ng/L n = 126	1.8	10.6	0.006
Quintile 5 395.41–3083 ng/L n = 41	13.8	19.7	0.35
* A combination of 200 mg/day of coenzyme Q10 and 200 µg/day of organic selenium.			

Alehagen et al. 2015 analysed cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years of the participants of the KiSel-10 study. Since this literature review focuses on patients with cardiovascular diseases, it will not take into account the overall treatment effect on cardiovascular mortality but only focus on the subgroup analysis. The authors divided the participants into subgroups. Namely, those with a history of ischemic heart disease and according to the different New York Heart Association (NYHA) classes (6).

Of the patients with a history of ischemic heart disease, 19 out of 47 in the active treatment group experienced cardiovascular mortality, while 31 out of 53 experienced cardiovascular mortality in the placebo group. Even though cardiovascular mortality was lower in the treatment group, this is not a statistically significant difference, 19/47 vs. 31/53; Chi-Square (χ^2): 3.25; P = 0.071. After the authors performed further analysis, using a multivariate model, a statistically significant reduction in the risk of cardiovascular mortality was found in the treatment group. Hazard Ratio (HR): 0.51; 95%Confidence Interval (CI) 0.27–0.97; P = 0.04 (6).

A statistically significant reduction in cardiovascular mortality was observed across all functional classes of the NYHA classification. “NYHA I: active treatment: 19/119 vs. placebo: 26/111; χ^2: 3.83; P = 0.05; NYHA II: active treatment: 14/61 vs. placebo: 26/64; χ^2: 4.48; P = 0.03; NYHA III; active treatment: 16/41 vs. placebo: 34/47; χ^2: 9.91; P = 0.002.” (6). If all subgroups are combined the results are as follows: active treatment: 68/268 vs. placebo 117/275; χ^2: 17.82; P = 0.000024.

This proves a statistically significant reduction of cardiovascular mortality when all patients with cardiovascular diseases in this study are pooled together.

TABLE 4 – Cardiovascular mortality 10 years after supplementation with selenium and coenzyme Q10 for four years by subgroup (6)

Group	Active treatment mortality	Placebo mortality	χ^2	p - value
Ischemic heart disease	19/47	31/53	3.25	0.071
NYHA class I	19/119	26/111	3.83	0.05
NYHA class II	14/61	26/64	4.48	0.03
NYHA class III	16/41	34/47	9.91	0.002
Overall	68/268	117/275	17.82	0.000024
χ^2 = Chi-Square; NYHA = New York Heart Association				

Alehagen et al. 2018 analysed cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four years of the participants of the KiSel-10 study. The authors divided that total study population into subgroups. In patients with ischemic heart disease there still was a statistically significantly decreased risk of cardiovascular mortality 12 years after the intervention. HR: 0.52; 95%CI: 0.30–0.90; P =0.02).

The same was seen in the hypertension group (HR: 0.60; 95% CI: 0.41–0.85; P =0.005) and in the NYHA functional class III group (HR: 0.49; 95% CI: 0.27–0.88; P =0.002). The authors also combined the patients with ischemic heart disease and with impaired systolic cardiac function (ejection fraction (EF) <40%). In this subgroup a statistically significant decrease in cardiovascular mortality risk was seen as well. HR of 0.56 (95% CI: 0.33–0.05; P =0.03). In a subgroup with patients with ischemic heart disease, impaired systolic function, and hypertension the risk of cardiovascular mortality was statistically significantly lower as well with an HR of 0.60 (95% CI: 0.42–0.84; P =0.004).

In the following table (Table 5) the effect of intervention after 12 years on risk for cardiovascular mortality in different groups is shown. The table was taken from the article “Still reduced cardiovascular mortality 12 years after supplementation with selenium and coenzyme Q10 for four years: A validation of previous 10-year follow-up results of a prospective randomized double-blind placebo-controlled trial in elderly” by Alehagen et al., published in the PLOS One journal in April 2018.

TABLE 5 – Model testing the effect of intervention after 12 years on risk for cardiovascular mortality in different groups (7).

Variable	HR	p-Value	95%CV
HT	0.59	0.005	0.41–0.85
IHD	0.52	0.02	0.30–0.90
NYHA III	0.49	0.02	0.27–0.88
IHD+EF<40%	0.56	0.03	0.33–0.95
IHD+EF<40%+HT	0.60	0.004	0.42–0.84
Note: CV: Coefficient of variation; HT: Hypertension; HR: Hazard ratio; IHD: Ischemic heart disease; NYHA III: New York Heart Association functional class III			

7.2 COENZYME Q10

Population	Intervention	Comparison	Outcome	Search Terms
Adults with current cardiovascular disease	Coenzyme Q10 supplementation	Adults with current cardiovascular disease who do not take coenzyme Q10 supplementation	Maximal oxygen consumption, exercise duration, left and right ventricular ejection fraction, subjective symptom improvement, major adverse cardiovascular events, cardiovascular mortality	("Ubiquinone"[Mesh]) AND "Cardiovascular Diseases"[Mesh]

TABLE 6 – Included reports (coenzyme Q10)

Authors	Year	Number of Participants	Age of Participants
Khatta et al.	2000	46	Mean of 64 years
Mortensen et al.	2014	420	Mean of 62 years
Mortensen et al.	2019	231	Mean of 65 years

The literature search yielded three reports of two studies that fitted the inclusion criteria for an intervention with coenzyme Q10. Khatta et al. 2000 investigated the effect of coenzyme Q10 on patients with congestive heart failure (8). They measured left ventricular ejection fraction and peak oxygen consumption and exercise duration at baseline and after six months of additional to standard treatment with coenzyme Q10, 200 mg/d, or placebo in patients with congestive heart failure with NYHA class III and IV, ejection fraction <40%, and peak oxygen consumption <17.0 mL/kg/min (or <50% of predicted) during standard therapy (8).

Maximal oxygen consumption increased by 0.21 ± 3.4 mL/kg per minute (95% CI: -1.25 to 1.68) for the treatment group and decreased by 0.49 ± 2.4 mL/kg per minute (95% CI: -1.54 to 0.55) for the placebo group. The difference between the change in the treatment and in the placebo group is not statistically significant (8).

Neither in the placebo nor in the treatment group a statistically significant change could be observed in terms of exercise duration. For the treatment group exercise duration increased from 8.5 ± 3.2 minutes to 9.1 ± 3.4 minutes. For the placebo group exercise duration decreased from 7.7 ± 3.2 minutes to 7.5 ± 2.9 minutes (8).

The mean left ventricular ejection fraction stayed the same in both groups at baseline and 6 months. Right ventricular ejection fraction remained more or less the same in the treatment group, 35% ± 13% at baseline and 35% ± 11% after six months. In the placebo group it slightly decreased from 39% ± 14% at baseline to 37% ± 8% after six months (8).

Symptoms improved in one patient of each group and remained unchanged in 16 patients in the treatment group and in 18 patients in the placebo group. In one patient of the treatment group symptoms worsened while they worsened in three patients of the placebo group (8).

These results suggest that additional treatment with coenzyme Q10 on top of standard treatment does not affect exercise duration, ejection fraction, or peak oxygen consumption in patients with congestive heart failure (8).

TABLE 7 – Maximal oxygen consumption, exercise duration, left ventricular ejection fraction, right ventricular ejection fraction, symptom improvement, and serum coenzyme Q10 levels 6 months after coenzyme Q10 200 milligram/day or placebo (8)

Outcome	Group	Baseline	6-Months Follow-Up
Maximal oxygen consumption	Coenzyme Q10	Not reported	Increase by 0.21 ± 3.4 mL/kg per minute (95% CI: -1.25 to 1.68)
	Placebo	Not reported	Decrease by 0.49 ± 2.4 mL/kg per minute (95% CI: -1.54 to 0.55)
Exercise duration	Coenzyme Q10	8.5 ± 3.2 minutes	9.1 ± 3.4 minutes
	Placebo	7.7 ± 3.2 minutes	7.5 ± 2.9 minutes
Left ventricular ejection fraction	Coenzyme Q10	27%	27%
	Placebo	30%	30%
Right ventricular ejection fraction	Coenzyme Q10	35% ± 13%	35% ± 11%
	Placebo	39% ± 14%	37% ± 8%
Symptom improvement	Coenzyme 10	-	1 patient improved, 16 unchanged, 1 worsened
	Placebo	-	1 patient improved, 18 unchanged, 3 worsened
Serum Coenzyme Q10 Levels	Coenzyme Q10	0.95 ± 0.62 mg/mL	2.2 ± 1.2 mg/mL
	Placebo	0.92 ± 0.34 mg/mL	0.96 ± 0.45 mg/mL
CI = Confidence interval			

Two reports analyzed the effect of coenzyme Q10 as an additional treatment in patients with heart failure that were enrolled in the Coenzyme Q10 Symptoms, Biomarker status, and long-term Outcome (Q-SYMBIO) study. One focused on all results (9) while another focused on the subgroups of European patients with heart failure (10).

Mortensen et al. 2014 defined major adverse cardiovascular events (MACE) as primary long-term endpoint and NYHA functional class, NT-proBNP, echocardiography, and mortality as secondary endpoints after 106 weeks of adjuvant treatment with 300 mg/d coenzyme Q10 or placebo.
They found that the risk to suffer a major adverse cardiovascular event was 43% lower in the treatment group than in the placebo group (9). 30 out of 202 patients in the treatment group suffered MACEs which accounts to 15%, while 57 out of 218 (26%) in the placebo group suffered MACEs (9). Incidence of cardiovascular deaths during the 106 weeks of follow-up was also statistically significantly lower in the treatment group. 18/202 (9%) in the treatment group vs. 34/218 (16%), indicating a 43% lower risk for the treatment group to suffer a cardiovascular death.

TABLE 8 – Major adverse cardiovascular events and cardiovascular deaths (9)

Endpoint	Coenzyme Q10 (n = 202)	Placebo (n = 218)	p - value
MACE	30 (15%)	57 (26%)	0.005
Cardiovascular death*	18 (9 %)	34 (16 %)	0.039
Values are n (%). MACE = Major adverse cardiovascular events *According to the Protocol: Implantation of left ventricular assist device and urgent cardiac transplantation were counted as deaths			

In the following table (Table 9) the changes of clinical and echocardiographic assessments at week 106 are shown. The table was taken from the article “The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a randomized double-blind trial” by Mortensen et al., published in the Journal of the American College of Cardiology: Heart Failure in December 2014.

TABLE 9 – Clinical and Echocardiographic Assessments at Week 106 (9)

Change from baseline - Δ	**Coenzyme Q10 (n = 148)**	**Placebo (n = 150)**
NYHA classification – no. (%)		

TABLE 9 – Clinical and Echocardiographic Assessments at Week 106 (continued) (9)

Improvement Unchanged Deterioration	86* (58) 61 (41) 1 (1)	68 (45) 79 (53) 3 (2)
Heart rate (beats/min ± SD)	−2 (78 ± 13)	−4 (79 ± 14)
Systolic blood pressure (mm Hg ± SD)	−2 (125 ± 18)	−1 (122 ± 16)
Diastolic blood pressure (mm Hg ± SD)	−2 (76 ± 8)	−1 (77 ± 9)
Left ventricular EF (% ± SD)	+ 2 (35 ± 10)	+ 2 (33 ± 11)
Left ventricular EDD (mm ± SD)	−1 (63 ± 8)	−1 (64 ± 8)
Left ventricular ESD (mm ± SD)	−2 (52 ± 11)	−1 (53 ± 11)
EDD end-diastolic diameter; EF = ejection fraction; ESD = end-systolic diameter; NYHA = New York Heart Association. *p = 0.028.		

After 106 weeks, NYHA functional class improved by at least one grade for 86 patients in the coenzyme Q10 group, which accounts for 58%, while only improving for 68 patients in the placebo group, which accounts for 45%. This is a statistically significant higher improvement in the coenzyme Q10 group ($p = 0.028$) (9). Echocardiographic assessments did not change statistically significantly more in the coenzyme Q10 group (9).

Mortensen et al. 2019 looked at the European subgroup of the Q-SYMBIO study. They found that European patients with heart failure, who were taking 300 mg/d coenzyme Q10 for six months, had statistically significant improvements in walking distance after two years, measured by the 6-min walk test. They improved from 331 ± 91 meters at baseline by +19 ± 75 meters after 2 years (10). If the hypothesis is that the 6-min walk test will not improve at all, this would be a statistically significant improvement ($p \approx 0.025$). The placebo group did not improve by a statistically significant margin from 321 ± 90 meters at baseline by +2 ± 102 meters after 2 years ($p \approx 0.864$) (10). However, the improvement in the treatment group was not statistically significantly higher than in the placebo group. A Welch's t-tests yields a p-value of roughly 0.237.

7.3 MAGNESIUM

Population	Intervention	Comparison	Outcome	Search Terms
Adults with current cardiovascular disease	Magnesium supplementation	Adults with current cardiovascular disease who do not take magnesium supplementation	Blood pressure, exercise tolerance (Bruce protocol), left ventricular ejection fraction, maximal oxygen consumption	("Magnesium"[Mesh]) AND "Cardiovascular Diseases"[Mesh]

TABLE 10 – Included reports (magnesium)

Authors	Year	Number of Participants	Age of Participants
Dyckner T, Wester PO	1983	39	Treatment group: mean of 62 years; Control group: mean of 68 years
Shechter et al.	2000	50	Mean of 66 years
Shechter et al.	2003	187	42 – 83, mean of 63 years
Pokan et al.	2006	53	Treatment group: mean of 61 years; Control group: mean of 58 years

The literature search yielded four reports of four studies that fitted the inclusion criteria for an intervention with magnesium. Dyckner et al. 1983 analyzed the effect of 15 mmol magnesium

aspartate hydrochloride/day for six months on blood pressure in patients receiving long-term diuretic treatment for arterial hypertension and/or congestive heart failure (11).

TABLE 11 – Changes in blood pressure in patients receiving 15 millimole/day magnesium aspartate hydrochloride for six months vs. control (11)

	Position	Baseline	Six months	p-value
Treatment group (N = 20)	Supine:	152 ± 20/93 ± 11 mmHg	140 ± 15/85 ± 7 mmHg	<0.001
	Standing:	145 ± 17/93 ± 13 mmHg	139 ± 18/87 ± 10 mmHg	<0.05
Control group (N = 19)	Supine:	154 ± 26/90 ± 11 mmHg	154 ± 28/86 ± 13 mmHg	>0.05
	Standing:	152 ± 27/91 ± 10 mmHg	154 ± 27/89 ± 12 mmHg	>0.05

The researchers found that magnesium supplementation statistically significantly reduced both systolic and diastolic blood pressure. In the control group, no statistically significant reduction of systolic or diastolic blood pressure was observed (11).

Shechter et al. 2000 analyzed the impact of oral magnesium supplementation of 30 mmol per day or placebo for six months on patients with stable coronary artery disease. The researchers carried out an exercise stress test, using the Bruce protocol at baseline and after six months (12).

In the following table (Table 12) the exercise parameters at six months after oral magnesium therapy or placebo are shown. The table was taken from the article “Oral magnesium therapy improves endothelial function in patients with coronary artery disease” by Shechter et al., published in Circulation in November 2000 (12).

TABLE 12 – Exercise Parameters at 6 mo (12)

Variable	Placebo (n = 25)	Magnesium (n = 25)	p
Supine heart rate, bpm	65±15	59±8	0.14
Standing heart rate, bpm	70±18	63±9	0.15

TABLE 12 – Exercise Parameters at 6 mo (continued) (12)

SBP supine, mm Hg	140±19	143±20	0.64
DBP supine, mm Hg	68±7	69±10	0.92
Exercise duration, min	7.3±3.1	9.3±2.0	0.05
Heart rate at maximum exercise, bpm	129±20	128±23	0.90
METs achieved	8.5±3.6	10.2±2.8	0.08
Double-product, bpm * mm Hg	22 297±4 907	22 571±6 400	0.86
Exercise-induced chest pain, n (%)	5 (20)	4 (16)	0.30
ST-segment depression, n (%)	10 (40)	4 (16)	0.05
Cardiac arrhythmias, n (%)	4 (16)	0 (0)	0.05
Cardiac arrhythmias indicate ventricular premature beats of Lown grade II or higher; DBP, diastolic blood pressure; SBP, systolic blood pressure. Values are expressed as mean SD.			

At baseline, there was no statistically significant difference in any parameter. After six months of oral magnesium supplementation the treatment group had a statistically significant longer exercise duration (a mean of 9.3 minutes) in comparison to the placebo group (a mean of 7.3 minutes). Furthermore, a statistically significantly lower percentage of patients in the treatment group had ST-segment depressions (4%) and cardiac arrhythmias (0%) than in the placebo group (10% and 4% respectively). All other parameters showed no statistically significant differences (12).

Shechter et al. 2003 also performed exercise stress testing after six months of 15 mmol magnesium twice per day in coronary artery disease patients. This time, they expanded the patient population, with a multicentered and multinational population, from the initial sub study (Shechter et al. 2000) that only included patients from the United States of America (12,13).

In the following table (Table 13) the exercise parameters at six months after oral magnesium therapy or placebo are shown. The table was taken from the article “Effects of oral magnesium therapy on exercise tolerance, exercise-induced chest pain, and quality of life in patients with coronary artery disease” by Shechter et al., published in The American Journal of Cardiology in March 2003 (13).

TABLE 13 – Exercise Parameters at Six Months (13)

Variable	Placebo (n = 84)	Magnesium (n = 73)	p Value
Supine heart rate (beats/min)	72 ± 14	70 ± 14	0.4407
Standing heart rate (beats/min)	74 ± 14	72 ± 13	0.5955
Systolic blood pressure supine (mm Hg)	140 ± 19	139 ± 17	0.5190
Diastolic blood pressure supine (mm Hg)	80 ± 13	81 ± 14	0.6969
Heart rate at maximum exercise (beats/min)	135 ± 19	131 ± 18	0.6019
Double-product (beats/min * mm Hg)	22,695 ± 5,744	25,555 ± 5,326	0.3103
Exercise-induced chest pain	18 (21%)	6 (8%)	0.0237
Time to chest pain (min)	6.2 ± 1.5	6.9 ± 1.8	0.7196
Test termination due to angina	14 (17%)	5 (7%)	0.0522
ST-segment depression	42 (50%)	31 (42%)	0.5244
Time to 1 mm ST-segment depression (min)	3.6 ± 2.2	4.4 ± 2.6	0.1787
Cardiac arrhythmias*	3 (4%)	3 (4%)	1.0000
Values are expressed as mean ± SD. *Cardiac arrhythmias indicate ventricular premature beats of Lown grade ≥II.			

Initially, no parameter was statistically significantly different between the treatment and placebo group. However, after a six-month follow-up period, a statistically significantly lower number of patients had exercise-induced chest pain in the oral magnesium group with six cases than in the placebo group with 18 cases ($p = 0.0237$) (13). Also, exercise duration after six months was statistically significantly longer in the magnesium group with 8.7 ± 2.1 minutes than in the placebo group with 7.8 ± 2.9 minutes ($p = 0.0075$). All other parameters did not have any statistically significant differences after six months (13).
Pokan et al. 2006 analyses how 15 mmol of oral magnesium twice a day for six months impacts left ventricular ejection fraction and maximal oxygen consumption in patients with coronary artery disease (14).

TABLE 14 – Changes in left ventricular ejection fraction and maximal oxygen consumption (14)

	LVEF, %		Maximal oxygen consumption, mL/kg/min	
	Magnesium (n = 28)	Placebo (n = 25)	Magnesium (n = 28)	Placebo (n = 25)
Baseline	58±11	56±11	28.3±6.2	29.3±5.4
After six months	67±10	55±12	30.5±7.1	29.6±5.2
p-value	<0.001	≥0.05	<0.001	≥0.05
LVEF = Left ventricular ejection fraction				

The magnesium supplementation led to a statistically significant increase in left ventricular ejection fraction and maximal oxygen consumption. While the placebo treatment had no statistically significant effect on either outcome (14).

8. RISK OF BIAS ASSESSMENT

For the risk of bias assessment, five main sources of possible bias were considered. Bias arising from the randomization process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported results. The range goes from low risk, meaning that bias is unlikely, over some concerns, meaning there might be some issues, until high risk, meaning that bias is likely. This assessment was inspired by the Cochrane risk of bias 2 tool (15). Alehagen et al. 2015, Alehagen et al. 2018 and Johansson et al.2013 all reported on the same study (5–7). The underlying study used a

computerised block randomisation process resulting in a low risk of bias (4). Due to double blinding, it is likely that there were no deviations from the intended intervention resulting in a low risk of bias (4). The study had a high dropout rate of 29%. However, the reasons were clearly stated. Still the dropout rate was higher in the placebo group (112 vs. 95) (16). Therefore, there might be some concerns here. All reports used objective outcomes and reported on the outcomes that they had planned (5–7). There are no concerns for bias in both domains. Overall, I decided to give all studies a low risk of bias as the dropouts were all documented and numbers did not differ significantly for all the reasons but one which was taking too many pills (16). Khatta et al. 2000, Mortensen et al. 2014 and Mortensen et al. 2019 all followed a computerized randomization process, as well as double blinding, resulting in a low risk of bias in the first two domains (8–10). Also, there were no concerns about missing outcome data in any of the studies as the dropout rate was low and reasons were stated (8–10). All outcomes were measured with validated methods and all planned outcomes were reported (8–10). This leads to a low risk of bias in the last two domains and overall, for all three reports. Dyckner et al. 1983 had some concern in all domains but missing outcome data and selection of the reported results. The report claims to be randomized but does not describe the process further. Also, there is no mention of blinding. The blood pressure was measured by a nonblinded nurse. Therefore, detection bias is possible. However, there were prespecified and objective outcomes that were all reported on (11). Still, due to the missing information on randomization, the missing blinding and the possible detection bias, there are some concerns overall. Shechter et al. 2000 and Shechter et al. 2003 both followed a computerized randomization protocol. Also both of them were double blinded (12,13), resulting in a low risk of bias in the first two domains. Shechter et al. 2000 had no dropouts and therefore no missing outcome data, outcomes form this report, that are used in this review, were measured using standardized methods and were reported on according to a prespecified plan (12), leading to an overall low risk of bias. Shechter et al. 2003 showed some concerns of bias regarding missing outcome data. While the reasons were specified, the dropout rate was higher in the magnesium group (19 vs. 7) (13). Outcomes of the report, that are used in this review, were measured by standardized methods and all preplanned outcomes were reported on (13), leading to a low risk of bias in those two domains and to an overall low risk of bias. Pokan et al. 2006 stated to be randomized but did not provide further explanation, leading to some concerns about the randomization process. Due to double blinding, there is a low risk of bias in the deviation from intended interventions. Dropout reasons were described, and dropout numbers were similar in both groups. However, after dropouts the difference in group size was quite high. In the magnesium group, 21 people remained while only 15 remained in the placebo group (14). This leads to some concerns regarding missing outcome data. In the other domains there were no reasons for concerns

about bias. Overall, Pokan et al. 2006 has some concerns of bias due to missing description of the randomization process and due to missing outcome data.

TABLE 15 – Risk of bias assessment

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall Risk of Bias
Alehagen et al. 2015	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk
Alehagen et al. 2018	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk
Johansson et al. 2013	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk
Khatta et al. 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mortensen et al. 2014	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mortensen et al. 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Dyckner et al. 1983	Some concerns	Some concerns	Low risk	Some concerns	Low risk	Some concerns
Shechter et al. 2000	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shechter et al. 2003	Low risk	Low risk	Some concerns	Low risk	Low risk	Low risk of bias
Pokan et al. (2006)	Some concerns	Low risk	Some concerns	Low risk	Low risk	Some concerns

9. DISCUSSION

The results of the KiSel-10 study suggest that combined selenium and coenzyme Q10 supplementation can be beneficial for individuals with cardiovascular diseases. Regarding the reasoning of combining selenium and coenzyme Q10, selenium is required to help reducing coenzyme Q10 into its active form ubiquinol (6).
Khatta et al. 2000 was randomized, double-blinded and placebo controlled. However, the study population was small, and the follow-up period was short (8). The Q-SYMBIO study had the additional advantage of being multicentred. Therefore, its study population was diverse and spanning over several countries and continents. Also, its follow up period was long with 106 weeks. However, the researchers did not reach enrolment goals, which limits the study's power (9).
While being randomized, Dyckner et al. 1983 was not blinded. Furthermore, its sample size was small, the follow up period short, and the dosage of diuretic treatment was changed during the study period. These factors decrease the study's significance (11). Shechter et al. 2000 as well as Shechter et al. 2003 both followed a well-designed structure of double-blinding and placebo control. However, the small sample size limits their generalizability. Furthermore, both studies had a relatively short follow up period. (12,13). Also, exercise tolerance is not a specific clinical marker for cardiovascular health. Shechter et al. 2003 has the advantage of being multinational and multicentred and thereby reflecting a more diverse population (13). Pokan et al. 2006 was randomized, double-blinded and placebo controlled. Left ventricular ejection fraction and VO_2max are objective outcomes. However, the sample size was small and the population only men. Therefore, the results have a limited generalizability (14).
Overall, many studies in this literature review lack a large and heterogenous patient population. Therefore, more, multicentred and multinational studies are needed to evaluate the true effect of dietary supplements on adults with cardiovascular diseases. However, the results of the smaller studies are mostly promising.

10. CONCLUSION

For combined supplementation with 200 µg/day of selenium and 200 mg/day of coenzyme Q10 for four years on top of standard treatment, data suggests that there might be benefits for patients with cardiovascular diseases. Compared to placebo, the treatment might significantly reduce cardiovascular mortality and the increase of B-type natriuretic peptide in those who have B-type natriuretic peptide levels of 104.01 – 395.40 ng/L at baseline (5). Also, the supplementation might significantly reduce the risk of cardiovascular mortality within 10 years after the end of the

treatment period in patients with ischemic heart disease and heart failure across all functional classes of the New York Heart Association classification (6). Patients with hypertension, ischemic heart disease and heart failure with New York Heart Association III might have a lower risk of cardiovascular mortality 12 years after the end of a four-year intervention (7).

For supplementation with 200 mg/day of coenzyme Q10 on top of standard treatment in patients with congestive heart failure (New York Heart Association class III and IV), ejection fraction <40%, and peak oxygen consumption <17.0 mL/kg/min (or <50% of predicted) for six months, there seems to be no significant effect on any parameter. Exercise duration, ejection fraction, peak oxygen consumption as well as symptom severity do not seem to differ significantly in patients who are supplemented (8).

Supplementation with 300 mg/day of coenzyme Q10 on top of standard treatment in patients with heart failure for 106 weeks might significantly decrease the risk of cardiovascular death and major adverse cardiovascular events. Also, the improvement of symptom severity, measured by the New York Heart Association functional class, might be significantly higher in patients who are supplemented. However, there seems to be no significant effect on ejection fraction (9). In European patients with heart failure who receive 300 mg/day coenzyme Q10 for 106 weeks on top of standard treatment, walking distance seems to improve significantly compared to baseline. However, not significantly more than in those without supplementation (10).

Supplementation with 15 mmol/day of magnesium for six months on top of standard treatment seems to significantly reduce systolic and diastolic blood pressure in patients receiving long-term diuretic treatment for arterial hypertension and/or congestive heart failure (11).

Supplementation of 30 mmol/day of magnesium for six months on top of standard treatment in patients with stable coronary artery disease seems to significantly increase exercise duration compared to patients who only receive the standard treatment (12,13). Furthermore, supplementation on top of standard treatment seems to significantly increase left ventricular ejection fraction and maximal oxygen consumption (14). There is conflicting evidence whether supplementation on top of standard treatment might also reduce the incidence of exercise induced ST-segment depression, exercise induced chest pain and exercise induced cardiac arrhythmias compared to patients who only receive the standard treatment (12,13).

TABLE 16 – Level of Evidence

Level of Evidence	Meaning
A	Based on multiple RCTs (high quality evidence)
B	Based on one RCT (moderate quality evidence)

TABLE 17 – Class of Recommendation

Class of Recommendation	Meaning
I	Strongly recommended
IIa	Should be considered

TABLE 18 – Recommendations

Recommendation	Level of Evidence	Class of Recommendation
To slow progression of cardiac wall stress and to reduce the risk of cardiovascular mortality, combined supplementation with 200 μg/day of selenium and 200 mg/day of coenzyme Q10 for four years should be considered in elderly individuals that have B-type natriuretic peptide levels of 104.01 – 395.40 ng/L.	B	IIa
To reduce cardiovascular mortality, combined supplementation with 200 μg/day of selenium and 200 mg/day of coenzyme Q10 for four years should be considered in elderly individuals with ischemic heart disease, hypertension or heart failure with New York Heart Association class III	B	IIa
To reduce the risk of cardiovascular mortality and major adverse cardiovascular events and to improve symptom severity, supplementation with 300 mg/day of coenzyme Q10 for 106 weeks should be considered in patients with heart failure.	B	IIa
To increase exercise duration, supplementation with 30 mmol/day of magnesium should be administered in patients with stable coronary artery disease.	A	I

TABLE 18 – Recommendations (continued)

To increase left ventricular ejection fraction and maximal oxygen consumption, supplementation with 30 mmol/day of magnesium should be considered in patients with coronary artery disease.	B	IIa

11. SELENIUM

I will start this section by giving some general information about Selenium. It was discovered by Jöns Jacob Berzelius in 1817 (17). Because of its similarity to the earlier identified element tellurium (derived from the Latin "tellus" for earth), Brezelius named it after the Greek moon goddess Selene (17,18). Humans receive selenium through the diet. Most of the dietary selenium is absorbed in the small bowel as well as in the duodenum (17).

11.1 SELENIUM AND CARDIOVASCULAR HEALTH

Now, I will elaborate on the possible mechanism how coenzyme Q10 can be beneficial for people with cardiovascular disease. Studies have shown that selenium plays a role in various heart diseases like in the cardiomyopathy called Keshan disease or in heart failure (19). Supplementation of selenium slowed the progression of Keshan diseases and selenium deficiency was related to worse outcomes in patients with heart failure (19–22). The exact mechanisms behind the relationship of cardiovascular diseases and selenium are not fully understood (19).
One suggested mechanism is related the role of selenium in regulating the apoptosis of cardiomyocytes. Studies have found that selenium deficiency increases apoptosis (19).
The following illustration (Figure 1) summarizes how selenium is metabolized in the heart, and to what extend selenium deficiency can contribute to the development of various cardiovascular diseases (19). The illustration is taken from the article "The Impact of Selenium Deficiency on Cardiovascular Function" by Briana K Shimada, Naghum Alfulaij, and Lucia A Seale, published in the International Journal of Molecular Sciences on the 2nd of October 2021.
The illustration shows that a selenium deficiency leads to a decrease in selenoproteins that affect the heart and upregulates oxidative stress and atherogenesis by disturbing calcium homeostasis, redox regulation and metabolism of thyroid hormones. This leads to the development of various cardiovascular diseases (19).

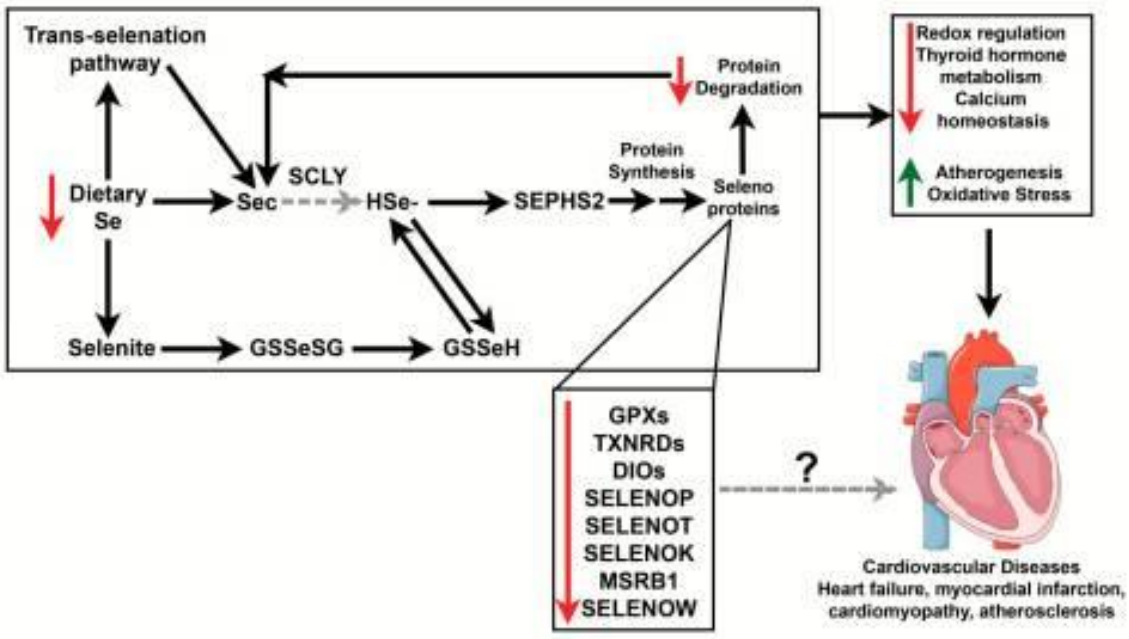


FIGURE 1 (19)

Briana et al. 2021 provided the following description and abbreviations: “Red arrows indicate processes and proteins that are decreased while green arrows indicate processes that are increased during Se deficiency. Black arrows point to known relationships, and dashed gray lines indicate the relationships that have not been established yet in the heart. The “?” indicates mechanisms that have not been determined. Sec, selenocysteine; HSe–, hydrogen selenide; SEPHS2, selenophosphate synthetase 2; GPX, glutathione peroxidase; TXNRDs, thioredoxin reductases; DIO, iodothyronine deiodinases; SELENOP, selenoprotein P; SELENOT, selenoprotein T; SELENOK, selenoprotein K; MSRB1, methionine sulfoxide reductase B1; SELENOW, selenoprotein W. The heart diagram is sourced from Servier Medical Art (smart.servier.com).” (19)

12. COENZYME Q10

I will start this section by giving some general information about coenzyme Q10. Coenzyme Q10 was discovered in 1957 by Frederik Crane. It occurs in three oxidation states (23).
The following illustration (figure 2) shows the three oxidation states of coenzyme Q10. It was taken from “Coenzyme Q_{10}” by Albert E Raizner, published in the Methodist DeBakey Cardiovascular Journal on the 1st of July 2019.

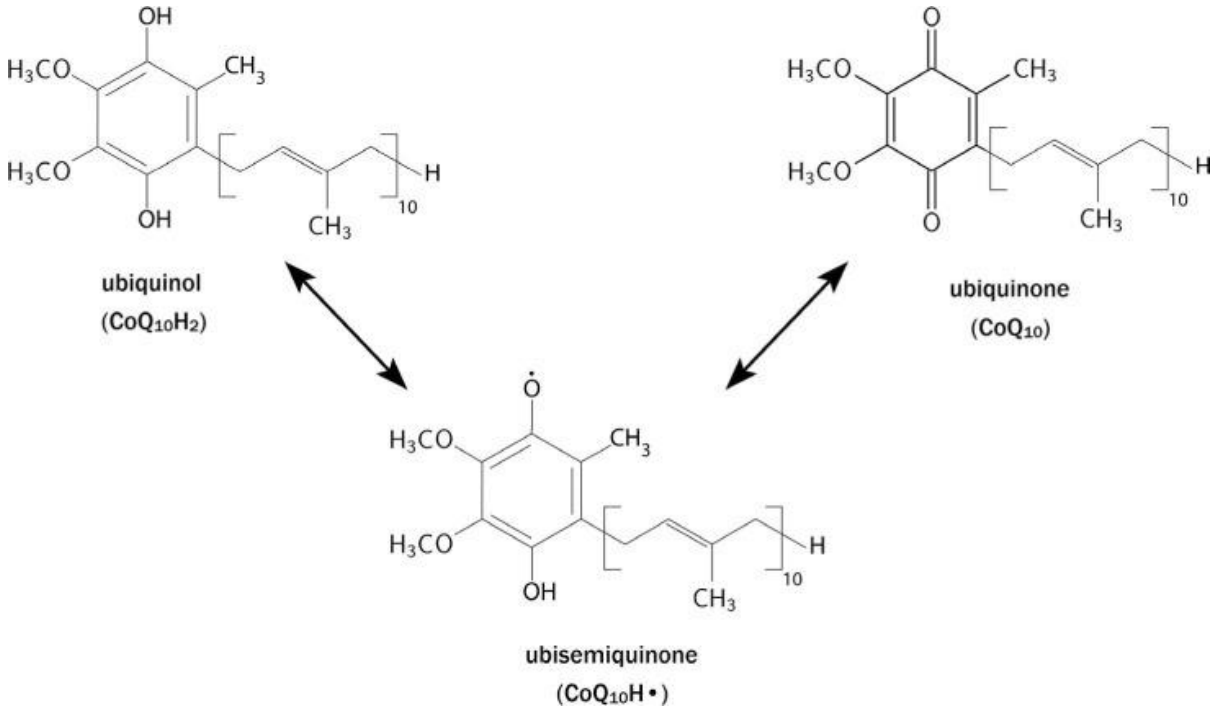


FIGURE 2 (23)

Humans can receive coenzyme Q10 through the diet. However, it is also naturally produced by the body itself. The absorption takes place in the small bowel (23,24). Afterwards, it is reduced to ubiquinol, this which accounts for around 95% of the coenzyme Q10 in the body (25). It plays a central role in the respiratory chain and therefore, in the formation of adenosine triphosphate (ATP) (25).

The following illustration (figure 3) shows the role of coenzyme Q10 in the mitochondrial respiratory transport chain. The illustration was taken from the article "Comparison of Coenzyme Q10 (Ubiquinone) and Reduced Coenzyme Q10 (Ubiquinol) as Supplement to Prevent Cardiovascular Disease and Reduce Cardiovascular Mortality" by Johannes-Paul Fladerer and Selina Grollitsch, published in the Current Cardiology Reports on the 16th of November 2023 (26). The illustration shows, that coenzyme Q10 is involved in complexes I, II, and III of the respiratory chain (26).

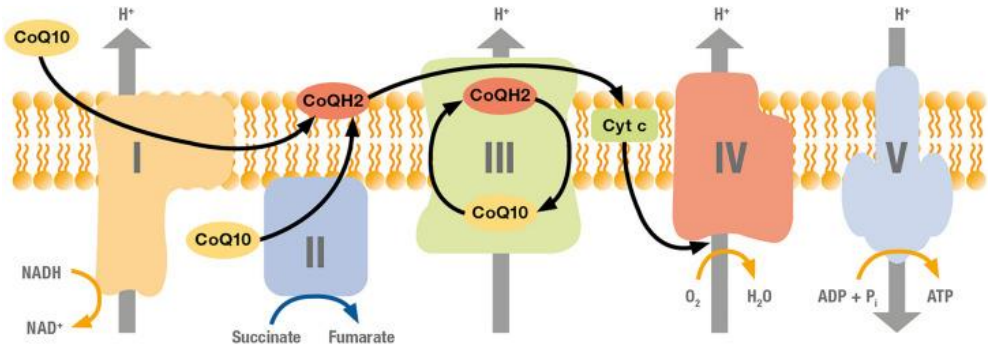


FIGURE 3 (26)

Furthermore, coenzyme Q10 can promote the production of antioxidants. One of them for example, is superoxide dismutase, which is beneficial in people with hypertension by decreasing oxidative stress on the blood vessels (25,27). Coenzyme Q10 is present in all organs. However, the heart has the highest concentration of ubiquinone (28).
In the following table (Table 19) the distribution of ubiquinone and ubiquinol in tissues is listed. The table was taken from the article "Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem" by Zozina et al., published in the journal Current Cardiology Reviews in August 2018.

TABLE 19 (28)

Organ	**Ubiquinone Concentration (μg/g)**	**Ubiquinol Concentration (μg/g)**	**Effects**	**References**
Heart	132.0	61.0	Antioxidant Bioenergetic Anti-inflammatory Membrane stabilizer Antiatherogenic	Aberg et al. (29) Miles et al. (30)
Kidneys	77.0	75.0		
Liver	63.6	95.0		
Muscle	39.7	65.0		
Brain	13.4	23.0		
Pancreas	32.7			
Spleen	24.6			
Lung	7.9	25.0		
Thyroidea	24.7			
Testis	10.5			
Intestine	11.5	95.0		
Colon	10.7			
Ventricle	11.8			
Plasma (μmol/ml)	1.1	96.0		

12.2 COENZYME Q10 AND CARDIOVASCULAR HEALTH

Now I will elaborate on the possible mechanism how coenzyme Q10 can be beneficial for people with cardiovascular disease. Research shows that at high dosage, coenzyme Q10 can be absorbed into all tissues, which also means into the heart, which could explain its positive effects in

cardiovascular diseases (24,25). Also, as previously mentioned, the heart has the highest concentration of ubiquinone (28). Furthermore, coenzyme Q10 can be beneficial for hypertensive people by promoting superoxide dismutase (25,27). Supporting the hypothesis that coenzyme Q10 is related to cardiovascular diseases, research showed that coenzyme Q10 was reduced in 75% of people with heart disease. Coenzyme Q10 was not only reduced, but the reduction also correlated with the degree of damage (28,31). Now, I will elaborate on some hypotheses on how exactly coenzyme Q10 might be involved in cardiovascular diseases.

One hypothesis is about the antioxidant effect of coenzyme Q10, or more specifically, its reduced form ubiquinol. By acting as an antioxidant, it inhibits reactive oxygen species and free radicals (28), which would normally lead to cell injury and hypertrophy of cardiomyocytes (28,32–34).

Another hypothesis is about coenzyme Q10's role in the electron transport chain. Coenzyme Q10 is needed to produce adenosine triphosphate. Adenosine triphosphate in turn is needed for the contraction of cardiomyocytes (28,35). If there is low coenzyme Q10, there is low adenosine triphosphate, which weakens the contraction of cardiomyocytes (28,31).

Finally, there are hypotheses that coenzyme Q10 has anti-inflammatory properties, probably due to its regulating impact on nitric oxide (28). As some cardiovascular diseases are associated with persistent inflammation, coenzyme Q10 could be a treatment option (28,36,37).

In the following table (Table 20) the main effects of COQ10 administration in different conditions are listed. The table was taken from the article "Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem" by Zozina et al., published in the journal Current Cardiology Reviews in August 2018.

TABLE 20 (28)

Condition	**Possible Effects**	**References**
Hypertension	Scavenging of ROS Vasodilatation Angiotensin effect adjustment Aldosterone level reducing	(38–40)
T2DM	Protection against ROS Antioxidant Fatty acid oxidation enhancement	(41–43)

TABLE 20 (continued) (28)

Metabolic Syndrome	Protection against ROS Antioxidant Tissue-protective The increase in triglyceride-rich lipoproteins (VLDL)	(44,45)
Overall role in cardiovascular disease	Antioxidant Protection against ROS Bioenergetic Anti-inflammatory	(32,35,46)

13. MAGNESIUM

I will start this section by giving some general information about magnesium. Joseph Black discovered magnesium (Mg^{2+}) in 1755 (47,48). Humans receive magnesium through the diet (47,49). Magnesium is mainly absorbed in the small bowel. However, some absorption also happens in the cecum and colon (50). It has a central function in several physiological processes of the human body, making it crucial for health. While being a calcium (Ca^{2+}) antagonist, magnesium also demonstrates anti-inflammatory capacities (47).
The following illustration (figure 4) shows the magnesium metabolism of a healthy adult (51,52). The illustration was taken from the article "Magnesium Metabolism" by Seo et al., published in Electrolytes & Blood Pressure in December 2008 (51).

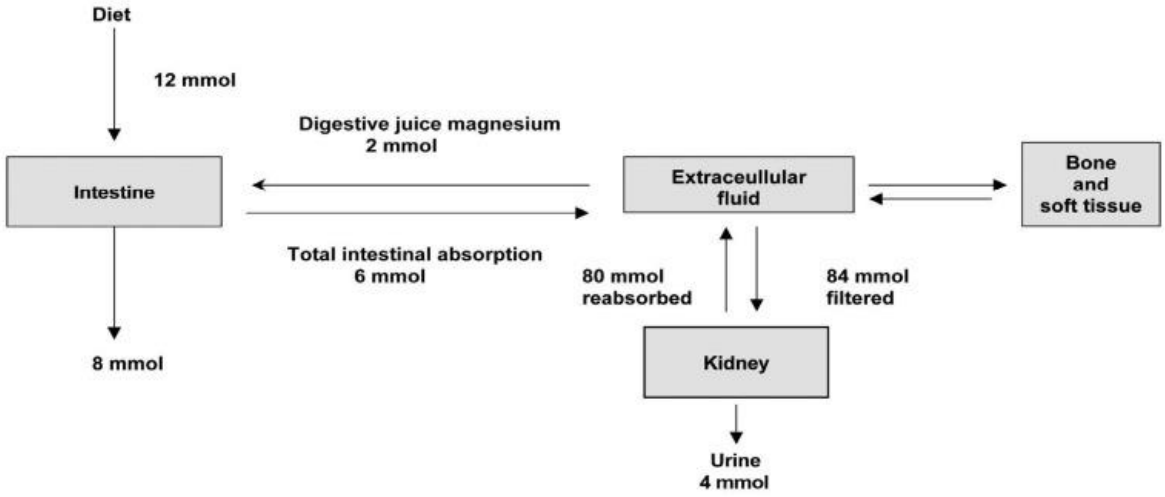


FIGURE 4 (51)

It should be noted that 99% of the magnesium in the human body is not circulating in the serum but is stored elsewhere. Namely, soft-tissues, bones, and muscles. Conclusively, even though magnesium serum levels might be normal, the body could be magnesium deficient (50).
The following illustration (figure 5) shows the roles of magnesium in different physiological processes of the human body. The illustration was taken from the article "Magnesium Deficiency and Cardiometabolic Disease" by Fritzen et al., published in Nutrients in May 2023 (50).

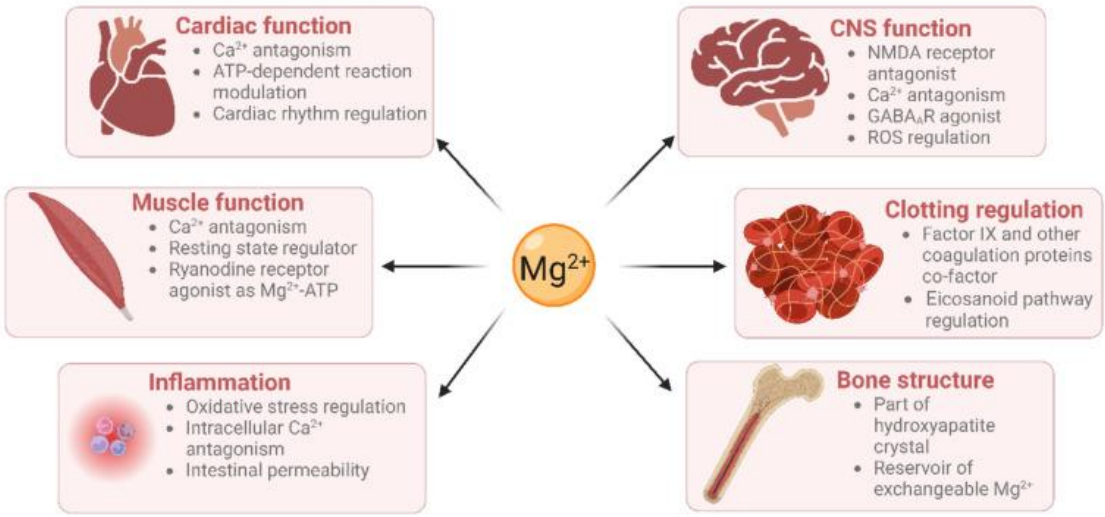


FIGURE 5 (50)

This illustration shows the previously mentioned, numerous functions that magnesium has in several physiological processes of the body. In the heart for example, it plays an important role in the regulation of the heart rhythm (50).

13.1 MAGNESIUM AND CARDIOVASCULAR HEALTH

Now I will elaborate on the possible mechanism how coenzyme Q10 can be beneficial for people with cardiovascular disease. Next to the numerous other physiological functions of magnesium in the human body, it is of central importance for the heart function. Magnesium has an impact on maintaining physiological calcium levels, peripheral vascular resistance, myocardial metabolism, vascular tone, and cardiac output (47). Magnesium exercises that influence by three mechanisms. Firstly, it alters the electrical characteristics of the heart muscle cells by affecting the action of their ion channels (47,53). Secondly, magnesium has an impact on calcium mobility inside of cardiac cells and thereby influencing myocardial contractility. Thirdly, magnesium leads to vasodilation and reduces inflammation (47).

The following illustration (figure 6) shows the role of magnesium in the heart. The illustration was taken from the article “Magnesium in man: implications for health and disease” by de Baaij et al., published in Physiological Reviews in January 2015 (47).

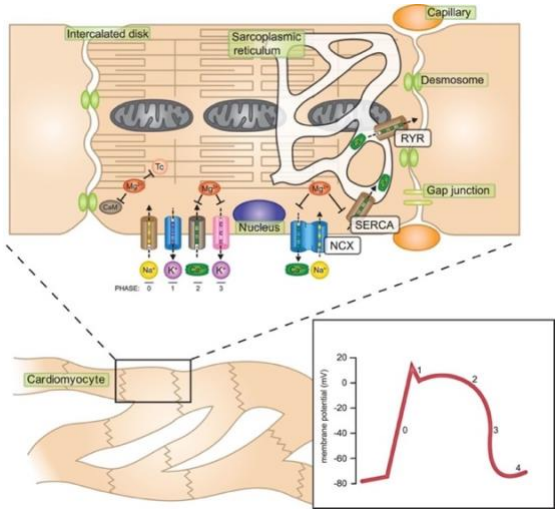


FIGURE 6 (47)

The following description was taken from the article “Magnesium in man: implications for health and disease” by de Baaij et al., published in Physiological Reviews in January 2015.
“Magnesium in heart. Mg2+ influences phase 2 and phase 3 of the cardiac action potential by inhibiting L-type Ca2+ channels (phase 2) and delayed rectifier K currents (phase 3). Moreover, Mg2+ directly influences the cardiac muscle contraction by antagonizing Ca2+ binding of troponin C and calmodulin. It further modifies Ca2+ availability by affecting NCX and SERCA activity. Inset: the cardiac action potential. The numbers indicate the phases of the action potential. Tc, troponin C; CaM, calmodulin; NCX, Na+-Ca2+-exchanger; SERCA, sarcoplasmatic/endoplasmic reticulum Ca2+-ATPase; RYR, ryanodine receptor.” (47)
Furthermore, there is some evidence that magnesium has favorable effects in coronary artery disease, myocardial infarction, arrhythmias, hypertension, and vascular calcification (47).
Both low magnesium intake, as well as low serum magnesium levels seem to be linked to a higher risk of developing coronary artery disease (47,54). Furthermore, the mortality in coronary artery disease patients is higher if they are magnesium deficient (47,55).
Multiple mechanisms of action could support the hypothesis that magnesium supplementation benefits coronary artery disease patients. Due to its significant anti-inflammatory effect, magnesium betters the lipid profile and endothelial function, while also decreasing free oxygen radicals (47,56,57). Additionally, magnesium decreases platelet aggregation (47,58) and thus protects against blood clotting. Coupled with its vasodilatory capacities (47,59,60), magnesium plays a central role in the occurrence and management of coronary artery disease.

A relationship between a higher risk for acute myocardial infarction and low serum magnesium levels has already been established (47,61). Magnesium's vasodilatory effect as well as its relaxing effect on cardiac endothelial and smooth muscle cells might explain its role in preventing acute myocardial infarction (47,59,62,63). Also, it is suggested that magnesium might protects against arrhythmias (47,61,64), which are a risk factor for acute myocardial infarction, due to heart rate variability.

Magnesium's antiarrhythmic potential might stem from its effect on calcium and potassium channels in the heart and thus also influencing the cardiac action potential. Some studies suggest that low serum magnesium levels themself are a trigger for arrythmias (47,65).

There may also be a relationship between reduced magnesium levels in the serum and hypertension (47,66–68). Intracellular magnesium can cause dilation of blood vessels by decreasing calcium in vascular smooth muscle cells, which then lowers blood pressure. This dilation is further facilitated by a decrease of endothelin-1 expression and a rise in prostacyclin due to increased extracellular magnesium (47,69–72). Furthermore, the creation of nitric oxide is reduced by magnesium (47,73).

Magnesium might also help to protect against vascular calcification (47). Decreased levels of magnesium in the serum are linked to vascular calcification (47). Why exactly magnesium protects against vascular calcification has yet to be fully established. However, two mechanisms are already outlined. First of all, formation and accumulation of calcium phosphate nanocrystals, along with the growth of apatite structures, are hindered by magnesium (47). Also, magnesium prevents the transformation of vascular smooth muscle cells into osteoblast-like cells within the vessel wall (47,74). Research has shown that in order to decrease the calcification of blood vessels, giving a combination of calcium and magnesium leads to comparable treatment results as the traditional treatment (47,75).

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