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Different anthracycline derivates for reducing cardiotoxicity in cancer patients (Review)

van Dalen EC, Michiels EMC, Caron HN, Kremer LCM

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[Intervention Review]

Different anthracycline derivates for reducing cardiotoxicity in cancer patients

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ABSTRACT

Background

The use of anthracyclines is limited by the occurrence of cardiotoxicity. In an effort to prevent this cardiotoxicity, different anthracycline derivates have been studied.

Objectives

To determine the occurrence of cardiotoxicity with the use of different anthracycline derivates in cancer patients.

Search methods

We searched The Cochrane Central Register of Controlled Trials (CENTRAL), (The Cochrane Library, Issue 2, 2009), MEDLINE (1966 to 29 May 2009) and EMBASE (1980 to 2 June 2009). In addition, we searched reference lists of relevant articles, conference proceedings and ongoing-trials-databases.

Selection criteria

Randomised controlled trials (RCTs) in which different anthracycline derivates were compared in cancer patients (children and adults).

Data collection and analysis

Two authors independently performed study selection, assessment of risk of bias and data-extraction including adverse effects.

Main results

We identified five RCTs of varying quality addressing epirubicin versus doxorubicin (1036 patients) with the same dose. The meta-analysis showed no evidence for a significant difference in the occurrence of clinical heart failure between the treatment groups (RR = 0.36, 95% CI 0.12 to 1.11). However, there is some suggestion of a lower rate of clinical heart failure in patients treated with epirubicin.

We identified two RCTs with varying quality addressing liposomal-encapsulated doxorubicin versus conventional doxorubicin (521 patients). The meta-analysis showed a significantly lower rate of both clinical heart failure and clinical and subclinical heart failure combined in patients treated with liposomal-encapsulated doxorubicin (RR = 0.20, 95% CI 0.05 to 0.75 and RR = 0.38, 95% CI 0.24 to 0.59 respectively). It should be noted that in one of the studies patients in the liposomal-encapsulated doxorubicin group received a higher cumulative anthracycline dose than patients in the doxorubicin group.

For the other possible combinations of different anthracycline derivates only one RCT (epirubicin versus liposomal-encapsulated doxorubicin) or no RCT was identified.

Authors' conclusions

We are not able to favour either epirubicin or doxorubicin when given with the same dose. Based on the currently available evidence on heart failure, we conclude that in adults with a solid tumour liposomal-encapsulated doxorubicin should be favoured over doxorubicin. For both epirubicin versus doxorubicin and liposomal-encapsulated doxorubicin versus conventional doxorubicin no conclusions can be made about the effects of treatment in children treated with anthracyclines and also not in patients diagnosed with leukaemia. More research is needed. For other combinations of anthracycline derivates not enough evidence was available to make definitive conclusions about the occurrence of cardiotoxicity in patients treated with anthracyclines.

PLAIN LANGUAGE SUMMARY

Different anthracycline derivates for reducing cardiotoxicity in cancer patients

Anthracyclines are among the most effective chemotherapy treatments available for various types of cancer. However, there is a risk of damage to the heart depending on the cumulative dose. In an effort to prevent heart damage different anthracycline derivates (like doxorubicin, daunorubicin, and epirubicin) are being used.

The authors found that for the use of many different combinations of anthracycline derivates there was no high quality evidence available and it was impossible to draw conclusions.

For the use of epirubicin versus doxorubicin, there was some suggestion of a lower rate of clinical heart failure in patients treated with epirubicin. There is no evidence which suggests a difference in anti-tumour response rate and survival between epirubicin and doxorubicin. No conclusions can be made regarding adverse effects. There are no data for children and patients with leukaemia. Further research is needed. For the use of doxorubicin versus liposomal-encapsulated doxorubicin, the authors found a significantly lower rate of both clinical heart failure and subclinical heart failure (i.e. various cardiac abnormalities, diagnosed with different diagnostic methods like echocardiography in asymptomatic patients) in patients treated with liposomal-encapsulated doxorubicin. There is no evidence which suggests a difference in anti-tumour response rate and survival between doxorubicin and liposomal-encapsulated doxorubicin. A lower rate of adverse effects was identified in patients treated with liposomal-encapsulated doxorubicin. There are no data for children and patients with leukaemia. Further research is needed.

BACKGROUND

Anthracyclines are among the most effective chemotherapeutic agents and have gained widespread use in the treatment of numerous solid tumours and hematologic malignancies in both adult and paediatric patients. However, their use is limited by a dose-dependent cardiotoxicity (Bonadonna 1969; Lefrak 1973).

According to the time of presentation, the heart damage after anthracycline therapy can be divided into early and late cardiotoxicity: early cardiotoxicity refers to heart damage that develops during anthracycline therapy or in the first year after its completion, and late cardiotoxicity manifests itself at least one year after the completion of anthracycline therapy (Shan 1996). The risk of developing heart failure remains a lifelong threat, especially for children and young adults who have a long life-expectancy after successful antineoplastic treatment. The risk of developing clinical heart failure 20 years after anthracycline therapy for childhood cancer is estimated to be approximately 5.5 per cent (Van Dalen 2006a).

Heart damage can become manifest in patients as either subclinical cardiotoxicity or clinical cardiotoxicity. The term subclinical cardiotoxicity is used to describe various cardiac abnormalities, diagnosed with different diagnostic methods in asymptomatic patients. Examples are histological abnormalities according to the Billingham score (Billingham 1978) or abnormalities in cardiac function measured by echocardiography or radionuclide ventriculography. Clinical cardiotoxicity is defined on the basis of symptoms of clinical heart failure, confirmed by an abnormal diagnostic test. In the end stage of clinical heart failure, heart transplantation is the only remaining option to avoid cardiac death.

In the literature, there is a wide variation in the reported frequency of both clinical and subclinical cardiotoxicity; in children, the prevalence of subclinical cardiac dysfunction has been reported to be more than 57% at a median of 6.4 years after treatment (Kremer 2002a) and the incidence of clinical heart failure as high as 16% 0.9 to 4.8 years after treatment (Kremer 2002b). In adults the prevalence of subclinical cardiac dysfunction has been reported to be 36% during anthracycline therapy (Nousiainen 2002) and the incidence of clinical heart failure 30% at a median of 37 months after treatment (Meinardi 2002). However, we did not perform systematic reviews on the frequency of anthracycline-induced cardiotoxicity in adults. Possible risk factors (Kremer 2002b; Ng 2006; Simbre 2005) are the type of anthracycline used, the cumulative anthracycline dose, and the presence of additional risk factors for developing heart damage such as radiation therapy involving the heart region, type of tumour, exposure to cyclophosphamide, iphosphamide, amsacrine, trastuzumab or taxanes or the presence of pre-existing heart damage. There also seems to be a higher risk for females, children and elderly people.

Clinicians confront a clinical dilemma as they balance the efficacy of higher anthracycline doses against the cardiotoxicity associated with these higher doses. In an effort to prevent or reduce this toxicity, extensive research has been devoted to the identification of anthracycline derivates with less cardiotoxic effects than doxorubicin, such as daunorubicin, epirubicin and idarubicin (Muggia 1991) and liposomal anthracyclines (Batist 2001).

An important question regarding any anthracycline derivate is whether it has a lower cardiotoxic effect without reducing the anti-tumour efficacy and without negative effects on toxicities other than cardiac damage, such as alopecia, nausea, vomiting, stomatitis, diarrhoea, fatigue, anaemia, leukopenia and thrombocytopenia.

This is an update of the first systematic review on the cardiotoxicity of different anthracycline derivates.

OBJECTIVES

Primary objective

To determine the cardiotoxicity of any type of anthracycline derivate in patients with cancer when compared to another type of anthracycline derivate.

Secondary objectives:

1. To determine possible effects of these anthracycline derivates on tumour response and patient survival (i.e. antitumour efficacy).
2. To determine possible effects of these anthracycline derivates on toxicities other than cardiac damage as well as quality of life (QOL).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing the occurrence of heart damage with the use of any type of anthracycline derivate with another type of anthracycline derivate.

Types of participants

Patients with cancer (both adults and children) who received anthracycline chemotherapy.

Types of interventions

Different types of anthracycline derivates with the same infusion duration and peak dose (i.e. the maximal dose received in one week). Chemotherapy other than anthracyclines and radiotherapy involving the heart region should be the same in both treatment groups. The cumulative anthracycline dose received in both treatment groups should have been mentioned, since otherwise it was impossible to correctly interpret the results of the study.

Types of outcome measures

Primary outcomes

Anthracycline-induced heart failure (i.e. clinical heart failure (as defined by the authors) and subclinical cardiac dysfunction (defined as either histological abnormalities according to the Billingham-score on myocardial biopsy (Billingham 1978) or abnormalities in cardiac function measured by echocardiography or radionuclide ventriculography)). If possible, both early and late cardiotoxicity were assessed (early cardiotoxicity refers to heart damage that develops during anthracycline therapy or in the first year after its completion, and late cardiotoxicity manifests itself at least one year after the completion of anthracycline therapy).

Secondary outcomes

Secondary outcomes included potential adverse effects of the different types of anthracycline derivates on:

1. Tumour response (defined as the number of complete and partial remissions)
2. Patient survival (progression-free survival (PFS) and overall survival (OS))
3. Toxicities other than cardiac damage
4. QOL

Search methods for identification of studies

Electronic searches

See: Review Group search strategy.

The electronic databases of CENTRAL (Cochrane Library, Issue 2, 2009), MEDLINE/PubMed (from 1966 to 29 May 2009), and EMBASE/Ovid (from 1980 to 2 June 2009) were searched. The search strategies for the different databases (using a combination of subject headings and text word terms) are stated in Appendix 1, Appendix 2 and Appendix 3. The search strategies were designed and executed by the author team. For the update of this review we adapted the search strategies used in the original version of the review (until April 2005). The exact changes are stated in the appendices.

Searching other resources

Information about trials not registered in CENTRAL, MEDLINE, or EMBASE, either published or unpublished, was located by searching the reference lists of relevant articles and review articles. In addition, the conference proceedings of the International Society for Paediatric Oncology (SIOP) and the American Society of Clinical Oncology (ASCO) were handsearched from 2000 to 2008. We searched for ongoing trials by scanning the ISRCTN register and the National Institute of Health Register (both screened June 2009 on www.controlled-trials.com). If possible, we contacted the investigators of possible eligible trials of which the available data did not provide all data needed to assess whether the study was truly eligible for inclusion in the review. Language restriction was not imposed.

Data collection and analysis

Selection of studies

After employing the search strategy described previously, identification of studies meeting the inclusion criteria was undertaken by two authors independently. Discrepancies between authors were resolved by consensus. No third party arbitration was needed. Any study seemingly meeting the inclusion criteria on grounds of the title, or abstract, or both, was obtained in full for closer inspection.

Data extraction and management

Data extraction was performed independently by two authors using standardised forms. Data of the characteristics of participants (such as age, sex, tumour type), of interventions (such as individual peak dose, cumulative dose), of outcome measures and of length of follow-up were extracted. Discrepancies were resolved by consensus. No third party arbitration was needed.

Assessment of risk of bias in included studies

The risk of bias in the included trials was assessed by two authors independently according to the following criteria: method of randomization, concealment of treatment allocation, blinding of the care provider, blinding of the patients, blinding of the outcome assessor (for each outcome separately), and completeness of follow-up (for each outcome separately). The adequacy of allocation concealment was assessed using the criteria proposed by Schulz and colleagues (Schulz 1995). See additional Table 1 for the complete criteria list for the assessment of risk of bias. Discrepancies were resolved by consensus. No third party arbitration was needed.

Data synthesis

Data were entered into RevMan and analysed according to the guidelines of the Cochrane Handbook (Higgins 2005). Dichotomous variables were related to risk using the relative risk / risk ratio (RR). If possible, data were extracted by allocation intervention, irrespective of compliance with the allocated intervention, in order to allow an 'intention-to-treat' analysis. If this was not possible, this was stated. Heterogeneity was assessed both by visual inspection of the forest plots and by a formal statistical test for heterogeneity, i.e. the I^2-test (I^2 > 50% was considered substantial heterogeneity). If there was evidence of substantial heterogeneity, this was reported. We used a random effects model throughout the review. All results are presented with the corresponding 95% confidence interval (95% CI). If pooling was not possible we provided descriptive results for these studies. We used the generic inverse variance function of RevMan to combine logs of the hazard ratios (HR) for progression-free survival and overall survival. Where necessary, Parmar's method was used to extract the log of the HR and its standard error (SE) (Parmar 1998). Otherwise, survival was summarised descriptively. An outcome measure was only included in this systematic review if it was the intention of the study to perform the necessary assessments in all randomised patients (i.e. not only optional or only performed in some centers). When less than 50% of the patients of a study had an acceptable follow-up for a particular outcome measure, due to associated the high risk of attrition bias, we did not report the results of this outcome measure. The risk of bias in studies included in the analyses was taken into account in the interpretation of the review's results. For all outcomes for which pooling was possible we performed sensitivity analyses for all risk of bias criteria separately. We excluded studies with a high risk of bias and studies for which the presence of bias was unclear and compared the results of studies with a low risk of bias with the results of all available studies. It was our intention to perform subgroup analyses for children and adults and for leukaemias and solid tumours, but unfortunately this was not possible (see Results for reasons).

RESULTS

Description of studies

After performing the searches of the electronic databases of CENTRAL, MEDLINE/PubMed and EMBASE/Ovid (2925 references: 684 identified in the update) we included a total of seven articles which fulfilled all the criteria for considering studies for this review (no new studies were identified in the update). From the currently available data of one study it is unclear if this study is eligible for inclusion in this review (identified in the update; see

Studies awaiting classification). Fifty-two articles were excluded after assessing the full text article for reasons described in the Characteristics of excluded studies. The remaining 2865 articles were excluded based on the title and / or abstract since they were not a RCT, were laboratory studies, were animal studies, did not include patients with cancer, did not describe anthracycline therapy with different derivates, were duplicate publications, there was a difference in anthracycline peak dose and / or infusion duration between the treatment groups, there was a difference in chemotherapy other than anthracyclines and / or radiotherapy involving the heart region between the treatment groups, and / or did not have heart failure as an outcome measure.

From scanning the reference lists of relevant articles and reviews one additional article was included in this review. From the currently available data of one study it is unclear if this study is eligible for inclusion in this review (identified in the update; see Characteristics of studies awaiting classification) Ten other articles were added to the Characteristics of excluded studies.

No extra information was obtained from scanning the conference proceedings of SIOP and ASCO, although two additional studies were excluded and thus added to the Characteristics of excluded studies (one identified in the update). Also, from the currently available data of one study it is unclear if this study is eligible for inclusion in this review (identified in the update; see Studies awaiting classification).

Searching the ongoing trial databases identified nine studies, of which one was eligible for this review (identified in the update; see Characteristics of ongoing studies). From five other trials (three identified in the update) we were not able to obtain all the information necessary to assess the eligibility of these trials (see Studies awaiting classification). After obtaining additional information it became clear that the other three studies were not eligible for inclusion in the review (all identified in the update; see Excluded studies).

Therefore, the total number of identified RCTs was eight. Five studies addressed doxorubicin versus epirubicin, two studies addressed conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet) and one study addressed epirubicin versus liposomal-encapsulated doxorubicin (myocet). For the other combinations of different anthracycline derivates no adequate RCTs were identified.

Description of studies addressing doxorubicin versus epirubicin

Our analysis of the cardiotoxicity of doxorubicin when compared with that of epirubicin included five trials (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988; Mouridsen 1984) with a total of 1036 patients. Five-hundred-and-fifteen patients were randomised to treatment with doxorubicin, whereas 521 patients were randomised to treatment with epirubicin. There were no important differences in cumulative anthracycline doses received in both treatment arms of the different RCTs. All studies included adult patients with a solid tumour. In four studies patients were diagnosed with breast cancer (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988), and in the other study with soft tissue sarcoma (Mouridsen 1984). In 2 studies the follow-up of the included patients was more than one year (Brambilla 1986; FESG 1988) and in one study this was possible for at least part of the included patients (IMBSWE 1988). Therefore it is possible that these studies included cases of both early and late cardiotoxicity. In the other studies the length of follow-up was not mentioned and as a result we don't know if the cases of cardiotoxicity in these studies are early or late. However, based on the fact that all patients included in these trials had advanced or metastatic disease and the associated effect on survival duration, we presume that cases of heart failure in these trials were early cardiotoxicity.

Description of studies addressing conventional doxorubicin versus liposomal-encapsulated doxorubicin

Our analysis of the cardiotoxicity of conventional doxorubicin when compared with that of liposomal-encapsulated doxorubicin included two trials (Batist 2001; Harris 2002) with a total of 521 patients. Two-hundred-and-seventy-one patients were randomised to treatment with doxorubicin, whereas 250 patients were randomised to treatment with liposomal-encapsulated doxorubicin. Both studies mentioned the cumulative anthracycline dose patients in the treatment groups received: in the study of Batist 2001 patients in both treatment groups received a median cumulative dose of 360 mg/m^2, whereas in the study of Harris 2002 patients in the doxorubicin group received a median cumulative dose of 570 mg/m^2 and patients in the liposomal-encapsulated doxorubicin group received a cumulative dose of 785 mg/m^2. Both studies included adult patients with breast cancer. In one study the follow-up of the included patients was more than one year (Batist 2001) and therefore it is possible that this study included cases of both early and late cardiotoxicity. In the other study the length of follow-up was not mentioned and as a result we don't know if the cases of cardiotoxicity in this study are early or late. However, based on the fact that all patients included in this trial had metastatic disease and the associated effect on survival duration, we presume that cases of heart failure in this trial were early cardiotoxicity.

Description of the study addressing epirubicin versus liposomal-encapsulated doxorubicin

Our analysis of the cardiotoxicity of epirubicin when compared with that of liposomal-encapsulated doxorubicin included one trial (Chan 2004) with a total of 160 patients. Eighty patients were randomised to treatment with epirubicin, whereas 80 patients were randomised to treatment with liposomal-encapsulated doxorubicin. The cumulative anthracycline dose patients in both treatment groups received was comparable. All patients included in this study were adults with breast cancer. The follow-up of at least part of the included patients was more than one year and therefore it is possible that this study included cases of both early and late cardiotoxicity.

Risk of bias in included studies

See additional Table 1 for the criteria list for the assessment of risk of bias.

Risk of bias in studies addressing doxorubicin versus epirubicin

In all five studies the allocation of patients to the treatment groups was randomised, but none of the studies did specify the presence of a concealed treatment allocation (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988; Mouridsen 1984).

It was unclear if the care provider and patients were blinded to treatment in all five studies.

For blinding of the outcome assessor we scored each different outcome, with the exception of overall survival, since for that outcome blinding was not relevant. For all evaluated outcomes (i.e. clinical heart failure, subclinical heart failure, response rate, progression-free survival and adverse effects) it was unclear if the outcome assessor was blinded to treatment in all studies evaluating the outcome.

Patients lost to follow-up were also scored for each different outcome. For clinical heart failure the number of patients lost to follow-up was described and acceptable (i.e. less than 20%) in three studies (FESG 1988; Gasparini 1991; IMBSWE 1988), in one study it was unclear (Brambilla 1986) and in one study it was unacceptable (Mouridsen 1984). For subclinical heart failure (both as a dichotomous and continuous outcome) the number of patients lost to follow-up was unacceptable in the one study describing this outcome (Brambilla 1986). For response rate the number of patients lost to follow-up was described and acceptable in four studies (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988), whereas in one study it was not (Mouridsen 1984). For progression-free survival the number of patients lost-to-follow-up was described and acceptable in three studies (FESG 1988; Gasparini 1991; IMBSWE 1988), whereas in two studies it was not (Brambilla 1986; Mouridsen 1984). Overall survival was evaluated in five studies, in four of them the number of patients lost to follow-up was described and acceptable (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988), whereas in the other study it was not (Mouridsen 1984). Finally, for the assessment of adverse effects the number of patients lost-to-follow-up was described and acceptable in two studies (Gasparini 1991; IMBSWE 1988), whereas in the other study it was not (FESG 1988). Please note that in the study of IMBSWE 1988 the number of patients lost-to-follow-up was described and acceptable for all adverse effects, with the exception of alopecia.

See additional Table 2 for the exact scores per included study.

In conclusion, the risk of bias in the included studies varied and bias could not be ruled out in the following percentages of included studies: selection bias (based on method of randomisation and concealment of allocation) 100%, performance bias (based on blinding of the care provider and patient) 100%, detection bias (based on blinding of the outcome assessor) 100% for all evaluated outcomes, and finally attrition bias (based on the completeness of follow-up) 40% for clinical heart failure, 100% for subclinical heart failure (both as a dichotomous and continuous outcome), 20% for response rate, 40% for progression-free survival, 20% for overall survival, and 33% for adverse effects.

Risk of bias in studies addressing conventional doxorubicin versus liposomal-encapsulated doxorubicin

In both studies the allocation of patients to the treatment groups was randomised, but it was unclear if the treatment allocation was concealed (Batist 2001; Harris 2002). It was unclear if the care provider and patients were blinded to treatment in both studies.

For blinding of the outcome assessor we scored each different outcome, with the exception of overall survival, since for that outcome blinding was not relevant. In one of the two studies evaluating clinical heart failure it was unclear if the outcome assessor was blinded to treatment (Harris 2002). The outcome assessor was blinded to treatment in both studies evaluating subclinical heart failure, response rate and progression-free survival. It was unclear if the outcome assessor was blinded to treatment in both studies evaluating adverse effects.

Patients lost to follow-up were also scored for each different outcome. For clinical heart failure, subclinical heart failure, tumour response, progression-free survival, overall survival and adverse effects the number of patients lost to follow-up was described and acceptable (i.e. less than 20%) in both studies.

See additional Table 2 for the exact scores per included study.

In conclusion, bias could not be ruled out in the following percentages of included studies: selection bias (based on method of randomisation and concealment of allocation) 100%, performance bias (based on blinding of the care provider and patient) 100%, detection bias (based on blinding of the outcome assessor) 50% for clinical heart failure, 0% for subclinical heart failure, response rate and progression-free survival and 100% for adverse effects, and finally attrition bias (based on the completeness of follow-up) 0% for all evaluated outcomes.

Risk of bias in the study addressing epirubicin versus liposomal-encapsulated doxorubicin

The allocation of patients to the treatment groups was randomised, but it was unclear if the treatment allocation was concealed (Chan 2004). It was unclear if the care provider and patients were blinded to treatment.

For blinding of the outcome assessor we scored each different outcome, with the exception of overall survival, since for that outcome blinding was not relevant. For clinical heart failure, subclinical heart failure, tumour response, progression-free survival, and adverse effects it was unclear if the outcome assessor was blinded to treatment.

Patients lost to follow-up were also scored for each different outcome. For all outcomes evaluated in this study (i.e. the above mentioned and overall survival) the number of patients lost to follow-up was described and acceptable (i.e. less than 20%). See additional Table 2 for the exact scores per included study.

In conclusion, in this study selection bias, performance bias, and detection bias (for all evaluated outcomes) could not be ruled out.

Effects of interventions

Not all articles allowed data extraction for all outcomes (see Characteristics of included studies for a more detailed description of the extractable outcomes of each study).

Studies addressing doxorubicin versus epirubicin

Clinical heart failure

We could collect data on clinical heart failure from five trials with a total of 1036 adult patients with a solid tumour (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988; Mouridsen 1984). There were three cases of clinical heart failure among 521 patients randomised to epirubicin and 12 cases among 515 patients randomised to doxorubicin. The meta-analysis showed no

significant difference in the occurrence of clinical heart failure in the treatment groups (RR = 0.36, 95% CI 0.12 to 1.11, P = 0.07). However, there is some suggestion of a lower rate of clinical heart failure in patients treated with epirubicin. No heterogeneity was detected (I^2 = 0%).

In two studies the follow-up of the included patients was more than one year (Brambilla 1986; FESG 1988) and in one study it was possible that part of the included patients had a follow-up of more than one year (IMBSWE 1988), therefore it is possible that these studies included cases of both early and late cardiotoxicity. In the other studies the length of follow-up was not mentioned (Gasparini 1991; Mouridsen 1984) and as a result we don't know if the cases of cardiotoxicity in these studies are early or late. However, based on the fact that all patients included in these trials had metastatic or advanced disease and the associated effect on survival duration, we presume that cases of heart failure in these trials were early cardiotoxicity.

Clinical and subclinical heart failure combined

Data on clinical and subclinical heart failure combined could be extracted from one trial including adult patients with a solid tumour (Brambilla 1986). However, due to the high risk of attrition bias (less than 50% of the patients had an acceptable follow-up), results of this study are not reported.

Subclinical heart failure as a continuous outcome

We could collect data on subclinical heart failure described as a continuous outcome from one trial including adult patients with a solid tumour (Brambilla 1986). However, due to the high risk of attrition bias (less than 50% of the patients had an acceptable follow-up), results of this study are not reported.

Tumour response

Data on response rate could be extracted from five trials with a total of 1036 adult patients with a solid tumour (Brambilla 1986; FESG 1988; Gasparini 1991; IMBSWE 1988; Mouridsen 1984). These trials used comparable criteria to assess tumour response (see Characteristics of included studies). There were 210 complete or partial responses among 521 patients randomised to epirubicin and 221 among 515 patients randomised to doxorubicin. The meta-analysis showed no significant difference in the response rate between the treatment groups (RR = 0.94, 95% CI 0.82 to 1.08, P = 0.40). No heterogeneity was detected (I^2 = 0%). Only one study mentioned that the response rate was determined by at least two observers (Mouridsen 1984).

Please note that due to the nature of this measurement (i.e. the percentage of patients with a remission) a high event rate is favourable. Therefore, in the figure of this analysis, "favours doxorubicin" is on the left and "favours epirubicin" is on the right, as opposed to the figures of the other analyses.

Survival

Data on progression-free survival were presented in 5 trials, but only 2 trials with a total of 446 adults with a solid tumour (FESG 1988; Mouridsen 1984) could be included in the meta-analysis. The meta-analysis showed no significant difference between the treatment groups (HR=1.05; 95% CI 0.76 to 1.44; P = 0.78). However, unexplained heterogeneity was detected (I^2 = 59%).

We excluded the study of Brambilla 1986 from this analysis due to the high risk of attrition bias (less than 50% of the patients had an acceptable follow-up). We excluded the studies of Gasparini 1991 and IMBSWE 1988 from this analysis because we were not able to reliably extract data needed to use Parmar's method for the assessment of survival for this study. However, for descriptive results see additional Table 3. In all individual studies no significant differences between the treatment arms were identified.

Data on overall survival were presented in 5 trials, but only 2 trials with a total of 245 adults with a solid tumour (Gasparini 1991; Mouridsen 1984) could be included in the meta-analysis. The meta-analysis showed no significant difference between the treatment groups (HR=0.95; 95% CI 0.65 to 1.39; P=0.79). No heterogeneity was detected (I^2=0%).

We excluded the studies of Brambilla 1986, FESG 1988 and IMBSWE 1988 from this analysis because we were not able to reliably extract data needed to use Parmar's method for the assessment of survival for this study. However, for descriptive results see additional Table 3. In all individual studies no significant differences between the treatment arms were identified.

Adverse effects

Since all patients receiving chemotherapy will suffer from side effects, we decided to analyse only the severe and life threatening effects. We defined this as grade 3 or 4 toxicity. All studies used the WHO criteria (Miller 1981; WHO Handbook 1979). Therefore, it was possible to perform meta-analyses for adverse effects for which more than 1 RCT was available. For adverse effects for which 1 RCT was available, we provide descriptive results (all the mentioned RR, 95%CI and P-values are calculated in RevMan with the random effects model).

Anaemia

Data on anaemia could be extracted from two trials with a total of 546 adult patients with a solid tumour (Gasparini 1991; IMBSWE 1988). However, in one study there were no cases of anaemia in both treatment groups and therefore, the not significantly different results of this study were not estimable for analysis of the RR (Gasparini 1991). As a result, pooling of results was not possible. In the other study (IMBSWE 1988), there was one case of anaemia grade 3 or 4 among 250 patients randomised to epirubicin and nine among 247 patients randomised to doxorubicin. This was a significant difference in favour of epirubicin (RR = 0.11, 95% CI 0.01 to 0.86, P = 0.04).

Leukopenia

Data on leukopenia could be extracted from two trials with a total of 546 adult patients with a solid tumour (Gasparini 1991; IMBSWE 1988). There were 23 cases of leukopenia grade 3 or 4 among 275 patients randomised to epirubicin and 46 among 271 patients randomised to doxorubicin. The meta-analysis showed a significantly lower rate of leukopenia grade 3 or four in patients treated with epirubicin as compared to patients treated with doxorubicin (RR = 0.50, 95% CI 0.31 to 0.80, P = 0.004). No heterogeneity was detected (I^2 = 0%).

Nausea and vomiting

Data on nausea / vomiting could be extracted from two trials with a total of 546 adult patients with a solid tumour (Gasparini 1991;

IMBSWE 1988). There were 79 cases of nausea / vomiting grade 3 or 4 among 275 patients randomised to epirubicin and 102 among 271 patients randomised to doxorubicin. The meta-analysis showed a significantly lower rate of nausea / vomiting grade 3 or 4 in patients treated with epirubicin as compared to patients treated with doxorubicin (RR = 0.77, 95% CI 0.61 to 0.97, P = 0.03). No heterogeneity was detected (I^2 = 0%).

Alopecia

Data on alopecia could be extracted from three trials with a total of 796 adult patients with a solid tumour (Gasparini 1991; FESG 1988; IMBSWE 1988). There were 128 cases of alopecia grade 3 or 4 among 402 patients randomised to epirubicin and 139 among 394 patients randomised to doxorubicin. The meta-analysis showed no significant difference in the occurrence of alopecia grade 3 or 4 between the treatment groups (RR=0.85, 95% CI 0.52 to 1.38, P=0.51). However, unexplained heterogeneity was detected (I^2 = 71%).

Thrombocytopenia

Two trials with a total of 546 adult patients with a solid tumour evaluated thrombocytopenia grade 3 or 4. However, in one study (Gasparini 1991) there were no cases of thrombocytopenia grade 3 or 4 in both treatment groups and therefore, the results of this study are not estimable for analysis of the RR. As a result, pooling of results was not possible. In the other study (IMBSWE 1988) there were four cases of thrombocytopenia grade 3 or 4 in both treatment groups (RR = 0.99, 95% CI 0.25 to 3.91, P=0.99), so in both studies no significant difference in the occurrence of thrombocytopenia grade 3 or 4 between the treatment groups was detected.

Infection

One trial with a total of 49 adult patients with a solid tumour evaluated infection grade 3 or 4 (Gasparini 1991). However, there were no cases of infection grade 3 or 4 in both treatment groups and therefore, the results of this study are not estimable for analysis of the RR, but no significant difference in the occurrence of infection grade 3 or 4 between the treatment groups was detected.

Stomatitis and mucositis

Two trials with a total of 546 adult patients with a solid tumour evaluated stomatitis / mucositis grade 3 or 4. However, in one study (Gasparini 1991) there were no cases of stomatitis / mucositis grade 3 or 4 in both treatment groups and therefore, the results of this study are not estimable for analysis of the RR. As a result, pooling of results was not possible. In the other study (IMBSWE 1988) there were six cases of stomatitis / mucositis grade 3 or 4 among 250 patients randomised to epirubicin and 8 among 247 patients randomised to doxorubicin. This was not a significant difference (RR = 0.74, 95% CI 0.26 to 2.10, P = 0.57), so in both studies no significant difference in the occurrence of stomatitis / mucositis grade 3 or 4 between the treatment groups was detected.

Thrombophlebitis

One trial with a total of 49 adult patients with a solid tumour evaluated thrombophlebitis grade 3 or 4 (Gasparini 1991). However, there were no cases of thrombophlebitis grade 3 or 4 in both treatment groups and therefore, the results of this study are not estimable for analysis of the RR, but no significant difference in the occurrence of thrombophlebitis grade 3 or 4 between the treatment groups was detected.

Other adverse effects

For hepatic dysfunction related to drug administration (Gasparini 1991), and renal dysfunction related to drug administration (Gasparini 1991), there were no cases in both treatment groups of the one study evaluating the adverse effect, and thus no significant differences in the occurrence of the evaluated outcome.

Quality of life

None of the studies evaluated QOL.

Subgroup analyses

Since all patients were adults with a solid tumour, subgroup analyses for children versus adults and leukaemias versus solid tumours were not performed.

Sensitivity analyses

The results of the sensitivity analyses for the risk of bias criteria were consistent among the trials and did not differ from the overall analyses.

Studies addressing conventional doxorubicin versus liposomal-encapsulated doxorubicin

Clinical heart failure

We collected data on clinical heart failure from two trials with a total of 521 adult patients with breast cancer (Batist 2001; Harris 2002). There were 14 cases of clinical heart failure among 271 patients randomised to conventional doxorubicin and two cases among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed a statistically significant lower rate of clinical heart failure in patients treated with liposomal-encapsulated doxorubicin as compared to treatment with conventional doxorubicin (RR = 0.20, 95% CI 0.05 to 0.75, P = 0.02). No heterogeneity was detected (I^2 = 0%).

In one study the follow-up of the included patients was more than one year (Batist 2001) and therefore it is possible that this study included cases of both early and late cardiotoxicity. In the other study the length of follow-up was not mentioned and as a result we do not know if the cases of cardiotoxicity in these studies are early or late. However, based on the fact that all patients included in this trial had metastatic disease and the associated effect on survival duration, we presume that cases of heart failure in these trials were early cardiotoxicity.

Clinical and subclinical heart failure combined

Data on clinical and subclinical heart failure combined could be extracted from 2 trials with a total of 521 adult patients with breast cancer (Batist 2001; Harris 2002). There were 67 cases of clinical and subclinical heart failure combined among 271 patients randomised to conventional doxorubicin and 23 cases among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed a statistically significant lower rate of clinical and subclinical heart failure combined in patients treated with liposomal-encapsulated doxorubicin as compared to treatment with conventional doxorubicin (RR = 0.38, 95% CI 0.24 to 0.59, P < 0.0001). No heterogeneity was detected (I^2 = 0%).

In one study the follow-up of the included patients was more than one year (Batist 2001) and therefore it is possible that this study

included cases of both early and late cardiotoxicity. In the other study the length of follow-up was not mentioned and as a result we don't know if the cases of cardiotoxicity in these studies are early or late. However, based on the fact that all patients included in this trial had metastatic disease and the associated effect on survival duration, we presume that cases of heart failure in these trials were early cardiotoxicity.

For both studies it should be noted that patients who suffered from clinical heart failure are also included in the meta-analysis of clinical heart failure as mentioned above.

Tumour response

Data on response rate could be extracted from two trials with a total of 521 adult patients with breast cancer (Batist 2001; Harris 2002). These trials used comparable criteria to assess tumour response (see Characteristics of included studies). There were 96 complete or partial responses among 271 patients randomised to conventional doxorubicin and 89 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the response rate between the treatment groups (RR = 1.01, 95% CI 0.80 to 1.26, P = 0.95). No heterogeneity was detected (I^2 = 0%). None of the studies mentioned that the response rate was determined by at least two observers.

Please note that due to the nature of this measurement (i.e. the percentage of patients with a remission) a high event rate is favourable. Therefore, in the figure of this analysis, "favours doxorubicin" is on the left and "favours liposomal-encapsulated doxorubicin" is on the right, as opposed to the figures of the other analyses.

Survival

Data on survival could be extracted from two trials with a total of 521 adult patients with breast cancer (Batist 2001; Harris 2002). Both studies presented HRs with 95% CIs, making it possible to use Parmar's method for the assessment of survival (Parmar 1998).

For the progression-free survival the meta-analysis showed no significant difference between patients treated with liposomal-encapsulated doxorubicin and patients treated with conventional doxorubicin (HR = 1.01, 95% CI 0.83 to 1.24, P=0.89). No heterogeneity was detected (I^2 =0%).

For the overall survival the meta-analysis also showed no significant difference between patients treated with liposomal-encapsulated doxorubicin and patients treated with conventional doxorubicin (HR = 1.12, 95% CI 0.83 to 1.53, P = 0.46). No heterogeneity was detected (I^2 = 50%).

Adverse effects

Data on adverse effects could be extracted from two trials with a total of 521 adult patients with breast cancer (Batist 2001; Harris 2002). Since all patients receiving chemotherapy will suffer from side effects, we decided to analyse only the severe and life threatening effects. We defined this as grade 3 or 4 toxicity. Both studies used the CTC (common toxicity criteria) of the National Cancer Institute. Therefore it was possible to perform meta-analyses.

Anaemia

There were 73 cases of anaemia grade > =3 among 271 patients randomised to conventional doxorubicin and 56 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of anaemia grade > =3 between the treatment groups (RR = 0.83, 95% CI 0.61 to 1.13, P = 0.23). No heterogeneity was detected (I^2 =0 %).

Thrombocytopenia

There were 20 cases of thrombocytopenia grade >=3 among 271 patients randomised to conventional doxorubicin and also 20 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of thrombocytopenia grade > =3 between the treatment groups (RR = 1.09, 95% CI 0.60 to 1.97, P = 0.78). No heterogeneity was detected (I^2 = 0%). Please note that thrombocytopenia grade >=3 in this meta-analysis was defined as platelets < $20*10^9$/L, whereas according to the CTC-criteria grade 3 starts with platelets <$50*10^9$. The study of Batist 2001 also reported patients with platelets <$50*10^9$ and again no significant difference between the treatment groups was identified (P = 0.78 as reported by the authors).

Neutropenia

There were 184 cases of neutropenia grade 4 among 271 patients randomised to conventional doxorubicin and 140 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed a significantly lower rate of neutropenia grade 4 in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with conventional doxorubicin (RR = 0.82, 95% CI 0.72 to 0.94, P = 0.005). No heterogeneity was detected (I^2 =0%). The study of Batist 2001 also reported patients with prolonged neutropenia grade 4 (defined as seven days or longer) and again no significant difference between the treatment groups was identified (P = 0.18 as reported by the authors).

Neutropenic fever

There were 31 cases of neutropenic fever (i.e fever > = 38°C, neutropenia grade 4 and IV antibiotics and/or hospitalisation) among 271 patients randomised to conventional doxorubicin and 25 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of neutropenic fever between the treatment groups (RR = 0.88, 95% CI 0.53 to 1.45, P = 0.61). No heterogeneity was detected (I^2 = 0%).

Nausea and vomiting

There were 53 cases of nausea / vomiting grade > =3 among 271 patients randomised to conventional doxorubicin and 32 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed a significantly lower rate of nausea / vomiting grade >=3 in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with conventional doxorubicin (RR = 0.65, 95% CI 0.44 to 0.98, P = 0.04). No heterogeneity was detected (I^2 = 0%).

Stomatitis and mucositis

There were 28 cases of stomatitis / mucositis grade > =3 among 271 patients randomised to conventional doxorubicin and

15 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of stomatitis / mucositis grade > =3 between the treatment groups (RR = 0.58, 95% CI 0.32 to 1.05, P = 0.07). No heterogeneity was detected (I^2 = 0%).

Diarrhoea

There were 17 cases of diarrhoea grade >=3 among 271 patients randomised to conventional doxorubicin and 5 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed a significantly lower rate of diarrhoea grade >=3 in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with conventional doxorubicin (RR = 0.33, 95% CI 0.12 to 0.87, P = 0.03). No heterogeneity was detected (I^2 = 0%).

Asthenia and fatigue

There were 30 cases of asthenia / fatigue grade 3 among 271 patients randomised to conventional doxorubicin and 24 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of asthenia / fatigue grade 3 between the treatment groups (RR = 0.85, 95% CI 0.52 to 1.41, P = 0.54). No heterogeneity was detected (I^2 = 0%).

Cutaneous

There were two cases of cutaneous toxicity grade 3 among 271 patients randomised to conventional doxorubicin and one among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of cutaneous toxicity grade 3 between the treatment groups (RR = 0.68, 95% CI 0.08 to 5.45, P = 0.71). No heterogeneity was detected (I^2 =0%).

Infection

There were 26 cases of infection grade > =3 among 271 patients randomised to conventional doxorubicin and 21 among 250 patients randomised to liposomal-encapsulated doxorubicin. The meta-analysis showed no significant difference in the occurrence of infection grade >=3 between the treatment groups (RR=0.78, 95% CI 0.21 to 2.89, P=0.71). However, unexplained heterogeneity was detected (I^2 = 78%).

Quality of life

None of the studies evaluated QOL.

Subgroup analyses

Since all patients were adults with a solid tumour, subgroup analyses for children versus adults and leukaemias versus solid tumours were not performed.

Study addressing epirubicin versus liposomal-encapsulated doxorubicin

Due to the absence of more than one RCT, for epirubicin versus liposomal-encapsulated doxorubicin pooling of results was not possible. We therefore provide descriptive results of this study. All the mentioned RR, 95% CI and P-values are calculated in RevMan with the random effects model.

Clinical heart failure

In the study of Chan 2004 there were no cases of clinical heart failure in both treatment groups and therefore, the results of this study are not estimable for analysis of the RR. However, no significant difference in the occurrence of clinical heart failure between the treatment groups was identified. All patients included in this study were adults with breast cancer.

Clinical and subclinical heart failure combined

In the study of Chan 2004 there were eight cases of clinical and subclinical heart failure combined among 80 patients randomised to epirubicin and nine cases among 80 patients randomised to liposomal-encapsulated doxorubicin. The analysis showed no significant difference in the occurrence of clinical and subclinical heart failure between the treatment groups (RR = 1.13, 95% CI 0.46 to 2.77, P = 0.80). All patients included in this study were adults with breast cancer. The follow-up of at least part of the included patients was more than one year and therefore it is possible that this study included cases of both early and late cardiotoxicity.

Tumour response

In the study of Chan 2004 there were 31 complete or partial responses among 80 patients randomised to epirubicin and 37 among 80 patients randomised to liposomal-encapsulated doxorubicin. The analysis showed no significant difference in the response rate between the treatment groups (RR = 1.19, 95% CI 0.83 to 1.72, P = 0.34). It was not mentioned that the response rate was determined by at least two observers. All patients included in this study were adults with breast cancer. Please note that due to the nature of this measurement (i.e. the percentage of patients with a remission) a high event rate is favourable.

Survival

In the study of Chan 2004 a significant difference in progression-free survival in favour of liposomal-encapsulated doxorubicin was identified. Patients randomised to epirubicin had a median progression-free survival of 5.6 months and patients randomised to liposomal-encapsulated doxorubicin 7.7 months (HR = 1.52, 95% CI 1.06 to 2.20 as reported by the authors). However, no significant differences in overall survival were found between the treatment arms. Patients randomised to epirubicin had a median overall survival of 16 months and patients randomised to liposomal-encapsulated doxorubicin 18.3 months (HR = 1.15, 95% CI 0.77 to 1.72 as reported by the authors).

Adverse effects

Since all patients receiving chemotherapy will suffer from side effects, we decided to analyse only the severe and life threatening effects. We defined this as grade 3 or 4 toxicity. Chan 2004 used the common toxicity criteria (CTC) of the National Cancer Institute. Results are shown in additional Table 4. Neutropenia grade 4 occurred significantly more often in the patients randomised to treatment with liposomal-encapsulated doxorubicin. For all the other evaluated adverse effects no significant differences between the treatment groups were identified.

Quality of life

QOL was not evaluated in this study.

Subgroup analyses

Since all patients were adults with a solid tumour, subgroup analyses for children versus adults and leukaemias versus solid tumours were not performed.

DISCUSSION

Heart damage due to anthracycline chemotherapy is a considerable and serious problem. It reduces QOL and can even cause premature death. Also, when heart damage occurs during therapy the maximum cumulative dose of anthracyclines needs to be limited and as a result the efficacy of anthracycline chemotherapy will be reduced. This is an update of the first systematic review evaluating the existing evidence on different anthracycline derivates for reducing cardiotoxicity. Only RCTs were included since it is widely recognized that a RCT is the only study design which can be used to obtain unbiased evidence on the use of anthracycline derivates, provided that the design and execution are adequate.

We could identify RCTs for three combinations of different anthracycline derivates, i.e. epirubicin versus doxorubicin, liposomal-encapsulated doxorubicin (myocet) versus doxorubicin and liposomal-encapsulated doxorubicin (myocet) versus epirubicin. For the other 25 combinations of different anthracycline derivates (see search strategy) no adequate RCTs could be identified.

For **epirubicin versus doxorubicin** five trials were identified.

Our meta-analysis of five trials showed no evidence for a significant difference in the occurrence of clinical heart failure between the treatment groups (RR=0.36, 95% CI 0.12 to 1.11, P = 0.07). However, based on the low value of the RR and the wide 95% CI there is some suggestion of a lower rate of clinical heart failure in patients treated with epirubicin as compared to patients treated with doxorubicin. The reason that this difference is not statistically significant could be a result of a low power of the included studies. No results are available on the occurrence of clinical and subclinical heart failure combined in patients treated with either epirubicin or doxorubicin, since none of the included studies adequately evaluated subclinical heart failure.

Our meta-analysis of tumour response showed no significant difference in response rate between the treatment groups (RR = 0.94, 95% CI 0.82 to 1.08, P=0.40). The same was true for our meta-analyses of both progression-free and overall survival (HR = 1.05; 95% CI 0.76 to 1.44; P = 0.78 and HR = 0.95; 95% CI 0.65 to 1.39; P = 0.79 respectively). However, please note that in the meta-analysis of progression-free survival substantial heterogeneity was detected. Individual studies not included in the meta-analysis also showed no significant differences in survival between the treatment groups.

For three evaluated adverse effects it was possible to perform a meta-analysis. A significantly lower rate of leukopenia and nausea/vomiting was identified in patients treated with epirubicin as compared to patients treated with doxorubicin. No significant difference in the occurrence of alopecia between the treatment groups was identified; please note that for this outcome substantial heterogeneity was present. For the other evaluated adverse effects pooling of results was not possible. As a result, this review does not allow for any definitive conclusions regarding those adverse effects in patients treated with either epirubicin or doxorubicin. However, for thrombocytopenia, infection, stomatitis/mucositis, thrombophlebitis, and hepatic or renal dysfunction related to drug administration, results were consistent among the individual studies evaluating the outcome (either one or two studies). None of the studies identified a significant difference in the occurrence of the evaluated adverse effects between the treatment groups. For anaemia the results were not consistent among the individual studies evaluating the outcome. The reason that some studies did not identify a significant difference between the treatment groups could be due to the fact that the number of patients included in these studies were too small to detect a difference between the treatment groups (i.e. low power).

The cumulative anthracycline dose received in both treatment groups was comparable. Therefore, the results of the different outcomes are direct comparisons of equimolar doses of epirubicin and doxorubicin. No conclusions can be made regarding treatment with epirubicin and doxorubicin with different cumulative doses.

The risk of bias in the included studies varied; in many studies bias could not be ruled out due to a lack of reporting. However, at the moment this is the best available evidence of RCTs evaluating epirubicin and doxorubicin.

For **liposomal-encapsulated doxorubicin versus conventional doxorubicin** two trials were identified.

Our meta-analysis of the two trials showed a significantly lower rate of both clinical heart failure and clinical and subclinical heart failure combined in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with doxorubicin (RR = 0.20, 95% CI 0.05 to 0.75, P = 0.02 and RR = 0.38, 95% CI 0.24 to 0.59, P < 0.0001 respectively).

However, an important question regarding any cardioprotective intervention during anthracycline therapy is whether the intervention could selectively decrease the heart damage without reducing the anti-tumour efficacy (i.e. tumour response and patient survival) and without negative effects on toxicities other than cardiac damage. Our meta-analysis of two trials for response rate showed no significant difference between the treatment groups (RR = 1.01, 95% CI 0.80 to 1.26, P = 0.95). The same was true for our meta-analyses of both progression-free and overall survival (HR=1.01, 95% CI 0.83 to 1.24, P=0.89 and HR = 1.12, 95% CI 0.83 to 1.53, P = 0.46 respectively). However, it should be noted that in the study of Harris 2002 there was a non-significant trend toward a shorter overall survival in patients treated with liposomal-encapsulated doxorubicin (P = 0.09). The authors state that although this finding cannot be ignored, it seems unlikely, given the other efficacy parameters, that this is a consequence of reduced efficacy of liposomal-encapsulated doxorubicin compared with conventional doxorubicin. It is possible that the excess of progesterone receptor positivity in the conventional doxorubicin arm may denote a better prognostic group. Other unmeasured prognostic factors (e.g. HER-2 expression) also may have played a role in the natural history of the disease. In the study of Batist 2001 there were no significant differences in progesterone receptor positivity between the treatment groups.

For all adverse effects it was possible to perform a meta-analysis. For neutropenia, nausea/vomiting and diarrhoea a significantly lower rate of the adverse effect was observed in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with doxorubicin. For

anaemia, thrombocytopenia, neutropenic fever, stomatitis/mucositis, asthenia/fatigue, cutaneous toxicity and infection no significant differences between the treatment groups were identified. Please note, that there was heterogeneity present in the analysis of infection.

It should be emphasised that the cumulative anthracycline dose received in both treatment groups was the same in the study of Batist 2001, whereas in the study of Harris 2002 patients in the liposomal-encapsulated doxorubicin group received a higher cumulative anthracycline dose than patients in the doxorubicin group. So despite a higher cumulative anthracycline dose received in the liposomal-encapsulated doxorubicin group, there was still a lower rate of both heart failure and adverse effects in the liposomal-encapsulated doxorubicin group as compared to the doxorubicin group. However, no significant differences in both tumour response and survival were identified between both treatment groups, whereas it might be expected that those outcomes would improve with a higher cumulative anthracycline dose. As a result, we are not able to provide definitive conclusions on tumour response and survival.

The risk of bias in the included studies varied; in many studies bias could not be ruled out due to a lack of reporting. However, at the moment this is the best available evidence of RCTs evaluating liposomal-encapsulated doxorubicin and doxorubicin.

For **liposomal-encapsulated doxorubicin versus epirubicin** one trial was identified. Pooling of results was therefore not possible, and as a result this review does not allow for any definitive conclusions regarding the effects of treatment with liposomal-encapsulated doxorubicin or epirubicin. No significant difference in the occurrence of both clinical heart failure and clinical and subclinical heart failure combined was identified. The same was true for response rate and overall survival, whereas progression-free survival was significantly better in patients treated with liposomal-encapsulated doxorubicin as compared to patients treated with doxorubicin. We cannot explain this difference.

This review does not allow for any definitive conclusions regarding adverse effects in patients treated with either epirubicin or liposomal-encapsulated doxorubicin. However, only for neutropenia a significant difference in favour of epirubicin was identified. For all other evaluated adverse effects no significant difference between the treatment groups was found.

The reason that in this study for most evaluated outcomes no significant difference between the treatment groups was identified could be due to the fact that the number of patients included in this study was too small to detect a difference between the treatment groups (i.e. low power).

The cumulative anthracycline dose received in both treatment groups was comparable. Therefore, the results of the different outcomes are direct comparisons of equimolar doses of liposomal-encapsulated doxorubicin and epirubicin. No conclusions can be made regarding treatment with epirubicin and liposomal-encapsulated doxorubicin with different cumulative doses.

The risk of bias in the included trial was unclear due to a lack of reporting, only the presence of attrition bias was ruled out. However, at the moment this is the best available evidence of RCTs evaluating epirubicin and liposomal-encapsulated doxorubicin.

Regarding early and late cardiotoxicity, we must conclude the following for all 3 comparisons. In some studies the follow-up of (at least part of) the included patients was more than 1 year, therefore it is possible that these studies included cases of both early and late cardiotoxicity. In the other studies the length of follow-up was not mentioned and as a result we don't know if the cases of cardiotoxicity in these studies are early or late. However, based on the fact that all patients included in these trials had metastatic or advanced disease and the associated effect on survival duration, we presume that cases of heart failure in these trials were early cardiotoxicity.

For all three comparisons of different anthracycline derivates it should be emphasised that all included patients were adults with a solid tumour, mainly breast cancer. As a result no conclusions can be made about the effects of treatment with epirubicin and doxorubicin in children treated with anthracyclines and also not in patients diagnosed with leukaemia.

It should be kept in mind that the inclusion of studies for this systematic review was limited to RCTs describing cardiotoxicity, and as a result, the analyses of response rate, survival, adverse effects and QOL were possibly based on only a subgroup of trials comparing different anthracycline derivates.

We are awaiting the results of the currently ongoing study evaluating liposomal-encapsulated doxorubicin versus conventional doxorubicin in adults with B-cell lymphoma (see Ongoing studies table). We are also awaiting (additional) results of the eight trials currently awaiting assessment (see Studies awaiting classification table): epirubicin versus doxocrubicin (n=3; all in patients with breast cancer), liposomal-encapsulated doxorubicin versus conventional doxorubicin (n = 2; one study in adults with AIDS-related Kaposi's sarcoma and one in adults with lymphoma), liposomal-encapsulated doxocrubicin versus epirubicin (n = 2; all in patients with breast cancer) and liposomal-encapsulated doxocrubicin versus liposomal daunorubicin (n=1; patients with AIDS-related Kaposi's sarcoma). From the currently available data it is unclear if these studies are eligible for inclusion in this systematic review.

AUTHORS' CONCLUSIONS

Implications for practice

Combinations of different anthracycline derivates for which no adequate RCTs were identified

For all combinations of different anthracycline derivates for which no adequate RCTs were identified, no conclusions can be made about possible differences in preventing anthracycline-induced heart damage. Based on the current available evidence, we are not able to give recommendations for clinical practice.

Epirubicin versus doxorubicin

Based on the current available evidence, we are not able to favour either epirubicin or doxorubicin when given in equimolar doses. No conclusions can be made regarding treatment with epirubicin and doxorubicin with different cumulative doses.

It should be emphasised that all patients included in these studies were adults with advanced solid tumours. As a result no conclusions can be made about the effects of treatment with

epirubicin and doxorubicin in children treated with anthracyclines and also not in patients diagnosed with leukaemia.

Liposomal-encapsulated doxorubicin versus conventional doxorubicin

Based on our meta-analysis which clearly shows that treatment with liposomal-encapsulated doxorubicin reduces the risk of both clinical and subclinical heart failure as compared to treatment with doxorubicin despite the fact that patients treated with liposomal-encapsulated doxorubicin received a higher cumulative anthracycline dose than patients treated with doxorubicin, we conclude that in adults with a solid tumour liposomal-encapsulated doxorubicin should be favoured over doxorubicin. However, until more evidence becomes available on tumour response and survival in patients treated with liposomal-encapsulated doxorubicin or doxorubicin in equimolar doses, we recommend the use of a higher cumulative liposomal-encapsulated doxorubicin dose as compared to the standard cumulative doxorubicin dose. Despite the higher cumulative anthracycline dose received in the liposomal-encapsulated doxorubicin group, patients treated with liposomal-encapsulated doxorubicin suffered from less side effects than patients treated with doxorubicin.

It should be emphasised that all patients included in these studies were adults with advanced breast cancer. As a result no conclusions can be made about the effects of treatment with liposomal-encapsulated doxorubicin and doxorubicin in children treated with anthracyclines and also not in patients diagnosed with leukaemia.

Liposomal-encapsulated doxorubicin versus epirubicin

Since pooling of results was not possible for the comparison of epirubicin versus liposomal-encapsulated doxorubicin, no definitive conclusions can be made about the occurrence of anthracycline-induced heart damage with the use of these anthracycline derivates. Based on the currently available evidence, we are not able to give recommendations for clinical practice.

Implications for research

Combinations of different anthracycline derivates for which no adequate RCTs were identified

Before any conclusions can be made about the occurrence of anthracycline-induced heart damage with the use of the anthracycline derivates for which no adequate RCTs were identified, high quality RCTs need to be undertaken. These RCTs should be performed in homogeneous study populations treated for either a haematological malignancy or a solid tumour. Also, since data obtained in adults cannot be extrapolated to children, they should be evaluated in children. The number of included patients should be sufficient to obtain the power needed for the results to be reliable and also, there should be adequate reporting of the occurrence of cardiotoxicity in relation to follow-up time. We are awaiting results of the trial currently awaiting assessment which compares liposomal-encapsulated doxocrubicin with liposomal daunorubicin.

Epirubicin versus doxorubicin

Future trials in adults on epirubicin versus doxorubicin in equimolar doses should be performed in homogeneous study populations treated for either a haematological malignancy or a solid tumour. Also, since data obtained in adults cannot be extrapolated to children, epirubicin and doxorubicin in equimolar doses should be evaluated in children. Epirubicin and doxorubicin with different cumulative doses could also be evaluated in high quality RCTs. The number of included patients in all RCTs should be sufficient to obtain the power needed for the results to be reliable and also, there should be adequate reporting of the occurrence of cardiotoxicity in relation to follow-up time. We are awaiting results of the three trials currently awaiting assessment.

Liposomal-encapsulated doxorubicin versus conventional doxorubicin

Future trials in adults on doxorubicin versus liposomal-encapsulated doxorubicin should be performed in homogeneous study populations treated for either a haematological malignancy or a solid tumour. Also, since data obtained in adults cannot be extrapolated to children, doxorubicin and liposomal-encapsulated doxorubicin should be evaluated in children. The number of included patients in all RCTs should be sufficient to obtain the power needed for the results to be reliable and also, there should be adequate reporting of the occurrence of cardiotoxicity in relation to follow-up time. We are awaiting the results of the currently ongoing study and also results of the two trials currently awaiting assessment.

Liposomal-encapsulated doxorubicin versus epirubicin

Before any definitive conclusions can be made about the possible difference between epirubicin and liposomal-encapsulated doxorubicin in preventing anthracycline-induced heart damage, more high quality RCTs need to be undertaken. These RCTs should be performed in homogeneous study populations treated for either a haematological malignancy or a solid tumour. Also, since data obtained in adults cannot be extrapolated to children, they should be evaluated in children. The number of included patients should be sufficient to obtain the power needed for the results to be reliable and also, there should be adequate reporting of the occurrence of cardiotoxicity in relation to follow-up time. We are awaiting results of the two trials currently awaiting assessment.

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For the comparison of epirubicin versus doxorubicin, the hazard ratio and associated statistics were calculated using an Excel spreadsheet developed by the Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the MRC Clinical Trials Unit, London. For the comparison of liposomal-encapsulated doxorubicin and doxorubicin, the hazard ratio and associated statistics were calculated using an Excel spreadsheet provided by Heather Dickinson.

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WHO Handbook 1979

World Health Organization. WHO Handbook for reporting results of cancer treatment. Geneva: World Health Organization, 1979.

References to other published versions of this review

Van Dalen 2006b

van Dalen EC, Michiels EMC, Caron HN, Kremer LCM. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. *Cochrane Database of Systematic Reviews* 2006, Issue 4.

CHARACTERISTICS OF STUDIES

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

Batist 2001

Methods	Randomisations were performed on 1:1 basis with a balanced block design (stratified according to prior exposure to doxorubicin).
Participants	297 patients (aged 22 to 88 years; sex nm) with metastatic breast cancer treated with cyclophosphamide and either liposomal-encapsulated doxorubicin (myocet) or doxorubicin. Prior anthracycline therapy in 14 patients in the liposomal-encapsulated doxorubicin group (median cumulative doxorubicin dose of 240 mg/m2; range 50 to 294 mg/m2) and 15 patients in the doxorubicin group (median cumulative doxorubicin dose of 240 mg/m2; range 63 to 270 mg/m2). Prior cardiac radiotherapy possible for 15 patients in the liposomal-encapsulated doxorubicin group and 19 in the doxorubicin group (all less than 35 Gy on the mediastinum). Prior cardiac dysfunction in 5 patients in the liposomal-encapsulated doxorubicin group and 3 patients in the doxorubicin group.

Batist 2001 *(Continued)*

Interventions	Liposomal-encapsulated doxorubicin (n=142; median cumulative dose 360 mg/m2; range 60 to 2220 mg/m2) or doxorubicin (n=155; median cumulative dose 360 mg/m2; range 60 to 660 mg/m2) every 3 weeks (both peak dose 60 mg/m2 and infusion duration of 1 hour).
Outcomes	Heart failure (i.e. clinical heart failure defined as clinical evidence of congestive heart failure; subclinical heart failure defined as a decrease in resting LVEF of 20 EF units or more from baseline to a final value of 50% or more or a decrease of 10 EF units or more from baseline to a final value of less than 50% as measured by MUGA scan). Tumour response (i.e. CR defined as the complete disappearance of all evidence of disease, including disease-related signs and symptoms, for at least 6 weeks; PR was defined as a 50% or greater decrease in the sum of the products of the 2 longest perpendicular diameters of all measured lesions for at least 6 weeks with no evidence of progressive disease). Survival. Adverse effects (according to NCI-CTC criteria).
Notes	One patient randomised to doxorubicin was withdrawn from the study before the first dose of chemotherapy; however, we performed an intention-to-treat analysis. Length of follow-up minimal 1 year (median 20 months).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

Brambilla 1986

Methods	Randomisations were performed with random permuted blocks of length 4 (stratified according to site of dominant lesion).
Participants	44 patients (aged 28 to 69 years; all females) with advanced breast cancer treated with either doxorubicin or epirubicin and eventual radiotherapy to side of initial disease (3 in each group). No prior anthracycline therapy. Prior cardiac radiotherapy in 1 patient in the doxorubicin group and 4 patients in the epirubicin group (all left chest wall irradiation). No prior cardiac dysfunction.
Interventions	Doxorubicin (n=21; median cumulative dose 540 mg/m2; range 225 to 650 mg/m2) or epirubicin (n=23; median cumulative dose 565 mg/m2; range 150 to 600 mg/m2) every 3 weeks (both peak dose 75 mg/m2 and bolus infusion).
Outcomes	Heart failure (i.e. clinical heart failure defined as symptoms and signs of left ventricular failure; subclinical heart failure defined as a fall in MAS as measured by echocardiography or a fall in LVEF as measured by radionuclide angiography). Tumour response (according to WHO criteria). Survival.
Notes	Median length of follow-up 22 months (range 14 to 30 months).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

Chan 2004

Methods	Method of randomisation not clear (stratified according to country of treatment centre).
Participants	160 patients (aged 19 to 82 years; all females) with metastatic breast cancer treated with cyclophosphamide and either liposome-encapsulated doxorubicin (myocet) or doxorubicin. No prior anthracycline therapy. Prior cardiac radiotherapy possible for 47 patients in the liposomal-encapsulated doxorubicin group and 53 in the epirubicin group (all less than 35 Gy on the mediastinum). No prior cardiac dysfunction.
Interventions	Liposomal-encapsulated doxorubicin (n=80) or epirubicin (n=80) every 3 weeks (both peak dose 75 mg/m2 and infusion duration of 1 hour; median cumulative dose nm; cumulative anthracycline dose received in both treatment groups is comparable).
Outcomes	Heart failure (i.e. clinical heart failure defined as clinical evidence of congestive heart failure; subclinical heart failure defined as a decrease in resting LVEF of 20 units or more from baseline to a final value of 50% or more or a decrease of 10 units or more from baseline to a final value of less than 50% as measured by echocardiography). Tumour response (i.e. CR defined as the disappearance of all evidence of disease for 6 weeks or longer; PR defined as a 50% or more decrease in the sum of the products of the 2 longest perpendicular diameters of all measured lesions for 6 weeks or longer , with no evidence of progressive disease). Survival. Adverse effects (according to NCI-CTC criteria).
Notes	Six patients (4 in the liposomal-encapsulated doxorubicin group and 2 in the epirubicin group) never received treatment; however, we performed an intention-to-treat analysis. The median length of follow-up was 21 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

FESG 1988

Methods	Method of randomisation not clear.
Participants	250 patients (aged 26 to 70 years; sex nm) with advanced breast cancer treated with fluorouracil, cyclophosphamide and either epirubicin or doxorubicin. No prior anthracycline therapy. Prior cardiac radiotherapy in 65 patients in the epirubicin group and 59 patients in the doxorubicin group. No prior cardiac dysfunction.
Interventions	Doxorubicin (n=123) or epirubicin (n=127) every 3 weeks (both peak dose of 50 mg/m2 and infusion duration nm; cumulative anthracycline dose nm; cumulative anthracycline dose received in both treatment groups is comparable).
Outcomes	Heart failure (i.e. clinical heart failure defined as congestive heart failure). Tumour response (according to WHO criteria). Survival. Adverse effects (according to WHO criteria).
Notes	The data presented in this table are for 230 patients which were evaluable for efficacy (113 in the doxorubicin group and 117 in the epirubicin group). However, we performed an intention-to-treat analysis. Median follow-up 41 months (range 27 to 52 months).

Risk of bias

FESG 1988 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

Gasparini 1991

Methods	Randomisations were performed using a permuted blocks design (stratified according to number of organ sites involved, dominant site of disease and performance status).
Participants	49 patients (aged 30 to 77 years; sex nm) with advanced or metastatic breast cancer treated with either epirubicin or doxorubicin. No prior anthracycline therapy. Prior cardiac radiotherapy possible for 14 patients in the epirubicin group and 12 patients in the doxorubicin group. No prior cardiac dysfunction.
Interventions	Doxorubicin (n=24; median cumulative dose 240 mg/m2; range 160 to 860 mg/m2) or epirubicin (n=25; median cumulative dose 220 mg/m2; range 160-860 mg/m2) weekly (both peak dose 20 mg/m2 and bolus infusion).
Outcomes	Heart failure (i.e. clinical heart failure defined as congestive heart failure). Tumour response (according to WHO criteria). Survival. Adverse effects (according to WHO criteria).
Notes	Length of follow-up nm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

Harris 2002

Methods	Randomisations were performed using a balanced block design (stratified according to prior doxorubicin and institution).
Participants	224 patients (aged 26 to 85 years; sex nm) with metastatic breast cancer treated with either liposomal-encapsulated doxorubicin (TLC-D99; myocet) or doxorubicin. Prior anthracycline therapy in 18 patients in the liposomal-encapsulated doxorubicin group (median cumulative doxorubicin dose 240 mg/m2; range 167 to 300 mg/m2) and 21 patients in the doxorubicin group (median cumulative doxorubicin dose 240 mg/m2; range 70 to 360 mg/m2). Prior cardiac radiotherapy possible for 47 patients in the liposomal-encapsulated doxorubicin group and 44 patients in the doxorubicin group (all less than 35 Gy on the mediastinum). No prior cardiac dysfunction.
Interventions	Liposomal-encapsulated doxorubicin (n=108, median cumulative dose 785 mg/m2) or doxorubicin (n=116; cumulative dose 570 mg/m2) every 3 weeks (both peak dose 75 mg/m2 and 1 hour infusion duration).
Outcomes	Heart failure (i.e. clinical heart failure defined as clinical evidence of congestive heart failure; subclinical heart failure defined as a decrease in resting LVEF of 20 points or more from baseline to a final value of 50% or more or a decrease of 10 points or more from baseline to a final value of less than 50% as measured by MUGA-scan).

Harris 2002 *(Continued)*

	Tumour response (i.e. CR defined as the complete disappearance of all evidence of disease, including disease-related signs and symptoms, for at least 6 weeks; PR was defined as a 50% or greater decrease in the sum of the products of the 2 longest perpendicular diameters of all measured lesions for at least 6 weeks with no evidence of progressive disease). Survival. Adverse effects (according to NCI-CTC criteria).
Notes	Two patients randomised to the liposomal-encapsulated doxorubicin group were accidently treated with conventional doxorubicin and one patient in this group never received study treatment. However, we performed an intention-to-treat analysis. Length of follow-up nm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

IMBSWE 1988

Methods	Method of randomisation not clear.
Participants	497 patients (aged 28 to 75 years; sex nm) with advanced breast cancer treated with fluorouracil, cyclophosphamide and either epirubicin or doxorubicin. No prior anthracyclines. Prior cardiac radiotherapy possible for 90 patients in the epirubicin group and 83 patients in the doxorubcin group. No prior cardiac dysfunction.
Interventions	Doxorubicin (n=247; median cumulative dose 311 mg/m2; range 50 to 600 mg/m2) or epirubicin (n=250; median cumulative dose 330 mg/m2; range 25 to 700 mg/m2) every 3 weeks (both peak dose 50 mg/m2 and infusion duration nm).
Outcomes	Heart failure (i.e. clinical heart failure defined as congestive heart failure). Tumour response (according to WHO criteria). Survival. Adverse effects (according to WHO criteria).
Notes	The data presented in this table are for the 443 evaluable patients (221 in the doxorubicin group and 222 in the epirubicin group). However, we performed an intention-to-treat analysis. Length of follow-up 28 to 1400 days.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

Mouridsen 1984

Methods	Method of randomisation not clear (stratified according to institution).
Participants	196 patients (aged 16 to 80 years; 70 women and 80 men) with locally advanced or metastatic soft tissue sarcoma treated with either doxorubicin or epirubicin. No prior anthracycline therapy. Prior cardiac radiotherapy possible for 18 patients in the doxorubicin group and 27 in the epirubicin group. No prior cardiac dysfunction.

Mouridsen 1984 *(Continued)*

Interventions	Doxorubicin (n=100; median cumulative dose 342 mg/m2; range 141 to 916 mg/m2) or epirubicin (n=96; median cumulative dose 355 mg/m2; range 144 to 1683 mg/m2) every 3 weeks (both peak dose 75 mg/m2 and bolus infusion).
Outcomes	Heart failure (i.e. clinical heart failure defined as cardiac dysfunction). Tumour response (according to WHO criteria). Survival.
Notes	The data presented in this table are for 150 of the 196 patients who were evaluable, i.e. 75 patients in each group. However, we performed an intention-to-treat analysis. Length of follow-up nm.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Not mentioned in article.

nm = not mentioned; LVEF = left ventricular ejection fraction; EF = ejection fraction; MUGA = multiple gated acquisition scan; CR = complete remission; PR = partial remission; NCI-CTC = national cancer institute-common toxicity criteria; MAS = minor axis shortening; WHO = world health organisation

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

Study	Reason for exclusion
Al-Ismael 1987	Difference in anthracycline peak dose between intervention and control group.
Armand 1984	Duplicate publication of FESG 1988.
Aviles 1993	No randomized controlled trial.
Aviles 1995	Difference in anthracycline peak dose between intervention and control group.
Aviles 2005	Difference in anthracycline peak dose between intervention and control group.
Baldini 2004	Results of two randomized controlled trials presented, both evaluating only one anthracycline derivate.
Benjamin 1978	No randomized controlled trial.
Bertini 1997	Difference in anthracycline peak dose between intervention and control group.
Bezwoda 1986	Difference in anthracycline peak dose between intervention and control group.
Bhutani 2002	Difference in anthracycline peak dose between intervention and control group.
Bonadonna 1984	Duplicate publication of Brambilla 1986.
Bonfante 1986	Duplicate publication of Brambilla 1986.
Bontenbal 1998	Difference in anthracycline peak dose between intervention and control group.
Brugiatelli 1993	Difference in anthracycline peak dose between intervention and control group; duplicate publication of Federico 1998.

Study	Reason for exclusion
Burton 2005	Difference in anthracycline peak dose between intervention and control group.
Casper 1987A	Difference in anthracycline peak dose between intervention and control group; duplicate publication of Casper 1987B.
Casper 1987B	Difference in anthracycline peak dose between intervention and control group.
Cottin 1998	Difference in anthracycline peak dose between intervention and control group; probably no randomized controlled trial.
Creutzig 1988	Duplicate publication of Creutzig 2001C.
Creutzig 2001A	Duplicate publication of Creutzig 2001C.
Creutzig 2001B	Duplicate publication of Creutzig 2001C.
Creutzig 2001C	Difference in anthracycline peak dose between intervention and control group.
De Lena 1987	Not all patients in the intervention group (i.e. epirubicin) received the same anthracycline peak dose as patients in the control group (i.e. doxorubicin).
De Lena 1989	Duplicate publication of De Lena 1987.
Federico 1998	Difference in anthracycline peak dose between intervention and control group.
Gebbia 2003	Difference in anthracycline peak dose between intervention and control group.
Gregory 2000	Difference in anthracycline peak dose between intervention and control group.
Heidemann 1990	Duplicate publication Heidemann 1993.
Heidemann 1993	Cumulative anthracycline dose patients received in both treatment groups was not mentioned.
Hernadi 1988	Cumulative anthracycline dose patients received in both treatment groups was not mentioned.
Homesley 1992	Difference in anthracycline peak dose between intervention and control group.
Hortobagyi 1989	Difference in anthracycline peak dose between intervention and control group.
Jain 1985	Difference in anthracycline peak dose between intervention and control group; duplicate publication of Casper 1987B.
Keiling 1986	Duplicate publication of FESG 1988.
Klener 1973	No randomized controlled trial; difference in anthracycline peak dose between intervention and control group.
Lahtinen 1991	Cumulative anthracycline dose patients received in both treatment groups was not mentioned.
Lawton 1993	Cumulative anthracycline dose patients received in both treatment groups was not mentioned.
Lopez 1989	Duplicate publication IMBSWE 1988.

Study	Reason for exclusion
Lotrionte 2009	Difference in anthracycline peak dose between intervention and control group; difference in treatment other than anthracyclines between intervention and control group; protocol of planned study.
Mandelli 1991	Difference in anthracycline peak dose between intervention and control group.
Maung 2002	Difference in anthracycline peak dose between intervention and control group.
Moser 2005	Results of 4 different trials presented; in none of these trials a randomisation of different anthracycline derivates was performed.
Mouridsen 1987	Cardiotoxicity data not presented in this publication.
Nair 1998	Difference in anthracycline peak dose between intervention and control group.
Namer 2001	Results of patients treated with doxorubicin and epirubicin not presented seperately.
NCT00531973	Registration in an ongoing trials database of the Lotrionte 2009 study protocol.
NCT00589082Latagliata2008	Difference in anthracycline peak dose between intervention and control group.
NCT00854568	Difference in anthracycline peak dose between intervention and control group.
Neri 1989	No randomized controlled trial.
Nielsen 1998	Difference in anthracycline peak dose between intervention and control group.
Nielsen 2000	Update of studies (Nielsen 1988 and Mouridsen 1987); as mentioned elsewhere, both studies were excluded from this review.
Nikkanen 1988	Cardiotoxicity not mentioned.
O'Brian 2004	Difference in anthracycline peak dose between intervention and control group.
Perez 1991	Difference in anthracycline peak dose between intervention and control group.
Pinedo 1987	Cardiotoxicity not mentioned.
Rifkin 2006	Difference in anthracycline peak dose between intervention and control group.
Sculier 1995	Difference in anthracycline peak dose between intervention and control group.
Smith 1987	Cumulative anthracycline dose patients received in both treatment groups was not mentioned.
Stohr 2006	Difference in anthracycline peak dose and infusion duration between intervention and control group; difference in treatment other than anthracyclines between intervention and control group.
Suzuki 1984	Animal study.
Swenson 2003	Describes part of the patients of Batist 2001; no cardiac data presented.
Tanaka 1983	No randomized controlled trial.
Toda 1989	No randomized controlled trial.

Study	Reason for exclusion
Tsushima 1991	Difference in anthracycline peak dose between intervention and control group.
Ventura 2005	No randomized controlled trial.
Yates 1982	No definition of cardiotoxicity provided.
Zinzani 1995	Difference in anthracycline peak dose between intervention and control group.

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

Burnell 2007

Methods	Method of randomisation not clear.
Participants	Female patients with node-positive or high-risk node-negative breast cancer (maximal age 60 years).
Interventions	Doxorubicin versus epirubicin.
Outcomes	Survival and toxicity (including cardiotoxicity) (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

Knobloch 2008

Methods	Unclear if this is a randomized controlled trial.
Participants	Female patients with breast cancer, ovarial cancer, corpus carcinoma or collum carcinoma (age not specified).
Interventions	Epirubicin versus liposomal doxorubicin (caelyx).
Outcomes	Cardiotoxicity (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

NCT00002985

Methods	Method of randomisation not clear.
Participants	Patients with AIDS-related Kaposi's sarcoma (age not specified).
Interventions	Liposomal daunorubicin (daunoxome) versus liposomal doxorubicin (doxil).
Outcomes	Clinical benefit, tumour response and safety (definitions not provided).

NCT00002985 *(Continued)*

Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

NCT00022516

Methods	Method of randomisation not clear.
Participants	Patients with breast cancer (stage I, II or III) (age not specified).
Interventions	Doxorubicin versus epirubicin.
Outcomes	Toxic effects, survival and quality of life (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

NCT00431795

Methods	Method of randomisation not clear.
Participants	Female patients with advanced breast cancer (aged between 18 and 75 years).
Interventions	Epirubicin versus liposomal doxorubicin (caelyx).
Outcomes	Tumour response and toxicities (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

NCT00516425

Methods	Method of randomisation not clear.
Participants	Female patients with invasive breast cancer (minimal age 70 years).
Interventions	Doxorubicin versus epirubicin.
Outcomes	Survival and safety (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

NCT00536393

Methods	Method of randomisation not clear.
Participants	Patients with disseminated high grade lymphoma (aged between 60 and 75 years).

NCT00536393 *(Continued)*

Interventions	Doxorubicin versus liposomal doxorubicin.
Outcomes	Tumour response, survival, toxicities (including cardiotoxicity) (definitions not provided).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

Northfelt 1996

Methods	Method of randomisation not clear.
Participants	Patients with AIDS-related Kaposi's sarcoma (aged between 29 and 46 years).
Interventions	Doxorubicin versus liposomal doxorubicin.
Outcomes	Toxicity (according to WHO criteria).
Notes	We were not able to contact the investigators of this trial, therefore we are not certain if this trial fulfilled all criteria for considering studies for this review.

WHO = world health organisation

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

NCT00575406

Trial name or title	Multicentre study to determine the cardiotoxicity of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristin and prednisolone) compared to R-COMP (rituximab, cyclophosphamide, liposomal doxorubicin, vincristin and prednisolone) in patients with diffuse large B-cell lymphoma (NHL-14).
Methods	Method of randomisation not clear.
Participants	Patients with diffuse large B-cell lymphoma (minimal age 18 years).
Interventions	Doxorubicin versus liposomal doxorubicin (both given in a short infusion with a peak dose of 50 mg/m^2).
Outcomes	Cardiotoxicity (definition not provided).
Starting date	December 2007
Contact information	Prof. dr. MA Fridrik (michael.fridrik@akh.linz.at)
Notes	

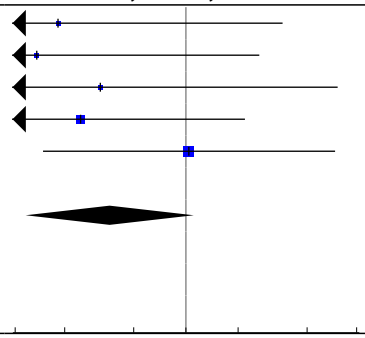
DATA AND ANALYSES

Comparison 1. Doxorubicin versus epirubicin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical heart failure	5	1036	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.12, 1.11]
2 Tumour response	5	1036	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.08]
3 Progression-free survival	2		Hazard ratio (Random, 95% CI)	1.05 [0.76, 1.44]
4 Overall survival	2		Hazard ratio (Random, 95% CI)	0.95 [0.65, 1.39]
5 Adverse effects: leukopenia grade 3 or 4	2	546	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.31, 0.80]
6 Adverse effects: nausea / vomiting grade 3 or 4	2	546	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.97]
7 Adverse effects: alopecia grade 3 or 4	3	796	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.38]

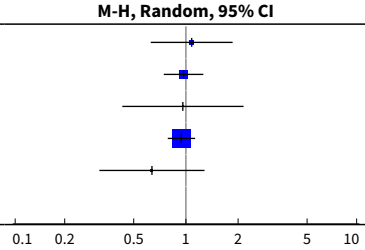
Analysis 1.1. Comparison 1 Doxorubicin versus epirubicin, Outcome 1 Clinical heart failure.

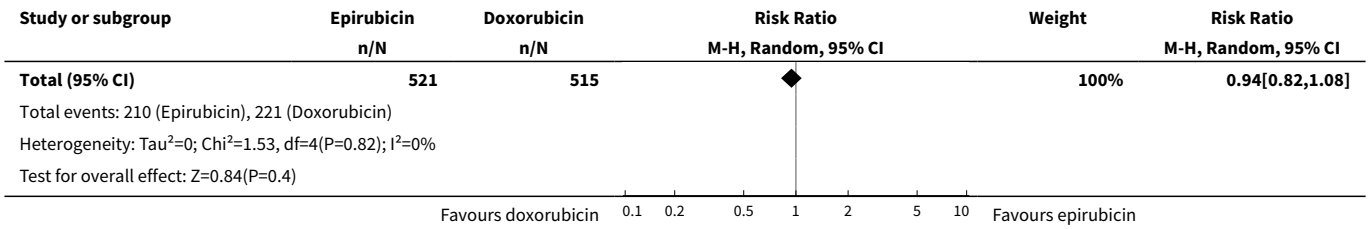
Study or subgroup	Epirubicin n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brambilla 1986	0/23	2/21		14.01%	0.18[0.01,3.61]
FESG 1988	0/127	3/123		14.28%	0.14[0.01,2.65]
Gasparini 1991	0/25	1/24		12.52%	0.32[0.01,7.5]
IMBSWE 1988	1/250	4/247		26.1%	0.25[0.03,2.19]
Mouridsen 1984	2/96	2/100		33.09%	1.04[0.15,7.25]
Total (95% CI)	**521**	**515**		**100%**	**0.36[0.12,1.11]**
Total events: 3 (Epirubicin), 12 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=1.9, df=4(P=0.75); I^2=0%					
Test for overall effect: Z=1.78(P=0.07)					



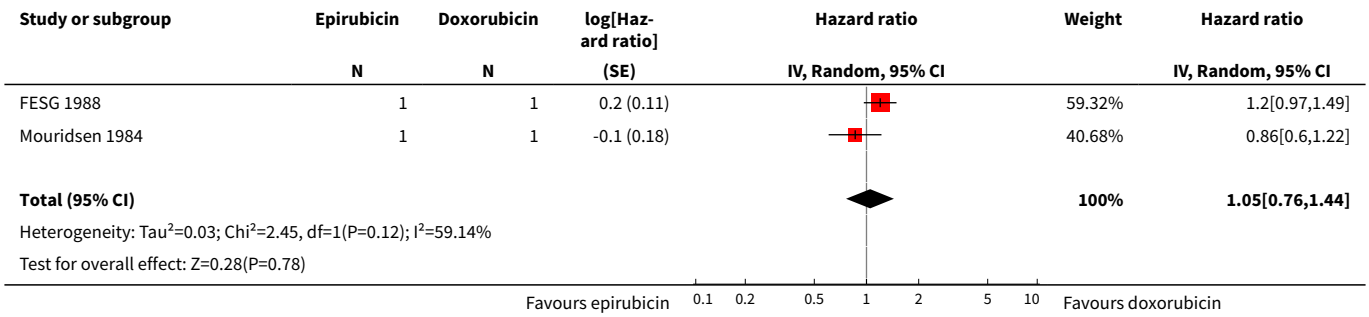
Analysis 1.2. Comparison 1 Doxorubicin versus epirubicin, Outcome 2 Tumour response.

Study or subgroup	Epirubicin n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Brambilla 1986	13/23	11/21		6.44%	1.08[0.63,1.86]
FESG 1988	59/127	59/123		27.6%	0.97[0.75,1.26]
Gasparini 1991	8/25	8/24		2.93%	0.96[0.43,2.15]
IMBSWE 1988	119/250	125/247		59.11%	0.94[0.79,1.13]
Mouridsen 1984	11/96	18/100		3.92%	0.64[0.32,1.28]

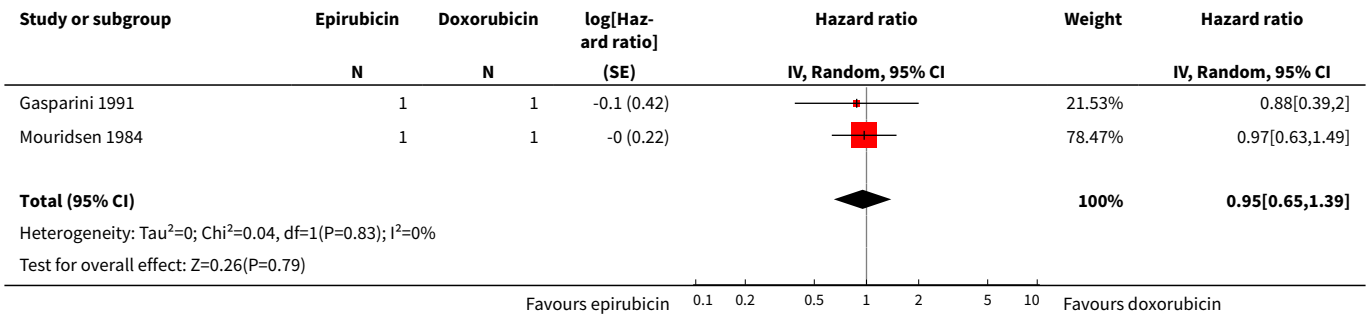




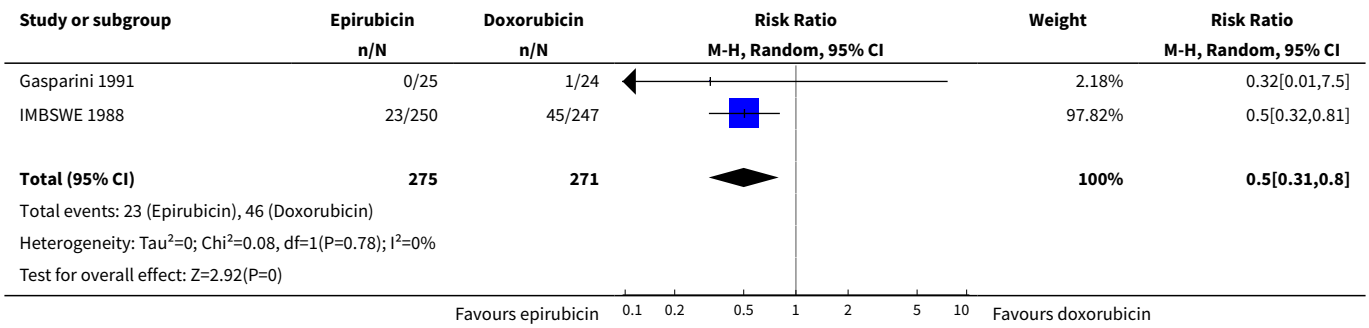
Analysis 1.3. Comparison 1 Doxorubicin versus epirubicin, Outcome 3 Progression-free survival.



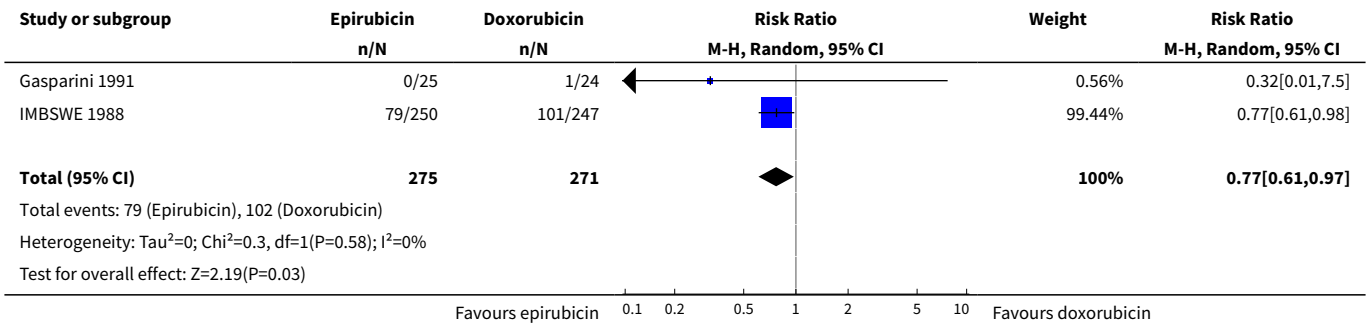
Analysis 1.4. Comparison 1 Doxorubicin versus epirubicin, Outcome 4 Overall survival.



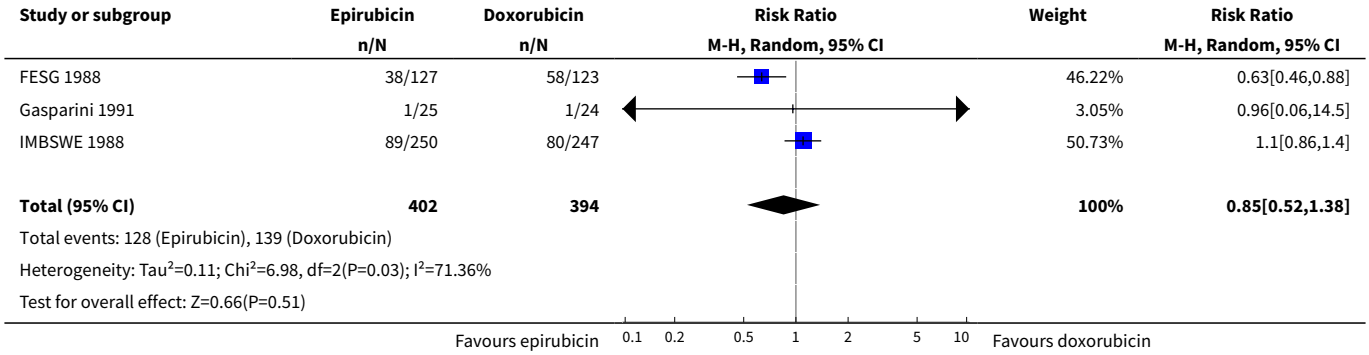
Analysis 1.5. Comparison 1 Doxorubicin versus epirubicin, Outcome 5 Adverse effects: leukopenia grade 3 or 4.



Analysis 1.6. Comparison 1 Doxorubicin versus epirubicin, Outcome 6 Adverse effects: nausea / vomiting grade 3 or 4.



Analysis 1.7. Comparison 1 Doxorubicin versus epirubicin, Outcome 7 Adverse effects: alopecia grade 3 or 4.



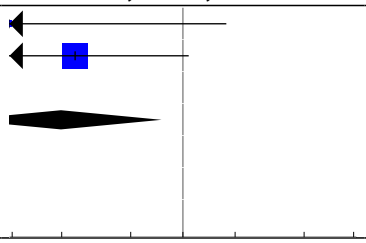
Comparison 2. Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical heart failure	2	521	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.75]
2 Heart failure combined	2	521	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.24, 0.59]
3 Tumour response	2	521	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.80, 1.26]
4 Progression-free survival	2		Hazard ratio (Random, 95% CI)	1.01 [0.83, 1.24]
5 Overall survival	2		Hazard ratio (Random, 95% CI)	1.12 [0.83, 1.53]
6 Adverse effects: anaemia grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.61, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Adverse effects: thrombocytopenia grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.60, 1.97]
8 Adverse effects: neutropenia grade 4	2	521	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.72, 0.94]
9 Adverse effects: neutropenic fever (fever >=38, neutropenia grade 4, IV antibiotics and/or hospitalisation)	2	521	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.53, 1.45]
10 Adverse effects: nausea/vomiting grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.98]
11 Adverse effects: stomatitis/mucositis grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.05]
12 Adverse effects: diarrhoea grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.12, 0.87]
13 Adverse effects: asthenia/fatigue grade 3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.41]
14 Adverse effects: cutaneous grade 3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.08, 5.45]
15 Adverse effects: infection grade >=3	2	521	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.21, 2.89]

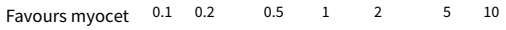
Analysis 2.1. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 1 Clinical heart failure.

Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	0/142	5/155		21.48%	0.1[0.01,1.78]
Harris 2002	2/108	9/116		78.52%	0.24[0.05,1.08]
Total (95% CI)	**250**	**271**		**100%**	**0.2[0.05,0.75]**
Total events: 2 (Myocet), 14 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=2.38(P=0.02)					



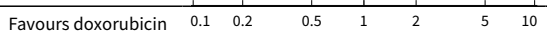
Analysis 2.2. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 2 Heart failure combined.

Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	9/142	33/155		39.34%	0.3[0.15,0.6]
Harris 2002	14/108	34/116		60.66%	0.44[0.25,0.78]
Total (95% CI)	**250**	**271**		**100%**	**0.38[0.24,0.59]**
Total events: 23 (Myocet), 67 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.75, df=1(P=0.39); I^2=0%					
Test for overall effect: Z=4.33(P<0.0001)					



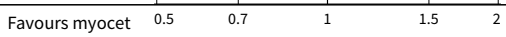
Analysis 2.3. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 3 Tumour response.

Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	61/142	66/155		73.92%	1.01[0.78,1.31]
Harris 2002	28/108	30/116		26.08%	1[0.64,1.56]
Total (95% CI)	**250**	**271**		**100%**	**1.01[0.8,1.26]**
Total events: 89 (Myocet), 96 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.98); I^2=0%					
Test for overall effect: Z=0.06(P=0.95)					

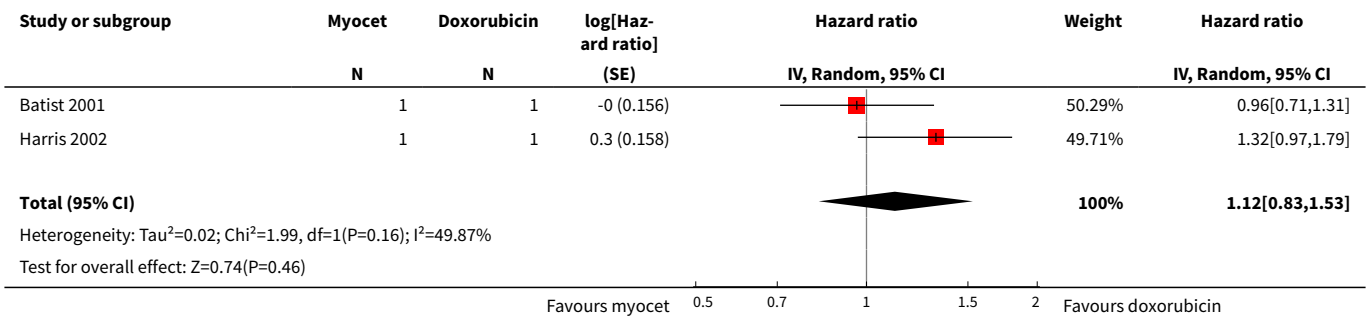


Analysis 2.4. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 4 Progression-free survival.

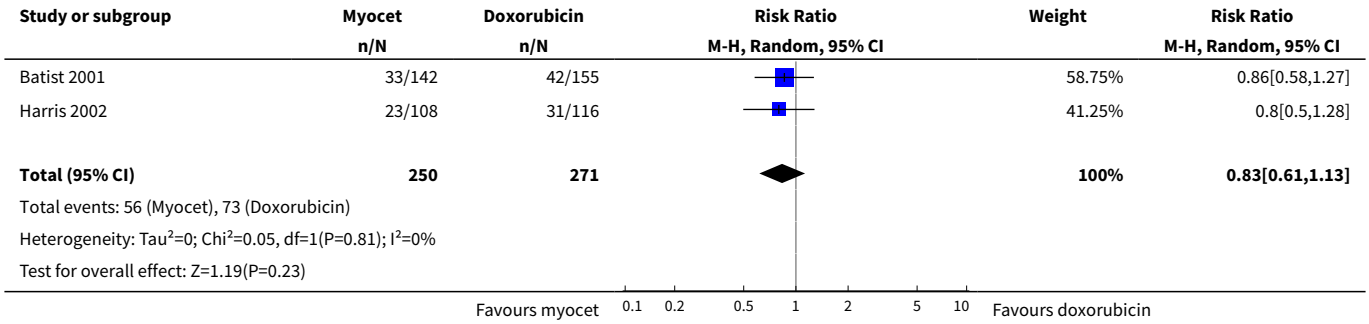
Study or subgroup	Myocet N	Doxorubicin N	log[Hazard ratio] (SE)	Hazard ratio IV, Random, 95% CI	Weight	Hazard ratio IV, Random, 95% CI
Batist 2001	1	1	-0 (0.13)		61.81%	0.97[0.75,1.25]
Harris 2002	1	1	0.1 (0.165)		38.19%	1.09[0.79,1.5]
Total (95% CI)					**100%**	**1.01[0.83,1.24]**
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%						
Test for overall effect: Z=0.13(P=0.89)						



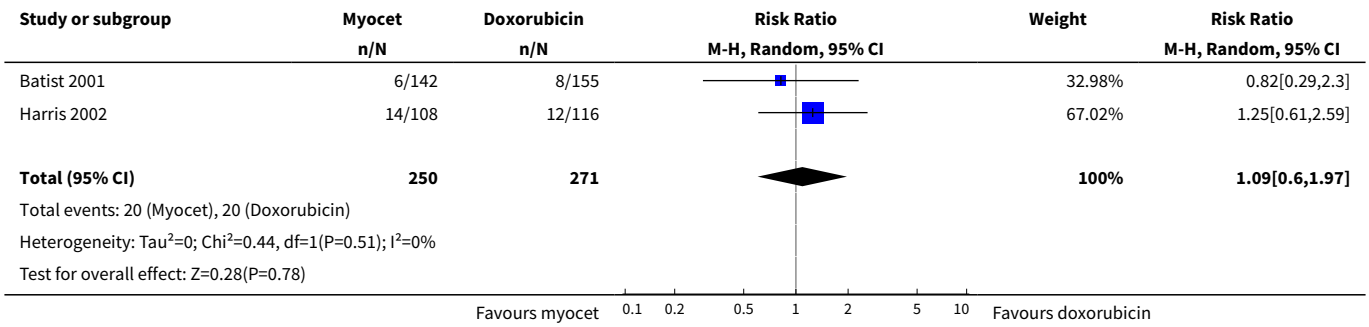
Analysis 2.5. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 5 Overall survival.



Analysis 2.6. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 6 Adverse effects: anaemia grade >=3.

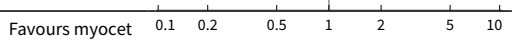


Analysis 2.7. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 7 Adverse effects: thrombocytopenia grade >=3.



Analysis 2.8. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 8 Adverse effects: neutropenia grade 4.

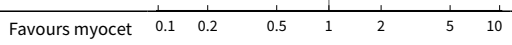
Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	87/142	116/155		70.33%	0.82[0.7,0.96]
Harris 2002	53/108	68/116		29.67%	0.84[0.65,1.07]
Total (95% CI)	**250**	**271**		**100%**	**0.82[0.72,0.94]**
Total events: 140 (Myocet), 184 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=2.84(P=0)					



Favours myocet — Favours doxorubicin

Analysis 2.9. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 9 Adverse effects: neutropenic fever (fever >=38, neutropenia grade 4, IV antibiotics and/or hospitalisation).

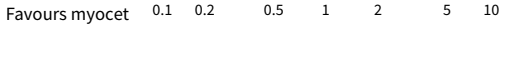
Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	13/142	20/155		57.96%	0.71[0.37,1.37]
Harris 2002	12/108	11/116		42.04%	1.17[0.54,2.54]
Total (95% CI)	**250**	**271**		**100%**	**0.88[0.53,1.45]**
Total events: 25 (Myocet), 31 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.93, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=0.52(P=0.61)					



Favours myocet — Favours doxorubicin

Analysis 2.10. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 10 Adverse effects: nausea/vomiting grade >=3.

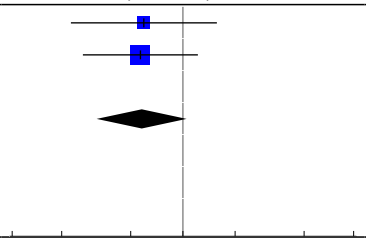
Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	18/142	25/155		52.1%	0.79[0.45,1.38]
Harris 2002	14/108	28/116		47.9%	0.54[0.3,0.96]
Total (95% CI)	**250**	**271**		**100%**	**0.65[0.44,0.98]**
Total events: 32 (Myocet), 53 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					



Favours myocet — Favours doxorubicin

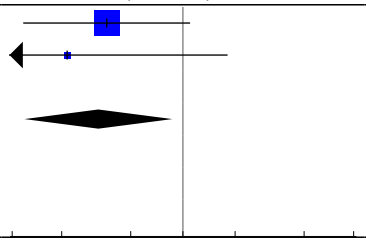
Analysis 2.11. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 11 Adverse effects: stomatitis/mucositis grade >=3.

Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	6/142	11/155		38.38%	0.6[0.23,1.57]
Harris 2002	9/108	17/116		61.62%	0.57[0.26,1.22]
Total (95% CI)	**250**	**271**		**100%**	**0.58[0.32,1.05]**
Total events: 15 (Myocet), 28 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%					
Test for overall effect: Z=1.79(P=0.07)					



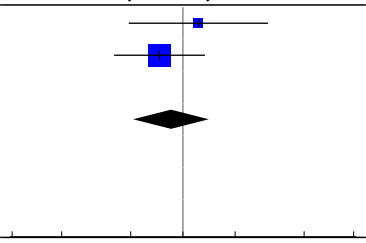
Analysis 2.12. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 12 Adverse effects: diarrhoea grade >=3.

Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	4/142	12/155		78.71%	0.36[0.12,1.1]
Harris 2002	1/108	5/116		21.29%	0.21[0.03,1.81]
Total (95% CI)	**250**	**271**		**100%**	**0.33[0.12,0.87]**
Total events: 5 (Myocet), 17 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.67); I^2=0%					
Test for overall effect: Z=2.24(P=0.03)					

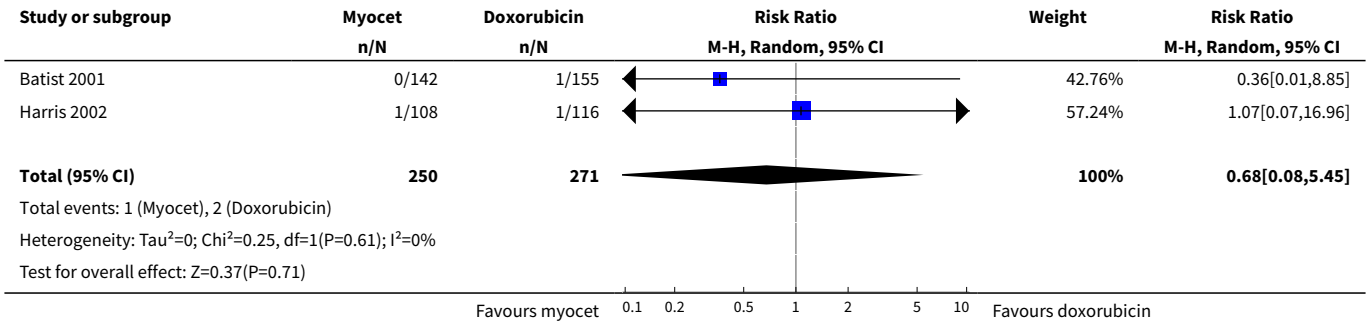


Analysis 2.13. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 13 Adverse effects: asthenia/fatigue grade 3.

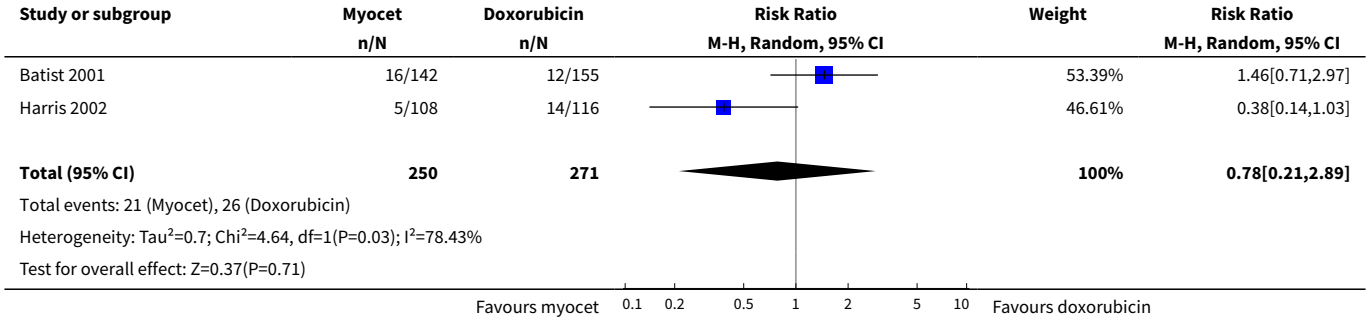
Study or subgroup	Myocet n/N	Doxorubicin n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Batist 2001	9/142	8/155		29.74%	1.23[0.49,3.1]
Harris 2002	15/108	22/116		70.26%	0.73[0.4,1.34]
Total (95% CI)	**250**	**271**		**100%**	**0.85[0.52,1.41]**
Total events: 24 (Myocet), 30 (Doxorubicin)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					



Analysis 2.14. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 14 Adverse effects: cutaneous grade 3.



Analysis 2.15. Comparison 2 Conventional doxorubicin versus liposomal-encapsulated doxorubicin (myocet), Outcome 15 Adverse effects: infection grade >=3.



ADDITIONAL TABLES

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

Item ID	Description	Implementation
Patient selection		Note: all criteria were scored yes (+), no (-) or unclear (?)
a	Was the allocation of participants to treatment groups randomised?	A random (unpredictable) assignment sequence must have been applied.
b	Was the treatment allocation concealed?	Allocation must have been performed by a person not responsible for determining eligibility of patients for inclusion.
Interventions		
c	Was the care provider blinded to the intervention?	Adequate information about blinding must have been provided.
d	Was the patient blinded to the intervention?	Adequate information about blinding must have been provided.

Table 1. Criteria list for the assessment of risk of bias in included studies *(Continued)*

Outcome assessments (for each outcome separately)		
e	Was the outcome assessor blinded to the intervention?	Adequate information about blinding must have been provided.
f	Were patients lost to follow-up described and acceptable?	For each outcome measure the number of evaluated patients must be mentioned. If the percentage of non-evaluable patients does not exceed 20% a "yes" (+) is scored.

Table 2. Risk of bias assessment in included studies

Study	a	b	c	d	e	f	Intervention
Batist 2001	+	?	?	?	Clinical heart failure, subclinical heart failure, tumour response, PFS: +; adverse effects: ?	Clinical heart failure, subclinical heart failure, tumour response, PFS, OS, adverse effects: +	Doxorubicin versus liposomal-encapsulated doxorubicin (myocet).
Brambilla 1986	+	?	?	?	Clinical heart failure, subclinical heart failure, tumour response, PFS: ?	Clinical heart failure: ?; subclinical heart failure, PFS: -; tumour response, OS: +	Doxorubicin versus epirubicin.
Chan 2004	+	?	?	?	Clinical heart failure, subclinical heart failure, tumour response, PFS, adverse effects: ?	Clinical heart failure, subclinical heart failure, tumour response, PFS, OS, adverse effects: +	Epirubicin versus liposomal-encapsulated doxorubicin (myocet).
FESG 1998	+	?	?	?	Clinical heart failure, tumour response, PFS, adverse effects: ?	Clinical heart failure, tumour response, PFS, OS: +; adverse effects: -	Doxorubicin versus epirubicin.
Gasparini 1991	+	?	?	?	Clinical heart failure, tumour response, PFS, adverse effects: ?	Clinical heart failure, tumour response, PFS, OS, adverse effects: +	Doxorubicin versus epirubicin.
Harris 2002	+	?	?	?	Clinical heart failure, adverse effects: ?; subclinical heart failure, tumour response, PFS: +	Clinical heart failure, subclinical heart failure, tumour response, PFS, OS, adverse effects: +	Doxorubicin versus liposomal-encapsulated doxorubicin (myocet).
IMBSWE 1988	+	?	?	?	Clinical heart failure, tumour response, adverse effects: ?	Clinical heart failure, tumour response, PFS, OS, adverse effects (with the exception of alopecia: -): +	Doxorubicin versus epirubicin.
Mouridsen 1984	+	?	?	?	Clinical heart failure, tumour response, PFS: ?	Clinical heart failure, tumour response, PFS, OS: -	Doxorubicin versus epirubicin.

PFS = progression-free survival; OS = overall survival

Table 3. Descriptive results of survival: epirubicin versus doxorubicin

Study	Progression-free survival	Overall survival
Brambilla 1986	Not evaluated in review	Median: in epirubicin group > 16 months (7-25+), in doxorubicin group > 18 months (6-28+) (no significant difference)
FESG 1988	Median: in epirubicin group 220 days (30-1230), in doxorubicin group 270 days (30-1380) (no significant difference)	Median: in epirubicin group 450 days (20-1582), in doxorubicin group 530 days (36-1681) (no significant difference)
Gasparini 1991	In epirubicin group range 2 to 11 months, in doxorubicin group 3 to 14 months (P=0.91)	Median: in epirubicin group 12 months, in doxorubicin group 11 months (no significant difference)
IMBSWE 1988	Median: in epirubicin group 273 days, in doxorubicin group 314 days (P=0.59)	Median: in epirubicin group 591 days, in doxorubicin group 613 days (P=0.75)
Mouridsen 1987	No significant differences between both treatment groups (P=0.41)	No significant differences between both treatment groups (P=0.90)

Table 4. Adverse effects: epirubicin versus liposomal-encapsulated doxorubicin (myocet)

Adverse effect	n/N myocet patients	n/N epirubicin patients	RR (95% CI)	P-value
Anaemia grade >=3	19/80	11/80	1.73 (0.88 - 3.39)	0.11
Thrombocytopenia grade >=3	3/80	2/80	1.50 (0.26 - 8.74)	0.65
Neutropenia grade 4	66/80	52/80	1.17 (1.05 - 1.53)	0.01
Prolonged neutropenia grade 4 (>=7 days)	20/80	24/80	0.83 (0.50 - 1.38)	0.48
Febrile neutropenia (fever >=38 C, neutropenia grade 4, IV antibiotics and/or hospitalisation)	4/80	1/80	4.00 (0.46 to 35.01)	0.21
Infection grade >=3	5/80	1/80	5.00 (0.60 - 41.85)	0.14
Nausea / vomiting grade >=3	16/80	15/80	1.07 (0.57 - 2.01)	0.84
Stomatitis / mucositis grade 3	5/80	0/80	11.00 (0.62 - 195.69)	0.10
Diarrhoea grade 3	1/80	1/80	1.00 (0.06 - 15.71)	1.00
Asthenia / fatigue grade 3	0/80	1/80	0.33 (0.01 - 8.06)	0.50
Cutaneous grade 3	0/80	1/80	0.33 (0.01 - 8.06)	0.50
Injection site toxicity grade 3	0/80	1/80	0.33 (0.01 - 8.06)	0.50

IV = intravenous; n = number of patients with adverse effect; N = total number of patients in group; RR = risk ratio/relative risk; CI = confidence interval

APPENDICES

Appendix 1. Search strategy for MEDLINE/PubMed

For **idarubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: 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*.

For **liposomal idarubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: (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*) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*).

For **epirubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: 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*.

For **liposomal epirubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: (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*) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*).

For **doxorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR DOXSL OR doxorubicin hydrochloride OR hydrochloride doxorubicin OR doxorubic* OR adriamyc*.

For **liposomal doxorubicin** the following subject headings and text words were used *(in the original version of the review)*: ((adriablastine OR adriblastin OR adriablastin OR adriamycin OR DOX-SL OR DOX SL OR DOXSL OR doxorubicin hydrochloride OR hydrochloride doxorubicin OR doxorubic* OR adriamyc*) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*)) OR (doxil OR caelyx OR liposomal doxorubicin OR doxorubicin, liposomal). *For the update we added the following to the search: OR myocet.*

For **daunorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: 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.

For **liposomal daunorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: ((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) AND (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*)) OR (daunoxome OR daunosom*).

Subject headings and text words of each type of anthracycline derivate were combined with an other type of anthracycline derivate, i.e. idarubicin versus liposomal idarubicin, idarubicin versus epirubicin, idarubicin versus liposomal epirubicin, idarubicin versus doxorubicin, idarubicin versus liposomal doxorubicin, idarubicin versus daunorubicin, idarubicin versus liposomal daunorubicin, liposomal idarubicin versus epirubicin, liposomal idarubicin versus liposomal epirubicin, liposomal idarubicin versus doxorubicin, liposomal idarubicin versus liposomal doxorubicin, liposomal idarubicin versus daunorubicin, liposomal idarubicin versus liposomal daunorubicin, epirubicin versus doxorubicin, epirubicin versus liposomal doxorubicin, epirubicin versus daunorubicin, epirubicin versus liposomal daunorubicin, epirubicin versus liposomal epirubicin, liposomal epirubicin versus doxorubicin, liposomal epirubicin versus liposomal doxorubicin, liposomal epirubicin versus daunorubicin, liposomal epirubicin versus liposomal daunorubicin, doxorubicin versus liposomal doxorubicin, doxorubicin versus daunorubicin, doxorubicin versus liposomal daunorubicin, liposomal doxorubicin versus daunorubicin, liposomal doxorubicin versus liposomal daunorubicin, and daunorubicin versus liposomal daunorubicin.

All the above mentioned combinations were combined with the following subject headings and text words for **heart damage** *(in the original version of the review)*: heart OR heart diseases OR heart disease OR disease, heart OR diseases, heart OR cardiac diseases OR cardiac disease OR diseases, cardiac OR disease, cardiac OR cardiotoxicity OR cardiomyopathy OR heart failure, congestive OR heart failure OR cardiomyopathy, congestive OR ventricular dysfunction OR ventricular dysfunction, left OR ventricular dysfunction, right. *For the update we added the following to the search: OR shortening fraction OR ejection fraction OR echocardiography OR radionuclide angiography OR radionuclide ventriculography OR ventriculography, radionuclide OR gated blood-pool imaging OR blood pool scintigraphy OR gated*

radionuclide ventriculography OR ventriculography, first pass OR cardiotox OR cardiomyop* OR echocardiogr* OR ventriculogr* OR scintigr* OR MUGA OR LVEF OR LVSF OR endomyocardial biopsy OR angiocardiography OR cardiomyopathies.*

Finally, the results of this search were combined with the **highly sensitive search strategy as described in the Cochrane Handbook** (*for the original review:* Higgins 2005 (all phases); *for the update*: Higgins 2009 (sensitivity-maximaizing version)).

Appendix 2. Search strategy for EMBASE/Ovid

For **idarubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or idarubicin.mp or (idarubicin derivative or IMI 30 or NSC 256439 or idarubicin hydrochloride or 4 demethoxydaunorubicin derivative).mp or idarubic$.mp.

For **liposomal idarubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: (exp IDARUBICIN DERIVATIVE/ or exp IDARUBICIN/ or idarubicin.mp or (idarubicin derivative or IMI 30 or NSC 256439 or idarubicin hydrochloride or 4 demethoxydaunorubicin derivative).mp or idarubic$.mp) and (liposomal or encapsulated or pegylated).mp.

For **epirubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: epirubicin.mp or exp EPIRUBICIN/ or epirubic$.mp or (4' epiadriamycin or 4' epidoxorubicin).mp or (farmorubicin or 4' epi DXR or epirubicin hydrochloride).mp OR (IMI 28 or NSC 256942).mp.

For **liposomal epirubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: (epirubicin.mp or exp EPIRUBICIN/ or epirubic$.mp or (4' epiadriamycin or 4' epidoxorubicin).mp or (farmorubicin or 4' epi DXR or epirubicin hydrochloride).mp OR (IMI 28 or NSC 256942).mp) and (liposomal or encapsulated or pegylated).mp.

For **doxorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: (adriamycin or doxorubicin).mp or exp Doxorubicin/ or (doxorubic$ or adriamyc$).mp or adriablastine.mp or (adriblastin or adriablastin or doxorubicin hydrochloride or DOX SL).mp.

For **liposomal doxorubicin** the following subject headings and text words were used *(in the original version of the review)*: (((adriamycin or doxorubicin).mp or exp Doxorubicin/ or (doxorubic$ or adriamyc$).mp or adriablastine.mp or (adriblastin or adriablastin or doxorubicin hydrochloride or DOX SL).mp) and (liposomal or encapsulated or pegylated).mp) or (caelyx or doxil or liposomal doxorubicin).mp. *For the update we added the following to the search: OR myocet.*

For **daunorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: exp DAUNORUBICIN DERIVATIVE/ or daunorubicin.mp or exp DAUNORUBICIN/ or (daunorubidomycine or rubidomycin or rubomycin or daunomycin or daynorubicin hydrochloride or daunoblastin or daunoblastine or cerubidine or NSC 82151).mp or (rubidomyc$ or daunorubic$).mp.

For **liposomal daunorubicin** the following subject headings and text words were used *(in both the original version of the review and the update)*: ((exp DAUNORUBICIN DERIVATIVE/ or daunorubicin.mp or exp DAUNORUBICIN/ or (daunorubidomycine or rubidomycin or rubomycin or daunomycin or daynorubicin hydrochloride or daunoblastin or daunoblastine or cerubidine or NSC 82151).mp or (rubidomyc $ or daunorubic$).mp) and (liposomal or encapsulated or pegylated).mp) or daunoxome.mp or daunosom$.mp.

Subject headings and text words of each type of anthracycline derivate were combined with an other type of anthracycline derivate, i.e. idarubicin versus liposomal idarubicin, idarubicin versus epirubicin, idarubicin versus liposomal epirubicin, idarubicin versus doxorubicin, idarubicin versus liposomal doxorubicin, idarubicin versus daunorubicin, idarubicin versus liposomal daunorubicin, liposomal idarubicin versus epirubicin, liposomal idarubicin versus liposomal epirubicin, liposomal idarubicin versus doxorubicin, liposomal idarubicin versus liposomal doxorubicin, liposomal idarubicin versus daunorubicin, liposomal idarubicin versus liposomal daunorubicin, epirubicin versus doxorubicin, epirubicin versus liposomal doxorubicin, epirubicin versus daunorubicin, epirubicin versus liposomal daunorubicin, epirubicin versus liposomal epirubicin, liposomal epirubicin versus doxorubicin, liposomal epirubicin versus liposomal doxorubicin, liposomal epirubicin versus daunorubicin, liposomal epirubicin versus liposomal daunorubicin, doxorubicin versus liposomal doxorubicin, doxorubicin versus daunorubicin, doxorubicin versus liposomal daunorubicin, liposomal doxorubicin versus daunorubicin, liposomal doxorubicin versus liposomal daunorubicin, and daunorubicin versus liposomal daunorubicin.

All the above mentioned combinations were combined with the following subject headings and text words for **heart damage** *(in the original version of the review)*: heart failure.mp or exp Heart Failure/ or exp Heart Ventricle Failure/ or exp Heart Ventricle Function/ or exp Congestive Heart Failure/ or cardiotoxicity.mp or exp CARDIOTOXICITY/ or exp Congestive Cardiomyopathy/ or exp CARDIOMYOPATHY/ or exp Heart Disease/ or exp Heart Failure/ or exp HEART LEFT VENTRICLE FUNCTION/ or exp HEART RIGHT VENTRICLE FUNCTION/ or exp HEART RIGHT VENTRICLE FAILURE/ or exp HEART/ or exp FORWARD HEART FAILURE/. *For the update we added the following to the search: heart.mp or exp HEART EJECTION FRACTION/ or exp HEART RIGHT VENTRICLE EJECTION FRACTION/ or exp HEART FUNCTION/ or exp HEART FUNCTION TEST/ or exp HEART LEFT VENTRICLE FAILURE/ or exp HEART VENTRICULOGRAPHY/ or exp HEART LEFT VENTRICLE EJECTION FRACTION/ or congestive heart failure.mp or cardiomyopathy.mp or heart disease.mp or cardiac disease.mp or ventricular dysfunction.mp or shortening fraction.mp or ejection fraction.mp or (MUGA or LVEF or LVSF).mp or echocardiography.mp or exp ECHOCARDIOGRAPHY/ or radionuclide angiography.mp or radionuclide ventriculography.mp or exp Radioisotope Ventriculography/ or gated blood-pool imaging.mp or endomyocardial biopsy.mp or*

exp Heart Muscle Biopsy/ or angiocardiography.mp or exp ANGIOCARDIOGRAPHY/ or blood pool scintigraphy.mp or (cardiotox$ or cardiomyop $ or echocardiogr$ or ventriculogr$ or scintigr$).mp.

Finally, the results of this search were combined with the search for **randomised controlled trials**. The following subject headings and text words were used (*in the original version of the review*; based on the highly sensitive search strategy for identifying reports of randomised controlled trials as described in the Cochrane Handbook (Higgins 2005)): Randomized Controlled Trial/ or exp RANDOMIZATION/ or Controlled Study/ or Clinical Trial/ or Single Blind Procedure/ or Double Blind Procedure/ or exp PLACEBO/ or exp Comparative Study/ or exp Prospective Study/. *For the update we used the following strategy (based on the highly sensitive search strategy for identifying reports of randomised controlled trials as described in the Cochrane Handbook (* Higgins 2009 *)): (Randomized Controlled Trial/ or Controlled Clinical Trial/ or randomized.ti,ab. or placebo.ti,ab. or randomly.ti,ab. or trial.ti,ab. or groups.ti,ab. or drug therapy.sh.) not (animal/ not human/).*

[mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]; [ti,ab=title, abstract]; [sh=subject heading]

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

For **idarubicin** the following subject headings and text words were used *(in the original version of the review)*: idarubicin OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR idarubicin hydrochloride OR idarubic*. *For the update we added the following to the search: OR IMI 30 OR IMI30 OR IMI-30 OR NSC 256439 OR NSC-256439 OR NSC256439.*

For **liposomal idarubicin** the following subject headings and text words were used *(in the original version of the review)*: (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*) and (idarubicin OR 4-demethoxydaunorubicin OR 4 demethoxydaunorubicin OR 4-desmethoxydaunorubicin OR 4 desmethoxydaunorubicin OR idarubicin hydrochloride OR idarubic*). *For the update we added the following to the search: OR IMI 30 OR IMI30 OR IMI-30 OR NSC 256439 OR NSC-256439 OR NSC256439*

For **epirubicin** the following subject headings and text words were used *(in the original version of the review)*: 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 epirubicin OR epirubic*. *For the update we added the following to the search: OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942.*

For **liposomal epirubicin** the following subject headings and text words were used *(in the original version of the review)*: (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*) and (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 epirubicin OR epirubic*). *For the update we added the following to the search: OR IMI-28 OR IMI 28 OR IMI28 OR NSC 256942 OR NSC-256942 OR NSC256942.*

For **doxorubicin** the following subject headings and text words were used *(in the original version of the review)*: adriablastine OR adriblastin OR adriablastin OR adriamycin OR doxorubicin hydrochloride OR doxorubicin OR doxorubic* OR adriamycin*. *For the update we added the following to the search: OR DOX-SL OR DOX SL OR DOXSL OR hydrochloride doxorubicin; for the update we changed adriamycin* into adriamyc*.*

For **liposomal doxorubicin** the following subject headings and text words were used *(in the original version of the review)*: (pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*) AND (adriablastine OR adriblastin OR adriablastin OR adriamycin OR doxorubicin hydrochloride OR doxorubicin OR doxorubic* OR adriamycin*). *For the update we added the following to the search: OR DOX-SL OR DOX SL OR DOXSL OR hydrochloride doxorubicin OR doxil OR caelyx OR liposomal doxorubicin OR myocet; for the update we changed adriamycin* into adriamyc*.*

For **daunorubicin** the following subject headings and text words were used *(in the original version of the review)*: daunorubidomycine OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR daunorubicin OR daunorubic* OR rubidomyc*. *For the update we added the following to the search: OR NSC-82151 OR NSC 82151 OR NSC82151; for the update we changed daunorubidomycine in dauno-rubidomycine OR dauno rubidomycin.*

For **liposomal daunorubicin** the following subject headings and text words were used *(in the original version of the review)*: daunoxome OR daunosom* OR ((pegylated OR pegyl* OR encapsulated OR encapsul* OR liposomal OR liposom*) AND (daunorubidomycine OR rubidomycin OR rubomycin OR daunomycin OR cerubidine OR daunoblastin OR daunoblastine OR daunorubicin hydrochloride OR daunorubicin OR daunorubic* OR rubidomyc*). *For the update we added the following to the search: OR NSC-82151 OR NSC 82151 OR NSC82151; for the update we changed daunorubidomycine in dauno-rubidomycine OR dauno rubidomycin.*

Subject headings and text words of each type of anthracycline derivate were combined with an other type of anthracycline derivate, i.e. idarubicin versus liposomal idarubicin, idarubicin versus epirubicin, idarubicin versus liposomal epirubicin, idarubicin versus doxorubicin, idarubicin versus liposomal doxorubicin, idarubicin versus daunorubicin, idarubicin versus liposomal daunorubicin, liposomal idarubicin versus epirubicin, liposomal idarubicin versus liposomal epirubicin, liposomal idarubicin versus doxorubicin, liposomal idarubicin versus liposomal doxorubicin, liposomal idarubicin versus daunorubicin, liposomal idarubicin versus liposomal daunorubicin, epirubicin versus doxorubicin, epirubicin versus liposomal doxorubicin, epirubicin versus daunorubicin, epirubicin versus

liposomal daunorubicin, epirubicin versus liposomal epirubicin, liposomal epirubicin versus doxorubicin, liposomal epirubicin versus liposomal doxorubicin, liposomal epirubicin versus daunorubicin, liposomal epirubicin versus liposomal daunorubicin, doxorubicin versus liposomal doxorubicin, doxorubicin versus daunorubicin, doxorubicin versus liposomal daunorubicin, liposomal doxorubicin versus daunorubicin, liposomal doxorubicin versus liposomal daunorubicin, and daunorubicin versus liposomal daunorubicin.

All the above mentioned combinations were combined with the following subject headings and text words for **heart damage** *(in the original version of the review)*: heart OR heart diseases OR heart disease OR cardiac diseases OR cardiac disease OR cardiotoxicity OR cardiomyopathy OR heart failure OR congestive heart failure OR ventricular dysfunction. *For the update we added the following to the search: congestive cardiomyopathy OR shortening fraction OR ejection fraction OR echocardiography OR radionuclide angiography OR radionuclide ventriculography OR gated blood-pool imaging OR blood pool scintigraphy OR gated radionuclide ventriculography OR cardiotox* OR cardiomyop* OR echocardiogr* OR ventriculogr* OR scintigr* OR MUGA OR LVEF OR LVSF OR endomyocardial biopsy OR angiocardiography OR cardiomyopathies.*

WHAT'S NEW

Date	Event	Description
21 September 2016	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 4, 2006

Date	Event	Description
24 February 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.
27 November 2009	New citation required but conclusions have not changed	Unfortunately, no new studies could be included in the review. However, eight studies are awaiting classification as the current available data is unclear regarding inclusion (six studies are identified in the update): epirubicin versus doxocrubicin (n = 3), liposomal-encapsulated doxorubicin versus conventional doxorubicin (n = 2), liposomal-encapsulated doxocrubicin versus epirubicin (n = 2) and liposomal-encapsulated doxocrubicin versus liposomal daunorubicin (n = 1). Also, we identified an ongoing trial evaluating liposomal-encapsulated doxorubicin versus conventional doxorubicin (new in the update).
27 November 2009	New search has been performed	The search for eligible studies was updated to May/June 2009 using an updated search strategy.
14 October 2008	Amended	Converted to new review format.
17 July 2006	New search has been performed	Minor update
29 June 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Elvira van Dalen designed the study. She developed the search strategy and undertook the searches in the different electronic databases. She searched for unpublished and ongoing studies and identified the studies meeting the inclusion criteria. She performed the data-extraction and risk of bias assessment of the included studies. She analyzed the data and interpreted the results. She wrote and revised the manuscript.

Erna Michiels identified the studies meeting the inclusion criteria. She performed the data-extraction and risk of bias assessment of the included studies. She contributed to the data-analysis and the interpretation of the results.She critically reviewed the manuscript.

Huib Caron contributed to the data-analysis and the interpretation of the results. He critically reviewed the manuscript.

Leontien Kremer designed the study. She performed the data-extraction and risk of bias assessment of the included studies. She contributed to the data-analysis and the interpretation of the results. She critically reviewed the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

None known.

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Internal sources

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External sources

- Foundation of Pediatric Cancer Research (SKK) Amsterdam, Netherlands.
- Stichting Steun Emma Kinderziekenhuis AMC, Netherlands.
- Stichting Kinderen Kankervrij (KIKA), Netherlands.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotics, Antineoplastic [administration & dosage] [*adverse effects]; Cardiac Output, Low [chemically induced]; Doxorubicin [administration & dosage] [*adverse effects]; Epirubicin [administration & dosage] [*adverse effects]; Heart [*drug effects]; Liposomes; Neoplasms [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans