Coenzyme Q10 to manage chronic heart failure with a reduced ejection fraction: a systematic review and economic evaluation

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Scientific summary

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Background

Chronic heart failure is a debilitating condition that presents a significant and growing health-care challenge. In the UK, chronic heart failure accounts for approximately 5% of emergency hospital admissions, 2% of bed-days and an annual NHS spend of around £2.3B.

Coenzyme Q10 is an endogenous vitamin-like substance that is involved in cellular energy production. Low levels of coenzyme Q10 in heart muscle may lead to, or exacerbate, chronic heart failure. Taking coenzyme Q10 supplements might improve outcomes for patients with chronic heart failure and, because statins are thought to block the production of coenzyme Q10, supplementation could be particularly beneficial for those using statins. Although it has a long history of use, and shows therapeutic promise, there is considerable uncertainty about the clinical effectiveness of coenzyme Q10 in chronic heart failure. There is no existing evaluation of cost-effectiveness.

Objectives

This project aimed to assess the clinical effectiveness and cost-effectiveness of coenzyme Q10 in managing chronic heart failure with a reduced ejection fraction, and whether or not further research would be cost-effective, through a systematic review, a meta-analysis, economic modelling and a value-of-information analysis.

Methods

Systematic review and meta-analysis

A systematic review compared coenzyme Q10 plus standard care with standard care alone (with or without placebo) in patients with heart failure with a reduced ejection fraction. Randomised controlled trials evaluating coenzyme Q10 alone or as part of a multi-micronutrient supplement were included. Trials restricted to patients with chronic heart failure with preserved ejection fraction were excluded. Outcomes of interest included all-cause and cardiovascular mortality, major cardiovascular events, hospitalisation, quality of life, functional class and adverse events, as well as several intermediate outcomes.

Comprehensive searches of MEDLINE, EMBASE and trial registers were last updated in March 2020. At least two researchers screened all references and independently extracted data from published and unpublished trial reports. Critical appraisal of included studies was based on the assessment of trial publications and, where available, protocols and individual patient data sets. Risk-of-bias assessments were made by at least two researchers using the Cochrane Risk of Bias tool (version 5.2).

An individual participant data meta-analysis was planned; however, despite considerable efforts to obtain data from trial investigators, the data available were insufficient to support a full individual participant data meta-analysis. Therefore, meta-analyses were mostly based on aggregate data from publications.

For all outcomes, individual-trial effect estimates were combined in two-stage inverse-variance random-effects meta-analyses using the DerSimonian–Laird approach. Heterogeneity was examined using the I^2-statistic. One-stage analyses of aggregate data were also carried out for all-cause mortality and the risk of being in New York Heart Association class III or IV at the end of treatment. Potential effect modification was examined using meta-regression. A network meta-analysis compared multi-micronutrient

supplements containing coenzyme Q10 with coenzyme Q10 alone, with standard care plus placebo and with standard care alone.

Economic evaluation

A systematic review of existing cost-effectiveness evidence for coenzyme Q10 was conducted to identify key issues and areas of uncertainty in any existing decision-analytic models of coenzyme Q10, and to identify any potentially relevant data sources in heart failure with a reduced ejection fraction that could be used in the development of a new decision-analytic model. A de novo Markov model was developed to estimate the cost-effectiveness of coenzyme Q10 as an adjunct to standard therapy, compared with standard therapy alone, for the management of heart failure with a reduced ejection fraction. The model incorporated a lifetime horizon, with clinical outcomes, costs and quality-adjusted life-years estimated using treatment effects from the meta-analysis and baseline mortality and cardiovascular-related hospitalisations from an observational UK cohort. Costs were evaluated from an NHS and Personal Social Services perspective and expressed in Great British pounds at a 2019/20 price base. Costs were estimated from UK Reference Costs and published resource utilisation. Outcomes were expressed in terms of quality-adjusted life-years, with utility values estimated from journal publications. Both costs and outcomes were discounted at a 3.5% annual rate.

Cost-effectiveness was assessed using incremental cost-effectiveness ratios. Uncertainty in the cost-effectiveness results was presented, with a probabilistic sensitivity analysis and a value-of-information analysis, based on the expected value of perfect information. Population expected value of perfect information estimates over a 10-year time horizon were calculated from national incidence statistics for chronic heart failure and an assumption that 50% of these would be heart failure with a reduced ejection fraction. Subgroup analyses were undertaken on populations with more severe symptoms.

Results

Systematic review and meta-analysis

Bibliographic searches identified 2672 unique references. A total of 26 trials (2250 participants) were included in the systematic review (17 trials had a parallel design and nine were crossover trials). Crossover trials were mainly old and small and contributed little to the analyses. All except three trials used a placebo control. Twenty trials were included in at least one meta-analysis. Six trials could not be included in any meta-analyses.

Trial inclusion criteria varied, although most patients had New York Heart Association class II or III chronic heart failure. All except four trials used coenzyme Q10 as a single agent supplement. Coenzyme Q10 doses ranged from 32 mg to 400 mg daily and treatment lasted from 4 weeks to 2 years. Most trials were reported poorly and, for many, risk of bias could not be assessed fully. Risk of patient selection bias was assessed as low in only eight trials, unclear in 12 trials and high in six trials. Potential publication and reporting bias could not be excluded.

One-stage meta-analysis of data from seven trials suggested a possible large benefit of coenzyme Q10 on all-cause mortality (relative risk 0.68, 95% confidence interval 0.45 to 1.03), although confidence intervals crossed unity and so this was uncertain. A similar large benefit was seen for cardiovascular mortality, although this was derived from a single trial (relative risk 0.57, 95% confidence interval 0.33 to 0.98). Survival benefit was also shown in time-to-event analyses.

By contrast, the results for short-term functional outcomes were more modest or unclear. Coenzyme Q10 produced improvements in left ventricular ejection fraction of around 1–2% (mean difference 1.76%, 95% confidence interval 0.21% to 3.31%), which are within measurement error and likely to be clinically irrelevant unless progressive. Results for improvement by one or more class in the New York Heart Association functional scale suggested a modest, but uncertain, improvement for coenzyme Q10

(relative risk 1.19, 95% confidence interval 0.93 to 1.52). Admission to hospital for chronic heart failure, which is a driver of both costs to health systems and individual well-being, was reduced by 39% (relative risk 0.61, 95% confidence interval 0.49 to 0.77), although this was based on data from only two trials. Results for other outcomes were generally limited by a lack of data. Although most data were in the direction of favouring coenzyme Q10, they were not conclusive. Quality-of-life data were very limited, but there was no evidence of benefit. There was no evidence that coenzyme Q10 led to increased adverse events.

There was no evidence that coenzyme Q10 dose, trial duration, values of outcomes at baseline or age of the trial had any impact on the relative effectiveness of coenzyme Q10. In particular, there was no evidence that taking statins alongside coenzyme Q10 altered the effectiveness of coenzyme Q10, but this was based on meta-regression, which lacks power to detect such interactions. The intent to explore potential interactions between statins and coenzyme Q10 was a major motivation for seeking individual participant data and this important question remains largely unaddressed.

As only four trials combined coenzyme Q10 with selenium or other micronutrients, analyses were limited, but they provided no evidence that additional supplements modified the effectiveness of coenzyme Q10, either in subgroup analyses or in network meta-analyses.

Economic evaluation

The review of cost-effectiveness studies identified no previous economic analyses of coenzyme Q10 in chronic heart failure. Base-case cost-effectiveness results produced incremental costs of £4878, incremental quality-adjusted life-years of 1.34 and an incremental cost-effectiveness ratio of £3650 per quality-adjusted life-year, based on a lifetime treatment duration and associated benefit. Probabilistic sensitivity analyses at cost-effectiveness thresholds of £20,000 and £30,000 per quality-adjusted life-year showed high probabilities (95.2% and 95.8%, respectively) that adjunct coenzyme Q10 was a cost-effective option relative to standard therapy alone. The cost-effectiveness results remained robust to a range of scenario analyses that varied the characteristics of the population, used differing statistical models to extrapolate survival, and used alternative assumptions about treatment effectiveness and duration of effect. These demonstrated that the incremental cost-effectiveness ratio was consistently under the threshold of cost-effectiveness £20,000–30,000 per quality-adjusted life-year conventionally used to establish value for money in the NHS. The decision uncertainty in the cost-effectiveness results was relatively low. However, with a large patient population who could potentially benefit from coenzyme Q10, the consequence of the uncertainty was of high value, producing sizeable expected value of perfect information estimates that ranged from £116M to £209M across a range of cost-effectiveness thresholds. This suggests that a new trial could potentially offer value for money to the NHS in reducing the uncertainty surrounding the use of coenzyme Q10.

Limitations and uncertainties

Most trials were poorly reported. The majority of trials did not report sufficient information on randomisation methods, and most were rated as having a high or unclear risk of bias in at least one domain. Individual participant data could not be obtained and independently scrutinised, as intended, for most trials. For most outcomes, data were available from only a few trials, and different trials contributed to different outcomes, making it difficult to draw inferences or make comparisons across outcomes. Several key outcomes, including mortality, New York Heart Association class and left ventricular ejection fraction, were missing for a number of trials, raising the possibility that outcomes might have been more likely to be published if they were positive. A lack of individual participant data meant that planned detailed analyses of effect modifiers were not possible. The mortality reduction estimated by the meta-analysis for coenzyme Q10, given as an adjunct to standard treatment, was surprisingly large and comparable to those for disease-modifying interventions, compared with no intervention. Meta-analyses results were highly influenced by one large trial that reported better than

expected survival and itself suggested the possibility that New York Heart Association class may have been lower than recorded, raising questions about whether or not the meta-analysis results are applicable to a typical UK population.

The cost-effectiveness and expected value of perfect information results depend on the validity of the evidence entering the model, and limitations reflect the concerns about the existing evidence from coenzyme Q10 trials related to the treatment effect on both mortality and hospitalisations. Expected value of perfect information analysis only quantifies the decision uncertainty predicted by the model. It does not address structural or methodological uncertainty that is inherent in the model assumptions. Expected value of perfect information results depend on the model assumptions and the additional assumptions regarding the size of the patient population that could ultimately benefit from additional research over an appropriate time horizon.

Conclusions

The results from the systematic review and meta-analysis suggested that coenzyme Q10 given in addition to standard care gave a possible large reduction in mortality, contrasting with more modest or uncertain benefits for short-term outcomes. The results of the economic model found that, if prescribed, coenzyme Q10 could be highly cost-effective (compared with usual treatment alone) for heart failure with a reduced ejection fraction. However, given concerns about risk of bias, plausibility of effect sizes and applicability of the existing evidence, there is a need to establish whether or not coenzyme Q10 is genuinely effective and delivers the size of treatment benefit suggested by the meta-analysis in a typical UK population. Stronger evidence may be needed before considering prescription in the NHS.

Expected value of perfect information results present an expected upper bound on the value of further research. Although inexpensive and potentially cost saving to the NHS, the potentially large budget impact of prescribing coenzyme Q10 to all patients with heart failure with a reduced ejection fraction means that it is important to understand whether or not these costs would be defrayed by reduced hospitalisation and justified by extending or improving quality of life.

Implications for service provision

Currently, coenzyme Q10 is not available on NHS prescription. Patients with chronic heart failure who wish to use coenzyme Q10 purchase it at their own expense. Coenzyme Q10 would be relatively inexpensive if prescribed, costing around £30 per month, and appears to have few side effects. This is still considerably more costly than standard drug treatment, which has a cost of around £2 per month. Our analyses have shown that coenzyme Q10 has the potential to be a clinically effective and cost-effective intervention from an NHS perspective. However, given concerns about possible bias, applicability and plausibility of meta-analysis effect sizes, additional evidence may be needed before considering the use of coenzyme Q10 use in the NHS, particularly as it has not been through the rigour and scrutiny of drug-licensing processes.

Should further research confirm the benefits of coenzyme Q10 suggested by our meta-analysis, and cost-effectiveness suggested by our economic model, it would seem appropriate to consider NHS prescribing, making coenzyme Q10 available to all relevant patients with heart failure with a reduced ejection fraction and providing equity of access. Conversely, if further research found benefit to be limited, then this would be important information for those who currently purchase coenzyme Q10 at their own expense.

Suggested research priorities

Given the concerns about possible bias, applicability and plausibility of the effect size, and as coenzyme Q10 has never been through the rigour and scrutiny of drug-licensing processes, an adequately powered placebo-controlled randomised controlled trial of coenzyme Q10 in a typical UK population with heart failure with a reduced ejection fraction may be warranted. Our value-of-information analysis suggested that the value of reducing decision uncertainty is highly likely to outweigh the costs of a new trial. However, the amount of uncertainty that is likely to be resolved by a new trial would need to be assessed against the cost of the trial (based on its design features) to ensure that any further research is an efficient use of NHS resources.

Study registration

This study is registered as PROSPERO CRD42018106189.

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This report

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