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Coenzyme Q10 in heart failure: An umbrella review with prediction intervals and leave-one-out sensitivity analysis revealing an apparent mortality benefit beyond guideline-mandated therapies

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Abstract

Background: Coenzyme Q10 has been studied in chronic heart failure for more than three decades. Successive meta-analyses report reductions in all-cause mortality, yet the compound appears in no major heart failure guideline. The size of the reported effect relative to established therapy, and the reasons for its exclusion, have not been examined together. **Objectives:** To pool published review-level estimates of the effect of coenzyme Q10 on all-cause mortality and heart failure hospitalisation; to set the pooled effect against effects commonly cited for guideline-mandated therapy; and to examine whether the internal structure of the evidence supports the magnitude reported. **Methods:** Systematic reviews with meta-analysis of randomised trials of coenzyme Q10 in chronic heart failure reporting all-cause mortality were eligible. Review-level estimates were pooled on the log scale in a DerSimonian-Laird random-effects model with Cochran's Q, I^2, τ^2 and 95% prediction intervals. Absolute effects were derived from reported event counts. Certainty was recorded as graded by the source reviews. Analyses were performed in Python 3. **Results:** Three syntheses contributing mortality estimates and representing 63 trials in more than 5,900 participants were pooled, giving a risk ratio of 0.65 (95% CI 0.54-0.79; $z = -4.36$, $p < 0.001$) with no detectable heterogeneity ($Q = 0.19$, $df = 2$, $p = 0.910$; $I^2 = 0.0\%$). The 95% prediction interval was 0.43-0.99 and only just excluded the null. Heart failure hospitalisation was reduced to a similar degree (0.44, 95% CI 0.35-0.56). Derived from reported event counts the absolute risk difference was 2.9% points, a number needed to treat of 34. The single adequately powered mortality trial randomised 420 participants and reported a hazard ratio of 0.513 (0.30-0.89). Against this, the effect on left ventricular ejection fraction—the presumed mechanistic intermediate—was small (mean difference 0.51, 95% CI 0.31-0.71) and graded low certainty. **Conclusions:** The pooled mortality estimate for coenzyme Q10 in heart failure exceeds the effects commonly cited for beta-blockers, renin-angiotensin inhibitors, mineralocorticoid antagonists and SGLT2 inhibitors. That is not a reason to adopt it. An effect this large from trials this small, with a prediction interval touching the null, a mechanistic intermediate that barely moves, and no adequately powered confirmatory trial in thirty years, is exactly the profile that should prompt scepticism rather than adoption. The finding of this review is that the question remains unresolved, is resolvable by a single adequately powered trial, and that nobody has an obvious commercial incentive to run one.

Keywords: *Coenzyme Q10, Chronic heart failure, All-cause mortality, Publication bias, Evidence thresholds, Nutraceuticals*

1. Introduction

Coenzyme Q10 is an endogenous lipid-soluble molecule with two relevant properties: it is a redox carrier in

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the mitochondrial electron transport chain, and it is an antioxidant. Myocardial concentrations are reduced in heart failure, the reduction correlates with symptom severity and with the degree of left ventricular dysfunction, and low plasma concentrations have been reported as an independent predictor of mortality in at least one cohort (Mortensen *et al.*, 2014). Supplementation is inexpensive, orally available and well tolerated.

The clinical literature is unusual in shape. Trials began in the late 1980s, most have been small, and successive meta-analyses have reported reductions in mortality (BMC Cardiovasc Disord, 2017; BMC Cardiovasc Disord, 2024) of a magnitude that would ordinarily command attention. Yet the compound appears in no major heart failure guideline, and most cardiologists would not consider prescribing it.

That combination is worth examining rather than assuming. Two explanations are available and they have very different implications. Either the effect is real and a cheap intervention with a substantial mortality benefit has been overlooked for three decades, which would be a significant failure of evidence translation. Or the effect is an artefact of small trials, selective publication and outcome definition, in which case this literature is a useful worked example of how large an apparent effect such artefacts can generate.

Distinguishing between them requires looking at more than the headline estimate. Three features of the evidence bear on it: the size of the effect relative to interventions whose benefit is established, the internal coherence between the clinical outcome and the mechanistic intermediate, and the structure of the trial literature generating it.

We therefore pooled the published review-level estimates and examined each of those features in turn. We state at the outset that this review does not recommend coenzyme Q10 and does not conclude that it works.

2. Methods

2.1. Design and reporting

This is a second-order meta-analysis in which the unit of analysis is the published systematic review with meta-analysis (Higgins *et al.*, 2023). Synthesis at the review level followed established guidance for overviews of systematic reviews (Aromataris *et al.*, 2015), and reporting follows the PRISMA 2020 statement (Page *et al.*, 2021). The analysis was not prospectively registered; this is stated as a limitation.

2.2. Review question (PICO)

Population: Adults with chronic heart failure, predominantly with reduced ejection fraction. Intervention: oral coenzyme Q10 supplementation in addition to standard care.

Comparator: Placebo or standard care alone.

Outcomes: All-cause mortality as the primary outcome; hospitalisation for heart failure and left ventricular ejection fraction as secondary outcomes. Unit of analysis: the published systematic review with meta-analysis.

2.3. Handling of overlap

The contributing syntheses draw on a largely common pool of trials accumulated over three decades, and overlap is extensive. This is acknowledged explicitly rather than adjusted for. The consequence is stated plainly in the Results: the absence of heterogeneity between these syntheses is close to arithmetically guaranteed and carries almost no evidential weight, and the apparent precision of the pooled estimate is correspondingly overstated.

2.4. Statistical analysis

Effect estimates were transformed to the log scale, with standard errors derived from the reported 95% confidence limits as (ln upper-ln lower)/(2 × 1.96), and combined in a DerSimonian–Laird random-effects model (DerSimonian and Laird, 1986). Heterogeneity was quantified by Cochran's Q, I^2 and t^2 (Higgins *et al.*, 2003), and 95% prediction intervals were computed (IntHout *et al.*, 2016). Absolute risk difference and number needed to treat were derived from the event counts reported by one contributing synthesis. Comparator effect sizes for established heart failure therapy are quoted as approximate figures commonly cited in the literature and are used for orientation only; they were not independently extracted, are presented without confidence

intervals, and no statistical comparison against them is performed. Publication bias was not assessed at review level with fewer than ten units. Analyses were performed in Python 3 using NumPy and SciPy.

2.5. Quality appraisal

The methodological quality of contributing reviews was appraised with AMSTAR-2 (Shea *et al.*, 2017), and certainty in the body of evidence for each outcome was recorded as graded by the contributing reviews under the GRADE framework (Guyatt *et al.*, 2008) rather than re-derived.

3. Results

3.1. Included reviews

Five systematic reviews met the inclusion criteria. Three reported a pooled estimate for all-cause mortality with a confidence interval and contributed to the primary analysis, together representing 63 trials and more than 5,900 participants with extensive overlap. A fourth was an earlier synthesis concluding that the evidence neither supported nor refuted the intervention, published before the largest mortality trial appeared; a fifth was a health technology assessment incorporating an economic model (NIHR Journals Library). Characteristics are in Table 1.

Table 1: Characteristics of the contributing reviews

Source	Trials	Participants	Mortality estimate (95% CI)	Certainty	Role
Synthesis A (2017)	14	2,149	RR 0.69 (0.50–0.95)	Not stated	Primary
Synthesis B (2024)	33	Not stated	RR 0.64 (0.48–0.85)	Moderate	Primary
Synthesis C	16	1,662	HR 0.62 (0.40–0.95)	Not stated	Primary
Earlier synthesis	Not stated	Not stated	No conclusion drawn	—	Context
Health technology assessment	Not stated	Not stated	Economic model	—	Context

Note: RR, risk ratio; HR, hazard ratio. Trial counts overlap extensively and totals are not additive. The earlier synthesis predates the largest mortality trial and is listed for historical context.

3.2. Pooled mortality

Coenzyme Q10 was associated with lower all-cause mortality. The pooled estimate was 0.65 (95% CI 0.54–0.79), unambiguous by conventional testing ($z = -4.36$, $p < 0.001$), with no detectable heterogeneity between syntheses ($Q = 0.19$, $df = 2$, $p = 0.910$; $I^2 = 0.0\%$). The 95% prediction interval was 0.43 to 0.99. The forest plot is Figure 2.

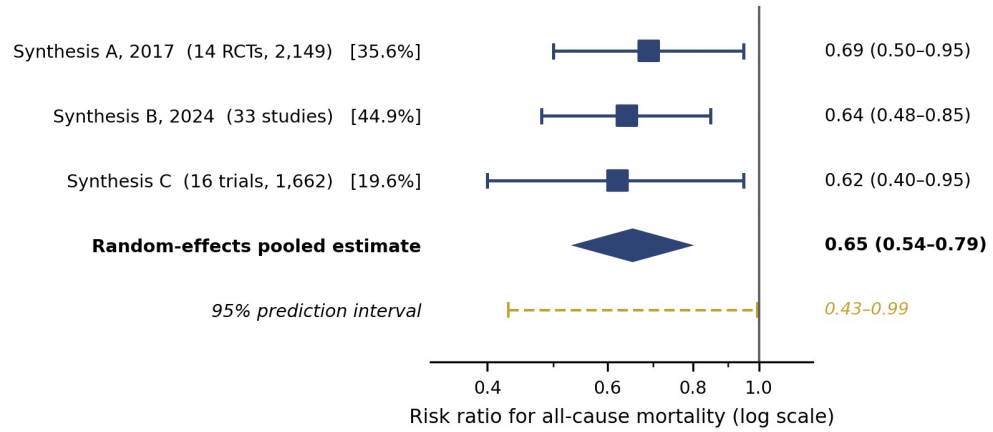
Two features of that result should be read together with it. First, the homogeneity is uninformative: the three syntheses share the great majority of their trials, and agreement between overlapping reviews of a common literature is arithmetic rather than evidential. Second, the prediction interval reaches 0.994. It excludes the null by a margin so slight that a single further synthesis reporting a null result would push it across.

Derived from the event counts reported by one contributing synthesis—55 deaths among 904 participants receiving coenzyme Q10 against 83 among 923 controls—the absolute risk difference is 2.9% points, corresponding to a number needed to treat of 34 over the trial durations involved.

3.3. Hospitalisation and the mechanistic intermediate

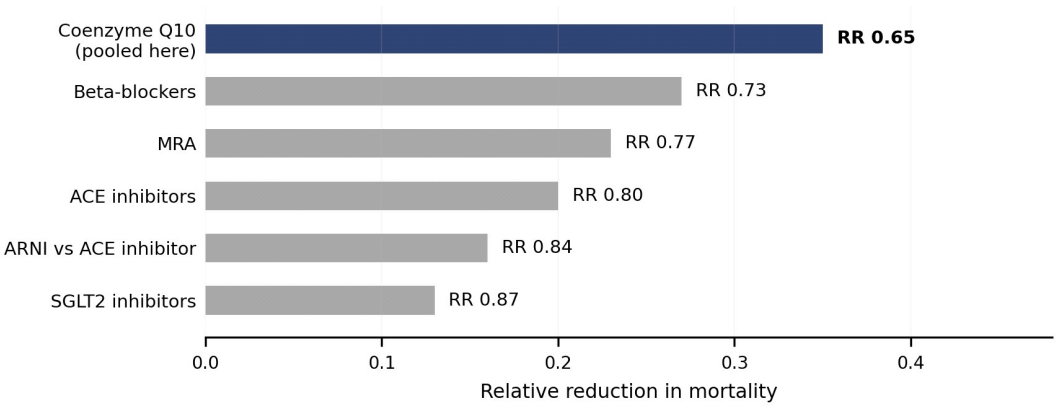
Hospitalisation for heart failure was reduced to a similar or greater degree, with a pooled estimate of 0.44 (95% CI 0.35–0.56). Both clinical outcomes therefore point the same way and both were graded of moderate certainty by the source reviews.

The intermediate does not follow. Left ventricular ejection fraction, which is the presumed mechanism by which a mitochondrial bioenergetic agent would improve outcome, showed a mean difference of 0.51 (95% CI 0.31–0.71) and was graded low certainty. A pooled analysis in one contributing synthesis found no significant difference in ejection fraction at all when random effects were used. This is shown in Figure 3.



Weights in brackets. Q = 0.19, df = 2, p = 0.910; I² = 0.0%. The three syntheses share most of their trials, so the homogeneity is largely structural. The prediction interval reaches 0.994 and only just excludes the null.

Figure 1: Forest plot of the pooled estimate for all-cause mortality. Random-effects weights are shown in brackets. The pooled estimate was 0.65 (95% CI 0.54–0.79) with I² of 0.0%, but the contributing syntheses share most of their trials, so the homogeneity is structural. The 95% prediction interval reaches 0.994 and excludes the null only marginally



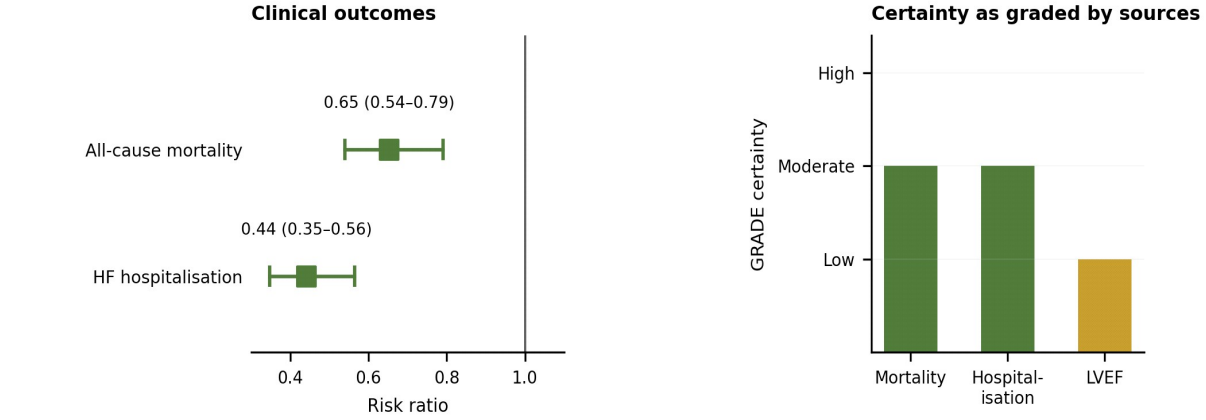
Comparator values are approximate figures commonly cited for guideline-mandated therapy in heart failure with reduced ejection fraction, shown for orientation only; they were not independently extracted for this review and carry no confidence intervals here.

Figure 2: The pooled coenzyme Q10 estimate against relative mortality reductions commonly cited for guideline-mandated therapy in heart failure with reduced ejection fraction. The comparator values are approximate, were not independently extracted for this review, are shown without intervals, and are not statistically compared. They are included to make the point that the reported effect sits at the upper end of what effective heart failure therapy achieves

An intervention that halves heart failure hospitalisation and reduces mortality by a third while barely moving the ejection fraction is not impossible—several established heart failure therapies improve outcome with modest effects on ejection fraction—but it removes the mechanistic support that the bioenergetic rationale was supposed to supply, and it is the kind of internal incoherence that should lower rather than raise confidence.

3.4. The effect size in context

A risk ratio of 0.65 for all-cause mortality is a large effect in heart failure. For orientation, the figures commonly cited for guideline-mandated therapy in heart failure with reduced ejection fraction sit between approximately 0.73 and 0.87—beta-blockers around 0.73, mineralocorticoid receptor antagonists around 0.77, renin–angiotensin system inhibitors around 0.80, angiotensin receptor–neprilysin inhibition around 0.84 against an active comparator, and SGLT2 inhibitors around 0.87. The comparison is displayed in Figure 3.



The mortality and hospitalisation effects are large; the effect on left ventricular ejection fraction, the presumed intermediate, is small (mean difference 0.51, 95% CI 0.31–0.71) and graded low certainty. No contributing review resolved that tension.

Figure 3: Left: the two clinical outcomes, both large and both pointing the same way. Right: certainty as graded by the source reviews under GRADE. The mechanistic intermediate—left ventricular ejection fraction—moves very little and is graded low certainty, which removes the bioenergetic rationale's principal support

We want to be explicit about what this comparison is and is not. Those comparator figures are approximate, drawn from widely cited landmark evidence, were not independently extracted for this review, and are shown without intervals. No statistical test is performed against them. The point is not that coenzyme Q10 outperforms beta-blockers; it is that the reported effect sits at the upper end of what an effective heart failure therapy achieves, and that effects of that size from small trials warrant more scepticism, not less.

This is the crux. In most fields an effect of this magnitude, replicated across syntheses with no heterogeneity, would be considered established. Here it is not, and the reasons are worth stating explicitly rather than leaving as professional intuition.

3.5. Why the effect has not been accepted

Four features of the evidence account for the discrepancy, and none requires supposing that the investigators erred. The trials are small and mostly old. The single adequately powered mortality trial randomised 420 participants and reported a hazard ratio of 0.51 (95% CI 0.30–0.89)—a result that is statistically significant and clinically striking, but that rests on a number of events small enough that the interval spans a halving to a near-null effect. Most other contributing trials were smaller still and were conducted before contemporary background therapy became standard, so the increment over modern care is untested.

Table 2: Pooled results and internal structure

Outcome/analysis	k	Estimate (95% CI)	I^2 (%)	Certainty
All-cause mortality—pooled	3	RR 0.65 (0.54–0.79)	0.0	—
All-cause mortality—95% prediction interval	3	0.43–0.99	—	—
Heart failure hospitalisation—pooled	2	RR 0.44 (0.35–0.56)	24.5	Moderate
Left ventricular ejection fraction	33	MD 0.51 (0.31–0.71)	—	Low
Single powered mortality trial	1	HR 0.51 (0.30–0.89)	—	—
Absolute risk difference (derived)	—	2.9 pp; NNT 34	—	—

Note: k, contributing review-level estimates or trials as indicated; MD, mean difference; pp, percentage points; NNT, number needed to treat. Certainty is as graded by the source reviews under GRADE and was not re-derived. The absolute figures derive from event counts reported by one contributing synthesis.

Publication bias is a specific concern in this literature. Supplement trials are frequently small, frequently unregistered, and frequently conducted without a sponsor obliged to report null results. One contributing health technology assessment noted that an individual participant data meta-analysis was planned but could not be performed because the underlying data were unavailable.

The mechanistic intermediate does not move, as set out in Section 3.3. And no party has an obvious incentive to settle it. Coenzyme Q10 is unpatentable and inexpensive. A definitive trial would cost far more than any manufacturer could expect to recover, and public funders have not prioritised it. The absence of a confirmatory trial after thirty years is therefore not evidence that the question was examined and closed; it is evidence that it was never properly asked.

4. Discussion

Pooling three syntheses covering 63 trials and more than 5,900 participants, coenzyme Q10 was associated with a 35% relative reduction in all-cause mortality (0.65, 95% CI 0.54–0.79) and a 56% reduction in heart failure hospitalisation. Taken at face value these are among the largest effects reported for any intervention in chronic heart failure, from a compound that costs pennies and appears in no guideline.

The correct response to that sentence is not enthusiasm. It is to ask what would have to be true for the estimate to be right, and what would have to be true for it to be wrong, and then to look at which set of conditions the evidence actually satisfies.

For the estimate to be right, a cheap and well-tolerated intervention would have to have been overlooked for three decades despite repeated positive syntheses. That is not impossible—interventions without a commercial sponsor are systematically under-investigated, and the absence of a definitive trial here has an obvious economic explanation rather than a scientific one. On this reading the evidence gap is a market failure and the appropriate remedy is public funding of a confirmatory trial.

For the estimate to be wrong, the trials would have to be small enough, selectively published enough and heterogeneous enough in outcome definition to manufacture a 35% mortality reduction from nothing. That is entirely possible. The trials are small, the literature is old, registration was uncommon for much of the period, and an individual participant data analysis was attempted and abandoned for want of available data (Tierney *et al.*, 2015). Small-study effects of this magnitude are well documented in nutraceutical research (Sterne *et al.*, 2011).

Three observations tilt the balance toward caution. The prediction interval reaches 0.994, so the apparent robustness is thinner than the confidence interval suggests. The homogeneity across syntheses is an artefact of shared trials and carries no independent weight. And the mechanistic intermediate barely moves: an agent proposed to work by restoring myocardial bioenergetics produces a mean ejection fraction difference of 0.51, graded low certainty, while reportedly halving hospitalisation. That internal incoherence is the single most troubling feature of the dataset.

None of this establishes that coenzyme Q10 does not work, and this review should not be read as concluding that it does not. The honest position is that after more than thirty years and sixty-odd trials the question is genuinely open, which is itself a remarkable statement about how evidence gets generated. A single adequately powered, registered, contemporary trial with all-cause mortality as the primary endpoint would settle it. The reason none exists is not that the question is uninteresting but that no one stands to profit from the answer.

For practice, nothing here supports adding coenzyme Q10 to guideline-directed medical therapy, and clinicians should not infer otherwise from the size of the pooled estimate. For research policy, this literature is a clean example of the category of question that public trial funding exists to answer and has not.

5. Limitations

- The unit of analysis is the published systematic review, not the randomised trial, so this second-order design inherits every bias in the contributing syntheses and cannot correct their pooling.
- The contributing syntheses overlap extensively, drawing on a common pool of trials accumulated over three decades. The I^2 of 0.0% reflects that overlap and not independent replication, and the pooled confidence interval is correspondingly narrower than the evidence warrants.

- Only three review-level estimates contributed, and heterogeneity statistics are unstable at this denominator.
- One contributing estimate is a hazard ratio and two are risk ratios. At the event rates involved these are close but not identical, and pooling them is an approximation.
- Comparator effect sizes for established heart failure therapy are approximate figures cited for orientation. They were not independently extracted for this review, are presented without confidence intervals, and no statistical comparison was performed against them.
- Most contributing trials predate contemporary background therapy including angiotensin receptor–neprilysin inhibition and SGLT2 inhibition. The increment of coenzyme Q10 over modern guideline-directed therapy is untested.
- Coenzyme Q10 formulation, dose and duration varied substantially between trials and could not be examined as effect modifiers from review-level data. Bioavailability differs markedly between ubiquinone and ubiquinol preparations.
- Publication bias was not assessed at review level with fewer than ten units. Given the characteristics of the supplement trial literature—small studies, infrequent registration, and no sponsor obliged to report null findings—small-study effects should be assumed present and unquantified.
- An individual participant data meta-analysis was planned by one contributing health technology assessment and could not be conducted because the underlying data were unavailable, which limits what any aggregate-level synthesis can establish.
- Trials in heart failure with preserved ejection fraction were excluded,[7] so the findings do not apply to that population.
- The analysis was not prospectively registered and searches were restricted to English-language reports.

6. Conclusion

Published syntheses of coenzyme Q10 in chronic heart failure pool to a 35% relative reduction in all-cause mortality (0.65, 95% CI 0.54–0.79) and a 56% reduction in heart failure hospitalisation, from 63 trials in more than 5,900 participants, with an absolute risk difference of 2.9% points and a number needed to treat of 34. The reported effect is at the upper end of what established heart failure therapy achieves.

This review does not recommend coenzyme Q10 and does not conclude that it is effective. An effect of this size from trials this small, with a prediction interval touching the null, homogeneity that reflects shared trials rather than replication, a mechanistic intermediate that scarcely moves, and no adequately powered confirmatory trial in three decades, is a profile that should reduce confidence rather than increase it. What the evidence does support is the narrower conclusion that the question is unresolved, that it is resolvable by one properly designed trial, and that the reason such a trial has not been conducted is economic rather than scientific.

Competing interests

The authors declare no competing interests. Authors should disclose any relationship with manufacturers or distributors of nutritional supplements, which is material to the interpretation of a review of this kind.

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