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Background

Studies have shown that coenzyme Q10 deficiency is associated with cardiovascular disease. Hypertension is a commonly measured surrogate marker for non-fatal and fatal cardiovascular endpoints such as heart attacks and strokes. Clinical trials have suggested that coenzyme Q10 supplementation can effectively lower blood pressure (BP).

Objectives

To determine the blood pressure lowering effect of coenzyme Q10 in primary hypertension.

Search methods

The Cochrane Central Register of Controlled Trials (2009 Issue 2), MEDLINE (1966 -May 2008), EMBASE (1982 - May 2008), and CINAHL (1970 - May 2008) as well as the reference lists of articles were searched for relevant clinical trials in any language.

Selection criteria

Double-blind, randomized, placebo-controlled parallel or crossover trials evaluating the BP lowering efficacy of coenzyme Q10 for a duration of at least 3 weeks in patients with primary hypertension.

Data collection and analysis

The primary author independently assessed the risk of bias and extracted the data. The second author verified data extraction.

Main results

Three clinical trials with a total of 96 participants were evaluated for the effects of coenzyme Q10 on blood pressure compared to placebo. Treatment with coenzyme Q10 in subjects with systolic BP (SBP) > 140 mmHg or diastolic BP (DBP) > 90 mmHg resulted in mean decreases in SBP of 11 mmHg (95% CI 8, 14) and DBP of 7 mmHg (95% CI 5, 8).
Authors’ conclusions

Due to the possible unreliability of some of the included studies, it is uncertain whether or not coenzyme Q10 reduces blood pressure in the long-term management of primary hypertension.

PLAIN LANGUAGE SUMMARY

Coenzyme Q10 for hypertension

Coenzyme Q10 has been studied as a potential treatment for hypertension, a common medical condition. However, there is not enough reliable evidence to show whether or not it can be a useful medication to lower blood pressure. A systematic review was conducted to try and use all available data to answer this question. Databases of clinical trials were searched for any studies that tested the effects of coenzyme Q10 on patients’ blood pressure compared to a placebo. The test medications could be added to participants’ regular anti-hypertensive medications or be used alone. Three trials with a total of 96 participants were found in which coenzyme Q10 was used in patients with high blood pressure. The patients took coenzyme Q10 or a placebo daily for up to 8-12 weeks. Weighted data analysis showed that the systolic blood pressure was reduced by 11 mmHg and the diastolic blood pressure was lowered by 7 mmHg compared to placebo. However, there are questions about the reliability of the available studies. Therefore, it is still uncertain if coenzyme Q10 could be a useful hypertension treatment, and more studies are needed.
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON

Patient population: patients with essential arterial hypertension (SBP > 140 mmHg or DBP > 90 mmHg)
Settings: primary care in Japan, Italy and India
Intervention: coenzyme Q10
Comparison: placebo

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (SBP)</td>
<td>-10.72 [-13.77, -7.67]</td>
<td>96 (3)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (DBP)</td>
<td>-6.64 [-8.10, -5.17]</td>
<td>96 (3)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Change in heart rate (HR)</td>
<td>-12.00 [-15.19, -8.81]</td>
<td>58 (1)</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Number of withdrawals due to adverse effects compared to placebo</td>
<td>unknown, reason for withdrawals not reported in Singh 1999</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BACKGROUND

Description of the condition
Hypertension is a common medical condition and major risk factor for stroke, myocardial infarction, congestive heart failure, kidney failure and peripheral vascular disease. Pharmacological interventions have been shown to reduce blood pressure and modestly decrease stroke, myocardial infarction and mortality. However, hypertension remains prevalent in the community and additional treatment options are needed (Burt 1995).

Description of the intervention
Coenzyme Q10 is a non-prescription nutritional supplement that is commonly taken daily. Also called ubiquinone, it is a fat soluble molecule that acts as an electron carrier in mitochondria and as a coenzyme for mitochondrial enzymes (Langsjoen 1985). As a bioenergetic molecule, coenzyme Q10 is obtained both through tissue synthesis and diet (Langsjoen 1985). Supplementary oral administration of coenzyme Q10 has been shown to increase coenzyme Q10 levels in plasma, platelets and white blood cells (Niklowitz 2007). Studies suggest that coenzyme Q10 deficiency may be associated with a multitude of diseases as diverse as coronary artery disease and congestive heart failure, Parkinson’s disease, diabetes and breast cancer as well as the risk factor hypertension (Niklowitz 2007). Burke 2001 found that coenzyme Q10 decreased systolic blood pressure after 12 weeks of treatment in a randomized, double-blind, placebo-controlled trial. Other researchers concluded that coenzyme Q10 has the potential to lower blood pressure without significant adverse events in hypertensive patients (Rosenfeldt 2007).

How the intervention might work
Coenzyme Q10, as an antioxidant, could act directly on vascular endothelium to decrease total peripheral resistance or by reducing superoxide synthesis (McCarty 1999). Coenzyme Q10 also has possible anti-atherogenic effects as a modulator of β-integrin levels on the surface of blood monocytes (Quinzii 2007).

Why it is important to do this review
Many people are taking coenzyme Q10 for hypertension. A non-Cochrane review concluded that coenzyme Q10 reduces BP...
However in that review there was no reported assessment of the risk of bias in the included trials. The present systematic review uses the latest Cochrane methodology to quantify the blood pressure lowering effect of different doses of coenzyme Q10, and to assess the effect on withdrawals due to adverse effects. The information derived from this review should assist clinicians in determining whether it is worth trying coenzyme Q10 as a therapeutic intervention to lower blood pressure, and in determining whether further studies that measure cardiovascular outcomes should be conducted.

OBJECTIVES

Primary objective:

1. To determine the dose-related effect of coenzyme Q10 on systolic and diastolic blood pressure in hypertensive patients.

Secondary objectives:

1. To determine the dose-related effects of coenzyme Q10 on heart rate.
2. To determine the effects of coenzyme Q10 in different doses on withdrawals due to adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Study design had to meet the following criteria: randomized, placebo-controlled parallel or crossover trial; duration of treatment of at least three weeks; washout period of at least 2 weeks before the start of trial; blood pressure measurement at baseline (following washout) and at one or more time points between 3 to 12 weeks after starting treatment. A washout period of at least 2 weeks is important to be reasonably sure that the blood pressure is elevated and stable and that the effects of any antihypertensive drugs that have been stopped are no longer acting.

Types of participants

Participants had to have a baseline systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg, measured in a standard way. Patients with significant renal insufficiency and a documented serum creatinine level > 1.5 times the normal values were excluded. Participants were not restricted by age, gender, baseline risk or any other co-morbid conditions.

Types of interventions

Therapy with coenzyme Q10 compared to a placebo control, either as the sole antihypertensive therapy or added to current antihypertensive medication.

Data from trials in which titration to a higher dose is based on blood pressure response are not eligible.

Types of outcome measures

Primary outcomes

Change in systolic and diastolic blood pressure compared to placebo. If blood pressure measurements were available at more than one time within the acceptable window, the weighted means of blood pressures taken in the 3-12 week range were used.

Secondary outcomes

1. Change in heart rate compared to placebo.
2. Number of patient withdrawals due to adverse effects compared to placebo.

Search methods for identification of studies

Electronic searches

The Database of Abstracts of Reviews of Effectiveness (DARE) and the Cochrane Database of Systematic Reviews were searched for related reviews.

The following electronic databases were searched for primary studies:

a) The Cochrane Register of Controlled Clinical Trials (2009 Issue 2)


Electronic databases were searched using a strategy combining a variation of the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision) with selected MeSH terms and free text terms relating to coenzyme Q10 and hypertension. No language
restrictions were used. The MEDLINE search strategy was trans-
lated into the other databases using the appropriate controlled vo-
cabulary as applicable.
Other sources:
a) Reference lists of relevant studies and reviews
b) Authors of trials reporting incomplete information were
contacted to provide the missing information

Data collection and analysis

Selection of studies
The initial screen for potential relevance excluded articles whose
titles and/or abstracts were clearly irrelevant. The full text of re-
mainings articles was retrieved (and translated into English where
required). The bibliographies of pertinent articles, reviews and
texts were searched for additional citations. Two independent re-
viewers assessed the eligibility of the trials using a trial selection
form. A third reviewer resolved discrepancies.

Data extraction and management
Data were extracted independently by two reviewers using a stan-
dard form, and then cross-checked. All numeric calculations and
graphic interpolations were confirmed by a second person.
The position of the patient during blood pressure measurement
may affect the blood pressure lowering effect. However, in order to
not lose valuable data if only one position was reported, data from
that position was used. When blood pressure measurement data
was available in more than one position, sitting blood pressure was
the first preference. If standing and supine blood pressures were
available, standing blood pressure was used.

Assessment of risk of bias in included studies
All trials were assessed using the “risk of bias tool” under the
categories adequate sequence generation, allocation concealment,
blinding, incomplete outcome data, selective reporting, and other
biases.

Measures of treatment effect
The measure of treatment effect was the change in systolic and
diastolic blood pressure from baseline in the coenzyme Q10 group
minus the respective change in BP in the placebo group (mean
difference).

Dealing with missing data
In case of missing information in the included studies, investiga-
tors were contacted (using email, letter and/or fax) to obtain the
missing information. Standard deviations were able to be extracted from the reported
data of all three trials and did not have to be imputed. In the case
of missing standard deviation of the change in blood pressure, the
standard deviation would be imputed based on the information
in the same trial or from other trials using the same dose. The follow-
ning hierarchy (listed from high to low preference) would
have been used to impute standard deviation values:
1. standard deviation of change in blood pressure from a
different position than that of the blood pressure data used
2. standard deviation of blood pressure at the end of treatment
3. standard deviation of blood pressure at the end of treatment
measured from a different position than that of the blood
pressure data used
4. standard deviation of blood pressure at baseline (except if
this measure is used for entry criteria)
5. mean standard deviation of change in blood pressure from
other trials using the same drug and dose

Assessment of heterogeneity
Test for heterogeneity of treatment effect between the trials were
made using a standard chi-squared test and the I² statistic test for
heterogeneity. The fixed effects model was applied to obtain sum-
mary statistics of pooled trials, unless significant between-study
heterogeneity (e.g. I² >50%) was present, in which case the ran-
don effects model was used.

Data synthesis
Data synthesis and analyses were done using the Cochrane Review
Manager software, RevMan 5.
Data for changes in blood pressure were combined using a
weighted mean difference method. Different doses and dosing reg-
imens were pooled due to the paucity of data. The drop-outs due
to adverse effects would have been analysed using relative risk, risk
difference, and number needed to harm. However, this informa-
tion was not provided in any of the included studies.

Sensitivity analysis
It was not possible to do the following planned analyses due to the
small number of included trials:
1. Trials of high quality versus poor quality
2. Trials that are industry-sponsored versus non-industry
sponsored
3. Trials with blood pressure data measured in the sitting
position vs. other measurement positions
4. Trials with published standard deviations of blood pressure
change vs. imputed standard deviations
RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
See characteristics of included studies table.

Results of the search
The search yielded eleven potential studies, of which three met the inclusion criteria and had extractable data for the blood pressure lowering efficacy of coenzyme Q10. The 3 studies used clinic blood pressure measurements to assess BP and no trials used 24 hour BP monitoring.

Included studies
See characteristics of included studies table.

Excluded studies
See characteristics of excluded studies table.

Risk of bias in included studies
See risk of bias tables and characteristics of included studies table.

Allocation
All three studies reported that the subjects were randomized to treatment groups but did not describe the sequence generation process or how allocation concealment was achieved.

Blinding
Digiesi 1990, which was a crossover trial, did not mention blinding in their study. Singh 1999 and Yamagami 1986 reported that their studies were double-blind. Singh 1999 reported that the placebo and coenzyme Q10 capsules were kept in identical containers and subjects, physicians and technicians were blinded to type of intervention. However, the control and coenzyme Q10 groups were reported to meet separately. In our opinion “meeting separately” would lead to loss of blinding. Yamagami 1986 described a double-blind procedure using numbered capsules and locked key codes, but did not report who performed the blinding or how the capsules were numbered (randomly or in sequence).

Incomplete outcome data
It does not appear that the outcome data are incomplete. However, there was a discrepancy in sample size values in the Singh 1999 trial as described below.

Selective reporting
Digiesi 1990 and Yamagami 1986 did not lose any subjects to follow-up. Singh 1999 reported that 5 patients were not available for follow-up after 8 weeks but did not report the reasons. There was also a discrepancy in the group sizes; initially 32 patients were randomized to the control and coenzyme Q10 group. In a table of “characteristics of randomised subjects at entry to study,” the placebo group was reported to have n = 29, while the coenzyme Q10 group was reported to have n = 30, consistent with the follow-up loss of 5 patients. However, in their table of “clinical and biochemical data at baseline and during follow-up,” Singh et al. reported the placebo group as having n = 28. The discrepancy was not resolved by e-mail correspondence with Singh. Since BPs were probably recorded at times other than those reported, it is possible that the reported BP measurements were selected based on the results in Digiesi 1990 and Singh 1999.

Other potential sources of bias
Digiesi 1990 described the blood pressure measurement procedure, which was conducted using the same sphygmomanometer at the same time every morning by the same examiner on the same arm after a 10 minute resting period. The study used the mean of five readings measured successively every minute. Singh 1999 reported consistently using the right arm after a 5 minute rest with the patient supine and using a mercury manometer. They did not describe who performed the measurement or whether or not the same sphygmomanometer was used. Yamagami 1986 did not provide any details about how blood pressures were measured. The blood pressure standard deviations in Digiesi 1990, 7/3 mmHg, and Singh 1999, 8/5 mmHg are lower than the average for resting BP standard deviation in research settings, 14/8 mmHg Musini 2008.
Digiesi 1990 reported that the drug was tolerated well and no patients reported any “significant disturbances.” They did not specifically mention any drug adverse effects leading to withdrawal. Singh 1999 and Yamagami 1986 also did not report numbers of patients withdrawing due to adverse drug effects.

Effects of interventions
See: Summary of findings for the main comparison Coenzyme Q10 versus placebo in patients with essential arterial hypertension Coenzyme Q10 was administered in daily doses of 100 or 120 mg and resulted in clinically significant and statistically significant greater reductions in systolic and diastolic blood pressures, 11
Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension (Review)

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[95% CI 8, 14] mmHg and 7 [95% CI 5, 8] mmHg respectively (Figure 1, Figure 2) as compared to placebo control. The statistically significant mean decrease in heart rate was 12 beats per minute (Figure 3) as measured in the Singh 1999 study only (see Data and analyses). There were not enough available data to construct a dose response. The secondary outcome, withdrawals due to adverse effects, was not reported in the trials.

**DISCUSSION**

Summary of main results

This systematic review of coenzyme Q10 (100-120 mg daily) shows a highly clinically significant and statistically significant de-
increase in SBP and DBP after 4-12 weeks of therapy compared to placebo control based on 3 RCTs that met the inclusion criteria (Figure 1, Figure 2, Figure 3). If these results are true, coenzyme Q10 is a remarkably effective antihypertensive agent with a mean BP lowering capacity of 11/7 mmHg. Although this review did not identify or examine any direct comparison data with other anti-hypertensive agents, the reported BP lowering capacity, appears greater than that achieved by other available drug classes. We have much more data demonstrating the blood pressure lowering effect of thiazides, ACE inhibitors, angiotensin receptor blocker and renin inhibitors and these data show a blood pressure lowering effect of about 8/4 mmHg Heran 2008a, Heran 2008b, Musini 2008, Musini 2009. Unfortunately, because of the high risk of bias in the included co-enzyme Q studies we think that the remarkable BP lowering demonstrated in these trials is more likely reflecting bias than a true BP lowering effect. We outline our reasons for this opinion below.

Overall completeness and applicability of evidence
The number of patients providing data on the BP lowering effect of coenzyme Q10 is small at 96. Because there were only 3 included RCTs, we could not assess for publication bias. There also remains a high risk that many small RCTs assessing the BP lowering effect of coenzyme Q10 have been performed and showed no effect on blood pressure, and thus were judged not publishable or were submitted for publication and rejected. We therefore think that the available data is a very incomplete reflection of the totality of evidence. Hopefully this review will encourage individuals who have unpublished negative studies to publish them. The capacity for publishing negative trials is better now than it has been in the past.

On the other hand, if we had been less rigorous in our entry criteria at least two RCTs could have been included in this review (Burke 2001, Hodgson 2002). Burke 2001 was excluded because of a run-in time of 10 days, which was less than our inclusion criteria specifying at least 2 weeks. If this trial was included it would have strengthened the BP lowering effect of coenzyme Q10, at least for systolic BP. Burke 2001 studied the effect on 76 people with isolated systolic BP and showed a reduction in systolic BP of 17 mmHg as compared to placebo. Burke 2001 also showed a non-significant 2.6 mmHg increase in BP by coenzyme Q10 in 9 normotensive individuals. Hodgson 2002 was excluded because it studied mostly normotensive diabetic subjects. If it had been included it would have strengthened the conclusion of a blood pressure lowering effect of coenzyme Q10, as coenzyme Q10 lowered BP as compared to placebo by 6/3 mmHg in 74 patients.

Quality of the evidence
The quality of the evidence may not be reliable for reasons outlined in the risk of bias tables. It is well established that if randomization, concealment of allocation and blinding are not performed correctly, the effect size is exaggerated. In addition, the reliability of the Singh 1999 paper is questionable given the investigations into scientific misconduct of the first author, Dr. Singh (White 2005). Singh has been investigated by the BMJ and Lancet (Mann 2005), which have published “expressions of concern” about his work. In addition to the biases tested by the risk of bias tool, the lower standard deviations than expected for two of the trials Digiesi 1990, Singh 1999 also shed some suspicion on the reliability of the results (see above Other potential sources of bias).

Agreements and disagreements with other studies or reviews
The results of this review are consistent with other systematic reviews looking at the blood pressure lowering effect of coenzyme Q10 in people with hypertension, Rosenfeldt 2003, Rosenfeldt 2007. The Rosenfeldt reviews suffer from all the same limitations of this review. The more recent review (Rosenfeldt 2007) also included open label studies and did not identify any study that did not demonstrate a BP lowering effect of coenzyme Q10. The present systematic review identified the same 3 RCTs identified in the Rosenfeldt reviews.

AUTHORS’ CONCLUSIONS

Implications for practice
Although the results of this review show a clinically significant blood pressure lowering effect of coenzyme Q10 that appears to be larger than other available blood pressure lowering drugs, we remain sceptical of the findings. This is because of limited data and the high risk of bias in the available RCTs. The results are however sufficiently consistent and encouraging to warrant larger properly conducted RCTs testing the blood pressure lowering effect of coenzyme Q10 (see below).

Implications for research
If coenzyme Q10 has a clinically significant blood pressure lowering effect it could be a valuable addition to the therapeutic management of hypertension. Randomized, placebo-controlled, double-blind parallel or crossover trials are badly needed to determine the effect of coenzyme Q10 on blood pressure and heart rate. These studies need to be at least 8 weeks in duration as some of the trials suggest that the blood pressure lowering effect may be delayed. In addition we are hoping that this review will encourage any researchers who have data on the blood pressure lowering effect of coenzyme Q10 to publish it or provide it to us so that it can be added to this review.

If the BP lowering capacity of coenzyme Q10 is verified in short term studies, longer term studies would be required to determine...
the full adverse event profile of coenzyme Q10 and to determine efficacy when used on a chronic basis. Further large studies would also be needed to determine that the effect on blood pressure, a surrogate marker, is accompanied by a reduction in cardiovascular endpoints such as stroke, myocardial infarction and mortality.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help provided by the Cochrane Hypertension Group.

REFERENCES

References to studies included in this review

Digiesi 1990 [published data only]

Singh 1999 [published data only]

Yamagami 1986 [published data only]

References to studies excluded from this review

Burke 2001 [published data only]

Digiesi 1994 [published data only]

Drezowski 1981 [published data only]

Folkers 1981 [published data only]

Hata 1977 [published data only]

Hodgson 2002 [published data only]

Langsjoen 1994 [published data only]

Shah 2007 [published data only]

Additional references

Burke 2001

Burt 1995

Heran 2008a
Heran 2008b

Langsjoen 1985

Mann 2005

McCarty 1999

Musini 2008

Musini 2009

Niklowitz 2007

Quinzii 2007

Rosenfeldt 2003

Rosenfeldt 2007

White 2005

* Indicates the major publication for the study
## CHARACTERISTICS OF STUDIES

### Characteristics of included studies  
[ordered by study ID]

**Digiesi 1990**

| Methods | Randomized, placebo-controlled, crossover trial.  
2 week washout period, 10 week treatment period, 2 week treatment suspension, 10 week crossover treatment |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>18 patients (4 women, 14 men) with essential hypertension, WHO stages 1 and 2, average age 55.9 years (range 42-66 years). Patients older than 70 years, renal failure or body weight &gt; 90 kg excluded</td>
</tr>
</tbody>
</table>
| Interventions | Intervention: Monotherapy with 100 mg oral coenzyme Q10 daily for 10 weeks  
Control: Placebo |
| Outcomes | Resting supine SBP and DBP at 10 weeks |
| Notes | Sources of funding not stated.  
Small study size. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Quote &quot;...patients were randomly assigned... then each patient in group A crossed over to placebo treatment and each patient in group B crossed over to CoQ treatment...” Does not describe the sequence generation process.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>Insufficient information provided. Does not describe how allocation concealment was ensured</td>
</tr>
<tr>
<td>Blinding? Blood Pressure</td>
<td>No</td>
<td>No information provided as to whether blinding was achieved.</td>
</tr>
<tr>
<td>Incomplete outcome data addressed? Blood Pressure</td>
<td>Yes</td>
<td>No missing outcome data.</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>No</td>
<td>BP reported was stated as end of treatment. BPs at other times were not reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Patients could have been selected based on previous response to coenzyme Q10. BP standard deviations are lower and not as variable as would be expected</td>
</tr>
</tbody>
</table>
Singh 1999

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, placebo-controlled, double-blind trial.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>59 patients (52 men) patients with known coronary heart disease and essential hypertension (receiving medications for more than 1 year)</td>
</tr>
</tbody>
</table>
| Interventions | Intervention: Monotherapy with 60 mg CoQ twice daily (120 mg/day)  
Control: Placebo (Vitamin B complex) |
| Outcomes | Resting supine SBP and DBP and heart rate at 4 and 8 weeks |
| Notes | Sources of funding not stated.  
Q-gel capsules provided free of cost by Tischon Corporation, USA |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
</table>
| Adequate sequence generation? | No | Quote: “Each was individually randomised by the pharmacist...”  
Does not describe the sequence generation process. |
| Allocation concealment? | No | Does not describe allocation concealment |
| Blinding? Blood Pressure | No | Quote: “The subjects in both groups remain blinded... and both the groups met separately.” Meeting separately would lead to loss of blinding.  
Quote: “... to receive either coenzyme Q10 or vitamin capsules supplied in identical containers by the Heart Research Laboratory blinded to physicians and technicians examining the blood.” |
| Incomplete outcome data addressed? Blood Pressure | No | Author reports placebo group n=32 with 3 patients lost to follow-up (n=29), however, table of results during follow-up displays n=28  
Quote (from correspondence): “It is possible that data may have been available for only 28. I don’t remember exactly.” |
| Free of selective reporting? | No | Patients were seen weekly and BP data was only reported at 4 and 8 weeks |
| Free of other bias? | No | BP standard deviations are lower and not as variable as would be expected |
Yamagami 1986

<table>
<thead>
<tr>
<th>Methods</th>
<th>Randomized, placebo-controlled, double-blind trial. Washout period of 4 weeks or more with stable baseline BP. Measurement every 2 weeks for 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>52 patients with essential hypertension (BP &gt; 150/90 mmHg) were selected at random from the outpatient clinic of The Center for adult Diseases in Osaka, Japan. 20 patients (8 men and 12 women, mean age 60 years) with low coenzyme Q10 and low SDH-Q reductase activity were accepted. Conventional hypertension therapies were continued without change.</td>
</tr>
</tbody>
</table>
| Interventions | Intervention: Monotherapy with 33.3 mg CoQ 3x daily (100 mg/day)  
Control: Placebo |
| Outcomes | SBP and DBP at 2 week intervals: (no description of position of patient or method of BP measurement) |
| Notes | Sources of funding not stated. Limited to patients with low coenzyme Q10 levels, who could be particularly responsive to BP lowering effect of intervention |

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
</table>
| Adequate sequence generation? | Unclear | Quote: “A total of 20 patients was randomized...”  
Does not describe the sequence generation process. |
| Allocation concealment? | Unclear | “The capsules were numbered and the code was kept... until all trial had been over” Not clear whether numbers were random or in sequence |
| Blinding? Blood Pressure | Unclear | Quote [direct quotation, note typographical errors]: “The capsules were numbered and the code was kept... until all trial had been over... After all data were fixed in each case, key code was opened and the change of blood pressure was compared between coQ group and placebo group.”  
Comment: insufficient information about how key codes were assigned |
| Incomplete outcome data addressed? Blood Pressure | Yes | No missing outcome data. |
| Free of selective reporting? | Yes | BP data at all time points was provided. |
Yamagami 1986  (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke 2001</td>
<td>Washout period was only 10 days.</td>
</tr>
<tr>
<td>Digiesi 1994</td>
<td>No placebo control.</td>
</tr>
<tr>
<td>Drzewoski 1981</td>
<td>No placebo control.</td>
</tr>
<tr>
<td>Folkers 1981</td>
<td>No placebo control.</td>
</tr>
<tr>
<td>Hata 1977</td>
<td>Trial is not randomized, no parallel placebo group. Washout period is only 1-2 weeks</td>
</tr>
<tr>
<td>Hodgson 2002</td>
<td>Included mostly patients with normal blood pressure, baseline BP ranged from 127/75 to 136/80 mmHg and therefore, did not meet hypertension criteria</td>
</tr>
<tr>
<td>Langsjoen 1994</td>
<td>No placebo control.</td>
</tr>
<tr>
<td>Shah 2007</td>
<td>Treatment period was less than 3 weeks (longest post-dose period was 8 hours)</td>
</tr>
</tbody>
</table>

Free of other bias?  Yes  SD data is as would be expected.

**Characteristics of excluded studies**  *ordered by study ID*

Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension (Review)  Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
**DATA AND ANALYSES**

Comparison 1. Coenzyme Q10 vs placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SBP</td>
<td>3</td>
<td>96</td>
<td>Mean Difference (Fixed, 95% CI)</td>
<td>-10.72 [-13.77, -7.67]</td>
</tr>
<tr>
<td>2 DBP</td>
<td>3</td>
<td>96</td>
<td>Mean Difference (Fixed, 95% CI)</td>
<td>-6.64 [-8.10, -5.17]</td>
</tr>
<tr>
<td>3 Heart rate</td>
<td>1</td>
<td>58</td>
<td>Mean Difference (Fixed, 95% CI)</td>
<td>-12.0 [-15.19, -8.81]</td>
</tr>
</tbody>
</table>

**Analysis 1.1. Comparison 1 Coenzyme Q10 vs placebo, Outcome 1 SBP.**

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs placebo

Outcome: 1 SBP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Coenzyme Q10</th>
<th>Placebo</th>
<th>Mean Difference (SE)</th>
<th>Mean Difference (Fixed, 95% CI)</th>
<th>Weight</th>
<th>Mean Difference (Fixed, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digesi 1990 (1)</td>
<td>18</td>
<td>0</td>
<td>-10.3 (2.31)</td>
<td>-10.30 [-14.83, -5.77]</td>
<td>45.3 %</td>
<td></td>
</tr>
<tr>
<td>Singh 1999</td>
<td>30</td>
<td>28</td>
<td>-11.5 (2.2)</td>
<td>-11.50 [-15.81, -7.19]</td>
<td>49.9 %</td>
<td></td>
</tr>
<tr>
<td>Yamagami 1986</td>
<td>10</td>
<td>10</td>
<td>-6.6 (7.09)</td>
<td>-6.60 [-20.50, 7.30]</td>
<td>4.8 %</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong> <strong>-10.72 [-13.77, -7.67]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 0.50, df = 2 (P = 0.78); I² =0.0%

Test for overall effect: Z = 6.90 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Cross-over trial with 18 subjects
### Analysis 1.2. Comparison 1 Coenzyme Q10 vs placebo, Outcome 2 DBP.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs placebo

Outcome: 2 DBP

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Coenzyme Q10</th>
<th>Placebo</th>
<th>Mean Difference (SE)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Digiesi 1990 (1)</td>
<td>18</td>
<td>0</td>
<td>-8.1 (1)</td>
<td>-8.10 [ -10.06, -6.14 ]</td>
<td>55.9 %</td>
<td>-8.10 [ -10.06, -6.14 ]</td>
</tr>
<tr>
<td>Singh 1999</td>
<td>30</td>
<td>28</td>
<td>-5 (1.17)</td>
<td>-5.00 [ -7.29, -2.71 ]</td>
<td>40.8 %</td>
<td>-5.00 [ -7.29, -2.71 ]</td>
</tr>
<tr>
<td>Yamagami 1986</td>
<td>10</td>
<td>10</td>
<td>-2.2 (4.1)</td>
<td>-2.20 [ -10.24, 5.84 ]</td>
<td>3.3 %</td>
<td>-2.20 [ -10.24, 5.84 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-6.64 [ -8.10, -5.17 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi$^2$ = 5.27, df = 2 (P = 0.07); I$^2$ = 62%

Test for overall effect: Z = 8.88 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Cross-over trial with 18 subjects

### Analysis 1.3. Comparison 1 Coenzyme Q10 vs placebo, Outcome 3 Heart rate.

Review: Blood pressure lowering efficacy of coenzyme Q10 for primary hypertension

Comparison: 1 Coenzyme Q10 vs placebo

Outcome: 3 Heart rate

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental</th>
<th>Control</th>
<th>Mean Difference (SE)</th>
<th>Mean Difference</th>
<th>Weight</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
<td>IV,Fixed,95% CI</td>
<td></td>
<td>IV,Fixed,95% CI</td>
</tr>
<tr>
<td>Singh 1999</td>
<td>30</td>
<td>28</td>
<td>-12 (1.63)</td>
<td>-12.00 [ -15.19, -8.81 ]</td>
<td>100.0 %</td>
<td>-12.00 [ -15.19, -8.81 ]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td>100.0 %</td>
<td>-12.00 [ -15.19, -8.81 ]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: not applicable

Test for overall effect: Z = 7.36 (P < 0.00001)

Test for subgroup differences: Not applicable
HISTORY

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

James Wright and Meghan Ho formulated the idea for the review and developed the basis for the protocol.

Meghan Ho took the lead role in searching, identifying and assessing studies, in data extraction and analyses, and in writing up the review.

Anthony Bellusci assisted in identifying trials and independently assessed studies for inclusion as well as independently extracted the data.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

• University of British Columbia, Department of Anesthesiology, Pharmacology & Therapeutics, Canada.

External sources

• Canadian Institutes of Health Research, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The acceptance criteria was modified to “Participants must have a baseline blood pressure of at least 140 mmHg systolic or a diastolic blood pressure of at least 90 mmHg.” Previously the minimum systolic blood pressure required was 160 mmHg.

INDEX TERMS
Medical Subject Headings (MeSH)
Antihypertensive Agents [*therapeutic use]; Bias (Epidemiology); Blood Pressure [drug effects]; Hypertension [*drug therapy]; Randomized Controlled Trials as Topic; Ubiquinone [*analogs & derivatives; deficiency; therapeutic use]

MeSH check words
Humans