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Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

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Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer (Review)

Sieswerda E, van Dalen EC, Postma A, Cheuk DKL, Caron HN, Kremer LCM

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Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

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A B S T R A C T

Background

Anthracyclines are frequently used chemotherapeutic agents for childhood cancer that can cause cardiotoxicity during and after treatment. Although several medical interventions in adults with symptomatic or asymptomatic cardiac dysfunction due to other causes are beneficial, it is not known if the same treatments are effective for childhood cancer patients and survivors with anthracycline-induced cardiotoxicity.

Objectives

To compare the effect of medical interventions on anthracycline-induced cardiotoxicity in childhood cancer patients or survivors with the effect of placebo, other medical interventions or no treatment.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011, issue 1), MEDLINE/PubMed (1949 to May 2011) and EMBASE/Ovid (1980 to May 2011) for potentially relevant articles. We additionally searched reference lists of relevant articles, conference proceedings and ongoing trial databases.

Selection criteria

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) comparing the effectiveness of medical interventions to treat anthracycline-induced cardiotoxicity with either placebo, other medical interventions or no treatment.

Data collection and analysis

Two review authors independently performed the study selection. One review author performed the data extraction and 'Risk of bias' assessments which were checked by another review author.

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Main results

We identified two RCTs. One trial (135 patients) compared enalapril with placebo in childhood cancer survivors with asymptomatic anthracycline induced cardiac dysfunction. The other trial (68 patients) compared a two-week treatment of phosphocreatine with a control treatment (vitamin C, ATP, vitamin E, oral coenzyme Q10) in leukaemia patients with anthracycline-induced cardiotoxicity. Both studies had methodological limitations.

The RCT on enalapril showed no (statistically) significant differences in overall survival, mortality due to heart failure, development of clinical heart failure and quality of life between treatment and control group. A post-hoc analysis showed a decrease (i.e. improvement) in one measure of cardiac function (left ventricular end systolic wall stress (LVESWS): -8.62% change) compared with placebo (+1.66% change) in the first year of treatment (P = 0.036), but not afterwards. Patients treated with enalapril had a higher risk of dizziness or hypotension (RR 7.17, 95% CI 1.71 to 30.17) and fatigue (Fisher's exact test, P = 0.013).

The RCT on phosphocreatine found no differences in overall survival, mortality due to heart failure, echocardiographic cardiac function and adverse events between treatment and control group.

Authors' conclusions

For the effect of enalapril in childhood cancer survivors with asymptomatic cardiac dysfunction, only one RCT is available. Although there is some evidence that enalapril temporarily improves one parameter of cardiac function (LVESWS), it is unclear whether it improves clinical outcomes. Enalapril was associated with a higher risk of dizziness or hypotension and fatigue. Clinicians should weigh the possible benefits with the known side-effects of enalapril in childhood cancer survivors with asymptomatic anthracycline-induced cardiotoxicity.

For the effect of phosphocreatine in childhood cancer patients with anthracycline-induced cardiotoxicity, only one RCT is available. Limited data with a high risk of bias showed no significant difference between phosphocreatine and control treatment on echocardiographic function and clinical outcomes.

We did not identify any RCTs or CCTs studying other medical interventions for symptomatic or asymptomatic cardiotoxicity in childhood cancer patients or survivors.

High-quality studies should be performed.

PLAIN LANGUAGE SUMMARY

Treatment for cardiac problems caused by anthracycline chemotherapy for childhood cancer

Anthracyclines are anti-cancer drugs that are used in the treatment of different types of childhood cancer. An important adverse effect of anthracyclines is damage to the heart that can lead to asymptomatic (without complaints) or symptomatic (with complaints) cardiac problems during and after cancer treatment. There are several drugs available to treat other types of cardiac problems in adults, but it is not known if these drugs are beneficial in treating cardiac problems caused by anthracyclines in childhood cancer patients and survivors. If a physician is confronted with a childhood cancer patient or survivor with anthracycline-induced cardiac problems, he or she should be able to make an informed decision to treat this patient based on high-quality evidence about the beneficial and adverse effects of the treatment options. We searched for and summarised studies that evaluated drugs for treating anthracycline-induced cardiac problems in childhood cancer patients and survivors.

We identified two randomised studies evaluating two different drugs in two different types of patients. One of these drugs, an ACE-inhibitor (enalapril), had a short-term beneficial effect on heart function in survivors of childhood cancer with asymptomatic cardiac problems caused by anthracyclines compared with placebo. However, the drug had no significant beneficial effect on other important outcomes and was associated with side effects such as dizziness and fatigue. This study was of reasonable/good quality. The other study was of low quality and found no effect of a short treatment with phosphocreatine in childhood leukaemia patients with symptomatic or asymptomatic cardiac problems compared with a control treatment with vitamin C, ATP, vitamin E, and oral coenzyme Q10.

No definitive conclusions can be made about treatment options for anthracycline-induced cardiac problems in childhood cancer patients and survivors. High-quality studies are necessary to show if there are drugs that improve heart function in these patients.

BACKGROUND

Description of the condition

Anthracyclines are frequently used chemotherapeutics for childhood cancer that can cause serious cardiac dysfunction (Lefrak 1973; Von Hoff 1977). This so-called anthracycline-induced cardiotoxicity can develop during, or many years after, treatment and may present clinically, with symptoms of heart failure, or subclinically, with abnormalities found only in diagnostic tests (Ganame 2007; Lipshultz 1991; Van Dalen 2006a). It is estimated that almost 10% of childhood cancer patients treated with anthracycline doses of 300 mg/m² or more will eventually develop symptomatic cardiotoxicity, a condition that is associated with high morbidity and mortality (Steinherz 1995; Van Dalen 2006a). Asymptomatic signs of cardiotoxicity are found in up to 57% of survivors of childhood cancer and are often progressive over time, but the long-term prognosis of these abnormalities is not known (Kremer 2002; Lipshultz 2005a; Sorensen 2003). In the general adult population individuals with asymptomatic cardiac dysfunction are at increased risk of developing symptomatic heart failure and death (Wang 2003). These findings raise the concern that children and young adults with asymptomatic cardiac dysfunction caused by anthracyclines are also at risk of progression to symptomatic heart failure in the long term.

Description of the intervention

Several cardiovascular drugs have been studied in patients with cardiac dysfunction due to other causes. Studies in adult patients with symptomatic as well as asymptomatic heart failure due to causes other than anthracyclines have shown that treatment with an average treatment duration of three years with angiotensin-converting enzyme (ACE) inhibitors reduces long-term morbidity and mortality, regardless of the aetiology of heart failure (Abdulla 2006; Garg 1995; Jong 2003; SOLVD 1991; SOLVD 1992). The SOLVD studies also showed an improvement in quality of life in symptomatic patients and no negative effect in quality of life in asymptomatic patients (Rogers 1994; SOLVD 1991; SOLVD 1992). A cost-effectiveness study was done in symptomatic SOLVD patients and showed survival benefit as well as cost savings (Glick 1995). Treatment with beta-blocking agents in addition to an ACE-inhibitors improves the outcome in patients with symptomatic cardiac failure (CIBIS-II 1999; Foody 2002; Packer 1996a; Packer 1996b; Waagstein 1993) and improves cardiac function in asymptomatic heart failure patients (Colucci 2007; Exner 1999). Other medical interventions also have the potential to improve prognosis in patients with symptomatic or asymptomatic heart failure, such as angiotensin receptor blockers (Granger 2003; Maggioni 2002) or combinations of heart failure medication such as angiotensin receptor blockers, ACE-inhibitors and beta-blockers (Cohn 2001; McMurray 2003).

Why it is important to do this review

Many collaborative groups have advocated screening for cardiac dysfunction in childhood cancer patients and survivors (COG 2006; SIGN 2004; Skinner 2005; Steinherz 1992). However, for appropriate screening for a disease, an effective treatment should be available (Wilson 1968). In addition, physicians who are confronted with childhood cancer patients and survivors with cardiac dysfunction should be able to make a well-informed decision regarding the risks and benefits of treatment options. Currently the optimal treatment for patients with anthracycline-induced cardiotoxicity, and how to decrease morbidity and mortality, is unclear (Lipshultz 2002; Silber 2004; Van Dalen 2003). Although medical interventions in populations with symptomatic and asymptomatic heart failure due to causes other than anthracyclines are beneficial, we cannot assume that the efficacy of this treatment is similar in childhood cancer patients and survivors (Kay 2001; Shaddy 2007). The different aetiology of the cardiac dysfunction as well as the different age distribution make it necessary to study the benefits and risks of treatment of symptomatic and asymptomatic anthracycline-induced cardiotoxicity in this specific population. Treatment of patients with anthracycline-induced cardiotoxicity should ideally decrease morbidity and mortality, improve cardiac function, reverse disease progression and improve quality of life.

This systematic review evaluated the current available evidence on medical interventions in both symptomatic and asymptomatic anthracycline-induced cardiotoxicity during and after treatment for childhood cancer.

OBJECTIVES

To compare the effect of medical interventions in childhood cancer patients or survivors with anthracycline-induced cardiotoxicity with the effect of placebo, other medical interventions or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and controlled clinical trials (CCTs) (as defined by the *Cochrane Handbook for Systematic*

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Reviews of Interventions (Higgins 2008)), including non-inferiority and cross-over trials, comparing a medical intervention for treating anthracycline-induced cardiotoxicity with either placebo, other medical intervention(s) or no treatment.

Types of participants

Patients and survivors (previously) diagnosed with any type of childhood cancer (defined as a diagnosis of cancer at age 18 years or younger) and with symptomatic or asymptomatic anthracycline-induced cardiotoxicity. RCTs or CCTs including both children and adults were only eligible for inclusion in this review if the majority of participants were 18 years or younger at cancer diagnosis. Anthracycline-induced cardiotoxicity, as defined by the authors of the original study, could be diagnosed both during and after anthracycline treatment for childhood cancer. Due to the low number of patients expected, we did not exclude patients who also had been treated with mediastinal radiotherapy.

Types of interventions

Medical (i.e. drug) interventions given with the intention to change the course of anthracycline-induced symptomatic or asymptomatic cardiotoxicity. We excluded surgical interventions such as heart transplantation.

Types of outcome measures

Primary outcomes

- Overall survival.
- Mortality due to heart failure.
- Development of clinical heart failure as defined by authors.
- Occurrence of adverse events and tolerability as defined by authors.

Secondary outcomes

- Change in cardiac function measured by different diagnostic tests as defined by authors.
- (Duration of) hospitalisation for heart failure.
- Change in NYHA (New York Heart Association) stage of heart failure (NYHA 1994).
- Change in quality of life as defined by author.
- Costs as defined by authors.

Outcomes may have been assessed at any time during follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2011, issue 1), MEDLINE/PubMed (1949 to 26 May 2011) and EMBASE/Ovid (1980 to 26 May 2011) for potentially relevant articles.

We scanned the ISRCTN Register, the National Institute of Health (NIH) Register and the trials register of the World Health organization (WHO) in May 2010 for ongoing trials (http://www.controlled-trials.com and http://apps.who.int/trialsearch/). There were no language restrictions. All electronic searches have been developed in co-operation with the Trials Search Co-ordinator of the Cochrane Childhood Cancer Group.

The search strategy for PubMed is shown in Appendix 1. We used the highly sensitive search strategy for identifying reports of RCTs and CCTs (sensitivity-maximizing version) as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008).

For EMBASE and CENTRAL we used adaptations of the same search strategy (see Appendix 2, Appendix 3).

Searching other resources

We located information about trials not registered in MEDLINE/PubMed, EMBASE/Ovid or CENTRAL, either published or unpublished, by searching the reference lists of relevant articles and review articles. In addition, we handsearched conference proceedings from 2005 to 2009 of the International Society for Paediatric Oncology (SIOP), the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), the International Conference on Long-Term Complications of Treatment of Children & Adolescents for Cancer and the European Symposium on Late Complications from Childhood Cancer. Again, there were no language restrictions.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, two review authors independently identified studies meeting the criteria for this review. We obtained in full any study which seemed to meet the inclusion criteria on the grounds of the title, abstract or both for closer inspection. Based on full text assessment, the review authors included or excluded studies for this review. Two of the studies that we selected for full text evaluation were not in a language the authors were familiar with. For these, we contacted Cochrane collaborators from Russia and China, who individually determined if the studies were eligible. We recorded the reasons for exclusion of any study considered for the review. We resolved discrepancies in the selection process between authors by consensus. In case of doubt, we consulted a third-party arbitrator for final resolution.

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One review author performed the search in reference lists of relevant articles and review articles as well as the search within the conference proceedings.

Data extraction and management

One review author performed data extraction using standardised forms and these were checked by a second review author. For the study that was published in Chinese, this was done by a review author from China based on full text and checked by another review author based on the abstract only. We abstracted information on the following items:

1. study design;
2. risk of bias items;
3. number of study patients;
4. participants, including:
    i) age at diagnosis;
    ii) age at study entry;
    iii) sex;
    iv) time since diagnosis;
    v) study performed during cancer treatment or in survivors;
    vi) in case of survivors, time since end of cancer treatment;
    vii) prior anthracycline treatment, including:
        a) type of anthracycline;
        b) cumulative anthracycline dose;
    viii) other previous treatment, including:
        a) chemotherapy;
        b) cardioprotective interventions;
        c) radiotherapy on heart region;
    ix) co-morbidities, including:
        a) cardiovascular disease (specification disease, cause and duration of disease before start of intervention);
        b) other (specification disease, cause and duration of disease before start of intervention);
    x) other treatment, including:
        a) other cardiovascular medication (agent, dose, frequency, mode of administration and duration);
        b) other medication (agent, dose, frequency, mode of administration and duration);
        c) cardiovascular surgery (location and procedure);
5. interventions, including:
    i) type of medical intervention (substance name, brand name);
    ii) dose and frequency of medical intervention;
    iii) mode of administration (oral, intravenous etc.);
    iv) duration of medical intervention;
    v) duration between diagnosis of anthracycline-induced cardiotoxicity and start of medical intervention;
6. outcome measures, including:
    i) outcome definition;
    ii) timing of outcome measurement;
7. length of follow-up.

In cases of disagreement, we re-examined the abstracts and articles and discussed the topic until consensus was achieved. No third-party arbitration was needed.

Assessment of risk of bias in included studies

One review author assessed the risk of bias using a standardised form and this was checked by another review author. The study that was published in Chinese was assessed by a review author from China based on full text and checked by another review author based on the (English) abstract only. We evaluated the studies according to the following criteria: generation of allocation sequence, concealment of treatment allocation, blinding of the study participants, blinding of personnel, blinding of outcome assessors, completeness of follow-up, intention-to-treat (ITT) analysis, selective outcome reporting and other sources of bias. We determined the items blinding of outcome assessors, completeness of follow-up and ITT analysis for all reported study outcomes. Only for overall survival, we regarded blinding of the outcome assessor not relevant. For all risk of bias items, we used definitions based on the module of the Cochrane Childhood Cancer Group at the time our protocol was published (Module CCG) and on the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008) (see additional Table 1). We resolved discrepancies between authors by consensus. In case of doubt, we consulted a third-party arbitrator.

Measures of treatment effect

We related dichotomous outcomes to risk using the risk ratio (RR) and presented all results with the corresponding 95% confidence interval (CI). When only one study was available and there were no events in one of the treatment groups, it was not appropriate to calculate the RR, its 95% CI and the corresponding P value. For these outcomes, we calculated the Fischer's exact P value instead, using PASW Statistics (SPSS) for Windows version 18 (SPSS Inc, Chicago, IL). We planned to analyse continuous outcomes using the mean difference (MD). However, this was not possible since no standard deviation (SD) of change in the continuous outcomes were provided by the included studies. For the assessment of survival, we planned to use Parmar's method if hazard ratio's had not been explicitly presented in the study (Parmar 1998). This was not applicable, since we could not pool the included studies.

Dealing with missing data

When information relevant to study selection was missing, we attempted to contact the authors in order to obtain the missing data.

We extracted data by allocation intervention, irrespective of compliance with the allocated intervention, in order to allow an ITT analysis. If this was not possible, we stated this and performed an as-treated analysis.

Assessment of heterogeneity

Assessing heterogeneity was not applicable, since we did not pool the included studies.

Assessment of reporting biases

We were not able to construct a funnel plot to evaluate the existence of publication bias graphically (Higgins 2008), since only two trials could be included in this review and pooling of results was not possible. As a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis. When there are fewer studies, the power of the tests is too low to distinguish chance from real asymmetry (Higgins 2008).

Data synthesis

We entered the data into RevMan 5.0 (RevMan 2008) and analysed according to the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). We used a random-effects model for the estimation of treatment effects throughout the review.

We included outcome measures in this systematic review only if it was the intention of the study authors to perform the necessary assessments in all randomised patients (i.e. not optional or only performed in some centres). When less than 50% of the patients in a study had an acceptable follow-up for a particular outcome measure, due to the associated high risk of attrition bias we did not report the results of this outcome measure.

We did not perform a pooled analysis since the included trials were not comparable with regard to important study characteristics, i.e. age, sex, cardiac dysfunction, treatment, used different outcome definitions and length of follow-up. We therefore summarised the results descriptively.

We planned to analyse data separately for clinical heart failure alone versus no clinical heart failure and for clinical and subclinical cardiotoxicity combined versus normal heart function. However, this was not applicable, since pooling was not possible and the study that included both patients with clinical and subclinical heart failure did not provide enough information to allow for such an analysis.

Subgroup analysis and investigation of heterogeneity

We hypothesised that treatment with mediastinal radiotherapy may cause other cardiac pathology, such as heart valve problems and that it is therefore possible that treatment effects would differ between patients treated with and without mediastinal radiotherapy. However, we were not able to investigate this type of heterogeneity by performing a subgroup analysis with regard to previous mediastinal radiotherapy, because pooling was not possible and because the individual studies did not provide outcomes separately for patients treated with and without previous radiotherapy.

Sensitivity analysis

Since results could not be pooled, performing a sensitivity analysis using the risk of bias criteria was not applicable.

RESULTS

Description of studies

Results of the search

Our searches in the electronic databases of MEDLINE/PubMed, EMBASE/Ovid and CENTRAL identified 1429 titles with or without an abstract (Figure 1). Of these, we selected eight references reporting on five studies for full text assessment. The remaining 1421 papers were not included because they were not RCTs or CCTs, were a laboratory study, an animal study, did not include children with cancer or survivors of childhood cancer or were preventive intervention studies of patients without signs of cardiotoxicity. While going through the reference lists of relevant papers, we additionally found five papers, reporting on two studies (of which one was already identified in the electronic database search), which we also assessed in full text. In total, we assessed the full text of 13 papers reporting on six studies.

Figure 1.   Flow diagram.
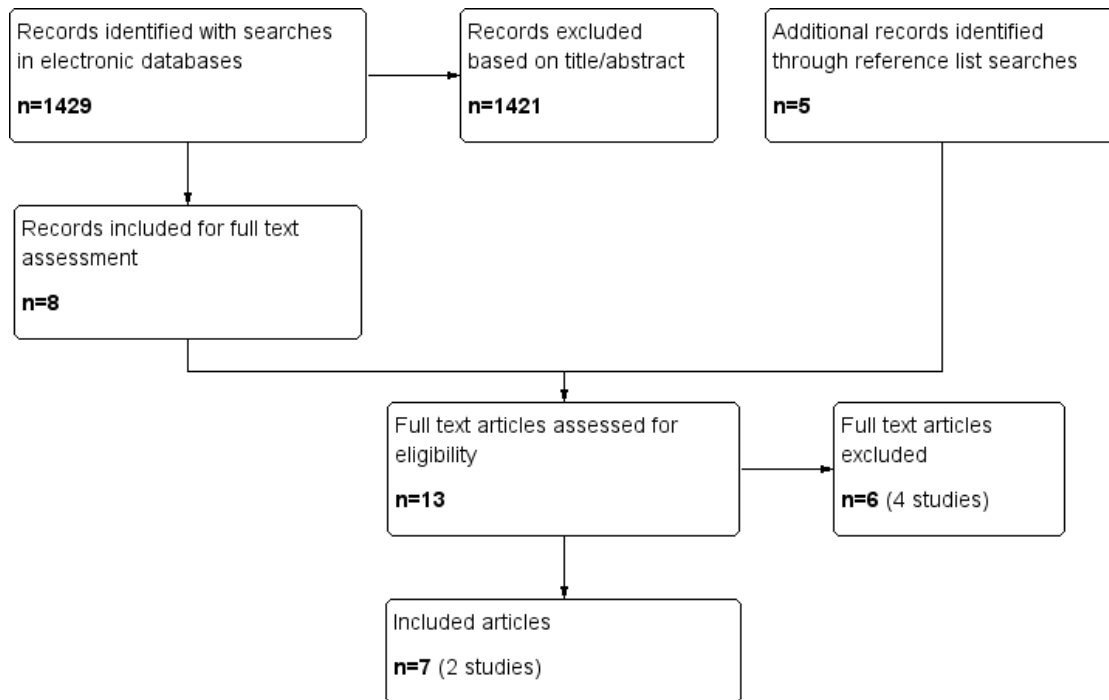
Based on full text assessment, we finally included in this review seven papers reporting on two studies. We excluded six papers reporting on four studies. Reasons for exclusion are listed in the Characteristics of excluded studies table.

By scanning the conference proceedings of the relevant conferences, we identified two papers that have not been published yet in full text and are awaiting further assessment (see the table Characteristics of studies awaiting classification). By scanning the ongoing trials databases we identified one additional ongoing trial (see the table Characteristics of ongoing studies).

Included studies

In summary, the total number of included RCTs was two (Chen 2008, Silber 2004). Six papers provided information on one trial (see all references under Silber 2004). We extracted information about the study from all six papers.

The total number of patients included in the two RCTs was 203. In one trial, 69 patients received enalapril and 66 patients received placebo (Silber 2004). Patients were childhood cancer survivors with asymptomatic decline of cardiac function at some time during follow-up after anthracycline exposure. Follow-up time was a median of 2.80 (range 2 weeks to 6.1) years.

In the other trial, 35 patients received phosphocreatine and 33 patients received a control treatment with vitamin C, adenosine tri-phosphate (ATP), vitamin E, and oral coenzyme Q10 (Chen

2008). Patients were children with acute leukaemia and anthracycline-induced cardiotoxicity, of which part was symptomatic. The duration of treatment was 14 days and assessment of cardiac function was done one day after the end of treatment, but it is unclear if there was longer follow-up, for example for the clinical outcomes.

For more information see the Characteristics of included studies table.

Excluded studies

In total, the number of excluded papers based on full text evaluation was six, reporting on five studies. The table Characteristics of excluded studies summarises the excluded studies.

Risk of bias in included studies

The evaluation of the risk of bias in the included studies is summarised below. An additional overview of the exact scores per included study is provided in the table Characteristics of included studies ('Risk of bias' section).

Allocation

In the *enalapril* study, allocation to treatment or control group was at random. For the allocation sequence random permuted blocks with equal allocation were used within each stratum of pre-specified variables (Silber 2004). Allocation was described to be concealed, but the method of allocation concealment was not stated and was therefore unclear.

In the *phosphocreatine* study allocation to treatment or control group was also at random, but the method used to generate the allocation sequence was not described (Chen 2008). It was not stated if there was allocation concealment.

Blinding

The *enalapril* trial reported to be a double-blind study (Silber 2004). Although it was not clearly stated how the blinding was done, in one of the additional papers regarding the trial, it is said that patients truly did not know which of the two treatments they had received (Silber 2004), indicating that blinding of patients was effective. It was also clearly stated that investigators were blinded to the intervention. However, it was not specified if the blinding of investigators regarded personnel as well as outcome assessors, if it was applicable to all studied outcomes, and if it was effective. Based on the effectiveness of blinding of the patients and the statement that patients and investigators were blinded, we judged that this probably was the case. We consulted a third party for this judgement, who agreed with it.

In the *phosphocreatine* trial blinding was not described and based on the different types of route of administration per treatment and control group, we judged that blinding of patients and personnel was very unlikely (Chen 2008). It was not stated if the investigators or outcome assessors were blinded and therefore we judged it unclear.

Incomplete outcome data

In the *enalapril* trial, follow-up was complete for overall survival, mortality due to heart failure and the development of clinical heart failure (Silber 2004). There was complete follow-up for change in cardiac function for the study outcomes maximal cardiac index (MCI) and left ventricular end-systolic wall stress (LVESWS), which were both measured in at least one post-baseline measurement in more than 80% of the patients. However, it should be noted that it was unclear if follow-up was complete for these parameters at the end of follow-up. For other measures of cardiac function (shortening fraction (SF) and stress-velocity index (SVI)) and the other outcomes that were reported (occurrence of adverse events and change in quality of life), it was unclear if the there was complete follow-up. In one of the additional papers about this trial it was stated that a considerable fraction of the study participants ended participation, but not what the exact numbers and timing of study dropouts were (Silber 2004). It was clearly stated that for the trial's primary and secondary outcomes ITT analysis

was performed. An extra per-protocol analysis was performed on LVESWS. For the other measures of cardiac function (SF and SVI) it was unclear if an ITT analysis was done. For overall survival, mortality due to heart failure and development of clinical heart failure, change in quality of life and occurrence of adverse events, ITT analysis was possible, since the treatment allocation was abstractable for the reported outcomes.

In the *phosphocreatine* trial, complete assessment was done for overall survival, mortality due to heart failure and the occurrence of adverse events (Chen 2008). For change in cardiac function, two parameters (echocardiography and hyper sensitivity C-reactive protein (hsCRP)) were reported in all patients, while for the other parameters of change in cardiac function outcomes (electrocardiogram (ECG), creatine kinase (CK), creatine kinase MB (CK-MB), lactate dehydrogenase (LDH1) and alpha hydroxybutyrate dehydrogenase (alphaHBDH)), were only assessed in some of the patients and therefore not reported in this review. For overall survival, mortality due to heart failure, two parameters of change in cardiac function (echocardiography and hsCRP) and the occurrence of adverse events, ITT analysis was possible, since the treatment allocation was abstractable for all reported outcomes.

Selective reporting

There was no sign of selective reporting in the *enalapril* trial (Silber 2004). A protocol was published that presented the outcomes that were planned to be studied as well as the planned data-analyses (Silber 2004). All outcomes were reported and the analyses done in the final report (Silber 2004). The authors clearly explained that they performed some additional analyses based on exploration of the data.

In the *phosphocreatine* trial, there was no published protocol and we therefore can not exclude selective reporting bias in the study (Chen 2008).

Other potential sources of bias

In the *enalapril* trial, we were not aware of other potential problems that could put the study at a high risk of bias (Silber 2004).

In the *phosphocreatine* study, we had concerns about the comparability of the study participants especially with regard to potential confounders such as gender, age, cumulative anthracycline dose, type of anthracycline, other cardiotoxic treatment, number of symptomatic patients and the provision of other treatments during the study (Chen 2008).

Effects of interventions

Both trials did not allow data extraction for all endpoints. See the table Characteristics of included studies for a more detailed description of the extractable endpoints of each study.

Overall survival and mortality due to heart failure

We could extract data on overall survival and mortality due to heart failure from both studies.

In the *enalapril trial*, there were no deaths in both the intervention and the control group during the study (Silber 2004). However, one patient from the placebo group (1.5%) died eight months after the end of the study, as a result of congestive heart failure. Because it was unclear if both the intervention group and placebo group had been followed longer than the end of the study, we did not calculate an RR of death due to heart failure including this late death.

In the *phosphocreatine* trial, there were no deaths in both the intervention and the control group during the study (Chen 2008).

Development of clinical heart failure (as defined by authors)

The *enalapril* trial provided data on the occurrence of clinical heart failure, which the authors pre-defined as a clinically significant decline in cardiac performance (Silber 2004). In the intervention group, one patient (1%) developed such a significant decline, while in the control group this occurred in six (9%) patients (RR = 0.16, 95% CI 0.02 to 1.29, P = 0.09). See also Analysis 1.1 and Figure 2.

Figure 2. Forest plot of comparison: 1 Enalapril versus placebo, outcome: 1.1 Development of clinical heart failure.
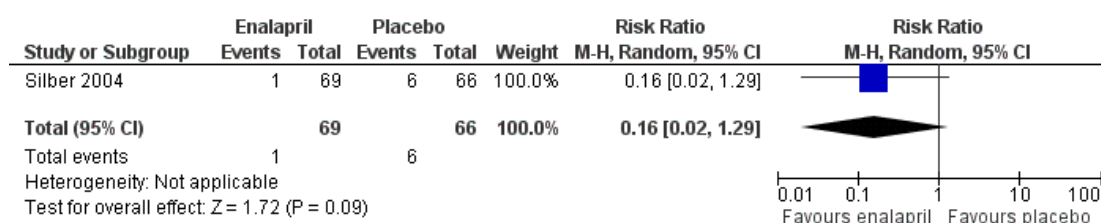
Occurrence of adverse events and tolerability (as defined by authors)

Both studies reported on the occurrence of adverse events. Severity or grading was not reported in either study.

In the *enalapril* trial, all patients were evaluated on the occurrence of adverse events (Silber 2004). The number of adverse events in patients was presented per adverse event and many events were recorded (see Analysis 1.2 until Analysis 1.13 for RRs and corresponding 95% CI, and Table 2 for Fischer's exact P values in outcomes with no event in one of the two groups). A notable difference in adverse events between groups was the higher occurrence of dizziness or hypotension (RR 7.17, 95% CI 1.71 to 30.17, P = 0.007; Analysis 1.2, Figure 3) and fatigue (Fisher's exact test, P = 0.013, Table 2) in the enalapril group. Other reported adverse events were not statistically different between groups (Analysis 1.3 until Analysis 1.13, and Table 2).

Figure 3. Forest plot of comparison: 1 Enalapril versus placebo, outcome: 1.2 Dizziness or hypotension.

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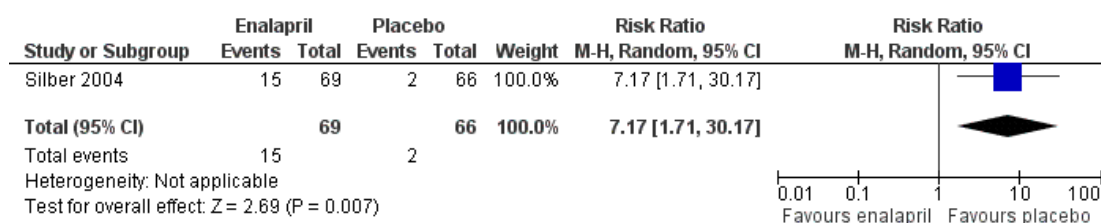
In the *phosphocreatine* trial, all patients were also evaluated for adverse events (Chen 2008). It was not stated what type of adverse events were assessed. No adverse events were found in the patients of either the phosphocreatine group or the control group during the trial.

Change in cardiac function measured by a diagnostic test

Both studies provided several measures of change in cardiac function in treatment and control groups.

The *enalapril* trial presented their results in unadjusted and adjusted linear mixed models of the change over time of maximal cardiac index (MCI), left ventricular end-systolic wall stress (LVESWS), stress-velocity index (SVI) and shortening fraction (SF) (Silber 2004). Since the authors did not present dichotomous outcomes, we were not able to calculate RRs and we therefore describe the outcomes as presented in the original study (reported as ITT analyses). All analyses were adjusted for anthracycline dose, age at diagnosis, follow-up time, gender and cardiac irradiation. No differences were detected in the rate of change of all outcome parameters between intervention and control group (adjusted model coefficient and P value of effect of enalapril: MCI 0.17, P = 0.36; LVESWS -1.41, P = 0.24; SVI 0.004, P = 0.68; SF 0.07, P = 0.81). After the data became available, the authors of the study explored the data and subsequently performed a piecewise linear model on LVESWS. In this per-protocol analysis (adjusted for the same covariates) they found that enalapril caused a decrease (i.e. improvement) in LVESWS (-8.62 g/cm² change) compared with placebo (+1.66g/cm² change) in the first year of treatment (P = 0.036). After the first year, there was no statistically significant difference in LVESWS change between enalapril and placebo group (-0.30 versus +0.49 g/cm², P = 0.56).

In the *phosphocreatine* trial, complete baseline and outcome parameters were provided for echocardiographic cardiac function and the cardiac marker hsCRP (Chen 2008). All patients had normal echocardiograms before and at the end of treatment (not further specified). In the phosphocreatine group, mean (SD) baseline levels of hsCRP was 8.79 (1.36) mg/L compared with 7.88 (2.08) mg/L in the control group, while post treatment levels were 2.23 (0.82) mg/L in the phosphocreatine group compared with 4.2 (1.52) mg/L in the control group. Since the SDs of the difference before and after treatment within each group were not provided, we could not estimate the MD. It is therefore unclear if the change in hsCRP was significantly different between treatment groups. For the cardiac enzymes CK, CK-MB, LDH1 and alphaHBDH, only post treatment levels were provided and are therefore not presented in this review. For the outcomes ECG, troponin I and the combined outcome of all cardiac enzymes together (hsCRP, CK, CK-MB, LDH1, alphaHBDH, troponin I) numbers of patients with normal or abnormal outcomes after the intervention were only provided for those patients with abnormal values at baseline. Since these outcomes were only assessed in a specific subgroup of the studied cohort, we did not present them in this review.

(Duration of) hospitalisation for heart failure

None of the studies provided outcome data on the (duration of) hospitalisation for heart failure.

Change in NYHA stage for heart failure

None of the studies provided change in NYHA stage for heart failure as an outcome parameter.

The *phosphocreatine* trial did provide change in symptoms after the intervention of the patients with symptoms at baseline (Chen 2008). However, since this outcome was reported in less than 50% of the patients, we did not present them in this review.

Change in quality of life (as defined by authors)

The *enalapril* study provided some information on quality of life (Silber 2004). There were no differences between groups on any of the dimensions of the Short-Form 36 General Health Survey or the Childhood Health Questionnaire-85. No further information was provided.

Costs as defined by authors

None of the included studies provided outcome data on costs.

DISCUSSION

As a result of survival rates of childhood cancer patients now approximating 75%, there is a steadily growing group of young childhood cancer survivors who are confronted with asymptomatic or even symptomatic anthracycline-induced cardiac dysfunction. Many collaborative groups have advocated screening for cardiac dysfunction in childhood cancer patients and survivors (COG 2006, SIGN 2004, Skinner 2005). However, for appropriate screening for a disease, an effective treatment should be available (Wilson 1968). In addition, physicians who are confronted with childhood cancer patients and survivors with cardiac dysfunction should be able to make a well-informed decision regarding the risks and benefits of treatment options. Although ACE-inhibitors and beta-blockers in adult populations with symptomatic and asymptomatic cardiac dysfunction due to other causes improve subclinical and clinical outcomes (Abdulla 2006; CIBIS-II 1999; Foody 2002; Garg 1995; Jong 2003; Packer 1996a; Packer 1996b; SOLVD 1991; Waagstein 1993), the different aetiology makes it difficult to extrapolate these beneficial effects to childhood cancer patients and survivors with anthracycline-induced cardiotoxicity. This is the first systematic review summarising all evidence on

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medical interventions for anthracycline-induced cardiotoxicity in childhood cancer patients and survivors.

For a reliable evaluation of the effects of medical interventions for the treatment of anthracycline-induced cardiotoxicity, the best study design is an RCT in which the only difference between the intervention and control group is the use of the medical intervention. However, because of the relative rareness of childhood cancer and therefore of survivors with cardiac dysfunction, we expected low number of studies and therefore decided that both RCTs and CCTs were eligible for this review, keeping in mind the limitations of CCTs.

We identified two eligible RCTs investigating different medical interventions in different study populations and with different lengths of follow-up. Since for both medical interventions only one study was available, no definitive conclusions about their effects on anthracycline-induced cardiotoxicity can be made. One RCT on *enalapril* (Silber 2004) in childhood cancer survivors with asymptomatic anthracycline-induced cardiotoxicity showed no significant effect of enalapril on overall survival, mortality due to heart failure, development of clinical heart failure and quality of life compared with placebo. Only a post-hoc, per-protocol analysis of the study investigators themselves showed an improvement in a measure of cardiac function (LVESWS) in the enalapril group compared with the placebo group in the first year of treatment. No effect was found after one year nor in other echocardiographic parameters of cardiac function over time. Patients treated with enalapril had a higher risk of dizziness or hypotension and fatigue. No conclusions can be made about the effect of enalapril on (duration) of hospitalisation, change in NYHA stage of heart failure and costs, since these outcomes were not studied. The other RCT on *phosphocreatine* (Chen 2008) in children with acute leukaemia and symptomatic or asymptomatic anthracycline-induced cardiotoxicity showed no significant differences in overall survival, mortality due to heart failure, echocardiographic cardiac function and adverse events compared with a control treatment with vitamin C, ATP, vitamin E, and oral coenzyme Q10 (in all outcomes no events/abnormalities in both groups). The effect of the intervention on one marker (hsCRP) was unclear. The study did not report on development of clinical heart failure, (duration of) hospitalisation for heart failure, change in NYHA stage for heart failure or costs. Therefore, no conclusions can be drawn for these outcomes.

It should be noted that reasons for not finding significant beneficial effects in the *enalapril* trial (Silber 2004), could be due to the low number of patients (i.e. low power), and potentially patient compliance and loss-to-follow-up. Also, the fact that there was a low threshold for patients to be classified as having anthracycline-induced cardiotoxicity could have influenced the identified effects of treatment. Patients with minor and sometimes temporary abnormalities were included, in which large benefits of the intervention were unlikely. In the so-called SOLVD trial on enalapril in adults with asymptomatic cardiac dysfunction due to other causes

than anthracyclines (SOLVD 1992), a clear benefit of enalapril was found on the occurrence of clinical heart failure. This trial had a much larger sample size (4228 patients) and used a more strict definition to classify patients as having cardiac dysfunction (i.e. a left ventricular ejection fraction (LVEF) of 35% or less). The *enalapril trial* had a relatively short length of follow-up (median 2.80 years). It is therefore unknown if there is a beneficial effect of enalapril on the longer term. In comparison, a follow-up study (Jong 2003) of the earlier mentioned SOLVD trial (SOLVD 1992), showed beneficial effects of enalapril treatment on mortality during a 12-year follow-up. In the *phosphocreatine* trial (Chen 2008), reasons for not identifying significant effects of the intervention could also be the low power and the very short duration of treatment and presumably also maximum follow-up (i.e. 14 days). Also, the most optimal dosage schedule of phosphocreatine is currently unknown. Suboptimal dosages of study treatment could have led to the fact that no differences between treatment groups were found.

The *enalapril* study (Silber 2004) had a low/moderate risk of bias. There was a low/moderate risk of selection bias, performance bias and detection bias. For most outcomes there was a low risk of attrition bias, but for some outcomes (the post-hoc analysis of LVESWS, other parameters of cardiac function (SF and SVI), the change in quality of life and the risk of adverse events) ITT analysis was not possible or it was unclear if follow-up was complete, leading to a possible risk of attrition bias for these other outcomes. There were no other risks of bias, nor unexpected outcomes or inconsistencies in the data. The *phosphocreatine* study (Chen 2008) had a high risk of bias. We concluded there was a high risk of selection bias, performance and detection bias. There was no sign of attrition bias. There was a risk of reporting bias and we had concerns about the comparability of the two groups. We found no unexpected outcomes or other inconsistencies in the data.

The external validity of a study indicates how well the results of the study can be generalised to individual patients with anthracycline-induced cardiotoxicity during and after treatment for childhood cancer. Although we did not systematically assess this in this review, we regarded the external validity of the *enalapril* trial (Silber 2004) as reasonable. Patient characteristics were well-defined and the study population seemed to be a representative sample of childhood cancer survivors who can present with asymptomatic cardiotoxicity during follow-up. However, it should be noted that a large proportion of patients had been treated previously with cardiac radiotherapy. It is not unlikely that the pathophysiology, course and response to treatment of cardiac dysfunction that is induced by both anthracyclines and radiotherapy is different from cardiac dysfunction caused by anthracyclines only. Also other study characteristics could have influenced the effects of treatment. An observational study in adults with anthracycline-induced cardiotoxicity (Cardinale 2010) suggested that time between the end of anthracycline treatment and start of heart failure

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treatment (including at least enalapril) influenced the chance of response to ACE-inhibitors, with a longer follow-up time associated with a lower chance of a beneficial effect. Another issue regarding the generalisability of the *enalapril* trial is that the diagnostic tools to determine cardiotoxicity that were used in this study are not easily used in daily practice. Especially equipment and expertise to determine MCI, LVESWS and SVI may not be widely available in the follow-up settings of childhood cancer survivors. As previously mentioned, the duration of follow-up precludes extrapolation to follow-up longer than three years. Finally, clear outcome definitions were provided, making it easy to extrapolate the study outcomes to daily practice. The *phosphocreatine* trial (Chen 2008) was less well generalisable to daily practice. Not all patient characteristics were described, including age and gender of the control group, time since leukaemia diagnosis and information on (previous) cardiotoxic cancer treatment. No clear definitions (i.e. cut-off values of abnormal diagnostic tests) of cardiotoxicity were provided. No patient had an abnormal echocardiogram, and since most research on anthracycline-induced cardiotoxicity as well as guidelines on detection of cardiotoxicity include echocardiographic examination of childhood cancer patients and survivors, we feel that the study group is not very representative with regard to cardiotoxicity (COG 2006; SIGN 2004; Skinner 2005; Steinherz 1992; Van Dalen 2006b). In addition, phosphocreatine is an experimental therapy and not a registered agent at the European Medicines Agency (EMA) or Food and Drug Administration (FDA). Both the intervention and the control treatments are not common practice in most countries. Treatment duration and outcome assessment of cardiac function in this trial were only two weeks, so we only know the immediate effects of the intervention studied and not any long-term benefits or harms. Based on these arguments, we feel that the outcomes of the *phosphocreatine* trial (Chen 2008) can hardly be extrapolated to daily clinical practice and care for childhood cancer patients.

There is no evidence from RCTs or CCTs available for other medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer (for a complete list of evaluated interventions, see the search strategy in the appendices (Appendix 1, Appendix 2, Appendix 3).

Please note that in this review RCTs and CCTs were only eligible for inclusion when the patients (previously) had a type of childhood cancer (defined as a diagnosis of cancer at age 18 years or younger). RCTs or CCTs including both children and adults were only eligible for inclusion in this review if the majority of participants were 18 years or younger at cancer diagnosis. It is possible that there are RCTs or CCTs in adults that evaluate the effects of medical interventions on anthracycline-induced cardiotoxicity in cancer patients or survivors. Although we did not systematically search for them, we are not aware that studies in survivors of adult cancers exist, apart from non-controlled observational stud-

ies (Cardinale 2010; Jensen 1996; Jensen 2002). One of these studies evaluated ACE-inhibitor (with or without a beta-blocker) treatment in all study participants (Cardinale 2010). This study was a prospective cohort study with a mean follow-up of 36 months in 201 adults with symptomatic and asymptomatic cardiac dysfunction after anthracycline therapy, who were all treated with at least an ACE-inhibitor as soon as cardiac impairment was noted. The study showed a (pre-specified) response of cardiac function in 42%, a partial response in 13% and no response in 45% of the study group. Responders had fewer cardiac events and a relationship was found between the duration of cardiac dysfunction and the probability to respond to the therapy. The authors did not report if side-effects occurred. It was concluded that beneficial effects of modern heart failure treatment are expected when treatment is started early after the detection of anthracycline-induced cardiotoxicity. It should be noted that it is not always appropriate to extrapolate adult cancer (survivor) studies to childhood cancer (survivor) studies. Other age ranges, pharmacokinetics, pharmacodynamics as well as comorbidities and co-treatments may influence the effect of interventions for cardiotoxicity as well as the generalisability of studies to the clinical care of childhood cancer patients and survivors. Similarly, RCTs in other childhood populations are also difficult to generalise to childhood cancer patients and survivors. For example, in an RCT of the beta-blocker carvedilol in children with symptomatic heart failure (Shaddy 2007), almost 40% of the study population had symptomatic heart failure due to congenital heart disease, with often a very different anatomy of the heart.

Even though RCTs provide the highest levels of evidence, observational studies can sometimes be useful when no, or few, RCTs or CCTs are available. A retrospective cohort study (Lipshultz 2002) described clinical and echocardiographic follow-up of 18 childhood cancer survivors with symptomatic and asymptomatic anthracycline-induced cardiotoxicity from the start of enalapril treatment during a median follow-up of 10 years. There were no serious side effects during the long-term enalapril treatment in the cohort. The authors found an initial improvement of cardiac function, but a deterioration of cardiac function and clinical parameters after six years of follow-up. However, the study was small, had no control group and is highly prone to selection, detection and performance bias. Another retrospective study of childhood cancer survivors treated with anthracyclines compared a group of 34 growth-hormone (GH) treated children to a group of 86 children not treated with GH therapy (Lipshultz 2005b). Echocardiographic assessments done during routine clinical follow-up were re-analysed by an investigator blinded for the intervention. From repeated measurements analyses adjusted for baseline characteristics and non random missingness of data, the authors' main conclusion was that GH therapy increased LV wall thickness during but not after therapy. It should be noted that among other issues, the retrospective construction of the control group, several confounding factors that were not adjusted for (such as, co-treatment

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with cardiovascular medication) and the missing outcome data for a large part of the two groups, put this study at high risk for selection and attrition bias. Therefore, no (careful) conclusions can be drawn from these two observational studies.

We are awaiting the results of the ongoing study (NCT00003070) and also more information from the three studies that currently did not provide enough information for inclusion (see Table Characteristics of studies awaiting classification).

AUTHORS' CONCLUSIONS
Implications for practice

We identified only one RCT (Silber 2004) comparing enalapril and placebo in childhood cancer survivors with asymptomatic cardiotoxicity. Although there is some evidence that enalapril temporarily improves one parameter of cardiac function (LVESWS), the current evidence did not show a statistically significant improvement of other parameters of cardiac function nor of clinical outcomes such as overall survival, mortality due to heart failure, occurrence of clinical heart failure and quality of life. However, "no evidence of effect" should not be confused with "evidence of no effect". The RCT showed that enalapril treatment is associated with a higher risk of dizziness or hypotension and fatigue. Effects of enalapril on (duration of) hospitalisation, change in NYHA stage of heart failure and costs were not studied. Also, no evidence is available on the effects of enalapril beyond 2.8 years of follow-up and on the effects of enalapril for treating symptomatic cardiotoxicity. Based on the currently available evidence in childhood cancer survivors with asymptomatic anthracycline-induced cardiac dysfunction, we are not able to give appropriate recommendations for clinical practice. Clinicians should weigh the potential benefits of enalapril with the known side-effect in childhood cancer survivors with asymptomatic anthracycline-induced cardiac dysfunction.

We identified one RCT (Chen 2008) comparing phosphocreatine and a control treatment of vitamin C, ATP, vitamin E, and oral coenzyme Q10 in childhood leukaemia patients with symptomatic and asymptomatic cardiotoxicity. Limited data with a high risk of bias and poor generalisability showed no difference of phosphocreatine compared with a control treatment on overall survival, mortality due to heart failure, echocardiographic function, and adverse events. The effect of the intervention on one marker (hsCRP) was unclear and effects on occurrence of clinical heart failure, (duration) of hospitalisation, change in NYHA stage of heart failure and costs were not studied. No evidence is available of the effects of phosphocreatine beyond two weeks of treatment or on the effects of phosphocreatine in survivors of childhood cancer with symptomatic or asymptomatic cardiotoxicity. Based on the currently available evidence, we do not recommend the use of phosphocreatine in clinical practice.

We did not identify RCTs or CCTs studying other medical interventions for symptomatic or asymptomatic cardiotoxicity in childhood cancer patients or survivors. Therefore, no conclusions can be made about the effect of other medical interventions in these patients and we are not able to give appropriate recommendations for clinical practice.

Implications for research

One RCT (Silber 2004) has studied the effect of enalapril in childhood cancer survivors with asymptomatic anthracycline-induced cardiac dysfunction and found no clear effect on clinical outcomes, possibly due to, among other things, low power of the study. Because there is strong evidence that ACE-inhibitors are beneficial for asymptomatic cardiac dysfunction in other populations, we urge the scientific community to start high-quality studies evaluating the effect of enalapril in childhood cancer patients and survivors with symptomatic or asymptomatic anthracycline-induced cardiotoxicity. These studies should preferably be RCTs, within homogenous populations and with long-term follow-up using valid and clinically relevant selection criteria and outcome definitions. Previous treatment with radiotherapy, duration since cancer diagnosis, duration of cardiotoxicity, the age of the patient, the severity of cardiotoxicity and comorbidity should ideally be taken into account. The number of included patients should be sufficient for the power that is needed for reliable results. In addition, a long-term follow-up study of the *enalapril* trial (Silber 2004), evaluating the long-term effects of enalapril treatment versus placebo, would be very contributory to the current evidence.

One low-quality RCT (Chen 2008) has studied the effect of phosphocreatine in childhood leukaemia patients with symptomatic or asymptomatic anthracycline-induced cardiac dysfunction. Other medical interventions for symptomatic or asymptomatic cardiotoxicity in childhood cancer patients or survivors have not been studied in RCTs or CCTs, even though several potentially beneficial treatment options are available. Especially for symptomatic childhood cancer patients and survivors, evidence on potential treatments for this severe complication is needed. Therefore, also studies with the above mentioned criteria should be started evaluating different treatment options in childhood cancer patients and survivors with symptomatic cardiotoxicity.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chen 2008

Methods	RCT using simple random allocation to intervention and control groups
Participants	68 childhood cancer patients, receiving phosphocreatine or control treatment of a combination of vitamin C, ATP, vitamin E and coenzyme Q10 Included patients had anthracycline related cardiotoxicity based on cardiac enzymes (CK, CK-MB, LDH1, alphaHBDH, troponin I, hsCRP), ECG and / or echocardiogram Median (range) age of the phosphocreatine group was 5 (1 to 15) years and 15 of 35 were males. Age and gender of the control group were not mentioned. Median time since cancer diagnosis was not mentioned. Patients had a diagnosis of acute lymphatic leukaemia or acute myeloid leukaemia Information on (previous) cardiotoxic cancer treatment (cumulative anthracycline dose, cardiac radiotherapy and dose and cardioprotective interventions) were not mentioned for both groups. Other cardiovascular comorbidities and treatments were also not mentioned At the start of the study, distribution of abnormalities in cardiac symptoms and signs in the treatment group (n = 35) was: cardiac symptoms 18, abnormal cardiac enzymes 28, abnormal troponin I 7, abnormal ECG 20 and abnormal echocardiogram 0. Mean (SD) hsCRP in the treatment group was 8.79 (1.36) mg/L. For the control group (n = 33) this distribution was: cardiac symptoms 16, abnormal cardiac enzymes 25, abnormal troponin I: 7, abnormal ECG 18 and abnormal echocardiogram 0. Mean (SD) hsCRP in the control group was 7.88 (2.08) mg/L. Time since diagnosis of cardiotoxicity was not mentioned
Interventions	Phosphocreatine 1 g intravenously over 30 to 40 minutes once to twice per day (n = 35) or a combination treatment of vitamin C 150 mg/kg and ATP 20 mg into 5% glucose 100ml intravenously once per day, oral vitamin E 50 mg once per day and oral coenzyme Q10 (ubidecarenone) 10 mg 3 times per day. All treatment durations were 14 days
Outcomes	*Overall survival.* *Mortality due to heart failure* (no definitions provided). *Occurrence of adverse events* (no definition provided). *Change in cardiac function* (normal / abnormal echocardiography, change in hsCRP, normal / abnormal ECG, normal / abnormal cardiac enzymes (CK, CK-MB, LDH1, alphaHBDH, troponin I and hsCRP), post-intervention levels of CK, CK-MB, LDH1, alphaHBDH and Troponin I. No definitions were provided)
Notes	The abstract (in English) mentions "retrospectively assessed". However, we think the study is an RCT, because there is a statement in the methods section (in Chinese) that "all patients have entered the clinical trial with simple random allocation to treatment and control groups." Duration of follow-up was not mentioned, but it seems that it was 15 days for the assessment of cardiac function, since that was done at the beginning and one day after the intervention. For clinical outcomes it is unclear. There was no loss to follow-up of patients

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding of participants?	High risk	Blinding of participants was not mentioned but seemed inadequate or very unlikely since the intervention and control treatment had different routes of administration
Blinding of personnel?	High risk	Blinding of personnel was not mentioned but seemed inadequate or very unlikely since the intervention and control treatment had different routes of administration
Blinding of outcome assessors? Mortality due to heart failure	Unclear risk	Blinding of outcome assessors was not mentioned
Blinding of outcome assessors? Occurrence of adverse events and tolerability (as defined by authors)	Unclear risk	Blinding of outcome assessors was not mentioned
Blinding of outcome assessors? Change in cardiac function measured by a diagnostic test (as defined by authors)	Unclear risk	Blinding of outcome assessors was not mentioned
Completeness of follow-up Overall survival	Low risk	Outcome could be abstracted for all patients
Completeness of follow-up Mortality due to heart failure	Low risk	Outcome could be abstracted for all patients
Completeness of follow-up Occurrence of adverse events and tolerability (as defined by authors)	Low risk	Outcome was provided for all patients
Completeness of follow-up Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For echocardiography (normal/abnormal) change in outcome was provided for all patients
Completeness of follow-up Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For one biomarker (hsCRP) change in outcome was provided for all patients
Intention-to-treat-analysis? Overall survival	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Mortality due to heart failure	Low risk	Allocation was provided for the reported outcome

Intention-to-treat-analysis? Occurrence of adverse events and tolerability (as defined by authors)	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For echocardiography (normal/abnormal) treatment allocation was provided
Intention-to-treat-analysis? Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For the biomarker (hsCRP) treatment allocation was provided
Free of selective reporting?	Unclear risk	We found no published protocol in which the reported outcomes and analyses were pre-specified
Free of other bias?	High risk	The baseline characteristics were not fully described. For example, there was no data about the gender and age distribution of the control group. We do not know what type of anthracycline and what doses of medications were used in each group of the patients. We have no information on whether radiation therapy was given. Therefore, we were not certain whether the intervention and control groups were comparable/similar at baseline. We are not certain whether co-interventions were different between the intervention and control groups
Random sequence generation?	Unclear risk	No description of sequence generation
Allocation concealment?	Unclear risk	No description of allocation concealment

Silber 2004

Methods	ACE inhibitor After Anthracycline (AAA) trial. Double-blinded RCT. Randomisations were performed using random permuted blocks (random size between 2 and 8) with equal allocation to each treatment (stratified according to the variables age at treatment (under 3 year old versus 3 year or older), total cumulative anthracycline dose (under 300 mg/m2 versus 300 mg/m2 or higher) and time from diagnosis (less than 10 years versus 10 years or more))
Participants	135 childhood cancer survivors (aged 8.3 to 30.6 years, 78 males) with asymptomatic decline of cardiac function at some time after anthracycline exposure, detected with echocardiography, resting or exercise GNA, MCI at peak exercise and / or resting ECG Median (range) time since cancer diagnosis 9 (4.2 to 22.3) years in the enalapril group

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Silber 2004 *(Continued)*

	and 9.6 (4.3 to 25.8) years in the placebo group. Patients had been treated for various types of cancer diagnosis at a median (range) age of 7.2 (3 to 21.8) years in the enalapril group and 8.2 (0.3 to 10.3) years in the placebo group. Median (range) age at study entry 17 (8.3 to 31.5) years in enalapril and 18.9 (8.1 to 30.6) years in placebo group Previous anthracycline treatment with median (range) cumulative anthracycline dose 305 (75 to 396) mg/m² in enalapril and 300 (75 to 738) mg/m² in placebo group (types of anthracyclines not mentioned). Previous cardiac radiotherapy in enalapril group: 26 (38%), unknown in 1 (1.4%). In placebo group: 23 (35%), unknown in 0 (0%) . Other previous potential cardiotoxic treatment or cardioprotective interventions not mentioned. Total radiotherapy dose, other cardiovascular comorbidities and treatments were not mentioned. 1 patient in enalapril group required a growth hormone supplement, 1 patient in placebo group required a testosterone supplement. At the start of the study, 111 patients had echocardiographic abnormalities (based on SF, LVESWS and/or SVI) and/or abnormalities during resting or exercise GNA (based on EF). Of the remaining 24 patients, 7 had (only) abnormalities on cycle ergometry (based on MCI) and 17 had any of the abnormalities (possibly including an abnormal QTc interval on ECG) before study entry. Mean (SD) cardiac function in enalapril group was: MCI (L/min/m²): 8.39 (2.66) (68 patients), LVESWS (g/cm²): 73.2 (19.0) (69 patients), EF (%): 59.1 (7.4) (69 patients), SF (%): 69: 30.7 (4.9) (69 patients), QTc (ms): 418 (23.4) (69 patients). Mean (SD) cardiac function in placebo group was: MCI (L/min/m²): 8.24 (2.57) (65 patients), LVESWS (g/cm²): 68.4 (20.4) (66 patients), EF (%): 58.3 (7.1) (64 patients), SF (%): 30.6 (3.9) (66 patients), QTc (ms): 411 (17.6) (66 patients). Time since diagnosis of cardiotoxicity was not mentioned
Interventions	Oral enalapril once daily (n = 69) or oral placebo once daily (n = 66). Dosing of study medication was as follows: at start 0.05 mg/kg/day, escalation after 14 days to 0.10 mg/kg/day and escalation at 3 months visit to 0.15 mg/kg/day if no side effects occurred
Outcomes	*Overall survival.* *Mortality due to heart failure* (no definitions provided). *Development of clinical heart failure* (defined as a clinically significant decline in cardiac performance: documented acute congestive heart failure, SF decline 20% (and below 28%) from baseline in 2 measures or MCI decline by 30% (and 2 SD below the mean) from baseline in 2 measures) *Occurrence of adverse events* (no definition provided). *Change in cardiac function* (Primary outcome: rate of decline over time of MCI. Secondary outcome: rate of increase over time in LVESWS. Other outcomes first-year reduction in LVESWS (post-hoc and ITT analysis), % of change in SF and change in SVI over time) *Quality of life:* based on the Short-Form 36 General Health Survey (age above 14 years) or the Childhood Health Questionnaire-85 (age equal or younger than 14 years). No definition for an abnormal outcome was provided
Notes	Median (range) follow-up time was 2.80 years (2 weeks to 6.1 years). Loss of follow-up was not mentioned Since the authors did not present dichotomous outcomes, we were not able to define RRs for the outcome change in cardiac function; we therefore describe the outcomes as presented in the original study

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Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding of participants?	Low risk	Participants were effectively blinded to the intervention
Blinding of personnel?	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the personnel was effectively blinded
Blinding of outcome assessors? Mortality due to heart failure	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the outcome assessors were effectively blinded
Blinding of outcome assessors? Development of clinical heart failure (as defined by authors)	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the outcome assessors were effectively blinded
Blinding of outcome assessors? Occurrence of adverse events and tolerability (as defined by authors)	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the outcome assessors were effectively blinded
Blinding of outcome assessors? Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the outcome assessors were effectively blinded
Blinding of outcome assessors? Change in quality of life (as defined by authors)	Low risk	Investigators were blinded to the intervention. Based on this statement and the effective blinding of patients, we judged that the outcome assessors were effectively blinded
Completeness of follow-up Overall survival	Low risk	Outcome could be abstracted from all patients
Completeness of follow-up Mortality due to heart failure	Low risk	Outcome could be abstracted from all patients
Completeness of follow-up Development of clinical heart failure (as defined by authors)	Low risk	Outcome was provided for all patients

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Completeness of follow-up Occurrence of adverse events and tolerability (as defined by authors)	Unclear risk	Completeness of follow-up not mentioned
Completeness of follow-up Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For MCI any follow-up measurement was done in 83% of the patients. Completeness of follow-up at the end of the study was not mentioned
Completeness of follow-up Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For LVESWS follow-up was 93% in the first year. Follow-up after the first year was not mentioned
Completeness of follow-up Change in cardiac function measured by a diagnostic test (as defined by authors)	Unclear risk	For other outcomes of cardiac function (SF and SVI) completeness of follow-up was not mentioned
Completeness of follow-up Change in quality of life (as defined by authors)	Unclear risk	Completeness of follow-up not mentioned
Intention-to-treat-analysis? Overall survival	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Mortality due to heart failure	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Development of clinical heart failure (as defined by authors)	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Occurrence of adverse events and tolerability (as defined by authors)	Low risk	Allocation was provided for the reported outcome
Intention-to-treat-analysis? Change in cardiac function measured by a diagnostic test (as defined by authors)	Low risk	For change in MCI and LVESWS intention-to-treat-analyses were performed by the study
Intention-to-treat-analysis? Change in cardiac function measured by a diagnostic test (as defined by authors)	High risk	For the extra post-hoc analysis of change in LVESWS (piecewise model), a per protocol analysis was performed by the study
Intention-to-treat-analysis? Change in cardiac function measured by a diagnostic test (as defined by authors)	Unclear risk	For other outcomes of cardiac function (SF and SVI) it was not stated if intention-to-treat-analyses were performed by the study

Intention-to-treat-analysis? Change in quality of life (as defined by authors)	Low risk	Allocation was provided for the reported outcome
Free of selective reporting?	Low risk	There was a published protocol in which the reported outcomes and analyses were pre-specified. All outcomes were reported and the analyses were done in the final report. The authors clearly explained that they performed some additional analyses based on exploration of the data
Free of other bias?	Low risk	
Random sequence generation?	Low risk	Randomizations were performed using random permuted blocks (random size between 2 and 8) with equal allocation to each treatment
Allocation concealment?	Unclear risk	It was stated that there was allocation concealment, but the method of allocation concealment was not mentioned

alphaHBDH: alpha hydroxybutyrate dehydrogenase
ATP: adenosine tri-phosphate
CK: creatine kinase
CK-MB: creatine kinase MB
ECG: electrocardiogram
EF: ejection fraction
GNA: gated nuclear angiography
hsCRP: hyper sensitivity C-reactive protein
ITT: intention-to-treat
LDH1: lactate dehydrogenase
LVESWS: left ventricular end-systolic wall stress
MCI: maximal cardiac index
RCT: randomised controlled trial
RR: risk ratio
SD: standard deviation
SF: shortening fraction
SVI: stress-velocity index

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

Study	Reason for exclusion
Garcia 2007	No RCT or CCT.
Ginsberg 2004	Health related quality of life was assessed in patients of the AAA trial (Silber 2004), but outcomes were not related to the treatment allocation
Shaddy 2007	In consultation with the authors of the paper: patients with anthracycline-induced cardiomyopathy were included in the trial, but it was not possible to separate the data of these patients from the data of all included patients
Tallaj 2005	No RCT or CCT.
Vatutin 2001	Exclusion based on adult age.

AAA trial: ACE inhibitor After Anthracycline trial
CCT: controlled clinical trial
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Mandric 2008

Methods	CCT comparing enalapril to placebo
Participants	30 survivors of paediatric haematological malignancies, aged between 6 and 14 years and treated with doxorubicin. All patients had at least one cardiac abnormality identified at any time after anthracyclines exposure Enalapril group:10 children, mean age at diagnosis 6 years, mean or median follow-up 16 months Placebo group: 20 children. Mean age and follow-up not mentioned Both groups had been treated with similar doses of anthracyclines. No further patient characteristics were provided. Duration of follow-up was unclear
Interventions	Enalapril (dose range between 0.2 and 0.5 mg/kg/day) Placebo (not further specified)
Outcomes	Cardiac evaluation (including echocardiography) at baseline and at 3, 6, 12, 16 month after initiation of enalapril/placebo therapy In the enalapril group, progressive improvement in LV dimensions (end-systolic and end-diastolic), fractional shortening, LV mass, LV percent posterior wall thickening, interventricular percent septal thickening and Tei index was found In the placebo group, the same echocardiographic parameters were constant or worsened in the course of follow-up (not further specified)
Notes	This study has not been published in full text, but has been presented at the SIOP conference 2008 (abstract L.030). It seems that patients were not randomised. Completeness of follow-up was not mentioned

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Mandric 2009

Methods	Unclear (possibly a CCT).
Participants	27 children aged between 3 and 18 years Enalapril group: 10 children with subclinical cardiotoxicity on echocardiography No "cardioprotector" group: 6 children with a chemotherapeutic protocol completed. It was not specified if this group suffered from cardiotoxicity Third group: 11 children with newly diagnosed cancer. It was not specified if this group received an intervention No further patient characteristics were provided. Duration of follow-up was unclear
Interventions	Enalapril (not further specified) No "cardioprotector" (not further specified)
Outcomes	Periodic history and physical examination, electrocardiogram, chest X-ray, 2 dimensional/Doppler echocardiography, cardiac biomarkers (BNP, cTnI, ALAT, CPK) "Clinical manifestations": heart failure: 1 patient; "untypical manifestation": 15 patients; "echocardiographic modifications": 6 patients; electrocardiographic changes: 5 patients; high values of plasma BNP (cut-off value of 100 microgram/ml): 11 patients It was not mentioned what the differences in these outcomes were between subgroups, except that all children on "cardioprotector" treatment had normal values of BNP and cTnI
Notes	This study has not been published in full text, but has been presented at the SIOP conference 2009 (abstract PQ. 020). The title suggested that cardiotoxicity in children in group B (and possibly also in group C) was caused by anthracyclines. It seems that patients were not randomised. Completeness of follow-up was not mentioned

ALAT: alanine transaminase
BNP: brain natriuretic peptide
CCT: controlled clinical trial
CPK: creatine phosphokinase
cTnI: cardiac troponin I
LV: left ventricular
SIOP: Société Internationale d'Oncologie Pédiatrique (International Society of Paediatric Oncology)

Characteristics of ongoing studies *[ordered by study ID]*

NCT00003070

Trial name or title	Afterload Reduction Therapy for Late Anthracycline Cardiotoxicity: A Pediatric Oncology Group Cancer Control Study
Methods	Randomized double-blinded phase III trial to compare the effectiveness of enalapril with a placebo in treating heart damage in patients who received anthracycline chemotherapy for childhood cancer
Participants	Patients with histologically diagnosed childhood malignancy that had prior anthracycline therapy and echocardiographic evidence of reduced fractional shortening, reduced contractility, or increased afterload, or any combination. At least 6 months oncologic disease free. At least 8 years old at study entry and less than 22 years at diagnosis. At least 1 year since prior cumulative anthracycline therapy of at least 200 mg/m^2.

Interventions	Enalapril maleate and placebo
Outcomes	Body surface area-adjusted left ventricular mass, ventricular function, quality of life
Starting date	15 Aug 1997
Contact information	Stephen Lipshultz, James P. Wilmot Cancer Center
Notes	On the ongoing trial website there is a note about the recruitment status: completed. However, we found no publication of this trial. One of the authors (LK) learned from contacts in the US that this trial has as yet not been executed

DATA AND ANALYSES

Comparison 1. Enalapril versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Development of clinical heart failure	1	135	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.29]
2 Dizziness or hypotension	1	135	Risk Ratio (M-H, Random, 95% CI)	7.17 [1.71, 30.17]
3 Rash or hives	1	135	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.25, 3.67]
4 Heart palpitations	1	135	Risk Ratio (M-H, Random, 95% CI)	3.83 [0.44, 33.35]
5 Anxiety or depression	1	135	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.18, 20.60]
6 Headache	1	135	Risk Ratio (M-H, Random, 95% CI)	3.83 [0.44, 33.35]
7 Gastrointestinal disturbance	1	135	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.20, 4.57]
8 Hepatitis C	1	135	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.11, 3.70]
9 Neutropenia	1	135	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.04, 5.15]
10 Musculoskeletal pain	1	135	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.20, 4.57]
11 Dry cough	1	135	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.06, 14.98]
12 Shortness of breath	1	135	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.14, 6.59]
13 Chest pain	1	135	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.51, 5.45]

Analysis 1.1.   Comparison 1 Enalapril versus placebo, Outcome 1 Development of clinical heart failure.

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Comparison: 1 Enalapril versus placebo

Outcome: 1 Development of clinical heart failure

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Silber 2004	1/69	6/66		100.0 %	0.16 [0.02, 1.29]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.16 [0.02, 1.29]**

Total events: 1 (Enalapril), 6 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.72 (P = 0.085)

Test for subgroup differences: Not applicable

```
        0.01    0.1    1    10    100
      Favours enalapril    Favours placebo
```

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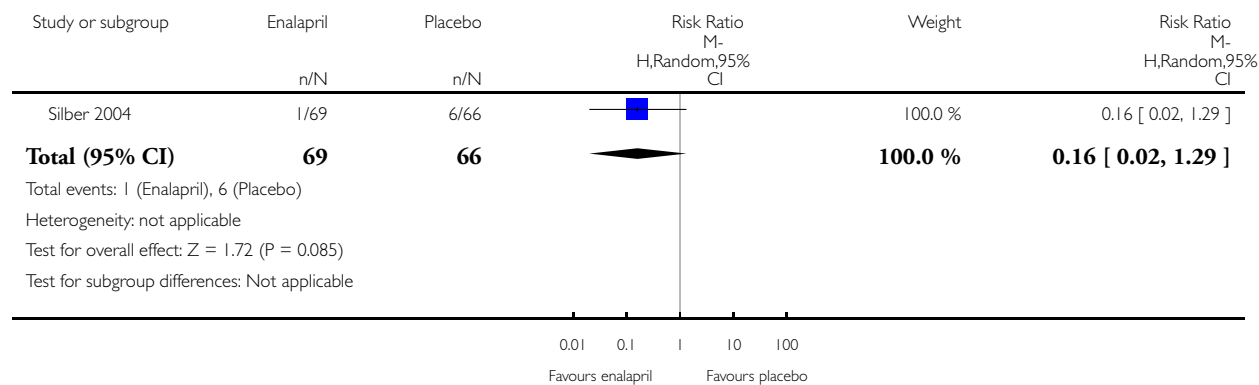
Analysis 1.2.   Comparison 1 Enalapril versus placebo, Outcome 2 Dizziness or hypotension.

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Comparison: 1 Enalapril versus placebo

Outcome: 2 Dizziness or hypotension

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Silber 2004	15/69	2/66		100.0 %	7.17 [1.71, 30.17]
Total (95% CI)	**69**	**66**		**100.0 %**	**7.17 [1.71, 30.17]**

Total events: 15 (Enalapril), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 2.69 (P = 0.0072)

Test for subgroup differences: Not applicable

```
          0.01   0.1    1    10   100
          Favours enalapril    Favours placebo
```

Analysis 1.3.   Comparison 1 Enalapril versus placebo, Outcome 3 Rash or hives.

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Comparison: 1 Enalapril versus placebo

Outcome: 3 Rash or hives

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Silber 2004	4/69	4/66		100.0 %	0.96 [0.25, 3.67]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.96 [0.25, 3.67]**

Total events: 4 (Enalapril), 4 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.06 (P = 0.95)

Test for subgroup differences: Not applicable

```
          0.01   0.1    1    10   100
          Favours placebo    Favours enalapril
```

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Analysis 1.4. Comparison 1 Enalapril versus placebo, Outcome 4 Heart palpitations.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

Comparison: 1 Enalapril versus placebo

Outcome: 4 Heart palpitations

Study or subgroup	Enalapril	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Silber 2004	4/69	1/66		100.0 %	3.83 [0.44, 33.35]
Total (95% CI)	**69**	**66**		**100.0 %**	**3.83 [0.44, 33.35]**
Total events: 4 (Enalapril), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.22)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1    10   100
      Favours enalapril   Favours placebo
```

Analysis 1.5. Comparison 1 Enalapril versus placebo, Outcome 5 Anxiety or depression.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

Comparison: 1 Enalapril versus placebo

Outcome: 5 Anxiety or depression

Study or subgroup	Enalapril	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Silber 2004	2/69	1/66		100.0 %	1.91 [0.18, 20.60]
Total (95% CI)	**69**	**66**		**100.0 %**	**1.91 [0.18, 20.60]**
Total events: 2 (Enalapril), 1 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.59)					
Test for subgroup differences: Not applicable					

```
        0.01   0.1    1    10   100
      Favours enalapril   Favours placebo
```

Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer (Review)

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Analysis 1.6. Comparison 1 Enalapril versus placebo, Outcome 6 Headache.

Comparison: 1 Enalapril versus placebo

Outcome: 6 Headache

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Silber 2004	4/69	1/66		100.0 %	3.83 [0.44, 33.35]
Total (95% CI)	**69**	**66**		**100.0 %**	**3.83 [0.44, 33.35]**

Total events: 4 (Enalapril), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.21 (P = 0.22)

Test for subgroup differences: Not applicable

```
       0.01    0.1     1      10     100
       Favours enalapril    Favours placebo
```

Analysis 1.7. Comparison 1 Enalapril versus placebo, Outcome 7 Gastrointestinal disturbance.

Comparison: 1 Enalapril versus placebo

Outcome: 7 Gastrointestinal disturbance

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Silber 2004	3/69	3/66		100.0 %	0.96 [0.20, 4.57]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.96 [0.20, 4.57]**

Total events: 3 (Enalapril), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.06 (P = 0.96)

Test for subgroup differences: Not applicable

```
       0.01    0.1     1      10     100
       Favours enalapril    Favours placebo
```
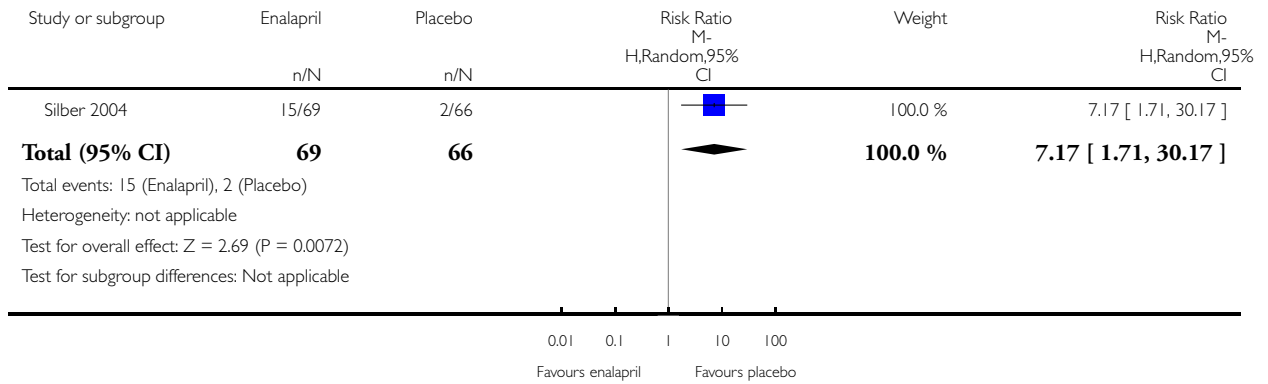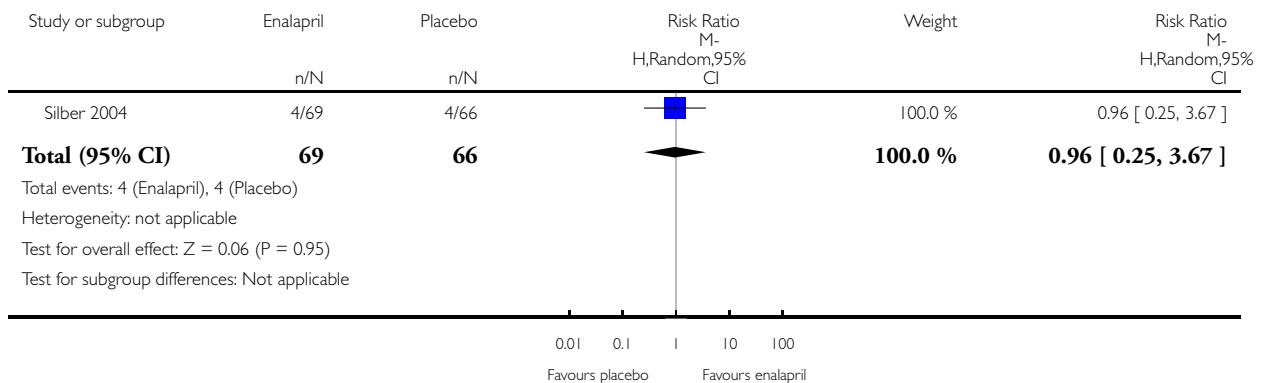
Analysis 1.8. Comparison I Enalapril versus placebo, Outcome 8 Hepatitis C.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer
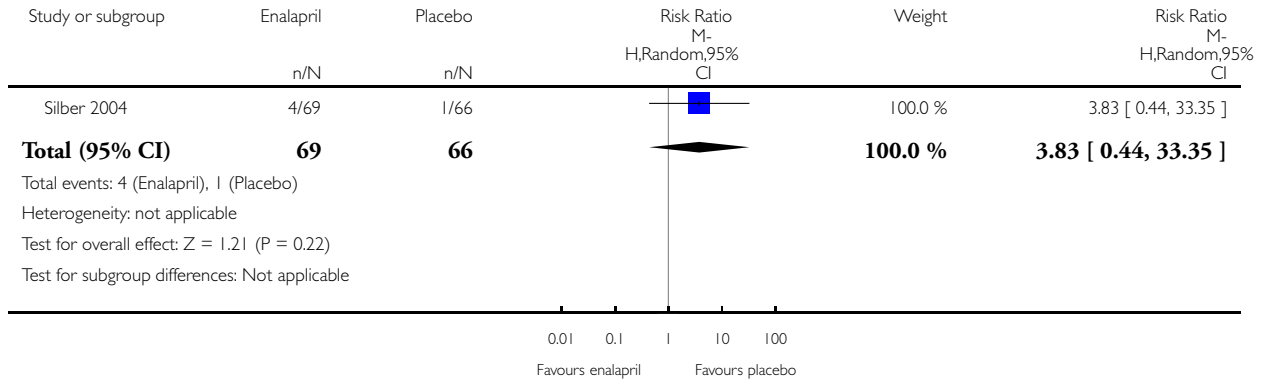
Comparison: 1 Enalapril versus placebo

Outcome: 8 Hepatitis C

Study or subgroup	Enalapril	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Silber 2004	2/69	3/66		100.0 %	0.64 [0.11, 3.70]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.64 [0.11, 3.70]**

Total events: 2 (Enalapril), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.50 (P = 0.62)

Test for subgroup differences: Not applicable

```
        0.01   0.1    I    I0   100
        Favours enalapril   Favours placebo
```

Analysis 1.9. Comparison I Enalapril versus placebo, Outcome 9 Neutropenia.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer
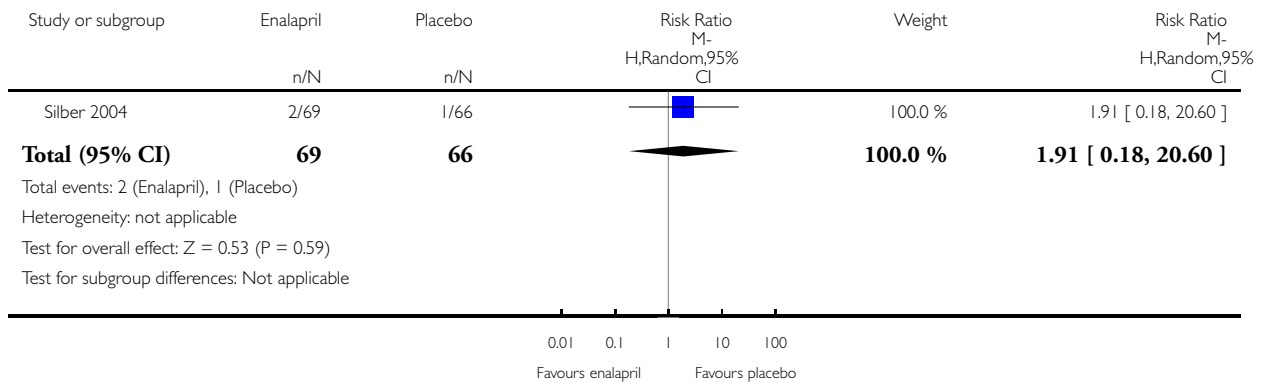
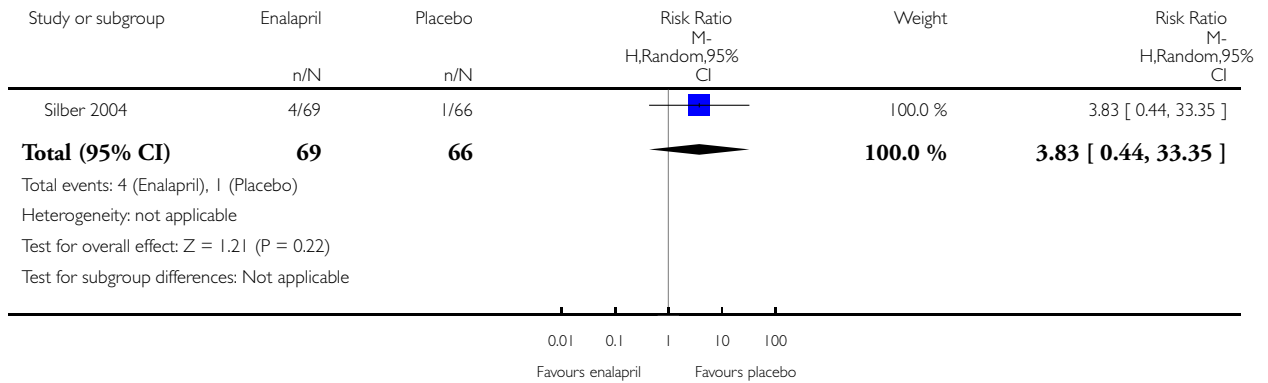Comparison: 1 Enalapril versus placebo

Outcome: 9 Neutropenia

Study or subgroup	Enalapril	Placebo	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Silber 2004	1/69	2/66		100.0 %	0.48 [0.04, 5.15]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.48 [0.04, 5.15]**

Total events: 1 (Enalapril), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.61 (P = 0.54)

Test for subgroup differences: Not applicable

```
        0.01   0.1    I    I0   100
        Favours enalapril   Favours placebo
```

Analysis 1.10. Comparison 1 Enalapril versus placebo, Outcome 10 Musculoskeletal pain.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer
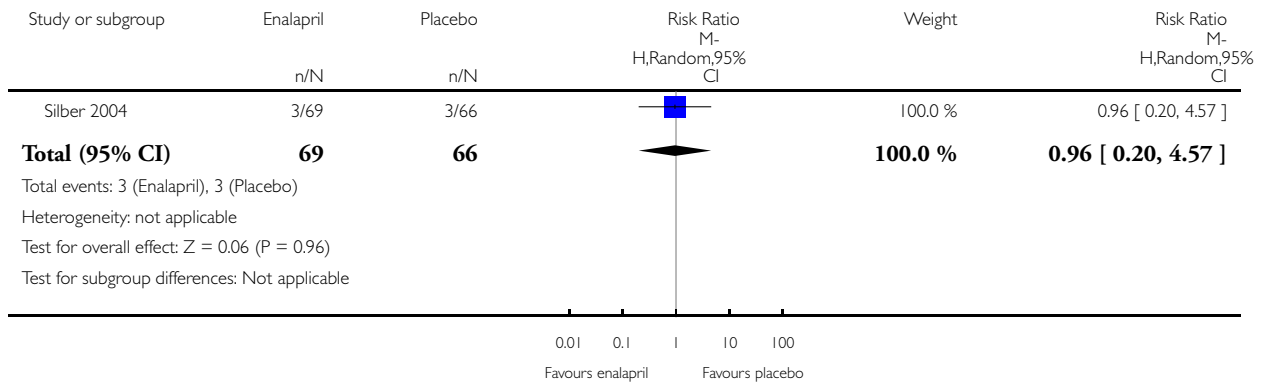
Comparison: 1 Enalapril versus placebo

Outcome: 10 Musculoskeletal pain

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Silber 2004	3/69	3/66		100.0 %	0.96 [0.20, 4.57]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.96 [0.20, 4.57]**

Total events: 3 (Enalapril), 3 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.06 (P = 0.96)

Test for subgroup differences: Not applicable

```
      0.01   0.1    1    10   100
    Favours enalapril   Favours placebo
```
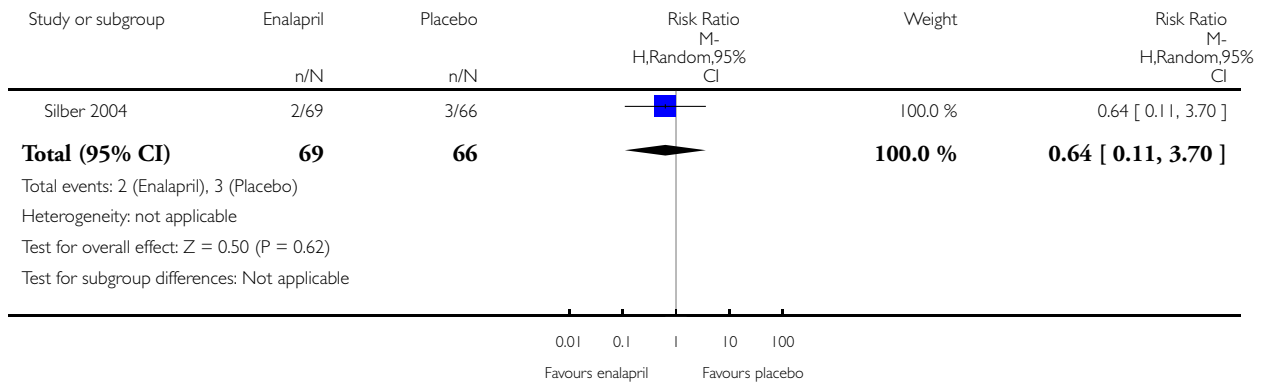
Analysis 1.11. Comparison 1 Enalapril versus placebo, Outcome 11 Dry cough.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer
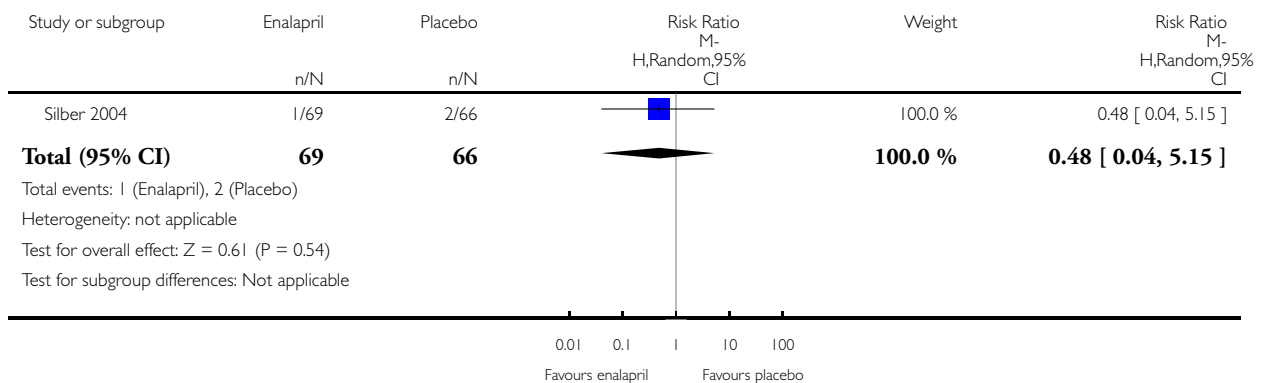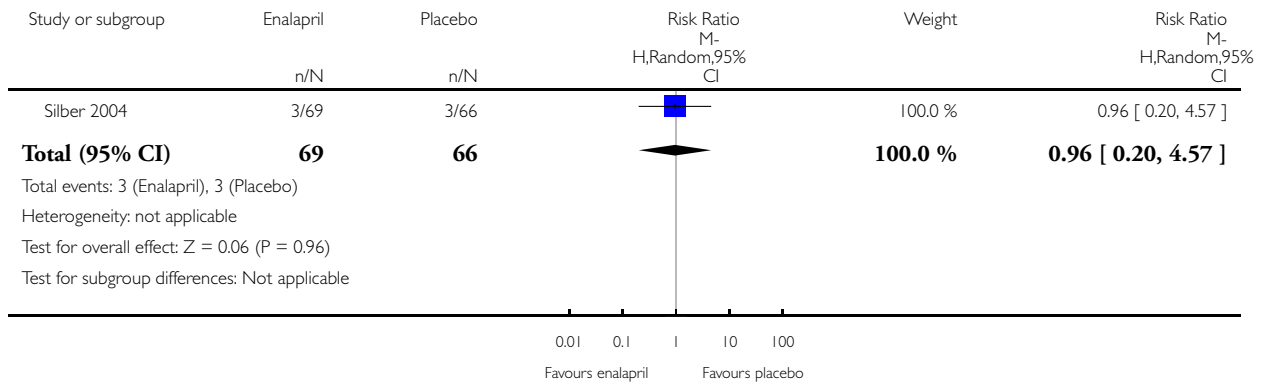
Comparison: 1 Enalapril versus placebo

Outcome: 11 Dry cough

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Silber 2004	1/69	1/66		100.0 %	0.96 [0.06, 14.98]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.96 [0.06, 14.98]**

Total events: 1 (Enalapril), 1 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.03 (P = 0.97)

Test for subgroup differences: Not applicable

```
      0.01   0.1    1    10   100
    Favours enalapril   Favours placebo
```

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Analysis 1.12.   Comparison 1 Enalapril versus placebo, Outcome 12 Shortness of breath.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

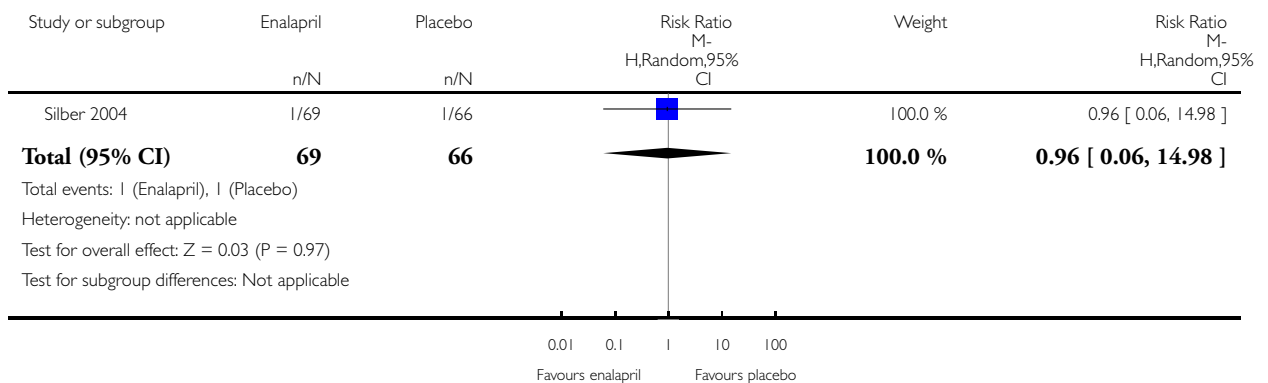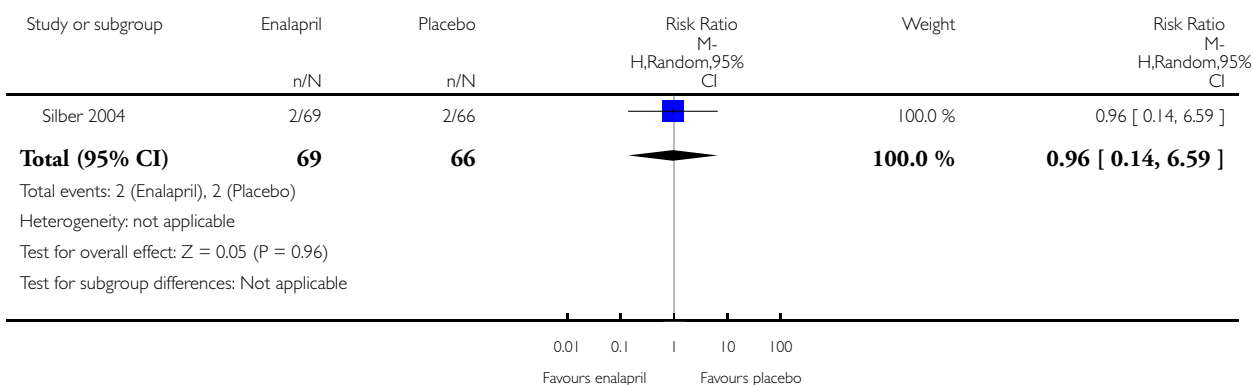Comparison: 1 Enalapril versus placebo
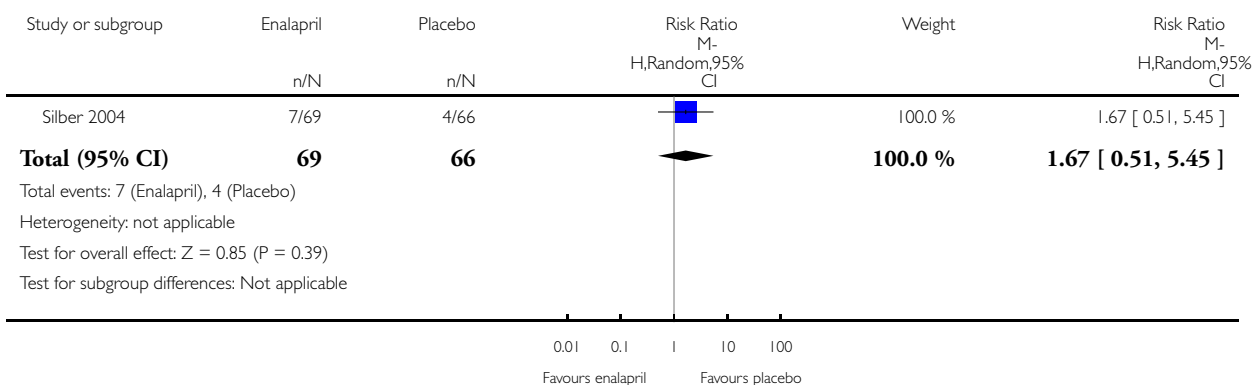
Outcome: 12 Shortness of breath

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Silber 2004	2/69	2/66		100.0 %	0.96 [0.14, 6.59]
Total (95% CI)	**69**	**66**		**100.0 %**	**0.96 [0.14, 6.59]**

Total events: 2 (Enalapril), 2 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

```
          0.01   0.1    1    10   100
          Favours enalapril   Favours placebo
```

Analysis 1.13.   Comparison 1 Enalapril versus placebo, Outcome 13 Chest pain.

Review: Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer

Comparison: 1 Enalapril versus placebo

Outcome: 13 Chest pain

Study or subgroup	Enalapril n/N	Placebo n/N	Risk Ratio M- H,Random,95% CI	Weight	Risk Ratio M- H,Random,95% CI
Silber 2004	7/69	4/66		100.0 %	1.67 [0.51, 5.45]
Total (95% CI)	**69**	**66**		**100.0 %**	**1.67 [0.51, 5.45]**

Total events: 7 (Enalapril), 4 (Placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.85 (P = 0.39)

Test for subgroup differences: Not applicable

```
          0.01   0.1    1    10   100
          Favours enalapril   Favours placebo
```

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Table 1.   Criteria list for the assessment of risk of bias of included studies

Item ID	Description	Implementation
Selection bias		
a	*Was the allocation sequence adequately generated?*	Adequate when a random (and therefore unpredictable) sequence was used to allocate the intervention to the participants
b	*Was allocation adequately concealed?*	Adequate when the upcoming allocations of participants were masked from those involved in enrolment into the trial
Performance bias		
c	*Was knowledge of the allocated intervention by participants adequately prevented during the study?*	Adequate when the participants were unaware of the intervention they received
d	*Was knowledge of the allocated intervention by personnel adequately prevented during the study?*	Adequate when the personnel involved in the care of the participants were unaware of the intervention a participant received
Detection bias (for each outcome separately)		
e	*Was knowledge of the allocated intervention by the outcome assessor adequately prevented during the study?*	Adequate when the outcome assessor was unaware of the intervention a participant received
Attrition bias (for each outcome separately)		
f	*Was the follow-up of the outcome complete?*	Complete when the outcome was assessed in at least 80% of the study cohort
g	*Was an intention-to-treat-analysis performed?*	Adequate when all participants were analysed in the treatment group to which they were randomised, regardless of whether or not they received the allocated intervention
Reporting bias		
h	*Are reports of the study free of suggestion of selective outcome reporting?*	Adequate when a study protocol was available that pre-specified study outcomes and analyses which were all reported in the final study report.
Other sources of bias		
i	*Was the study apparently free of other problems that could put it at a high risk of bias?*	Adequate when there were no other important personal concerns about bias not addressed in the other domains in the tool

All items were scored yes, no or unclear

Table 2. Fisher's exact test of outcomes with no events in the enalapril or placebo group

Outcome	Enalapril (n = 69)	Placebo (n = 66)	P value
Dehydration	0	1	0.49
Fatigue	7	0	0.013
Fever	0	1	0.49
Alopecia	1	0	1.00
Severe sunburn	0	1	0.49
Wolf-Parkinson-White syndrome	0	1	0.49
Anorexia	0	2	0.24
Cholecystitis or gallstones	2	0	0.50
Elevated bilirubin	1	0	1.00
Ulcerative colitis	0	1	0.49
Diabetes	0	1	0.49
Hypokalemia	0	1	0.49
Hyperthyroidism	1	0	1.00
Second cancer	2	0	0.50
Tumour recurrence	0	1	0.49
Proteinuria	1	0	1.00
Renal stones	1	0	1.00
Epistaxis	1	0	1.00
Impotence	0	1	0.49
Taste disturbance	1	0	1.00

APPENDICES

Appendix 1. Search strategy for MEDLINE (PubMed)

Medical interventions:

1. **ACE-inhibitor**

(ace inhibitor OR ace-inhibitor OR ace inhibitor* OR ace-inhibitor* OR Angiotensin-Converting Enzyme Inhibitors OR Angiotensin-Converting Enzyme Inhibitors[Pharmacological Action] OR Angiotensin Converting Enzyme Inhibitors OR Angiotensin-Converting Enzyme Antagonists OR Angiotensin Converting Enzyme Antagonists OR Enzyme Antagonists, Angiotensin-Converting OR Antagonists, Angiotensin-Converting Enzyme OR Antagonists, Angiotensin Converting Enzyme OR Antagonists, Kininase II OR Inhibitors, Kininase II OR Inhibitors, ACE OR ACE Inhibitors OR Kininase II Inhibitors OR Kininase II Antagonists OR Angiotensin I-Converting Enzyme Inhibitors OR Angiotensin I Converting Enzyme Inhibitors OR Inhibitors, Angiotensin-Converting Enzyme OR Enzyme Inhibitors, Angiotensin-Converting OR Inhibitors, Angiotensin Converting Enzyme OR Angiotensin-Converting Enzyme Inhibitor* OR Angiotensin Converting Enzyme Inhibitor* OR Angiotensin-Converting Enzyme Antagonist* OR Angiotensin Converting Enzyme Antagonist* OR Kininase II Inhibitor* OR Kininase II Antagonist* OR Angiotensin I-Converting Enzyme Inhibitor* OR Angiotensin I Converting Enzyme Inhibitor* OR captopril OR enalapril OR fosinopril) OR (peptidyl dipeptidase OR Peptidyl Dipeptidase A OR Angiotensin I-Converting Enzyme OR Angiotensin I Converting Enzyme OR Carboxycathepsin OR Kininase A OR CD143 Antigen OR CD143 Antigens OR Dipeptidyl Peptidase A OR Antigens, CD143 OR Angiotensin Converting Enzyme OR Kininase II)

2. **Angiotensin receptor blocker**

(angiotensin receptor blocker OR angiotensin receptor blockers OR angiotensin receptor blocker* OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin II Type 1 Receptor Antagonists OR Type 1 Angiotensin Receptor Antagonists OR Type 1 Angiotensin Receptor Blockers OR Selective Angiotensin II Receptor Antagonists OR Sartans OR Angiotensin II OR Angiotensin Receptors/antagonists & inhibitors OR Angiotensin II Type 1 Receptor Blocker* OR Type 1 Angiotensin Receptor Antagonist* OR Type 1 Angiotensin Receptor Blocker* OR Selective Angiotensin II Receptor Antagonist* OR losartan OR valsartan)

3. **Beta-blocker**

(beta blocker OR beta blockers OR beta-blockers OR beta-blocker OR beta-blocker* OR beta blocker* OR Adrenergic beta Antagonists OR adrenergic beta-antagonists OR adrenergic beta-antagonists[Pharmacological Action] OR beta-Antagonists, Adrenergic OR Adrenergic beta-Receptor Blockaders OR Adrenergic beta Receptor Blockaders OR Blockaders, Adrenergic beta-Receptor OR beta-Receptor Blockaders, Adrenergic OR beta-Adrenergic Receptor Blockaders OR Blockaders, beta-Adrenergic Receptor OR Receptor Blockaders, beta-Adrenergic OR beta Adrenergic Receptor Blockaders OR beta-Adrenergic Blocking Agents OR Agents, beta-Adrenergic Blocking OR Blocking Agents, beta-Adrenergic OR beta Adrenergic Blocking Agents OR beta-Adrenergic Blockers OR Blockers, beta-Adrenergic OR beta Adrenergic Blockers OR beta-Blockers, Adrenergic OR Adrenergic beta-Blockers OR beta Blockers, Adrenergic OR Sympatholytics OR Sympatholytics[Pharmacological Action] OR Sympathetic-Blocking Agents OR Agents, Sympathetic-Blocking OR Sympathetic Blocking Agents OR Sympatholytic Agents OR Agents, Sympatholytic OR Sympatholytic Drugs OR Drugs, Sympatholytic OR Sympatholytic* OR Adrenergic beta Antagonist* OR Adrenergic beta-Receptor Blockader* OR Adrenergic beta Receptor Blockader* OR beta-Adrenergic Receptor Blockader* OR beta Adrenergic Receptor Blockader* OR beta-Adrenergic Blocking Agent* OR beta Adrenergic Blocking Agent* OR beta Adrenergic Blocker* OR beta-Adrenergic Blocker* OR Adrenergic beta-Blocker* OR Sympathetic-Blocking Agent* OR Sympathetic Blocking Agent* OR Sympatholytic Agent* OR Sympatholytic Drug* OR carvedilol OR atenolol OR metoprolol OR propranolol)

4. **Calcium channel blocker**

(calcium channel blocker OR calcium channel blockers OR calcium channel blockers[Pharmacological Action] OR calcium channel blocker* OR Exogenous Calcium Antagonists OR Antagonists, Exogenous Calcium OR Calcium Antagonists, Exogenous OR Exogenous Calcium Blockaders OR Blockaders, Exogenous Calcium OR Calcium Inhibitors, Exogenous OR Calcium Channel Blocking Drugs OR Exogenous Calcium Inhibitors OR Inhibitors, Exogenous Calcium OR Calcium Blockaders, Exogenous OR Channel Blockers, Calcium OR Blockers, Calcium Channel OR Exogenous Calcium Antagonist* OR Exogenous Calcium Blockader* OR Calcium Channel Blocking Drug* OR Exogenous Calcium Inhibitor* OR Exogenous Calcium Blockader* OR Calcium Channel Blocking Drug* OR Exogenous Calcium Inhibitor* OR diltiazem OR nifedipine)

5. **Digoxin**

(digoxin OR digoxin* OR Lanoxin)

6. **Vasodilator agent**

(vasodilator OR vasodilators OR vasodilator* OR vasodilator agents OR vasodilator agents[Pharmacological Action] OR Agents, Vasodilator OR Vasodilator Drugs OR Drugs, Vasodilator OR Vasoactive Antagonists OR Antagonists, Vasoactive OR Vasoactive

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Antagonist* OR vasodilator agent* OR Vasodilator Drug* OR nitroglycerin OR Glyceryl Trinitrate OR Trinitrate, Glyceryl OR Nitroglycerin* OR diazoxide OR adenosine)

7. **Diuretic**

(diuretic OR diuretics OR diuretic* OR diuretics[Pharmacological Action] OR furosemide)

8. **Aldosterone antagonist**

(aldosteron antagonist OR aldosteron antagonists OR aldosterone antagonist OR aldosterone antagonists OR aldosterone antagonist* OR aldosteron antagonist* OR "Aldosterone antagonists"[Pharmacological Action] OR Antagonists, Aldosterone OR spironolactone)

9. **(Other) antihypertensive agents**

(antihypertensiva OR anti-hypertensive OR anti hypertensive OR anti hypertensive drugs OR antihypertensive drugs OR antihypertensive agents OR antihypertensive agents[Pharmacological Action] OR Agents, Antihypertensive OR Anti-Hypertensive Agents OR Agents, Anti-Hypertensive OR Anti Hypertensive Agents OR Anti-Hypertensive Drugs OR Anti Hypertensive Drugs OR Drugs, Anti-Hypertensive OR Anti-Hypertensives OR Anti Hypertensives OR Antihypertensive Drugs OR Drugs, Antihypertensive OR Antihypertensives OR antihypertensiv* OR antihypertensive drug* OR anti hypertensive drug* OR antihypertensive agent* OR anti hypertensive agent* OR clonidine)

10. **Inotropic**

(inotropics OR inotropic OR inotropic* OR dopamine OR dobutamine OR epinephrine OR norepinephrine)

11. **Growth hormone**

(growth hormone OR Growth Hormone, Pituitary OR Pituitary Growth Hormone OR Somatotropin OR Growth Hormone, Recombinant OR Growth Hormones Pituitary, Recombinant OR Pituitary Growth Hormones, Recombinant OR Recombinant Pituitary Growth Hormones OR Somatotropin, Recombinant OR Recombinant Somatotropin OR Recombinant Growth Hormone OR Recombinant Growth Hormones OR Growth Hormones, Recombinant OR Recombinant Somatotropins OR Somatotropins, Recombinant OR growth hormon* OR Somatotropin* OR Pituitary Growth Hormon* OR Recombinant Pituitary Growth Hormon* OR Recombinant Somatotropin* OR Recombinant Growth Hormon*)

Total search strategy for medical interventions:

12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

13. **Anthracyclines**

(anthracyclines OR anthracyclin* OR anthracycline antibiotics OR antibiotics, anthracycline OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI30 OR IMI-30 OR idarubicin hydrochloride OR hydrochloride, idarubicin OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-epidoxorubicin OR 4' epidoxorubicin OR 4'-epi-doxorubicin OR 4' epi doxorubicin OR 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR hydrochloride, epirubicin OR farmorubicin OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR hydrochloride, doxorubicin OR doxorubic* OR adriamyc* OR dauno-rubidomycine OR dauno rubidomycin OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR doxorubicin, liposomal OR myocet OR doxorubicin OR daunorubicin)

14. **Childhood cancer**

(((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology)) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (cancer or neoplasms or tumor or cancers or neoplasm or tumors)

15. **RCTs, CCTs**

(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) AND humans[mh]

The final combined search was:

16. **12 AND 13 AND 14 AND 15**

[pt = publication type; tiab = title, abstract; sh = subject heading; mh = MeSH term; *=zero or more characters; RCT = randomized controlled trial; CCT = controlled clinical trial]

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Appendix 2. Search strategy for EMBASE (OVID)

1. Medical interventions

1. (ace inhibitor or ace-inhibitor or ace inhibitor$ or ace-inhibitor$).mp.

2. Dipeptidyl Carboxypeptidase Inhibitor/ or (angiotensin converting enzyme inhibitor or angiotensin converting enzyme inhibitors or angiotensin converting enzyme inhibitor$).mp.

3. (angiotensin-converting enzyme inhibitor or angiotensin-converting enzyme inhibitors or angiotensin-converting enzyme inhibitor$).mp.

4. (angiotensin-converting enzyme antagonist or angiotensin-converting enzyme antagonists or angiotensin-converting enzyme antagonist$ or angiotensin converting enzyme antagonist or angiotensin converting enzyme antagonists or angiotensin converting enzyme antagonist$).mp.

5. (kininase II inhibitor or kininase II inhibitors or kininase II inhibitor$ or kininase II antagonist or kininase antagonists or kininase antagonist$).mp.

6. (angiotensin I-converting enzyme inhibitors or angiotensin I converting enzyme inhibitors or angiotensin I-converting enzyme inhibitor$ or angiotensin I converting enzyme inhibitor$).mp.

7. (peptidyl dipeptidase or peptidyl dipeptidase A).mp. or exp Dipeptidyl Carboxypeptidase/

8. exp Kininase/ or Kininase A.mp.

9. (Angiotensin I-Converting Enzyme or Angiotensin I Converting Enzyme).mp.

10. exp Dipeptidyl Peptidase/ or Dipeptidyl Peptidase A.mp.

11. (Carboxycathepsin or Angiotensin Converting Enzyme or Kininase II).mp.

12. (CD143 Antigen or CD143 Antigens).mp.

13. (captopril or enalapril or fosinopril).mp. or exp Captopril Plus Hydrochlorothiazide/ or exp Captopril/ or exp Enalapril Maleate/ or exp Enalapril Plus Hydrochlorothiazide/ or exp Enalapril/ or exp Enalapril Maleate Plus Nitrendipine/ or exp Enalapril Maleate Plus Felodipine/ or exp Diltiazem Plus Enalapril Maleate/ or exp Fosinopril/ [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

14. (angiotensin receptor blocker or angiotensin receptor blockers or angiotensin receptor blocker$).mp.

15. (angiotensin II type 1 receptor blockers or angiotensin II type 2 receptor blocker$).mp. or exp Angiotensin Receptor Antagonist/

16. (angiotensin II type 1 receptor antagonists or type 1 angiotensin receptor antagonists or type 1 angiotensin receptor blocker$ or type 1 angiotensin receptor blockers or type 1 angiotensin receptor antagonist$).mp.

17. exp Angiotensin Antagonist/ or exp Angiotensin/ or exp Angiotensin 2 Receptor Antagonist/ or exp Angiotensin II Antagonist/

18. (selective angiotensin II receptor antagonists or selective angiotensin II receptor antogonist$ or sartans or angiotensin II).mp.

19. (losartan or valsartan).mp. or exp Losartan/ or exp Hydrochlorothiazide Plus Losartan/ or exp Losartan Potassium/ or exp Hydrochlorothiazide Plus Valsartan/ or exp Amlodipine Plus Valsartan/ or exp Valsartan/

20. (beta blocker or beta blockers or beta blocker$ or beta-blocker or beta-blockers or beta-blocker$).mp.

21. exp Beta Adrenergic Receptor Blocking Agent/

22. (adrenergic beta-antagonists or adrenergic beta antagonists).mp.

23. (adrenergic beta-receptor blockaders or adrenergic beta receptor blockaders or beta-adrenergic receptor blockaders or beta adrenergic receptor blockaders).mp.

24. (beta-adrenergic blocking agents or beta adregenic blocking agents or beta-adrenergic blockers or beta adrenergic blockers or adrenergic beta-blockers or adrenergic beta blockers).mp.

25. (sympatholytics or sympathetic-blocking agents or sympathetic blocking agents or sympatholytic agents or sympatholytic drugs or sympatholytic$).mp.

26. (adrenergic beta antagonist$ or adrenergic beta-receptor blockader$ or adrenergic beta receptor blockader$ or beta-adrenergic receptor blockader$ or beta adrenergic receptor blockader$ or beta-adrenergic blocking agent$ or beta adrenergic blocking agent$).mp.

27. (beta adrenergic blocker$ or beta-adrenergic blocker$ or adrenergic beta-blocker$ or sympathetic-blocking agent$ or sympathetic blocking agent$ or sympatholytic agent$ or sympatholytic drug$).mp.

28. (carvedilol or atenolol or metoprolol or propanolol).mp. or exp carvedilol/ or exp atenolol plus chlortalidone/ or exp atenolol/ or exp atenolol plus nifedipine/ or exp metoprolol tartrate/ or exp metoprolol/ or exp metoprolol fumarate/ or exp metoprolol succinate/ or exp propranolol/

29. (calcium channel blocker or calcium channel blockers or calcium channel blocker$).mp.

30. exp Calcium Channel Blocking Agent/

31. exp Calcium Antagonist/ or (exogenous calcium antagonists or exogenous calcium blockaders or calcium channel blocking drugs).mp.

32. (exogenous calcium inhibitors or exogenous calcium antagonist$ or exogenous calcium blockader$ or calcium channel blocking drug$).mp.

33. (exogenous calcium inhibitor$ or exogenous calcium blockader$ or calcium channel blocking drug$ or exogenous calcium inhibitor$).mp.

34. exp Diltiazem Derivative/ or exp Diltiazem/ or exp Diltiazem Plus Enalapril Maleate/ or exp Nefedipine/ or (diltiazem or nefedipine).mp.

35. exp DIGOXIN/

36. (digoxin or digoxin$ or lanoxin).mp.

37. (vasodilator or vasodilators or vasodilator$).mp.

38. exp Vasodilator Agent/ or (vasodilator agents or vasodilator agent$ or vasodilator drugs or vasodilator drug$ or vasoactive antagonists or vasoactive antagonist$).mp.

39. (nitroglycerin or glyceryl trinitrate or nitroglycerin$ or diazoxide or adenosine).mp.

40. exp diazoxide/ or exp glyceryl trinitrate/

41. (diuretic or diuretics or diuretic$).mp.

42. exp Diuretic Agent/ or exp Furosemide Plus Triamterene/ or exp Furosemide/ or furosemide.mp.

43. (aldosteron antagonist or aldosteron antagonists or aldosterone antagonist aldosterone antagonists or aldosterone antagonist$).mp.

44. exp Aldosterone Antagonist/ or spironolacton.mp. or exp Spironolactone/

45. (antihypertensiva or antihypertensive or anti hypertensive or anti-hypertensive).mp.

46. exp Antihypertensive Agent/

47. (anti hypertensive drugs or anti-hypertensive drugs or antihypertensive drugs or antihypertensive agents or anti-hypertensive agents or anti hypertensive agents).mp.

48. (anti-hypertensives or anti hypertensives or antihypertensives).mp.

49. (antihypertensiv$ or antihypertensive drug$ or anti hypertensive drug$ or antihypertensive agent$ or anti hypertensive agent$).mp.

50. exp Clonidine Derivative/ or clonidine.mp. or exp Clonidine/ or exp Clonidine Displacing Substance/

51. (inotropic or inotropics or inotropic$).mp.

52. exp dopamine/ or exp dobutamine/ or exp adrenalin/ or exp noradrenaline/ or (dopamine or dobutamine or epinephrine or norepinephrine).mp.

53. (growth hormone or pituitary growth hormone).mp. or exp Growth Hormone/

54. (somatropin or recombinant somatotropin).mp. or exp recombinant growth hormone/ or recombinant pituitary growth hormones.mp.

55. (recombinant growth hormone or recombinant growth hormones or recombinant somatotropins).mp.

56. (growth hormon$ or somatotropin$ or pituitary growth hormon$ or recombinant pituitary growth hormon$ or recombinant somatotropin$ or recombinant growth hormon$).mp.

57. or/1-56

2. Anthracyclines

1. (anthracyclin$ or anthracyclines).mp. or exp Anthracycline/

2. anthracycline antibiotics.mp. or exp Anthracycline Antibiotic Agent/

3. exp Anthracycline Derivative/

4. (4-demethoxydaunorubicin or 4 demethoxydaunorubicin or 4-desmethoxydaunorubicin or 4 desmethoxydaunorubicin).mp. or exp idarubicin/

5. (IMI 30 or IMI30 OR IMI-30 or idarubicin hydrochloride).mp.

6. (NSC 256439 or NSC-256439 or NSC256349 or idarubicin or idarubic$).mp.

7. (4'-epiadriamycin or 4' epiadriamycin or 4'-epidoxorubicin or 4' epidoxorubicin or 4'-epi-doxorubicin or 4' epi doxorubicin).mp.

8. (4'-epi-adriamycin or 4' epi adriamycin or 4'-epi-DXR or 4' epi DXR).mp.

9. exp epirubicin/ or (epirubicin or epirubicin hydrochloride or epirubic$ or farmorubicin).mp.

10. (IMI-28 or IMI 28 or IMI28 or NSC 256942 or NSC-256942 or NSC256942).mp.

11. (adriablastine or adriblastin or adriablastin or adriamycin).mp.

12. (DOX-SL or DOX SL or doxorubicin hydrochloride or doxorubic$ or adramyc$).mp.

13. (dauno-rubidomycine or dauno rubidomycin or rubidomycin or rubomycin or daunomycin).mp.

14. (cerubidine or daunoblastin or daunoblastine or daunorubicin hydrochloride or daunorubic$).mp.

15. (NSC-82151 or NSC 82151 or NSC82151).mp.

16. (daunoxome or daunoxom$ or daunosom$ or doxil or caelyx or liposomal doxorubicin or myocet or doxorubicin or daunorubicin).mp.

17. exp DAUNORUBICIN DERIVATIVE/ or exp DAUNORUBICIN/ or exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or exp DOXORUBICIN DERIVATIVE/ or exp DOXORUBICIN/ or exp EPIRUBICIN/

18. or/1-17

3. Childhood cancer

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.

2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.

3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.

4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.

5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.

6. (pediatric oncology or paediatric oncology).mp.

7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.

8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.

9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.

10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.

11. intracranial neoplasm$.mp.

12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/

13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/

14. or/1-13

4. RCTs, CCTs

1. Randomized Controlled Trial/

2. Controlled Clinical Trial/

3. randomized.ti,ab.

4. placebo.ti,ab.

5. randomly.ti,ab.

6. trial.ti,ab.

7. groups.ti,ab.

8. drug therapy.sh.

9. or/1-8

10. Human/

11. 9 and 10

The final combined search was:

5. 1 AND 2 AND 3 AND 4

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; sh = subject heading; ti,ab = title, abstract; / = Emtree term; $=zero or more characters ; RCT = randomized controlled trial; CCT = controlled clinical trial]

Appendix 3. Search strategy for Central Register of Controlled Trials (CENTRAL)

Medical interventions:

1. **ACE-inhibitor**

(ace inhibitor OR ace-inhibitor OR ace inhibitor* OR ace-inhibitor* OR Angiotensin-Converting Enzyme Inhibitors OR Angiotensin Converting Enzyme Inhibitors OR Angiotensin-Converting Enzyme Antagonists OR Angiotensin Converting Enzyme Antagonists OR ACE Inhibitors OR Kininase II Inhibitors OR Kininase II Antagonists OR Angiotensin I-Converting Enzyme Inhibitors OR Angiotensin I Converting Enzyme Inhibitors OR Angiotensin-Converting Enzyme Inhibitor* OR Angiotensin Converting Enzyme Inhibitor* OR Angiotensin-Converting Enzyme Antagonist* OR Angiotensin Converting Enzyme Antagonist* OR Kininase II Inhibitor* OR Kininase II Antagonist* OR Angiotensin I-Converting Enzyme Inhibitor* OR Angiotensin I Converting Enzyme Inhibitor* OR captopril OR enalapril OR fosinopril OR peptidyl dipeptidase OR Peptidyl Dipeptidase A OR Angiotensin I-Converting

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Enzyme OR Angiotensin I Converting Enzyme OR Carboxycathepsin OR Kininase A OR CD143 Antigen OR CD143 Antigens OR Dipeptidyl Peptidase A OR Angiotensin Converting Enzyme OR Kininase II)

2. **Angiotensin receptor blocker**

(angiotensin receptor blocker OR angiotensin receptor blockers OR angiotensin receptor blocker* OR Angiotensin II Type 1 Receptor Blockers OR Angiotensin II Type 1 Receptor Antagonists OR Type 1 Angiotensin Receptor Antagonists OR Type 1 Angiotensin Receptor Blockers OR Selective Angiotensin II Receptor Antagonists OR Sartans OR Angiotensin II OR Angiotensin Receptors/ antagonists & inhibitors OR Angiotensin II Type 1 Receptor Blocker* OR Type 1 Angiotensin Receptor Antagonist* OR Type 1 Angiotensin Receptor Blocker* OR Selective Angiotensin II Receptor Antagonist* OR losartan OR valsartan)

3. **Beta-blocker**

(beta blocker OR beta blockers OR beta-blockers OR beta-blocker OR beta-blocker* OR beta blocker* OR Adrenergic beta Antagonists OR adrenergic beta-antagonists OR Adrenergic beta-Receptor Blockaders OR Adrenergic beta Receptor Blockaders OR beta-Adrenergic Receptor Blockaders OR beta Adrenergic Receptor Blockaders OR beta-Adrenergic Blocking Agents OR beta Adrenergic Blocking Agents OR beta-Adrenergic Blockers OR beta Adrenergic Blockers OR Adrenergic beta-Blockers OR Sympatholytics OR Sympathetic-Blocking Agents OR Sympathetic Blocking Agents OR Sympatholytic Agents OR Sympatholytic Drugs OR Sympatholytic* OR Adrenergic beta Antagonist* OR Adrenergic beta-Receptor Blockader* OR Adrenergic beta Receptor Blockader* OR beta-Adrenergic Receptor Blockader* OR beta Adrenergic Receptor Blockader* OR beta-Adrenergic Blocking Agent* OR beta Adrenergic Blocking Agent* OR beta Adrenergic Blocker* OR beta-Adrenergic Blocker* OR Adrenergic beta-Blocker* OR Sympathetic-Blocking Agent* OR Sympathetic Blocking Agent* OR Sympatholytic Agent* OR Sympatholytic Drug* OR carvedilol OR atenolol OR metoprolol OR propranolol)

4. **Calcium channel blocker**

(calcium channel blocker OR calcium channel blockers OR calcium channel blocker* OR Exogenous Calcium Antagonists OR Exogenous Calcium Blockaders OR Calcium Channel Blocking Drugs OR Exogenous Calcium Inhibitors OR Exogenous Calcium Antagonist* OR Exogenous Calcium Blockader* OR Calcium Channel Blocking Drug* OR Exogenous Calcium Inhibitor* OR Exogenous Calcium Blockader* OR Calcium Channel Blocking Drug* OR Exogenous Calcium Inhibitor* OR diltiazem OR nifedipine)

5. **Digoxin**

(digoxin OR digoxin* OR Lanoxin)

6. **Vasodilator agent**

(vasodilator OR vasodilators OR vasodilator* OR vasodilator agents OR Vasodilator Drugs OR Vasoactive Antagonists OR Vasoactive Antagonist* OR vasodilator agent* OR Vasodilator Drug* OR nitroglycerin OR Glyceryl Trinitrate OR Trinitrate, Glyceryl OR Nitroglycerin* OR diazoxide OR adenosine)

7. **Diuretic**

(diuretic OR diuretics OR diuretic* OR furosemide)

8. **Aldosterone antagonist**

(aldosteron antagonist OR aldosteron antagonists OR aldosterone antagonist OR aldosterone antagonists OR aldosterone antagonist* OR aldosteron antagonist* OR spironolactone)

9. **(Other) antihypertensive agents**

(antihypertensiva OR anti-hypertensive OR anti hypertensive OR anti hypertensive drugs OR antihypertensive drugs OR antihypertensive agents OR Anti-Hypertensive Agents OR Anti Hypertensive Agents OR Anti-Hypertensive Drugs OR Anti Hypertensive Drugs OR Anti-Hypertensives OR Anti Hypertensives OR Antihypertensive Drugs OR Antihypertensives OR antihypertensiv* OR antihypertensive drug* OR anti hypertensive drug* OR antihypertensive agent* OR anti hypertensive agent* OR clonidine)

10. **Inotropic**

(inotropics OR inotropic OR inotropic* OR dopamine OR dobutamine OR epinephrine OR norepinephrine)

11. **Growth hormone**

(growth hormone OR Pituitary Growth Hormone OR Somatotropin OR Recombinant Pituitary Growth Hormones OR Recombinant Somatotropin OR Recombinant Growth Hormone OR Recombinant Growth Hormones OR Recombinant Somatotropins OR growth hormon* OR Somatotropin* OR Pituitary Growth Hormon* OR Recombinant Pituitary Growth Hormon* OR Recombinant Somatotropin* OR Recombinant Growth Hormon*)

Total search strategy for medical interventions:

12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11

13. **Anthracyclines**

anthracyclines OR anthracyclin* OR anthracycline antibiotics OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR IMI 30 OR IMI30 OR IMI-30 OR idarubicin hydrochloride OR NSC 256439 OR NSC-256439 OR NSC256439 OR idarubicin OR idarubic* OR 4'-epiadriamycin OR 4' epiadriamycin OR 4'-

epidoxorubicin OR 4' epidoxorubicin OR 4'-epi-doxorubicin OR 4' epi doxorubicin OR 4'-epi-adriamycin OR 4' epi adriamycin OR 4'-epi-DXR OR 4' epi DXR OR epirubicin hydrochloride OR farmorubicin OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942 OR epirubicin OR epirubic* OR adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR doxorubicin hydrochloride OR doxorubic* OR adriamyc* OR dauno-rubidomycine OR dauno rubidomycin OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR hydrochloride, daunorubicin OR daunorubic* OR rubidomyc* OR NSC-82151 OR NSC 82151 OR NSC82151 OR daunoxome OR daunoxom* OR daunosom* OR doxil OR caelyx OR liposomal doxorubicin OR myocet OR doxorubicin OR daunorubicin

14. **Childhood cancer**

(leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR cancer or neoplasms or tumor or cancers or neoplasm or tumors)

The final combined search was:

15. **12 AND 13 AND 14**

All searches in Title, Abstract or Keywords in Cochrane Central Register of Controlled Trials (CENTRAL).

[*=zero or more characters]

WHAT'S NEW

Last assessed as up-to-date: 7 November 2010.

Date	Event	Description
29 January 2015	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Elske Sieswerda designed the study and wrote the protocol. She developed the search strategy. She identified the studies meeting the inclusion criteria and searched for unpublished and ongoing studies. She performed the data-extraction and 'Risk of bias' assessment of the included study in English and checked the data-extraction and 'Risk of bias' assessment of the included study in Chinese, performed by the fourth author. She analysed the data and interpreted the results. She wrote and revised the manuscript.

Elvira van Dalen supervised in the design of the study and the writing of the protocol. She critically reviewed the protocol. She developed the search strategy. She identified the studies meeting the inclusion criteria and searched for unpublished and ongoing studies. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Aleida Postma critically reviewed the protocol. She identified studies meeting the inclusion criteria and checked the data-extraction and 'Risk of bias' assessment of the included study in English, performed by the first author. She contributed to the interpretation of the results. She critically reviewed the manuscript.

Daniel Cheuk performed the data-extraction and 'Risk of bias' assessment of the included study in Chinese. He contributed to the interpretation of the results. He wrote and revised the manuscript. He critically reviewed the manuscript.

Huib Caron critically reviewed the protocol. He contributed to the interpretation of the results. He critically reviewed the manuscript.

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Leontien Kremer supervised in the design of the study, the development of the search strategy, the writing of the protocol, the selection of studies, the data-extraction and the 'Risk of bias' assessment. She critically reviewed the protocol. She contributed to the interpretation of the results. She critically reviewed the manuscript.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Dutch Cochrane Centre, Netherlands.

External sources

- Foundation of Paediatric Cancer Research (SKK), Netherlands.
- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As opposed to the protocol in which it was stated that we would use the criteria and definitions stated in the module of the Cochrane Childhood Cancer Group (as available in 2008: Module CCG), the 'Risk of bias' assessment was based both on the earlier mentioned module and on information provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). New items (i.e. generation of allocation sequence, selective outcome reporting and other sources of bias) were added and some definitions were adjusted.

Based on a peer-reviewer's comment, we added to the methods section the Fisher's exact test, P for situations in which only one study was available and there were no events in one of the treatment groups.

The data-extraction and 'Risk of bias' assessment of included studies was done by one review author and checked by another review author.

We did not contact authors in order to obtain missing data during the data-extraction and 'Risk of bias' assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

Adult Survivors of Child Adverse Events; Angiotensin-Converting Enzyme Inhibitors [adverse effects; *therapeutic use]; Anthracyclines [*administration & dosage; adverse effects]; Antibiotics, Antineoplastic [*adverse effects]; Cardiotonic Agents [*therapeutic use]; Enalapril [adverse effects; *therapeutic use]; Heart Failure [chemically induced; *drug therapy; mortality]; Neoplasms [drug therapy]; Phosphocreatine [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans