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The research reported in this monograph was commissioned by the HTA Programme as project number 05/34/01. The contractual start date was in September 2005. The draft report began editorial review in March 2006 and was accepted for publication in February 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review

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Objectives: To evaluate the technologies used to reduce anthracycline-induced cardiotoxicity in children. Also to evaluate cardiac markers to quantify cardiotoxicity, and identify cost-effectiveness studies and future research priorities

Data sources: Eight electronic databases were searched from inception to January 2006. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

Review methods: A systematic review of the evidence was undertaken using a priori methods.

Results: Four randomised controlled trials (RCTs) met the inclusion criteria of the review, each considering a different cardioprotective intervention; all trials included children with acute lymphoblastic leukaemia, and one also included children with non-Hodgkin's lymphoma. However, all had methodological limitations. No cost-effectiveness studies were identified. One RCT and six cohort studies on the use of cardiac markers met the inclusion criteria of the review, but also had methodological limitations. Of the two RCTs that considered continuous infusion versus bolus (rapid) infusion, one found that continuous infusion of doxorubicin did not offer any cardioprotection over bolus; the other suggested that continuous infusion of daunorubicin had less cardiotoxicity than bolus. Two studies considered cardioprotective agents, one concluded that dexrazoxane prevents or reduces cardiac injury without compromising the antileukaemic efficacy of doxorubicin and the other reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy. One RCT suggested that cardiac troponin T can be used to assess the effectiveness of the cardioprotective agent dexrazoxane. Two cohort studies considering atrial natriuretic peptide and two considering brain (B-type) natriuretic peptide suggested that these chemicals are elevated in some subgroups of children treated with anthracyclines for cancer. N-terminal B-type natriuretic peptide levels were significantly elevated in children treated with anthracyclines who had cardiac dysfunction. One cohort study found that serum lipid peroxide was higher in younger children treated with doxorubicin than correspondingly aged children not receiving doxorubicin. No differences in carnitine levels were found in children treated with doxorubicin and a group of healthy children in one cohort study.

Conclusions: It is difficult to draw conclusions about the effectiveness of technologies for reducing or preventing cardiotoxicity and about the use of cardiac markers in children as the evidence is limited in quantity and quality. The lack of standardisation for monitoring and reporting cardiac performance is problematic. Not all studies report effectiveness in terms of cardiac outcomes and event-free survival with supporting statistical analyses. Studies are mostly small and of short duration, making generalisation difficult. Increasing numbers of survivors of childhood cancer treated with anthracyclines will experience cardiac damage and require long-term surveillance and management. This will have an impact on cardiac services and costs. Diverse medical problems and other late sequelae that affect cardiac outcome will have an impact on other specialist services. Mechanisms to reduce or prevent cardiotoxicity from anthracycline therapy and cardiac markers to improve monitoring could alter the extent of this impact on service provision. RCTs of the different methods for reducing or preventing cardiotoxicity in children treated with anthracyclines for cancer with long-term follow-up are needed to determine whether the technologies influence the development of cardiac damage. Cost-effectiveness research is also required.

Contents

List of abbreviations

6-MP	6-mercaptopurine
A-CHF	anthracycline-induced clinical heart failure
ADR	adriamycin (doxorubicin)
AEIOP	Associazione Italiana di Ematologia ed Oncologia Pediatrica
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ANP	atrial or A-type natriuretic peptide
AS	acceleration slopes of early filling velocity
AT	acceleration time of early filling velocity
BNP	brain or B-type natriuretic peptide
CCRG	Childhood Cancer Research Group
CHF	congestive heart failure
CI	confidence interval
CO	cardiac output
CoQ/CoQ_{10}	coenzyme Q10
CPK	creatine phosphokinase
CRD	Centre for Reviews and Dissemination
CSF	cerebrospinal fluid
cTnI	cardiac troponin I
cTnT	cardiac troponin T
DAUN	daunorubicin
DBP	diastolic blood pressure
DFS	disease free survival
DOX	doxorubicin
DS	deceleration slopes of early filling velocity
DT	deceleration time of early filling velocity
DZX	dexrazoxane (ICRF-137)
E/A	early peak filling velocity atrial peak filling velocity
echo	echocardiography
EF	ejection fraction
EFS	event-free survival
EPI	epirubicin
FAB	French–American–British
FS	fractional shortening
HD	Hodgkin's disease
HR	high risk
i.m.	intramuscularly
i.v.	intravenously
ITT	intention-to-treat
IVRT	isovolumetric relaxation time
LDH	lactate dehydrogenase

continued

List of abbreviations *continued*

LV	left ventricular
LV-A	left ventricular mitral atrial peak filling velocity
LVC	left ventricular contractility
LVDD	left ventricular diastolic dimension or left ventricle end-diastolic diameter
LVDS/SD	left ventricular systolic dimension
LV-E	left ventricular mitral early peak filling velocity (mitral E)
LVEDd	left ventricular at end of diastole dimension or left ventricular chamber dimension at the end of diastole
LVEDs	left ventricular at end of systole dimension
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
LVID	left ventricular internal diameter in short axis
LVIDd	left ventricular internal dimension at end-diastole or left ventricular end-diastolic dimension
LVIDs	left ventricular internal dimension at end-systole
LVPWS	left ventricular posterior wall thickness systolic
LVPWTd	left ventricular posterior wall thickness at end-diastole
LVPWTs	left ventricular posterior wall thickness at end-systole
LVWT	left ventricular wall thickness
MRI	magnetic resonance imaging
NA	not applicable
ND	not determined
NHL	non-Hodgkin's lymphoma
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NR	not reported
ns	not significant
NT-pro-BNP	N-terminal B-type natriuretic peptide
PEG	pegylated
RCT	randomised controlled trial
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF	shortening fraction
SWT	septal wall thickness
TDF	total diastolic filling time
UKCCSG	UK Children's Cancer Study Group
WBC	white blood count
WS	wall stress

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Anthracyclines are potent cytotoxic antibiotics widely used in the treatment of malignancies in children. Their use has improved survival rates, but been limited by cardiotoxic side-effects which may cause myocardial damage and lead to congestive heart failure and risk of death from cardiac causes. Prevention of anthracycline-induced clinical heart failure (A-CHF) and cardiotoxicity is particularly important in children because they can be expected to survive for decades after treatment. Attempts to minimise cardiotoxicity of anthracyclines include dose limitation and schedule modification, and the use of less cardiotoxic analogues and cardioprotective agents. Cardiac markers released by myocyte cells during anthracycline treatment have been suggested as early markers for the quantification of cardiac damage.

Objectives

The main objective of this study was to evaluate the technologies used to reduce anthracycline-induced cardiotoxicity in children. Other objectives included evaluating cardiac markers to quantify cardiotoxicity, and identifying cost-effectiveness studies and future research priorities.

Methods

A systematic review of the evidence was undertaken using a priori methods.

Data sources

Eight electronic databases were searched from inception to January 2006. Bibliographies of related papers were assessed for relevant studies and experts contacted to identify additional published references.

Study selection

Studies were included if they fulfilled the following criteria:

- Interventions: studies that evaluated different dosing schedules for anthracyclines, anthracycline derivatives or cardioprotective agents were considered for inclusion.
- Participants: studies on children aged up to 18 years being treated for cancer with anthracyclines were included.
- Outcomes: subclinical cardiac failure, clinical (symptomatic) heart failure, arrhythmias and death were the primary outcome measures considered in the systematic review.
- Design: randomised controlled trials (RCTs) were included. For the section considering cardiac markers controlled cohort studies were also included.

Studies identified were assessed for inclusion through two stages with titles and abstracts and full papers of retrieved studies assessed independently by two reviewers, with differences in decisions resolved through discussion or through recourse to a third, independent reviewer.

Data extraction and quality assessment

Data were extracted by one reviewer using a data extraction form developed a priori, and checked by a second reviewer. Any disagreements were resolved through discussion or through recourse to independent assessment by a third reviewer. The methodological quality of the studies included in the systematic review was assessed using recognised quality assessment tools using individual components of methodological quality rather than relying on summary scores. The quality criteria were applied by two reviewers, with any disagreements resolved through discussion or through recourse to a third, independent reviewer.

Data synthesis

Studies were synthesised using a narrative approach with full tabulation of results from all included studies.

Results

Number and quality of studies

Four RCTs met the inclusion criteria of the review, each considering a different cardioprotective intervention; all trials included children with acute lymphoblastic leukaemia, and one also included

children with non-Hodgkin's lymphoma. The RCTs had methodological limitations owing to inadequacy of randomisation and assessment of outcomes, or insufficient details of methods and incomplete reporting of results. No cost-effectiveness studies were identified. One RCT and six cohort studies on the use of cardiac markers met the inclusion criteria of the review. These studies also had methodological limitations.

Summary of clinical effectiveness of technologies for reducing A-CHF

Two RCTs considered continuous infusion versus bolus (rapid) infusion. One found that continuous infusion of doxorubicin did not offer any cardioprotection over bolus; the other suggested that continuous infusion of daunorubicin had less cardiotoxicity than bolus infusion. Two studies considered cardioprotective agents. One concluded that dexrazoxane prevents or reduces cardiac injury as reflected in levels of a cardiac marker during doxorubicin therapy without compromising the antileukaemic efficacy of doxorubicin. The other reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy.

Summary of cardiac markers to quantify cardiotoxicity

One RCT suggested that cardiac troponin T can be used to assess the effectiveness of the cardioprotective agent dexrazoxane. Two cohort studies considering atrial natriuretic peptide and two considering brain (B-type) natriuretic peptide suggested that these chemicals are elevated in some subgroups of children treated with anthracyclines for cancer compared with healthy children. N-terminal B-type natriuretic peptide levels were significantly elevated in children treated with anthracyclines who had cardiac dysfunction compared with patients who did not have cardiac dysfunction and healthy controls in one cohort study. One cohort study found that serum lipid peroxide was higher in younger children treated with doxorubicin than correspondingly aged children not receiving doxorubicin. No differences in carnitine levels were found in children treated with doxorubicin and a group of healthy children in one cohort study.

Conclusions

It is difficult to draw conclusions about the effectiveness of technologies for reducing or preventing cardiotoxicity and about the use of cardiac markers in children as the evidence is limited in quantity and quality. The lack of standardisation for monitoring and reporting cardiac performance is problematic. Not all studies report effectiveness in terms of cardiac outcomes and event-free survival with supporting statistical analyses. Studies are mostly small and of short duration, making generalisation difficult.

Implications for service provision

Increasing numbers of survivors of childhood cancer treated with anthracyclines will experience cardiac damage and require long-term surveillance and management. This will have an impact on cardiac services and costs. Diverse medical problems and other late sequelae which affect cardiac outcome will have an impact on other specialist services. Mechanisms to reduce or prevent cardiotoxicity from anthracycline therapy and cardiac markers to improve monitoring could alter the extent of this impact on service provision.

Recommendations for research

RCTs of the different methods for reducing or preventing cardiotoxicity in children treated with anthracyclines for cancer with long-term follow-up are needed to determine whether the technologies influence the development of cardiac damage. It is likely that the studies will require a range of outcomes, including event-free survival in terms of the whole treatment protocol, cardiac measurements such as echocardiographic findings and potential cardiac markers, side-effects and measures of anthracycline antitumour efficacy. Cost-effectiveness research is also required.

Chapter 1
Background

Cytotoxic antibiotics, known as anthracyclines, are highly potent chemotherapeutic agents and are widely used in the treatment of solid and haematological malignancies in children. Their introduction has improved survival rates, but their use has been limited by their cardiotoxic side-effects during and after treatment.[1,2] The cardiotoxic risk increases with higher cumulative doses of anthracycline therapy.[3] Many survivors of anthracycline treatment have long-term problems of myocardial damage such as impaired left ventricular contractility and cardiomyopathy, which may lead to congestive heart failure (CHF) and an increased risk of sudden cardiac death and death from cardiac causes. The toleration of anthracyclines and the occurrence of toxicity vary considerably between individuals and for some patients cardiotoxicity may develop at doses below the generally accepted threshold levels. Prevention of anthracycline-induced clinical heart failure (A-CHF) and cardiotoxicity is particularly important in children because they can be expected to survive for decades after treatment.

Description of health problem

Cardiotoxicity

The mechanism underlying A-CHF and cardiotoxicity is not fully understood. It is thought that lipid peroxidation and the generation of free radicals by anthracycline–iron complexes play a major role. The heart is vulnerable to free radical injury because protective antioxidant enzymes are present at lower levels than in other tissues, such as the liver and kidney,[4] and the resulting damage to myocardial cells may eventually lead to irreversible heart failure.

Heart damage can present as either subclinical cardiotoxicity, which is the development of various asymptomatic cardiac abnormalities in previously healthy survivors of cancer, or clinical toxicity, which is defined on the basis of symptoms of clinical heart failure confirmed by diagnostic tests. Subclinical cardiotoxicity is progressive. The only treatment option for end-stage heart failure is heart transplantation.

Heart damage after anthracycline therapy is 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, while late cardiotoxicity presents at least 1 year after completion of anthracycline therapy.[5] The risk of developing heart failure remains a lifelong threat.

Epidemiology

Cancers are rare in children aged less than 15 years old.[6] The annual rate of new cases in those aged 0–14 years is 122 per million,[6] the equivalent of about 1500 new cases in England and Wales each year. An increase in the incidence of childhood and adolescent cancers has been demonstrated for a wide range of different cancer diagnoses.[6] Improvements in cancer therapies and expertise at dedicated children's cancer centres mean that the number of long-term survivors of childhood cancer is increasing. The majority of children (about 70%) can realistically expect long-term survival.

The most common diagnoses among children are leukaemia (42.9 per million, about 515 cases a year), brain and spinal neoplasms (31.4 per million, about 377 cases a year) and lymphoma (12.0 per million, about 144 cases a year).[6] Cases of childhood cancer diagnosed in England, Wales and Scotland, between 1991 and 2000, according to the 3rd edition of the International Classification of Childhood Cancer, are shown in *Table 1*.

Anthracyclines are incorporated into more than 50% of childhood cancer treatment protocols, including those for young infants. Therefore, more than 750 child patients per year receive anthracyclines.[6] The risk of cardiotoxicity increases with cumulative dose, so efforts have been made to limit both peak levels and cumulative dose of anthracyclines while maintaining treatment efficacy. Protocols for the treatment of tumours with a good prognosis, such as acute lymphoblastic leukaemia (ALL), Hodgkin's disease (HD) and Wilms' tumour, incorporate moderate doses of anthracyclines (less than 250 mg/m^2), while those tumours with a poor prognosis, such as hepatoblastoma, oesteogenic

TABLE I *Cases of childhood cancers diagnosed in England, Wales and Scotland, 1991–2000*

Diagnostic group	Age (years)				
	0	1–4	5–9	10–14	0–14
Leukaemias, myeloproliferative and myelodysplastic diseases	274	2,276	1,267	879	4,696
Lymphomas and reticuloendothelial neoplasms	8	232	477	712	1,429
CNS and miscellaneous intracranial and intraspinal neoplasms	252	1,048	1,296	978	3,574
Neuroblastoma and other peripheral nervous cell tumours	256	510	110	21	897
Retinoblastoma	182	228	18	2	430
Renal tumours	113	507	145	45	810
Hepatic tumours	41	64	12	20	137
Malignant bone tumours	5	24	150	383	562
Soft-tissue and other extraosseous sarcomas	106	324	296	302	1,028
Germ-cell tumours, trophoblastic tumours and neoplasms of gonads	81	123	81	202	487
Other malignant epithelial neoplasms and malignant melanomas	10	46	106	318	480
Other and unspecified malignant neoplasms	15	28	18	31	92
Total	**1,343**	**5,410**	**3,976**	**3,893**	**14,622**

Data extracted from The National Registry of Childhood Tumours; registry details.[7]

and Ewing's sarcoma, incorporate high-dose anthracyclines. Children with tumours that have a poor prognosis and who are therefore more likely to be treated with higher anthracycline doses are at particular risk of cardiotoxicity, and children less than 2 years of age are particularly at risk of anthracycline-induced cardiomyopathy (Levitt G: personal communication, 2006).

The reported frequency of subclinical heart failure after anthracycline therapy in children varies between 0% and 57%[8] and that of clinical heart failure between 0% and 16%.[9] Potential risk factors include the type of anthracycline used, higher cumulative and peak doses, female gender, radiation therapy involving the heart region, type of tumour and, in adults, pre-existing heart disease.

Anthracyclines are associated with late-onset cardiac morbidity in about 25% of childhood ALL and other cancer survivors. About 5% develop overt heart failure, with some requiring heart (or heart/lung) transplantation. In Britain between 1970 and 1996 there were 31,992 cases of childhood malignancy and of these 16 patients (0.05%) required a heart (14 cases) or heart/lung (two cases) transplant.[10] Levitt and colleagues found that the 14 children who were potential heart transplant patients between 1970 and 1994 had definite anthracycline cardiomyopathy.[10]

Each year in the UK more than 1200 survivors of childhood cancer become eligible for long-term follow-up, half of whom may have received anthracyclines during their treatment. The National Institute for Health and Clinical Excellence (NICE) guideline *Improving outcomes in children and young people with cancer* states that there should be "robust and appropriate surveillance of survivors, which will be intensive for those with significant anticipated adverse late effects of therapy and minimal for others who are likely to remain well." In all, there are now over 20,000 adults living in the UK who had cancer in childhood. The health of 14,000 of these survivors is being investigated in the British Childhood Cancer Survivor Study (BCCSS) at the Centre for Childhood Cancer Survival Studies, University of Birmingham, in collaboration with the Childhood Cancer Research Group (CCRG).

Costs

Costs can be divided into two categories relating to the monitoring and the management of cardiac dysfunction resulting from anthracycline use, and are significant. Cardiac monitoring of all survivors of anthracyclines requires regular echocardiography, with high-risk patients receiving more regular follow-up and a requirement for cardiological specialist input, which is costly. The cost of management includes more extensive cardiac function tests and drug treatment in those with abnormal cardiac function to ameliorate the progression to irreversible heart failure and may continue for many years. Heart transplantation is also costly.

The reduction of cardiotoxic side-effects of anthracycline therapy in children with cancer is likely to reduce costs to the NHS. In addition, the ability to assess accurately the damage caused by

anthracyclines at the end of treatment may well reduce the need for lifelong monitoring.

Current service provision

Anthracyclines are used extensively in childhood cancer treatment protocols, even in very young children. Doxorubicin and daunorubicin have become a standard component of therapy for many paediatric malignancies.

Cardioprotective agents have been used in an ad hoc way owing in part to the lack of funded trials (Levitt G: personal communication, 2006). Although dexrazoxane has been shown to prevent heart damage in adults treated with anthracycline[11] it is not routinely used in children because of potential side-effects, such as possible interference with anti-tumour efficacy. It is not licensed for this indication in children in the UK at the time of writing.

The UK Children's Cancer Study Group (UKCCSG) Practice statement for long-term follow-up and the Scottish Intercollegiate Guidelines Network (SIGN) guidelines suggest that all patients should be monitored every 3–5 years and more frequently if cardiac problems are found. However, it is likely that current practice varies across the UK depending on the follow-up systems and the availability of cardiac services to provide echocardiograms. Wallace and colleagues suggest that follow-up of childhood cancer patients should be lifelong,[12] although evidence for this practice is not clear and will depend on the patient's condition and methods of treatment.

Patient pathway

All patients have echocardiograms performed within 3–6 months of last anthracycline administration. This may not fall at the end of treatment as, for example, ALL regimens continue for many months after anthracycline treatment. For a normal echocardiogram the patient would then have 5-yearly echocardiograms. If abnormal then the patient would have yearly echocardiograms; if echocardiograms return to normal the follow-up interval is increased. Patients are referred to a cardiologist if fractional shortening is less than 25% and treatment would only be given by a cardiologist after careful consideration in asymptomatic patients with abnormal echocardiograms, as it is usually given for life. There is some variation in threshold for starting treatment. Patients with clinical signs of heart failure would be treated and if severe and thought not to be reversible then referral to a transplant unit would be considered.

Children doing competitive sports at a high level and particularly those required to do weight training need more careful surveillance, which would include exercise testing. Women who have received anthracyclines require careful monitoring throughout pregnancy.[13,14] During pregnancy patients should be under a consultant obstetrician with access to cardiology. An echocardiogram should be performed at least once with a watch on cardiac status and delivery should be in a hospital with cardiac cover.

Description of technology under assessment

Much research has been conducted to identify methods or agents capable of preventing or reducing the cardiotoxicity resulting from anthracycline therapy, mostly undertaken in adults. These attempts have focused on three main approaches: first, by decreasing myocardial concentrations of anthracyclines and their metabolites by dose limitation and schedule modification,[15,16] secondly, by developing less cardiotoxic anthracycline analogues and formulations,[17] and thirdly, by the administration of cardioprotective agents during and after chemotherapy to attenuate the effects of anthracyclines on the heart.[18]

Dose limitation and schedule modification

The main anthracyclines used which have related cardiotoxicity include doxorubicin (DOX) and daunorubicin (DAUN). It has been shown that there is a close correlation between cumulative anthracycline dose and risk of heart failure.[19] Changing the dose schedule to a smaller weekly bolus and prolonged infusion to avoid peak anthracycline levels may minimise cardiotoxicity and provide some cardioprotection. This is based on the hypothesis that chronic cardiotoxicity is primarily related to peak dose anthracycline concentration, and that antitumour efficacy is more related to total drug exposure (concentration $\times$ time, area under the concentration–time curve).[20]

Anthracycline derivatives

Many anthracycline structural analogues have been developed which have similar antitumour activity but reduced cardiotoxicity. Two have been

widely used: epirubicin (EPI), an analogue of doxorubicin, and idarubicin, an analogue of daunorubicin. Liposomal anthracyclines are a class of drugs that may permit more specific targeting of anthracyclines with less systemic and cardiac toxicity.[17] Alternative formulations available for use in children include pegylated (PEG) coated doxorubicin (DOXIL) for the treatment of Kaposi's sarcoma, and daunorubicin (DaunoXome) in acute myeloid leukaemia (AML). Although total plasma levels may be relatively high for several days after liposomal administration, the majority of the dose is sequestered within liposomes and is not bioavailable to distribute (as free drug molecules) to tissue, including the myocardium, to cause cardiotoxic effects. A key feature of liposomal formulations is the ability to accumulate in solid tumours.[21]

Cardioprotective agents

Another approach to reduce anthracycline-induced heart damage is the use of cardioprotective agents during and after chemotherapy which will attenuate the cardiotoxicity without altering the anti-tumour activity of the drug. Dexrazoxane (DZX, ICRF-137) is the most commonly used cardioprotective agent.[11] Other agents include classic antioxidants such as tocopherol (vitamin E), ascorbic acid (vitamin C) and *N*-acetylcysteine. Other antioxidant cardioprotectants are probucol, L-carnitine, coenzyme Q_{10} (CoQ_{10}), digoxin, enalapril, phenethylamines, deferoxamine, ethylenediaminetetraacetic acid, superoxide dismutase and monohydroxyethylrutoside and dietary glutamine supplementation. These agents act as free-radical scavengers, but a disadvantage is that they may protect tumour cells from chemotherapy.[22]

Dexrazoxane differs from other antioxidant cardioprotective agents in that it acts by preventing free-radical formation rather than acting after free radicals are formed.[23] It provides cardiac protection by the systemic chelation of free iron and iron bound in anthracycline complexes, which can contribute to the formation of cardiotoxic reactive oxygen radicals during anthracycline exposure.[23,24]

The main issue of concern in the use of cardioprotective interventions during anthracycline therapy is that the cardioprotective agent reduces the heart damage by anthracyclines without reducing the antitumour efficacy and without causing other toxic effects. If the antitumour effect of anthracyclines depends to any extent upon free radical-induced injury to the tumour cells, compounds such as dexrazoxane, which act by prevention of free radical formation, may reduce antitumour efficacy since they are systemically administered.

Chapter 2

Overall aims and objectives of assessment

The aim of this project is to conduct a systematic review of the clinical effectiveness and cost-effectiveness of cardioprotection against the toxic effects of anthracyclines given to children with cancer. The research also aims to highlight deficiencies in current knowledge and to generate recommendations for future research.

The objectives are:

- to evaluate the technologies that have the potential to reduce anthracycline-induced cardiotoxicity in children, including:
  - different dosage schedules
  - different anthracycline derivatives
  - use of cardioprotective agents, such as dexrazoxane
  - use of antioxidant protection, such as probucol or nutritional supplementation with glutamine
- to identify markers to quantify cardiotoxicity in children
- to refine outcome measures for use in longer term studies
- to identify studies evaluating the cost-effectiveness of cardioprotection against the toxic effects of anthracyclines given to children with cancer
- to identify priorities for future primary research.

Chapter 3
Methods

The a priori methods used for the review are outlined in the research protocol (Appendix 1). This was sent to members of the advisory group for the review for expert comments (see Acknowledgements). Helpful comments were received relating to the general content of the research protocol; there were none that identified specific problems with the proposed methods of the review.

Some changes, additions or points of clarification were made to the methods discussed in the original protocol.

- Only randomised controlled trials (RCTs) were included in the section on the effectiveness of cardioprotective technologies, as the potential for confounding by indication is high. Children for whom there is a concern about cardiac damage could be treated differently, in terms of choice of drug and dose, from those for whom there are no such concerns, and non-randomised studies would not be helpful.
- The aim of the section of the review dealing with markers was to identify studies that evaluated the effectiveness of cardiac markers to quantify cardiac damage in children receiving anthracyclines for cancer. As such, the highest level of evidence was sought, that is studies with a control or comparison group. Studies evaluating diagnostic tests of cardiac damage by comparing cardiac markers with other measures such as biopsy were outside the remit of this assessment and were not included.

The research methods for the review are summarised below. These apply to both the clinical effectiveness of cardioprotective technologies and cardiac marker sections, apart from the inclusion criteria, which are presented separately for the two elements of the review.

Search strategy

The following databases were searched for published studies and ongoing research, from inception to January 2006: The Cochrane Library (Database of Systematic Reviews and Controlled Trials Register), MEDLINE (OVID), EMBASE (OVID), Web of Science Proceedings, NHS Economic Evaluations Database (NHS CRD databases), NHS HTA database (NHS CRD databases), NHS Database of Abstracts of Reviews of Effectiveness (NHS CRD databases), National Research Register (NRR) and American Society for Clinical Oncology Abstracts database (ASCO). Searches were restricted to the English language and human. Bibliographies of related papers were assessed for relevant studies. Investigators of studies were not contacted due to time constraints. Further details, including key search terms, can be found in Appendix 2.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were screened independently for inclusion by two reviewers. The full text of potentially eligible studies was obtained and examined independently for inclusion by two reviewers. Data were extracted by one reviewer on standard data extraction forms and checked by a second reviewer.

The process for identifying and including studies for assessment of effectiveness and for cardiac markers is illustrated in *Figure 1*. The primary reason for excluding studies was that they did not meet the inclusion criteria (for clinical effectiveness they were not RCTs, did not compare a cardioprotective technology with an alternative or did not include outcomes of interest in children; for cardiac markers they were uncontrolled studies). A list of studies excluded at various stages of the process can be found in Appendix 3. Ongoing research is shown in Appendix 4.

Quality assessment

RCTs were quality assessed using the criteria recommended in CRD Report 4 (2nd ed.)[25] (Appendix 5) and cohort studies were assessed for quality using the criteria developed by Spitzer and colleagues[26] (Appendix 6). Quality criteria were applied by one reviewer and checked by a second reviewer.

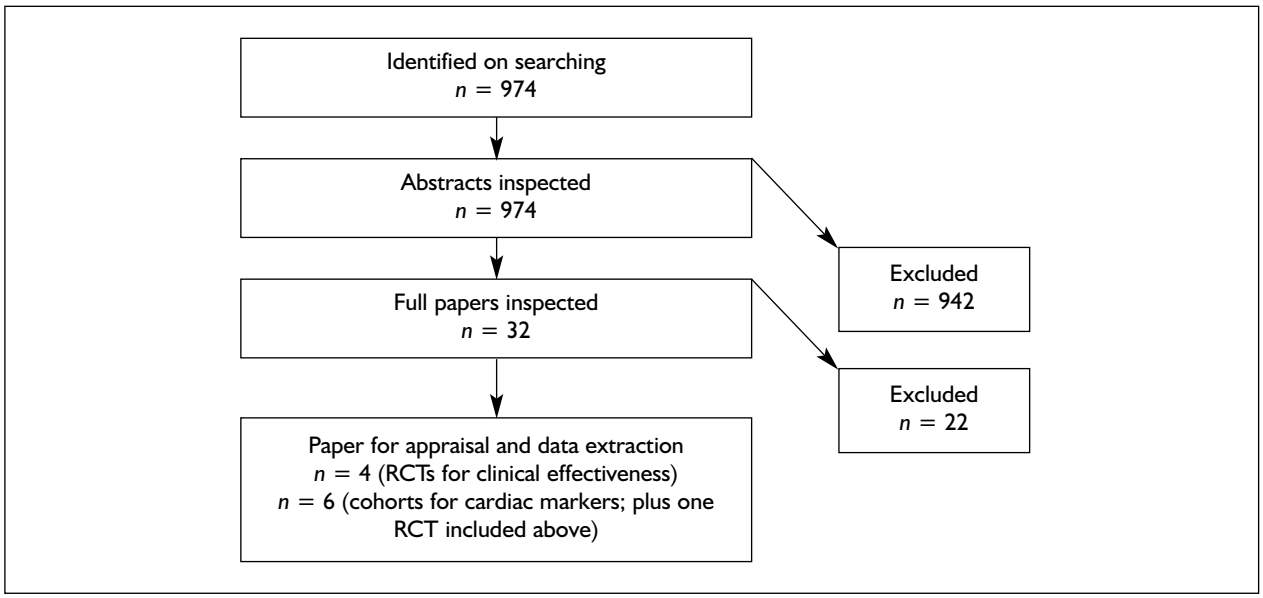

FIGURE 1 *Flowchart of identification of studies for clinical effectiveness systematic review (RCTs) and cardiac marker studies (controlled cohorts)*

At each stage, any differences in opinion were resolved through discussion or if necessary by arbitration by a third reviewer.

Inclusion criteria

Inclusion criteria for studies on clinical effectiveness and cost-effectiveness and for cardiac markers are shown below.

Clinical effectiveness and cost-effectiveness

- *Intervention*
  - different dosage schedules for anthracyclines aclarubicin, daunorubicin, doxorubicin, epirubicin and idarubicin
  - different anthracycline derivatives (liposomal anthracyclines such as liposomal doxorubicin and mitozantrone)
  - cardioprotective technologies, such as dexrazoxane and amifostine, probucol, coenzyme Q and dietary glutamine supplementation, during and after anthracycline use.
- *Comparator*
  - standard treatment protocols or an alternative cardioprotective technology.
- *Population*
  - children aged 0–18 years being treated for cancer with anthracyclines.
- *Outcomes*
  - subclinical cardiac failure, measured by echocardiography
  - clinical (symptomatic) heart failure
  - arrhythmias
  - death.

Tumour recurrence and length of remission information will be extracted where reported.

- *Study type*
  - RCTs
  - economic evaluations of cardioprotective technologies for use during or after anthracycline treatment in children.

Markers of cardiac damage

- *Marker*
  - any cardiac marker including atrial or A-type natriuretic peptide (ANP), brain or B-type natriuretic peptide (BNP), cardiac troponin T (cTnT), lipid peroxide and carnitine.
- *Population*
  - children with cancer given anthracyclines.
- *Study type*
  - RCTs or cohorts with controls.

Data synthesis

Synthesis of data was through narrative review with full tabulation of results of all included studies. Full data extraction forms are shown in Appendices 7 and 8. Meta-analysis was not possible owing to the different interventions considered and different characteristics of participants.

Chapter 4

Assessment of clinical effectiveness

Quantity and quality of research available

Four RCTs met the inclusion criteria for the review and are shown in *Table 2* and Appendix 7.

Each considered a different cardioprotective technology. All trials included children with ALL, and one also included children with non-Hodgkin's lymphoma (NHL).[29] The cardiac outcomes reported in the trials were various echocardiographic measures which were presented in different ways, and not all trials reported overall survival.[28,29]

Owing to the complex nature of the trials and different interventions investigated, details of each trial are presented separately, with a description of the study methodology, the participants, the intervention, duration of the trial and the outcomes used to assess effectiveness. In general, the studies were of poor quality with methodological limitations, as can be seen from *Table 3*, which reports quality assessment of the included studies.

Continuous infusion versus rapid (bolus) infusion of doxorubicin[27]

This study by Lipshultz and colleagues[27] reports the results of one treatment randomisation that

TABLE 2 *Clinical effectiveness studies*

Study	Intervention and comparator
Lipshultz *et al.*, 2002[27]	Continuous infusion of doxorubicin versus bolus infusion
Steinherz *et al.*, 1993[28]	Continuous infusion of daunorubicin versus bolus infusion
Iarussi *et al.*, 1994[29]	Coenzyme Q_{10} versus no coenzyme Q_{10}
Lipshultz *et al.*, 2004[30]	Dezraxozane versus no dezraxozane

TABLE 3 *Quality assessment of included experimental studies*

Criterion	Lipshultz, 2002[27]	Steinherz, 1993[28]	Iarussi, 1994[29]	Lipshultz, 2004[30]
Was the assignment to the treatment groups really random?	Unknown	Unknown	Unknown	Adequate
Was the treatment allocation concealed?	Unknown	Unknown	Unknown	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Reported only for the participants for whom there were outcome data	Unknown	Reported	Reported
Were the eligibility criteria specified?	Adequate	Adequate	Partial	Adequate
Were outcome assessors blinded to the treatment allocation?	Adequate	Unknown	Unknown	Adequate
Was the care provider blinded?	Unknown	Unknown	Unknown	Inadequate
Cointerventions	Inadequate	Adequate	Partial	Partial
Was the patient blinded?	Unknown	Unknown	Unknown	Inadequate
Were the point estimates and measure of variability presented for the primary outcome measure?	Partial	Inadequate	Adequate	Adequate
Did the analyses include an intention-to-treat analysis?	Inadequate	Inadequate	Adequate	Inadequate
Were withdrawals and dropouts completely described?	Inadequate	Inadequate	Adequate	Adequate

took place within a larger multicentre study (reported in a separate paper[31]). Randomisation was to doxorubicin administration by continuous infusion or by bolus infusion in children with ALL and was designed to detect a reduction in toxicity. Patients could participate in a further four treatment randomisations. Study details are shown in Appendix 7.

Study methodology

Randomisation was performed centrally; it is not known whether treatment allocation was concealed. The impact on the outcome of this part of the study of the other four treatment randomisations is unknown. Eligibility criteria were specified, but it is not known whether the groups were similar at baseline in terms of prognostic factors because baseline data were only reported for the participants who contributed outcome data. There were no significant differences in terms of age at diagnosis, follow-up since completion of therapy, percentage of females, or cumulative doxorubicin dose received. It is not known whether treating physicians were blinded to treatment allocation, so it may have been possible to observe which participants were receiving continuous infusions and which bolus infusions. The echocardiographic data were assessed in a blinded fashion as these were remeasured centrally by a technician who was unaware of the treatments participants had received. Results are given as median scores, but no indication of variability (such as the range or interquartile range) is provided. *p*-Values are reported both for the comparison with the reference value for healthy individuals and for the between-group comparison. Final echocardiograms were only available for about half of the participants. Reasons why final echocardiograms were not available for the remainder of the participants are given. However, some data from the final echocardiograms that were available are missing, and no explanation for this is given.

Participants

Only patients newly diagnosed with ALL who were classed as high risk were eligible for this randomisation ($n = 240$). To be classed as high risk, patients had to meet one or more of the following pretreatment characteristics: (1) white blood cell (WBC) count of at least 20×10^9 cells/litre (20,000 cells/μl); (2) age between 1 year and less than 2 years or at least 9 years; (3) presence of leukaemia blasts in a cytocentrifuged cerebrospinal fluid (CSF) specimen regardless of CSF WBC count (CNS-2 or CNS-3); (4) presence of a mediastinal mass; or (5) T-cell immunophenotype. Patients with the Ph1 chromosome t(9;22)(q34; q11) were also treated as high-risk patients. The rationale for restricting eligibility to high-risk patients is not stated explicitly, but the treatment protocol reveals that only high-risk patients received doxorubicin during the intensification phase of therapy as well as during induction. Therefore, their exposure to doxorubicin would presumably have been greater, putting them at an increased risk of cardiac toxicity in comparison to patients classified as standard risk.

Intervention

The primary efficacy intervention of the main study[31] (not reported in this publication) was randomisation (of standard-risk patients and high-risk patients) to either conventional 50 mg/m^2 per day oral 6-mercaptopurine (6-MP) on days 1–14 of every 3-week cycle during the first year of postremission therapy or high-dose 1000 mg/m^2 i.v. 6-MP delivered as a continuous infusion for 20 hours on weeks 1 and 2 of every 3-week chemotherapy cycle. In addition to this randomisation, patients were entered in four further randomisations which were all designed to detect a reduction in toxicities: (1) doxorubicin 360 mg/m^2 in 30 mg/m^2 doses every 3 weeks by bolus (within 1 hour) or doxorubicin 360 mg/m^2 in 30-mg/m^2 doses every 3 weeks by continuous infusion (over 48 hours) (only for high-risk patients, the subject of this paper and the intervention of interest); (2) 40 mg/m^2 per day prednisolone or 6, 18, or 150 mg/m^2 per day dexamethasone before the initiation of multiagent remission induction therapy; (3) 2500 IU/m^2 PEG asparaginase intramuscularly (i.m.) every other week for 15 doses or native 25,000 IU/m^2 *Escherichia coli* asparaginase i.m. every week for 30 doses during the intensification phase of therapy; or (4) cranial radiation consisting of twice-daily fractions of 90 cGy (hyperfractionated) or once-daily fractions of 180 cGy (conventional).

Outcomes

The main outcomes reported are a range of cardiac characteristics measured from the post-treatment echocardiogram such as left ventricular (LV) mass and left ventricular fractional shortening (LVFS). For some participants pretreatment results were available which enabled differences between pre- and post-treatment cardiac characteristics to be calculated. One centre made an additional measurement, left ventricular contractility (LVC), and also took systolic and diastolic blood pressures at the final echocardiogram. The 5-year event-free survival

(EFS) was reported (with EFS defined as the time from complete remission to the first outcome event) by Lipshultz and colleagues[27] for those patients for whom there was a final echocardiogram and by Silverman and colleagues[31] for all high-risk patients (i.e. including early treatment failures for whom there was no final echocardiogram).

Duration

Length of follow-up since completion of therapy was reported. This was variable, with a median value of 17.8 months (range 0.0–52) for the bolus infusion group and a median of 18.4 months (range 0.0–56) for the continuous infusion group.

Continuous infusion versus rapid (bolus) infusion of daunorubicin[28]

The study by Steinherz and colleagues[28] reports the results of a pilot trial designed to explore the effects of dose-intensive multidrug therapy and concurrently compare the antileukaemic efficacy of continuous daunorubicin with rapid intravenous infusion. Patients were randomised to one of four regimens varying only in the sequence and mode of administration of drugs during the first 48 hours of therapy (using a modified New York regimen plus daunorubicin bolus on days 2 and 3, daunorubicin continuous infusion on days 2 and 3, daunorubicin bolus days 0 and 1, and daunorubicin infusion on days 0 and 1.) Study details are shown in Appendix 7.

Study methodology

Randomisation was stratified to ensure even distribution of participants with regard to risk group, degree of leucocyte count elevation, age, French–American–British (FAB) morphology and the presence or absence of lymphoma syndrome. No details are provided to illustrate the characteristics of the participants in each study arm or methods of randomisation. Eligibility criteria were specified and individual patient characteristics presented for high risk (age at start of protocol, presence of lymphoma syndrome, leucocyte count, FAB morphology, CNS leukaemia and T cell) and average risk (age at start of protocol, presence of lymphoma syndrome, leucocyte count, platelet count, FAB morphology and CNS leukaemia) participants, together with information on the ethnicity of the patients. No details are provided to indicate whether allocation was concealed or whether outcome assessors, care-givers or patients were blinded to treatment. However, it may have been possible to observe which participants were receiving continuous infusions and which bolus infusions of daunorubicin and on which days (either days 2 and 3 or days 0 and 1). A primary outcome measure is not defined. Where point estimates are provided these are not accompanied by measures of variability. The number of participants contributing to the reported outcomes is stated, and from this one can deduce that there are missing data. No details of withdrawals are provided and missing data are not accounted for.

Participants

All the participants were newly diagnosed with ALL, but only those defined as having an average or high risk of early relapse (Children's Cancer Group criteria) were eligible to participate in the study (n = 44). The following four factors qualified a patient as having a high risk of early relapse: (1) age 1 year or younger or 10 years or older; (2) leucocyte count greater than or equal to 50,000/μl; (3) greater than 25% L_2 FAB morphology; (4) lymphomatous features. Everyone who was not high risk or good risk (good risk defined as children 2–10 years of age with leucocyte count less than 10,000/μl) was considered average risk and therefore also eligible for the study. The rationale for these eligibility criteria appears to have been to focus on a population requiring intensive therapy which is therefore at risk of cardiotoxicity owing to its significant exposure to anthracyclines.

Intervention

The full treatment protocol (induction, consolidation, first and subsequent maintenance cycles) is reported, which details the cointerventions that all patients received. The four trial arms varied only in the sequence and mode of administration of the drugs during the first 48 hours of therapy (the start of the induction phase of therapy). Group 1 received cyclophosphamide on day 0, vincristine/prednisone on day 1, and daunorubicin push (bolus) on days 2 and 3; group 2 received the same treatment as group 1, on days 0 and 1, but then received daunorubicin by continuous infusion on days 2 and 3 (48 hours); group 3 received daunorubicin push (bolus) first on days 0 and 1 followed by vincristine/prednisone on day 2, and cyclophosphamide also on day 2; and group 4 received daunorubicin by 48-hour continuous infusion on days 0 and 1, followed by vincristine/prednisone and cyclophosphamide on day 2. After the first 2 days therapy was identical for all patients, with the exception of the mode of administration of daunorubicin, which continued to be given by the method used during the first 48 hours of treatment.

Outcomes

Many of the results are presented for the participants either generally (without reference to their treatment group) or as a comparison of high-risk and average-risk patient outcomes (also without reference to their treatment group). The only outcomes that are compared between treatment groups are reductions in leukaemic cells measured at days 2, 7 and 14 of therapy, and deterioration in cardiac function. Point estimates are provided without a measure of variability and the outcomes from some groups have been merged together.

Duration

The minimum duration of follow-up was 25 months and the maximum 73 months. The length of follow-up is presented for each participant in a table.

Addition of CoQ_{10} to anthracycline therapy[29]

The aim of this small study by Iarussi and colleagues[29] was to evaluate the protective effect of exogenous CoQ_{10} on anthracycline-induced cardiotoxicity (n = 20). Study details are shown in Appendix 7.

Study methodology

Block randomisation was used to allocate patients to one of two groups, with or without CoQ_{10}, but no details of the methods are given. No power calculation was reported to demonstrate that the stated aim could be met. Little information is provided regarding the eligibility criteria for this study and therefore it is difficult to know whether the groups were comparable at the beginning of the study, particularly in terms of disease severity. Although not stated, it appears likely that investigators, patients and carers were not blind to treatment allocation as the protocol states that informed consent was obtained only from the parents of the children due to take CoQ_{10}. Results were expressed as mean ± standard deviation and although not stated explicitly there do not appear to have been any dropouts from this study. There is some contradictory reporting of results in the abstract and text of the paper.

Participants

All the participants were 15 years or under, the majority were diagnosed with ALL, but a few cases of children with NHL were also included. No information is provided regarding disease severity, except that the treatment protocol is described for those with ALL with standard, high and very high risk, and the treatment protocol for NHL is described for those with stage II, III and IV disease. Presumably these disease severities were represented in the participants of the study.

Intervention

Patients were treated with standard protocols. Those with ALL were treated with Associazione Italiana di Ematologia ed Oncologia Pediatrica (AEIOP) ALL protocols and those with LNH were treated according to the protocols of the Societé Française d'Oncologie Pédiatrique for lymphome malins de Burkitt. These protocols had fixed cumulative dose limits which were higher for the most severe ALL and NHL disease categories. In addition to treatment by the standard protocol, one group received CoQ_{10} (100 mg by mouth twice daily).

Outcomes

Two outcome measures were used to assess the effectiveness of the intervention in preventing cardiotoxicity. These were left ventricular global function and left ventricular regional wall motion by echocardiography following the recommendations of the American Society of Echocardiography. Echocardiography was performed in both groups before the start of therapy, during therapy at a cumulative anthracycline dose of 180 mg/m^2 and again at the end of therapy. Data are presented as mean values with standard deviation, but no p-values are reported.

Duration

No information is given regarding the period over which participants were recruited to the study or the duration of the intervention. Although outcomes were assessed at the end of therapy no further follow-up of the participants is reported.

Addition of dexrazoxane (ICRF-187) to doxorubicin therapy[30]

This study by Lipshultz and colleagues[30] was part of a multiagent chemotherapy regimen in the Dana-Farber Cancer Institute childhood ALL consortium protocol 95-2001. It was conducted to determine whether dexrazoxane therapy reduces myocardial injury as measured by serum cTnT levels in children with newly diagnosed ALL being treated with doxorubicin. Study details are shown in Appendix 7.

Study methodology

Randomisation involved a permuted-block design and was carried out centrally at the Dana-Farber Cancer Institute's Quality Assurance Office for Clinical Trials. Patients were randomly assigned to receive doxorubicin alone or dexrazoxane

immediately followed by doxorubicin. Local centres and patients were not blinded to the assignment with respect to dexrazoxane, but central investigators performing outcome measurements and providing summary study results remained blinded throughout the study. Treatment groups did not differ significantly with respect to baseline characteristics. No sample size or power calculation is mentioned. Details of dropouts and sample attrition were reported. Results are expressed as point estimates with a measure of variability and *p*-values are stated. To adjust echocardiographic data for changes associated with growth, *z*-scores were calculated using a regression model.

Participants

Patients were children under 18 years of age who had newly diagnosed and previously untreated high-risk ALL. Patients with standard risk disease, defined as aged between 1 and 10 years, a WBC of less than 50,000 cells/mm^3 at presentation, and the absence of T-cell markers, an anterior mediastinal mass and CNS disease, were excluded.

Intervention

In addition to receiving multiagent chemotherapy and CNS radiation, patients received two doses of doxorubicin (30 mg/m^2 of body surface area per dose) during remission induction, followed by eight more doses (30 mg/m^2 every 3 weeks) during induction therapy (cumulative dose 300 mg/m^2). No doxorubicin was given after 9 months of therapy. Patients were randomly assigned to receive doxorubicin alone (n = 101) or dexrazoxane (300 mg/m^2) immediately followed by doxorubicin (n = 105). There were no cross-overs.

Outcomes

The primary end-point of the study was elevated cTnT, defined as above 0.01 ng/ml. Extremely elevated levels (defined as above 0.025 ng/ml) were also reported. cTnT results were reported for 76 of 101 patients in the doxorubicin group and 82 of 105 patients in the group given dexrazoxane and doxorubicin. Measurements were taken at diagnosis before doxorubicin therapy, daily after induction doses of doxorubicin, 7 days after a dose of doxorubicin during induction therapy and at completion of therapy.

Secondary end-points were echocardiographic measurements and event-free survival.

Duration

The latest echocardiogram for each patient before, during and after doxorubicin therapy was analysed, and each study consisted of two-dimensional echocardiography and Doppler evaluation. Median length of follow-up was 2.7 years.

Assessment of effectiveness

Table 4 summarises the effectiveness of the cardioprotective technologies in preventing or reducing cardiotoxicity in children treated with anthracyclines for cancer.

The results of each study are detailed below.

Continuous infusion versus rapid (bolus) infusion of doxorubicin[27]

Effectiveness could only be assessed by Lipshultz and colleagues[27] where there was a follow-up echocardiogram of sufficient quality for remeasurement at a central location. Of the 240 participants randomised to continuous or bolus doxorubicin infusion, outcome data were only available for half of these (n = 121). All early treatment failures were excluded from the analysis, but Lipshultz and colleagues report that there was no congestive heart failure among this group.

Cardiac characteristics

Five measures of left ventricular structure and function are reported for participants from all centres, with a further three left ventricular measures, blood pressure and heart rate reported for participants at the main centre. No measure of variability is given for the median scores presented.

Before the start of treatment there were no significant differences in measures of left ventricular structure and function between the two groups. However, statistically significant left ventricular mass and LVFS abnormalities were observed in both treatment groups in comparison to reference data from healthy subjects.

After doxorubicin treatment no significant difference between the two groups for any cardiac characteristic was demonstrated, although both groups showed abnormalities of LV structure and function compared with normal and baseline (see Appendix 7). For example, median LVFS fell significantly by approximately 2 SD in both the continuous infusion and bolus infusion groups, but when the groups were compared, no statistical significance was found (see Appendix 7).

Event-free survival

The lack of data in this study from early treatment failures meant that the 5-year event-free survival

TABLE 4 *Summary of effectiveness from included studies*

Study details	Cardiac outcomes	Anthracycline treatment effectiveness	Survival
Lipshultz *et al.*, 2002[27] *Intervention:* DOX bolus ($n = 64$) vs DOX continuous infusion ($n = 57$) *Patients:* ALL *Study design:* RCT *Follow-up:* 0–56 months	LVFS median z-score after treatment DOX bolus: –0.47 DOX infusion: –0.44, $p = 0.60$ LV diastolic dimension median z-score DOX bolus: 0.285 DOX infusion: –0.015, $p = 0.79$ LV systolic dimension median z-score DOX bolus: 0.365 DOX infusion: 0.345, $p = 0.72$ LV wall thickness median z-score DOX bolus: –0.525 DOX infusion: –0.690, $p = 0.88$ LV mass median z-score DOX bolus: –0.37 DOX infusion: –0.270, $p = 0.50$ No CHF in either group	NR	5-year EFS (excluding early treatment failures, mean ± SE): DOX bolus: 89.0 ± 3.9% DOX infusion: 87.3 ± 4.5% $p = 0.50$ 5-year EFS (including early treatment failures, mean ± SE): DOX bolus: 80 ± 4% DOX infusion: 86 ± 4% $p = 0.23$
Steinhertz *et al.*, 1993[28] *Intervention:* DAUN bolus ($n = 22$) vs DAUN continuous infusion ($n = 22$) *Patients:* ALL *Study design:* RCT *Follow-up:* Minimum 25 months	Change in LVFS: DAUN bolus: –6.5 units DAUN infusion: +1 unit, *p*-value NR Significant deterioration in cardiac function: DAUN bolus: 4/18 DAUN infusion: 0/18, $p = 0.10$	Not reported separately for each group	With only two relapses at the time of reporting the authors were unable to see any effects on long-term survival
Iarussi *et al.*, 1994[29] *Intervention:* Addition of CoQ_{10} ($n = 10$) versus no CoQ_{10} ($n = 10$) *Patients:* ALL or NHL *Study design:* RCT *Follow-up:* NR	% LVFS (mean ± SD) decrease from baseline to end value: CoQ_{10}: 40.36 ± 4.60 to 35.82 ± 5.02 ($p < 0.05$) No CoQ_{10}: 39.89 ± 4.37 to 33.43 ± 3.46 ($p < 0.002$) Difference between groups described as significant, but *p*-value NR % SWT (mean ± SD) decrease from baseline to end value: CoQ_{10}: 44.10 ± 13.20 to 40.10 ± 15.30 (ns) No CoQ_{10}: 46.10 ± 10.10 to 27.0 ± 18.54 ($p < 0.01$) LVFS decreased at end of therapy CoQ_{10}: 7/10 No CoQ_{10}: 8/10 SWT decreased at end of therapy CoQ_{10}: 5/10 No CoQ_{10}: 9/10 Septal wall motion abnormalities CoQ_{10}: 0/10 No CoQ_{10}: 2/10 LV posterior wall thickening; no significant changes reported for either group	NR	NR

continued

TABLE 4 *Summary of effectiveness from included studies (cont'd)*

Study details	Cardiac outcomes	Anthracycline treatment effectiveness	Survival
Lipshultz *et al.*, 2004[30] *Intervention:* DOX (n = 101) vs DZX and DOX (n = 105) *Patients:* ALL *Study design:* RCT *Follow-up:* Median 2.7 years	Patients with elevated cTnT levels: At any time: DOX: 50% (95% CI 38 to 62) DZX and DOX: 21% (95%CI 13 to 31), $p < 0.001$ During treatment: DOX: 46% (95%CI 35 to 58) DZX and DOX: 15% (95% CI 8 to 25), $p < 0.001$ After treatment: DOX: 38% (95% CI 21 to 58) DZX and DOX: 17% (95% CI 6 to 36), $p = 0.14$ Multiple elevations: DOX: 37% (95% CI 26 to 49) DZX and DOX: 12% (95% CI 6 to 21), $p < 0.001$ Any extreme elevation: DOX: 32% (95% CI 21 to 43) DZX and DOX: 10% (95% CI 4 to 18), $p < 0.001$ Multiple extreme elevations: DOX: 20% (95% CI 11 to 30) DZX and DOX: 7% (95% CI 3 to 15), $p = 0.03$ Echocardiographic data: No significant differences between groups in LVFS, LVD or LVC LVFS was significantly depressed in both groups during and after treatment (mean z-score –1.06, $p < 0.001$)	Continuous complete remission: DOX: 81% DZX + DOX: 81%	EFS at 2.5 years DOX: 83% DZX and DOX: 83%, $p = 0.87$

CHF, congestive heart failure; CI, confidence interval; cTnT, cardiac troponin T; CoQ/CoQ_{10}, coenzyme Q10; DAUN, daunorubicin; DOX, doxorubicin; DZX, dexrazoxane (ICRF-137); EFS, event-free survival; LV, left ventricular; LVFS, left ventricular fractional shortening; NR, not reported; ns, not significant; RCT, randomised controlled trial; SWT, septal wall thickness.

for the 121 patients who contributed data was high, at 89.0 ± 3.9% for the bolus group and 87.3 ± 4.5% for the continuous group. There was no difference in event-free survival between the two groups ($p = 0.50$).

Continuous infusion versus rapid (bolus) infusion of daunorubicin[28]

The primary effectiveness measure assessed by Steinherz and colleagues[28] was the reduction in leukaemic cells during the first 2 weeks of therapy. Cardiac function was monitored in only 36 of the 44 participants.

Cardiac characteristics

LVFS data are reported, but not separately for each of the four treatment arms. Instead, a median change in LVFS of –6.5 units is reported for all the participants who received a bolus infusion of daunorubicin (a combination of two groups, those receiving bolus daunorubicin on days 0 and 1 or on days 2 and 3) and a change in LVFS of +1 unit for the two groups of participants combined who received the continuous infusion of daunorubicin. No measure of variability is given for the median scores presented. It is not reported whether the change in LVFS was significantly different in the bolus and continuous infusion groups.

LVFS was also used to identify participants who had experienced a significant deterioration in cardiac function. Significant deterioration was defined as decrease of LVFS on two consecutive evaluations to abnormal levels (less than 29%) or by 10 or more percentile units from the baseline level for that particular patient to borderline function (29%) at any time during treatment or follow-up. Four of the 18 participants who received the bolus infusion of daunorubicin were identified as having a significant deterioration in cardiac function in comparison to none of those who received a continuous infusion of the drug. This difference was statistically significant ($p = 0.10$).

Reduction in leukaemic cells

A larger and more rapid reduction in leukaemic cells was observed in the two trial arms where

daunorubicin was administered at the start of the induction phase of treatment (groups 3 and 4). Results are provided for groups 3 and 4 combined versus groups 1 and 2 (reduction in $\log_{10}$ cells/mm^2 of marrow biopsy: day 2, –0.74 versus –0.26, $p = 0.03$; and day 14, –1.82 versus –0.86, $p = 0.03$). The between-group comparison for groups 3 and 4 is also presented. This indicates that a more rapid cytoreduction occurred when daunorubicin was delivered by continuous infusion rather than by rapid (bolus) infusion (reduction in $\log_{10}$ cells/mm^2 of marrow biopsy: day 2, –1.21 versus –0.54, $p = 0.03$; day 14, –1.83 versus –1.78).

Addition of coenzyme Q_{10} to anthracycline therapy[29]

Two cardiac outcomes, left ventricular and septal wall structure and function, are reported for all 20 participants in the study by Iarussi and colleagues.[29]

Cardiac characteristics

Before the start of treatment no significant differences in echocardiographic parameters between the two groups were reported, although *p*-values are not given. After anthracycline treatment % LVFS was significantly decreased in both groups. In the anthracycline-only group, % LVFS decreased from 39.89 ± 4.37 at baseline to 33.43 ± 3.46 at the end of therapy ($p < 0.002$), while in the anthracycline plus coenzyme Q_{10} group % LVFS decreased from 40.36±4.60 at baseline to 35.82±5.02 at the end of therapy ($p < 0.05$). The study reports that "mean % LVFS was significantly lower in the group that received coenzyme Q_{10} compared to the mean value in the group that did not receive coenzyme Q_{10}", but probably refers to mean reduction in % LVFS, which was lower in treated patients, although no *p*-value is given for this comparison. The number of participants whose LVFS was decreased at the end of therapy is also reported. In the group that received coenzyme Q_{10} seven participants (70%) had decreased LVFS at the end of therapy in comparison to eight participants (80%) in the control group. No *p*-value is reported.

SWT and septal wall motion abnormalities are also presented, but no between-group statistical comparison is reported. No statistical reduction in % SWT was reported in the group that received coenzyme Q_{10}, but in the group that did not receive coenzyme Q_{10} % SWT was statistically decreased from 46.10 ± 10.1 at baseline to 27.00 ± 18.54 at the end of therapy ($p < 0.01$). In the group that received coenzyme Q_{10} five participants (50%) had decreased % SWT at the end of therapy, but no participants had septal wall motion abnormalities. In comparison, nine participants (90%) had decreased % SWT at the end of therapy and two participants had septal wall motion abnormalities in the control group. No *p*-values are reported for a between-group comparison. The authors state that there was no significant left ventricular posterior wall thickening in either group, but no data are provided.

Addition of dexrazoxane (ICRF-187) to doxorubicin therapy[30]

The primary outcome of cTnT levels and secondary cardiac outcomes are reported in the study by Lipshultz and colleagues[30] on the cardioprotective effect of dexrazoxane.

cTnT

Significantly fewer patients in the group given dexrazoxane and doxorubicin compared with patients in the doxorubicin group had any elevations in cTnT (21% versus 50%, $p < 0.001$), any extreme elevations in cTnT (10% versus 32%, $p<0.001$) or multiple elevations in cTnT (12% versus 37%, $p < 0.001$).

Differences between the groups in the percentage of patients with at least one elevated cTnT level began to emerge between 61 and 120 days after the start of therapy and persisted throughout the treatment period, becoming significant during the interval 121 and 180 days ($p < 0.001$). Patients in the doxorubicin group also had a higher rate of elevation over time than those in the group given dexrazoxane and doxorubicin ($p = 0.003$).

Cardiac outcomes

Echocardiographic results were available for a subgroup of patients who underwent randomisation. There were no significant differences between the children who received doxorubicin alone and those who received dexrazoxane and doxorubicin in terms of mean left ventricular dimension, fractional shortening or contractility, before, during or after therapy. Fractional shortening was significantly depressed in both randomised groups during and after treatment (mean *z*-score, –1.06, $p < 0.001$).

Event-free survival and remission rates

The rate of event-free survival at 2.5 years was 83% in both groups and continuous remission was 81% in both groups.

Summary of the effectiveness of cardioprotective technologies

- Four RCTs met the inclusion criteria of the review. All were described as randomised but none was double blind. There were methodological limitations in most studies owing to inadequacy of randomisation and assessment of outcomes, or insufficient details of methods and results.
- Each RCT considered a different intervention: doxorubicin bolus versus continuous infusion, daunorubicin bolus versus continuous infusion, anthracyclines with or without coenzyme Q_{10}, and doxorubicin with or without dezraxozane.
- Participants included in the studies were mostly patients with average- or high-risk ALL, although specific criteria differed between studies.
- Outcomes measures were cardiac characteristics from echocardiography and survival in all trials, and cardiac troponin levels and reduction in leukaemic cells, each in one trial.
- Duration of follow-up was variable within and between studies, ranging from 0 to 56 months.
- One study[27] found that doxorubicin infusion over 48 hours for childhood leukaemia did not offer cardioprotection over bolus infusion. Both regimens were associated with progressive subclinical cardiotoxicity. Fractional shortening fell by approximately 2 SD in both groups and left ventricular contractility was depressed in both groups. Dilated cardiomyopathy and inadequate left ventricular hypertrophy were noted in both groups. Clinical manifestations and event-free survival did not differ between groups.
- One study[28] concluded that "continuous infusion of daunorubicin had less cardiotoxicity with faster antileukaemic activity than bolus infusion". However, statistical results are not reported separately for the different treatment arms of the study for all outcomes so there are no comparable groups for leukaemic cell reduction and cardiac function for statistical comparison.
- One small study[29] reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy, but there are no statistical data to support this conclusion. Reduction in mean % LVFS was reported to be significantly lower in the group receiving coenzyme Q_{10} compared with the mean value in the group not receiving coenzyme Q_{10}, but there are no between-group statistical comparisons, only before and after within-treatment groups. The LVFS parameter is never reported to be less than normal in either group.
- One study[30] concluded that dexrazoxane prevents or reduces cardiac injury as reflected by elevations of cTnT during doxorubicin therapy for childhood ALL without compromising the antileukaemic efficacy of doxorubicin.

Cost-effectiveness

No cost-effectiveness studies considering cardioprotection in children receiving anthracyclines for cancer were identified.

Chapter 5

Markers of cardiac damage

Anthracyclines are toxic to tumour cells, largely owing to irreversible damage to tumour cell DNA. This damage is caused by intercalation of the anthracycline into DNA, which results in inhibition of macromolecular biosynthesis, and by the generation of highly reactive oxygen-derived free radicals.[24] Oxygen-derived free radicals can cause direct injury to cell membranes through lipid peroxidation, which is known to kill cardiac myocytes, thus leading to cardiomyopathy. Another mechanism thought to be involved in cardiac injury is the disruption of the expression of genes encoding enzymes critical for energy production in cardiac myocytes.[24] The free-radical hypothesis and the disruption of cardiac gene expression hypothesis are not mutually exclusive.

Since anthracyclines cause disruption of cardiac myocyte cell membranes, resulting in the release of intracellular proteins such as lactate dehydrogenase (LDH), creatine phosphokinase (CPK) and cTnT, these substances have been used to assay for the presence and extent of myocyte injury. In the absence of myocardial injury, cTnT levels are usually below the limit of detection of current analytical methods.[30] It has been demonstrated that low-level elevations of cTnT induced by doxorubicin are associated with histological evidence of myocardial injury which may be clinically meaningful.[32] Consequently, cTnT has been suggested to be an early marker of anthracycline-induced myocardial injury.[33] Another cardiac marker that may be useful is cardiac troponin I (cTnI).

Plasma levels of circulating natriuretic peptides, such as ANP and BNP, are elevated in left ventricular dysfunction and heart failure. They cause natriuresis (excretion of abnormal amounts of sodium in the urine), diuresis, vasodilatation and suppression of the renin–angiotensin–aldosterone system.[34] N-terminal BNP (NT-pro-BNP) is secreted from the cardiac ventricles in response to volume expansion and pressure overload.[35] These peptides are under investigation as non-invasive markers in the early detection of A-CHF before other signs of cardiac damage, such as decreased left ventricular ejection fraction (LVEF), appear.

Clinical evidence shows that carnitine has an important function in the management of cardiovascular disorders, and that clinical presentation of carnitine deficiency includes cardiomyopathy which improves after carnitine replacement. A relationship between serum carnitine concentrations and cardiac dysfunction is postulated,[36] which could be useful for monitoring the cardiotoxic effects of doxorubicin. Elevated serum lipid peroxide levels have been shown in animals given doxorubicin. It has been suggested that this increase reflects a release of lipid peroxide from heart tissues exposed to doxorubicin,[37] which could also be useful for assessing A-CHF and cardiotoxicity.

Echocardiography and magnetic resonance imaging (MRI) scanning can be used to follow the progression of myocardial damage. However, echocardiographic measurements have poor sensitivity and specificity in identifying subclinical abnormalities of left ventricular structure and function in children with cancer who are receiving doxorubicin.[38] This may be due to various transient confounding factors. The gold standard for determining whether cardiac dysfunction is due to anthracycline toxicity is endomyocardial biopsy to assess pathology.

The use of serum cardiac markers to quantify A-CHF in children would be of value owing to their minimally invasive nature and ease of analysis and reproducibility. A systematic review of the evidence of the use of cardiac markers in children receiving anthracyclines for cancer was performed (see 'Inclusion criteria', p. 8). Quality assessment of included studies was undertaken using criteria developed by Spitzer and colleagues[26] (Appendix 6).

Quantity and quality of research available

One RCT[30] and six cohort studies[34–37,39,40] met the inclusion criteria for the review. Quality assessment of the studies is shown in *Table 5* and a summary of the studies in *Table 6*.

TABLE 5 *Quality assessment of cardiac marker studies*

Criterion	Lipshultz *et al.*, 2004[30]	Bauch *et al.*, 1992[39]	Hayakawa *et al.*, 2001[40]	Pinarli *et al.*, 2005[34]	Soker *et al.*, 2005[35]	Horino *et al.*, 1983[37]	Yaris *et al.*, 2002[36]
Proper random assignment	U (no details)	NA	NA	NA	NA	NA	NA
Proper sampling	Y	NR	NR	NR	NR	NR	NR
Adequate sample size	U	N	N	N	N	N	N
Objective outcomes	Y	Y	Y	Y	Y	Y	Y
Blind assessment	Y	NR	NR	NR	NR	NR	NR
Objective eligibility criteria	Y	NR	NR	NR	NR	NR	NR
Reported attrition	I	NR	NR	N	NR	NR	NR
Comparability of groups	Y	N	N	U	N	N	U
Generalisability	U	U	U	U	U	U	U

I, incomplete; N, no; NA, not applicable; NR, not reported; U, uncertain; Y, yes.

The RCT considered the effect of dexrazoxane on myocardial injury in doxorubicin-treated children with ALL as measured by cTnT levels. Details of the RCT are reported in the section of the review reporting clinical effectiveness of cardioprotection in children (Chapter 4, p. 12), and Appendix 7.

Of the six cohort studies, two measured plasma ANP levels, to determine whether these levels could indicate cardiac damage.[39,40] One of these also measured BNP levels.[40] One study examined BNP levels alone,[34] one measured plasma levels of NT-pro-BNP and cTnI,[35] another serum lipid peroxide levels[37] and one serum carnitine levels.[36] Details are shown in Appendix 8.

Sampling, blind assessment, objective eligibility criteria and sample attrition were not discussed or reported in any of the cohort studies.[34–37,39,40]

None of the cohort studies achieved an adequate sample size.[34–37,39,40] Numbers ranged from 15 to 34, with three control groups in two studies totalling only 10, 11 and 12 patients, respectively.[34,39] In one study the results for some diastolic functions are given for 33 out of 34 patients, and for half of the controls (6/12), but it is not stated why this is the case.[34]

One cohort study did not report what type of cancer the patients had, or whether they were in remission.[39] In two studies, the patients were in complete remission,[35,40] and in one of these most patients had ALL.[35] In a fourth they were asymptomatic, with no evidence of residual malignancy.[34] A fifth study describes the patients as having NHL[36] and the sixth as "patients with various types of neoplasms".[37]

Generalisability was difficult to determine in all the included studies. No inclusion criteria were stated explicitly.[34–37,39,40] Two cohort studies[35,40] reported that if patients were in complete remission and a month after their last dose of chemotherapy they would be invited to take part. Four cohort studies stated that they had excluded patients; the first for illnesses such as infections,[39] another where patients had cardiovascular disease or were using any drugs affecting the cardiovascular system,[36] the third excluded patients who had received mediastinal radiation therapy, developed congestive heart failure or had other illnesses such as infections,[40] and the fourth where patients had received radiation therapy to the mediastinum or had other illnesses such as infections.[35] Although not part of explicit exclusion criteria, none of the patients in the Yaris study[36] and the Bauch study[39] received mediastinal radiation therapy. In the study by Horino and colleagues,[37] it was stated that participants did not receive vitamin E. It is not clear whether this referred to both groups.

In each of the cohort studies, the groups were incomparable at baseline, or the comparability of the groups was uncertain. All cohort studies used some healthy volunteers as part of the control groups. Pinarli and colleagues[34] used two healthy control groups, one to compare the echocardiographic results and the second to compare BNP levels. The age and size of the echocardiographic controls were younger and smaller than those of the BNP controls, and the authors stated that they had adjusted the

TABLE 6 *Summary of cardiac marker studies*

Study details	Intervention group	Control group
Authors: Lipshultz *et al.*[30] *Design:* RCT *Outcomes:* cTnT and echocardiographic studies	DZX 300 mg/m^2 followed by DOX 2 × 30 mg/m^2 during induction, then 8 × 30 mg/m^2 every 3 weeks (cumulative dose 300 mg/m^2) *n* = 105 Age: Median 7.5 years Male (%): 61	DOX alone 2 × 30 mg/m^2 during induction, then 8 × 30 mg/m^2 every 3 weeks (cumulative dose 300 mg/m^2) *n* = 101 *Age:* median 7.3 years Male (%): 55
Authors: Bauch *et al.*[39] *Design:* Cohort *Outcomes:* ANP and LVEF	Combination chemotherapy, including DOX (ADR); total cumulative dose 80–480 mg/m^2 *n* = 16 *Age:* Mean 13.3 years; Male (%): 44	(1) Treatment controls: Oncology patients, undergoing chemotherapy but never received doxorubicin, *n* = 10 (2) Untreated controls: Healthy volunteers, *n* = 11 Age: (1) Mean 10.5 years; (2) 24–38 years Male (%): (1) 40; (2) 27
Authors: Hayawaka *et al.*[40] *Design:* Cohort *Outcomes:* Echocardiographic cardiac dysfunction; ANP and BNP levels; correlation between systolic and diastolic functions of LV and ANP and BNP	In complete remission, receiving combination chemotherapy including DOX *n* = 34 Age: Mean 11.5 years Male (%): NR	Healthy control group *n* = 19 Age: Mean 10.6 years Male (%): NR
Authors: Pinarli *et al.*[34] *Design:* Cohort *Outcome:* Cardiac functions and BNP	Asymptomatic having received DOX, DAUN and EPI for solid tumours *n* = 34 Age: Mean 12.2 ± 3.44 years Male (%): 68	Healthy volunteers (1) Echo controls, *n* = 12 (2) BNP controls, *n* = 16 Age: (1) Mean 8.2 ± 3.0 years; (2) Mean 11.3 ± 3.64 years Male (%): (1) 42; (2) 62.5
Authors: Soker *et al.*[35] *Design:* Cohort *Outcomes:* NT-pro-BNP and cTnI levels; echocardiographic cardiac dysfunctions	In complete remission receiving chemotherapy regimens including DOX. Total cumulative dose 30–600 mg/m^2. *n* = 31: ALL (27), AML (2), HD (1), NHL (1) Age: 8.16 ± 3.48 years Male (%): 45	Healthy volunteers *n* = 30 *Age:* NR Male (%): 52
Authors: Horino *et al.*[37] *Design:* Cohort *Outcome:* Serum lipid peroxide	Various types of neoplasms treated with chemotherapeutic regimens including DOX *n* = 21 Age: 1–16 years Male (%): NR	Did not receive DOX *n* = 44 Age: 0 to adult Male (%): NR
Authors: Yaris *et al.*[36] *Design:* Cohort *Outcomes:* Serum carnitine levels and relationship with cardiac dysfunction	NHL given combination chemotherapy including DOX *n* = 15 Age: Mean 9.04 ± 2.08 years Male (%): 60	Healthy volunteers *n* = 20 Age: Mean 9.8 ± 4.3 years Male (%): 60

ADR, adriamycin (doxorubicin); ANP, atrial or A-type natriuretic peptide; AML, acute myeloid leukaemia; BNP, brain or B-type natriuretic peptide; DAUN, daunorubicin; DOX, doxorubicin; DZX, dexrazoxane (ICRF-137); echo; echocardiography; EPI, epirubicin; LV, left ventricular; LVEF, left ventricular ejection fraction; NHL, non-Hodgkin's lymphoma; RCT, randomised controlled trial.

parameters to account for this. However, in this study[34] haemoglobin, heart rate and blood pressure of the patients were not significantly different from controls. In the study by Yaris and colleagues,[36] healthy controls were also used. Age, gender, weight, heart rate and blood pressure were not significantly different in the patient and control groups at each evaluation time.[36] Soker and colleagues[35] used a healthy control group that was reported to be age and gender matched, although age was not reported for the control group. As no echocardiography results are reported for the controls, it is unclear whether they underwent echocardiography in addition to the blood sampling.[35] The control group in the study by Horino and colleagues[37] comprised patients receiving chemotherapy without doxorubicin, patients with unrelated disorders and healthy adult volunteers. The adults' age range is not given. Hayakawa and colleagues[40] used a healthy, age-matched control group, and Bauch and colleagues[39] used a control group of healthy adults aged 24–38 years.

Three of the cohort studies included participants over the age of 18 in the treated groups,[34,39,40] although mean ages in the treated groups were 13.3 years,[39] 11.5 years[40] and 12.2 ± 3.44 years.[34]

A large range of cumulative anthracycline dose was given to patients in four of the six cohort studies: 80–480 mg/m^2,[39] 42–696 mg/m^2,[40] 90–490 mg/m^2,[34] and 30–600 mg/m^2.[35] In another study the regimen administered was doxorubicin every 4–7 weeks in a dose of 15–30 mg/m^2.[37] In the remaining study, all patients had received a total cumulative doxorubicin dose of 300 mg/m^2 at the end of the study.[36]

The timing of blood sampling for cardiac markers may not have been comparable between the studies. In one study[39] samples were taken when children came to the outpatient clinic or when they were admitted to hospital for chemotherapy administration. As different treatment protocols were followed there was variation in the time interval between administering a dose of doxorubicin and obtaining blood samples for ANP levels.[39] The last dose of anthracycline was more than 1 month previously in two studies,[35,40] and 1–7 weeks before in another.[37] One study reported that blood sampling was 3–4 weeks after cumulative doses of doxorubicin[36] and another that the mean time between the last dose of anthracycline and cardiac evaluation was 45.7 ± 27.9 months (range 3–122 months).[34]

Assessment of cardiac markers to quantify cardiotoxicity

Table 7 summarises the effectiveness of cardiac markers in the included studies. Details of the RCT are reported in the clinical effectiveness section of the review (Chapter 4, p. 16).

Levels of ANP, BNP and NT-pro-BNP

Two studies measured plasma ANP levels.[39,40] One of these[40] also measured BNP levels and a further study[34] examined BNP levels alone. A further study measured NT-pro-BNP levels, along with cTnI levels (see below).[35]

Bauch and colleagues[39] found that six children (37.5%) had transiently elevated plasma levels of ANP 3 SD above control levels, and ten patients had no increase in ANP. Patients in the group treated with doxorubicin were then put into two groups for additional analysis, one with high ANP levels recorded at some time after receiving doxorubicin (group I, six patients) and one with normal ANP throughout the treatment (group II, ten patients). The results were then compared with those of the two control groups. Group I results were the average of the highest levels for each patient. For the controls the mean ANP level was used.

In the group with high ANP levels, all six children had received the highest cumulative doses of doxorubicin (200–480 mg/m^2). In the group with normal ANP levels nine out the ten patients had received less than 160 mg/m^2 of doxorubicin. The other patient in this group had received a larger cumulative dose without a significant change in ANP levels.

In the group with high ANP, ANP levels were time dependent and a peak ANP was found 19–24 days after patients had received a dose of doxorubicin. There was no similar peak in the group with normal ANP levels, and when ANP levels in that time-frame were compared the two groups were significantly different ($p < 0.05$).[39]

No significant difference was found between the group with high ANP and the group with normal ANP in LVEF, although no results are given. There was no significant decline in LVEF in any of the children in either group. The authors state that despite the lack of evidence of cardiotoxic effects by LVEF, CHF developed in two patients; these were both in the group with high ANP levels.[39]

TABLE 7 *Summary of effectiveness of cardiac markers in included studies*

Lipshultz *et al,* 2004[30]	**Intervention group**		**Control**		***p*-Value**
Patients with any elevated cTnT	DZX+DOX 21% (95% CI 13 to 31)		DOX 50% (95% CI 38 to 62)		$p < 0.001$
Patients with many elevated cTnT	DZX+DOX 12% (95% CI 6 to 21)		DOX 37% (95% CI 26 to 49)		$p < 0.001$
LVFS, LVD or LVC	No significant differences between groups LVFS significantly depressed in both groups during and after treatment				NR
Bauch et al., 1992[39]	**Intervention**		**Control**		***p*-Value**
	Group I (n = 6) High ANP	**Group II (n = 10) Normal ANP**	**Group 1 (n = 10)**	**Group 2 (n = 11)**	
ANP (pg/ml), mean ± SE	136.2 ± 23.3	33.3 ± 4.1	34.6 ± 7.9	25.1 ± 2.4	$p < 0.01$, Group I significantly higher than any other group
LVEF	No results reported		No results reported		
Hayakawa *et al.*, 2001[40]	**Intervention**		**Control (n = 19)**		***p*-Value**
	Cardiac dysfunction (n = 26)	**Normal cardiac function (n = 8)**			
ANP (pg/ml), mean ± SD	28.8 ± 14.6	17.6 ± 8.6	14.8 ± 5.8		$p < 0.01$ (dysfunction compared with control) $p < 0.05$ (dysfunction compared with normal)
BNP (pg/ml), mean ± SD	29.0 ± 31.2	9.0 ± 14.8	5.6 ± 3.8		$p < 0.01$ (dysfunction compared with control) $p < 0.05$ (dysfunction compared with normal)
Peak E filling velocity (m/s), mean ± SD	0.82 ± 0.15	0.70 ± 0.12	0.78 ± 0.16		ns
Peak A filling velocity (m/s), mean ± SD	0.54 ± 0.11	0.40 ± 0.11	0.40 ± 0.09		$p < 0.05$
Pinarli *et al.*, 2005[34]	**Intervention (n = 34)**		**Healthy control group (n = 16)**		***p*-Value**
BNP before exercise testing (pg/ml), mean ± SD	10.56 ± 10.22		4.09 ± 2.26		$p = 0.016$
BNP after exercise testing (pg/ml), mean ± SD	15.70 ± 14.0 (n = 31)		NA		

continued

TABLE 7 *Summary of effectiveness of cardiac markers in included studies (cont'd)*

Pinarli et *al.*, 2005[34]	**Intervention (n = 34)**	**Healthy control group (n = 12)**	***p*-Value**
LVEF (%)	72.50	75.50	$p > 0.05$
LVFS	34.97	37.46	$p > 0.05$
LVWS (g/cm^2)	54.90	36.50	$p < 0.001$
CO (L/min/m^2)	9.77	2.88	$p < 0.001$
LV-E (m/s)	1.17	1.02	$p = 0.007$
LV-A (m/s)	0.66	0.51	$p = 0.039$

Soker et *al.*, 2005[35]	**Intervention**			**Healthy control group (n = 30)**	***p*-Value**
	Cardiac dysfunction (n = 4)	**Normal cardiac function (n = 27)**	**Total (n = 31)**		
NT-pro-BNP level (pg/ml), mean ± SD	299.03 ± 264.97	107.55 ± 131.82	135.92 ± 166.16	47.17 ± 19.48	Cardiac dysfunction group compared with: control group $p < 0.001$; normal cardiac function group $p < 0.008$
Range (pg/ml)	62.2–550	5–501	5–550	15–95.1	

	Intervention		
	Normal cardiac function (n = 27)	**Cardiac dysfunction (n = 27)**	**Total (n = 31)**
LVEF, mean ± SD (range)	68.16 ± 4.43 (62.30–80.60)	55.72 ± 3.63 (50.70–59.40)	66.25 ± 6.25 (50.70–80.60)
LVFS, mean ± SD (range)	37.24 ± 3.43 (33–47.2)	27.30 ± 1.77 (25–29.2)	35.71 ± 4.86 (25–47.2)

Horino et *al.*, 1983[37]	**Age group (years)**	**DOX+**	**DOX–**	***p*-Value**
Serum lipid peroxide level (malondialdehyde nmol/ml of serum)	0–2	2.65 ± 0.37 (n = 5)	1.68 ± 0.44 (n = 7)	$p < 0.01$
	3–5	2.73 ± 0.23 (n = 7)[a]	2.00 ± 0.31 (n = 7)	$p < 0.001$
	6–10	2.23 ± 0.32 (n = 8)	1.78 ± 0.32 (n = 14)	$p < 0.01$
	11–15	1.95 (n = 1)	2.23 ± 0.31 (n = 5)	
	16 to adult	ND	2.59 ± 0.55 (n = 11)[b]	

continued

TABLE 7 *Summary of effectiveness of cardiac markers in included studies (cont'd)*

Yaris et *al.*, 2002[36]	**Patients (*n* = 15)**			**Healthy control group (*n* = 20)**	***p*-Value**
	0 (base-line)	**180 mg/m^2 DOX**	**300 mg/m^2 DOX**		
Carnitine (μmol/l)	31.05 ± 11.54	29.60 ± 12.85	28.43 ± 11.2	32.0 ± 8.2	
EF (%) (normal range 64–83%)	62.2 ± 3.09	68.5 ± 4.9	66.0 ± 5.4**	70.1 ± 4.8	**$p < 0.05$ (but within normal limits)
SF (%)	38.0 ± 2.6	37.7 ± 3.7	35.5 ± 3.1**	39.1 ± 3.3	**$p < 0.05$ (but within normal limits)
LVIDd (mm)	36.6 ± 6.3*	39.1 ± 6.6	40.3 ± 6.5*	39.4 ± 4.8	*$p < 0.05$ (baseline to post treatment)
LVIDs (mm)	22.7 ± 3.6*	24.9 ± 5.6	26.1 ± 4.6*	24.5 ± 4.7	*$p < 0.05$ (baseline to post treatment)

[a] Serum lipid peroxide level of DOX+ age 3–5 years significantly higher than that in the DOX+ 6–10-year group ($p < 0.01$).
[b] Serum lipid peroxide level of DOX– age 16 to adult significantly higher than in the DOX– 0–2, 3–5, and 6–10-year age groups ($p < 0.01$).
ANP, atrial or A-type natriuretic peptide; BNP, brain or B-type natriuretic peptide; cTnT, cardiac troponin T; DOX, doxorubicin; DZX, dexrazoxane (ICRF-137); EF, ejection fraction; LVFS, left ventricular fractional shortening; LVDS/SD, left ventricular systolic dimension; LVC, left ventricular contractility; LVIDd, left ventricular internal dimension at end-diastole; LVIDs, left ventricular internal dimension at end-systole; ND, not determined; SD, standard deviation; SF, shortening fraction.

Hayakawa and colleagues[40] measured ANP and BNP levels and the correlation of these levels with systolic and diastolic functions of the left ventricle. The overall incidence of cardiac dysfunction as assessed by echocardiography was 23.5% (8/34 treated participants) and results are presented for this subgroup of patients versus normal cardiac patients and healthy controls. There were no significant differences between the group with normal cardiac function on echocardiography and that with cardiac dysfunction with regard to age or gender.

Mean ANP plasma levels were 28.8 ± 14.6 pg/ml in the cardiac dysfunction group, 17.6 ± 8.6 pg/ml in the normal cardiac function group ($p < 0.05$ compared with the cardiac dysfunction group) and 14.8 ± 5.8 in the healthy control group ($p < 0.01$ compared with the cardiac dysfunction group). Mean BNP plasma levels were 29.0 ± 31.2 pg/ml in the cardiac dysfunction group, 9.0 ± 14.8 pg/ml in the normal cardiac function group ($p < 0.05$ compared with the cardiac dysfunction group) and 5.6 ± 3.8 pg/ml in the healthy control group ($p < 0.01$ compared with the cardiac dysfunction group).[40]

The elevated ANP and BNP plasma levels, which were defined as greater than the mean + 2 SD of the healthy controls, were greater than 26 pg/ml and 13 pg/ml, respectively. No correlation between the cumulative anthracycline dose and ANP plasma level was found. The authors state that there was a tendency for BNP plasma level to correlate with the cumulative anthracycline dose.

BNP levels correlated significantly with cardiac systolic function and ANP levels with LVEF and LVFS. Peak A filling velocity in patients with cardiac dysfunction was elevated significantly, compared with normal healthy controls and the patients with normal cardiac function ($p < 0.05$). There were no significant relationships between levels of natriuretic peptides and diastolic function.[40]

Pinarli and colleagues[34] assessed cardiac functions of 34 children with solid tumours, by measuring plasma BNP levels, electrocardiography, exercise

electrocardiography testing and echocardiography. Two different control groups were used for echocardiography and BNP measurements.

The mean BNP levels were significantly higher in patients (10.56 ± 10.22 pg/ml) than in the healthy controls (4.09 ± 2.26 pg/ml) ($p = 0.016$) before exercise testing.[34] After exercise testing there was a non-significant increase in mean BNP levels in patients, with no data reported for the control group. No correlation was found between BNP levels, the total cumulative anthracycline dose and the mean duration after the last dose of chemotherapy.[34]

In echocardiography, the cardiac systolic functions of cardiac output (CO) and wall stress (WS) were significantly higher in the patients than in the controls ($p < 0.001$). Other systolic functions such as LVEF and LVSF were not significantly different between patients and controls ($p > 0.05$). No significant relationships were found between the total cumulative anthracycline dose, the mean duration after treatment and cardiac systolic functions.[34] Diastolic filling patterns showed various abnormalities, some of which were significantly higher than those of controls, such as left ventricular mitral early peak filling velocity (LV-E) and left ventricular mitral atrial peak filling velocity (LV-A).

Soker and colleagues[35] assessed the incidence of echocardiographically diagnosed doxorubicin-induced cardiac dysfunction in children with cancer, and its association with the secretion of NT-pro-BNP and cTnI (cTnI is discussed below).

The incidence of cardiac dysfunction in this study was 12.9% (4/31 patients). The NT-pro-BNP plasma levels in patients with cardiac dysfunction were elevated significantly compared with the control group ($p < 0.001$) and the patients with normal cardiac function ($p < 0.008$).[35]

The authors report that there were no statistically significant changes in the left ventricular systolic indices, or in peak A and peak E wave velocities or E/A ratio. However, it is not clear which comparison is being referred to here.[35] No significant correlations were found between any of the echocardiographic parameters with natriuretic peptides and cumulative doxorubicin dose.[35]

cTnI

The serum cTnI values of all patients were below the detection limit (<0.50 ng/ml).[35] There was no difference between serum cTnI levels of all the patients with normal and abnormal echocardiographic findings. Results for the control group are not reported.[35]

Serum lipid peroxide

The serum lipid peroxide levels in children with malignancies treated with combination chemotherapies with or without doxorubicin were reported by Horino and colleagues.[37]

All patients were examined periodically for left ventricular performance by echocardiography (systolic time intervals, ejection fraction by Pombo's method, mean circumferential fibre shortening velocity). The results were all normal.

In the control group, lipid peroxide values of patients with any type of neoplasm did not differ from one another or from those of patients with unrelated disorders or from the combined value. The younger three age groups receiving doxorubicin showed significantly higher levels of serum lipid peroxide than the corresponding group not receiving doxorubicin. There was no correlation between the serum lipid peroxide level and the number of injections or interval after the last doxorubicin injection. In addition, the authors found when coenzyme Q_{10} was given to patients receiving doxorubicin, lipid peroxide levels remained elevated.[3]

Serum carnitine levels

Serum carnitine levels during treatment with doxorubicin and the relationship between serum carnitine levels and cardiac dysfunction were measured by Yaris and colleagues.[36] Physical examination of the cardiovascular system, chest X-ray and ECG of patients before therapy and after each dose of drug were normal, as in the control subjects. Mean left ventricular at end of diastole dimension (LVEDd) and left ventricular at end of systole dimension (LVEDs) of patients increased significantly after doxorubicin therapy compared with the initial values, but were still not significantly different from those of control subjects. Mean ejection fraction (EF) and shortening fraction (SF) of patients after completion of therapy were significantly lower than those of the control group, but remained within normal limits.

The mean carnitine values of the patient group before treatment, and after cumulative doses of 180 mg/m^2 and 300 mg/m^2 were not significantly different from the mean value of the control group. A decrease was observed in mean serum levels with the higher cumulative doses of the

drugs, although it was not statistically significant. There was no correlation between carnitine values and echocardiographic subclinical abnormalities.

Summary of cardiac markers

- One RCT and six cohort studies met the inclusion criteria for the review. The RCT reported on cTnT levels; one cohort study reported on ANP, one on ANP and BNP, one on BNP alone, one on NT-pro-BNP and cTnI, and one each on serum lipid peroxide levels and serum carnitine levels.
- The RCT was described as randomised but no details are given, and it was not double blind.
- The cohort studies all had methodological limitations. Sampling, blind assessment, objective eligibility criteria and sample attrition were not discussed or reported by any of the studies. The studies were small, with different patient groups which were not stated to be comparable at baseline. A variety of control groups was used, including healthy controls in some studies, which may not have been appropriate. Generalisability of these studies is difficult to determine.
- The RCT found that patients who had been treated with doxorubicin alone were significantly more likely to have elevated cTnT levels than those treated with dexrazoxane and doxorubicin. No significant differences in echocardiography between the groups were found and EFS was similar in both groups.
- One study (Bauch[39]) looking at ANP found that 37% of children treated with doxorubicin had transiently elevated ANP levels which were associated with high cumulative doses of doxorubicin. Two children in a subgroup of children with high ANP levels developed CHF; no children in the subgroup with normal ANP levels did. No statistically significant differences in LVEF were found and no children had abnormal LVEF.
- One study (Hayakawa[40]) found that both ANP and BNP levels were significantly elevated in a subgroup of doxorubicin-treated patients who had cardiac dysfunction compared with healthy controls or patients with normal cardiac function. ANP and BNP levels were significantly correlated with cardiac systolic function, but not with diastolic function.
- One study (Pinarli[34]) found that BNP levels were significantly higher in patients than in healthy controls before exercise testing; echocardiographic results showed no significant differences between patients and controls except for cardiac output and wall stress, which were significantly higher in patients than controls. Diastolic filling patterns showed various abnormalities, some of which were significantly higher than those of controls. Different controls were used for different outcomes.
- One study (Soker[35]) found that NT-pro-BNP plasma levels in patients with cardiac dysfunction were elevated significantly compared with a healthy control group and the patients with normal cardiac function. cTnI levels were under normal value for all patients. No significant correlations were found between any of the echocardiographic parameters with natriuretic peptides and cumulative doxorubicin dose.
- One study (Horino[37]) found that younger age groups of patients treated with doxorubicin had significantly higher levels of serum lipid peroxide than a corresponding age group not receiving doxorubicin. All echocardiographic results were normal and no cardiotoxicity was observed.
- One study (Yaris[36]) found no significant differences in carnitine levels between children treated with doxorubicin and a control group of healthy children. A decrease in serum carnitine levels with higher cumulative doses of doxorubicin was observed, but was not statistically significant. There was no correlation between carnitine values and subclinical echocardiographic abnormalities.

Chapter 6

Assessment of factors relevant to the NHS and other parties

Monitoring and treating cardiac problems relating to anthracycline treatment during childhood will have an impact on the NHS in terms of costs and the availability of scarce resources. There would be implications for service provision in terms of bed usage, staffing and other costs, if further research results suggest that longer infusions of anthracyclines should become mandatory (although unlikely) during the primary treatment of children with cancer. Longer term surveillance of treated children for cardiac effects, well into adulthood, will have implications for resources.

There are social costs to relatives of childhood cancer sufferers and economic losses to society resulting from survivors of childhood cancer developing heart failure in later life. Non-productivity and financial/social dependence of sick long-term survivors are important indirect costs, but these factors are difficult to quantify.

Those with cardiac dysfunction may be limited in their occupations, productivity, quality of life and social independence. Medication is usually required for life and can cause side-effects. The burden on society as these survivors approach third and subsequent decades is uncertain. The worst scenario is progression to irreversible heart failure requiring heart transplantation with all its inherent problems. Life expectancy will probably be shortened.

Chapter 7
Discussion

Statement of principal findings

Clinical effectiveness and cost-effectiveness

Four RCTs met the inclusion criteria of the review. The RCTs had methodological limitations owing to inadequacy of randomisation and assessment of outcomes, or insufficient details of methods and incomplete reporting of results.

Each RCT considered a different intervention: doxorubicin bolus versus continuous infusion, daunorubicin bolus versus continuous infusion, anthracyclines with or without coenzyme Q_{10}, and doxorubicin with or without dexrazoxane. The participants in all the trials were children with acute leukaemia or NHL.

One study[27] found that doxorubicin infusion over 48 hours for childhood leukaemia did not offer cardioprotection over bolus infusion. Both regimens were associated with progressive subclinical cardiotoxicity. Fractional shortening fell by approximately 2 SD in both groups and left ventricular contractility was depressed in both groups. Dilated cardiomyopathy and inadequate left ventricular hypertrophy were noted in both groups. Clinical manifestations and event-free survival did not differ between groups.

The study considering daunorubicin[28] concluded that "continuous infusion of daunorubicin had less cardiotoxicity with faster antileukaemic activity than bolus infusion". However, statistical results are not reported separately for the different treatment arms of the study for all outcomes, so there are no comparable groups for leukaemic cell reduction and cardiac function for statistical comparison.

The small study[29] which investigated the effects of coenzyme Q_{10} reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy, but there are no statistical data to support this conclusion. Reduction in mean % LVFS was reported to be significantly lower in the group receiving coenzyme Q_{10} compared with the mean value in the group not receiving coenzyme Q_{10}, but there are no between-group statistical comparisons, only before and after within-treatment groups. The LVFS parameter is never reported to be less than normal.

One study[30] concluded that dexrazoxane prevents or reduces cardiac injury, as reflected by elevations of cTnT during doxorubicin therapy for childhood ALL without compromising the antileukaemic efficacy of doxorubicin.

No cost-effectiveness studies which met the inclusion criteria of the review were identified.

Cardiac markers

Seven studies considering cardiac markers in children are included in the review: one RCT which was reported in the clinical effectiveness section of the review and six controlled cohort studies. The RCT reported on cTnT levels, one cohort study reported on ANP, one on ANP and BNP, one on BNP alone, one NT-proBNP and cTnI, and one each on serum lipid peroxide levels and serum carnitine levels.

The cohort studies all had methodological limitations. Sampling, blind assessment, objective eligibility criteria and sample attrition were not discussed or reported by any of the studies. The studies were small, with different patient groups which were not stated to be comparable at baseline. A variety of control groups was used, including healthy controls in some studies which may not have been appropriate. Generalisability of these studies is difficult to determine.

The RCT found that patients who had been treated with doxorubicin alone were significantly more likely to have elevated cTnT levels than those treated with dexrazoxane and doxorubicin. No significant differences in echocardiography between the groups were found and event-free survival was similar in both groups.

A proportion (37%) of children treated with doxorubicin had transiently elevated ANP levels which were associated with high cumulative doses of doxorubicin in one cohort study. Two children in a subgroup of children with high ANP levels developed CHF; no children in the subgroup with normal ANP levels did. No statistically significant

differences in LVEF were found and no children had abnormal LVEF.

Both ANP and BNP levels were significantly elevated in a subgroup of doxorubicin-treated patients who had cardiac dysfunction compared with healthy controls or patients with normal cardiac function in one cohort study. ANP and BNP levels were significantly correlated with cardiac systolic function, but not with diastolic function.

BNP levels were significantly higher in patients than healthy controls before exercise testing in one cohort study; echocardiographic results showed no significant differences between patients and controls except for cardiac output and wall stress, which were significantly higher in patients than controls. Diastolic filling patterns showed various abnormalities, some of which were significantly higher than those of controls.

NT-pro-BNP levels were significantly elevated in a subgroup of anthracycline-treated patients who had cardiac dysfunction compared with healthy controls or patients with normal cardiac function in one cohort study. cTnI levels were below normal values in all patients.

Serum lipid peroxide levels were found to be significantly higher in younger age groups of patients treated with doxorubicin than in those of corresponding age groups not receiving doxorubicin. All echocardiographic results were normal and no cardiotoxicity was observed.

No significant differences in carnitine levels between children treated with doxorubicin and a control group of healthy children were found in one cohort study. A decrease in serum carnitine levels with higher cumulative doses of doxorubicin was observed, but was not statistically significant. There was no correlation between carnitine values and subclinical echocardiographic abnormalities.

Strengths and limitations of the assessment

The review has certain strengths:

- It is independent of any vested interest.
- The review brings together the evidence for the clinical effectiveness of cardioprotection for children receiving anthracyclines for cancer, applying consistent methods of critical appraisal, presentation and transparency.
- The review was guided by the principles for undertaking a systematic review. Before the review was undertaken, the methods were set out in a research protocol (Appendix 1), and this was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.
- The review of clinical effectiveness relied on evidence from RCTs that reported various cardiac outcomes.
- The quality of the RCTs was assessed using criteria recommended in CRD Report No. 4 (2nd ed.).[25]

In contrast, certain limitations were placed on the review:

- Synthesis of the included studies was through narrative review. Owing to differences in the cardioprotective technologies and reported outcomes of the trials, meta-analysis was not possible.
- The effectiveness of cardiac markers relied on evidence from controlled cohort studies, apart from one RCT which was also included in the clinical effectiveness section of the review.

Other relevant factors

Clinical effectiveness

- There are two major problems regarding the investigation of cardiotoxicity which make comparisons of study results difficult. First, there is no agreed consensus of the definition of cardiotoxicity, making categorisation for data analysis difficult. Secondly, there is a lack of standardisation for monitoring cardiac performance, in terms of the variety of cardiac outcomes being used to assess cardiotoxicity and the inconsistent reporting of those methods. These need to be addressed to make synthesis of evidence possible.
- Several of the studies were of a complicated design or were part of a larger study, and it is not clear what the impact of this may have been on the outcomes of interest for this review.
- The reporting of some studies lacked clarity. For example, it was noted that in some studies there were discrepancies between the abstract and tables and text, numbers were exchanged

between groups, and there was contradictory text and numerical results. This brings into question the reliability of results.
- Several studies have problems with the data analysis or data presentation. In some cases there are incomplete or missing data for some of the outcomes, or outcomes from some groups have been merged together. Point estimates do not all have a measure of variability and *p*-values are not always reported, although results are stated to be statistically significant. Where power calculations have not been undertaken it is not possible to assess whether the studies are underpowered to detect any differences between groups.
- The studies do not all report the effect of the cardioprotective agent in preventing or reducing anthracycline-induced cardiotoxicity in terms of both subclinical and long-term cardiac damage and anti-tumour/cancer effectiveness through event-free survival and remission rates.
- Longer-term follow-up is needed to determine whether the cardioprotective technologies influence echocardiographic outcomes and event-free survival, as most of the studies are of short duration.
- The study that assessed cardiac injury by the measurement of cTnT levels assumes that this cardiac marker is a surrogate for cardiac damage. This is on the basis of an uncontrolled study which suggests that the cumulative dose of anthracyclines correlates with subsequent structural abnormalities of the left ventricle as seen by echocardiography. As elevations of cTnT correlate with cumulative dose of doxorubicin, cTnT levels are therefore assumed to correlate with cardiac damage. The lack of direct correlation with echocardiographic measures of cardiac abnormality suggests that any cardioprotection afforded was subtle and of doubtful long-term significance in comparison with other aspects of the original disease or its treatment.

Cardiac markers

- Studies of cardiac markers are small, with few participants, and generally give preliminary results. They are of short duration, with the timing of assessment of outcomes problematic, being too early for the conditions of interest to have developed.
- Both control and treatment groups in the studies of cardiac markers often comprised mixed groups with different baseline characteristics. Treatment groups received different interventions or dosages, and timings of samples taken after anthracycline therapy varied because patients were on different protocols. Different control groups for different outcome measures were also used. These methodological problems make comparisons between groups difficult.
- Some of the cardiac marker studies suffer from poor reporting, making the text difficult to interpret and understand, and inappropriate analysis of results, such as post-hoc subgroup analysis. For example, patients were arbitrarily split into those receiving higher and lower anthracycline dosages for subsequent analyses in one study, and in another study patients were grouped according to cardiac marker levels. It is unclear whether similar calculations were made in each group for comparisons between groups in another study.
- The studies of cardiac markers appear to be measuring an association of levels of serum chemicals with anthracycline treatment rather than a statistical correlation with cardiotoxicity. As cardiac outcomes are not always reported, or if reported show no significant difference between groups, or are significant through post-hoc analysis, it is difficult to see how these substances can be used as surrogate markers for later cardiac damage without further evaluation.
- The cardiac marker studies have a high risk of confounding due to study type employed and the use of healthy controls. In addition, it is not known how much levels of cardiac markers may be influenced by factors other than anthracycline therapy, such as exercise.
- The timing of blood samples from last anthracycline dose is an issue in trying to assess the usefulness of markers of cardiac damage. It is known that echocardiographic abnormalities detected after anthracycline administration can normalise and the precise timing may be important as the heart compensates for the damage. The time taken for a return to normal or the lack of return to normal may be predictive of late cardiac damage.

Chapter 8
Conclusions

Technologies for reducing A-CHF

It is difficult to draw conclusions about the effectiveness of technologies for reducing or preventing anthracycline-induced cardiotoxicity in children as the evidence is limited in both quantity and quality, with four RCTs considering different interventions, each of which had methodological limitations.

Two RCTs considered continuous infusion versus bolus infusion: one found that continuous infusion of DOX did not offer cardioprotection over bolus; the other suggested that continuous infusion of DAUN had less cardiotoxicity than bolus infusion, but did not report results separately for all outcomes for the different treatment arms of the study.

Two studies investigated protective agents: one concluded that dexrazoxane prevents or reduces cardiac injury, as reflected in elevation of a cardiac marker (cTnT) during doxorubicin therapy for childhood ALL without compromising the antileukaemic efficacy of doxorubicin; the other reported a protective effect of coenzyme Q_{10} on cardiac function during anthracycline therapy, but did not support this conclusion with statistical data.

No cost-effectiveness studies of cardioprotective technology in children treated with anthracyclines for cancer were identified.

Markers to quantify cardiotoxicity in children

Evidence on the use of cardiac markers for quantifying cardiac damage is also limited in quantity and quality, making conclusions problematic. One RCT suggests that cTnT can be used to assess the effectiveness of the cardioprotective agent dexrazoxane; cohort studies suggest that ANP (two studies) and BNP (two studies) are elevated in some subgroups of children treated with anthracyclines compared with healthy controls, but not all studies report all appropriate outcomes such as cardiac dysfunction. NT-pro-BNP levels were significantly elevated in children treated with anthracyclines who had cardiac dysfunction compared with patients who did not have cardiac dysfunction and healthy controls in one cohort study. One cohort study found that serum lipid peroxide was higher in younger children treated with doxorubicin than in correspondingly aged children not receiving doxorubicin, but all echocardiographic results were normal. No differences were found in carnitine levels between children treated with doxorubicin and a healthy control group in one cohort study.

Outcome measures for use in longer term studies

There is no standardisation of reporting or outcome measures in studies of cardioprotection during anthracycline use for cancer in children. All clinically relevant outcomes should be reported, including antitumour efficacy of the anthracycline in terms of event-free survival and remission rates, and cardiac measures including echocardiographic data and potential cardiac markers to identify and quantify subclinical and clinical events.

Overall, the most important outcome measure is event-free survival in terms of the whole treatment protocol. This is because although the anthracycline tumour killing activity may not be impaired, if cardioprotection causes increased morbidity, other treatments may not be given in a timely manner. For example, increased myelosuppression resulting from anthracycline use means that treatment intensity is reduced, which could impact on the final outcome.

In addition, acute and chronic side-effects of cardioprotective measures need monitoring. Liposomal anthracyclines in certain formulations give severe side-effects, such as palmar plantar syndrome (painful soreness and redness or darkening of the palms of the hand and soles of the feet).[41]

Until reliable surrogate markers of late toxicity are available, studies will have to look at cardiac outcome over many years or even decades.

Implications for service provision

The implications for service provision relate to the long-term surveillance and the management of cardiac damage resulting from anthracycline treatment in childhood. Monitoring requires well-organised cardiac facilities to deliver the service described previously, with good recall and referral pathways, followed up by suitable treatment, which may be lifelong. With increasing numbers of survivors of childhood cancer, demands on cardiac services are also likely to increase, which could impact on cardiac services for other patient groups.

In addition, many of these survivors have diverse medical problems in association with other organ treatment-induced late sequelae, which may complicate the treatment of their cardiac decompensation and require follow-up in highly specialised hospitals with late effects expertise in other specialities. Other late sequelae, such as gonadal or growth hormone failure, may make cardiac problems worse and thus compromise their treatment, rather than the treatment for the cardiac abnormalities. Atherosclerosis may complicate the anthracycline cardiotoxicity by affecting the blood supply to the overworked myocytes.

In the unlikely case that future research results suggest that longer infusions of anthracyclines should become mandatory, there would be implications for service provision, such as bed usage, during the primary treatment of children with cancer.

All of these resource implications will have an impact on the cost of service provision and therefore on the cost-effectiveness of any cardioprotective technology given to children with cancer.

Suggested research priorities

Intensive chemotherapy protocols have improved survival for children with cancer. However, this has made it more difficult to assess new protocols to improve results further because it necessitates accrual of more patients and longer follow-ups to demonstrate differences, and there may be a risk to survival rates. Protocols have become more complex and there are more short-term toxicities and increased potential for delayed side-effects such as cardiac damage. Cancer treatment protocols are dynamic and will have moved on by the time late effects of previous treatment can be assessed, which is why a marker of acute cardiac damage would be valuable. Therefore, although further research is required in this area it is not without difficulties.

Well-designed RCTs of the various cardioprotective technologies within the context of treatment protocols with longer follow-up are necessary to determine whether they influence event-free survival and cardiac outcomes. Alternative anthracycline preparations, such as liposomal doxorubicin, and cardioprotective agents are likely to be the technologies of particular interest. Participants should include children with solid tumours as well as ALL. The most important outcome is event-free survival in terms of the whole treatment protocol, although a range of outcomes is likely to be required, including different measures of cardiac function, potential cardiac markers, side-effects, measures of antitumour efficacy and remission rates.

Further research is needed to evaluate potential cardiac markers in terms of cardiotoxicity, by linking short-term changes in cardiac markers to longer term damage. Key to this is dialogue between specialists treating children with cancer and cardiologists treating adults to develop a framework that links early cardiac changes to later events. These results could then be incorporated in the evaluation of cardioprotectants. Research is also needed on novel measures of cardiac damage such as MRI and tissue Doppler, which may prove useful in determining the progression of myocardial damage, but are expensive and labour intensive.

An economic evaluation would be worthwhile to assess the cost-effectiveness of cardioprotective technologies should further evidence become available on their effectiveness and that of cardiac markers for quantification of cardiac damage, along with data to inform all the necessary elements of a model.

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Contribution of authors

J Bryant (Senior Research Fellow, SHTAC) developed the research protocol, assisted in the development of the search strategy, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence, drafted and edited the final report, and project managed the study. J Picot (Research Fellow, SHTAC) developed the research protocol, assessed studies for inclusion, extracted data from and quality assessed included studies, synthesised evidence and drafted the report. G Levitt (Consultant in Oncology, GOSH) developed the research protocol and drafted the report. I Sullivan (Consultant in Cardiology, GOSH) developed the research protocol and drafted the report. L Baxter (Research Fellow, SHTAC) extracted data from and quality assessed included studies, synthesised evidence and drafted the report. A Clegg (Principal Research Fellow and Director of SHTAC) developed the research protocol, assisted in the development of the search strategy, quality assessed included studies and drafted the report.

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39. Bauch M, Ester A, Kimura B, Victorica BE, Kedar A, Phillips MI. Atrial natriuretic peptide as a marker for doxorubicin-induced cardiotoxic effects. *Cancer* 1992;**69**:1492–7.
40. Hayakawa H, Komada Y, Hirayama M, Hori H, Ito M, Sakurai M. Plasma levels of natriuretic peptides in relation to doxorubicin-induced cardiotoxicity and cardiac function in children with cancer. *Med Pediatr Oncol* 2001;**37**:4–9.
41. Marina NM, Cochrane D, Harney E, Zomorodi K, Blaney S, Winick N, *et al*. Dose escalation and pharmacokinetics of pegylated liposomal doxorubicin (Doxil) in children with solid tumours: a pediatric oncology group study. *Clin Cancer Res* 2002;**8**:413–18.
42. Drummond M, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83.
43. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. New York: Oxford University Press; 1997.
44. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. A review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).

Appendix 1

Review methods from the research protocol

Methods for reviewing effectiveness

The a priori methods used for the review are outlined below. The sources of information used are outlined in Appendix 2.

Inclusion and exclusion criteria

- Technologies:
  - different dosage schedules for anthracyclines (aclarubicin, daunorubicin, doxorubicin, epirubicin, idarubicin)
  - different anthracycline derivatives (liposomal anthracyclines such as liposomal doxorubicin, mitozantrone)
  - cardioprotective technologies, such as dexrazoxane and amifostine during and after anthracycline use
  - antioxidant protection during and after anthracycline use, such as probucol and coenzyme Q
  - dietary glutamine supplementation during and after anthracycline use.

  Comparator intervention will be standard treatment (i.e. no additional cardioprotective agent) or an alternative cardioprotective technology.
- Participants should be children aged 0–18 years being treated for cancer with anthracyclines.
- Primary outcomes are subclinical cardiac failure, clinical (symptomatic) heart failure, arrhythmias and death. Tumour recurrence and length of remission information will be extracted where reported.
- Study design: RCTs; economic evaluations of cardioprotective technologies for use during or after anthracycline treatment in children.

Studies will be selected for inclusion through a two-stage process. The full literature search results will be screened by one reviewer and checked by a second reviewer to identify all citations that may meet the inclusion criteria. Full manuscripts of all selected citations will be retrieved and assessed independently by two reviewers against the inclusion criteria. An inclusion flowchart will be developed and used for each paper assessed. These criteria will be piloted on a sample of papers and agreement between reviewers will be measured. Any disagreements over study inclusion will be resolved by consensus or if necessary by arbitration by a third reviewer.

Data extraction

The extraction of studies' findings will be conducted independently by two reviewers using a predesigned and piloted data extraction form to avoid any errors. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Quality assessment strategy

The methodological quality of RCTs and controlled clinical trials will be assessed using recognised quality assessment tools.[25] Quality assessment of economic evaluations will be conducted using a checklist adapted from those developed by Drummond and colleagues[42,43] and Philips and colleagues.[44] Study quality will be assessed independently by two reviewers. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration involving a third reviewer.

Methods of analysis/synthesis

Studies will be synthesised through a narrative review with tabulation of results of included studies. The methods of data synthesis will be determined by the nature of the studies identified through searches and included in the review. Meta-analysis will be undertaken if appropriate. This will be judged in terms of quality and quantity of studies, as well as the effects of heterogeneity. Subgroup analysis will be undertaken where appropriate.

Appendix 2

Sources of information, including databases searched and search terms

Clinical effectiveness and cost-effectiveness

The following databases were searched for published studies and ongoing research.

Searches were restricted to the English language and human studies. Bibliographies of related papers were assessed for relevant studies.

Search terms used for anthracyclines were as follows:
Anthracyline(s)/, Antibiotics Anthracycline, Anthracyline derivative/, Anthracycline Antibiotic Agent/, Anthracycline adj 2 analogue$, Aclarubicin/, Daunorubicin/, daunorubicin derivative/, Doxorubicin/ , doxorubicin derivative/, Epirubicin/, epirubicin derivative, Idarubicin/, Idarubicinol/, Pirarubicin/, Pirarubicin derivative/, Mitoxantrone, Mitoxantrone derivative. Antineoplastic Combined chemotherapy protocols/ad administration & dosage, Anthracyclines/cb, Anthracycline derivative/cb, Anthracycline Antibiotic Agent/cb.

Search terms for cardioprotective technologies were as follows:
razoxane/, probucol/, ferric compounds/, oxidative stress/, oxidative reduction/, antioxidant(s)/, antioxidant activity/ oxidation reduction/, sodium hydrogen antiporter/, guanidine(s)/, vitamin/ vitamin e/, Ascorbic Acid/, Reactive Oxygen Species/, Phytoestrogen(s)/, Plant Extract(s)/, Isoflavone(s)/, Dietary Supplements/, Diet Supplementation/ Glutamine/, Glutathione/, Free Radical Scavenger(s)/, Free Radical(s)/, Polyunsaturated Fatty Acid/ Iron chelate/ Chelation Therapy/ Heart Protection/ Cardiotoxicity/pc Deferiprone/ Nutritional Support/ Iron Therapy/ Betacarotene/ Fish Oil/ (dexarazone or cardio?protect? or cardiac) adj sparing) or iron) adj chelator) or free) adj radical) or short) adj infusion$) or long) adj infusion$) or herceptin or guanidine$).ti,ab.

Databases searched	Clinical effectiveness: Issues or dates searched	Cost-effectiveness: Issues or dates searched
Cochrane Library (Database of Systematic Reviews and Controlled Trials Register)	Cochrane Library Issue 1, 2006 (9 January 2006)	
MEDLINE (OVID)	1966 to January 2006 (9 January 2006)	
EMBASE (OVID)	1980 to January 2006 (9 January 2006)	1980 to January 2006
Web of Science Proceedings	1970 to January 2006 (9 January 2006)	
NHS Economic Evaluations Database (NHS CRD databases)	1994 to January 2006 (9 January 2006)	1994 to January 2006 (9 January 2006)
NHS HTA database (NHS CRD databases)	All years (9 January 2006)	
NHS DARE database (NHS CRD databases)	All years (9 January 2006)	
National Research Register (NRR)	All years (9 January 2006)	
American Society for Clinical Oncology Abstracts database (ASCO) http://www.asco.org/ac	1995 to July 2005 (9 January 2006)	

Primary search terms for economic searches and outcome/risk were as follows:
Technology Assessment Biomedical Treatment Protocols/, Treatment Outcome/, Health Outcome/, Survival/, Cost effectiveness/, Health Economics/, Economic Evaluation/ Health Care Cost/,Cost/ Drug Cost/ Cost of Illness/ Cost Effectiveness Analysis/, Cost Utility Analysis/, Cost Benefit Analysis/ Cost Minimization Analysis/ Cost Control/, Follow up/, late effect$, follow up, fee(s) financ$ cost (effective$ or utlilty or benefit or minimi$), budget, economic(s), price or pricing pharmacoeconomic(s), resource use. (The subheading pe (this is the tag for pharmacoeconomics) was additionally appended to the drug terms)

Full search strategies are available upon request.

Appendix 3

List of excluded studies

Clinical effectiveness studies

Aviles A, Neri N, Nambo JM, Huerta-Guzman J, Talavera A, Cleto S. Late cardiac toxicity secondary to treatment in Hodgkin's disease. A study comparing doxorubicin, epirubicin and mitoxantrone in combined therapy. *Leuk Lymphoma* 2005;**46**:1023–8 (adults).

Berrak SG, Ewer MS, Jaffe N, Pearson P, Ried H, Zietz HA, *et al*. Doxorubicin cardiotoxicity in children: reduced incidence of cardiac dysfunction associated with continuous-infusion schedules. *Oncol Rep* 2001;**8**:611–14 (cohort study).

Bu'Lock FA, Gabriel HM, Oakhill A, Mott MG, Martin RP. Cardioprotection by ICRF187 against high dose anthracycline toxicity in children with malignant disease. *Br Heart J* 1993;**70**:185–8 (cohort study).

Burgert EO Jr, Nesbit ME, Garnsey LA, Gehan EA, Herrmann J, Vietti TJ, *et al*. Multimodal therapy for the management of nonpelvic, localized Ewing's sarcoma of bone: intergroup study IESS-II. *J Clin Oncol* 1990;**8**:1514–24 (multimodal therapy and not all children).

Chavez GA, Hernandez IM, Ollarve CF, Natera YM. Myocardial protection by L-carnitine in children treated with adriamycin. *Revista Latina de Cardiologia Euroamericana* 1997;**18**:208–14 (not randomised).

Ewer MS, Jaffe N, Ried H, Zietz HA, Benjamin RS. Doxorubicin cardiotoxicity in children: comparison of a consecutive divided daily dose administration schedule with single dose (rapid) infusion administration. *Med Pediatr Oncol* 1998;**31**:512–15 (not randomised).

Gupta M, Steinherz PG, Cheung N-K, Steinherz L. Late cardiotoxicity after bolus versus infusion anthracycline therapy for childhood cancers. *Med Pediatr Oncol* 2003;**40**:343–7 (cohort study).

Kraft J, Grille W, Appelt M, Hossfeld DK, Eichelbaum M, Koslowski B, *et al*. Effects of verapamil on anthracycline-induced cardiomyopathy: preliminary results of a prospective multicenter trial. *Haematol Blood Transfus* 1990;**33**:566–70 (adults).

Levitt GA, Dorup I, Sorensen K, Sullivan I. Does anthracycline administration by infusion in children affect late cardiotoxicity? *Br J Haematol* 2004;**124**:463–68 (not randomised).

Lipshultz SE, Colan SD, Gelber RD, Perez-Atayde AR, Sallan SE, Sanders SP. Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991;**324**:808–15 (cohort study).

Mladosievicova B, Foltinova A, Petrasova H, Bernadic M, Hulin I. Signal-averaged electrocardiography in survivors of Hodgkin's disease treated with and without dexrazoxane. *Neoplasma* 2001;**48**:61–5 (not randomised).

Myers C, Bonow R, Palmeri S, Jenkins J, Corden B, Locker G, *et al*. A randomized controlled trial assessing the prevention of doxorubicin cardiomyopathy by *N*-acetylcysteine. *Semin Oncol* 1983;**10**(1 Suppl 1):53–5 (adults).

Schiavetti A, Castello MA, Versacci P, Varrasso G, Padula A, Ventriglia F, *et al*. Use of ICRF-187 for prevention of anthracycline cardiotoxicity in children: preliminary results. *Pediatr Hematol Oncol* 1997;**14**:213–22 (not randomised).

Villani F, Galimberti M, Comazzi R, Crippa F. Evaluation of cardiac toxicity of idarubicin (4-demethoxydaunorubicin). *Euro J Cancer Clin Oncol* 1989;**25**:13–18 (adults).

Wexler LH, Andrich MP, Venzon D, Berg SL, Weaver-McClure L, Chen CC, *et al*. Randomized trial of the cardioprotective agent ICRF-187 in pediatric sarcoma patients treated with doxorubicin. *J Clin Oncol* 1996;**14**:362–72 (adults).

Cardiac marker studies

Fink FM, Genser N, Fink C, Falk M, Mair J, Maurer-Dengg K, *et al*. Cardiac troponin T and creatine kinase MB mass concentrations in children receiving anthracycline chemotherapy. *Med Pediatr Oncol* 1995;**25**:185–9 (no controls).

Kismet E, Varan A, Ayabakan C, Alehan D, Portakal O, Buyukpamukcu M. Serum troponin T levels and echocardiographic evaluation in children treated with doxorubicin. *Pediatr Blood Cancer* 2004;**42**:220–4 (no controls).

Koseoglu V, Berberoglu S, Karademir S, Kismet E, Yurttutan N, Demirkaya E, *et al*. Cardiac troponin I: is it a marker to detect cardiotoxicity in children treated with doxorubicin? *Turk J Pediatr* 2005;**47**:17–22 (no controls).

Kremer LCM, Bastiaansen BAJ, Offringa M, Lam J, Van Straalen JP, De Winter RJ, *et al*. Troponin T in the first 24 hours after the administration of chemotherapy and the detection of myocardial damage in children. *Eur J Cancer* 2002;**38**:686–9 (no controls).

Lipshultz SE, Rifai N, Sallan SE, Lipsitz SR, Dalton V, Sacks DB, *et al*. Predictive value of cardiac troponin T in

pediatric patients at risk for myocardial injury. *Circulation* 1997;**96**:2641–8 (no controls).

Mathew P, Suarez W, Kip K, Bayar E, Jasty R, Matloub Y, *et al*. Is there a potential role for serum cardiac troponin I as a marker for myocardial dysfunction in pediatric patients receiving anthracycline-based therapy? A pilot study. *Cancer Invest* 2001;**19**:352–9 (no controls).

Stohr W, Paulides M, Brecht I, Kremers A, Treuner J, Langer T, *et al*. Comparison of epirubicin and doxorubicin cardiotoxicity in children and adolescents treated within the German Cooperative Soft Tissue Sarcoma Study (CWS). *J Cancer Res Clin Oncol* 2006;**132**:35–40 (not prospective RCT).

Appendix 4

Research in progress identified from the National Research Register

A randomised Phase II study on the treatment of children and adolescents with refractory or relapsed acute myeloid leukaemia

Randomised control trial with random allocation to: [A] liposomal daunorubicin and [B] idarubicin. Patients will be randomised to either receive or not liposomal daunorubicin with the first course of FLAG chemotherapy for relapsed or refractory AML. All patients will then go on to have a BMT. Although this does not really represent a new approach and would be our treatment of choice anyway, all patients across Europe will now receive this standard therapy and the results will be recorded centrally in Germany. Participants will be children with relapsed or refractory AML. Outcomes remission rates and overall survival

Central Manchester and Manchester Children's University Hospitals NHS Trust
North West Regional Office
Start: 1 February 2004; end date:1 May 2007
NHS R&D Support Funding

SIOP Nephroblastoma Clinical Trial and Study-SIOP WT 2001

Randomised controlled trial. Random allocation to [a] treatment a [b] treatment b. To assess whether stage II and stage III tumours need treatment with two or three drugs. Standard treatment is with three drugs. However, an uncommon side-effect of doxorubicin is weakening of the heart muscle and therefore it is a drug we would like to reduce or avoid using in the treatment of Wilms' tumour. Outcome: 2-year event-free survival, with an event being a patient's relapse or death from any cause.

Paediatric Oncology Unit, Childrens Day Hospital, Leeds Teaching Hospitals NHS Trust, Beckett Street, Leeds LS9 7TF, UK
Northern/Yorkshire Regional Office
Start: 1 December 2001; End date:1 December 2008
NHS R&D Support Funding

A randomised Phase III study on the treatment of children and adolescents with refractory or relapsed acute myeloid leukaemia

Randomised test intervention versus standardised intervention. Each year in the UK, only about 20 to 25 paediatric patients with acute myeloid leukaemia (AML) will either be refractory to primary therapy or relapse following primary treatment. At present there is no standard approach to the further treatment of these patients. Most units will use schedules based on fludarabine and granulocyte colony-stimulating factor (G-CSF), referred to as the FLAG regimen. Some paediatricians add in the anthracycline drug idarubicin (FLAG-Ida). If the patient goes into second remission following usually two courses of FLAG ± Ida, the patient will then undergo some form of bone marrow transplant. The small number of suitable patients has made it impossible to design relevant studies at a national level. This study represents the first international approach to this rare clinical problem. The major aim of this study is to combine the resources of the major European paediatric leukaemia working parties and also some non-European countries, so that a meaningful study can be performed in an attempt to improve the outlook for this small but important group of patients. In the UK all refractory or relapsed paediatric patients will have already been treated on regimens, which include anthracycline drugs, usually mitoxantrone or daunorubicin. These anthracycline drugs are effective in AML but are cardiotoxic, particularly in children. For that reason many paediatricians use FLAG on its own, rather than FLAG-Ida, for relapsed or refractory AML patients. It is in this situation that the potentially less cardiotoxic anthracycline, DaunoXome, may offer the possibility of increased efficacy without excessive cardiotoxicity and with possible reduction in other side-effects as well.

The primary objective is to assess whether the addition of DaunoXome improves the efficacy of the FLAG regimen in paediatric patients with

refractory or relapsed AML. The secondary objectives are to determine the short- and long-term toxicity of FLAG-DaunoXome compared to FLAG alone and to determine the long-term outcome prospectively in a large group of children with refractory and relapsed AML. Subjects are also being asked for permission for surplus cells from diagnostic and monitoring samples to be stored for use in present or future research. At present the 'add on' research studies potentially available are to study minimal residual disease, cellular drug resistance and a study to assess the importance if any of Fanconi anaemia genes in the development of resistant AML. Participation in these 'add on' studies is not necessary for inclusion on the main study.

The Royal Marsden NHS Foundation Trust
Paediatrics, Royal Marsden NHS Trust, Downs Road, Sutton, Surrey SM2 5PT, UK
Start: 26 September 2003; end date: 1 September 2007
NHS R&D Support Funding

Appendix 5

Quality assessment of experimental studies

TABLE 8 *Quality criteria for assessment of experimental studies: CRD Report 4*[25]

1. Was the assignment to the treatment groups really random?
2. Was the treatment allocation concealed?
3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient blinded?
8. Were the point estimates and measure of variability presented for the primary outcome measure?
9. Did the analyses include an intention-to-treat analysis?
10. Were withdrawals and dropouts completely described?

TABLE 9 *Some instructions for using a checklist for RCTs*

Quality item	Coding	Explanation
1. Was the assignment to the treatment groups really random?		
Random sequence generation	Adequate Partial Inadequate Unknown	Adequate: random numbers table or computer and central office or coded packages Partial: (sealed) envelopes without further description or serially numbered opaque, sealed envelopes Inadequate: alternation, case record number, birth date or similar procedures Unknown: just the term 'randomised' or 'randomly allocated', etc.
2. Was the treatment allocation concealed?		
Concealment of randomisation The person(s) who decide on eligibility should not be able to know or be able to predict with reasonable accuracy to which treatment group a patient will be allocated. In trials that use good placebos this should normally be the case; however, different modes or timing of drug administration in combination with the use of small block sizes of known size may present opportunities for clinicians who are also involved in the inclusion procedure to make accurate guesses and selectively exclude eligible patients in the light of their most likely treatment allocation; in centres with very low inclusion frequencies combined with very brief follow-up times this may also present a potential problem because the outcome of the previous patient may serve as a predictor of the next likely allocation	Adequate Inadequate Unknown	Adequate: when a paper convinces you that allocation cannot be predicted (separate persons, placebo really indistinguishable, clever use of block sizes (large or variable). Adequate approaches might include centralised or pharmacy-controlled randomisation, serially numbered identical containers, on-site computer based system with a randomisation sequence that is not readable until allocation, and other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients Inadequate: this option is often difficult. You have to visualise the procedure and think how people might be able to circumvent it. Inadequate approaches might include use of alternation, case record numbers, birth dates or week days, open random numbers lists, serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation) and any other measures that cannot prevent foreknowledge of group allocation Unknown: no details in text. Disagreements or lack of clarity should be discussed in the review team

continued

TABLE 9 *Some instructions for using a checklist for RCTs (cont'd)*

Quality item	Coding	Explanation
3. Were the groups similar at baseline regarding the prognostic factors?		
Baseline characteristics Main aim is to enable the reviewer to see which patients were actually recruited. It enables one to get a rough idea on prognostic comparability. A real check on comparability requires multivariable stratification (seldom shown)	Reported Unknown	Consult the list of prognostic factors or baseline characteristics (not included in this appendix). Reviewer decides
4. Were the eligibility criteria specified?	Adequate Partial Inadequate Unknown	
Prestratification Consult the list of prognostic factors or baseline characteristics (not included in this appendix)	Adequate Partial Inadequate Unknown	*Single-centre study* Adequate: prestratification on at least one factor from the list or no prestratification if the number of patients exceeds a prespecified number Partial: leave judgement to reviewer Inadequate: stratification on a factor(s) not on our list or no stratification, whereas the number of patients is less than the prespecified number Unknown: no details in text and no way to deduce the procedure from the tables *Multicentre study* Adequate: must prestratify on centre. Within each centre the criteria for single centre studies also apply Partial: impossible option Inadequate: no prestratification on centre or violating the criteria for single-centre studies (see above) Unknown: no details in text and no way to deduce the procedure from the tables
5. Were outcome assessors blinded to the treatment allocation?		
Blinding of assessors The assessor may be the patient (self-report), the clinician (clinical scale, blood pressure, etc.) or, ideally, a third person or a panel. Very important in judgement of cause of death, but unimportant in judgement of death	Adequate Inadequate Unknown	Adequate: independent person or panel or (self) assessments in watertight double-blind conditions Inadequate: clinician is assessor in trial on drugs with clear side-effects or a different influence on laboratory results, ECGs etc. Unknown: no statements on procedures and not deducible
6. Was the care provider blinded?		
Blinding of caregivers Look out for good placebos (see, hear, taste, feel, smell), tricky unmasking side-effects accounting for the subjectivity of the outcome measurements and the accessibility of cointerventions by the caregivers	Adequate Partial Inadequate Unknown	Adequate: placebo described as 'indistinguishable' and procedures watertight (use your imagination with the 'cheat' in mind; e.g. statement that sensitive/unmasking laboratory results were kept separate from ward personnel) Partial: just 'double blind' in text and no further description of procedures or nature of the placebo Inadequate: wrong placebo (e.g. fructose in trial on ascorbic acid) Unknown: no details in text

continued

TABLE 9 *Some instructions for using a checklist for RCTs (cont'd)*

Quality item	Coding	Explanation
Cointerventions		
Register when they may have an impact on any of the outcome phenomena. Consult the list of cointerventions (not included in this appendix)	Adequate Partial Inadequate Unknown	Adequate: percentages of all relevant interventions in all groups Partial: one or more interventions omitted or omission of percentages in each group Inadequate: not deducible Unknown: no statements
7. Was the patient blinded?		
Blinding of patients This item is hard to define. Just the statement 'double blind' in the paper is really insufficient if the procedure to accomplish this is not described or reasonably deducible by the reviewer. Good placebos (see, hear, taste, feel, smell), tricky unmasking side-effects accounting for the subjectivity of the outcome measurements and the accessibility of cointerventions by the patient are required	Adequate Partial Inadequate Unknown	Adequate: placebo described as 'indistinguishable' and procedures watertight Partial: just 'double blind' in text and no further description of procedures or nature of the placebo Inadequate: wrong placebo Unknown: no details in text
Compliance Dosing errors and timing errors	Adequate Partial Inadequate Unknown	Adequate: Medication Event Monitoring System (MEMS or eDEM) Partial: blood samples, urine samples (use of indicator substances) Inadequate: pill count or self-report Unknown: not mentioned
Check on blinding Questionnaire for patients, caregivers, assessors and analysis of the results; the (early) timing is critical because the treatment effect may be the cause of unblinding, in which case it may be used as an outcome measure	Reported Unknown	Reviewer decides
8. Were the point estimates and measure of variability presented for the primary outcome measure?		
Results for the primary outcome measure	Adequate Partial Inadequate Unknown	Adequate: mean outcome in each group together with mean difference and its standard error (SE) or standard deviation (SD) or any CI around it or the possibility to calculate those from the paper. Survival curve with log rank test and patient numbers at later time points Partial: partially reported Inadequate: no SE or SD, or SD without *N* (SE = SD/*N*) Unknown: very unlikely
9. Did the analysis include an intention-to-treat analysis?		
ITT analysis Early dropout can make this very difficult. Strictest requirement is sensitivity analysis including early dropouts	Adequate Inadequate	Reviewers should not just look for the term ITT but assure themselves that the calculations were according to the ITT principle

continued

TABLE 9 *Some instructions for using a checklist for RCTs (cont'd)*

Quality item	Coding	Explanation
Dealing with missing values The percentage of missing values on potential confounders and outcome measurements (seldom given) is a rough estimate of a trial's quality. One can carry them forward, perform sensitivity analysis assuming the worst and best case scenarios, use statistical imputation techniques, etc. Note that the default option (deletion) assumes that the value is randomly missing, which seems seldom justified	Adequate Partial Inadequate Unknown	Adequate: percentage of missing values and distribution over the groups and procedure of handling this stated Partial: some statement on numbers or percentages Inadequate: wrong procedure (a matter of great debate) Unknown: no mention at all of missing data and not deducible from tables
Loss to follow-up This item examines both numbers and reasons; typically an item that needs checking in the methods section and the marginal totals in the tables. Note that it may differ for different outcome phenomena or time-points. Some reasons may be reasons given by the patient when asked and may not be the true reasons. There is no satisfactory solution for this	Adequate Partial Inadequate Unknown	Adequate: number randomised must be stated. Number(s) lost to follow-up (dropped out) stated or deducible (from tables) for each group and reasons summarised for each group Partial: numbers, but not the reasons (or vice versa) Inadequate: numbers randomised not stated or not specified for each group Unknown: no details in text

ITT, intention-to-treat.

Appendix 6

Quality assessment of observational studies

An assessment was used for included studies that were not RCTs. These quality criteria were adapted from Spitzer and colleagues.[26] The original checklist was modified to include items of particular relevance to assessing observational studies.

1. Does the trial use proper random assignment?
   A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g. random numbers table, computer generated) with allocation concealment.
2. Did the study use proper sampling?
   A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g. patients selected consecutively or randomly sampled).
3. Was the sample size adequate?
   Proper sample size enables adequately precise estimates of priority variables found to be significant (e.g. can compute CI within relatively small range or relatively small SEM).
4. Were the criteria for definition or measurement of outcomes objective or verifiable?
   Good outcome measures would be defined by clear methods for measuring outcomes (i.e. an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment?
   In studies with blind assessment those evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of subjects?
   Good eligibility criteria would use clear, public, verifiable characteristics that are applied for inclusion and exclusion.
7. Were attrition rates (%) provided?
   A study should report the number of patients who could not be contacted for outcome measures or later (e.g. dropouts or withdrawals due to treatment toxicity).
8. Were groups under comparison comparable?
   Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalisable?
   Generalisable results come from a sample population that is representative of the population to which results would be applied.

Appendix 7

Data extraction of clinical effectiveness studies

Study and design	Intervention	Participants	Outcome measures
Authors: Lipshultz *et al*.[27] Year: 2002 Countries: USA, Canada, Puerto Rico Study design: Multicentre RCT No. of centres: 10 Funding: In part NIH grants. No further information provided	*Comparisons of different interventions:* (1) DOX 360 mg/m^2 in 30-mg/m^2 doses every 3 weeks by bolus (within 1 hour) (2) DOX 360 mg/m^2 in 30-mg/m^2 doses every 3 weeks by continuous infusion (over 48 hours) Other interventions used: The protocol included more intense postremission therapy than previous protocols, dexamethasone was substituted for prednisone, and intensified asparaginase administration was prolonged from 20 to 30 weeks Patients were eligible to participate in five randomisations, one of which was to bolus or continuous DOX administration. The other four randomisations were: corticosteroids: 40 mg/m^2/day prednisolone or 6, 18 or 150 mg/m^2/day dexamethasone before the initiation of multiagent remission induction therapy. Asparaginase: 2500 IU/m^2 PEG asparaginase i.m. every other week for 15 doses or native 25,000 IU/m^2 *E. coli* asparaginase i.m. every week for 30 doses during the intensification phase of therapy 6-MP: high-dose 1000 mg/m^2 i.v. 6-MP delivered as a continuous infusion for 20 hours on weeks 1 and 2 of every 3-week chemotherapy cycle or conventional 50 mg/m^2/day oral 6-MP on	*Number of participants:* Recruitment $n = 386$ to the main study, but only 377 eligible to participate. Of these only the 240 classed as high risk (HR) were eligible for the randomisation to bolus or continuous DOX therapy Allocation $n = 240$, number randomised to each group unknown Analysis $n = 121$ (1) $n = 64$; (2) $n = 57$ *Sample attrition/dropout:* 63 HR patients of the initial 240 did not complete treatment protocol so no follow-up ECG available (five relapsed, six non-cardiac deaths, 46 dose reductions, five still receiving treatment, and one premature discontinuation) Of the 177 patients who did complete treatment, 56 sets of results were not included in the analysis: 32: echocardiographic data missing 24: echocardiographic data of too low quality Data are also missing from the final results tables, but no reasons are given for this. *Sample cross-overs:* None *Inclusion criteria for study entry:* Children aged 0–18 years with newly diagnosed ALL Only children categorised as HR were included in the randomisation to bolus or continuous infusion with DOX. *Exclusion criteria for study entry:* Mature B-cell ALL, pretreatment with other antileukaemia therapy *Characteristics of participants:* HR patients presented with one or more of the following pretreatment characteristics: (1) WBC count $\geq 20 \times 10^9$ cells/litre (20,000 cells/μl); (2) age between 1 year and <2 years or ≥ 9 years; (3) presence of leukaemia blasts in a cytocentrifuged CSF specimen regardless of CSF WBC count (CNS-2 or CNS-3); (4) presence of a mediastinal mass; or (5) T-cell immunophenotype. Patients with the Ph+ chromosome t(9;22)(q34; q11) were treated as HR patients, but they received an allogeneic BMT during first remission.	*Primary outcomes:* The primary outcome of the main study is not reported in this paper *Secondary outcomes:* Only one of the secondary outcomes, reduction in toxicity to DOX is reported in this paper. Cardiac outcomes (LVFS, LVEDd, LVEDs, LVWT and mass) were reported *Method of assessing outcomes:* Echocardiographic data submitted to a central technician for remeasurement *Adverse symptoms*: Not reported *Length of follow-up:* Varied between 0 and 56 months *Recruitment dates:* Participants to the main study recruited between 1991 and 1995. Centres informed about the follow-up echocardiographic data that should be submitted beginning in August 1996 and submissions complete by December 1996

continued

Study and design	Intervention	Participants	Outcome measures
	days 1–14 of every 3-week cycle during the first year of postremission therapy Cranial radiation: twice-daily fractions of 90 cGy (hyperfractionated) or once-daily fractions of 180 cGy (conventional)	The 121 HR patients whose echocardiographic data were evaluated had the following characteristics [median (range)]: (1) Age at diagnosis 5.2 years (0.4–17.9); follow-up since completion of therapy 17.8 months (0.0–52), cumulative DOX dose 336 mg/m^2 (228–360). % female 45.3 (2) Age at diagnosis 5.4 years (0.6–17.6); follow-up since completion of therapy 18.4 months (0.0–56), cumulative DOX dose 340 mg/m^2 (222–360); % female 42.1 DOX dose intensity was stated to be the same for both groups (no details provided) No patient had clinically evident cardiac disease before, during, or after chemotherapy	

BMT, bone-marrow transplantation; HR, high risk; NIH, National Institutes of Health.

Results

Secondary outcomes Cardiac characteristics at post-treatment echocardiogram	Bolus DOX infusion (n = 64)			Continuous doxorubicin infusion (n = 57)			p-Value
	No.	Median z-score	p^b	No.	Median z-score	p^b	p^c
LVFS	62	–0.47	0.008	55	–0.44	0.09	0.60
LVEDd	62	0.285	0.36	56	–0.015	0.55	0.79
LVEDs	62	0.365	0.01	56	0.345	0.02	0.72
LVWT	62	–0.525	<0.001	56	–0.690	<0.001	0.88
LV mass	59	–0.37	0.006	53	–0.270	0.02	0.50
LV contractility[a]	25	–0.70	0.006	22	–0.765	0.005	0.99
SBP[a]	27	–0.44	0.04	22	–0.095	0.24	0.67
DBP[a]	27	0.46	0.06	22	0.11	0.52	0.38
End-SBP[a]	27	–0.48	0.005	22	–0.795	<0.001	0.70
LV afterload[a]	27	0.33	0.24	22	–0.215	0.89	0.32
LV peak stress[a]	27	0.84	0.007	22	0.92	0.05	0.49
Heart rate[a]	25	0.24	0.17	22	0.465	0.10	0.70

z-Scores of LV measurements were based on measurements collected from a healthy population. A z-score of 0 is at the healthy population mean, whereas a z-score of 2 represents 2 SDs above normal mean.

[a] These results gathered only for patients treated at the Dana-Farber Cancer Institute (the lead centre where a total of 67 children were treated).

[b] p, Significance of difference from the normal population (in which, by definition, z-score = 0).

[c] p, Significance of difference between the two treatments.

continued

Differences between pre- and post-treatment echocardiographic z-scores	Bolus DOX infusion $n = 45$			Continuous (DOX) Infusion ($n = 44$)			p^c
	No.	Median z-score difference	p^b	No.	Median z-score difference	p^b	
LVEDd	36	-0.12	0.39	37	–0.23	0.06	0.41
LVWT	35	–0.32	0.11	35	–0.28	0.09	0.94
LVEDs	36	0.85	<0.001	37	0.38	0.04	0.20
LVFS	37	–2.34	<0.001	37	–1.77	<0.001	0.34
LV mass	35	–0.65	<0.001	31	–0.47	0.001	0.98

z-Scores of LV measurements were based on measurements collected from a healthy population. A *z*-score of 0 is at the healthy population mean, whereas a *z*-score of 2 represents 2 SDs above normal mean.
[b] *p*, Test that the median *z*-score is equal to zero for a given treatment.
[c] *p*, Test that the median *z*-scores are equal for the two treatments.

Additional	Bolus DOX infusion $n = 64$	Continuous DOX Infusion $n = 57$	*p*
5-year EFS excluding early treatment failures (%)	89.0 ± 3.9% (NS but believe ± SE)	87.3 ± 4.5% (NS but believe ± SE)	0.50

Additional	Bolus DOX infusion		Continuous DOX Infusion		*p*
	Events/patient (no.)	5-year EFS ± SE (%)	Events/patient (no.)	5-year EFS ± SE (%)	
5-year EFS including early treatment failures	20/102	80 ± 4	14/102	86 ± 4	0.23

Because late echocardiograms were needed and, therefore, early treatment failures were removed, the 5-year EFS reported for all high-risk patients ($n = 240$) on this protocol was not as high (81 ± 3%). The study authors report no significant differences between bolus and continuous infusion patients based on early treatment failures (no further information provided). There was no CHF in either group.

Methodological comments

- *Allocation to treatment groups:* Randomisations were performed centrally and occurred following enrolment, before the initiation of therapy. In the main study there were five randomisations, one of which was the randomisation to bolus or continuous DOX therapy.
- *Blinding:* Both the technician and echocardiographer were unaware of the treatment status of the patients during remeasurement of the echocardiograms.
- *Comparability of treatment groups:* Patients in the two arms similar in terms of five risk factors for late doxorubicin cardiotoxicity: age, duration of post-therapy follow-up, gender, cumulative DOX dose and dose intensity. No differences between groups in baseline echocardiography, both had abnormalities of LV structure and function, i.e. increased fractional shortening and mass, compared with healthy controls.
- *Method of data analysis:* (1) To ensure uniformity all echocardiograms were submitted by each institution to a central technician for remeasurement at the central location. Institutions were sent sample echocardiographic strip chart recordings to assist them in determining what information would be most useful to the technician during remeasurement. A random sample of 10% was spot-checked by one echocardiographer for quality assurance. Discrepant measurements of tracings were redone or discarded from the data set, depending on the quality of the tracing. Only 45 of the 64 subjects who received bolus DOX and 44 of the 57 who received continuous infusions were assessed at baseline. The study authors selected the post-treatment measurements of patients who had pretreatment measurements and found that the median *z*-scores of this group were similar to those of the entire group. Thus, they considered the subjects who did have pretreatment measurements to be a random sample of all subjects, and they expected no bias from using their data to estimate pre-DOX echocardiographic parameters. The similarity also suggested to the study authors that the pre-treatment and post-treatment differences from the entire patient data set are an unbiased estimate of the true differences in the population.
- *Sample size/power calculation:* The primary efficacy of the main study (not reported in this publication) was defined prospectively as the standard-dose versus high-dose 6-MP. Given the smaller sample sizes available for the bolus or continuous DOX randomisation this comparison was designed to detect a reduction in toxicity. The DOX

continued

randomisation analysis was performed on approximately 60 patients in treatment group. The study authors report that this had an 80% power to detect a 0.5 SD difference between post median z-scores of echocardiographic abnormalities (LVFS, LVEDd, LVEDs, LVWT, and LV mass) using a Wilcoxon rank-sum test at a 5% level of significance. For the additional outcomes reported only for patients at the lead centre (LV contractility, SBP, DBP, end-SBP, LV afterload, LV peak stress, heart rate) where the report authors state there are approximately 30 patients per group (in fact only 22 and 25–27 per group) the study had an 80% power to detect a 1 SD difference between post median z-scores in the two treatment arms using a Wilcoxon rank-sum test at a 5% level of significance. The test for equal pre–post differences between the two treatment groups, with approximately 35 patients per group, had 80% power to detect a 1 SD difference between median pre–post differences across the two treatment groups using a Wilcoxon rank-sum test at a 5% level of significance. The study authors state that they believe anything less than a 1 SD difference (and particularly 0.5 SD difference for the main comparisons) is not clinically important, so they believed their study had sufficient power to find clinically meaningful differences.

- *Attrition/dropout:* The study authors described the reasons why there was no follow-up echocardiogram for 63 of the initial 240 HR patients. They also accounted for a further 56 sets of results that were not included in the analysis. However, for the echocardiographic abnormalities (LVFS, LVEDd, LVEDs, LVWT and LV mass) there are between two and five missing data points from the bolus infusion group, and between one and four missing data points from the continuous infusion group. Similarly, there are between eight and ten data points from the bolus infusion group, and between seven and 13 data points from the continuous infusion group missing from the differences between pre- and post-treatment echocardiographic z-score results. No explanation is given for these missing data.

General comments

- *Generalisability:* Specific patient group: high-risk ALL following defined protocol
- *Outcome measures:* Institutions were recontacted until sufficient data were submitted, reasons for unsubmitted data were provided or the period of data collection ended. Some centres called patients back for a follow-up echocardiogram specifically for this analysis.
- *Intercentre variability:* The study authors state that 46 patients at one centre received dose reductions before the last echocardiogram and could not be included in the analysis. This suggests that processes at this centre differed from the other nine centres. There is no other information to indicate how intercentre variability may have been minimised or controlled for. As all echocardiograms were submitted by each institution to the central location for remeasurement this eliminated any intercentre variability in the echocardiographic outcomes.
- *Conflict of interests:* Supported in part by three grants from the NIH. No further information provided and no conflict of interest declaration reported.

Quality criteria for assessment of experimental studies

Was the assignment to the treatment groups really random?	Unknown
Was the treatment allocation concealed?	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Reported only for the participants for whom there were outcome data
Were the eligibility criteria specified?	Adequate
Were outcome assessors blinded to the treatment allocation?	Adequate
Was the care provider blinded?	Unknown
Cointerventions	Inadequate
Was the patient blinded?	Unknown
Were the point estimates and measure of variability presented for the primary outcome measure?	Partial
Did the analyses include an intention-to-treat analysis?	Inadequate
Were withdrawals and dropouts completely described?	Inadequate

Study and design	Intervention	Participants	Outcome measures
Steinherz *et al.*[28] Year: 1993 Country: USA Study design: Four-arm pilot RCT No. of centres: 1 Funding: NR	*Comparisons of different interventions:* (1) Cyclophosphamide day 0, vincristine/prednisone day 1, DAUN push (bolus) day 2 and 3 (2) Cyclophosphamide day 0, vincristine/prednisone day 1, DAUN continuous infusion days 2 and 3 (48 hours) (3) DAUN push (bolus) day 0 and 1, vincristine/ prednisone day 2, cyclophosphamide day 2 (4) DAUN 48-hour infusion day 0 and 1, vincristine/prednisone/ cyclophosphamide day 2 Therapy after day 2 was identical, with the exception of anthracycline administration. Patients randomised to receive continuous infusion continued to receive the drug that way throughout maintenance unless their central line had to be removed temporarily due to infection or other reasons *Other interventions used:* Asparaginase therapy was spread out evenly over the induction and consolidation phases of therapy and continued weekly during the first cycle of maintenance. CNS irradiation was introduced at the first maintenance chemotherapy phase Patients who developed life-threatening complications after induction or consolidation and who were deemed by their physician not able to resume full protocol maintenance therapy were given standard maintenance consisting of daily 6-MP 75 mg/m^2, weekly oral methotrexate 25 mg/m^2 with monthly pulses of vincristine 1.5 mg/m^2, and prednisone 40 mg/m^2 until they were able to resume full protocol therapy. All such cases were included in the analysis The duration of therapy was 2 years of maintenance Consolidation therapy was reduced by 1 week (days 28–34 were eliminated) for the last six patients entered in the programme	*Number of participants:* Recruitment $n = 46$ Allocation $n = 44$ (1) $n = 11$; (2) $n = 9$; (3) $n = 11$; (4) $n = 13$ *Analysis:* Number of patients included in analysis varied (see Results section) *Sample attrition/dropout:* Two not randomised because of prolonged pretreatment with corticosteroids. Other dropouts not described *Sample cross-overs:* None *Inclusion criteria for study entry:* Children's Cancer Group criteria for the definition of risk group were used. Patients with newly diagnosed ALL who were at average or high risk of early relapse at diagnosis were eligible. The following four factors qualified a patient as having a high risk of early relapse: • age ⩽1 year or younger or ⩾10 years • leucocyte count ⩾50,000/μl • >25% L_2 FAB morphology • lymphomatous features *Exclusion criteria for study entry:* Good-risk children 2–10 years of age with leucocyte count <10,000/μl *Characteristics of participants:* Gender: 11 girls, 33 boys Age: range 1–19 years (median 7 years) with 28 (64%) ⩽2 years or ⩾10 years Risk: 31 high-risk, 13 average-risk patients Ethnicity: 32 (73%) white, 20% Hispanic, 5% Asian and 2% African–American	*Primary outcomes:* Kinetics of bone marrow cell reduction over the first 14 days of therapy *Secondary outcomes:* Echocardiograms *Method of assessing outcomes:* NR *Adverse symptoms:* Reported but not by treatment group *Length of follow-up:* Minimum 25 months *Recruitment dates:* November 1986 to February 1991

continued

Results

Outcomes	Group 1 DAUN bolus days 2 and 3 (n = 11)	Group 2 DAUN infusion days 2–3 (n = 9)	Group 3 DAUN bolus days 0 and 1 (n = 11)	Group 4 DAUN infusion days 0–1 (n = 13)	p-Value
Reduction in leukaemic cells day 0–2 (log_{10} cells/mm^2 of marrow biopsy)	–0.26 (n = 9)		–0.74 (n = 15)		0.03
Reduction in leukaemic cells day 0–7 (log_{10} cells/mm^2 of marrow biopsy)	–1.10 (n = 9)		–1.30 (n = 15)		0.03
Reduction in leukaemic cells day 0–14 (log_{10} cells/mm^2 of marrow biopsy)	–0.86 (n = 9)		–1.82 (n = 15)		0.03
Reduction in leukaemic cells day 0–2 (log_{10} cells/mm^2 of marrow biopsy)			–0.54 (n = 8)	–1.21 (n = 7)	0.03
Reduction in leukaemic cells day 0–7 (log_{10} cells/mm^2 of marrow biopsy)			–1.39 (n = 8)	–1.19 (n = 7)	ns
Reduction in leukaemic cells day 0–14 (log_{10} cells/mm^2 of marrow biopsy)			–1.78 (n = 8)	–1.83 (n = 7)	ns

With only two relapses to date, no effect on long-term EFS can be seen due to the differences in induction therapy.

Outcomes	Group 1 DAUN bolus days 2 and 3 (n = 11)	Group 3 DAUN bolus days 0 and 1 (n = 11)	Group 2 DAUN infusion days 2–3 (n = 9)	Group 4 DAUN infusion days 0–1 (n = 13)	p-Value
Significant deterioration in cardiac function (cardiac function monitored in 36 patients only)	4/18 (dose 120–585 mg/m^2, median dose 360 mg/m^2)		0/18 (dose 120–558 mg/m^2, median dose 400 mg/m^2)		0.10
Change in LVFS (median change)	–6.5 units		+1 unit		NR

Significant deterioration in cardiac function was defined as decrease of LVFS on two consecutive evaluations to abnormal levels (<29%) or by ⩾10 percentile units from the baseline level for that particular patient to borderline function (29%) at any time during treatment or follow-up.

Additional outcomes	Group 1	Group 2	Group 3	Group 4	p-Value
Deaths during induction			3		
Deaths after relapse			2		
Deaths during remission			1		

One other patient was removed from the study after remission and then received alternative therapy.

continued

Methodological comments

- *Allocation to treatment groups:* Stratified randomisation.
- *Blinding:* No information reported.
- *Comparability of treatment groups:* Stratified randomisation ensured even distribution with respect to risk group, degree of leucocyte count elevation, age, FAB morphology, and presence or absence of lymphoma syndrome.
- *Method of data analysis:* The methods by which data were collected and analysed are not reported. Event-free survival EFS and disease-free survival were estimated by the method of Kaplan–Meier. Differences between groups were tested using the log-rank statistic. The non-parametric Wilcoxon rank test was used for the statistical evaluation of the cell kinetic data. Comparison between proportions tested using Fisher's exact test.
- *Sample size/power calculation:* The authors state that in this pilot study they were not trying to demonstrate superiority for the infusion.
- *Attrition/dropout:* There were six deaths at different stages of the study: three died during the induction phase of treatment, two relapsed and subsequently died, and one died during remission. One other patient was removed from the study after remission and then received alternative therapy. The authors did not report which treatment groups these patients had been assigned to. Some of the results present data from only 24 of 44 and 36 of 44 patients so it is clear that, in addition to the deaths and one patient removed, other data were not available, but the reasons for this are unknown.

General comments

- *Generalisability:* Children with ALL on defined protocol. Small study.
- *Outcome measures:* Kinetics of bone-marrow cell reduction measured by bone-marrow aspiration and biopsy on days 0, 2, 7 and 14.
- *Intercentre variability:* NA
- *Conflict of interests:* Source of funding not reported and no statement regarding potential conflicts of interest made.

Quality criteria for assessment of experimental studies

Was the assignment to the treatment groups really random?	Unknown
Was the treatment allocation concealed?	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Unknown
Were the eligibility criteria specified?	Adequate
Were outcome assessors blinded to the treatment allocation?	Unknown
Was the care provider blinded?	Unknown
Cointerventions	Adequate
Was the patient blinded?	Unknown
Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate
Did the analyses include an intention-to-treat analysis?	Inadequate
Were withdrawals and dropouts completely described?	Inadequate

Study and design	Intervention	Participants	Outcome measures
Authors: Iarussi *et al*.[29] Years: 1994 Country: Italy Study design: RCT No. of centres: 1 (although not stated explicitly) Funding: NR	*Comparisons of different interventions:* (1) CoQ_{10} 100 mg by mouth twice daily (2) No CoQ_{10} treatment *Other interventions used:* Patients with ALL were treated with AEIOP ALL protocols (1991) fixing anthracycline at different cumulative doses in relation to the risk. The cumulative dose was fixed at 240 mg/m^2 (120 mg/m^2 daunorubicin and 120 mg/m^2 adryblastin) in the standard-risk and high-risk groups. Only DAUN was used at a cumulative dose of 270 mg/m^2 in the very high-risk group. Patients with NHL were treated according to SFOP LMB protocols (Protocols of the Société Française d'Oncologie Pédiatrique for lymphome malins de Burkitt), fixing an adryblastin cumulative dose at 180 mg/m^2 at stages II and III and 210 mg/m^2 at stage IV	*Number of participants:* $n = 20$ (1) $n = 10$; (2) $n = 10$ *Sample attrition/dropout:* Not specifically reported, but it appears that there were no dropouts *Sample cross-overs:* None *Inclusion criteria for study entry:* Children or young people with ALL or NHL. No further information provided *Exclusion criteria for study entry:* NR *Characteristics of participants:* (1): Mean age 5.6 years (range 3–12 years, eight with ALL and two with NHL, cumulative anthracycline dose range 210–270 mg/m^2 (mean 240 ± 20.0) (2): Mean age 5.1 years (range 1–15 years), nine with ALL and one with NHL, cumulative anthracycline dose range 210–270 mg/m^2 (mean 252.0 ± 20.1) Authors state no statistically significant differences of echocardiographic parameters found in the two groups at baseline	*Primary outcomes:* LV global function and LV regional wall motion *Method of assessing outcomes:* Echocardiography performed according to the recommendations of the American Society of Echocardiography *Adverse symptoms:* NR *Length of follow-up:* NR *Recruitment dates:* NR

Results

Primary outcomes	Group 1: intervention mean ± SD			Group 2: Control mean ± SD			*p*-Value
	Baseline	180 mg/m^2	End therapy	Baseline	180 mg/m^2	End therapy	
LVFS (%)	40.36 ± 4.6 Statistically lower ($p < 0.05$) than end value, but no difference detected vs 180 mg/m^2 value	39.67 ± 5.66 No difference detected vs end value	35.82 ± 5.02	39.89 ± 4.37 Statistically lower ($p < 0.03$) than 180 mg/m^2 value and higher significant difference ($p < 0.002$) detected vs end value	35.85 ± 3.18	33.43 ± 3.46	Mean % LVFS described as significantly lower in group 1 compared to the mean value in group 2, but no *p*-value reported

Note that there is contradictory reporting in the paper. Abstract states % LVFS decreased from baseline (40.36 ± 4.6) to end value (35.82 ± 5.02) ($p < 0.05$) in group I; % LVFS decreased from baseline (39.89 ± 4.37) to end value (33.43 ± 3.46) ($p < 0.002$) in group II. In main body of text results reported as above. LVFS parameter never less than normal (⩾28%).

continued

LVFS decreased at the end of therapy, *n* (%)		***n* = 7 (70%)**			**n=8 (80%)**		**No *p*-value reported**
Septal wall thickness (SWT) %	44.10 ± 13.2	43.11 ± 14.4	40.10 ± 15.3	46.10 ± 10.1 Statistically lower ($p<0.01$) than end value	45.2 ± 14.53 No difference detected vs end value	27.00 ± 18.54	No between group comparison reported. No statistically significant differences between any of the group 1 values
Note that there is contradictory reporting in the paper. Abstract states % SWT decreased only in group 2 from baseline (46.10 ± 10.1) to end of therapy (27.00 ± 18.54) ($p < 0.01$).							
SWT decreased at the end of therapy, *n* (%)		***n* = 5 (50%)**			***n* = 9 (90%)**		**No *p*-value reported**
Septal wall motion abnormalities (*n*/*N*)		0/10			2/10		No *p*-value reported
Left ventricular posterior wall thickening (LVPWT) %	63.00 ± 15.5	62.50 ± 19.90	61.25 ± 18.40	65.50 ± 19.90	58.00 ± 10.40	57.13 ± 14.40	No significant changes within groups and no between-group comparison reported

Echocardiology was performed in both groups before, at a cumulative dose of 180 mg/m^2 and at the end of therapy with anthracyclines.
% LVFS = 100 × (LVIDd – LVIDs)/LVIDd
% LVPWT = 100 × (LVPWTs – LVPWTd)/LVPWTd

where LVIDd is left ventricular internal dimension at end-diastole, LVIDs is left ventricular internal dimension at end-systole, LVPWTs is left ventricular posterior wall thickness at end-systole, and LVPWTd is left ventricular posterior wall thickness at end-diastole.

Methodological comments

- *Allocation to treatment groups:* Block randomisation was used to assign the patients to the two groups, but no further details are given.
- *Blinding:* Whether or not blinding took place is not specifically reported. However, informed consent was only obtained from the parents of group 1 children before starting treatment with CoQ, which suggests that treating physicians and parents were not blinded to treatment group allocation.
- *Comparability of treatment groups:* The authors of this study do not state whether they believe the groups to be comparable. From the limited information that is provided in the paper the groups seem to be comparable in terms of age and cumulative dose of anthracyclines received. No information is provided to indicate whether disease severity was comparable between the two groups.
- *Method of data analysis:* Although echocardiography was performed according to the recommendations of the American Society of Echocardiography, no details are provided regarding who performed the measurements. Statistical analysis was performed using properly paired and unpaired Student's *t*-test.
- *Sample size/power calculation:* NR.
- *Attrition/dropout:* NR, but appears from results that there were no dropouts.

continued

General comments

- *Generalisability:* Children with ALL or NHL on defined protocols. Small study.
- *Outcome measures:* Echocardiology was performed in both groups before, at a cumulative dose of 180 mg/m^2 and at the end of therapy with anthracyclines.
- *Intercentre variability:* NA.
- *Conflict of interests:* No information regarding funding of the study is provided and no statements are made declaring whether any of the authors had a conflict of interest.

Quality criteria for assessment of experimental studies

Was the assignment to the treatment groups really random?	Unknown
Was the treatment allocation concealed?	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Reported
Were the eligibility criteria specified?	Partial
Were outcome assessors blinded to the treatment allocation?	Unknown
Was the care provider blinded?	Unknown
Cointerventions	Partial
Was the patient blinded?	Unknown
Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
Did the analyses include an intention-to-treat analysis?	Adequate
Were withdrawals and dropouts completely described?	Adequate

Study and design	Intervention	Participants	Outcome measures
Authors: Lipshultz *et al.*[30] Year: 2004 Country: USA Study design: RCT No. of centres: NR Funding: Grants from NIH, Pfizer and Roche Diagnostics	*Comparisons of different interventions:* (1) DOX alone (2×30 mg/m^2 during remission induction, then eight more doses of 30 mg/m^2 every 3 weeks during induction therapy (cumulative dose 300 mg/m^2). No DOX after 9 months (2) DZX (300 mg/m^2) followed by DOX (as above) *Other interventions used:* Multiagent chemotherapy and CNS radiation	*Number of participants:* 213 enrolled. 13 not randomised (1) DOX: 101; (2) DZX + DOX: 105 *Sample attrition/dropout:* Nine patients (five DOX and four DZX+DOX) did not have complete remission. 39 (20 DOX and 19 DZX+DOX) did not have data on cTnT values at time of analysis. Remaining 158 patients were cohort for cTnT analyses *Sample cross-overs:* none *Inclusion criteria for study entry:* Aged <18 years, newly diagnosed untreated high-risk ALL *Exclusion criteria for study entry:* Standard-risk patients (defined as age between 1 and 10, WBC <50,000 cells/mm^3 at presentation, and the absence of T-cell markers, an anterior mediastinal mass and CNS disease) *Characteristics of participants:* Median age at diagnosis (years): DOX: 7.3; DZX + DOX: 7.5 Gender (M/F): DOX: 56/45; DZX + DOX: 64/41 Received less than median dose of DOX (300 mg/m^2): DOX: 26/96 (27%); DZX + DOX: 19/101 (19%) cTnT samples: Median no./patient: DOX: 15.0; DZX + DOX: 15.1 Total no. that could be evaluated: DOX: 1139; DZX + DOX: 1238	*Primary outcomes:* cTnT levels *Secondary outcomes:* Echocardiograms; EFS *Method of assessing outcomes:* cTnT at diagnosis, daily after induction doses of DOX, 7 days after a dose of DOX during induction therapy, and at completion of therapy. Serum assayed at central core laboratory. Evaluated as elevated (>0.01 ng/ml) or extremely elevated (>0.025 ng/ml). Echocardiograms before, during and after DOX therapy for subset of patients. Consisted of two-dimensional echocardiography and Doppler evaluation. Fractional shortening and stress-velocity index were measured *Dose-limiting adverse symptoms:* None *Length of follow-up:* Median 2.7 years *Recruitment dates:* January 1996 to September 2000

Results

Primary outcomes	DOX		DZX + DOX		*p*-Value
cTnT	**No. with finding/ total no.**	**% (95% CI)**	**No. with finding/ total no.**	**% (95% CI)**	
Any elevation	38/76	50 (38 to 62)	17/82	21 (13 to 31)	<0.001
During DOX treatment	35/76	46 (35 to 58)	12/80	15 (8 to 25)	<0.001
After DOX treatment ended	11/29	38 (21 to 58)	5/29	17 (6 to 36)	0.14
Multiple elevations	28/76	37 (26 to 49)	10/82	12 (6 to 21)	<0.001
Any extreme elevation	24/76	32 (21 to 43)	8/82	10 (4 to 18)	<0.001
Multiple extreme elevations	15/76	20 (11 to 30)	6/82	7 (3 to 15)	0.03
No pretreatment elevations subgroup results	71/76		75/82		
Any subsequent elevation	33/71	46 (34 to 58)	10/75	13 (7 to 23)	<0.001
Any elevation during DOX treatment	32/71	45 (33 to 57)	9/74	12 (6 to 22)	<0.001
Any elevation after DOX treatment	10/27	37 (19 to 58)	4/26	15 (4 to 35)	0.12

continued

Primary outcomes cTnT	DOX No. with finding/ total no.	DZX + DOX % (95% CI)	*p*-Value No. with finding/ total no.	% (95% CI)	
Multiple elevations	24/71	34 (23 to 46)	5/75	7 (2 to 15)	<0.001
Any extreme elevations	21/71	30 (19 to 42)	4/75	5 (1 to 13)	<0.001
Multiple extreme elevations	15/71	21 (12 to 32)	4/75	5 (1 to 13)	0.006
Timings of elevations[a] (%)					
(read from graph)					
Overall	50		21		<0.001
Before treatment	9		12		0.77
0–60 days of DOX	9		11		0.99
61–120 days of DOX	22		8		0.06
121–180 days of DOX	38		8		<0.001
181–240 days of DOX	46		7		<0.001

Elevated cTnT level >0.01 ng/ml; extremely elevated cTnT >0.025 ng/ml.
10% of children for whom cTnT levels were measured before DOX therapy had elevated levels. They had a higher rate of elevated levels after treatment began compared with those who did not have elevated levels before treatment (73% vs 27%, $p = 0.004$) and of extremely elevated levels (58% vs 17%, $p = 0.003$).
[a] Timings of elevations results were for patients with at least one elevated cTnT level during the specified intervals. Patients in the DOX group had a higher rate of elevation compared with those in the DOX + DZX group ($p = 0.003$). The same pattern was evident for differences in the incident of extremely elevated cTnT levels over time.

Secondary outcomes Echocardiographic data	DOX	DZX + DOX
Median no. per patient	2.0	3.0
Before DOX treatment	Normal LVFS (84 echograms, mean *z*-score 0.19, $p = 0.51$) Normal contractility (22 echograms, mean z score –0.02, $p = 0.96$) Slight LV dilatation (79 echograms, mean *z*-score 0.28, $p = 0.03$)	
After DOX treatment (164 echograms, median 198 days after therapy completion)	Depressed LVFS (91 echograms, mean *z*-score –1.06, $p < 0.001$) Depressed contractility (29 echograms, mean *z*-score –0.82, $p = 0.02$) Normal LV dimension (89 echograms, mean *z*-score 0.01, $p = 0.92$)	

462 echocardiograms were obtained for patients for whom cTnT data were available and who had a complete remission. No significant differences between DOX and DZX + DOX groups in mean LV dimension, fractional shortening or contractility before, during or after DOX therapy. Fractional shortening significantly depressed in both groups during and after therapy.

	DOX	DZX + DOX	*p*-Value
EFS rate at 2.5 years	83%	83%	0.87
Continuous complete remission	82/101 (81%)	85/105 (81%)	ns

Additional prognostic factors

Covariates were: gender (male vs female), race (white vs non-white), age (<10 vs ⩾10 years), cumulative dose of DOX (<300 vs ⩾300 mg/m^2)

Logistic regression analysis to determine covariates associated with elevated cTnT. None significant.

Methodological comments

- *Allocation to treatment groups:* Permuted-block design carried out centrally before any therapy received.
- *Blinding:* Local centres and patients not blinded to assignment. Central investigators performing cTnT measurement and echocardiographic evaluations remained blinded throughout study.
- *Comparability of treatment groups:* No difference between groups with respect to baseline characteristics.
- *Method of data analysis:* Fisher's exact test and the Kruskal–Wallis test for comparison of baseline characteristics and cTnT levels between treatment groups. Logistic regression analysis to identify covariates associated with elevates cTnT levels. EFS estimated by Kaplan–Meier method, with data on the time to event censored for patients who were in complete

continued

continuous remission at the time of data analysis. Echocardiographic data analysed by *t*-tests and repeated measures analysis. To adjust for changes associated with growth, *z*-scores calculated (number of standard deviations a measurement is above or below the predicted value) by dividing the differences between a child's observed cardiac outcome and normal predicted value by the standard deviation of a distribution of normal values (using 285 children evaluated at same centre and in same manner). *z*-Scores for LV dimension were adjusted for body surface area, and those for fractional shortening for age. Two-sided *p*-values reported.
- *Sample size/power calculation:* NR
- *Attrition/dropout:* Reported.

General comments
- *Generalisability:* Inclusion criteria specified.
- *Outcome measures:* Appropriate.
- *Intercentre variability:* Not reported how many centres involved, no report of inter-centre variability.
- *Conflict of interests:* Reported.

Quality criteria for assessment of experimental studies

Was the assignment to the treatment groups really random?	Adequate
Was the treatment allocation concealed?	Unknown
Were the groups similar at baseline in terms of prognostic factors?	Reported
Were the eligibility criteria specified?	Adequate
Were outcome assessors blinded to the treatment allocation?	Adequate
Was the care provider blinded?	No
Cointerventions	Partial
Was the patient blinded?	No
Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
Did the analyses include an intention-to-treat analysis?	Inadequate
Were withdrawals and dropouts completely described?	Adequate

Appendix 8

Data extraction of cardiac marker studies

Study and design	Intervention	Participants	Outcome measures
Authors: Bauch *et al.*[39] Year: 1992 Country: USA Study design: Cohort Funding: NIH grant	*Intervention:* Combination chemotherapy, including doxorubicin hydrochloride (Adriamycin); the total cumulative dose ranged between 80 and 480 mg/m^2 Variations in time intervals between administration of dose and obtaining ANP levels *Control:* Two groups of controls: (1) Treatment controls: ten oncological patients, undergoing chemotherapy but never received DOX (2) Untreated healthy controls, 11 healthy volunteers	*Number of participants:* Intervention: 16 patients *Control:* (1) ten patients; (2) 11 healthy volunteers *Sample attrition/dropout:* NR *Sample cross-overs:* NA *Inclusion criteria for study entry:* NR *Exclusion criteria for study entry:* Other illnesses such as infections *Characteristics of participants:* Intervention: nine female, seven male, 5–19 years of age, mean 13.3 years Food, salt and oral fluid intakes were unrestricted. Patients did not have hepatic or renal dysfunction, and none of them received mediastinal radiation therapy *Control:* (1) six female; four male, 3–23 years of age, mean 10.5 years; (2) eight female, three male controls, 24 to 38 years of age	Levels of plasma ANP (pANP); does this become elevated during doxorubicin therapy as a result of changes in ventricular diastolic function, and before LVEF is decreased as a sign of cardiac damage? LVEF measured by radionuclide angiography before administration of DOX and compared with ANP levels Blood samples were obtained by venipuncture or from central lines every time the children came to the outpatient clinics or admitted to hospital *Adverse symptoms:* Two patients went into CHF, one died *Length of follow-up:* Study period was 7 months *Recruitment dates:* NR

Results

Outcomes	Group I (n = 6)	Group II (n = 10)	Treatment without DOX (n = 10)	Healthy volunteers (n = 11)	p-Value
ANP levels (pg/ml), mean ± SE	136.2 ± 23.3	33.3 ± 4.1	34.6 ± 7.9	25.1 ± 2.4	< 0.01, group I significantly higher than any other group

No significant differences between group 2 and controls and between controls.
Six children (37.5%) had transiently elevated plasma levels of ANP 3 SD above control levels, and ten patients had no increase in ANP. Patients who had been treated with DOX were then put into two groups for additional analysis, one with high ANP levels recorded at some time after DOX (group I, n = 6 patients) and one with normal ANP levels throughout treatment (group II, n = 10 patients). The data were then compared with those of the two control groups (see above). Group I is the highest levels for each patient averaged. In the controls the mean pANP level is used.
In the group with high ANP levels, all six children had received the highest cumulative doses of DOX (200–480 mg^2). In group II nine out of ten patients had received < 160 mg/m^2 of DOX. The other patient in this group had tolerated a larger cumulative dose without any significant changes in ANP levels.
To determine whether the higher values of group I were time dependent, data from multiple samples were plotted, as time from last dose, and curves were fitted by the Stineman interpolation to the data points. In group I patients, ANP levels were time dependent and a pANP peak was found 19–24 days after group I had received a dose. There was no such peak in group II, and when ANP levels in that time-frame were compared, the two groups were significantly different ($p < 0.05$).

continued

LVEF	**See below**

LVEFs of groups I and II were compared, and no significant difference was found between the groups. No results are given. LVEF measured before drug administered. Individual LVEF studies showed no significant decline in ejection fraction in any of the children. Despite the lack of evidence of cardiotoxic effects by LVEF, CHF developed in two patients, both of whom were in the group with high ANP levels. One case is described: a 5-year-old boy with T-cell leukaemia. ANP levels increased to 208 pg/ml but LVEF remained unchanged at 58%. This patient lived; LVEF is not given for patient who died.

Methodological comments

- *Allocation to treatment groups:* NA
- *Blinding*: NR
- *Comparability of treatment groups:* One group treated with chemotherapy including DOX. Group of 16, aged between 5 and 19 years. One control group had received chemotherapy without DOX, aged 3–23 years. Mean ages 13.3 years and 10.5 years, respectively. Second control group: healthy adults aged 24–38 years.
- *Method of data analysis:* Student's *t*-test and analysis of variance. A *p*-value <0.05 was considered significant. Consecutive levels were analysed by curve fitting with the interpolation of Stineman.
- *Sample size/power calculation:* NA
- *Attrition/dropout:* NR

General comments

- *Generalisability:* No inclusion criteria stated. Small group ($n = 16$), large range of cumulative dose (between 80 and 480 mg/m^2)
- *Outcome measures:* The outcome measures were relevant to the study area; LVEF measured before drug administered.
- *Inter-centre variability:* NA.
- *Conflict of interests:* NR. Funded by NIH grant HL 2335 to MI Phillips.

Quality criteria for assessment of observational studies (revised from Spitzer *et al.*)[26]

	Yes	**U/I/S**	**No**	**DK/NR**	**NA**	**Comments**
Proper random assignment					NA	
Proper sampling				NR		Sampling methods NR
Adequate sample size			N			16 in treatment group, 10 in treatment control, 11 in healthy control
Objective outcomes	Y					
Blind assessment				NR		Blind assessment NR
Objective eligibility criteria				NR		
Reported attrition				NR		
Comparability of groups			N			Treatment group 5–19 years, treatment control 3–23 years, healthy volunteers 24–38 years
Generalisability		U				No inclusion criteria stated. Small group (16), large range of cumulative dose (between 80 and 480 mg/m^2)

DK/NR, don't know/not reported; U/I/S, uncertain/incomplete/substandard.

Study and design	Intervention	Participants	Outcome measures
Authors: Hayakawa *et al.*[40] Year: 2001 Country: Japan Study design: Cohort/cross-sectional Number of centres: NA Funding: NR	*Intervention:* Combination chemotherapy including DOX; the total cumulative dose of DOX ranged between 42 and 696 mg/m^2 (mean 315 mg/m^2 median 314 mg/m^2) *Control:* Healthy control group; no treatment	*Number of participants:* Intervention: $n = 34$ Control: $n = 19$, healthy controls *Sample attrition/dropout:* None stated *Sample cross-overs:* NA *Inclusion criteria for study entry:* None stated *Exclusion criteria for study entry:* Patients who had received mediastinal radiation therapy, developed CHF or had other illnesses such as infections *Characteristics of participants:* 34 patients who had received their last dose of anthracycline >1 month previously and continued to be in complete remission. Aged 0.7–21.7 years mean age 11.5 years Healthy control group: $n = 19$, aged 4.1–16.4 years, mean 10.6 years. Normal cardiac function, and had not received any treatment affecting the heart, kidneys or fluid balance before and throughout the study period	Incidence of echocardiographically diagnosed DOX-induced cardiac dysfunction in Japanese children previously treated with cancer Elevated ANP and BNP levels in children with DOX-induced cardiac dysfunction Correlation between systolic and diastolic functions of left ventricle and plasma levels of natriuretic peptides *Method of assessing outcomes:* Levels of ANP and BNP were measured using double antibody radioimmunometric assay kits Pulsed-wave Doppler ad M-mode echocardiography were performed in a standard manner with a Hewlett Packard Sonos 2000 ultrasound system by a single observer *Adverse symptoms:* 8/34 patients had DOX induced cardiac dysfunction *Length of follow-up:* NR, but had received chemotherapy between 1994 and 1999, and had received their last dose >1 month previously, and continued to be in complete remission *Recruitment dates:* NR

Results

Outcomes	Intervention ($n = 34$)	Healthy control ($n = 19$)	*p*-Value
Incidence of DOX-induced cardiac dysfunction	8/34 (23.5%)	NA	
	Cardiac dysfunction	**Normal cardiac function**	
Mean cumulative dose (mg/m^2)	475 ± 177	274 ± 174	$p < 0.01$
	Anthracycline ≤300 mg/m^2	**Anthracycline >300 mg/m^2**	
Incidence of cardiac dysfunction	2/18 (11.1%)	6/16 (37.5%)	$p < 0.05$

There were no significant differences between the groups with normal cardiac function on echocardiography and cardiac dysfunction with regard to age or gender. The overall incidence of cardiac dysfunction was 23.5% and increased with increasing cumulative anthracycline dose. The authors note that one patient with 142 mg/m^2 cumulative anthracycline dose had diffuse hypokinesis of interventricular septum on echocardiography.

continued

	Intervention: (n = 34)		Normal, healthy controls (n = 19)	
	Cardiac dysfunction (n = 26)	**Normal cardiac function (n = 8)**		
ANP plasma levels (pg/ml), mean ± SD	28.8 ± 14.6	17.6 ± 8.6	14.8 ± 5.8	<0.01 (dysfunction vs control) <0.05 (dysfunction vs normal)
BNP plasma levels (pg/ml), mean ± SD	29.0 ± 31.2	9.0 ± 14.8	5.6 ± 3.8	<0.01 (dysfunction vs control) <0.05 (dysfunction vs normal)

The elevated ANP and BNP plasma levels, which were defined as greater than the mean + 2 SD, of the 19 healthy controls were >26 and 13 pg/ml, respectively. 3/8 patients with cardiac dysfunction had normal ANP and BNP plasma levels, whereas only 1/26 patients with normal cardiac function had elevated peptide levels. No correlation between the cumulative anthracycline dose and ANP plasma level was found. There is a tendency for BNP plasma level to correlate with the cumulative anthracycline dose. Since the authors found that ANP and BNP plasma levels were elevated in patients with cardiac dysfunction, they investigated correlations between these levels, and various indicators for left ventricle systolic or diastolic function, in patients with or without cardiac dysfunction.

	LVEF	**LVFS**	**Mean velocity of circumferential fibre shortening (mVcf)**	**Left ventricle time interval (LVSTI)**
BNP plasma levels	$r = -0.43$, $p < 0.01$	$r = -0.45$, $p < 0.01$	$r = -0.42$, $p < 0.01$	$r = 0.59$, $p < 0.01$
ANP plasma levels	$r = -0.32$, $p < 0.05$	$r = -0.34$, $p < 0.05$	NR	NR

Comments:

	Cardiac dysfunction	**Normal systolic function**	**Normal healthy controls**	***p*-Value**
Mean values of peak E filling velocity ± SD (m/s)	0.82 ± 0.15	0.70 ± 0.12	0.78 ± 0.16	ns
Mean values of peak A filling velocity ± SD (m/s)	0.54 ± 0.11	0.40 ± 0.11	0.40 ± 0.09	<0.05

	E/A ratio (>2) (7 patients)	**Normal E/A ratio**	
Mean values of ANP plasma level ± SD (pg/ml)	19.7 ± 8.6	19.8 ± 11.9	ns
Mean value of BNP plasma level ± SD (pg/ml)	18.0 ± 21.3	12.6 ± 21.6	ns

Peak A filling velocity in patients with cardiac dysfunction was elevated significantly, compared with normal health controls, and the patients with normal cardiac function ($p < 0.05$). Seven patients had an E/A ratio >2 and five of these seven patients had normal systolic function. No patient had an E/A ratio <1. There were no significant relationships between levels of natriuretic peptides and diastolic function.

continued

Methodological comments
- *Allocation to treatment groups:* NA.
- *Blinding:* NR.
- *Comparability of treatment groups:* One treatment group of 34. Control group: 19, age matched, healthy.
- *Method of data analysis:* Values were expressed as mean ± SD. The unpaired Student's *t*-test was used to assess differences between each group with respect to the plasma levels of ANP and BNP. The correlations between variables were studied using Pearson's correlation test. $p < 0.05$ was considered statistically significant.
- *Sample size/power calculation:* NA.
- *Attrition/dropout:* NR.

General comments
- *Generalisability:* No inclusion criteria stated. Small group (34).
- *Outcome measures:* Outcomes were relevant to study area.
- *Intercentre variability:* NA
- *Conflict of interests:* None stated.

Quality criteria for assessment of observational studies (revised from Spitzer *et al.*)[26]

	Yes	U/I/S	No	DK/NR	NA	Comments
Proper random assignment					NA	
Proper sampling				NR		Not discussed
Adequate sample size			N			34 in intervention group, 19 healthy controls
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria				NR		
Reported attrition				NR		
Comparability of groups				N		One treatment group of 34. Control group: 19, age matched, healthy
Generalisability		U				No inclusion criteria stated, other than were included if and continued to be in complete remission. Small group (34)

Study and design	Intervention	Participants	Outcome measures
Authors: Horino *et al*.[37] Year: 1983 Country: Japan Study design: Cohort No. of centres: NR Funding: Supported by a grant-in-aid for scientific research from the Ministry of Education, Science and Culture of Japan and from the Japan Medical Research Foundation	*Intervention:* (ADR+ group) Regimen including DOX (ADR). Given ADR every 4–7 weeks in a dose of 15–30 mg/m^2 body surface area and CoQ_{10} daily, 30–60 mg/m^2 *Control:* (ADR– group) Did not receive ADR Did not receive vitamin E (not clear whether this refers to both groups)	*Number of participants:* Intervention: $n = 21$ Control: $n = 44$ *Sample attrition/dropout:* NR *Sample cross-overs:* NR *Inclusion criteria for study entry:* NR *Exclusion criteria for study entry:* NR *Characteristics of participants:* Intervention: Patients with various types of neoplasms, age 1–16 years Control: Age-matched patients with the same kinds of neoplasms who did not receive ADR, children with unrelated disorders, and healthy adult volunteers The clinical and immunological aspects of the patients studied here have been published elsewhere	To determine the serum lipid peroxide values in children with various types of neoplasms treated with chemotherapeutic regimens including ADR, to try to identify their significance in the evaluation of adverse reactions to ADR *Method of assessing outcomes*: Echocardiography; capillary or venous blood was obtained 1–7 weeks after the last ADR injection, and the serum was separated and assayed on the same day *Adverse symptoms:* None stated *Length of follow-up:* NR *Recruitment dates:* NR

ADR, adriamycin.

Results

Serum lipid peroxide levels in children with malignancies treated with combination chemotherapies with or without ADR. It is not stated how these results are reported, i.e. mean ± SD or mean ± SE.

Primary outcomes	Age group	ADR+	ADR–	*p*-Value
Serum lipid peroxide level (malondialdehyde nmol/ml of serum)	0–2	2.65 ± 0.37 ($n = 5$)	1.68 ± 0.44 ($n = 7$)	< 0.01
	3–5	2.73 ± 0.23 ($n = 7$)[a]	2.00 ± 0.31 ($n = 7$)	<0.001
	6–10	2.23 ± 0.32 ($n = 8$)	1.78 ± 0.32 ($n = 14$)	<0.01
	11–15	1.95 ($n = 1$)	2.23 ± 0.31 ($n = 5$)	
	16 to adult	ND	2.59 ± 0.55 ($n = 11$)[b]	

[a] Serum lipid peroxide level of ADR+ age 3–5 years significantly higher than that in the ADR+ 6–10-year group ($p < 0.01$).
[b] Serum lipid peroxide level of ADR– age 16 to adult significantly higher than those of the ADR– 0–2, 3–5, and 6–10-year age groups ($p < 0.01$).

ADR+: Patients treated with chemotherapies including ADR. ADR–: patients treated with chemotherapies without ADR and controls.
All patients were examined periodically for LV performance by echocardiography (systolic time intervals, ejection fraction by Pombo's method, mean circumferential fibre shortening velocity). The results were all normal.
In the ADR– group, lipid peroxide values of patients with any type of neoplasm did not differ from one another or from those of patients with unrelated disorders or from the combined value.
The youngest three ADR+ groups showed significantly higher levels of serum lipid peroxide than the corresponding ADR– group.
There was no correlation between the serum lipid peroxide level and the number of injections or interval after the last ADR injection.
When CoQ_{10} was given to patients receiving ADR, lipid peroxide levels remained elevated.

continued

Methodological comments
- *Allocation to treatment groups:* NR.
- *Blinding:* NR.
- *Comparability of treatment groups*: Age matched, with one control group having "the same kinds of neoplasms"; the other two groups are children with unrelated disorders and healthy adults.
- *Method of data analysis:* Student's *t*-test.
- *Sample size/power calculation:* NA.
- *Attrition/dropout:* NR.

General comments
- *Generalisability:* Inclusion criteria not stated. 21 in treatment group, controls in total were 44.
- *Outcome measures:* Outcomes were relevant: echo results not discussed or reported, described as 'normal'
- *Inter-centre variability:* NA.
- Conflict of interests: None stated.

Quality criteria for assessment of observational studies (revised from Spitzer *et al.*)[26]

	Yes	U/I/S	No	DK/NR	NA	Comments
Proper random assignment					N/A	
Proper sampling				NR		Numbers in each group are not discussed, but are found in table of results
Adequate sample size			N			Small intervention group (21)
Objective outcomes	Y					
Blind assessment					NR	
Objective eligibility criteria				NR		Eligibility NR
Reported attrition				NR		
Comparability of groups			N			Control group comprised of patients receiving chemotherapy, patients with unrelated disorders and healthy volunteers (adults, age range not given)
Generalisability		U				Inclusion criteria not stated. 21 in treatment group, controls in total were 44. Control results were not reported separately

Study and design	Intervention	Participants	Outcome measures
Authors: Pinarli *et al*.[34] Year: 2005 Country: Turkey Study design: Cohort No. of centres: NR Funding: NR	Intervention: Three anthracycline types: DOX, DAUNO and EPI; Cumulative dose was range 90–490 mg/m^2 (mean 259 ± 127 mg/m^2). Patients were separated into two groups on the basis of the cumulative anthracycline dose received: group 1 <250 mg/m^2; group 2 >250 mg/m^2. This cut-off value was very close to the median value (260 mg/m^2) of the patients, and gave the opportunity to divide the patients into two equal groups. Group 1 mean cumulative dose 148.82 ± 46.49 mg/m^2; group 2 mean cumulative dose 369.70 ± 73.92 mg/m^2 In patients who received cyclophosphamide according to chemotherapy regimens, the dose of the drug was below the cardiotoxic range Two patients had received thoracic irradiation (2000 and 2400 cGy) All of the patients underwent detailed cardiac examination, resting electrocardiography, exercise testing and echocardiography *Control:* Healthy volunteers	*Number of participants:* Intervention: n = 34 patients Control: Echocardiographic controls, 12 healthy children Plasma BNP controls, 16 healthy children *Sample attrition/dropout:* NR. Some of the results are for 33 people, or half the controls (six), but does not state why this might be the case *Sample cross-overs:* NA *Inclusion criteria for study entry:* NR *Exclusion criteria for study entry:* NR *Characteristics of participants:* Intervention: 11 girls, 23 boys, age range 5–20 years (mean age 12.2 ± 3.44, median 12.5 years), had completed chemotherapy including anthracyclines. All asymptomatic and had no evidence of residual malignancy Control: The echocardiographic studies were compared with those of a group of 12 healthy children; seven girls, five boys (mean age 8.2 ± 3.0, median 6.75 years). Age range not given The age and size of these controls were smaller than of the patients; this inconvenience was eliminated by the adjustment of echocardiographic parameters according to body surface area The plasma BNP measurements were obtained from 16 healthy children, six girls, ten boys, age range 6–17 years (mean age 11.3 ± 3.64, median 11 years) All of the patients were haemodynamically stable: haemoglobin, heart rate and blood pressure of the patients were not statistically different from those of controls ($p > 0.05$). The mean cumulative doses of anthracyclines received by the patients in groups 1 and 2 were 148.82 ± 46.49 and 369.70 ± 73.92 mg/m^2, respectively	In this prospective study, cardiac functions of 34 children with solid tumours who received anthracyclines drugs were assessed *Method of assessing outcomes:* Electrocardiography, exercise electrocardiography testing, echocardiography, and plasma BNP levels measurements. BNP samples were obtained in the fasting state at 08.00 h (BNP1) and after exercise testing (BNP2) *Adverse symptoms:* None stated *Length of follow-up:* NR, but the mean time between last dose of drug and cardiac evaluation was 45.7 ± 27.9 months (3–122 months) *Recruitment dates*: NR

continued

Results

Electrocardiography: All of the patients showed normal sinus rhythm by 12-lead electrocardiography. Fourteen of them (eight in group 1 and six in group 2) revealed right axis deviation and two patients (in group 2) had Rr' waves in lead V1. Borderline LV hypertrophy was observed in only one patient (in group 2, cumulative anthracycline dose: 300 mg/m^2). Neither ST-segment–T-wave abnormalities nor decreased QRS voltage were seen. Prolongation of corrected QT interval (QT_C >0.44 SEC) was observed in two patients (0.47 and 0.49 s) in group 1, who had received cumulative anthracycline doses of 100 and 200 mg/m^2, respectively.

Electrocardiographic exercise testing: All of the patients completed the exercise testing without any complications. The duration of exercise of each patient was within normal limits. The mean maximum heart rate was 90.8% of the predicted value. ST segment depression of 1.1–2.1 mm was seen in five patients (two in group 1 and three in group 2).

Cardiac systolic functions of patients and controls (medians) (echocardiography)	**Intervention (*n* = 34)**	**Control (*n* = 12)**	***p*-Value**
LVDD (cm/m^2)	3.19	3.89	>0.05
LVDS (cm/m^2)	2.09	2.29	>0.05
EF (%)	72.50	75.50	>0.05
SF (%)	34.97	37.46	>0.05
WS (g/cm^2)	54.90	36.50	<0.001
CO (l/minute/m^2)	9.77	2.88	<0.001
LVPWS (cm)	1.16	1.10	>0.05

LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; EF, ejection fraction; SF, shortening fraction; WS, wall stress; CO, cardiac output; LVPWS, left ventricular posterior wall thickness.

Cardiac diastolic functions of patients and controls (medians)			
IVRT (ms)	71.04 (*n* = 34)	53.85 (*n* = 12)	<0.001
AT (ms)	64.22 (*n* = 34)	47.69 (*n* = 12)	0.006
DT (ms)	136.87 (*n* = 34)	155.78 (*n* = 12)	>0.05
E/A	1.78 (*n* = 34)	1.94 (*n* = 12)	>0.05
LV-E (m/s)	1.17 (*n* = 33)	1.02 (*n* = 12)	0.007
LV-A (m/s)	0.66 (*n* = 33)	0.51 (*n* = 12)	0.039
RV-E (m/s)	0.89 (*n* = 33)	0.73 (*n* = 6)	0.02
RV-A (m/s)	0.71 (*n* = 33)	0.34 (*n* = 6)	0.001

This is a different control group to that used for the BNP work.
IVRT, LV isovolumetric relaxation time; AT, acceleration time; DT, deceleration time; E/A, early peak filling velocity; LV-E, mitral early peak filling velocity; LV-A, mitral atrial peak filling velocity; RV-E, tricuspid early peak filling velocity; RV-A, tricuspid atrial peak filling velocity.
Although SF was reduced in one patient, (22.75%) and borderline in two others (30.26% and 30.93%), LVDD, LVDS, EF, SF and LVPWS were not significantly different between patients and controls ($p > 0.05$). CO and WS were significantly higher in the patients than in controls ($p < 0.001$). WS was negatively correlated with SF ($r = –0.34$, $p < 0.05$). LVDD, LVDS, EF, SF, LVPWS, CO and WS did not differ between groups. No significant relations were found between the total cumulative anthracycline dose, mean duration after treatment and cardiac systolic functions.
Diastolic filling patterns showed various abnormalities. Mitral E, mitral A, tricuspid atrial (TA) and tricuspid early (TE) peak filling velocity, AT, and IVRT were significantly higher than those of controls. Mitral and tricuspid systolic insufficiency respectively (MS and TS) were observed in 12 and 11 patients, respectively. Diastolic variables were not different between groups 1 and 2. The total cumulative dose was negatively correlated with AT ($r = –0.349$, $p = 0.043$).

Serum BNP levels in patient and control groups	**Intervention (*n* = 34)**	**Control (*n* = 16)**	***p*-Value**
BNP before exercise testing (pg/ml), mean ± SD	10.56 ± 10.22	4.09 ± 2.26	0.016
BNP before exercise testing (pg/ml), median	6.52	3.85	
BNP after exercise testing (pg/ml), mean ± SD	15.70 ± 14.0 (*n* = 31)	–	
BNP after exercise testing (pg/ml), median	9.08 (*n* = 31)		>0.05 (ns)

The mean BNP1 levels were significantly higher in patients (10.56 ± 10.22 pg/ml) than in the healthy controls (4.09 ± 2.26 pg/ml) ($p = 0.016$).
16/34 (47%, seven in group 1 and nine in group 2) exceeded the 95 percentile BNP concentration (9.27 pg/ml) of the controls.

continued

Although the mean BNP2 plasma levels (15.70 ± 14.0 pg/ml) were higher than the BNP1 plasma levels, this difference was not statistically significant ($p > 0.05$).
No correlation was found between BNP levels, the total cumulative anthracycline dose and the mean duration after the last dose of chemotherapy.

Methodological comments
- *Allocation to treatment groups:* NA.
- *Blinding:* NR.
- *Comparability of treatment groups:* Two control groups comprised of healthy children. Echo group younger and smaller; authors state they have accounted for this by adjusting parameters. BNP measurements were taken from a different group.
- *Method of data analysis:* Data are presented as means ± SD. Mann–Whitney *U*-test and Wilcoxon test were used to compare differences between and within groups. Spearman correlation test was used to evaluate correlation between parameters. A *p*-value of <0.05 was considered statistically significant.
- *Sample size/power calculation:* NR.
- *Attrition/dropout:* No information, but some results were reported for groups smaller than the patient and control groups.

General comments
- *Generalisability:* No inclusion/exclusion criteria reported.
- *Outcome measures:* Outcomes relevant to study area. Electrocardiography and electrocardiographic exercise testing no control group. BNP measurements taken from different people than the echo control (in healthy people).
- *Intercentre variability:* NA.
- *Conflict of interests:* Funding not stated.

Quality criteria for assessment of observational studies (revised from Spitzer *et al.*)[26]

	Yes	U/I/S	No	DK/NR	NA	Comments
Proper random assignment					NA	
Proper sampling				NR		
Adequate sample size			N			34 patients, 12 and 16 in controls
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria				NR		
Reported attrition			N			Some results reported where the group appears to be smaller than the numbers stated earlier for each group. No comment made about this
Comparability of groups		U				Two control groups comprised healthy children. Echo group younger and smaller; authors state they have accounted for this by adjusting parameters. BNP measurements were taken from a different group
Generalisability		U				No inclusion or exclusion criteria reported. Small groups

Study and design	Intervention	Participants	Outcome measures
Authors: Yaris *et al*.[36] Year: 2002 Country: Turkey Study design: Cohort No. of centres: NR Funding: No details	*Intervention:* Previously untreated patients were given a chemotherapy protocol containing DOX. DOX was administered by slow bolus injection in a dose of 60 mg/m^2 every 3 or 4 weeks in combination with vincristine, cyclophosphamide and high-dose methotrexate All patients received a total cumulative DOX dose of 300 mg/m^2 at the end of chemotherapy *Control:* Healthy volunteers. No treatment	*Number of participants*: Intervention: 15 previously untreated patients Control: 20 healthy children *Sample attrition/dropout:* NR *Sample cross-overs:* NR *Inclusion criteria for study entry:* NR *Exclusion criteria for study entry:* Patients who had cardiovascular disease or were using any drugs affecting the cardiovascular system were not included *Characteristics of participants:* Nine male and six female patients, mean age 9.04 ± 2.08 years (range 4–15 years). All were previously untreated with NHL. None of the cases received mediastinal radiotherapy Controls were groups of 20 healthy children, 12 male, eight female, mean age 9.8 ± 4.3 years (range 3–16 years). Age- and gender-matched volunteers, all in good health; none was receiving medication or on a special diet	Serum carnitine levels during treatment of doxorubicin; relationship between serum carnitine levels and cardiac dysfunction *Method of assessing outcomes:* Measurement of serum carnitine levels and cardiological evaluation were performed before therapy and 3 or 4 weeks after cumulative doses of both 180 mg/m^2 and 300 mg/m^2 Weight, height and body surface areas were obtained from every subject at each step Serum carnitine levels were measured by spectrophotometric method Cardiovascular evaluation consisted of physical examination, measurement of blood pressure, chest X-ray, electrocardiography, echocardiography including two-dimensional, M-mode, continuous and pulse-wave Doppler studies Normal values for EF and SF were considered as 64–83% and 28–40%, respectively. LV diastolic functions were evaluated by determination of the following parameters: mitral early filling velocity (mitral E), mitral late-atrial filling velocity (mitral A), mitral E/A ratio, LV IVRT, AT, DT, acceleration (AS) and deceleration slopes (DS) of early filling velocity, and total diastolic filling time (TDF). Three consecutive cardiac cycles were evaluated for all measurements and mean values were taken for further calculations *Adverse symptoms:* The authors did not observe any clinical manifestation of cardiotoxicity within the follow-up period *Length of follow-up:* Median 30 months (range 10–36 months) *Recruitment dates:* NR

continued

Results
Serum carnitine levels and cardiac functions of patients (data shown as mean ± SD)

	Patients: cumulative dose DOX (n = 15)			Healthy control group (n = 20)	p-Value
	0 (baseline)	180 mg/m^2	300 mg/m^2		
Carnitine (μmol/l)	31.05 ± 11.54	29.60 ± 12.85	28.43 ± 11.2	32.0 ± 8.2	
The mean carnitine values of the patient group before treatment, and after cumulative doses of 180 mg/m^2 and 300 mg/m^2 were not significantly different from the mean value of the control group. A decrease was observed in mean serum carnitine levels with the higher cumulative doses of drugs, although it was not statistically significant. There was no correlation between carnitine values and echocardiographic abnormalities.					
LVIDd (mm)	36.6 ± 6.3	39.1 ± 6.6[a]	40.3 ± 6.5[b]	39.4 ± 4.8	[a] $p = 0.02$ and [b] $p = 0.007$ vs baseline, so in both cases $p < 0.05$, but not significantly different from healthy controls
LVIDs (mm)	22.7 ± 3.6	24.9 ± 5.6	26.1 ± 4.6[c]	24.5 ± 4.7	[c] $p = 0.006$ vs baseline so $p < 0.05$, but not significantly different from healthy controls
EF (%) (normal range 64–83%)	62.2 ± 3.09	68.5 ± 4.9	66.0 ± 5.4[d]	70.1 ± 4.8	[d] $p = 0.04$ for vs healthy controls, so $p < 0.05$, but remains within normal limits
After the 300 mg/m^2 cumulative dose EF was decreased in seven patients. The reduction was >10% in three patients.					
SF (%) (normal range 28–40%)	38.0 ± 2.6	37.7 ± 3.7	35.5 ± 3.1[e]	39.1 ± 3.3	[e] $p = 0.007$ for vs healthy controls, so $p < 0.05$, but remains within normal limits
After the 300 mg/m^2 cumulative dose SF was decreased in seven patients. The reduction was >10% in five patients.					
IVRT (msn)	49.2 ± 13.3	45.3 ± 9.7	44.2 ± 9.3	46.7 ± 8.2	
Mitral E (cm/sn)	87.7 ± 0.1	85.5 ± 0.1	90.27 ± 0.1	76.2 ± 0.2	
Decrease in early mitral filling velocity observed at the end of treatment in six patients.					
Mitral A (cm/sn)	56.3 ± 0.2	60.7 ± 0.1[f]	63.1 ± 0.1[f]	46.3 ± 0.1	[f] $p < 0.05$ vs healthy controls
Decrease in early mitral filling velocity observed at the end of treatment in seven patients.					
Mitral E/A ratio	1.65 ± 0.48	1.44 ± 0.08	1.5 ± 0.4	1.6 ± 0.3	
Mitral E to mitral A ratio reduced in seven patients.					
AT (msn)	71.5 ± 12.7	71.7 ± 13.4	76.72 ± 15.69	72.3 ± 9.7	
DT (msn)	108.1 ± 45.1	92.0 ± 21.6	99.2 ± 24.0	89.5 ± 19.4	
AS (m/sn^2)	11.4 ± 2.7	11.5 ± 3.2	11.3 ± 4.4	11.1 ± 4.2	
DS (m/sn^2)	8.5 ± 5.2	8.4 ± 2.4	9.5 ± 4.4	7.5 ± 4.2	
TDF (msn)	304.7 ± 112.8	304.4 ± 96.7	325.0 ± 133.7	304.1 ± 59.4	

continued

Comments:
Age, gender, weight, heart rate and blood pressure were not significantly different in the patient and control groups at each evaluation time. Physical examination of cardiovascular system, chest X-ray and ECG of patients before therapy and after each dose of drug were normal, like the control subjects.
The mean initial LVIDd and LVIDs of the patients were not different from the control group. The EF and SF were within normal limits for all patients before therapy. The mean LVIDd of patients after cumulative doses of 180 mg/m^2 and 300 mg/m^2 of DOX increased significantly compared with the initial value ($p = 0.02$ and $p = 0.007$, respectively). The mean LVIDs in the patient group showed a significant increase after completion of therapy compared with pre-treatment values ($p = 0.006$). However, these values were still not significantly different from the control subjects.
The mean values of mitral E and mitral A after any cumulative doses of drug were not significantly different from baseline values. The difference between mean mitral E to mitral A ratio before and after treatment was not significant, although the ratio was reduced slightly while the cumulative doses of the drug increased. Significantly greater mean mitral A amplitude was demonstrated in patients after cumulative DOX doses of both 180 mg/m^2 and 300 mg/m^2 compared with those in the control group (0.005 and 0.003, respectively), but mean mitral E values of patients were not different from those in the control group. There was no difference in mean mitral E/A ratio between the patient and control groups after any cumulative doses of the drug. Prolongation of AT was observed at the end of treatment, although it was not statistically significant. Mean values of other parameters of diastolic functions in patients after cumulative DOX doses were not different from baseline values or from those of the control group.

Methodological comments
- *Allocation to treatment groups:* NA.
- *Blinding:* NR.
- *Comparability of treatment groups:* Age, gender, weight, heart rate and blood pressure were not significantly different between the patient and control groups at each evaluation time.
- *Method of data analysis:* A paired sample *t*-test was used to compare carnitine levels and echocardiographic measurements of patients obtained at three different times. Independent samples *t*-test was used to compare carnitine levels and echocardiographic measurements of patients and control groups.
- *Sample size/power calculation:* NR.
- *Attrition/dropout:* NR.

General comments
- *Generalisability:* Small groups. Inclusion criteria not reported, but all patients had NHL, and none received mediastinal radiotherapy.
- *Outcome measures:* Outcome relevant to the study.
- *Intercentre variability:* NA.
- *Conflict of interests:* NR.

Quality criteria for assessment of observational studies (revised from Spitzer *et al.*)[26]

	Yes	U/I/S	No	DK/NR	NA	Comments
Proper random assignment					NA	
Proper sampling				NR		
Adequate sample size			N			15 in treated group, 20 controls
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria				NR		
Reported attrition				NR		
Comparability of groups		U				Healthy controls, gender and age matched. Similar size, small groups (15/20)
						Age, gender, weight, heart rate and blood pressure were not significantly different in the patient and control groups at each evaluation time
Generalisability		U				Small groups. Inclusion criteria not reported, but all patients had NHL, and none received mediastinal radiotherapy

Study and design	Intervention	Participants	Outcome measures
Authors: Soker *et al*.[35] Year: 2005 Country: Turkey Study design: Cohort No. of centres: NR Funding: NR	*Intervention:* TRALL-BFM 2000 chemotherapy regimen administered in ALL and standard doses of DOX 30 mg/m^2. The total cumulative dose of DOX was 180 mg/m^2, (standard-risk group) 240 mg/m^2, (medium-risk group) and 300 mg/m^2 (high-risk group). AML-BFM 93 chemotherapy regimen administered in patients with AML. Standard doses of DOX 30 mg/m^2 and a total cumulative dose of 300 mg/m^2 was administered Adriamycin, Bleomycin, Vinblastine and Dacarbazine chemotherapy was administered in HD, standard doses of doxorubicin 25 mg/m^2 given on day 1 and day 15. The cycle was repeated every 2 weeks to the maximum of six cycles The NHL-BFM 90 chemotherapy regimen was administered in NHL. In this protocol DOX was used as 25 mg/m^2, total cumulative dose of 150 mg/m^2 All 31 patients underwent chemotherapy, and the total cumulative dose ranged between 30 and 600 mg/m^2 (mean ± SD 227.25 ± 111.09 mg/m^2, median 240 mg/m^2) *Control:* Healthy volunteers	*Number of participants:* Intervention: 31 Control: 30 *Sample attrition/dropout:* NR *Sample cross-overs:* NR *Inclusion criteria for study entry:* NR *Exclusion criteria for study entry:* Patients who received radiation therapy to mediastinum or had other illnesses such as infections *Characteristics of participants:* 31 patients who had received their last dose of anthracycline >1 month previously and continued to be in complete remission 14 boys, 17 girls, median age was 8.16 ± 3.48 years (range 4–15 years) Of the 31 patients, 27 had ALL (three relapsed ALL), two had AML, one HD and one NHL Control group of healthy volunteers: 16 boys, 14 girls. No abnormality on routine examination. In same age and gender distribution. Normal cardiac function. Had not received any treatment affecting the heart, kidneys or the fluid balance before and throughout the study period	Incidence of echocardiographically diagnosed DOX-induced cardiac dysfunction in children with cancer, and the association with the secretion of NT-pro-BNP and cTnI *Method of assessing outcomes:* Levels of cTnI were measured by an enzyme-linked one-step sandwich immunoassay method, and the lowest detectable level was 0.50 ng/ml. Levels of NT-pro-BNP were measured using an electrochemiluminescent immunoassay Pulsed-wave Doppler and M-mode echocardiography were performed by one experienced paediatric cardiologist with a Hewlett Packard Sonos 1000 ultrasound system using 2.5-MHz and 3.5-MHz transducers Considered abnormal when EF was <60% or FS was <30% *Adverse symptoms:* Two out of four patients with LV systolic dysfunction had clinical findings *Length of follow-up:* NR, but chemotherapy was received between October 2000 and December 2004 *Recruitment dates:* As above

Results

Outcomes	Intervention			Control (n = 30)	p-Value
	Cardiac dysfunction (n = 4)	Normal cardiac function (n = 27)	Total (n = 31)		
NT-pro-BNP level (pg/ml), mean ± SD	299.03 ± 264.97	107.55 ± 131.82	135.92 ± 166.16	47.17 ± 19.48	$p < 0.001$ cardiac dysfunction compared with control, $p < 0.008$ cardiac dysfunction compared with patients with normal cardiac function
Range	62.2–550	5–501	5–550	15–95.1	

continued

The time from the last DOX dose was 1–42 months (9.39 ± 12.3). The median cumulative doses of the patients with normal and abnormal echocardiographic parameters were 240 and 270 mg/m^2. The mean cumulative anthracycline dose was 217.04 ± 11.52 mg/m^2 in the patients with normal cardiac function (normal group). Four patients (one of AML and three of ALL) had cardiac dysfunction on echocardiography. The mean cumulative anthracycline dose in this group with dysfunction was 296.25 ± 77.82 mg/m^2, which was significantly higher than that in the normal group ($p < 0.01$).
Serum cTnI values of all patients were below the detection limit (<0.50 ng/ml). There was no difference between serum cTnI levels of the patients with normal and abnormal echocardiographic findings. The individual results for cTnI are not given.

Outcomes	**Intervention**									***p*-Value**
	Normal cardiac function (*n* = 27)			**Cardiac dysfunction (*n* = 4)**			**Total (*n* = 31)**			
	Mean ± SD	**Range**	**Median**	**Mean ± SD**	**Range**	**Median**	**Mean ± SD**	**Range**	**Median**	
LVEF	68.16 ± 4.43	62.30–80.60	67.85	55.72 ± 3.63	50.70–59.40	56.40	66.25 ± 6.25	50.70–80.60	66.35	
FS	37.24 ± –3.43	33–47.2	36.35	27.30 ± 1.77	25–29.2	27.50	35.71 ± 4.86	25–47.2	36	
Peak E filling velocity (cm/s)	94.38 ± 18.79	72–128	93	86.22 ± 9.79	75.1–98.2	85.80	93.17 ± 17.85	72–128	93	
Peak A filling velocity (cm/s)	53.16 ± 10.99	40.4–85.2	50.80	50.85 ± 12.38	39.8–68.6	47.50	51.33 ± 10.99	39.8–85.2	50	
E/A ratio	1.81 ± 0.38	1.1–2.8	1.98	1.77 ± 0.50	1.3–2.5	1.66	1.80 ± 0.39	1.1–2.8	1.82	
IVRT (s)	0.06 ± 0.01	0.05–0.08	0.06	0.08 ± 0.01	0.07–0.09	0.08	0.07 ± 0.01	0.05–0.09	0.06	
LVED (cm)	3.50 ± 0.48	2.5–4.2	3.48	3.92 ± 0.35	3.4–4.2	4.07	3.57 ± 0.48	2.5–4.2	3.60	

There were no statistically significant changes in the LV systolic indices ($p > 0.05$). There were no statistically significant changes in peak A and peak E wave velocities, or E/A ratio.
Unclear whether controls underwent echocardiography. No results for echocardiography for controls.
No significant correlations were found between any of the echocardiographic parameters with natriuretic peptides and cumulative DOX dose.

Methodological comments

- *Allocation to treatment groups:* NA.
- *Blinding:* NR.
- *Comparability of treatment groups:* One treatment group of 31, control group of 30. Reported to be age and gender matched, gender not reported for treatment group. Healthy control group.
- *Method of data analysis:* SPSS package used. Values were expressed as mean ± SD. The unpaired Student's *t*-test was used to assess differences between each group. The correlations between variables were found using Pearson's correlation test. $p < 0.05$ was considered statistically significant.
- *Sample size/power calculation:* NR.
- *Attrition/dropout:* NR.

General comments

- *Generalisability:* No specific inclusion criteria stated. Exclusion criteria excluded patients who received radiation therapy to mediastinum or had other illnesses such as infections. Small group of 31. Within that group were four types of cancer, two of these had one patient.
- *Outcome measures:* Outcomes were relevant to the study area.
- *Intercentre variability:* NR.
- *Conflict of interests:* NR.

Quality assessment(revised from Spitzer *et al*.)[26]

	Yes	U/I/S	No	DK/NR	NA	Comments
Proper random assignment					N/A	
Proper sampling				NR		Not discussed
Adequate sample size			No			31 in patient group, 30 healthy controls
Objective outcomes	Y					
Blind assessment				NR		
Objective eligibility criteria				NR		
Reported attrition				NR		
Comparability of groups			N			Healthy controls
Generalisability		U				No inclusion criteria stated other than received their last dose of anthracycline more than 1 month previously and continued to be in complete remission

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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