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Review article

Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews

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ABSTRACT

Introduction: This article is an attempt to provide an overview of systematic reviews to determine the efficacy of CQ10 supplementation in the treatment of patients with cardiovascular diseases (CVD).
Method and material: All reviews were identified through a systematic search of the following databases: Cochrane, DARE, Ovid, EMBASE, ISI Web of Knowledge, and PubMed. Check references studies and the quality of the studies was assessed by means of AMSTTAR. No meta-analyses were performed due to the heterogeneity of studies.
Result: Extracted data for Seven systematic reviews for primary outcomes, net changes in cardiac output, cardiac index, New York Heart Association functional classification, improved survival, based on existing evidence, there is a case for use of CoQ10 as an adjunctive therapy in congestive heart failure, especially in those patients unable to tolerate mainstream medical therapies.
Conclusion: Evidence suggests that the CoQ10 supplement may be a useful tool for managing patients with heart failure.

1. Introduction

Heart failure is a major cause of mortality and morbidity in the world.[1–4] Almost 50% of people who develop heart failure die within the first 5 years of diagnosis and it is a frequent cause of hospitalizations and disability[5] Patients with chronic heart failure (CHF) typically have a relapsing and remitting disease course, with periods of decompensation causing worsening symptoms, resulting in increased therapy or hospitalization.[6] Myocardial tissues of cardiovascular disease (CVD) patients are reported to be deficient in CoQ10.[7,8] Littarru first reported its deficiency in heart disease.[9] Myocardial CoQ10 deficiency has been observed in patients with congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, and hypertension.[10] Furthermore, although drug therapies can reduce morbidity and mortality, the management of chronic symptoms such as fatigue and exercise intolerance remains challenging. One novel therapeutic avenue is to modulate cardiac energetics. Therapies that can prevent myocardial energy depletion may play a role in the treatment and management of heart failure.[11]

The clinical benefits of CoQ10 supplementation in prevention and treatment of heart failure have been observed in many trials.[12–16] CoQ10 may be recommended to patients at risk of or diagnosed with cardiovascular disease as an adjunct to conventional treatment,[7,10,17] and long-term therapy with CoQ10 has been shown to improve heart failure symptoms and reduce major adverse cardiovascular events, while being safe and well-tolerated.[18–20]

Currently, Europe, Russia, the USA,[21] and Japan make up 85% of the total consumption of CoQ10 supplementation. In Japan, CoQ10 was approved as treatment for heart failure in 1974.[22,23] In 1982, it became one of the top five medications used in Japan.[1]

CoQ10 exists in two different forms: a reduced form, as Ubiquinol (CoQ10H2), and an oxidized form, ubiquinone (CoQ10). It is endogenously produced, and converts between the two forms, as the reduced or antioxidant form, and as the oxidized form, as part of normal cellular enzyme functions. it is an antioxidant, its main role is as an integral part of the mitochondria respiratory chain for energy production and deficiencies in coenzyme Q10 impair energy production.[24] As a therapeutic agent, CoQ10 may have a beneficial effect in patients with heart failure by three

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different actions: first, it increases adenosine triphosphate (ATP) generation and cellular energy by mediating electron transfer in the electron transport chain; second, by reducing oxidative stress, a well-known marker of mortality in heart failure, and by preventing membrane oxidation and lipid peroxidation; third, by stabilizing calcium dependent ion channels in the myocardium, thus enhancing ATP synthesis.[25–27]

CoQ10 has the potential for use in prevention and treatment of CVDs, particularly heart failure.[17, 19, 28, 29] This article is an attempt to provide an overview of evidence from systematic reviews to determine the efficacy of CoQ10 supplementation in the clinical outcomes of patients with heart failure.

2. Method and material

We searched electronic databases using a combination of MeSH and free-text terms. Searching lasted until 16 May 2017. The following terms were used as Medical Subject Headings and keywords: ("heart failure") and ("coenzyme Q10" or "ubiquinone" or "ubidecarenone"). The search strategies for all databases were specified and the following databases were searched across all included years: Ovid MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), ISI web of science, and PubMed.

In addition, the reference lists of all eligible reviews were manually searched. The bibliographies of all articles thus located were scanned for further relevant references. No language restrictions were applied. Only systematic reviews (including meta-analyses) of controlled clinical trials of CoQ10 with human samples were included. Non-systematic reviews, overviews, clinical trials, and reviews of non-clinical investigations were excluded. Two overview authors independently checked the search results and included eligible reviews. Initially, we reviewed the titles and abstracts of identified studies and excluded studies that were clearly not relevant. Where it was not clear from the abstract whether a study was relevant, we checked the full review to confirm its eligibility.

We included all systematic reviews of randomized controlled trials that assessed the effects of CoQ10 supplementation in heart failure patients. Data from original studies presented in more than one included review were only considered once in any analysis. Participants of studies were Adults 18 years or older described as suffering from heart failure or an alternative descriptor for this condition. Types of interventions were CoQ10 supplementation compared with placebo.

2.1. Data collection and analysis

2.1.1. Selection of reviews

Two overview authors independently applied the selection criteria to the full papers of identified reviews. Disagreement between the authors was resolved through discussion. Where resolution was not achieved, a third overview author considered the study(ies) in question.

2.2. Data extraction

Two overview authors extracted data independently using a standardized form. Discrepancies were resolved by consensus. We contacted the authors of the reviews or the original study reports in the event that the required information could not be extracted from the reports. The data extraction form included the following details:

- assessment of the methodological quality of the included review;
- objectives of the review;
- details of included participants;
- interventions studied;
- outcomes and time points assessed (primary and secondary);
- Comparisons performed and meta-analysis details.

2.3. Quality assessment

We used the AMSTAR tool to assess the methodological quality of the included reviews.[30] We applied this to both Cochrane and non-Cochrane reviews. In addition, included reviews assessed the methodological quality and risk of bias of included studies in a variety of ways. Therefore, we used the judgments made by the authors of the original reviews regarding the quality of evidence and risk of bias.

2.4. Data synthesis

Where possible, we extracted data from the included reviews and presented data in a tabular format. We planned to present and discuss important limitations within the evidence base and to consider the possible influence of publication and small study biases on review findings. No meta-analyses were performed due to the heterogeneity of studies.

3. Results

3.1. Included studies

Fig. 1 shows a flow diagram of the search process. Database searches identified 1266 records from which 207 duplicates were identified and removed. 5 additional records were identified from manual searching. From the remaining 1059 records, 1043 were removed following a screening of the titles and abstracts. The remaining 16 full-text articles were assessed for eligibility. Seven systematic reviews were included in the final overview.

3.2. Description of included reviews

We included 2 Cochrane reviews[25,31] and 5 non-Cochrane systematic reviews[32,33] See Table 1 for a list of the reviews and the characteristics of the included reviews which have contributed to this review. A total of 7 systematic reviews were finally identified and most of them were good quality. The seven systematic reviews reported data on articles describing 71 different randomized controlled trials including CVD patients.

3.3. CoQ10 levels and ejection fraction (EF)

There is recent evidence for a role of CoQ10 as a predictor of outcomes and also as an adjunctive clinical therapy.[37] A recent systematic review reported that with CoQ10 supplement, plasma Q10 level was significantly higher (mean difference of 1.44 mcg/dL, 95% confidence interval (CI) 1.16–1.73 mcg/dL, $p < 0.001$).[33] Another systematic review that combined data from two studies on the effect of CoQ10 on left ventricular ejection fraction showed that CoQ10 has no significant effect (MD −2.26;95% CI −15.49 to 10.97); in addition, the results showed that the use of CoQ10 increases its concentration in the blood (MD 1.46; 95% CI 1.19, 1.72).[38] One study showed that there was a 3.7% improvement in EF for subjects who received CoQ10 supplementation compared with a control group. Findings were consistent with those of previous studies, which reported a net increase in EF after supplementation with CoQ10.[39]

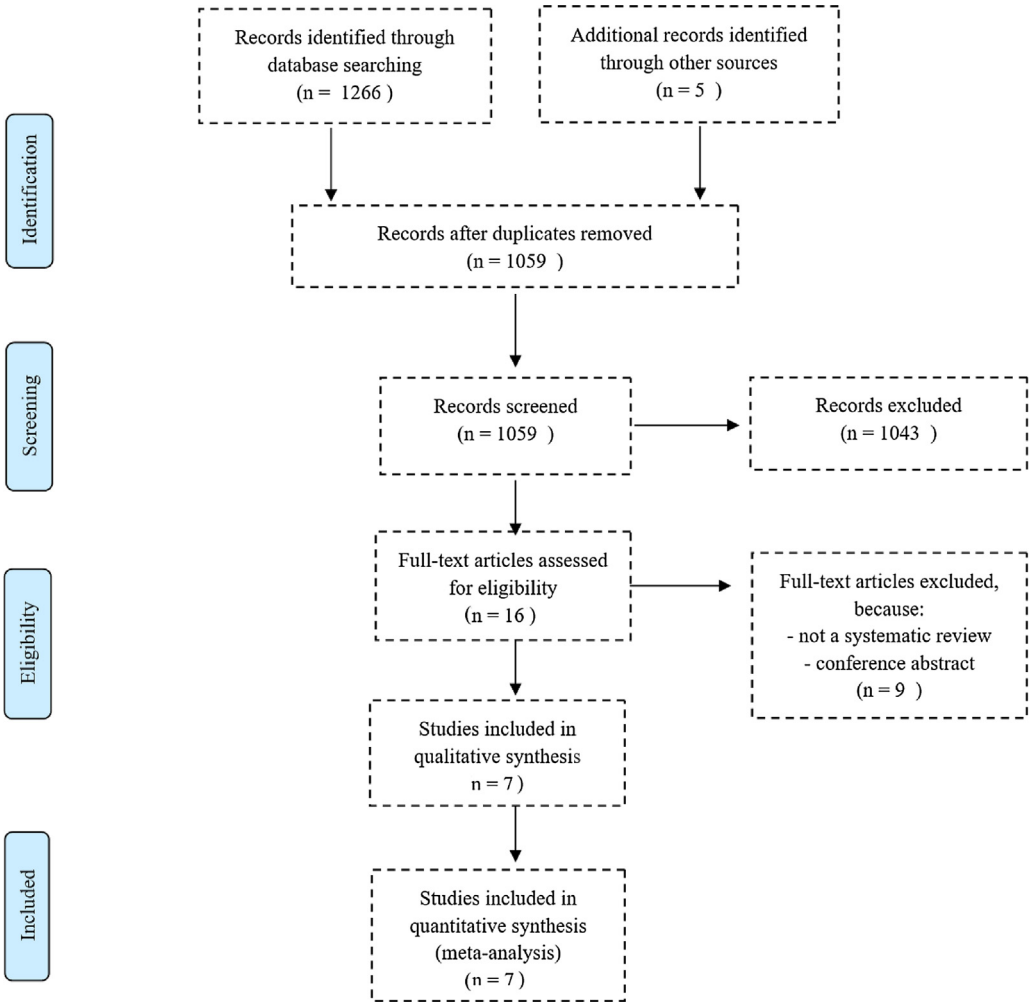

Fig. 1. PRISMA flow diagram.

A meta-analysis of nine randomized trials of CoQ10 in heart failure showed that for CoQ10 levels the weighted mean difference was 1.5, which was a 161% increase. For resting EF (384 patients), the weighted mean difference showed a trend of 1.9% in favor of CoQ10 (95% CI −0.13 to +3.9).[4] Upon meta-analysis, there was a 3.7% net improvement in EF (1.59 to 5.77; $p < 0.00001$).[35]

3.4. Net changes in, CO (Cardiac output), CI(Cardiac index), SV(Stroke volume)

The results of meta-analyses showed that CoQ10 treatment led to an increase in SV and a decrease in EDVI.[f] It was shown that the average patient in the CoQ10 group had a better SV score than 76% of the patients in the placebo group. During treatment, the EDVI was clearly improved in that the average patient in the CoQ10 group had a better score than 88% of the patients in the placebo group.[32] In a more recent meta-analysis, Trongtorsak et al reviewed 16 studies with a total of 1662 individuals, reporting that LVEF and LVESD[g] significantly improved by 2.9% with CoQ10 supplement, but not LVEDD.[33],[h] Cardiac output increased by an average of 0.28 L/min (0.03–0.53; P 0.96) for statistical heterogeneity. No statistically significant increase in CI could be found. There was a trend toward an increase in SV. Stroke index increased by an average of 5.68 mL/m2 (1.02–10.34; P 0.28 for statistical heterogeneity.[35]

3.5. New York Heart Association (NYHA) functional classification

Myocardial depletion of CoQ10 has been demonstrated in heart failure and the severity of the deficiency has been found to correlate with the severity of symptoms, with patients in NYHA class IV having significantly lower CoQ10 in endomyocardial biopsy samples than those in NYHA class I. Myocardial CoQ10 deficiency in patients with cardiomyopathy was reversed through CoQ10 supplementation therapy.[7]

Three studies investigated NYHA in relation to CoQ10. Results of meta-analysis showed that after 3 months of therapy, NYHA class in CoQ10 group (n = 17) showed a significant improvement of 0.5 class compared with the placebo group (n = 18) (p = 0.01).[34]

The results of the fives trials in the Cochran systematic review showed that the NYHA class in the CoQ10 group decreased, whereas no change was reported in the placebo group.[38] In another meta-analysis of net change in NYHA classification, using a random-effects model, CoQ10 supplementation resulted in a pooled mean net decrease of −0.30 (95% CI: −0.66, 0.06) for the NYHA functional class, although this change was not significant.[40] On the other hand, myocardial tissue data on the effective therapy

[f] Diastolic volume index.
[g] Left ventricular Systolic diameter.
[h] Left ventricular Diastolic diameter.

Table 1
The list of the reviews and the characteristics of the included reviews.

Ref.	Review	Objective	patient number	Intervention	QA	Meta-analysis	Overall conclusion	Comment
[32]	A. M. Soja (1997)	Investigate whether CoQl0 treatment of patients with CHF would lead to an improvement of certain cardio-physiological parameters.	356	CoQ10	N	Of eight trials which could be submitted to meta-analysis: the CoQl0 group achieved an improvement that was 0.71 SD. better than the placebo group	Treatment with CoQ10 led to a statistically significant improvement of SV, CO, EF, CI, and EDVI. The results of the meta-analyses support the hypothesis that CoQ10 can be used as an adjuvant treatment of CHF.	There is a need for additional randomized, double-blind studies for meta-analyses with a more restrictive and stratified basis and eliminate as many of the factors that produce heterogeneity as possible.
[34]	Franklin Rosenfeldt (2003)	A meta-analysis of nine randomized trials of CoQ10 in heart failure	824	CoQ10	N	Of nine trials which could be submitted to meta-analysis: CoQ10 in serum = 1.4 (1.3 to 1.5) EF rest = 1.9 (−0.13 to 3.9) EF exercise = −0.5 (−3.9 to 2.9) Maximum ex. capacity = 14.2 (−3.9 to 12.4) NYHA class = −0.09 (−0.037 to 0.18) Mortality = 0.76 (0.43 to 1.37) (odds ratio) Exercise duration = 1.0 (−0.54 to 2.54)	The meta-analysis showed a trend towards an improvement in ejection fraction.	Trials to detect a mortality difference would need to be prohibitively large, requiring 2000 or more patients per group.
[35]	Stephen Sander pharm D (2006)	To evaluate the impact of CoQ10 therapy on ejection fraction and cardiac output	319	CoQ10	N	Of eleven trials which could be submitted to meta-analysis: EF = 3.68 (1.59–5.77) CI = 0.32 (20.07–0.70) CO = 0.28 (0.03–0.53) SI = 5.80 (0.84–10.75) SV = 6.68 (20.41–13.78)	statistically significant change in EF, CO, and SI	Future studies looking at long-term outcomes are required Future studies with more homogeneous etiologies are also required to determine why some patients benefit and others do not.
[36]	A Domnica Fotino (2013)	To evaluate the impact of CoQ10 supplementation on the EF and NYHA functional classification in patients with CHF	395	CoQ10	Y	Of 13 trials which could be submitted to meta-analysis: EF = 3.67 (1.60, 5.74) (11 studies) NYHA = 0.30(0.66, 0.06) (3 studies)	Supplementation with CoQ10 may be of benefit in patients. The benefit may be limited to patients with less severe stages of CHF, such as patients with an EF $\geq$30% or those with an NYHA class of II or III.	Additional well-designed studies that include more diverse populations are needed. Additional larger studies are warranted and should examine whether there is an effect when this supplementation is added to the current standard of therapy for CHF or whether there is a dose-response effect between the stage of CHF at baseline and the dose of CoQ10 required for an improvement to be seen.
[25]	Mohammed E Mamdani (2013)	To review the safety and efficacy of Coenzyme Q10 in HF.	914	CoQ10	Y	Of 7 trials which could be submitted to meta-analysis: Exercise duration = 12.79 [−140.12, 165.70] (2studies) Left ventricular EF = −2.26 [−15.49, 10.97] (2studies) serum levels of Coenzyme Q10 = 1.46 [1.19, 1.72] (3studies)	The evidence collected shows no convincing evidence to support or refuse the use of Coenzyme Q10 for heart failure.	Adequately powered and long-term conducted RCTs with low risk of bias are needed to support or change the current results Although Coenzyme Q10 is associated with improvement in the NYHA of clinical status and exercise capacity, the evidence is based on small trial numbers and is thus incomplete.
[31]	Nadine Flowers (2013)	To determine the effects of coenzyme Q10 supplementation as a single ingredient for the primary prevention of CVD.	218	CoQ10	Y	Of 7 trials which could be submitted to meta-analysis: Systolic blood pressure = Totals not selected (2sttudies) Diastolic blood pressure = −1.62 [-5.20, 1.96] (2studies) Total cholesterol = 0.30 [−0.10, 0.70] (1study)	Our review produced few data with which to compare to previous studies and no conclusions can be drawn at present.	Due to the small number of trials included, with a small number of participant's randomized, short follow-up and trials at some risk of bias, the results should be treated with caution. High-quality trials are needed to examine the effects of CoQ10 Supplementation on

Table 1 (*Continued*)

Ref.	Review	Objective	patient number	Intervention	QA	Meta-analysis	Overall conclusion	Comment
						HDL-cholesterol = 0.02 [−0.13, 0.17] (1study) Triglycerides = 0.05 [−0.42, 0.52] (1study)		cardiovascular risk factors and events over a longer period of time.
[33]	Angkawipa Trongtorsak (2016)	To evaluate the effect of CoQ10 for left ventricular parameters and clinical outcomes in patients with HF	1662	CoQ10	NM	Of 16 trials which could be submitted to meta-analysis: Q10 level = 1.44 (1.16–1.73) LVEF = 2.9(1.3–4.5) LVESD = 2.1(3.5–0.6) LVEDD = 1.0 (3.74 to −1.82) All-cause death = HR: 0.62 (95% CI 0.40-0.95, p = 0.03). less hospitalization = HR: 0.39 95% CI 0.29 −0.53, $p < 0.001$).	This meta-analysis supports the use of combined CoQ10 with standard therapy in HF to reduce mortality. The benefit may partially explain by reversed remodeling of the left ventricle	With CoQ10 supplement, the plasma Q10 level was significantly higher, the LVEF and LVESD were significantly improved, respectively but not the LVEDD. Adding CoQ10 compared with placebo was associated with less hospitalization.

*CHF: Chronic Heart Failure; CoQ10: CoenzymeQ10; CO: Cardiac output; CI: Cardiac index; CHF: Chronic Heart Failure; EF: Ejection Fraction; LVEF: Left ventricular Ejection Fraction; HF: Heart Failure; HR: Hazard ratio; LVESD: Left ventricular Systolic diameter; LVEDD: Left ventricular Diastolic diameter; NYHA: New York Heart Association; SD: Standard deviation; SI: Systolic Index; SV: Stroke volume; QA: Quality Assessment.

of cardiomyopathy with CoQ10 showed that a more severe form of heart failure (NYHA Class IV) would benefit the most from CoQ10,[7] but subgroup analysis did not support this assumption.[35]

Overall, among the meta-analyses that have examined the effect of CoQ10 supplementation on the NYHA classification, two cases had similar results and reported a significant change in NYHA classification, which correlated with an improvement (a decrease in severity).[33, 34]

3.6. Clinical status, improved survival, quality of life

It was recently demonstrated that plasma levels of CoQ10 are an independent predictor of survival in patients with chronic heart failure.[3]

None of the included studies provided data on quality of life.[31] The results of a recent meta-analysis showed that CoQ10 was associated with less hospitalization compared to placebo (hazard ratio = 0.39 95% CI 0.29–0.53, $p < 0.001$).[33] None of the included studies provided data on cardiovascular and all-cause mortality and non-fatal cardiovascular events.[31] As for mortality, the odds ratio for reduction in the CoQ10 group was 0.76 (95% confidence limits 0.43–1.37). In this study, the meta-analysis showed a slight reduction in mortality from 6.4% to 5.0% (1.4% absolute risk reduction) with an odds ratio of 0.76.[34] In one of the meta-analyses, only one study reported no significant change in mortality between the placebo and CoQ10 group, and other studies did not report any change in mortality rate.[38]

A meta-analysis by Soja reported a significant improvement in stroke volume, ejection fraction, cardiac output, cardiac index, and end diastolic volume index, as a consequence of CoQ10 supplementation.[32]

An overview on CoQ10 has shown that it predicts mortality by heart failure, and in every intervention trial undertaken to date, those achieving higher plasma CoQ10 levels showed better clinical outcomes.[37]

Of the six HF reviews, three showed a positive result with statistically significant beneficial effects of coenzyme Q10 in HF, two showed trends towards beneficial effects and one showed no effect.

4. Discussion

Over the last few decades, numerous uncontrolled observational studies have been conducted in the heart failure population. Although these studies are large and show dramatic improvements, severe design flaws limit their usefulness.[7,8,41–43] There are, however, several small, randomized, blinded trials comparing CoQ10 with placebo dating back decades.[44–48] These studies may not have the power to express the benefits, or the results are exaggerated because of their small sample size. Pooling the results of these smaller trials through the use of meta-analyses may provide insight into its true effectiveness and may allow us to detect population differences in response.

Recently, many systematic reviews and meta-analyses have been published on the efficacy of CoQ10 supplementation as prevention or treatment tool for heart failure patients. While these reviews all share the same subject, they include different original studies. Conflicting results have been derived from heterogeneous studies and they have often concluded that additional studies are required. The present systematic review aimed to provide a complete overview of the evidence available from systematic reviews to determine the efficacy of CoQ10 supplementation for prevention or treatment of heart failure. From the 71 papers screened, we identified seven systematic reviews that included 4688 participants in studies with a duration of three or more months. All of the studied compared CoQ10 with placebo in controlled trials.

CoQ10 is an obligatory member of the respiratory chain in the mitochondria of all cells. CoQ10 is located in the mitochondria, lysosomes, and Golgi and plasma membranes, and provides a basis for antioxidant action either by direct reaction with free radicals or by regeneration of tocopherol and ascorbate from their oxidized state.[49]

It can be imagined that the different types of CHF result in different CoQ10 needs and therefore lead to different effects of CoQ10 treatment. It is also possible that certain patients respond to CoQ10 supplementation and others do not, depending on the severity or etiology of heart failure.[32]

There have been many controlled trials of the clinical effect of CoQ10 on CVD, a majority of which show benefit in subjective

(quality of life, decrease in hospitalizations) and objective (increased left ventricular ejection fraction, stroke index) parameters.[3]

It should be noted that many of the studies were analyzed in our systematic review. In Table 1, we summarize these trials. Overall, two studies evaluating symptoms showed benefits from CoQ10 versus placebo. Two other studies reported that supplementation with CoQ10 may be of benefit in CVD patients, and in one of these studies the evidence collected showed no convincing evidence to support or reject the use of CoQ10 for heart failure.[31] Collectively these data do not provide sound evidence that CoQ10 is clinically different from placebos.

Q-SYMBIO is the first PRCT with all of the following: adequate sample size, sufficient dosage of CoQ10 and long enough duration of follow-up to evaluate the efficacy of CoQ10 on major adverse cardiac events and mortality in HF. The results showed that after two years follow up there were 21 deaths (10%) from all causes in the CoQ10 group compared with 39 deaths (18%) in the placebo group, corresponding to a 42% relative reduction (p = 0.036). The total number of cardiovascular deaths was lower in the CoQ10 group (N = 18, 9%) compared to the placebo group (N = 34, 16%), corresponding to a 43% relative reduction (p = 0.039). The number of hospitalizations for HF (counted as MACE) was lower in the CoQ10 group (N = 17, 8%) versus the placebo group (N = 31, 14%) (p = 0.033). There were significantly fewer MACE in the CoQ10 group (N $^{1}/_{4}$ 30, 15%) than in the placebo group (N = 57, 26%), findings corresponding to a 43% relative reduction (p = 0.005).The conclusion was that treatment with CoQ10 in addition to standard therapy for patients with moderate to severe HF: is safe, well tolerated and is associated with a reduction in symptoms and major adverse cardiovascular events.[50]

Another meta-analysis supported the use of combined CoQ10 with standard therapy in HF to reduce mortality.[33] In addition, three of the meta-analyses showed a positive trend towards an improvement in ejection fraction and cardiac outputs. Groups could not be combined and compared using meta-analysis. However, to date, clinical trials do not show a consistent benefit for these parameters across studies and more work needs to be done in this area.

A strength of the current study is its systematic methodology regarding literature search and the subsequent steps involving independent selection of relevant articles, quality assessment, and extraction of data. Furthermore, it provides a comprehensive overview of the evidence available to date, which is emphasized by the fact that the included systematic reviews all involved different original studies that were relevant to our research question.

However, the present analysis has several limitations that should be kept in mind when interpreting its conclusions. It is worth mentioning that the reason for the large number of underpowered studies of CQ10 in heart failure in the six reviews is the lack of funding for non-patentable supplements such as CoQ10 which in turn is due to the lack of a return for a commercial company funding the trial. Whereas in the big Parma industry where monetary returns are huge if new drug is trial is successful, trials with several thousand patients are not uncommon. Another limitation in the predefined and systematic methodology is that the included systematic reviews were considered a starting point for data extraction and the original studies were checked for verification and to complement the data present in systematic reviews, if necessary. This allowed for maximal transparency and a systematic methodology, but may have led to the omission of some data of interest that were not presented in any of the systematic reviews. It can be said that the validity of conducting a systematic review of systematic reviews has its limitations; most importantly, it does not create any information that was not available before.

Our overview suggested that CoQ10 supplementation may be beneficial for patients with CHF. However, additional, well-designed studies that include more diverse populations are needed. To our knowledge, this study is the overview of all systematic reviews of the effect of CoQ10 on cardiovascular disease, and its results will provide additional information.

It can be argued that based on the current evidence and the excellent safety profile of CoQ10, there is a case for the use of CoQ10 as an adjunctive therapy in congestive heart failure, particularly for those patients unable to tolerate mainstream medical therapies.

In conclusion, It would appear from the results of this review that three out of four reviews showed a positive result, two showed a trend and one was neutral. Moreover, the Q Symbio trial results showed that treatment with CoQ10 in addition to standard therapy for patients with moderate to severe HF: is safe, well tolerated and is associated with a reduction in symptoms and major adverse cardiovascular events. Evidence suggests that CoQ10 supplementation can be a useful tool for managing patients with heart failure.

Conflict of interest

The author haven't conflicted of interest.

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Authors' contributions

Data Extraction; S.M.M, N.Y; Data Analysis: A.A, M.J. First Draft: A.A. Final Manuscript: S.M.M., A.A.

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