Assessing Cardiotoxicity in Randomised Trials of Anthracycline in Cancer Patients

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Trinity Term 2015

If you trust in yourself…
and believe in your
dreams… and follow your
star… you'll still get beaten
by people who spent their
time working hard and
learning things and
weren't so lazy. –

The Wee Free Men by
Terry Pratchett

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Amanda J. Kerr, Green Templeton College, Doctor of Philosophy, Trinity Term, 2015

ABSTRACT

Chemotherapy has improved survival in many types of cancer. However, it can lead to a range of toxic side effects that can occur while the patient is on treatment but may also appear months or years later. One of the more serious harmful side-effects of chemotherapy is heart disease and anthracycline chemotherapy is particularly implicated in this. Observational studies have shown that the risk of congestive heart failure in anthracycline treated patients rises rapidly after cumulative doses of about 400 mg/m^2, but that there is also some risk below this dose.

This thesis explored several methodological issues that affect meta-analyses of harms. First meta-analyses of harms often include terms for those harms in their search strategies. Evaluation of a trial search including cardiac terms against the trial list maintained by the Early Breast Cancer Trialists' Collaborative Group showed that only 48% of their trials were found. After cardiac terms were removed from the search strategy, 87% of the EBCTCG trials were found. Second, anthracycline cardiotoxicity is often not reported in a manner that enables data to be extracted for meta-analyses. To address this, risk of outcome reporting bias in trials included in this thesis was assessed. There was a high risk of outcome reporting bias for cardiac morbidity in 50% of trials, and 35% of trials had high risk of outcome reporting bias for cardiac mortality. Third, previous meta-analyses of anthracycline cardiotoxicity included only a limited number of trials. In order to increase the amount of information about anthracycline cardiotoxicity available for meta-analysis, a method was devised for including confounded trials in the meta-analysis, taking into account prior knowledge as to the likely effect of other drugs on cardiotoxicity.

Finally, published and individual patient data meta-analyses of cardiac death in randomised trials of anthracycline versus not were undertaken. The published data meta-analysis included 32 trials, 9 of which were unconfounded, and found a 36% (95% CI 1-83%) increased risk of cardiac death in anthracycline-allocated patients compared to those not allocated to anthracycline. No conclusions could be drawn about the effect of confounder drugs on the risk of cardiac death. A meta-analysis grouped by lower and higher dose showed that there was a statistically significant increase in risk of cardiac death in anthracycline allocated patients compared to those not allocated anthracyclines in the higher dose group only (OR=1.74, 95%CI 1.15 – 2.62).

In conclusion, this thesis has generated new insights into the methods used for meta-analyses of harms. It has also produced a new risk estimate of cardiac death in anthracycline-treated patients that clinicians can use to inform their treatment decisions.

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LIST OF ABBREVIATIONS

5-FU – 5-fluorouracil
ABVE – doxorubicin + bleomycin + vincristine + etoposide
AC – doxorubicin + cyclophosphamide chemotherapy
ALL – Acute Lymphoblastic Leukaemia
BCCSS – British Childhood Cancer Survivors Study
CCSS – Childhood Cancer Survivor Study
CHF – congestive heart failure
CI – confidence interval
CMF – cyclophosphamide + methotrexate + 5-FU chemotherapy
COD – cause of death
COG – Children's Oncology Group
CTCAE – common terminology criteria for adverse events
DEX – dexrazoxane
DOX – doxorubicin
EBCTCG – Early Breast Cancer Trialists' Collaborative Group
EMA – European Medicines Agency
EPI – epirubicin
FAC – 5-FU + doxorubicin + cyclophosphamide chemotherapy
FDA – United States Food and Drug Administration
IHD – ischemic heart disease
IPD – individual patient data
LVEF – left ventricular ejection fraction
MI – myocardial infarction
MS – multiple sclerosis
OR – odds ratio
ORB – outcome reporting bias
PFS – progression free survival
PHIS – Pediatric Health Information System database
PI – principal investigator
POG – Pediatric Oncology Group
RCT – randomised controlled trial
RR – rate ratio or risk ratio
SIR – standardised incidence rate
SMN – second malignant neoplasm
SMR – standardised mortality ratio
TOPII – topoisomerase II

CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

Cancer is one of the most common diseases across the world. In 2012 the world age standardised rate of new cancers in males was 204 per 100,000, and 165 per 100,000 in females.[1, 2] While cancer incidence has been rising, cancer mortality is falling. The current risk of dying from cancer before the age of 75 is 10.5% for both sexes combined.[1, 2] In the UK approximately 50% of adults will survive at least 10 years after their cancer diagnosis.[3] Current estimates also suggest that 80% of children survive at least 5 years after a diagnosis of cancer.[4]

The main methods of cancer treatment are surgery to remove tumours, radiotherapy, which uses radiation to kill cancer cells, and systemic therapy, which uses chemotherapy or other drugs to kill cancer cells. Systemic therapy and radiotherapy cure many patients of their cancer, but they can lead to a wide range of toxic side effects. Some of these side effects are acute, occurring while the patient is receiving treatment, but others can appear many months or years later.

Analysis of the late effects of cancer treatment in the Childhood Cancer Survival Study (CCSS) showed that childhood cancer survivors had 10.8 times higher all-cause mortality compared to the age and sex matched general population. Deaths from heart disease were 8.2 times higher, and deaths from second malignancies (SMN) were almost 20 times higher.[5, 6]

As cancer treatments improve and the number of people surviving their cancer grows, it becomes increasingly important to understand the long-term side effects of cancer treatments. One of the most serious side effects of cancer therapy is cardiac toxicity. This can be caused by both systemic therapy and radiotherapy. Different therapies may affect

the heart in different ways, impacting on muscle, structure, and/or function.[7, 8] Anthracycline chemotherapy is particularly implicated in cardiac toxicity.

1.2 ANTHRACYCLINE CHEMOTHERAPY

Anthracyclines are a form of antibiotic, the first of which, daunorubicin, was isolated in 1958 from a strain of streptomyces bacteria. Initial tests showed that daunorubicin was too toxic for use as an antibiotic, however, it was found to have activity against cancer cells in animal models.[9] The first human trials of anthracycline to treat cancer started in 1964 in lymphoma and leukaemia patients.[10] These trials showed promising results, with improvements in survival for some patients, although some of the patients receiving anthracyclines experienced some toxicity. Many anthracycline compounds have since been tested, but few have entered clinical use, due to toxicity.[11] Currently the most commonly used anthracyclines and anthracycline analogues are

- Daunorubicin and liposomal daunorubicin
- Doxorubicin and liposomal doxorubicin
- Epirubicin
- Idarubicin
- Mitoxantrone (an anthracycline analogue)

Mitoxantrone is included alongside the anthracyclines in this study as it also causes cardiotoxicity. Mitoxantrone has been used to treat multiple sclerosis as well as cancer.[12]

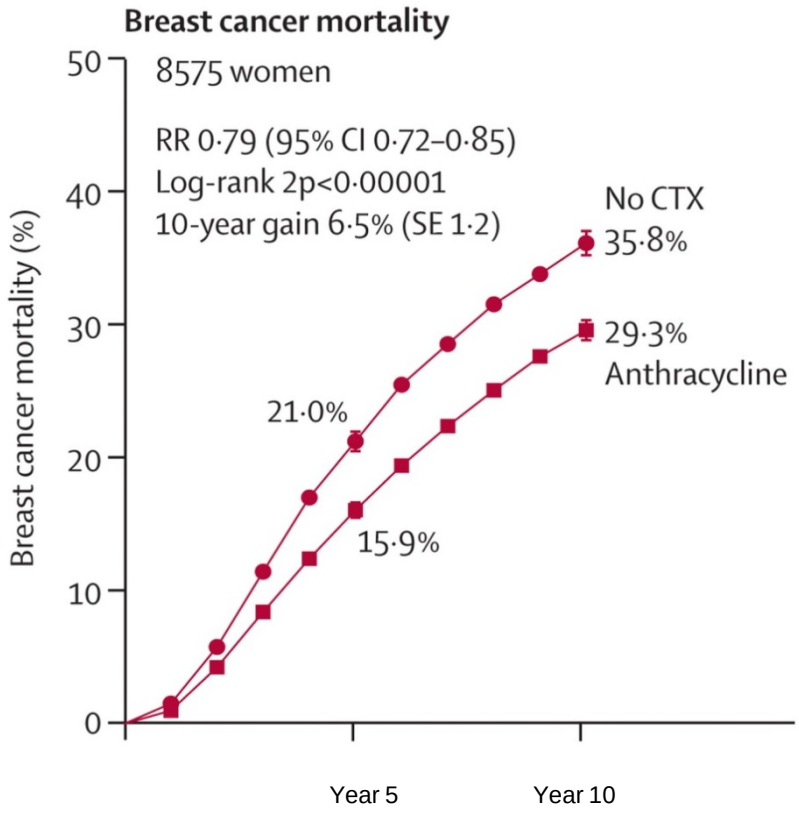
Anthracyclines have shown activity against a wide range of cancers, both solid tumours and haematological malignancies (see Table 1.1).

TABLE1.1 ANTHRACYCLINE INDICATIONS FOR USE

Anthracycline	Approved uses
Daunorubicin	Acute leukaemia
Liposomal Daunorubicin	AIDS related Kaposi's sarcoma
Doxorubicin	Acute leukaemias Hodgkin and non-Hodgkin lymphoma Paediatric malignancies Breast cancer Bladder instillation for transitional cell carcinoma, papillary bladder tumours and carcinoma in-situ Chronic lymphocytic leukaemia Kaposi's sarcoma Mantle cell lymphoma Mycosis fungoides Gastric cancer Ewing's sarcoma Prostate cancer Thyroid cancer Nephroblastoma Neuroblastoma Non-small cell lung cancer Ovarian cancer Bladder cancer Cervical cancer Langerhans' cell histiocytosis Multiple myeloma
Liposomal Doxorubicin	Ovarian cancer
Epirubicin	Breast cancer Gastric cancer Ovarian cancer Small cell lung cancer Lymphoma Soft tissue sarcoma
Idarubicin	Haematological malignancies
Mitoxantrone	Prostate cancer Acute myeloid leukaemia Acute non-lymphocytic leukaemia Multiple sclerosis Metastatic breast cancer Non-Hodgkin lymphoma Hepatocellular carcinoma

Table adapted from the US Food and Drug Administration[13], the UK Medicines and Healthcare products Regulatory Agency[14], and the Australian Therapeutic Goods Administration[15]

Anthracyclines are widely used and have contributed to improvements in cancer survival. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overviews of randomised trials showed that by 10 years post chemotherapy, there was an absolute reduction in breast cancer mortality of about 6% in women allocated to anthracycline compared to women allocated to no chemotherapy (10-year breast cancer mortality 29.3% versus 35.8%, rate ratio=0.79, 95% confidence interval [CI] 0.72 – 0.85, 2p<0.00001) (see Figure 1).[16]



Death rates (%/year: total rate–rate in women without recurrence) and log-rank analyses

Allocation	Years 0–4	Years 5–9	Year 10+
CTX	3·38 SE 0·13	3·57 SE 0·16	2·83 SE 0·19
No CTX	4·77 SE 0·17	4·31 SE 0·21	2·98 SE 0·22
Rate ratio	0·73 SE 0·05	0·83 SE 0·07	0·92 SE 0·11
(O–E)/V	−97·5/307·0	−35·9/193·2	−6·7/81·0

FIGURE 1 BREAST CANCER MORTALITY IN RANDOMISED TRIALS OF ANTHRACYCLINE VS NO CHEMOTHERAPY

Figure from EBCTCG (2012) [16]

1.3 ANTHRACYCLINE CARDIOTOXICITY

While anthracyclines are widely used in the treatment of cancer, there is concern over their cardiac effects. Cardiotoxicity was seen in preclinical animal models, and borne out in early human trials.[9, 10] The cardiac effects of anthracyclines vary from mild, asymptomatic declines in left ventricular ejection fraction (LVEF) to congestive heart failure (CHF) and death.[17, 18] Severe cardiotoxicity can present as restrictive or dilated cardiomyopathy.

Anthracycline cardiotoxicity is characterised by clinical features including transient changes in heart function tests, such as depressed contractility, i.e. a heart that has reduced strength to contract, and decreased LVEF, i.e. a lower than normal amount of blood being pumped out of the left side of the heart[19]. It may also present as restrictive cardiomyopathy, i.e. a heart that is smaller than normal, or as dilated cardiomyopathy, i.e. a large floppy heart[20]. Damage to heart muscle cells (cardiac myocytes) can also be seen on biopsy.

Anthracycline cardiotoxicity has been described as acute, early or late onset.[20] Acute cardiotoxicity occurs within a week of anthracycline treatment, may present as transient changes in heart function tests and usually resolves when anthracyclines are discontinued. Early cardiotoxicity occurs within 1 year of the end of anthracycline treatment, and late cardiotoxicity occurs any time after the first year has elapsed. Early and late onset anthracycline cardiotoxicity is usually not reversible and can be progressive. Table 1.2 summarises the key characteristics of acute, early and late anthracycline cardiotoxicity.

TABLE 1.2 CHARACTERISTICS OF ANTHRACYCLINE CARDIOTOXICITY

Characteristic	Acute cardiotoxicity	Early cardiotoxicity	Late cardiotoxicity
Time to onset	Within one week of anthracycline administration	<1 year from the last anthracycline dose	>1 year from the last anthracycline dose
Risk factor dependence	Unknown	Yes (see Table 1.3)	Yes (see Table 1.3)
Clinical presentation in adults	Depression of contractility, LVEF changes	Dilated cardiomyopathy	Dilated cardiomyopathy
Clinical presentation in children	Depression of contractility, LVEF changes	Restrictive or dilated cardiomyopathy	Restrictive or dilated cardiomyopathy
Course	Usually transient and reversible	Not reversible, likely progressive	Not reversible, likely progressive

Adapted from Adams et al. (2006)[20]

Acute onset anthracycline cardiotoxicity may improve initially, so that tests of heart function return to within the normal range. However, this may not be maintained over the long term. Lipshultz et al. (2005) studied long term cardiac health in a cohort of 115 childhood cancer survivors who had received anthracyclines while participating in one of six clinical trials run by the Dana-Farber Cancer Institute.[21] Children were eligible for this cohort if they were free of cancer two years after the end of their treatment, and also disease free when the cohort was first created. Cardiac health was tested with serial echocardiograms that assessed performance of the left ventricle of the heart, heart contractility, afterload, which measures pressure in the wall of the left ventricle, and blood pressure. One echocardiogram per patient was included at each of three time-points: before anthracycline therapy, at the end of anthracycline therapy, and the most recent echocardiogram taken during long term follow-up. Median follow-up for this cohort was 11.8 years (range 8.3 to 15.0 years). The cohort was divided into three groups. Patients in the low-dose group had received less than 300 mg/m^2 of doxorubicin, the medium dose group received 300 to 400 mg/m^2 and the high dose group more than 400 mg/m^2. This study found abnormalities in echocardiographic measures that were

persistent and progressive, indicating reduced cardiac output and cardiomyopathy in this cohort of anthracycline-treated children. Poor cardiac performance, as shown by echocardiographic abnormalities, was not only seen in the high and medium dose groups, but also in low dose group. Cardiac performance that worsens over time would be consistent with the injury, compensation, decompensation mechanism proposed by the "Multiple-Hit" hypothesis.

The "Multiple-Hit" hypothesis outlines a process by which the heart is initially able to compensate for anthracycline-related injury to the myocytes, but over time lifestyle factors and cardiac stressors decrease cardiac reserves until the heart is no longer able to compensate for damaged tissue. The patient presents for treatment of their cancer with underlying cardiovascular risk factors. Anthracyclines are received as part of their cancer treatment. They damage some cardiac myocytes leaving the patient with a decreased reserve of myocytes. Initially healthy myocytes are able to compensate for the anthracycline injury. Over time, factors such as hypertension and obesity, and stressors such as radiotherapy and advancing age, decrease the cardiac reserve, until it is no longer able to compensate for damaged myocytes. The heart then decompensates and clinical evidence of heart disease appears (see Figure 2).[22]

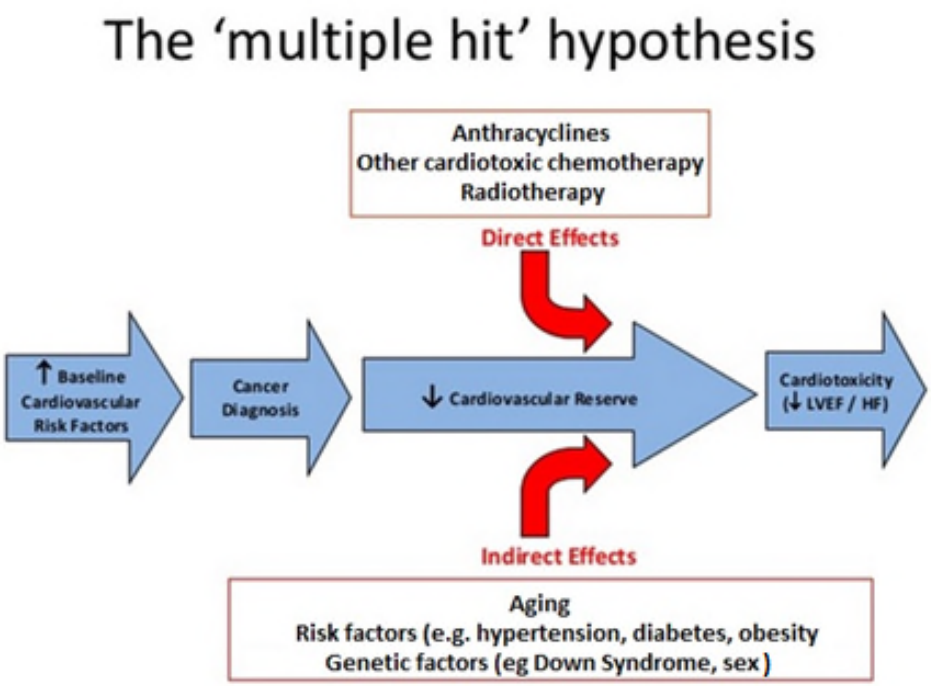


FIGURE 2 THE "MULTIPLE-HIT" HYPOTHESIS OF ANTHRACYCLINE CARDIOTOXICITY
Adapted from Jones et el (2007)[22]

Originally anthracyclines were thought to damage the heart by the action of iron-dependent free radicals, which damage cardiac myocytes leading to cell death.[23, 24] However, as Yeh (2014)[25] explains, it is now thought that topoisomerase II (TOPII) inhibition contributes to anthracycline cardiotoxicity. TOPII is an enzyme that resolves problems in the coiling of DNA strands by breaking the strands apart and sealing them back together once the coiling issue is resolved. Anthracyclines inhibit TOPII, and create DNA double strand breaks in tumour cells ultimately leading to cell death. TOPII is also expressed in cardiac myocytes, and contributes to DNA repair in these cells. There are two forms of TOPII, TOPIIα and TOPIIβ. TOPIIα is expressed in tumour cells, and by inhibiting TOPII expression, anthracyclines interfere with cell repair mechanisms in tumour cells, thus leading to tumour cell death. TOPIIβ is expressed in cardiac myocytes, and by inhibiting TOPII expression, anthracyclines also interfere with cell repair mechanism in these cells. To demonstrate the role of TOPII in anthracycline

cardiotoxicity, Lyu et al. (2007) used mice that lack TOPIIβ in their cardiac myocytes. They showed that these mice were less susceptible to cardiotoxicity compared to mice that did not lack TOPIIβ, supporting the hypothesis that TOPII is involved in anthracycline cardiotoxicity.[26]

1.4 RISK FACTORS FOR ANTHRACYCLINE CARDIOTOXICITY

In addition to the cumulative dose of anthracycline, several factors have been found to increase the risk of anthracycline-related cardiotoxicity (See Table 1.3).[7, 27-29] In children damage to cardiac myocytes in the developing heart results in Grinch Syndrome. The damaged heart does not reach its full growth potential so is smaller than normal.[29-31] These smaller than normal hearts are more susceptible to stressors, thus increasing the risk of heart disease. In the elderly, the heart has lower reserves to compensate for damaged myocytes, and is thus more susceptible to heart disease.[28, 32] Patients with pre-existing heart disease or cardiac risk factors such as diabetes or hypertension are also at greater risk of cardiotoxicity.[7, 17, 28] The method of anthracycline administration can also affect the risk of cardiotoxicity. Bolus administration (given as a single injection) increases the risk of cardiotoxicity compared to infusions that take place over a period of hours.[33, 34] Females appear to be at higher risk of cardiotoxicity than males.[35] Girls have more body fat than boys. This means that as anthracyclines do not accumulate in body fat, girls have higher concentrations of anthracycline in their blood for a longer time than boys do, leading to increased cardiotoxicity.[35] Treatment with other cardiotoxic agents such as radiotherapy[36, 37], paclitaxel[38, 39] or trastuzumab[40] can also increase the risk of anthracycline-related cardiotoxicity. A variety of genetic factors, such as Down's Syndrome and African ancestry, may increase the risk of anthracycline cardiotoxicity.[21,

[28, 41] The mechanisms for anthracycline cardiotoxicity in patients with these genetic factors are not yet well understood.

TABLE 1.3 RISK FACTORS ASSOCIATED WITH ANTHRACYCLINE CARDIOTOXICITY

Conditions that have damaged the heart prior to anthracycline administration
Prior anthracycline exposure
Prior treatment with other cardiotoxic agents
Older age
Underlying heart disease
Other cardiac risk factors (e.g. diabetes, hypertension)
Factors that increase the risk of cardiotoxicity during anthracycline treatment
Bolus dosing
Higher cumulative dose
Concomitant treatment with other cardiotoxic agents
Conditions that make the heart more susceptible to ongoing damage
Subsequent treatment with other cardiotoxic agents
Younger age
Genetic factors (e.g. Down's Syndrome, African ancestry, female sex)

Table adapted from Ewer (2013)[28]

1.5 EVIDENCE FROM OBSERVATIONAL STUDIES

There is ample evidence for acute and early anthracycline cardiotoxicity in adults. Von Hoff and colleagues (1979) conducted a retrospective review of cardiac outcomes in 4018 patients, of which 3941 were evaluable.[32] Patients were aged between 2 months and 99 years, with a median of 54 years. Most of the patients were more than 15 years old (n=3543, 89.9%). Mean length of follow-up was 2.35 years (range 0 to 6.4 years). Almost half (48%) of patients included in this study had cancers with poor prognosis (lung cancer or metastatic breast cancer). There were 88 cases of CHF, and of these 88, CHF was the immediate cause of death in almost half (n=38). In this case-series, Von Hoff et al. (1979) showed that the risk of CHF rises rapidly after a cumulative dose of about 500 mg/m^2 of doxorubicin, with smaller increases in the 300 to 500 mg/m^2 range (see Figure 3).[32]

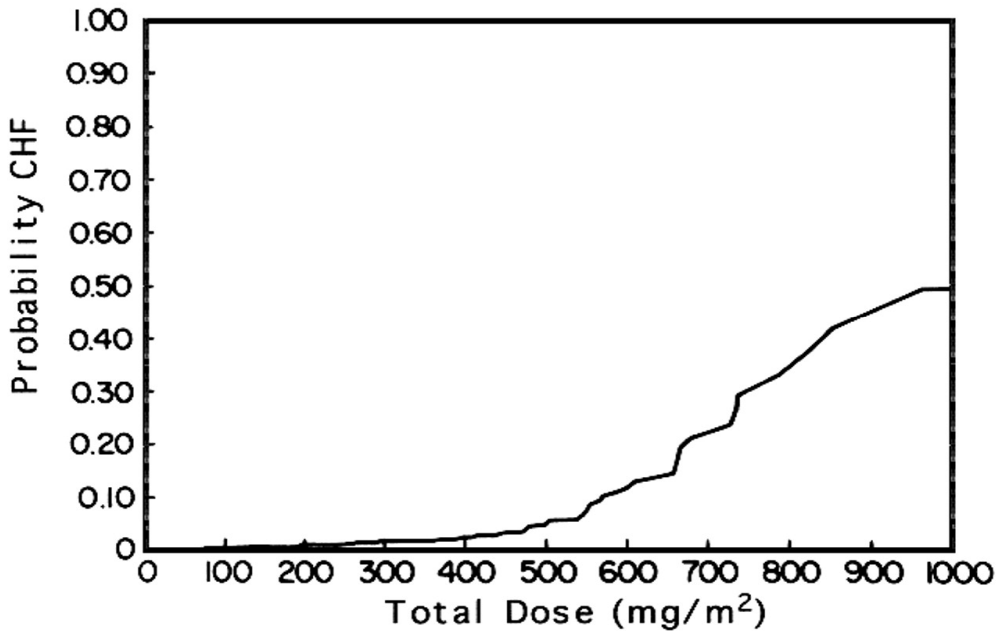


FIGURE 3 PROBABILITY OF CONGESTIVE HEART FAILURE AGAINST CUMULATIVE DOXORUBICIN DOSE (VON HOFF)
from Von Hoff et al. (1979)[32]

Swain et al. (2003) analysed the risk of CHF in a group of 630 patients who had participated in one of three trials.[42] Eligible patients were those randomised to the doxorubicin plus placebo arm of each trial. Included patients had either metastatic breast cancer (n=519 patients) or lung cancer (n=111 patients). Most patients were aged 65 years or less (n=458, 73%) and had no history of heart disease (n=557, 88%). Similar to the results of the Von Hoff study, Swain et al. (2003) found that the risk of CHF rises rapidly after a cumulative dose of about 400mg/m^2 of doxorubicin (see Figure 4).[42] The cumulative percentage of patients who experienced CHF was 5% at 400mg/m^2, 16% at 500mg/m^2, 26% at 550mg/m^2 and almost half (48%) at 700mg/m^2.

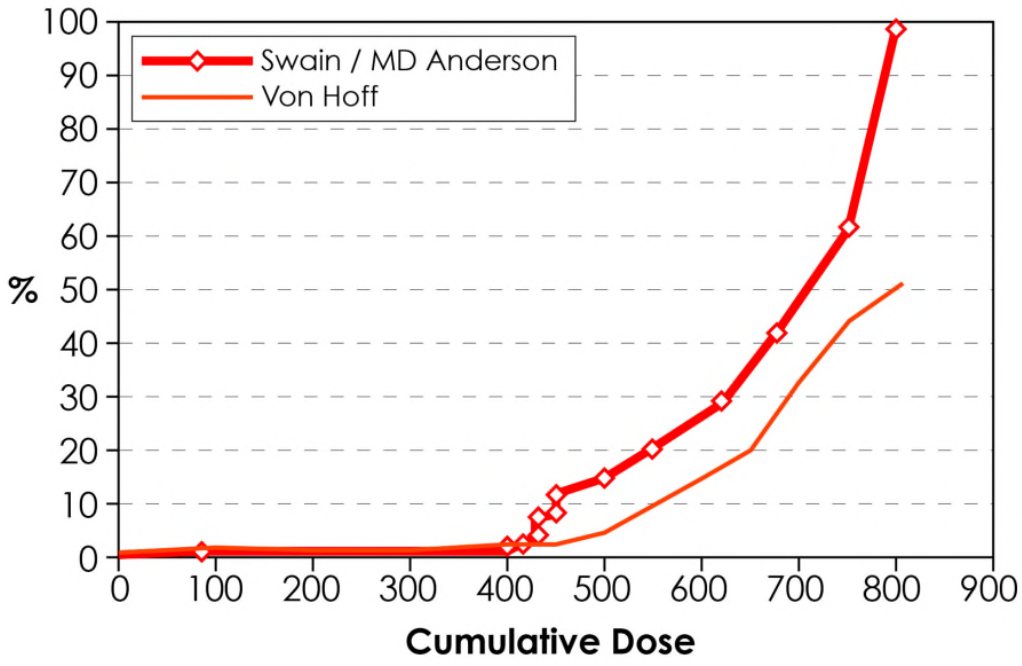


FIGURE 4 PROBABILITY OF CONGESTIVE HEART FAILURE AGAINST CUMULATIVE DOXORUBICIN DOSE (SWAIN AND VON HOFF)
from Ewer (2013)[28]

While the risk of CHF rises rapidly after about 400 mg/m^2 of doxorubicin, evidence suggests that there is damage to the heart below this dose. Increases in biomarkers such as cardiac troponin I can indicate cardiac damage. Increases in biomarkers have been demonstrated even after a single dose of anthracycline.[43] Similarly, measures of heart function, such as LVEF may also show changes after relatively low doses of anthracycline (<300 mg/m^2).[44] As such, current recommendations are that, where possible, the cumulative lifetime dose of anthracycline is limited to below 400 to 450 mg/m^2 of doxorubicin or the equivalent of other anthracyclines.[28, 32, 41, 45, 46]

1.5.1 EVIDENCE FOR LONG TERM OUTCOMES

Much of the evidence for long term cardiac outcomes in anthracycline-treated patients comes from adult survivors of childhood cancer. Lipshultz et al. (2005) studied long term survivors of childhood cancer who had been treated with anthracyclines. They found that at a median follow-up of 11.8 years there were a range of abnormalities on

echocardiogram.[21, 30, 31] These abnormalities were progressive, worsening over time, and even affected children who had received doses of anthracycline below 300 mg/m^2.

Van Dalen et al. (2006) reviewed a cohort of 830 children who had been treated with anthracyclines at one hospital in the Netherlands between January 1976 and December 2000.[47] Median follow-up was 7.1 years (range 0.01 to 28.4 years). The cumulative incidence of anthracycline-related CHF was 2.5%, and 1 in 10 children who had received 300 mg/m^2 of doxorubicin developed anthracycline-related CHF.

Kremer et al. (2002) conducted a systematic review of studies of subclinical(i.e. symptom free) cardiotoxicity in anthracycline treated children.[48] They identified 25 studies that investigated cardiac health in long term survivors of childhood cancer. In these studies, subclinical cardiotoxicity was present in 0% to 57% of patients.

Cutter et al. (personal communication)[49] investigated cardiac mortality in the British Childhood Cancer Survivor Study (BCCSS). This cohort included 17,981 5-year cancer survivors who were diagnosed with cancer between 1940 and 1991, when aged less than 15 years. Median follow-up was 27.1 years (range 5.0 to 69.6 years). This study found a ten-fold increased risk of death from all cardiac causes in anthracycline-treated patients compared to patients unlikely to have received anthracyclines (standardised mortality ratio [SMR] 10.8, 95% confidence interval [CI] 8.0 to 14.4). When considering different cardiac endpoints, there was a twenty-fold increased risk of death from CHF in this cohort (SMR 20.0, 95% CI 13.7 to 28.2). Risk of death from ischaemic heart disease (IHD) was also raised (SMR 5.2, 95% CI 2.3 to 9.6) as was risk of death from valvular heart disease (SMR 6.0, 95% CI 2.0 to 14.1). Clearly cardiac death due to anthracycline treatment is not limited to CHF.

Two cohort studies have investigated cardiac deaths in adults treated for Hodgkin Lymphoma. First, Swerdlow et al. (2007) studied a cohort of patients who had participated in clinical trials for Hodgkin Lymphoma conducted by a British lymphoma clinical trials collaboration. Included patients were diagnosed between March 1970 and February 1999.[50] There were 7033 patients in the cohort, aged between 25 and 44 years old when treated. In patients who had received anthracyclines there was an almost three-fold increased risk of death from myocardial infarction (SMR = 2.9, 95% CI 1.9 to 4.3).

Second, van Nimwegen et al. (2015) investigated cardiac deaths in a cohort of Hodgkin Lymphoma patients who had been treated in one of 5 Dutch hospitals between January 1965 and December 1995.[51] Included patients were aged less than 51 years at treatment, and had survived at least 5 years after diagnosis. There were 2064 patients in the cohort 41% of whom were aged between 30 and 50 years old at the time of treatment. There were statistically significant increases in death from both CHF (SMR 2.2, 95% CI 1.5 to 3.2) and valvular heart disease (SMR 2.0, 95% CI 1.5 to 2.6). The radiation fields used in Hodgkin lymphoma treatment often include the heart. Thus radiotherapy may be contributing to the increased risk of valvular heart disease in anthracycline treated patients found in this study.

Although long term cardiac outcome studies in anthracycline-treated adults are less common than studies in children, declines in LVEF have been found to be more common in the anthracycline arms of adult randomised trials than in the comparator non-anthracycline arms.[52, 53]

1.6 EVIDENCE FROM META-ANALYSES

There have been several meta-analyses of published data from randomised controlled trials (RCTs) of anthracycline that include cardiotoxicity as an outcome. Of these, 3 were meta-analyses of RCTs of anthracycline versus not, and 4 included other anthracycline comparisons such as one anthracycline versus another, dosing strategy comparisons, such as bolus versus continuous infusion, and comparisons of anthracycline with or without a cardioprotectant.

The diagnosis of CHF is based on a variety of signs, symptoms, medical history and test results. While diagnostic criteria have been developed, the definition of CHF varies across clinical settings, and between RCTs. Thus events that are defined as CHF or clinical cardiotoxicity in one RCT may be defined as subclinical cardiotoxicity in another. Any attempt to combine data from RCTs in a meta-analysis is limited by the extent to which the definitions of CHF, clinical and subclinical cardiotoxicity are comparable.

Van Dalen et al. (2012) conducted a Cochrane review of RCTs of anthracycline vs not for childhood cancer.[54] This review was primarily designed to assess efficacy outcomes. It also included analyses of non-fatal cardiotoxicity and cardiac deaths. To be included in the review RCTs had to be conducted in children aged 0-18 years, or 0-30 years provided the majority of participants were children. Trial arms could differ only in the presence or absence of anthracycline and the cumulative dose of each non-anthracycline drug could not differ by more than 25%. The timing of doses could differ but prior treatment had to be comparable in the different arms within each trial.

In this review, an extensive search found 8 RCTs including 2274 patients that fitted the inclusion criteria. However, of these 8 trials, only 2 could be included in the analysis of cardiac death, and a non-significantly increased risk of cardiac death in patients treated

with anthracyclines was found (Risk Ratio for comparison of control vs anthracycline [RR] = 0.41, 95%CI 0.04 - 3.89, p=0.44). Data on non-fatal cardiac events could only be extracted from one trial, and in this study there was a non-significantly increased risk of grade 3-4 cardiac toxicity in patients allocated to anthracycline (RR (control vs anthracycline) = 0.2, 95% CI 0.02 - 1.70, p=0.14).

Itchaki et al. (2013) conducted a Cochrane review of treatment with and without anthracyclines for follicular lymphoma.[55] The primary objective of this review was to compare efficacy in anthracycline regimens compared to other chemotherapy. It also included an analysis of cardiotoxicity. To be included in this review RCTs had to be conducted in adults at least 75% of whom were diagnosed with follicular lymphoma. Eligible RCTs could include patients who had had prior treatment for their cancer, and any grade of lymphoma.

The search for this review identified 8 RCTs, of which 4 were included in the analysis of non-fatal cardiotoxicity. Patients allocated to anthracycline were over four times more likely to have a cardiotoxic event than those not allocated to anthracycline, but the number of events was small, the confidence interval was wide and the difference was not statistically significant (RR = 4.55, 95% CI 0.92 - 22.49, p = 0.063).

Smith et al. (2010) conducted a published-data meta-analysis of cardiac outcomes in RCTs of anthracycline versus not.[56] This study included RCTs in patients of any age. It only included RCTs in cancers with good prognosis as they would be likely to have long-term survivors, with long follow-up. Diagnoses included breast cancer, ovarian cancer, sarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma and multiple myeloma. Of the 55 RCTs included in this study, 8 were of anthracycline versus not. Only 4 of these 8 RCTs could be included in analyses of cardiac outcomes as data on these outcomes could not be extracted from the other RCTs. Smith et al. (2010) found that patients allocated to

anthracycline were five times more likely to die of cardiac causes than patients allocated to other chemotherapies. This difference was statistically significant (Odds Ratio [OR] 4.94, 95% CI 1.23 - 19.87, p=0.025). Anthracycline-treated patients were also five times more likely to experience clinical cardiotoxicity, defined as any event reported in trial publications as CHF or drop in LVEF requiring treatment discontinuation (OR 5.43, 95% CI 2.34 - 12.62, p<0.0001). The definition of CHF or drop in LVEF requiring treatment discontinuation varied across trials.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have also analysed the risk of cardiac death in women randomised to anthracycline compared to those randomised to other chemotherapy or no chemotherapy.[16] In an Individual Patient Data (IPD) meta-analysis of 22 RCTs including 36,596 women, there was a 61% increased risk of cardiac death in patients allocated to anthracycline + cyclophosphamide (AC) compared to no chemotherapy (OR 1.61, SE 0.31). In a comparison of patients allocated to anthracycline compared to those allocated to cyclophosphamide + methotrexate + 5-fluorouracil (CMF), there were 20 RCTs including 17,569 women. This analysis showed a 50% increased risk of cardiac death in patients allocated to anthracycline-containing regimens compared to those allocated to CMF (OR 1.50, standard error 0.38).[16]

1.7 METHODS TO AMELIORATE ANTHRACYCLINE CARDIOTOXICITY

When anthracyclines are needed to treat cancer measures need to be taken to reduce the risk of cardiotoxicity. One method for reducing this risk is to use the lowest possible cumulative dose of anthracycline that still maintains adequate dose intensity to provide a cure. However, given the wide range of cancers which are treated with anthracyclines, and the number of patients at risk of cardiotoxicity, there have been ongoing efforts to find other methods to reduce cardiac risks without interfering with treatment efficacy.

Research has focused on three areas: finding less toxic anthracyclines, modifying the dosing strategy to find less toxic ways of administering anthracyclines, and adding cardioprotective agents to the chemotherapy regimen.

1.7.1 LESS TOXIC ANTHRACYCLINE AGENTS

Doxorubicin and daunorubicin are the anthracyclines with the longest history. More recently, research efforts have focussed on finding anthracyclines that are as effective as regards cancer treatment, but free from cardiotoxicity. Epirubicin was the first of the alternate anthracyclines to enter clinical practice. Epirubicin appears to be as effective as doxorubicin, with lower incidence of cardiotoxicity.[17, 57] Smith et al. (2010) found 8 RCTs that compared clinical cardiotoxicity of epirubicin to doxorubicin. Epirubicin decreased the risk of clinical cardiotoxicity compared to doxorubicin (OR = 0.39, 95% CI 0.20 - 0.78, p = 0.008).[56] Similarly, a Cochrane review of different anthracyclines for reducing cardiotoxicity found 5 RCTs of epirubicin vs doxorubicin including 1036 patients.[58] This review found no significant difference in CHF between patients allocated to epirubicin and doxorubicin (RR = 0.36, 95% CI 0.12 - 1.11, p=0.07). Although the difference was not statistically significant, the authors conclude that there is some suggestion that rates of CHF were lower in patients allocated to epirubicin.

Idarubicin is another anthracycline that has been developed in an effort to reduce cardiotoxicity and it is approved for use in some haematological malignancies.[17] Randomised trials have shown that the cardiac risk from idarubicin is smaller than for doxorubicin. In an RCT of an idarubicin chemotherapy regimen compared to a doxorubicin chemotherapy regimen in adults with non-Hodgkin lymphoma, fewer idarubicin than doxorubicin-allocated patients developed cardiac events. There were 3 cardiac events in idarubicin-allocated patients, and 7 cardiac events in doxorubicin-

allocated patients, and asymptomatic drops in LVEF were lower in idarubicin (median LVEF drop 8.3%) than doxorubicin patients (median LVEF drop 4.8%).[59]

Liposomal encapsulation of anthracyclines is another promising strategy in the development of less cardiotoxic analogues. Smith et al. (2010) found 4 RCTs of liposomal doxorubicin compared to conventional doxorubicin. Meta-analysis of these 4 studies showed that liposomal doxorubicin reduced the risk of clinical cardiotoxicity compared to conventional doxorubicin, and this difference was statistically significant (OR = 0.18, 95% CI 0.08 - 0.38, $p < 0.0001$).[56]

Mitoxantrone is a derivative of anthracyclines that was developed to reduce cardiotoxicity. It has been trialled in patients with cancer and patients with multiple sclerosis (MS). Smith et al. (2010) analysed the risk of clinical cardiotoxicity in 8 RCTs of anthracycline compared to mitoxantrone and found that anthracyclines had 3 times the risk of clinical cardiotoxicity (OR 2.88, 95% CI 1.29 - 6.44, p=0.01).[56]

1.7.2 MODIFICATIONS TO THE DOSING STRATEGY

There is some suggestion that modifying the way in which anthracyclines are administered could reduce the risk of cardiotoxicity. By increasing the duration of each individual anthracycline infusion, the peak serum concentration of anthracycline is reduced which may be less injurious to cardiac myocytes.[28] A Cochrane review of shorter (less than 6 hours) vs longer (more than 6 hours) infusion durations showed that in adults the risk of clinical heart failure was in patients that had longer infusion durations (RR = 0.27, 95% CI 0.09 - 0.81, p = 0.02).[60] However, although this strategy showed promise, the reduction in risk with longer infusion durations may not be maintained over the long term. Lipshultz et al. (2002) randomised children with Acute Lymphoblastic Leukaemia (ALL) to bolus administration of doxorubicin (<1 hour duration) vs 48 hour

infusion.[61, 62] At a median of 1.5 years after the end of anthracycline therapy, both groups showed abnormalities on echocardiogram and there was no statistically significant difference between them.

1.7.3 CARDIOPROTECTIVE DRUGS

One further method for protecting the heart during anthracycline therapy is to add a cardioprotective drug to the chemotherapy regimen. The aim is to reduce cardiotoxicity by adding a drug that protects the heart without interfering with anti-tumour activity. A number of different cardioprotectants have been investigated. Dexrazoxane is the most widely studied cardioprotectant, and is discussed in more detail in Chapter 8. In a meta-analysis of 7 RCTs including 1162 patients, Kalam and Marwick (2013) found a 65% reduction in the risk of CHF in patients allocated to dexrazoxane compared to those not allocated to dexrazoxane (RR 0.35, 95% CI 0.27 to 0.45, $p<0.00001$).[63] Drugs used to treat non-anthracycline-related heart failure have also been tested as cardioprotectants. This meta-analysis found a 69% reduction in risk of CHF in patients allocated to statins (RR=0.31, 95%CI 0.13 – 0.77), a 69% reduction in risk of CHF in patients allocated to beta-blockers (RR = 0.31, 95% CI 0.16 – 0.63) and an 89% reduction in risk of CHF in patients allocated to ACE Inhibitors (RR = 0.11, 95% CI 0.04 – 0.29), all compared to patients not allocated cardioprotectants. While statins, ACE inhibitors and beta-blockers all showed some reduction in cardiotoxicity when compared to patients not allocated cardioprotectants it is not clear whether this benefit is maintained over the long term.[63]

Dexrazoxane affords some cardioprotection even when given after the first 300 mg/m^2 of doxorubicin have been received. Swain et al. (1997) conducted two RCTs of anthracycline with and without dexrazoxane[64]. An interim analysis of these trials showed clear cardioprotection in the dexrazoxane arms. Subsequent to this analysis, patients in

the non-dexrazoxane arm of these trials were given dexrazoxane alongside their doxorubicin after a cumulative dose of 300 mg/m^2 of doxorubicin had been received (delayed dexrazoxane). Patients who had not received dexrazoxane were more than three times more likely to have a cardiac event than those who received delayed dexrazoxane (hazard ratio=3.5, 95% CI 2.2 – 5.7, $p<0.001$).

CHAPTER 2 MOTIVATION AND AIMS

2.1 MOTIVATION FOR THIS STUDY

Cancer patients are now surviving longer, thus it is desirable to increase the understanding of long term side-effects of cancer therapies. Anthracycline chemotherapy is widely used, and contributes to an increasing number of people surviving their cancer, but also carries the risk of cardiotoxicity. It is important to understand the extent of the cardiac risk to anthracycline patients, and to determine how that risk changes over time. There is clear evidence that anthracyclines are cardiotoxic, and that the risk of cardiotoxicity increases with increasing cumulative dose of anthracycline. Long term follow-up of childhood cancer survivors treated with anthracyclines show chronic and progressive abnormalities in heart function, and increased risk of congestive heart failure. Much of the evidence for cardiotoxicity in adults is for early anthracycline cardiotoxicity, with little understanding of how risk might change over the long-term. Certainly the "Multiple-Hit" hypothesis of an injury, compensation, decompensation process (as discussed in Chapter 1) suggests that the increased risk of a cardiac event continues across the lifespan

Prior meta-analyses of cardiotoxicity in RCTs of anthracycline vs not have been able to include very few trials in their analyses. Combining data from the small number of trials found may still have resulted in analyses that include too few patients to detect true differences between trial arms. The trials included in existing meta-analyses are a small subset of the anthracycline versus not RCTs that have ever been done. Many of the trials not found in earlier meta-analyses may have collected data on cardiac outcomes and could contribute to cardiotoxicity analyses.

Published-data meta-analyses have focussed on non-fatal cardiac events in their analyses. However, there is reason to believe that cardiac outcomes may be more closely

followed in anthracycline-treated patients. Given that clinicians know anthracyclines are cardiotoxic, they may be more likely to closely monitor the cardiac health of patients treated with or allocated to anthracyclines than those not treated with or allocated to anthracyclines. This would lead to ascertainment bias and a higher proportion of the cardiac events that occur being found in anthracycline-treated patients than in those not treated with anthracyclines. For this reason, an analysis of non-fatal cardiac events in trials of anthracycline versus not may be biased, and may overestimate the cardiotoxicity risk.

In addition, current clinical trial recommendations specify that data on adverse events that occur after the patient has stopped taking study medication need only be reported to regulatory authorities if they are deemed to be related to study drugs.[65] Adverse events deemed to be unrelated to study drugs need only be collected for the timeframe specified in the study protocol, which is often only until 30 days post treatment. After this time period it is unlikely that adverse events would be systematically followed up in all trial patients unless it was a pre-specified outcome of the trial. This suggests that the majority of adverse event data reported in trial publications reflect events that occur while the patient is on treatment, and that estimates of event rates during long-term follow-up of randomised trials may be unreliable. Sporadic reports of adverse events, including cardiotoxicity, may be collected, but as this data is not systematically collected, the trials are inherently biased.

While follow-up of non-fatal adverse events in cancer trials may not be systematic, this is less an issue for causes of death. Many cancer trials include cause of death (COD) as an outcome. There is no reason to suspect that data on COD would be collected less completely and systematically in non-anthracycline compared to anthracycline-allocated

patients. Given the greater potential for bias in non-fatal cardiac event data, this thesis will only analyse data on cardiac death and not data on non-fatal cardiac toxicity.

Current estimates of anthracycline-related cardiac risk that are calculated from aggregated data extracted from RCT publications can only convey information about cardiotoxicity incidence and nothing about the time-course of the disease. It is not possible to construct survival curves using aggregated data as there is no information as regards the time when cardiac events occur. A meta-analysis of individual patient data from RCTs would address this issue by collecting information on both the occurrence and date of cardiac events, which would enable the construction of survival curves. In addition, individual trials are usually too small to detect differences in cardiac outcomes reliably, and published trial reports rarely present cardiotoxicity data in a form that is appropriate for meta-analysis. An individual patient data meta-analysis avoids these problems by collating data from existing trials. This increases the power to detect differences in uncommon outcomes. Therefore, individual patient data meta-analyses of cardiotoxicity in RCTs of chemotherapy would be desirable.

2.2 AIMS OF THIS THESIS

The aims of this thesis are fourfold:

1. *To determine the extent of outcome reporting bias in randomised trials of anthracycline vs not*. Previous published-data meta-analyses mention that cardiac outcomes are not reported well, and that much data may be missing. It is important to gauge the extent to which cardiac outcomes are missing in published trial reports and how this may affect risk estimates generated in meta-analyses of published data. Thus outcome reporting bias will be investigated in all trials that fit the eligibility criteria for this thesis

2. *To determine the extent of risk of cardiac deaths in randomised trials of anthracycline vs not*. Prior published-data meta-analyses find and include only a very small number of trials. It seems unlikely that these few trials represent the majority of anthracycline vs not trials that have ever been conducted. Thus a more extensive search for anthracycline vs not trials will be conducted. The aim is to construct a complete list of all anthracycline vs not trials that have been done and to conduct a meta-analysis using individual patient data, to better establish the risk of cardiac death and how this changes across the lifespan.
3. *To determine the effect of other cancer treatments on anthracycline cardiotoxicity risk*. Prior published-data meta-analyses limit inclusion to trials where the only difference between trial arms is the anthracycline. In this thesis more liberal criteria that allow the inclusion of RCTs with multiple differences between trial arms will be used. The effect of this will be explored in meta-analyses of both published and individual participant data.
4. *To commence the process of conducting IPD meta-analyses of anthracycline cardiotoxicity in RCTs.* Individual RCTs may be too small to reliably detect differences in rare outcomes such as anthracycline cardiotoxicity. Published-data meta-analyses have greater power to detect these differences but, due to the aggregated nature of the data, cannot reveal anything about the time-course of anthracycline cardiotoxicity. Thus, this thesis will begin the process of conducting an IPD meta-analysis of cardiotoxicity in randomised trials of anthracycline vs not.

CHAPTER 3 TRIAL SEARCH

3.1 INTRODUCTION

The first steps in conducting a meta-analysis of data from randomised trials are to define the question of interest, the specific randomised comparisons to be considered, and the outcomes to be studied. Once these have been settled, literature searches are conducted to identify and compile a list of the trials that are eligible for the meta-analysis.

In this study, the question to be addressed was the cardiotoxicity of anthracycline when used in the treatment of cancer, and the specific randomised comparisons to be considered were the following:

- Anthracycline-containing chemotherapy regimen vs no chemotherapy
- Anthracycline-containing chemotherapy regimen vs non-anthracycline chemotherapy
- Anthracycline-containing chemotherapy regimen vs radiotherapy

Any of these comparisons may be confounded by the presence of non-anthracycline agents that are cardiotoxic, such as radiotherapy that includes the heart. This is discussed in more detail in Chapter 4.

Risk of cardiac death was the primary outcome for this study. While existing meta-analyses of published data from randomised controlled trials (RCTs) of anthracycline versus not have included cardiac death as an outcome, the primary analyses were of non-fatal cardiotoxicity. This study used cardiac death as the primary outcome for several reasons. Firstly, there is little to suggest that cardiac status is assessed systematically in all arms of randomised trials, or that data on this endpoint is routinely collected during follow-up. Even if data on non-fatal cardiac events were collected, it is often not reported. Reports of cardiac death may also be subject to lower levels of information bias than non-fatal cardiac events. Information bias occurs when there are differences between

study groups in the data collected on exposures or outcomes. Cause of death is a primary outcome of many cancer trials and thus would be collected for all patients for the full-length of follow-up. These issues were discussed in more detail in Chapter 2.

Randomised trials in any cancer, and in patients whose cancer was diagnosed at any age, were eligible. Trials were to be excluded for the following reasons:

- Anthracycline was given for the treatment of a non-cancer disease, such as multiple sclerosis
- The anthracycline was given by local administration, with limited systemic exposure to the drug (e.g. intravesical administration in bladder cancer, or trans-arterial chemo-embolization in hepatic cancer.)
- Trials in which patients in every trial arm were to receive anthracycline, i.e. there must have been at least one arm in the trial in which the patients were not to be given anthracycline.

Eligible RCTs were identified by a series of systematic searches of the published literature. The initial literature search employed a search strategy similar to that used in previous systematic reviews that have already been published[56, 58, 60, 66], and included terms for:

- Anthracyclines, i.e. daunorubicin, doxorubicin, epirubicin, idarubicin, liposomal daunorubicin, liposomal doxorubicin, and the anthracycline analogue mitoxantrone.

and

- Randomised controlled trials, using the Cochrane highly sensitive search strategy.

and

- Cardiotoxicity, including cardiac tests, cardiac anatomy and cardiac outcomes.

Searches were conducted of the databases MEDLINE and EMBASE for all years with no language restrictions applied (see Appendix A.1 for full search strategies). The search included terms from the controlled vocabulary thesauri of both databases, called MeSH terms in MEDLINE and Emtree terms in EMBASE, as well as terms generated from knowledge of the subject area.

3.2 INITIAL TRIAL SEARCH

The MEDLINE and EMBASE searches identified 6471 publications. After removal of duplicates there were 5442 publications remaining. Based on a review of the titles and abstracts, 4579 of these were excluded as they were either review papers, animal or in vivo cell studies, or non-randomised studies, leaving 1271 publications. Of these, 506 publications were not trials of anthracyclines, or were trials that included anthracycline but did not fit the inclusion criteria for this study. The publications that did report an anthracycline randomisation were then grouped according to the nature of the anthracycline comparison. There were 155 publications that reported a comparison of one anthracycline versus another. There were 214 papers that reported comparisons of dosing strategy, and there were 68 papers that reported comparisons of anthracycline with or without a cardioprotectant. These 437 trials were not considered further in this study. The 328 remaining publications represented 246 unique RCTs of anthracycline versus not and these were the subject of this study (see Figure 5).

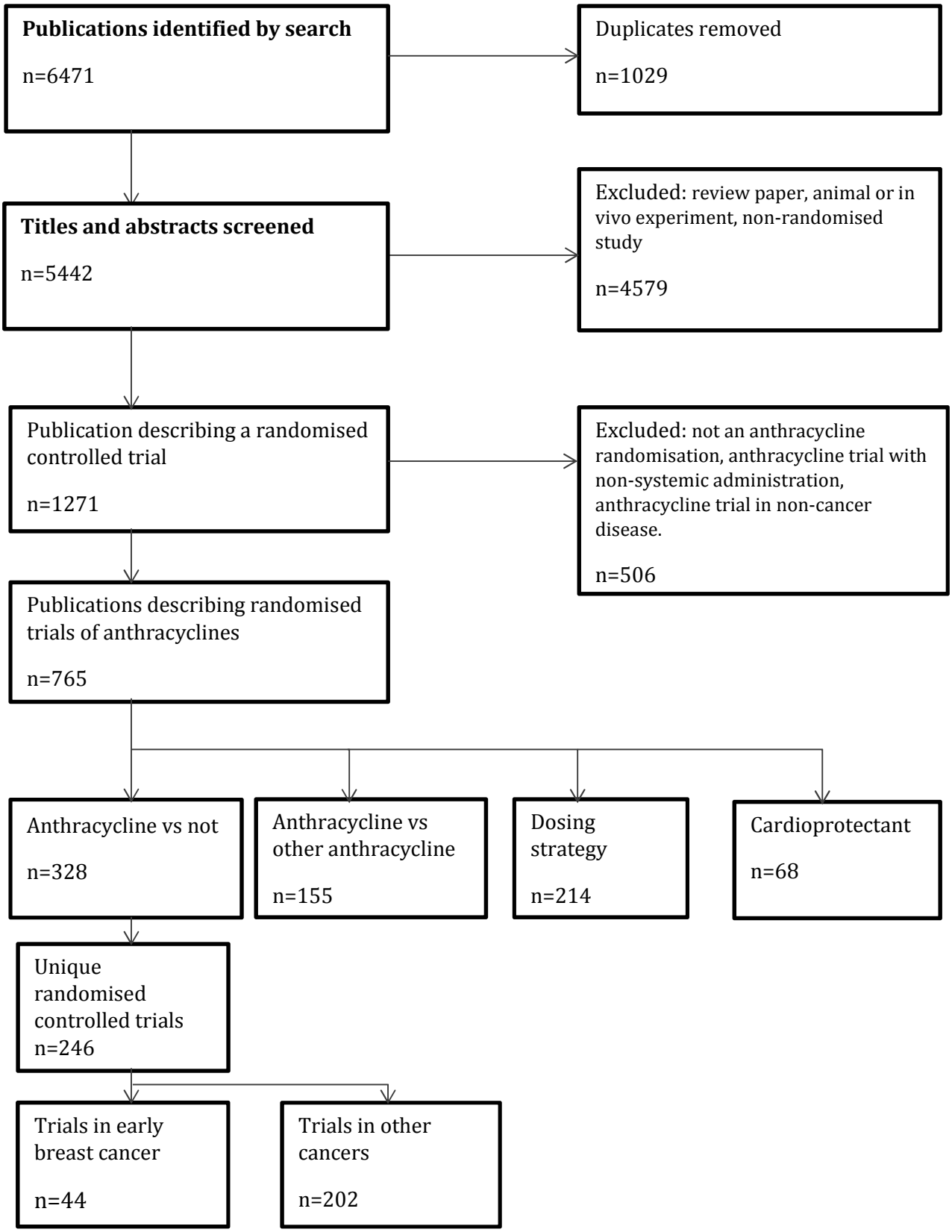


FIGURE 5 RESULTS OF THE INITIAL SEARCH TO IDENTIFY TRIALS ELIGIBLE FOR THE ANTHRACYCLINE CARDIOTOXICITY META-ANALYSIS

Of the 246 randomised trials of anthracycline versus not found by this initial literature search, the type of cancer with the largest number of trials was early breast cancer with 44 trials, while there were 202 trials of anthracycline versus not in other sites of solid cancer (metastatic breast, gynaecologic and other solid tumours) or haematological malignancies (leukaemia, lymphoma, and multiple myeloma) (see Table 3.1). The majority of the trials started in the 1980s-90s although the earliest started in the 1970s, and the most recent after 2005.

TABLE 3.1 TRIALS IDENTIFIED BY THE INITIAL TRIAL SEARCH

Site or type of cancer	Total number of trials	Trials with at least 100 patients per arm and median progression-free survival at least one year	Trials with less than 100 patients per arm or median progression-free survival less than one year
Pancreas	4	0	4
Wilms Tumor	4	3	1
Bladder	8	0	8
Other cancers	8	1	7
Other gynaecologic	8	1	7
Multiple myeloma	9	4	5
Hepatocellular	11	0	11
Sarcoma (soft tissue and osteosarcoma)	14	4	10
Prostate	14	3	11
Leukaemia	14	4	10
Lymphoma	17	7	10
Ovaries	19	7	12
Stomach	19	5	14
Lung	22	0	22
Metastatic breast	31	0	31
Early breast	44	37	7
Total	**246**	**76**	**170**

3.2.1 EVALUATION OF THE INITIAL SEARCH

It is possible to check the completeness of a trial search by comparing the list of RCTs identified to a pre-existing trial list. Of course no list exists that contains all randomised trials of anthracycline versus not in all cancers. However, there is a complete list for one disease. Since 1985, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has been carrying out regular literature searches and maintaining a list of all known randomised trials of treatments for early breast cancer. The EBCTCG were contacted and a copy of their complete trial list requested. This was provided and found to include over 500 trials, including 110 trials of anthracycline versus not.

All of these trials 110 trials should have been identified by the initial trial search. However, the search found only 44 of them, i.e. 40%. For 17 of these 44 trials, the search identified the trial from the MeSH or Emtree terms applied to the citation by MEDLINE or EMBASE. The other 27 trials were identified via a cardiac term in the title or abstract.

Several of the 66 trials that were on the EBCTCG list but were not identified by the search were missed because cardiac terms did not appear in the title or abstract of the publication, and did not have MEDLINE or EMBASE controlled vocabulary term applied to reflect this. Consequently a search strategy including cardiac terms would not be able to find these publications.

3.3 REVISION OF THE INCLUSION CRITERIA

Further evaluation of the initial trial search consisted of examining the number of patients randomised, and also the median progression-free survival (PFS). Most of the trials found were small or had rather short median PFS, and only 76 trials included at least 100 patients in each arm and also had median PFS of at least one year (see Table

3.1). Thirty seven of these were in early breast cancer and 39 in other cancer types, including 7 paediatric trials (3 Wilms tumour, 2 acute lymphoblastic leukaemia, 1 non-Hodgkin lymphoma, and 1 osteosarcoma) and 32 trials in adult patients, or patients of any age. Small trials will contain a limited number of cardiac deaths and hence only a small amount of information. Furthermore, as the focus of this meta-analysis is long-term cardiotoxicity, trials with short survival or follow-up have limited information to contribute to the analysis. Therefore, a decision was made to consider only trials of reasonable size and with reasonably long follow-up.

In the light of the findings of the initial trial search, it was decided to exclude trials which did not satisfy the following additional criteria:

- At least 100 patients per trial arm.
- Median progression-free survival of at least 12 months in all trial arms.

3.4 REVISED TRIAL SEARCH

In view of the low proportion of early-breast cancer trials identified, the trial search strategy was revised to include only the anthracycline and randomised controlled trial search terms and the cardiac terms were dropped (see Appendix A.2 for full search strategies). The revised search strategies were run in MEDLINE and EMBASE, for all years, with no language restrictions applied.

The revised MEDLINE and EMBASE searches identified an additional 21,528 unique publications after removal of those publications found by the initial search. After a further 4935 duplicate records were removed, 16593 publications remained. A team of 9 people each reviewed the title and abstract of approximately 2000 of these records, tagging any record that referred to a randomised trial. 10553 publications were excluded

at this point as they were review papers, animal or in vivo cell studies, or non-randomised studies, leaving 6040 publications that definitely referred to a randomised trial. Of these, 4968 publications were not trials of anthracyclines, or were trials that included anthracycline but did not fit the inclusion criteria for this study, i.e. there were less than 100 patients per trial arm, or had median progression free survival of less than 12 months, leaving 1072 publications. Of these, there were 682 publications that reported other anthracycline comparisons, i.e. anthracycline versus other anthracycline, anthracycline dosing strategy comparison, or anthracycline with or without a cardioprotectant. These categories were not considered further in this study. The 390 remaining publications included an additional 80 trials not found by the first search (see Figure 6).

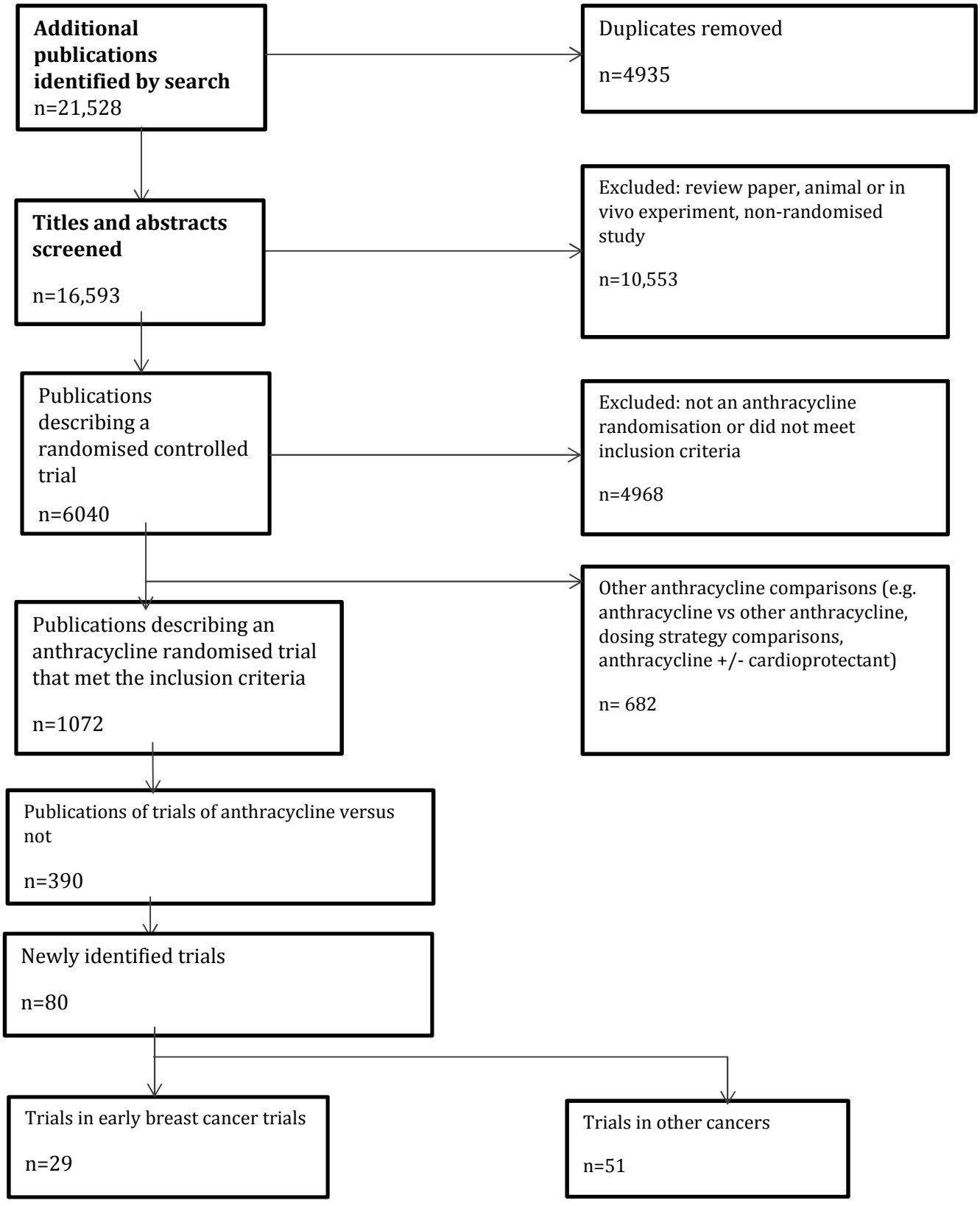


FIGURE 6 RESULTS OF THE REVISED SEARCH TO IDENTIFY TRIALS ELIGIBLE FOR THE ANTHRACYCLINE CARDIOTOXICITY META-ANALYSIS

3.5 COMBINED SEARCH RESULTS

The results of both the initial and revised trial searches were collated. The combined searches found 156 trials that fit the inclusion criteria for this study (see Table 3.2). An additional 15 trials were found by searching reference lists of meta-analyses, emailed alerts that search for anthracycline and cardiotoxicity in titles of newly published papers, and unpublished trials that were included on the EBCTCG trial list. Thus, there were 171 trials identified that fit the inclusion criteria for this study (see Appendix B.1 for full trial descriptions). The type of cancer with the largest number of trials was early breast cancer with 76 trials, while there were 95 trials of anthracycline versus not in other sites of solid tumour or haematological malignancies. The majority of the trials started in the 1980s-90s, with the earliest starting in the 1970s and the most recent in 2010.

TABLE 3.2 TRIALS IDENTIFIED BY THE COMBINED TRIAL SEARCHES

Cancer	Trials in first search	Additional second search trials	Total of both searches	Trials found by other methods (journal alerts, EBCTCG list etc.)	Total number of trials found
Hepatocellular	0	1	1	0	1
Wilms Tumor	3	0	3	0	3
Bladder	0	3	3	0	3
Nasopharyngeal	1	2	3	0	3
Prostate	3	0	3	0	3
Other gynaecologic	1	5	6	0	6
Sarcoma (soft tissue and osteosarcoma)	4	2	6	0	6
Multiple Myeloma	4	5	9	0	9
Ovarian	7	3	10	0	10
Gastric	5	6	11	1	12
Leukaemia	4	7	11	2	13
Lymphoma	7	17	24	2	26
Early breast	37	29	66	10	76
Total	**76**	**80**	**156**	**15**	**171**

3.5.1 EVALUATION OF COMBINED SEARCHES

The EBCTCG trial list was used once again to evaluate the completeness of the combined searches. Of the 110 trials of anthracycline versus not on the EBCTCG trial list, a total of 76 satisfied the revised inclusion criteria for this study, i.e. had at least 100 patients per trial arm and median progression-free survival of at least one year. The first search had found 37 of these 76 trials, which is 48%. The revised search found another 29 of the eligible trials on the EBCTCG list. Therefore, when the results of the two searches were combined, 66 of the 76 eligible EBCTCG trials were found, which is 87%. Further

investigation of the 10 eligible trials on the EBCTCG list that were not found by the searches, showed that four trials had only ever been published as conference abstracts not indexed by citation databases such as MEDLINE or EMBASE. The remaining 6 trials had never been published. Of the unpublished studies, one was a trial opened to recruitment in 2008 for which the final analysis had not taken place. Another of the unpublished studies had been referred to in other papers by the trial group, but results not published separately. The other four studies were smaller studies that only just met the patient numbers inclusion criteria for this study. The searches found 87% of the eligible EBCTCG trials, which represents more than 90% of the patients ever randomised who fit the inclusion criteria for this study, it seems likely that a similar proportion of trials in other cancers were also found by the search.

3.6 DISCUSSION

One of the first steps in conducting a meta-analysis of randomised trials is to construct a list of trials which are relevant to the question of interest. Clearly such a list needs to be as complete as possible, and one of the major elements in constructing such a trial list is a series of systematic searches of relevant citation databases. These searches need to be constructed carefully, including search terms for randomised trials, as well as terms for the intervention being investigated. Many meta-analyses also include search terms for the outcome being investigated, particularly when the purpose of the meta-analysis is to investigate outcomes other than the primary outcome of the included trials, such as treatment toxicities. However, if a trial was carried out in order to evaluate treatment efficacy rather than toxicity, toxicity may not have been included as a primary outcome of the trial, and so may not have been reported as fully as treatment efficacy. As a result,

terms for these toxicities often do not appear in the title, abstract or keywords of papers indexed in citation databases, i.e. the fields most often used when searching citation databases. Search strategies that include toxicity terms, will therefore miss many potentially relevant trials, as relevant terms do not appear in the citation for the paper in the database.

In the present study, a search that included toxicity terms found less than half the relevant trials on an existing trials list, and many of the trials on that list did not report cardiac outcomes in their papers. This is not surprising as, in the era when the majority of the eligible trials were published, there was no requirement to report negative side effects of treatment in publications reporting trial results. Furthermore, even when cardiac outcomes were reported, they were often not mentioned in the title, abstract or keywords of the paper. Therefore MEDLINE and EMBASE could not identify these trials when cardiac terms were included in the search. Even if toxicity is not reported in the trial publication, data relevant to that endpoint may have been collected, and could contribute to a meta-analysis of individual patent data. This topic is discussed further in Chapter 6.

The initial trial search revealed that many of the trials of anthracycline versus not that had been carried out were small or had short survival. Trials that included only small numbers of patients will only contain limited information on cardiac death. Furthermore, in order to investigate long-term cardiac mortality, patients included in trials need to survive their cancer for long enough to incur appreciable risk of dying of cardiac causes. Where survival from the cancer in question is poor, and median progression-free survival is less than 12 months, even trials of moderate size will provide little information on long-term cardiac death. Of the 246 trials found by the initial search in

this study, two thirds of them included less than 100 patients per trial arm, or had median progression-free survival less than 1 year.

In a previously published review of cardiac events in randomised trials of anthracycline versus not it was reported that patients allocated to anthracycline were four times as likely to die of cardiac causes as other patients, and the increase was significant[56]. That review included cardiac terms in its search strategy but was only able to include four trials in the cardiac death analysis. Furthermore, of these four trials, only one met the inclusion criteria for the present study. The other three trials did not meet the inclusion criteria for this study as the median survival of included patients was less than 12 months. The searches conducted for the present study suggest that considerably more information on cardiac mortality in trials of anthracycline treatment is available in the published literature which could be included in a meta-analysis of cardiac death.

CHAPTER 4 CONFOUNDING IN META-ANALYSES OF RANDOMISED TRIALS

4.1 INTRODUCTION

Meta-analysis of randomised trials involves the collation and analysis of data that may have been collected in different ways, at different times, with varying length of follow-up and also possibly with different primary outcomes.[67] The first steps in a meta-analysis of randomised trials are to formulate the research question, specify randomised comparisons to be considered, and the outcomes to be studied. Then study inclusion criteria are defined, and a search is conducted to identify potentially eligible studies. Each study is reviewed and a decision is made whether it meets the pre-defined eligibility criteria. Finally, decisions are made on whether the included studies can be considered together and whether, for some analyses, they should be divided into subgroups.

One advantage of conducting a meta-analysis is that it increases the statistical power to detect a treatment effect. This is important when investigating a rare outcome where individual studies may not be large enough to contain many events. Collating data from many studies improves the power to detect an effect. A meta-analysis of an outcome which is not the primary outcome of the included studies, such as a treatment harm, may be particularly at risk of low power. Harm outcomes may not be reported as often as efficacy outcomes, or reported in sufficient detail to enable data-extraction for meta-analysis. If the harms data is not reported, the trial may not be found by a trial search that includes terms for the harm. If the trial is found, but the harms data is not extractable, then it cannot be included in the meta-analysis. This could lead to low statistical power due to many potentially informative studies being excluded from the meta-analysis.

There are several potential sources of bias that may be introduced in the process of conducting a meta-analysis of harm outcomes. If the harm outcome is rare, then combining data from a small number of studies may not improve power to detect significant differences in the outcome. This can lead to false negative errors, whereby the meta-analysis fails to detect a true difference in the outcome. Combining a small number of trials also has the potential to introduce selection bias through the use of an unrepresentative sample. Publication bias occurs when trials with significant results are more likely to be published than trials with non-significant results. Positive trials are therefore more likely to be identified during a trial search than trials without significant result. This can lead to the effect estimate generated by the meta-analysis being more extreme than it should be.

The present chapter is going to consider how the problems outlined above can be overcome in a meta-analysis of anthracycline cardiotoxicity. The anthracyclines are a class of chemotherapy agent that are widely used in a variety of cancers. They are very effective at curing cancer but they can increase the risk of heart disease.[17, 18, 68] The primary outcome of anthracycline trials is often either recurrence or survival. Suppose a meta-analysis were designed to investigate the risk of heart disease after anthracyclines in randomised trials of anthracycline containing chemotherapy vs non anthracycline or no chemotherapy. In its simplest form, this meta-analysis would include those trials where the only difference between trial arms was the presence or absence of the anthracycline. Several meta-analyses of published data have used this design but were able to include only a small number of trials, as very few fit this pattern.[54, 56] However, if the eligibility criteria were widened to include trials with more than one difference between trial arms, many more trials could be included. To enable inclusion of

randomised trials with more than one difference between trial arms, a process has been devised to classify trials according to how additional differences between trial arms might affect the risk estimates generated.

4.2 DEFINITIONS

A confounder is a factor that is associated with both the exposure and the outcome being investigated. This can be applied to the comparison in a randomised trial where the test is of the association between a treatment (the exposure) and an outcome (e.g. improved survival). In many randomised trials in cancer, there are multiple treatments used in each trial arm, and each trial arm may use different combinations of treatments. Any treatment that is not common to all trial arms could potentially be a confounder of the association between the treatment of interest and the outcome. In a trial where the combination of treatments used in each trial arm is different, it can be difficult to decide whether to include the trial in the meta-analysis. If the trial is included, consideration should be given to how all of the randomised differences between arms affect the endpoint under investigation, which might not be the primary endpoint of the trial.

In order to decide if a particular treatment used in a trial acts as a confounder, a review of the evidence for the association between that treatment and the outcome must be made. If there is evidence that the treatment is associated with the outcome, then it can be considered active for the outcome, and is a confounder. If the effect of the treatment on the outcome is unknown, with no evidence for or against it, the treatment can be considered inactive for the outcome. When reviewing the evidence of association with the outcome, it is important to consider both the cumulative and individual doses of each treatment, as different doses of a treatment may affect the outcome differently. A

treatment that has no association with the outcome at a certain individual dose, may still affect the outcome above a specific cumulative dose. A treatment such as this would only be a confounder when the individual or cumulative dose was above the threshold dose level for association with the outcome, and would not be a confounder below those doses.

Definitions for each of the terms used to define confounding in this thesis are provided below (see Table 4.1). The outcome is the outcome being investigated in the meta-analysis and may or may not be the primary outcome of each included randomised trial. The test treatment is the intervention under investigation. It is assumed that the test treatment increases the incidence of the outcome of interest. Background treatment is that combination of drugs and/or radiotherapy given in addition to the test treatment. Background treatment may be different in each arm of the randomised trial. A harmful treatment is any treatment for which there is evidence that it increases the outcome of interest. A protective treatment is any treatment for which there is evidence that it decreases the outcome of interest. Other treatments are those for which there is no known evidence for the effect on the outcome of interest. In the following discussion, other treatments are therefore assumed not to affect the outcome of interest.

TABLE 4.1 DEFINITION OF TERMS

Term	Definition
Outcome	The outcome being investigated in the meta-analysis*
Test treatment	The treatment of interest
Background treatment	A treatment or combination of treatments given to both trial arms that are not the test treatment
Harmful treatment	There is evidence that this treatment increases the outcome of interest
Protective treatment	There is evidence that this treatment reduces the outcome of interest
Other treatments	There is no evidence for the effect of these treatments on the outcome of interest
Randomised difference	A treatment given to one treatment arm but not the other

*This is not necessarily a primary outcome of the original trials

For the present meta-analyses, a list of all the non-anthracycline drugs and other interventions in each trial was compiled. The anthracyclines included in the meta-analyses are listed in Table 4.2. A literature review of the evidence for cardiotoxicity of each of the non-anthracycline treatments that appeared in an included randomised trial was undertaken. Treatments were categorised as *Harmful* if there was any evidence that they were cardiotoxic, or *Protective* if there was evidence that they protect the heart (See Table 4.3). Any evidence of cardiotoxicity, regardless of the source or type was accepted, even from studies that provide very weak evidence. The type of evidence for cardiotoxicity and cardioprotection was classified by adapting the Oxford Centre for Evidence Based Medicine 2011 Levels of Evidence.[69, 70] Treatments for which there were no reports of cardiotoxicity or cardioprotection were classified as Other treatments (see Table 4.4). The existing published evidence on the effects of various chemotherapy treatments on the heart was mostly based on case series which reported only short term

effects. For the purposes of this meta-analysis, radiotherapy was included as a harmful treatment only if the heart was irradiated, and there was assumed to be no interaction effects between anthracyclines and cardiotoxic treatments.

TABLE 4.2 ANTHRACYCLINES AND ANTHRACYCLINE ANALOGUES USED IN RCTS INCLUDED IN THIS META-ANALYSIS

Anthracyclines			
Daunorubicin	Epirubicin	Liposomal doxorubicin	Mitoxantrone
Doxorubicin	Idarubicin	Liposomal daunorubicin	

TABLE 4.3 CARDIOTOXICITY IN HUMANS OF NON-ANTHRACYCLINE TREATMENTS USED IN RCTS OF ANTHRACYCLINES IN THIS META-ANALYSIS

Type of evidence	Harmful treatments (Evidence of cardiotoxicity)	Protective treatments (Evidence for protection from cardiotoxicity)
Meta-analysis or systematic review of randomised trials	Radiotherapy (if heart irradiated)[71]	Dexrazoxane[56, 63, 66]
Meta-analysis or systematic review of observational studies	Estramustine[72] Trastuzumab[4, 15]	
Randomised trial(s)	Docetaxel[73, 74] Paclitaxel[75-78] Thalidomide[79-83] Capecitabine[84]	ACE inhibitors[66, 85] Beta-blockers[66, 86]
Non-randomised controlled trial(s), or cohort studies	Androgen deprivation (e.g. Buserelin, Goserelin, Triptorelin)[87] 5-Fluorouracil [88-92] Bortezomib[93-95] Cyclophosphamide[96-100] Cisplatin[101, 102] Corticosteroids (e.g. dexamethasone, prednisone)[103] Ifosfamide[104-109] Rituximab[110-113]	
Case series, case control or historically controlled studies, or case reports	Bleomycin[114-120] Cytarabine[121-128] Etoposide[129-132] Fludarabine[133, 134] Gemcitabine[135] Melphalan[136, 137] Methotrexate[138-140] Mitomycin C[141-146] Tegafur[147] Vinblastine[148] Vincristine[149-152]	

*Evidence from human studies only

TABLE 4.4 TREATMENTS OF NO KNOWN CARDIOTOXICITY IN HUMANS USED IN RCTS OF ANTHRACYCLINES IN THIS META-ANALYSIS

Other Treatments (unknown effect on outcome)			
Actinomycin D	Cladribine	Leucovorin	Prednimustine
Asparaginase	Clodronate	Letrozole	Procarbazine
Bacillus calmette geurin	Dacarbazine	Mechlorethamine	Tamoxifen[153]
Bendamustine	Glutathione	Mercaptopurine	Thioguanine
Carboplatin	Hexamethylamine	MESNA	Thiotepa
Carmustine (BCNU)	Ketoconazole	Oxaliplatin	Topotecan
Chlorambucil	Lenograstim	Pamidronate	Zoledronate

4.3 UNCONFOUNDED COMPARISONS

A comparison is unconfounded when the only treatment used in the trial that is associated with the outcome of interest is the test treatment, and there is no evidence that other treatments in the comparison are related to the outcome. In unconfounded comparisons we can say that any increased risk of the outcome is likely to be caused by the test treatment (see Table 4.5).

TABLE 4.5 UNCONFOUNDED TRIAL DESIGNS

Trial design		Test arm	Control arm
A.	*Unconfounded comparisons*		
1	Simple	Test treatment	No treatment / placebo
		Test treatment + Background treatment	Background treatment only
2	Complex	Test treatment + Background treatment	No treatment/placebo
		Test treatment + Background treatment	Different background treatment
3	Involve dose differences – *where dose not associated with outcome*	Test treatment + Background treatment	Differently dosed background treatment

4.3.1 SIMPLE UNCONFOUNDED DESIGNS

In simple unconfounded comparisons (Table 4.5, A1 above) the only difference between trial arms is the presence or absence of the test treatment. There are two designs that fit this pattern:

Test treatment	vs	No treatment or placebo
Test treatment + Background treatment	vs	Background treatment alone

For both of these designs we can say that any difference in the outcome of interest is likely to be due to the test treatment, as there is no evidence that any of the other treatments affect the outcome of interest.

In the anthracycline cardiotoxicity meta-analysis the following are simple unconfounded comparisons:

Doxorubicin	vs	Observation
Doxorubicin + Cisplatin	vs	Cisplatin

In the first example, the only treatment used is doxorubicin. There is nothing to confound the association between doxorubicin and cardiotoxicity. In the second example there is some evidence that cisplatin is cardiotoxic[101, 102] but the only difference between the trial arms is the presence of doxorubicin in the test arm. In both these examples we can say that any increase in cardiotoxicity is due to the doxorubicin as this is the only difference between the test and control arms.

4.3.2 COMPLEX UNCONFOUNDED DESIGNS

In complex unconfounded designs (Table 4.5, A2 above), there are multiple differences between trial arms, but the only treatment with evidence of association with the outcome is the test treatment. There are two designs that fit this pattern:

Test treatment + Background treatment	vs	No treatment or placebo
Test treatment + Background treatment	vs	Different background treatment

It is assumed that all of the treatments in the background treatment are Other treatments, with no evidence of association with the outcome of interest. For both of these designs we can say that any increase in the risk of the outcome is due to the test treatment. In the second example the background treatment is different in each arm, but

as there is no evidence that any of these background treatments are associated with the outcome, they do not act as confounders.

In the anthracycline cardiotoxicity meta-analysis the following trial is a complex unconfounded comparison:

Daunorubicin + Cytarabine	vs	Amonafide L-malate + Cytarabine

In this example, there is some evidence that cytarabine is cardiotoxic, but it is used in both arms, and therefore it is not a confounder in this example. There is no known evidence that amonafide L-malate is cardiotoxic. Therefore, despite the background treatment being different in the test and control arms this trial is unconfounded, as the only cardiotoxic treatment is doxorubicin.

For this design we can say that any increase in the risk estimate is due to the anthracycline because there is no evidence that any of the other treatments that differ between arms are associated with cardiotoxicity.

4.3.3 UNCONFOUNDED COMPARISONS THAT INVOLVE DOSE DIFFERENCES

The final set of unconfounded designs are similar to simple unconfounded comparisons in that the main difference between trial arms is the presence or absence of the test treatment, but there are also differences in the dosing of background treatments in each trial arm (Table 4.5, A3 above). There are multiple designs that fit this pattern, such as the following:

Test treatment + Standard dose background	vs	Higher dose background
Test treatment + Higher dose background	vs	Standard dose background

Comparisons of these designs are unconfounded only where there is no evidence that higher doses of the background treatment are associated with the outcome of interest. If higher doses of the background are associated with cardiotoxicity, the trial would be classified as confounded.

For example, standard treatment for a particular cancer is a two treatment chemotherapy regimen. If a researcher wanted to investigate whether there was benefit to adding a third treatment to standard chemotherapy they might design a trial where the control arm used the standard treatment. In the test arm of this trial, the researcher adds the new treatment, but reduces the dose of the standard treatment. There are now multiple differences between the trial arms, which may confound the association between the test treatment and the outcome, such as in the following comparison:

Doxorubicin 300mg/m^2 + Actinomycin D 450mcg/m^2 + Vincristine 52.5mg/m^2	vs	Actinomycin D 600mcg/m^2 + Vincristine 60mg/m^2

Here doxorubicin plus lower doses of actinomycin D and vincristine are compared to standard doses of vincristine and actinomycin D. There is no evidence for actinomycin D cardiotoxicity (see Table 4.4). There is limited evidence from case reports that vincristine is cardiotoxic[149-152], but it does not appear to be dose dependent, higher doses are not more likely to be cardiotoxic than lower doses. As actinomycin D and vincristine are common to both arms, and there is no evidence of a dose relationship with

cardiotoxicity, we can still consider this trial unconfounded, despite the dose differences between trial arms. We can say that any increase in cardiotoxicity in this trial is likely due to the doxorubicin.

4.4 CONFOUNDED COMPARISONS

Many randomised trials, particularly in oncology, involve multiple treatments, any of which may be associated with the outcome of interest. If any of the background treatments in the trial are associated with the outcome, they act as confounders of the association between the test treatment and the outcome. Many meta-analyses would exclude such trials, as it may be difficult to interpret the risk estimates generated from them. This thesis suggests a method by which confounded trials can be included in meta-analyses, by considering how confounder treatments might affect the risk estimate. Comparisons which include confounders that affect the risk estimate in similar ways can be grouped in the analysis.

There are three main ways that confounders can affect the risk estimate: confounding that increases the risk estimate, confounding that reduces the risk estimate, and confounding that has unpredictable effects on the risk estimate (see Table 4.6).

TABLE 4.6 CONFOUNDED TRIAL DESIGNS

B	*Confounded comparisons*		
1	Positive confounding (increases the risk estimate)	Test treatment	Protective treatment
		Test treatment + Harmful treatment	No treatment / placebo
		Test treatment + Harmful treatment + Background treatment	Background treatment only (may be different to background in test arm)
2	Negative confounding (decreases the risk estimate)	Test treatment	Harmful treatment
		Test treatment + Background treatment	Harmful treatment + Background treatment
		Test treatment + Protective treatment	No treatment / placebo
		Test treatment + Protective treatment + Background treatment	Background treatment (may be different to background in test arm)
3	Unknown confounding (unpredictable effect on the risk estimate)	Test treatment + Harmful treatment(s)	Different harmful treatment(s)
		Test treatment + Protective treatment	Harmful treatment
		Test treatment + Harmful background	Protective treatment

4.4.1 POSITIVE CONFOUNDING

Positive confounding (Table 4.6, B1 above) occurs when potential confounders might increase the risk estimate (i.e. move the risk estimate away from the null). A confounder could increase the risk estimate in two ways, by the inclusion of a harmful treatment in the test arm or a protective treatment in the control arm. There are several designs that fit this pattern:

Test treatment	vs	Protective treatment
Test treatment + Harmful treatment	vs	No treatment or placebo
Test treatment + Harmful treatment + Background treatment	vs	Background treatment (may be different to test arm)
Test treatment + Background treatment	vs	Protective treatment + Background treatment (may be different to test arm)

In a trial with a harmful treatment in the test arm, the number of events in that arm could be higher than expected because of direct action of the harmful treatment, direct action of the background treatment(s) or by additive or multiplicative effects between the harmful and test treatments. Alternatively, if the test treatment is being compared to a protective treatment, the number of events in the control arm could be lower than expected. In either of these cases, the risk estimate would be increased and the test treatment could look worse than it really is.

In the anthracycline cardiotoxicity meta-analysis the following trial is positively confounded (increased risk estimate):

Epirubicin + Cisplatin + Leucovorin	vs	No treatment

There is some evidence that cisplatin is cardiotoxic[101, 102]. Cardiac events in the test arm could be caused by the epirubicin, by the cisplatin, or by the interaction of the two cardiotoxic treatments. If there are more cardiac events in the anthracycline arm than expected by anthracycline alone, the risk estimate will be larger than it should be due to the presence of cisplatin. The anthracycline (epirubicin) would look more cardiotoxic than it really is. We still gain some evidence for the cardiotoxicity of epirubicin, but it should be interpreted in a different way than evidence from an unconfounded trial.

There could also be confounding that increases the risk estimate if the test treatment is being compared to a protective treatment as in the following (hypothetical) anthracycline trial:

Doxorubicin + Carboplatin	vs	Enalapril (an ACE inhibitor)

There is no known evidence that carboplatin is cardiotoxic. Enalapril is an ACE inhibitor, and ACE inhibitors have been shown to reduce the risk of cardiovascular events, so there may be fewer cardiac events than expected in the enalapril arm. This will increase the risk estimate so that the anthracycline (doxorubicin) looks more cardiotoxic than it really is.

The mechanism for the effect on the risk estimate is different in both these example, but the direction of the effect is the same, so the trials can be grouped in the analysis and interpreted in similar ways.

4.4.2 NEGATIVE CONFOUNDING

Negative confounding (Table 4.6, B2 above) occurs when potential confounders might decrease the risk estimate (i.e. move the risk estimate towards the null). A confounder could decrease the risk estimate in two ways, by the inclusion of a protective treatment in the test arm or a harmful treatment in the control arm. There are several designs that fit this pattern:

Test treatment	vs	Harmful treatment
Test treatment + Protective treatment	vs	No treatment or placebo
Test treatment + Protective treatment + Background treatment	vs	Background treatment (may be different to test arm)
Test treatment + Background treatment	vs	Harmful treatment + Background treatment (may be different to test arm)

In a trial with a protective treatment in the test arm, the number of events in that arm could be lower than if the test treatment alone were used. Alternatively, if the test treatment is being compared to a harmful treatment, the number of events in the control arm could be higher than expected. In either of these cases, the risk estimate is decreased and the test treatment looks better than it really is.

In the anthracycline cardiotoxicity meta-analysis, the trial below is negatively confounded (reduced risk estimate):

Doxorubicin + Carboplatin	vs	Paclitaxel

There is some evidence that paclitaxel is cardiotoxic[75-78]. Here the anthracycline (doxorubicin) is being compared to another cardiotoxic treatment. The risk estimate may be lower than expected, due to an increase in cardiac events in the control arm, making the anthracycline (doxorubicin) look less cardiotoxic than it really is.

Negative confounding also occurs if there is a protective treatment in the test arm, such as the following (hypothetical) anthracycline trial:

Doxorubicin + Dexrazoxane	vs	Gemcitabine

Dexrazoxane is a cardioprotectant that significantly reduces the risk of doxorubicin cardiotoxicity.[56, 63, 66] There is no evidence that gemcitabine is cardiotoxic (see Table 4.4). The inclusion of dexrazoxane in the test arm will lower the number of cardiac events in that trial arm, meaning the risk estimate will be reduced, and the test treatment (doxorubicin) look less cardiotoxic than it really is.

The mechanism for the effect on the risk estimate is different in both these trials, but as the effect on the risk estimate is in a similar direction, the trials can be grouped in the analysis and interpreted in similar ways.

4.4.3 UNKNOWN CONFOUNDING

Unknown confounding occurs when the comparison includes multiple confounder treatments that might affect the risk estimate (Table 4.6, B3 above). Confounder treatments are distributed across both the test and control arms. There are many designs that fit this pattern, such as the following:

Test treatment + Harmful background treatment	vs	Different harmful background treatment
Test treatment + Protective treatment	vs	Harmful treatment
Test treatment + Harmful treatment	vs	Protective treatment

In a trial with harmful treatments in both the test and control arms, the number of events in both arms may be higher than expected, but it is not possible to predict how this might affect the risk estimate. In a trial with a protective treatment in the test arm and a harmful treatment in the control arm, the number of events in the test arm might be lower than expected and the number of events in the control arm higher than expected. These two sources of confounding do not cancel each other, and it is not possible to predict the overall effect on the risk estimate. A trial with harmful treatment in the test arm and protective treatment in the control arm appears similar to a positively confounded trial. There may be more events than expected in the test arm and less than expected in the control arm, leading to a risk estimate larger than it should be, and more extreme than a positively confounded trial. It is grouped with the complex confounded trials due to multiple sources of confounding.

Interpretation of complex confounded trials can be difficult. It may not be possible to tease out the relative contribution of each of the confounder treatments to the size or direction of the risk estimate. Any conclusions drawn from such trials must be made with caveats on the validity of the result.

In the anthracycline cardiotoxicity meta-analysis the trial below involves complex confounding:

Doxorubicin + Bleomycin + Vinblastine + Dacarbazine	vs	Radiotherapy (heart in the radiotherapy field)

There is evidence that radiotherapy to the heart causes cardiac disease[71]. In this trial the heart was irradiated, thus the anthracycline arm is being compared to something cardiotoxic. There is also limited evidence that bleomycin[114-120] and vinblastine[148] may be cardiotoxic, thus the anthracycline is being used in conjunction with other cardiotoxic treatments. On the one hand, radiotherapy in the control arm may increase the number of cardiac events in that arm and thereby reduce the risk estimate. On the other hand, additional cardiotoxic treatments in the test arm may increase the number of cardiac events in that arm and therefore increase the risk estimate. One source of confounding does not automatically cancel out the other, so it is not possible to predict the overall effect on the risk estimate.

In a large meta-analysis that includes many trials, including confounded trials and grouping them according to the effect on the risk estimate may be justified. Where there are many confounded trials, analysed separately from the unconfounded trials, we can learn about the effect of the test treatment alone and in the presence of the other potentially harmful treatments.

4.5 COMPARING ESTIMATES FOR EACH CONFOUNDING SUBGROUP

Grouping trials according to the direction of effect on the risk estimate will create four groups in the analysis: unconfounded trials, positively confounded trials (increased risk

estimate), negatively confounded trials (reduced risk estimate), and trials with unknown confounding (unpredictable effect on risk estimate). The unconfounded trial group provides the best evidence for the association between the test treatment and the outcome. Further evidence for this association is gained by comparing the risk estimate generated from each confounded group to the unconfounded group. Conclusions can be drawn about the extent to which confounder treatments affect the risk estimate generated in the meta-analysis.

If the risk estimate generated from each group of confounded trials does not differ significantly from the unconfounded risk estimate, we can conclude that confounder treatments did not affect the risk estimate, and are not true confounders. If this is the case, all trials can be considered together and grouping by confounding is not necessary. If there are significant differences between the unconfounded risk estimate and each of the confounded groups, conclusions can be drawn about the effect of confounders. If the risk estimate in the positive confounded group is larger than in the unconfounded group, or the risk estimate in the negative confounded group is smaller than in the unconfounded group, this suggests that non-test treatments are true confounders of the association between the harm under investigation and the test treatment. In this case the trials should be considered separately, grouped by confounding. By grouping trials in the analysis according to the non-test treatments, we have generated evidence not only for the association between the test treatment and the outcome, but also for the impact of non-test treatments.

Other potential sources of confounding should also be considered when interpreting risk estimates generated by the meta-analysis. In the anthracycline cardiotoxicity example the effect of anthracycline on cardiac outcomes may be confounded by the dose of

anthracycline. Higher anthracycline doses are associated with greater risk of cardiotoxicity, thus the median cumulative anthracycline dose in each anthracycline category should be calculated and compared. If the median cumulative anthracycline dose differs between categories then this may explain any differences found despite the presence of confounder drugs. Additionally, there is some evidence that some anthracyclines may be less cardiotoxic than others. The distribution of particular anthracyclines between the confounding categories could also be examined. The length of follow-up may also affect the risk of cardiotoxicity, as trials with longer follow-up may observe more cardiac events. Thus the length of follow-up in each category should also be examined. There may be sources of confounding other than confounder drugs, and these should be considered when interpreting differences between confounding categories.

4.6 DISCUSSION

This chapter has explored how confounding in randomised trials may influence risk estimates generated in a meta-analysis. A method for categorising confounders and grouping confounded comparisons according to the effect confounders may have on the risk estimate has been proposed. In a meta-analysis of harms in randomised trials that include multiple treatments there may be very few unconfounded trials. In order to learn more about the outcome of interest than is possible with a small number of unconfounded trials, it is desirable to include a larger number of trials. Using the above method will enable inclusion of trials that would otherwise be excluded from meta-analysis that only include unconfounded trials.

To determine whether treatments used in randomised trials in the meta-analysis are true confounders of the association between the test treatment and the outcome, risk estimates for confounded trials are compared to the risk estimate for unconfounded trials. If there are significant differences between risk estimates of confounded and unconfounded trials, conclusions can then be drawn as to whether treatments are true confounders or not. This provides evidence for both the association between the test treatment and the outcome, and for the influence of confounders on the risk estimate.

While interactions between the test treatment and confounder treatments, and effect on risk estimates have been mentioned, it is possible that these have a greater role in confounding than already discussed. Even in a simple unconfounded trial, where the only difference between trial arms is the test treatment, it is possible for interactions between the test and background treatments to occur, and to affect the risk estimate in unpredictable ways. For example, in the anthracycline meta-analysis, we would consider a trial of doxorubicin + cisplatin vs cisplatin alone, as unconfounded, because the only difference between trial arms is the doxorubicin. However, as there is evidence that cisplatin is cardiotoxic, there may be additive or multiplicative effects between doxorubicin and cisplatin that cannot be predicted based on existing evidence.

This chapter outlines a method for including confounded trials in meta-analyses of harms in randomised trials. It assumes that the test and any harmful treatments increase the outcome, and protective treatments reduce the outcome. This method will be demonstrated by applying confounding classifications to all trials identified by the trial search, and conducting a meta-analysis of cardiac death in randomised trials of anthracycline vs not (see Chapter 5).

CHAPTER 5 PUBLISHED-DATA META-ANALYSIS OF CARDIAC DEATHS IN RANDOMISED TRIALS OF ANTHRACYCLINE VS NOT

5.1 JUSTIFICATION FOR PUBLISHED-DATA META-ANALYSIS

Previous meta-analyses of cardiotoxicity in trials of anthracycline vs not that used published data included only trials that could be found by a search that included cardiotoxicity in its search terms. They also limited inclusion to those trials where the only difference between trial arms was the presence or absence of anthracycline, or to trials of multi-agent chemotherapy including anthracycline compared with no chemotherapy. As discussed in Chapter 3, few trials fit either of these two patterns. Many more trials have multiple differences between trial arms. This may result in some confounding of the effect of anthracycline and that of other drugs, but it may not preclude them contributing information regarding cardiotoxicity. The process for including trials of this nature was discussed in Chapter 4. Much may be learned about anthracycline cardiotoxicity by analysing both unconfounded and confounded trials. Thus, the purpose of this chapter is twofold. First, it aims to investigate the risk of cardiac death in randomised trials of anthracycline vs not using published-data meta-analysis, including a greater number of trials than in previous meta-analyses. Second, it is designed to evaluate the assertions regarding confounding made in Chapter 4, namely that confounding by the inclusion of cardiotoxic and cardioprotective agents in anthracycline trials will influence the risk estimate generated for cardiotoxicity. It will address the following questions:

1. What is the risk of cardiac death in anthracycline allocated patients?
2. Do confounder drugs influence the cardiotoxicity risk estimates in the predicted directions?
3. Is the size of the risk estimate similar to that found by other published data meta-analyses?

If positively confounded trials have a larger risk estimate than unconfounded trials, and negatively confounded drugs, a smaller risk estimate, as predicted in chapter 4, then confounding may be present and confounder drugs do influence the risk of cardiac death in anthracycline trials.

Cardiac death has been defined in different ways in different trials and has not been reported consistently in the trials included in this analysis. Definitions of cardiac death include deaths from a variety of causes such as congestive heart failure, myocardial infarction, stroke and pulmonary embolism. In addition, it is not clear from published reports whether those who adjudicated causes of death were blinded to treatment allocation. If those who attributed cause of death knew whether a patient had been allocated anthracycline or not, this may have affected whether they labelled a death as cardiac not. Thus there may be cardiac deaths missing from published trial reports. In addition there may be misclassification such that true cardiac deaths are not reported as such, and some deaths are labelled cardiac that should not have been. Due to these sources of imprecision in cardiac death reporting any death reported as due to a cardiac cause was included in this analysis. Care should be undertaken in interpreting the outcomes of analyses of cardiac death due to limited rigour in reporting of this endpoint.

5.2 METHODS

5.2.1 INCLUSION CRITERIA

To be eligible for inclusion in this analysis, trials had to fit the inclusion criteria outlined in Chapter 3. Progression free survival had to be at least 12 months in all trial arms. There also had to be at least 100 patients randomised in each trial arm, and trials that fit this criteria were included even if the number of patients in the published data were less

than 100 per arm. All trials that fit these criteria were eligible for inclusion in this meta-analysis provided that they had published the number of cardiac deaths in each trial arm, or the odds ratio for cardiac death and a measure of accuracy (standard error, confidence interval or precise p-value).

5.2.2 CONFOUNDING CATEGORISATION

All the trials that were to be included were categorised for degree of confounding and tagged as unconfounded, positively confounded, negatively confounded or of unknown confounding, using the process described in Chapter 4. For each trial, each drug in each trial arm was compared to the list of cardiotoxic and cardioprotective agents (see Table 4.2, Chapter 4). Every drug was tagged as cardiotoxic, cardioprotective, or not cardiotoxic (see below for example).

N Carboplatin +	vs	**T** Cisplatin +
T paclitaxel		**T** paclitaxel +
		A doxorubicin

In this example, carboplatin is tagged with an N to indicate no known cardiotoxicity, and doxorubicin is tagged with A to indicate that it is the anthracycline. Paclitaxel and cisplatin have been tagged with a T to indicate (cardio)toxicity. As paclitaxel appears in both arms it is not considered further. This assumes no interaction between paclitaxel and anthracycline (see Chapter 4 for further discussion of this assumption). The other cardiotoxic agent is cisplatin, and is in the same arm as doxorubicin. Therefore this trial is positively confounded according to the rules in Chapter 4.

For trials with more than two trial arms, each relevant comparison within the trial was categorised for confounding separately. For example, in a three arm trial there are three possible comparisons:

- arm 1 vs arm 2
- arm 1 vs arm 3
- arm 2 vs arm 3

In a trial such as this, it is possible that each of these comparisons is confounded in different ways. For example, arm 1 vs arm 2 may be unconfounded, arm 1 vs arm 3 positively confounded, and arm 2 vs arm 3 of unknown confounding. Thus, for a trial with multiple arms, each comparison within the trial would be considered separately and appear separately in the meta-analysis.

5.2.3 DATA EXTRACTION

For each trial, all publications and conference abstracts were examined for reports of cardiac deaths. Where more than one report was available, the largest number of cardiac deaths was used in this analysis. If a trial report stated "there were no cardiac deaths" then zero cardiac deaths were entered for each arm for that trial. Any death due to cardiac causes, regardless of the precise nature of the cardiac death, was included. Non-fatal cardiac events were not extracted or analysed due to the diversity of cardiac endpoints reported in trial papers, and the difficulty of combining these. As an intention to treat analysis was planned, data was extracted on all randomised patients. Some trials only reported per protocol analyses that excluded protocol violations and patient who did not receive their randomly allocated treatment. In a per protocol analysis, bias is introduced if the patients not included in the analysis dataset differ systematically from the evaluated patients. As such it is possible that some cardiac deaths may be missing from published papers and thus not included in the following analysis.

Each trial was assessed for methodological quality using the risk of bias tool described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[67] The domains selected for assessment from this tool were:

- selection bias - adequacy of random sequence generation and concealment of the allocation sequence
- performance bias - whether patients and trial personnel were blinded to treatment allocation
- detection bias - whether outcome assessors were blinded to treatment allocation
- attrition bias - the completeness of follow-up
- and other sources of bias

Reporting bias was assessed using the ORBIT II classifications of risk of outcome reporting bias for harm outcomes (discussed in Chapter 6).

5.2.4 STATISTICAL ANALYSIS

Data were analysed in Stata version 13.1 using the 'metan meta-analysis' macro using the Peto odds ratio fixed effects model. Odds ratios were calculated rather than rate ratios because the person years of follow-up were not available. Trials were grouped by confounding category (unconfounded, positively confounded, negatively confounded, unknown confounding), and I^2 tests for trend and heterogeneity between and within groups were undertaken. Statistical significance was set at the 0.05 level.

5.3 RESULTS

5.3.1 CHARACTERISTICS OF INCLUDED STUDIES

Of the 171 trials identified by the search outlined in Chapter 3, 58 were unconfounded, 51 were positively confounded, 27 were negatively confounded, 23 were of unknown

confounding, and 12 were multiple arm trials that included comparisons that fit in more than one confounding category. Only 32 of the 171 trials (18%) had published data on cardiac deaths with enough detail to allow data extraction. Of these 32 trials, 9 were unconfounded, 11 were positively confounded, 6 were negatively confounded and 6 were of unknown confounding (see Table 5.1).

TABLE 5.1 CONFOUNDING IN RCTS IN THE PUBLISHED-DATA META-ANALYSIS

Confounding category	Number of trials	Number with published data on cardiotoxicity
Unconfounded	40	8
Positively confounded	69	12
Negatively confounded	24	6
Unknown confounding	25	6
Multiple arm trials that contribute to more than one category	13	0
Total	171	32

Of the 32 trials that reported data on cardiac deaths, the largest number were in early breast cancer (n=11) followed by lymphoma (n=8). There were also 8 trials in other solid cancers and 5 trials in other haematological malignancies. The oldest trial started in 1968 and the most recent started in 2009. However the majority of the trials started in the 1980s and 1990s. The trials ranged in size from 200 to over 3000, with a median of 368 patients. The anthracycline used in most of the trials was doxorubicin (n=25). Most of the trials excluded patients with existing cardiac risk factors or prior therapy to treat cancer (see Appendix B.2 for full trial descriptions).

The methodological quality of the included trials varied from low to high quality. Many trials did not report randomisation methods and most trials were not blinded. It was unclear whether other biases may have affected trial outcomes.

5.3.2 RESULTS OF META-ANALYSIS

There were 98 cardiac deaths in 9320 patients allocated to anthracycline and 84 cardiac deaths in 9065 patients not allocated to anthracyclines. Meta-analysis of the 32 studies showed that the odds of dying from cardiac causes was almost 40% higher in patients allocated anthracycline compared with those not allocated anthracycline (odds ratio [OR] 1.36, confidence interval [CI] 1.01-1.83, 2p=0.04) and this increase was statistically significant (see Figure 7).

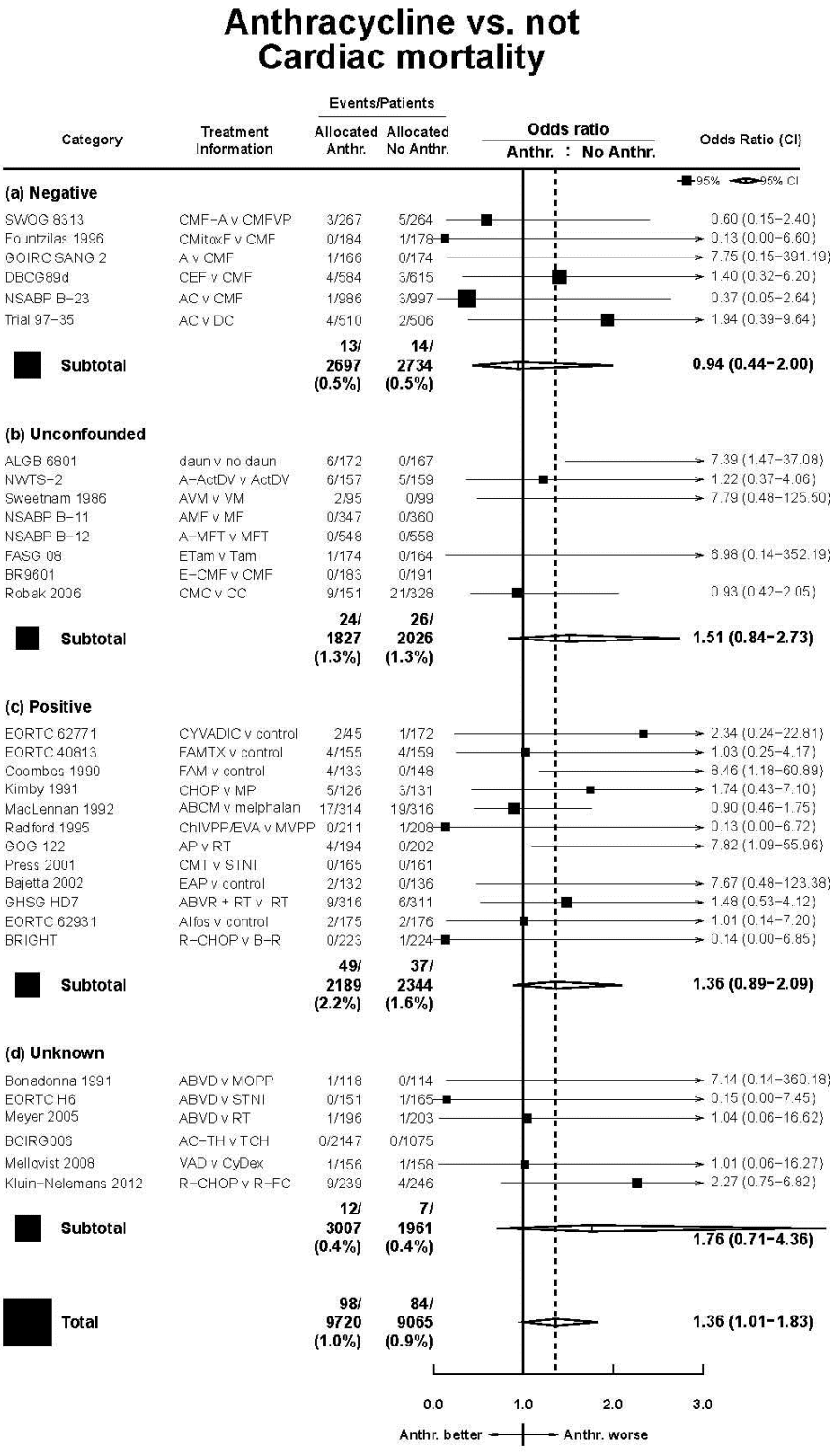


FIGURE 7 CARDIAC MORTALITY IN TRIALS OF ANTHRACYCLINE VS NOT

There was no significant heterogeneity detected (I^2 7.5%, p=0.353).

Odds ratios for each trial were plotted against total cumulative anthracycline dose to determine whether cumulative dose was associated with risk of cardiac death (see Figure 8)

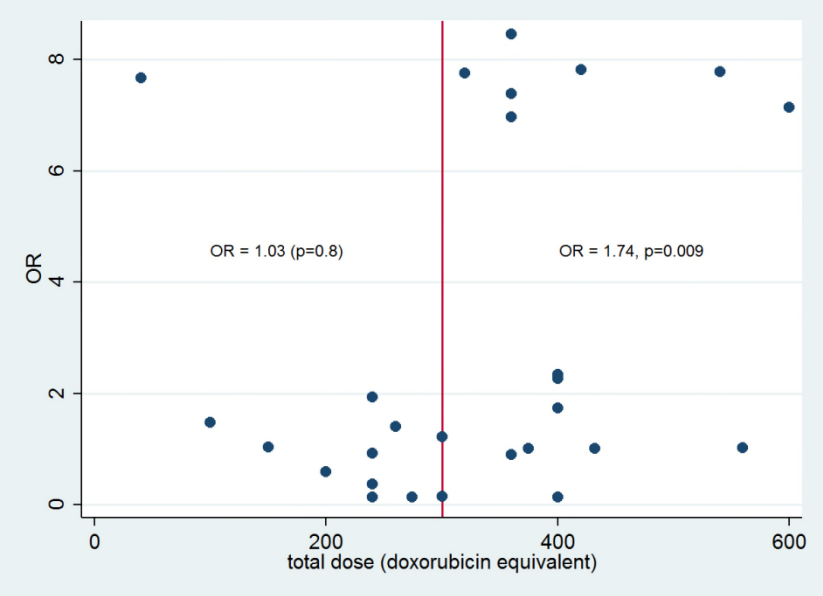


FIGURE 8 TOTAL CUMULATIVE ANTHRACYCLINE DOSE VS ODDS RATIO

Meta-analysis of the 32 trials grouped by dose less than 300mg/m^2 and cumulative dose greater than or equal to 300mg/m^2 showed that the for trials in the higher dose category, the risk of cardiac death in anthracycline allocated patients was almost 75% higher than for those not allocated anthracycline (OR=1.74, 95%CI 1.15 – 2.62, p=0.009) and this increase was statistically significant. There was no statistically significant difference in the lower dose group.

5.3.3 RESULTS OF ANALYSIS BY CONFOUNDING

There was no significant heterogeneity between the odds ratios for the different confounding categories, and the trend in the odds ratios was also not significant.

There was no statistically significant heterogeneity within any of the confounding categories, indicating that the odds ratio for the individual studies within each category differed from each other by no more than would be expected from random variability.

5.4 DISCUSSION

Overall, the risk of cardiac death was 36% higher in the anthracycline-allocated patients than those not allocated anthracyclines. This difference was statistically significant, suggesting that this is a true difference. Despite an increase in risk of cardiac death in patients allocated to anthracycline, the absolute risk of cardiac death was low. Only 1% of patients allocated to anthracycline died of cardiac causes in the trials included in this analysis, and the absolute difference in risk between those allocated anthracycline and those not allocated anthracycline was 0.7%.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have also analysed cardiac deaths in their individual patient data meta-analyses.[16] In 22 trials including 36,596 women, there was a 61% increased risk of cardiac death in patients allocated to anthracycline + cyclophosphamide compared to no chemotherapy (OR 1.61, SE 0.31). All 22 of these trials were positively confounded. In a further 20 trials, including 17,569 women, there was a 50% increased risk of cardiac death in patients allocated to anthracycline containing regimens compared to those allocated to cyclophosphamide + methotrexate + 5-fluorouracil (OR 1.50, SE 0.38).[16] Of these 20 trials, 12 were negatively confounded, 2 were positively confounded and 6 were unconfounded. The EBCTCG hold data from additional trials of anthracycline vs not that were not included in these analyses. Further information would be obtained from an analysis using individual patient data from trials of anthracycline vs not, using both data from non-early-breast-

cancer trials, and the data held by the EBCTCG. This would confirm the overall result, and it would also allow examination of the effect of confounding. It is also possible that information might be provided on the cardiotoxicity of non-anthracycline drugs, and possibly on interactions between anthracyclines and other drugs.

There was no statistically significant heterogeneity between confounding categories and thus no conclusions can be drawn about the effect of confounder drugs on the risk of cardiac death. The lowest median cumulative anthracycline dose was in the negatively confounded group (240 mg/m^2) and this group did produce a smaller odds ratio than the other confounding groups (OR = 0.94, 95% CI 0.44 – 2.00). The other confounding groups had larger odds ratios and higher median cumulative anthracycline dose than the negatively confounded group. The highest median cumulative anthracycline doses were in the positively confounded (360 mg/m^2) and unknown confounding groups (350 mg/m^2). Thus cumulative anthracycline dose was a better explanation for increases in risk of cardiac death than the presence of confounder drugs.

Only 32 of the 171 eligible trials reported fatal cardiac events and the confidence intervals for the odds ratios for each of the confounding categories were wide. Therefore this analysis had limited power to detect true differences between the confounding categories. When all trials were considered together, the odds of cardiac death was almost 40% higher in patients allocated to anthracycline than in those not allocated anthracyclines and the increase was only just significant. Therefore it would be unlikely for subgroup analyses based on a result such as this to be statistically significant. A larger number of non-fatal cardiac events would be expected than of fatal events, so an analysis that also included non-fatal events would have greater power to detect true differences between trial arms, provided that events in both arms had been equally thoroughly

recorded. However, as discussed in Chapter 2, non-fatal cardiac events may be recorded and followed-up more rigorously in anthracycline-treated patients than those treated without anthracyclines.

The current analysis confirms the increased risk of cardiac death in patients allocated to anthracycline compared to those not allocated to anthracycline found in previous meta-analyses. It included a much larger number of trials than was possible in previous meta-analysis, however further study is needed to determine whether there is an effect of confounder drugs as this analysis was underpowered.

It was not possible to determine the timeframe in which cardiac deaths occurred using information in RCT publications. In order to better understand the time-course of anthracycline cardiotoxicity, and to establish when the risk occurs, an individual patient data meta-analysis should be undertaken. Using IPD methods will allow investigation of when the risk of cardiac death occurs, and whether it persists across the lifespan.

CHAPTER 6 OUTCOME REPORTING BIAS IN RANDOMISED TRIALS OF ANTHRACYCLINE VS NOT

6.1 OUTCOME REPORTING BIAS AND ITS CLASSIFICATION

Publication bias occurs when published studies are systematically different in some way from unpublished studies. A recent review of publication bias in clinical trials found that studies where the main outcomes being compared differed significantly from each other were almost twice as likely to be published as studies where they did not.[154] Unpublished studies, therefore, lead to an evidence base that is not only incomplete but also biased, potentially leading to incorrect decisions about treatments.[155] However, publication bias is not the only source of missing data for individual outcomes, particularly for outcomes that are not the main objective of the trial. Studies that publish some but not all of the outcomes specified in the protocol are at risk of Outcome Reporting Bias (ORB).

ORB occurs when outcomes that are measured in a study are not reported, and the decision not to report is based on the results for those outcomes.[156] Chan (2004) assessed ORB in Canadian government-funded trials and found that almost all of the trials included had at least one unreported efficacy outcome and two thirds of the trials that measured harms had at least one unreported harm outcome.[157] In a Cochrane methodology review, Page et al. (2012) synthesised the results of systematic reviews that investigated selective reporting by comparing outcomes listed in trial registry entries or trial protocols to outcomes in published papers.[158] They found that 38% of systematic reviews had a change in outcomes between that specified in the review protocol and the published review. Kirkham et al. (2010) also examined the risk of ORB in a cohort of systematic reviews.[159] They found that around 70% of trials included in the reviews had fully reported the primary outcome of the review, and around 30% had not reported or partially reported the review primary outcome. Of those trials that had not fully reported the primary outcome, half were at high risk of ORB.

The ORBIT I study was designed to assess the prevalence of ORB in a cohort of all the systematic reviews published in the Cochrane Library during 2006 and 2007. ORBIT I developed a system for classifying the risk of ORB for the primary outcome of each trial in the cohort of systematic reviews included in the study (see Appendix C.1).[159] This system specifies nine categories that are used to classify the risk of ORB for missing outcome data. The coding system uses data for outcomes provided in trial publications, and information on how data for each outcome was collected. Where information is not provided on data collection, a judgement is made, based on clinical knowledge and results of similar trials, on whether the data were collected or not, and if no events were reported, whether this is attributable to no events having occurred. Trials are categorised as having outcomes likely to have been measured and analysed but only partially reported, for which codes A to D are applied. For trials were the outcome is likely to have been measured but not analysed, codes E to F are applied. For trials where it is unclear whether the outcome was measured or not, codes G to H are applied. There is a separate code applied for trials that clearly state the outcome was not measured (see Appendix C.1 for full a description of each code). This system is straightforward to apply to trials with efficacy outcomes or when assessing the primary outcome of a study, but more difficult when assessing secondary and harm outcomes.

Data on harm outcomes are often not reported in as much detail as data on efficacy outcomes.[160, 161] Similarly, methods of collecting data on harm outcomes are often reported in less detail than methods of collecting data on efficacy outcomes. This lack of reporting can lead to difficulties in assessing whether data on a harm outcome were collected. Where this information is not reported, judgements on whether these data were collected can be made based on whether harms data has been collected in similar

studies, and whether there were mandated data items that cover this outcome, at the time that study was run.

Although the ORBIT I study produced satisfactory ORB risk classifications for the primary outcome, it was more difficult to assess ORB risk for harm and non-primary outcomes. In order to address this issue, the ORBIT II study was designed to evaluate the prevalence of ORB for harm outcomes. ORBIT II assessed ORB for harm outcomes in two cohorts of systematic reviews. The first cohort included new reviews in 6 issues of The Cochrane Library published during 2012 and 2013. The second cohort included reviews for which the main outcomes were harm outcomes. ORBIT II developed an ORB classification system for harm outcomes (see Table 6.1) similar to that developed for primary outcomes in ORBIT I.[162] ORBIT II found that the primary harm outcome was not fully reported in three quarters of Cochrane reviews and in almost half of adverse event reviews. Outcome Reporting Bias was suspected in 63% of the clinical trials included in the reviews that were assessed. Outcome reporting bias is thus suspected in a higher proportion of trials when assessing harm outcomes than when assessing efficacy outcomes.

The ORBIT II review investigated ORB for the primary harm outcome of a study, and produced satisfactory ORB risk classifications for them. This classification system has not been used as yet to assess uncommon and non-primary harm outcomes. Rare outcomes may be at greater risk of ORB compared to more common harm outcomes. This thesis, however, focusses on the cardiotoxicity of anthracycline chemotherapy, which may not be the primary harm outcome reported in anthracycline trial publications. Two reviews of cardiotoxicity in anthracycline trials both suggest that cardiac outcomes are under-reported in publications for these trials, even though it is a clinically and patient relevant

outcome.[54, 56] If cardiac outcomes are reported only by those studies with more extreme results the relative risk of anthracycline cardiotoxicity may be overestimated, and the anthracycline look worse than it really it. In addition if some cardiac events are not reported then the absolute risk of anthracycline cardiotoxicity will be underestimated.

The trial search for this thesis found that few trials report cardiac outcomes in a way that citation databases can index (see Chapter 3). Such trials are not able to be found using methods that include cardiac items in the search terms. Prior meta-analyses of published data in this subject area report similar difficulties.[54, 56] A small number of trials were found, and only two trials in each review were able to be included in analyses of cardiac death. This reflects inadequacies both in how citation databases index harm outcomes, and in the extent to which harm outcomes are reported in trial publications. The purpose of this chapter is to assess the extent to which ORB might be contributing to under-reporting of cardiac outcomes in trials of anthracycline vs not. Outcome reporting bias for cardiac outcomes will be assessed in trials identified by the trial search for this thesis.

6.2 METHODS

6.2.1 TRIAL LIST

All trials identified by the trial search described in Chapter 3 were eligible for outcome reporting bias assessment if they had been published as a full paper at least once (see Appendix A for full search strategies). Trials were excluded for the following reasons:

- The trial had never been published.
- The trial had been published as a conference abstract only.

- The trial had published a methods paper or outline of trial design, but not a paper that included outcome data.
- The trial was briefly mentioned in a review paper, or was included in a meta-analysis, but a full paper describing the trial had not been published.

In each of these exclusion scenarios the information available on methods or outcomes would not be adequate for full assessment of outcome reporting bias.

6.2.2 OUTCOME REPORTING BIAS CLASSIFICATION SYSTEM

The ORBIT II system for classifying risk of ORB was selected for this study.[162] ORBIT II is designed to assess the risk of ORB for the primary harm outcome of a study. As anthracycline cardiotoxicity may not be the primary harm outcome in trials of anthracycline vs not, criteria were created to support the application of the ORBIT II classifications to this outcome, and this was done separately for cardiac morbidity and cardiac mortality (see Appendix C.2).

Prior meta-analyses of anthracycline cardiotoxicity conducted separate analyses for cardiac morbidity and cardiac mortality. A review of publications for a number of trials eligible for ORB assessment showed that cardiac morbidity and cardiac mortality were usually reported separately. Consequently, cardiac morbidity and cardiac mortality were assessed for the presence of ORB separately in this study. For example, a trial that reported cardiac morbidity but not cardiac mortality would have different ORBIT II classifications for these two endpoints. ORBIT II first classifies a trial as fully reported if the number of events and patients per trial arm are reported or a measure of effect is reported with a precise significance level, i.e. p value. Trials that do not meet these criteria are classified as partially or not reported. A trial that only partially reports an

outcome or does not report it is further classified based on information about whether the outcome was measured, and what information about the outcome is provided in the results. Each classification code specifies whether the trial is at risk of ORB for that outcome (see Table 6.1). The classifications are split according to the amount of information provided in publications for the outcome. Outcomes that were measured and compared across treatment groups are coded as **P**. Outcomes that were measured but not compared are coded **Q**. Outcomes that were measured but for which it is unclear whether treatment groups were compared are coded **R**. Outcomes which were not explicitly mentioned but clinical judgement suggests it would have been measured and compared across groups are coded **S**. Outcomes for which clinical judgement says it was likely measured but there were no events are coded **T**. Outcomes that were not mentioned and clinical judgement says there were probably no events are coded **U**. Finally, outcomes for which the publication explicitly states that it was not measured are coded **V**. The risk of ORB for each code is shown in Table 6.1.

TABLE 6.1 ORBIT II CLASSIFICATION CODES

Classification	Description	Level of reporting	Risk of bias
Explicit specific harm outcome			
Measured and compared across treatment groups			
P1	States outcome analysed but reported only that p>0.05	Partial	High risk
P2	States outcome analysed but reported only that p<0.05	Partial	High risk
P3	Insufficient reporting for meta-analysis or full tabulation	Partial	Low risk
Measured but not compared across treatment groups			
Q	Clear that outcome was measured and clear outcome was not compared	N/A	No risk
Measured, not clear whether compared or not across treatment groups			
R1	Clear that outcome was measured but no results reported	None	High risk
R2	Results reported globally across groups	None	High risk
R3	Results reported from some groups only	None	High risk
Specific harm outcome not explicitly mentioned			
Clinical judgement says likely measured and likely compared across treatment groups			
S1	Only pooled adverse events reported (could include specific harm outcome)	None	High risk
S2	No harms mentioned or reported	None	High risk
Clinical judgement says likely measured but there were no events			
T1	Specific harm not mentioned, all other specific harms fully reported	None	Low risk
T2	No description of specific harms	None	Low risk
Specific harm outcome not explicitly mentioned, clinical judgement says unlikely measured			
U	No harms mentioned or reported	None	Low risk
Explicit the specific harm was not measured			
V	Report clearly states that data on specific harm of interest not measured	N/A	No risk

* Table from Saini, P (2014)[162]

6.2.3 ASSESSMENT OF STUDIES

For the trials eligible for assessment for ORB, each full publication and, where available, the trial protocol, were examined in detail to determine whether information on cardiac morbidity and cardiac mortality were collected and whether data for these outcomes were reported in trial publications.

If cardiac morbidity or mortality were specified as outcomes, it was assumed that data were collected for these outcomes, and that they were compared between trial arms. If cardiac morbidity or cardiac mortality were not pre-specified outcomes of the trial, the methods section was examined in detail to determine if any data were collected on either cardiac morbidity or cardiac mortality. The results and discussion sections of each full paper, and any conference abstracts were examined, to determine the extent to which cardiac morbidity and cardiac mortality were reported.

6.2.3.1 ASSESSMENT OF CARDIAC MORBIDITY OUTCOME REPORTING BIAS

There was substantial variation in the way cardiotoxicity was reported across trials. Thus any mention of a non-fatal cardiac event, regardless of the type of event, was included in cardiac morbidity assessment.

Full reporting of cardiac morbidity was considered to have occurred if the number of patients per trial arm and the number of cardiac morbidity (i.e. non-fatal) events in each trial arm were reported. For example if text such as the following was seen, the trial would be classified as fully reported for cardiac morbidity:

> *"Six patients in the anthracycline arm developed congestive heart failure. Four patients in the non-anthracycline arm developed congestive heart failure (CHF). 3 patients in the non-anthracycline arm had myocardial infarctions (MI). There were no MIs in the anthracycline arm".*

If a trial reported a subset of cardiac events, for example Common Terminology Criteria for Adverse Events (CTCAE) grade III and IV cardiac events, this was also considered to be fully reported if it otherwise fitted the criteria for full reporting.

If any cardiac testing, such as measurement of ejection fraction, electrocardiography or other cardiac testing, was undertaken during the trial, it was deemed to have measured cardiac morbidity. If an adverse event coding scheme that included cardiotoxicity, such as CTCAE, was mentioned, the trial was also assumed to have collected data on cardiac events and thus was deemed to have measured cardiac morbidity. If there was no mention of cardiac testing or adverse event recording in the methods section of the paper, the results section of all publications for the trial were examined.

If any adverse events or toxicities were reported in the results section, it was assumed that adverse event data were collected on all patients. If a toxicity table was included, but no cardiotoxicity was noted on the table, it was assumed that cardiac morbidity was recorded, but that there had been no non-fatal cardiac events. If there was a description of adverse events in the text of the results, but no cardiac events were noted, it was also assumed that cardiac morbidity was collected but that there had been no non-fatal cardiac events.

6.2.3.2 ASSESSMENT OF CARDIAC MORTALITY OUTCOME REPORTING BIAS

Full reporting of cardiac mortality was considered to have occurred if the number of patients per trial arm and the number of cardiac deaths per trial arm was reported. If cardiac deaths were reported in one arm, but not the other, and if all non-cancer deaths in each arm were fully described, this was also considered to be fully reported. For

example, if text such as the following was seen, the trial would be classified as fully reported for cardiac mortality:

> *"There were 6 deaths before recurrence in the anthracycline arm and 4 deaths before recurrence in the non-anthracycline arm. Three patients in the anthracycline arm died of CHF and 3 died of severe infections. The 4 deaths in the non-anthracycline arm were all due to neutropenic sepsis".*

If the methods section of the trial publication stated that cause of death was recorded, it was assumed that cardiac mortality was measured. If the methods section stated that only data on cancer deaths but not data on other causes of death were collected, then it was deemed that cardiac mortality was not measured. If there was no information regarding mortality in the methods section of the publications, the results sections were examined.

If any non-cancer causes of death were reported in the results section, it was assumed that specific cause of death was collected on all patients, and that trial arms had been compared. If several non-cancer causes of death were mentioned for each trial arm, but no cardiac deaths were reported, it was assumed that there had been no cardiac deaths in the trial at the time of publication.

6.2.4 STATISTICAL ANALYSIS

Ordered logistic regression was used in order to determine if the risk of ORB could be predicted by any of:

- the size of the trial,
- the age of participants,
- or the year of trial publication,

as the outcome variable, risk of ORB, has three levels, which are ordered. Size of trial and age of participants were converted to categorical variables. For each trial, the risk of ORB was classified as:

1. No risk if the outcome was fully reported
2. Low risk, using the classifications outlined in table 6.1, if the outcome was partially or not reported
3. High risk using the classifications outlined in table 6.1, if the outcome was partially or not reported.

Trials were sorted into three size categories: small (200 to 499 patients), medium (500 to 999 patients), and large (1000 or more patients). Age of participants was classified as adult if included patients were 18 to 65 years of age, and extreme age if the trial included only patients aged 18 years or less or only patients over the age of 65 years. Year of publication was the year of the first full publication for the trial and was analysed as a continuous variable. It was hypothesised that larger trials would be at lower risk of ORB, that more recently published trials would be at lower risk of ORB, and that trials in paediatric or elderly patients would be at higher risk of ORB than trials in adult patients. Separate analyses were conducted for cardiac mortality ORB risk and cardiac morbidity ORB risk. Statistical significance of cardiac morbidity and cardiac mortality were not entered into the model as very few trials reported this information, meaning that statistical significance was unknown for the majority of trials. All analyses were conducted using Stata version 13.1.

6.3 RESULTS

6.3.1 DESCRIPTION OF STUDIES

Of the 171 RCTs on the trial list (see Chapter 3 for derivation of the trial list), 133 had been published as a full paper at least once and were assessed for Outcome Reporting Bias. Of the RCTs that had not been published as a full paper and were thus not eligible for ORB assessment, 25 had only ever been published as conference abstracts. The remaining 16 RCTs had never been published, or were recent trials that had published methods papers, but not papers that included results. The risk of ORB for cardiac morbidity and cardiac mortality were not correlated (ρ=0.14). Median trial size was 415 patients (range 200 to 4312). Eighty of the 133 eligible trials (60%) were small, including less than 500 patients. The majority of the trials included adult patients only (119/133, 89%). Median year of publication was 1999 (range 1974 to 2014). Ninety-seven of the 133 trials (73%) were published between 1990 and 2009. Almost half (59/133, 45%) the eligible trials had not published any data on cardiac outcomes, and only 19 of the 133 trials (14%) had published both cardiac morbidity and mortality data. A further 36 of the 133 trials (27%) reported cardiac morbidity only, and 19 of the 133 trials (14%) reported cardiac mortality only (See Table 6.2).

TABLE 6.2 CHARACTERISTICS OF INCLUDED RCTS

Characteristic	Number of trials
Trial size	
Small (200 – 499)	80 (60%)
Medium (500-999)	32 (24%)
Large (1000+)	21 (16%)
Age of participants	
Adult	119 (89%)
Age extremes (<18 years or >65 years)	14 (11%)
Year of publication	
Before 1990	24 (18%)
1990 to 1999	46 (35%)
2000 to 2009	51 (38%)
After 2009	12 (9%)
Cardiac event data reported	
Morbidity only	36 (27%)
Mortality only	19 (14%)
Morbidity and mortality	19 (14%)
No cardiac event data	59 (45%)
Total	133 (100%)

6.3.2 CLASSIFICATION OF STUDIES FOR CARDIAC MORBIDITY

Forty-five of the 133 trials that were assessed for ORB had fully reported at least one cardiac morbidity outcome. There were a large number of different cardiac morbidity outcomes reported including changes in left ventricular ejection fraction, congestive heart failure, and unspecified cardiotoxicity.

It was clear for 25 of the 45 (55%) fully reported studies that the cardiac events occurred while patients were on treatment. In these studies, data on cardiac morbidity were reported in a table of toxicities, which generally report events that occur while patients are on treatment. It was unclear, in these studies, whether data on late cardiac events were collected.

Eighty-eight of the 133 studies assessed for ORB had not reported or only partially reported cardiac morbidity. It was clear that cardiac morbidity data had been collected in 33 studies (P and R codes), the other 55 studies did not explicitly mention cardiac morbidity but it was likely that some cardiac morbidity data had been collected (S and T codes). Forty five of the 88 partially or not reported studies were judged to be at high risk of ORB (51%) (Codes P1, P3, R1, R2, R3, S1, S2). The other 43 studies were at judged to be at low risk of ORB (48%) (Codes P3, T1, T2) see Table 6.3.

TABLE 6.3 OUTCOME REPORTING BIAS CLASSIFICATIONS FOR CARDIAC MORBIDITY AND CARDIAC MORTALITY

ORBIT II classification	Number of trials		ORB risk
	Cardiac morbidity	Cardiac mortality	
P1 (analysed but only report p>0.05)	2	0	High
P2 (analysed but only report p<0.05)	0	0	High
P3 (insufficient reporting for full tabulation)	8	2	Low
Q (measured but clearly not compared)	0	0	None
R1 (measured but no results reported)	2	0	High
R2 (results reported globally)	6	2	High
R3 (results from some groups only)	15	3	High
S1 (only pooled events reported)	10	22	High
S2 (no harms mentioned or reported)	10	7	High
T1 (specific harm not mentioned but others fully reported)	27	14	Low
T2 (no description of specific harms)	8	47	Low
U (no harms mentioned or reported)	0	0	Low
V (states harm not measured)	0	0	None
Fully reported	45	36	
Partially reported low risk trials	43	63	
Partially reported high risk trials	45	34	
Total number of trials*	133	133	

*Most trials contributed to both the cardiac morbidity and cardiac mortality columns

6.3.3 CLASSIFICATION OF STUDIES FOR CARDIAC MORTALITY

Thirty-six of the 133 trials that were assessed for ORB had fully reported cardiac mortality. Cardiac deaths were reported as specific cardiac cause of death, total number of cardiac deaths reported or number of CTCAE grade 5 (i.e. fatal) cardiac events reported. In some studies it was clear that the reported deaths occurred before recurrence or progression of cancer. In others it was not clear if the cardiac deaths occurred before recurrence or after. Some trials only reported non-cancer deaths that occurred while patients were on treatment and may thus underestimate the true number of cardiac deaths.

Ninety-seven of the 133 studies assessed for ORB had not reported or partially reported cardiac mortality. Table 6.2 shows that ORBIT II classifications for these 88 studies.

It was clear that cardiac mortality had been collected in 7 studies (P and R codes). In 91 studies, cardiac deaths were not mentioned, but it was likely that some data on cardiac deaths had been collected (S and R codes). Thirty four of the 97 partially or not reported studies were judged to be at high risk of ORB (35%) (Codes R2, R3, S1, S2). The other 63 studies were judged to be at low risk of ORB (65%) (Codes P3, T1, T2) see Table 6.2.

6.3.4 PREDICTION OF RISK OF OUTCOME REPORTING BIAS

Neither age of participants nor year of publication predicted the risk of cardiac morbidity outcome reporting bias. However, trial size was a significant predictor of the risk of cardiac morbidity ORB irrespective of controlling for age of participants and year of publication, such that the risk of ORB decreased as the size of the trial

increased (OR 0.35, 95%CI 0.14 - 0.89, p=0.02) (see Table 6.4). The largest trials had the lowest risk of ORB and this was true for both the unadjusted and the adjusted model that included age of participants and year of publication.

TABLE 6.4 PREDICTION OF RISK OF ORB FOR CARDIAC MORBIDITY

Trial Characteristic	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)	p-value (unadjusted model)	p-value (adjusted model)
Trial size				
<500	1.00	1.00		
500 – 1000	0.50 (0.23 – 1.07)	0.48 (0.22 – 1.04)	0.07	0.06
1000+	0.33 (0.13 – 0.82) *	0.35 (0.14 – 0.89) *	0.02	0.03
Age of participants				
Adult	1.00	1.00		
Age extremes	1.69 (0.61 – 4.66)	1.54 (0.53 – 4.41)	0.31	0.42
Year of publication (per year)	0.99 (0.95 - 1.02)	0.99 (0.95 - 1.03)	0.42	0.55

* = significant at 0.05 level

Trials assessed for cardiac morbidity ORB varied in size from 200 to 4312 patients, with a median of 415 patients. 60% of the trials were small, 24% were medium and 16% were large (see Table 6.5)

TABLE 6.5 TABULATION OF TRIAL SIZE AND RISK OF ORB FOR CARDIAC MORBIDITY

	Risk of ORB – cardiac morbidity			
Trial size	No risk	Low risk	High risk	**Total**
Small	20 (45%)	28 (65%)	32 (71%)	80 (60%)
Medium	14 (31%)	9 (21%)	9 (20%)	32 (24%)
Large	11 (24%)	6 (14%)	4 (9%)	21 (16%)
Total	45	43	45	133

The largest trials were at lowest risk of ORB for cardiac morbidity and this result was expected as larger trials have greater power to detect rare events such as anthracycline cardiotoxicity. A trial with more events may be more likely to report that outcome. Similarly In a smaller trial, rare outcomes may not be observed and therefore not reported. If only a subset of the harm outcomes are reported, such as the 10 most common, or only those occurring in at least 5% of patients, then it is unlikely that a rare outcome such as anthracycline cardiotoxicity would be reported.

Neither trial size nor age of participants predicted the risk of cardiac mortality ORB. However, there was a positive association between risk of ORB for cardiac mortality and year of publication, such that more recently published trials were at higher risk of ORB than trials published earlier (OR = 1.05, 95%CI 1.01 to 1.09, p=0.02) (see Table 6.6). This was true for both the unadjusted and the adjusted model that included trial size, and age of participants.

TABLE 6.6 PREDICTION OF RISK OF ORB FOR CARDIAC MORTALITY

Trial Characteristic	Unadjusted model OR (95% CI)	Adjusted model OR (95% CI)	p-value (unadjusted model)	p-value (adjusted model)
Trial size				
<500	1.00	1.00		
500 – 1000	0.69 (0.32 – 1.49)	0.71 (0.33 – 1.55)	0.34	0.40
1000+	0.59 (0.24 –1.50)	0.51 (0.20 – 1.30)	0.27	0.16
Age of participants				
Adult	1.00	1.00		
Age extremes	0.85 (0.31 – 2.38)	0.94 (0.33 – 2.71)	0.76	0.91
Year of publication (per year)	1.00 1.05 (1.01 – 1.09)*	1.00 1.05 (1.01 – 1.09)*	0.02	0.02

*= significant at the 0.05 level

Year of publication varied between 1974 and 2014, with a median publication year of 2000. Of the 133 trials, 97 (73%) were published between 1990 and 2009 (see Table 6.7).

TABLE 6.7 TABULATION OF YEAR OF PUBLICATION AND RISK OF ORB FOR CARDIAC MORTALITY

	Risk of ORB – cardiac mortality			
Year of publication	No risk	Low risk	High risk	**Total**
Before 1989	8 (22%)	13 (21%)	3 (9%)	24 (18%)
1990 to 1999	11 (31%)	26 (41%)	9 (26%)	46 (35%)
2000 to 2009	14 (39%)	20 (32%)	17 (50%)	51 (38%)
2010 to 2014	3 (8%)	4 (6%)	5 (15%)	12 (9%)
Total	36	63	34	133

The most recently published trials were at highest risk of ORB for cardiac mortality and this result was unexpected. Reporting guidelines for randomised trials have become more stringent over time, and harm outcomes are now expected to be reported in trial publications. As such, it was expected that more recently published trials would be at the lowest risk of ORB. One explanation of this result is that more recently published trials are those conducted more recently, and thus have shorter length of follow-up. A trial with shorter follow-up may observe fewer or no cardiac events and not report cardiac mortality because of that. ORBIT II might still classify such a trial as at high risk of ORB if clinical judgement says there were likely some events. Thus the ORBIT II tool may misclassify more recently published trials.

6.4 DISCUSSION AND CONCLUSIONS

Half the trials included in this study were found to be at high risk of ORB for cardiac morbidity, and one third of the trials were at risk of ORB for cardiac mortality. The primary harm outcome of a study may be at higher risk of ORB than other harm outcomes, and cardiotoxicity was not the primary outcome in many of the trials included in this study. Cardiotoxicity is a clinically significant but not common harm outcome of anthracycline chemotherapy, so may not be observed in many studies, particularly if they are small. So studies with no events may be less likely to report that outcome and are at low risk of ORB.

If systematic reviews and meta-analyses only include trials that report the outcome under investigation they are at risk of introducing bias into their analyses. As trials with more events are more likely to publish that result, the absolute risk of the outcome may be overestimated if trials that do not publish the outcome are excluded. Relative risks may be less susceptible to this kind of bias as a trial with no events will not contribute to the calculation of relative risk. For these reasons it is important to include all trials in a meta-analysis, and to assess the impact of any ORB on the risk of the outcome.

A smaller proportion of trials in the current analysis were judged to be at high risk of ORB than in the ORBIT II study.[162] ORB was suspected in 63% of trials included in ORBIT II. In this study 51% of trials were at high risk of ORB for cardiac morbidity, which more closely reflected the risk of ORB for harms found in ORBIT II. However, 35% of trials were at high risk of ORB for cardiac mortality in this study. A smaller number of cardiac deaths would be expected than non-fatal cardiac events, therefore

ORB for mortality should be higher than ORB for morbidity, as was found in this analysis.

An alternate explanation for the moderate rate of ORB found in this study is that ascertainment bias rather than outcome reporting bias is responsible for infrequent publication of cardiotoxicity outcomes. Clinicians know that anthracyclines carry the risk of cardiotoxicity, and thus they may assess cardiac status more frequently and more completely in anthracycline-treated patients. This would lead to a greater number of cardiac events being found in anthracycline patients than in non-anthracycline-treated patients. Similarly, as clinicians know that anthracyclines cause cardiotoxicity, they may be more likely to record a death as due to cardiac causes if they know that the patient was treated with anthracyclines. In both these cases, cardiac events are more likely to be found in anthracycline patients.

The ORBIT II classification system showed some weaknesses in assessing cardiac morbidity and cardiac mortality ORB risk in the RCTs included in this study. There was no code that adequately fit several non-reporting situations. Some trials had reported grade 3 and 4 cardiac events but not grade 1 and 2 cardiac events, it was not clear whether this was because no grade 1 or 2 events had occurred, if there had been grade 1 or 2 events but they were not compared, or if grade 1 and 2 events had been analysed but not reported. If clinical judgement or similar trials suggested that there were no events then a T1 or T2 classification would be appropriate, but if no events were reported it and it were either of the other two scenarios then there is no code that adequately reflects this. In addition, non-fatal cardiac events were often reported in a table of toxicities, which largely reflects on treatment events and not events that occur after a patients is no longer taking study medication. As anthracycline

cardiotoxicity can occur at any time on or after treatment, it is possible that post treatment events are not reported. There is no ORBIT II classification that adequately describes this situation. Finally the toxicity table may only report frequently occurring harm outcomes and not uncommon or rare outcomes. Thus rare events may have occurred, may have been compared but not reported because of space limitations in the published paper. ORBIT II does not capture these types of non-reporting.

In 55% of trials included in this study, toxicity was reported only while patients were receiving anthracycline treatment, and not after. Cardiotoxicity can appear many years after treatment, thus many cardiac events may be missed in trials that only collect this data while patients are on treatment. In this instance, even trials with a low risk of ORB, may be under-reporting cardiotoxicity. Under-reporting is an important issue for this endpoint. Cardiac morbidity was fully reported in 45 of 133 (33%) of the trials included in this study. The other 88 studies either partially reported cardiac morbidity (n=33, 37%) or did not report it at all (n=55, 63%). This may reflect a lack of events, as there are few data collected on toxicity after patients finish treatment. In addition, trials that fully reported on-treatment events, or only grade III and IV events were classified as fully reported. If these trials had been classified as partially reported (as there could have been events that were not reported), the risk of outcome reporting bias in this cohort of studies may well have been higher.

Studies that do report cardiac outcomes may be those with more extreme results. There is evidence to suggest that statistically significant results are more likely to be reported than results that are not[154]. Thus an outcome with few or no events, for

which the analysis was not statistically significant, is less likely to be reported. In a cohort of studies of at least 200 patients, those trials reporting cardiotoxicity results may be those with more events. This is a form of outcome reporting bias not assessed by ORBIT II classifications, and can lead to an overestimation of the risk of the outcome.

This study found that the size of the trial may predict the risk of ORB for cardiac morbidity. Larger trials were at lower risk of cardiac morbidity ORB than smaller trials in this study. This is expected as anthracycline cardiotoxicity is not a common outcome cardiotoxicity. Less common outcomes are less likely to be observed in a smaller trial, underpowered to detect uncommon events, than it is to be observed in a larger trial. Thus, large trials are more likely to observe cardiac events. A trial that does not observe any events is not at risk of ORB. This pattern did not emerge when predictors of risk of ORB for cardiac mortality were analysed.

The present study found that the year of trial publication showed a positive association with risk of ORB for cardiac mortality, such that trials published more recently were at higher risk of ORB than were trials published earlier. This was unexpected, because reporting guidelines have become more stringent over time, and trialists more aware of the need to report adverse outcomes as well as efficacy outcomes. As such, one would expect that risk of ORB for harms would be lower in trials published more recently. This was not seen in this cohort of trials, and suggests that despite more stringent reporting guidelines, ORB for cardiac mortality is not improving. Another explanation could be that with better monitoring and lower anthracycline doses in more recent trials, far fewer anthracycline-treated patients die of cardiac causes than in the past. It is also possible that the follow-up time of more

recent trials is not long enough to have observed cardiac deaths. If this is the case, a trial may be categorised as at high risk of ORB for cardiac mortality, when in reality it was at no risk of ORB. It would be of interest to assess risk of ORB for cardiac mortality in other anthracycline comparisons, to establish if the same pattern emerged.

This study was limited by several factors. First, only one reviewer classified the studies. Ideally each study would be assessed by more than one reviewer and ORBIT II categorisations compared. Second, no contact was made with study authors to clarify what, if any, cardiac outcomes were measured or recorded. While it was assumed some information was recorded on cardiac morbidity and cardiac mortality in most studies, some may not have collected this data. If this were the case, there would be fewer studies at high risk of ORB than are reported here. In future studies, contact should be made with investigators, and study protocols obtained to determine what cardiac outcomes were measured, to enable a more accurate assessment of the risk of ORB for cardiac outcomes. Third, this study only assessed ORB for cardiac outcomes, not ORB for harms in general. It would be of interest to compare the risk of ORB for cardiac outcomes, to the risk of ORB for other harm outcome such as second malignancies in anthracycline vs not trials. This would allow examination of whether these trials are generally not reporting harm outcomes, or if the risk of outcome reporting bias is different for cardiac outcomes. Many of the trials included in this study of ORB had reported some harms, largely of harms that occurred while patients were on treatment. Some of the more common harms were mentioned, such as nausea and vomiting and a variety of abnormalities in standard blood tests. If other harms are reported but cardiac outcomes omitted from a report,

this could be due to no events. Where there are no events, the risk of ORB is low. This may be reflected in the lower risk of ORB for cardiac mortality than for cardiac morbidity, as the expected number of cardiac deaths in a trial is smaller than the expected number of non-fatal cardiac events.

To verify the results of this study, ORB for cardiotoxicity could be assessed in a cohort of trials for which cardiotoxicity is the primary harm outcome. Trials that compare one anthracycline with another, or that compare bolus and continuous dosing of anthracycline often include cardiotoxicity as a primary outcome and would fit these criteria. If a smaller proportion of trials were at high risk of ORB in comparisons such as these, it would support the contention that anthracycline vs not trials are at high risk of ORB for cardiac outcomes.

The current study assessed risk of ORB for cardiac morbidity and cardiac mortality in all trials of anthracycline vs not that included at least 200 patients, regardless of whether cardiac events were reported. This is the first time that the risk of cardiac ORB has been assessed for this group of trials. It showed that rare but clinically significant outcome that is not the primary harm outcome of a study, such as cardiotoxicity, are still at risk of ORB. A larger number of included patients reduced the risk of ORB for cardiac morbidity, but was not related to risk of ORB for cardiac mortality. The risk of ORB for cardiac mortality is not improving, despite more stringent reporting guidelines. It would be of interest to assess ORB for cardiac morbidity and mortality in trials of other anthracycline comparisons, to verify the degree of ORB risk.

CHAPTER 7 INDIVIDUAL PATIENT DATA META-ANALYSIS OF CARDIAC DEATHS IN RANDOMISED TRIALS OF ANTHRACYCLINE VS NOT: PRELIMINARY RESULTS

7.1 JUSTIFICATION FOR THE INDIVIDUAL PATIENT DATA META-ANALYSIS

Individual randomised controlled trials (RCTs) may be too small to detect modest differences in outcomes between trial arms. Published-data meta-analyses increase statistical power by combining results from individual RCTs, but are limited to including only those trials which have published data on the outcome under investigation. Provided that the data can be obtained, individual patient data (IPD) meta-analyses can avoid this issue by including data from all eligible trials, and not just those that publish the relevant outcome. These issues can be considerable for meta-analyses of harm outcomes, as they are less likely to be published than efficacy outcomes.

As seen in Chapter 3, trial search strategies that include the harm outcome in their search terms may find very few of the eligible RCTs. Search strategies such as this can only find trials for which the harm outcome appears in the title, keywords or abstract of the paper, and many publications do not report harm outcomes in this way. In addition, Chapter 6 demonstrated that outcome reporting bias (ORB) is a particular problem for harm outcomes. An IPD meta-analysis of harm outcomes can avoid ORB by using data on each patient included in every eligible RCT, leading to the generation of risk estimates that are free from publication and outcome reporting biases. Even when data from every eligible trial is not available, IPD meta-analyses may reduce ORB by including data from trials that have not published their harm outcomes as well as those that have.

Thus, the purpose of this chapter is to conduct an individual patient data meta-analysis of cardiac deaths in randomised trials of anthracycline vs not. It is designed to repeat the analysis conducted in Chapter 5 using IPD rather than published data. It will address the following questions:

1. Is there an excess risk of cardiac death in anthracycline allocated patients?
2. Is the size of the risk estimate similar to that found by published data meta-analyses?
3. Can the effect of any confounding by background treatment be seen?

7.2 METHODS

7.2.1 INCLUSION CRITERIA

All RCTs found by the trial search outlined in Chapter 3 were eligible for inclusion in the IPD meta-analysis. In order to accommodate the timeframe of a doctoral project, data were requested from the subset of trials that had published a paper since 2006, as it was more likely that the original data would exist in an easily extractable form, and investigators from these RCTs might be more easily found than investigators from RCTs published less recently. RCTs that had not published a paper since 2006, but that were run by large collaborative groups from whom other RCTs were being requested, were included in the data request.

7.2.2 CONFOUNDING CATEGORISATION

The confounding categorisations outlined in Chapter 4 (sections 4.3 and 4.4) were used in this analysis. Briefly, unconfounded trials are those in which the only cardiotoxic drug is the anthracycline. Positively confounded trials include cardiotoxic and/or cardioprotective drugs, the effect of which is to increase the risk estimate. Negatively confounded trials include cardiotoxic and/or cardioprotective drugs, the effect of which is to reduce the risk estimate. Trials categorised as unknown confounding include a pattern of cardiotoxic and/or cardioprotective drugs for which it is difficult to predict the effect on the risk estimate.

7.2.3 DATA ITEMS

A list of variables was designed to collect data on patient characteristics, details of therapy, outcomes of therapy, mortality, and second malignancies (For full variable list see Appendix D). Patient characteristic items included age, sex, diagnosis, date of diagnosis and date of randomisation. Therapy detail items requested information on both randomised and non-randomised therapy. Randomised therapy data items included the trial arm to which the patient had been randomised, and total dose received of each randomised therapy. As radiotherapy can cause heart disease, information was also requested on exposure to radiotherapy (as part of the RCT, or before or after), radiotherapy targets/fields, and radiotherapy modality. Information on other non-randomised systemic agents that the patient had received (before, during, or after the RCT) for treatment of their cancer was also requested. Therapy outcome items included whether the patient had had a relapse, recurrence or progression of their cancer. Outcome data items included vital status, date of death or

last follow up and cause of death. Information was also collected on second malignancies.

One anonymised record of data for each individual included in each eligible trial was requested. Once received, data were checked and collated into a uniform format.

7.2.4 STATISTICAL ANALYSIS

The statistical analyses used methods similar to those carried out by the Early Breast Cancer Trialists' Collaborative Group. All individuals ever randomised in each trial were included in the analysis. They were entered at the date of randomisation and censored at the earliest of death, end of follow-up, or recurrence, relapse or progression of their cancer. Censoring at relapse, recurrence or progression was used, as deaths after this date would be more likely due to the primary cancer, and patients may have received further non-randomised treatment at this point, which may contribute to cardiotoxicity. The person-years and deaths were stratified by trial, year of randomisation, sex, age at randomisation in 10-year groups, and time since randomisation in single years. The meta-analysis used Peto fixed effect log rank methods[163].

Two analyses were planned, mortality from any cause other than the original cancer before relapse, recurrence or progression, and cardiac mortality before relapse, recurrence or progression of the original cancer.

7.2.5 DATA REQUEST

In March, 2013 investigators for eligible RCTs were emailed to invite them to collaborate. If there was no response, or an email could not be found for the primary

investigator, other authors listed on published papers were contacted. If the trial had been run by a large collaborative trial group, the head office of the group was contacted. Once agreement to collaborate was reached, a data request was sent.

7.3 RESULTS

7.3.1 CHARACTERISTICS OF INCLUDED STUDIES

Of the 171 RCTs identified by the trial search outlined in Chapter 3, 60 had published papers since 2006, or were overseen by large collaborative trial groups who had published another eligible RCT since 2006. Data were not requested for early breast cancer RCTs, as these are requested by the EBCTCG breast cancer overview.

Of the 60 RCTs, 14 were in lymphoma, 13 in gynaecologic cancers, 9 in gastric cancer, 6 in multiple myeloma, 5 in sarcomas, 9 in other solid tumours, and 4 in leukaemias. Data were received by June 2015 (the cut-off date for inclusion in these preliminary analyses), from 12 of the 60 RCTs from whom data were requested (see Appendix B.3 for full trial descriptions). These 12 trials included 6788 patients. Of the 12 RCTs, 6 started in the 1990s (50%), 4 started before 1989, and 2 started in the 2000s. Most of the RCTs included adult patients over the age of 18 (n=10), and 2 included only children aged 18 or below. Four of the RCTs were in patients with lymphoma, 4 in patients with ovarian cancer and 4 in other solid tumours. The anthracycline used in half the RCTs was doxorubicin (n=6), the others used epirubicin (n=5) or mitoxantrone (n=1). The median number of included patients was 361, (range 208 to 1282). Of the 12 RCTs 4 were unconfounded and the others were confounded in various ways (n=8) (see Table 7.1). Median follow-up ranged from 20.8 months to more than 30 years.

TABLE 7.1 CHARACTERISTICS OF RCTS INCLUDED IN THE IPD META-ANALYSIS

Characteristic	All eligible RCTs (n=171)	RCTs for which data requested (n=60)	RCTs for which data received (n=12)
Diagnosis			
Early breast cancer	76	0	0
Lymphoma	26	14	4
Gynaecologic cancers	16	13	4
Leukaemia	13	4	0
Gastric cancer	12	9	1
Multiple myeloma	9	6	0
Sarcoma	6	5	0
Other solid tumours	13	9	3
Age of participants			
Paediatric	12	7	2
Adult	85	30	10
Elderly	4	1	0
Unspecified	70	22	
Median start year (range)	1990 (1968 – 2010)	1994 (1974 – 2009)	1994 (1975 – 2003)
Median number of patients (range)	422 (200 – 6600)	457 (200 – 4312)	361 (208 – 1282)
Range of follow-up	19 months – 30+ years	19 months – 30+ years	20.8 months – 30+ years
Confounding category			
Unconfounded	58	13	4
Positively confounded	51	27	2
Negatively confounded	27	4	3
Unknown confounding	23	12	3
Trials that contribute to more than one category	12	4	0

7.3.2 MORTALITY BEFORE RECURRENCE

There were 167 deaths before recurrence in 3329 patients allocated to anthracyclines and 192 deaths before recurrence in 3459 patients not allocated anthracyclines. Meta-analysis of the 12 included studies showed that there was no significant difference between trial arms in risk of death before recurrence (RR = 0.83, 97% CI 0.66 to 1.04, 1p>0.1) (see Figure 8).

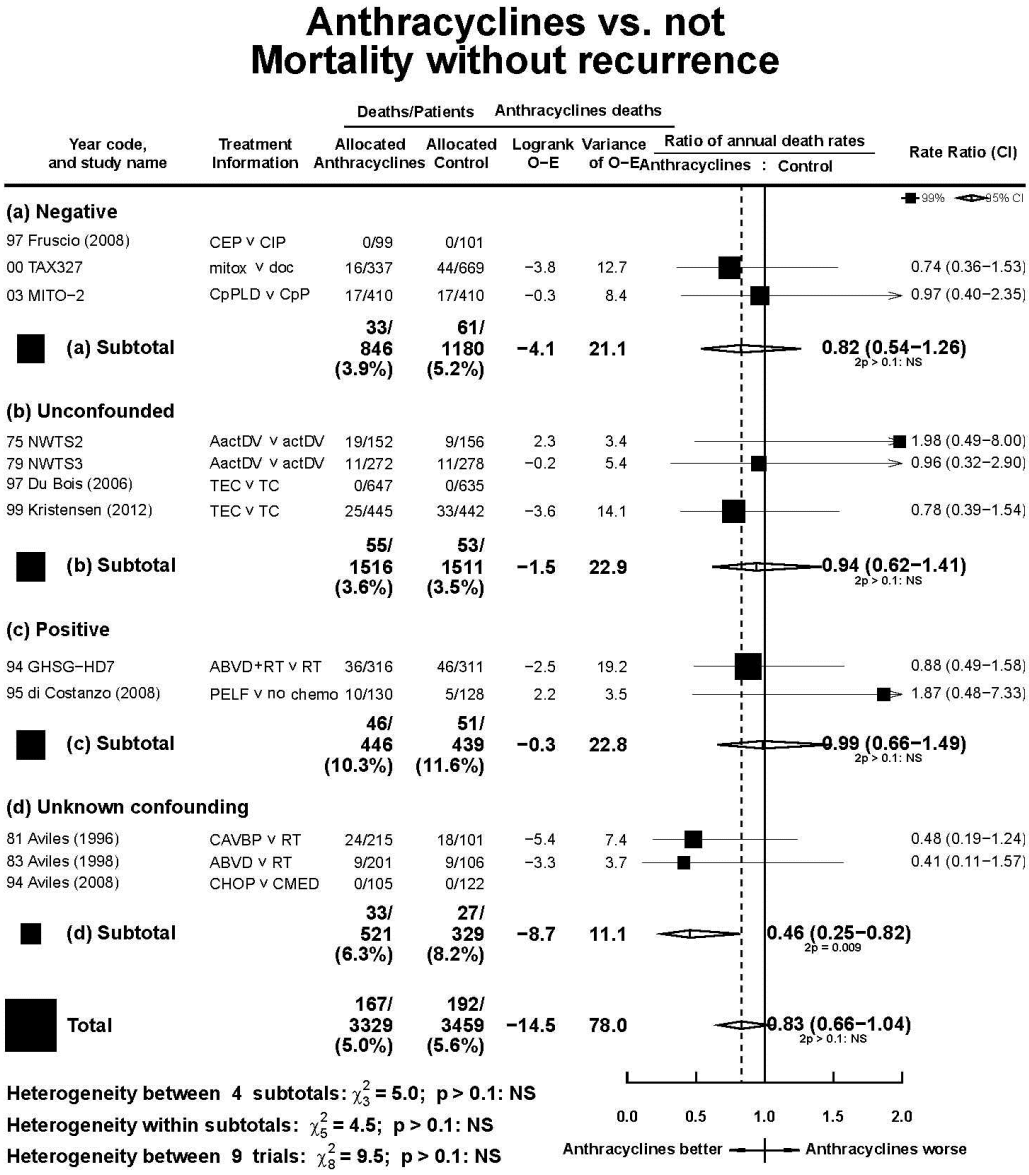


FIGURE 9 DEATH BEFORE RECURRENCE IN TRIALS OF ANTHRACYCLINE VS NOT (IPD)

There was no significant heterogeneity within each confounding category (χ^2_4=4.5, p>0.1), between each confounding category (χ^2_5=5.0, p>0.1) or between all trials considered together (χ^2_8=9.5, p>0.1). This analysis was underpowered to detect differences between anthracycline allocated patients and those not allocated

anthracyclines as the number of deaths before recurrence was small. Less than 20% of the deaths before recurrence were due to cardiac causes, and many of the others were due to second malignancies and infections. The effect of confounder drugs on these endpoints are likely different to the effect of confounder drugs on cardiac deaths. Thus the effect of anthracycline on death before recurrence is masked by the effect of confounder drugs on second malignancies and infections. There is no statistical evidence of heterogeneity and thus no evidence that confounder drugs affect the risk estimate for death before recurrence.

7.3.3 CARDIAC MORTALITY BEFORE RECURRENCE

There were 25 cardiac deaths before recurrence in 3329 patients allocated to anthracyclines and 31 deaths before recurrence in 3459 patients not allocated anthracyclines. Meta-analysis of the 12 included studies showed that there was no significant difference between trial arms in risk of cardiac death before recurrence (RR = 0.93, 97% CI 0.54 to 1.61) (see Figure 9).

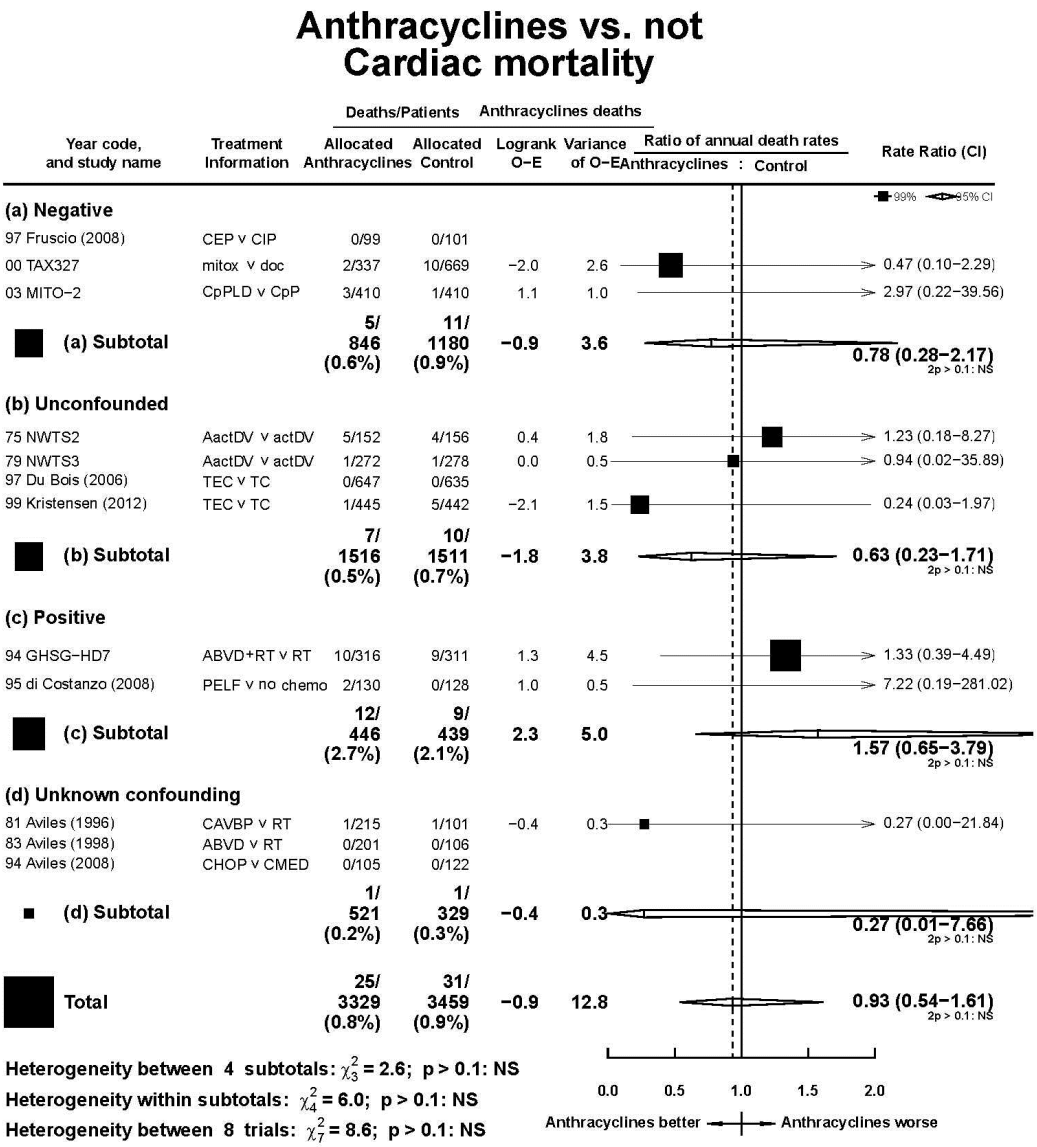


FIGURE 10 CARDIAC MORTALITY IN TRIALS OF ANTHRACYCLINE VS NOT (IPD)

There was no significant heterogeneity within each confounding category (χ^2_4=6.0, p>0.1), between each confounding category (χ^2_3=2.6, p>0.1) or between all trials considered together (χ^2_8=8.6, p>0.1). The analysis of cardiac death before recurrence lacked statistical power to detect true differences in cardiac mortality between those allocated anthracycline and those not allocated anthracycline. Similarly the analysis

was not powered to detect differences between confounding categories and the effect of confounder drugs. Thus no conclusions can be drawn about the effect of confounder drugs on cardiac deaths before recurrence.

7.4 DISCUSSION

In these analyses there was no effect of anthracyclines on risk of mortality before recurrence, or risk of cardiac mortality before recurrence. Very few of the deaths before recurrence were due to cardiac causes, and the majority were due to second malignancies and infections. The effect of confounder drugs on non-cardiac causes of death was not taken into account in the confounding categorisation thus the effect of confounders on cardiac deaths is masked by other non-cancer causes of death.

It is possible that there is no true difference between the confounded categories and that confounder drugs do not affect the risk of death before recurrence. There were no statistical differences between the rate ratios for each confounding category. However, this analysis had limited power to detect true differences between the confounding categories. Only 12 of the 60 trials from whom data was requested were able to provide data by the cut-off date. It is likely that the small number of events and patients included in this set of RCTs is too small to reliably detect differences in mortality before recurrence. The issue of low statistical power was exacerbated by an even smaller number of events in the analysis of cardiac mortality before recurrence.

It is not possible to draw conclusions about the effect of anthracyclines on cardiac mortality from this analysis. However, as more RCTs provide data and statistical power is increased, it is expected that differences in both mortality before recurrence, and cardiac mortality before recurrence, between anthracycline-allocated

patients and those not allocated anthracyclines will become clear. Negotiations are ongoing with representatives of 15 of the remaining 48 RCTs from whom data have been requested. It is anticipated that data will be forthcoming from these trials once the negotiations conclude. There are ongoing efforts to identify contacts for the 33 RCTs on the initial contact list that have not yet responded and for the 35 RCTs that have not yet been contacted.

CHAPTER 8 THE CARDIOPROTECTIVE EFFECTS OF DEXRAZOXANE

8.1 BACKGROUND

As discussed in Chapter 1, anthracyclines may damage the heart by the action of iron-dependent free radicals which damage cardiac muscle cells (myocytes) leading to cell death.[23, 24] Topoisomerase IIβ (TOPIIβ) is also thought to contribute to anthracycline cardiotoxicity.[164-167] TOPIIβ is an enzyme that is expressed in cardiac myocytes, and contributes to repair mechanisms in these cells. Anthracyclines are TOPII inhibitors, and thus interfere with cardiac myocyte repair mechanisms, as well as causing DNA damage in these cells. One method for protecting the heart during anthracycline therapy is to use a cardioprotectant drug while the patient is receiving therapy. One such drug, dexrazoxane (DEX), may provide protection to the heart during anthracycline therapy both by preventing the formation of iron-dependent free radicals, and by interfering with anthracycline effects on TOPIIβ.[164-167]

A number of preclinical studies in mice, rabbits, rats, pigs and dogs all showed reduced levels of cardiac myocyte damage in animals given dexrazoxane alongside anthracyclines compared to animals given anthracycline alone.[9] Initial non-randomised human trials of dexrazoxane as a cardioprotectant showed similar benefits.[168] Subsequent randomised controlled trials (RCTs) comparing anthracycline treatment with the same treatment without dexrazoxane, have all shown a reduction in risk of cardiotoxicity in patients allocated to dexrazoxane.[42, 64, 169-178] It is likely that this cardioprotective effect of dexrazoxane is maintained over time. Chow et al. (2015) studied children who had participated in three dexrazoxane RCTs. At a median of follow-up time of 12 years post-dexrazoxane treatment, no patients had died of cardiac causes.[179]

8.2 ONGOING CONCERNS

Although dexrazoxane has been shown to reduce the risk of cardiotoxicity, it is not widely used at present. Walker et al. (2012) compiled a retrospective cohort of children with AML or ALL from the Pediatric Health Information System (PHIS) database. [180] The PHIS database includes data on inpatient treatment from 43 hospitals in the US. Children in the cohort had been treated with chemotherapy for their cancer between 1999 and 2009 at one of the included hospitals. Of the 11289 patients newly diagnosed with ALL or AML during the study period, only 259 (2.3%) had been treated with dexrazoxane. Dexrazoxane use varied by both hospital and region. Almost 50% of patients prescribed dexrazoxane and who had ALL were treated at two of the 43 hospitals. The northeast US region had the highest proportion of dexrazoxane use, with 13.6% of ALL and 4.9% of AML patients from this region receiving DEX.

Current recommendations from national and international medicines regulatory agencies such as the US Food and Drug Administration (FDA)[181], and the European Medicines Agency (EMA)[182] limit the use of dexrazoxane. Guidelines issued by all these agencies recommend dexrazoxane for use only in adults with metastatic breast cancer, and only when more than 300mg/m^2 of doxorubicin or 450mg/m^2 of epirubicin are prescribed, and not at all in children. Evidence for these recommendations is sparse.

Swain et al. (1997) randomised 682 patients with metastatic breast cancer to treatment with fluorouracil, doxorubicin and cyclophosphamide chemotherapy (FAC) with or without dexrazoxane.[183] Response to treatment was coded as complete response if there was no evidence of disease, partial response if the cancer had

shrunk but not disappeared, stable disease if the tumour had not changed in size or progressive disease if the tumour had grown larger. Survival data were also collected. Progression-free survival is the amount of time the patient survives without their cancer getting worse. Overall survival is the number of patients still alive at a certain time point. The dexrazoxane arm of this study had a lower proportion of patients with complete or partial tumour responses (47%) than did patients in the control arm(63%), and this difference was statistically significant (p=.007). There were no differences between trial arms in either progression free or overall survival in this study. This difference in tumour response rate has not been found in any other randomised trial.

In addition, there is some concern that the risk of second malignancies (SMNs) is greater in children treated with dexrazoxane than in those not treated with dexrazoxane. The risk of SMNs was evaluated in a combined analysis of two Pediatric Oncology Group (POG) trials. In POG 9425[175] and POG 9426[176], children with Hodgkin lymphoma were randomised to receive doxorubicin, bleomycin, vincristine and etoposide (ABVE) with or without dexrazoxane, children with high risk disease also received prednisone and cyclophosphamide. Of the 513 children who were randomised into the POG 9425 and 9426 trials, there were 10 second malignancies, 8 of which occurred in children randomised to dexrazoxane. The standardized incidence rate (SIR) of SMNs was higher in dexrazoxane allocated patients (SIR 41.86) than in patients not allocated dexrazoxane (SIR 10.08) and this difference was statistically significant (p=0.0231). This difference has not been found in long-term follow-up in these or other paediatric dexrazoxane trials.

Chow et al. (2015) analysed data not only from POG 9425, POG 9426 but also POG 9404. POG 9404 randomised 537 children with ALL or non-Hodgkin lymphoma to receive or not receive dexrazoxane with each dose of doxorubicin[179]. Data on overall and cause-specific mortality were collated for all three trials. When all three trials were combined, there was no significant difference in the number of deaths from second cancers between those allocated to DEX (n = 10) and those not allocated DEX (n = 8), but the confidence interval was wide (hazard ratio 1.25, 95%CI 0.49 to 3.19). The evidence that dexrazoxane increases the risk of second malignancies is, therefore, not overwhelming.

8.3 PUBLISHED DATA META-ANALYSES OF ANTHRACYCLINE WITH AND WITHOUT DEXRAZOXANE

Three meta-analyses of published data have considered cardiac outcomes in patients allocated to dexrazoxane or not. A Cochrane review identified 10 RCTs of anthracycline with and without dexrazoxane.[66] Of the 10 RCTs, 6 included adults, 1 included only children, and 3 included both adults and children. Most of the patients included in these RCTs were women with metastatic breast cancer (n=6), and the anthracycline used in most of the trials was doxorubicin (n=6). Analyses of congestive heart failure (CHF), survival, tumour response and toxicities were carried out. 8 RCTs including 1561 patients were included in the analysis of CHF, which showed an 80% reduction in the risk of CHF in patients allocated to dexrazoxane compared to those not allocated dexrazoxane (Risk Ratio [RR] = 0.18, 95% CI: 0.10 – 0.32, $p<0.00001$). There was no significant difference in tumour response rate (RR =

0.89, 95%CI 0.78 – 1.02, p=0.08) or survival (hazard ratio = 1.04, 95%CI 0.88 – 1.23, p=0.65).

Smith et al. (2010) identified 6 RCTs of anthracycline with or without dexrazoxane including 1325 patients.[56] Of these, 4 included women with metastatic breast cancer, 1 included those aged 25 or less with sarcoma, and 1 included adults with breast cancer or sarcoma. All were treated with doxorubicin or epirubicin. Five RCTs were included in an analysis of clinical cardiotoxicity, defined as CHF or drop in LVEF requiring anthracycline treatment to be stopped. Dexrazoxane allocated patients had a lower risk of clinical cardiotoxicity than patients not allocated DEX (OR 0.21, 95%CI 0.13 to 0.33, p<0.0001).

Kalam and Marwick (2013) identified 7 RCTs of anthracycline with and without dexrazoxane including 1154 patients. 6 of the 7 RCTs only included adults, and the other included adults and older children.[63] Most of the adults in these RCTs were women with metastatic breast cancer (n=6), and the anthracycline used in most of the RCTs was doxorubicin (n=5). The outcome analysed in this study was drop in ejection fraction, development of CHF or both. This analysis showed a 65% reduction in the risk of cardiotoxicity in patients allocated to dexrazoxane compared to those not allocated dexrazoxane (RR =0.35, 95%CI: 0.27 – 0.45, P<0.0001).

Despite the above published data meta-analyses finding reduced risk of cardiotoxicity in patients allocated to dexrazoxane, it is not widely used as a cardioprotectant. Several investigations of dexrazoxane cardioprotection were planned and these are described below.

8.4 DEXRAZOXANE TRIAL SEARCH

In addition to the literature searches described in Chapter 3, MEDLINE and EMBASE were searched for publications of randomised trials of dexrazoxane. The search included terms from the controlled vocabulary thesauri of the databases, as well as synonyms for dexrazoxane. The full search strategy is provided in Appendix A.3. No language or date limits were applied. Reference lists of published data meta-analyses and other relevant articles were also searched to identify additional trials.

8.4.1 INCLUSION CRITERIA

To be included, RCTs had to fit the following criteria:

- Be an RCT of an anthracycline containing regimen with or without dexrazoxane
- Be conducted in human participants
- Include only patients diagnosed with cancer
- Have collected data on survival outcomes
- Have randomised at least 20 patients

8.4.2 RESULTS OF THE DEXRAZOXANE TRIAL SEARCH

The MEDLINE and EMBASE searches identified 408 publications. Ninety-six of the publications had been found by the searches described in Chapter 3. The initial trial search (see section 3.2) had found 68 publications that referred to an RCT of anthracycline with or without a cardioprotectant. Of these 68 publications, 38 referred to dexrazoxane. These 38 publications represented 20 unique dexrazoxane RCTs. The revised trial search (see section 3.3) did not find any additional

dexrazoxane RCTs. A further 3 RCTs were found by searching the clinicaltrials.gov trial index. No new RCTs were identified by the search conducted for this chapter.

Seven of the 23 dexrazoxane RCTs found by the trial search did not meet the inclusion criteria for this study. Three RCTs included less than 20 patients, 1 RCT included patients with multiple sclerosis (MS) and not cancer patients, and 3 RCTs only collected short term data and no survival outcomes.

8.4.3 CHARACTERISTICS OF ELIGIBLE DEXRAZOXANE RCTS

There were 7 RCTs in paediatric patients and 9 RCTs in adult patients (see Table 8.1). Half of the paediatric RCTs included patients with ALL, and the others included children with lymphoma, sarcoma or unspecified cancers. Six of the 8 adult RCTs included women with metastatic breast cancer, one included patients with metastatic breast cancer or advanced soft tissue sarcoma, one included patients with non-metastatic breast cancer and the other included patients with advanced small cell lung cancer. The median number of patients included in the paediatric RCTs was 205 (range 46 to 573), and the median number of patients included in the adult RCTs was 158 (range 112 to 682). The trials were all run in the late 1980s to early 2000s.

TABLE 8.1 CHARACTERISTICS OF INCLUDED DEXRAZOXANE RCTS

Trial	Diagnosis	Anthracycline	Anthracycline pre-treatment	Number of patients	Recruitment dates	Comparison	Dexrazoxane anthracycline ratio
Paediatric trials							
POG 94-04[174, 184]	ALL or advanced Non-Hodgkin lymphoma	Doxorubicin	Not allowed	573	1996-2001	Anthracycline in induction and consolidation +/- dexrazoxane	20:1
POG 9425[175, 176]	Hodgkin lymphoma	Doxorubicin	Not allowed	219	1997-2001	ABVE-CP[a] +/- dexrazoxane	10:1
POG 9426[176, 185]	Hodgkin lymphoma	Doxorubicin	Not allowed	294	1996-2000	ABVE[b] +/- dexrazoxane	12:1
DFCI 95-001[177, 186]	ALL	Doxorubicin	Not allowed	205	1996-2000	Doxorubicin in induction and intensification +/- dexrazoxane	Not mentioned
Wexler 1996[169]	Sarcoma	Doxorubicin	Not allowed	38	1989-2002	CAV/IE[c] +/- dexrazoxane	20:1
Cardenas 2003[187]	Paediatric cancer	Not mentioned	Not mentioned	52	2000-2002	Anthracycline +/- dexrazoxane	Not mentioned
Saad El-Din 2003[188]	ALL	Doxorubicin	Not mentioned	46	Not mentioned	Doxorubicin +/- dexrazoxane	15:1
Adult trials							
Swain 1997 (088001)[64]	Metastatic breast cancer	Doxorubicin	Not allowed	682	1988-1992	FAC[d] +/- dexrazoxane	10:1
Swain 1997 (088006)[183]	Metastatic breast cancer	Doxorubicin	Not allowed	326	1989-1992	FAC[d] +/- dexrazoxane	10:1
Ten Bokkel-Huinink 1990[189, 190]	Breast cancer	Doxorubicin	Not mentioned	112	Not mentioned	FAC[d] +/- dexrazoxane	20:1
Lopez 1998[171]	Metastatic breast cancer or advanced soft tissue sarcoma	Epirubicin	Not allowed	129	1993-1995	Epirubicin +/- dexrazoxane	6.25:1
Marty 2006[172]	Metastatic breast cancer	Doxorubicin Epirubicin	Required	164	2000-2003	Anthracycline +/- dexrazoxane	20:1 (dex:dox) 10:1 (dex:epi)
Venturini 1996[191]	Breast cancer	Epirubicin	Allowed	162	1992-1994	CEF[e] OR high dose epirubicin +/- dexrazoxane	10:1
Speyer 1992[173, 192]	Advanced breast cancer	Doxorubicin	Not allowed	150	1984-1989	FAC[d] +/- dexrazoxane	20:1
Tallarico 2003[193]	Breast cancer	Doxorubicin Epirubicin	Not allowed	112	1998-2000	Anthracycline +trimetazine Vs Anthracycline +dexrazoxane Vs Anthracycline +dexrazoxane + trimetazine	6:1 (dex:epi) 10:1 (dex:dox)
Feldmann 1992[194]	Advanced small cell lung cancer	Doxorubicin	Not mentioned	155	Not mentioned	CAV[f] +/- dexrazoxane	10:1

[a]ABVE-CP = Doxorubicin + bleomycin + vincristine + etoposide + cyclophosphamide + prednisone, [b]ABVE = Doxorubicin + bleomycin + vincristine + etoposide, [c]CAV/IE = Cyclophosphamide + doxorubicin + vincristine + mesna alternating with ifosfamide + etoposide, [d]FAC = 5-FU + doxorubicin + cyclophosphamide, [e]CEF = cyclophosphamide + epirubicin + 5-FU, [f]CAV = Cyclophosphamide + doxorubicin + vincristine

TABLE 8.2 CHARACTERISTICS OF EXCLUDED DEXRAZOXANE RCTS

Trial	Diagnosis	Anthracycline	Anthracycline pre-treatment	Number of patients	Recruitment dates	Comparison	Dexrazoxane anthracycline ratio
Short term endpoint							
Galetta[195]	Non-Hodgkin lymphoma	Epirubicin	Not allowed	20	2001-2002	ProMECEcytaBOM[g] +/- dexrazoxane	10:1
Massidda 1997[196]	Breast cancer	Epirubicin	Not mentioned	30	Not mentioned	Epirubicin Vs Epirubicin +coenzyme Q10 Vs Epirubicin + dexrazoxane	8.3:1
Jackowska[197]	ALL - paediatric	Daunorubicin	Not mentioned	107	Not mentioned	Anthracycline +/- dexrazoxane	Not mentioned
Less than 20 patients included							
De Berranger 2006[198]	ALL	Doxorubicin	Not mentioned	16	2000-2003	Doxorubicin regimen +/- dexrazoxane	20:1
CALGB 49808	Early breast cancer	Doxorubicin	Not allowed	6	2001-2002	AC +P[h] +/- trastuzumab +/- dexrazoxane	Not mentioned
Hu	Breast cancer	Not mentioned	Required	12	2009 - 2012	Anthracycline Vs Anthracycline + low dose dexrazoxane Vs Anthracycline + high dose dexrazoxane	10:1 15:1
Non cancer study							
RUB001 CARMS	Multiple sclerosis	Mitoxantrone	Allowed	50	2012-ongoing	Mitoxantrone +/- dexrazoxane	50:1

[g]ProMECEcytaBOM = Epirubicin + cyclophosphamide + etoposide + prednisolone + vincristine + methotrexate + cytarabine + bleomycin [h]AC+P = doxorubicin + cyclophosphamide + paclitaxel

8.4.4 PUBLISHED-DATA META-ANALYSES OF CARDIOTOXICITY IN DEXRAZOXANE RCTS.

This thesis analysed cardiac deaths in RCTs of anthracycline versus not rather than non-fatal cardiac events as it is not clear that cardiac outcomes are followed up systematically in the non-anthracycline arms of these trials. In contrast to this, dexrazoxane RCTs have cardiac outcomes as a primary outcome of the trial and assess cardiac status in both arms equally. Very few of the dexrazoxane RCTs publish data on cardiac deaths. Most of the adult dexrazoxane trials included patients with metastatic disease who do not survive their original cancer long enough to die of non-cancer causes. In addition the risk of cardiac death in paediatric populations is very low, so there may be very few if any cardiac deaths in the paediatric dexrazoxane trials. For these reasons the analyses undertaken in this chapter are of non-fatal cardiac events rather than cardiac deaths.

8.4.4.1 DATA EXTRACTION

Data were extracted for the following items: cancer diagnosis, dates of recruitment, number of patients, age of patients, inclusion and exclusion criteria, dexrazoxane to anthracycline ratio, treatment comparison, and cardiac outcomes. Cardiac outcomes extracted were number of congestive heart failures, unspecified cardiotoxicity, and changes of measures in cardiac function, such as drop in LVEF. For some but not all trials, unspecified cardiotoxicity included CHF and changes in measures of cardiac function. Where the number of patients randomised was specified, but the number randomised to each arm was not reported, it was assumed that there were an equal number of patients in each trial arm.

8.4.4.2 STATISTICAL ANALYSIS

Trials were grouped into two age categories (paediatric and adult) for the analyses. Paediatric trials included only patients aged 18 years or less. Adult trials included patients aged over 18 years, but may have included a small number of patients younger than 18. Data were analysed in Stata version 13.1 using the 'metan meta-analysis' macro using the Peto fixed effects model. Odds ratios were calculated rather than rate ratios because the person years of follow-up were not available. Analyses were conducted for risk of CHF, and risk of any cardiotoxicity (clinical or subclinical).

8.5 RESULTS

8.5.1 META-ANALYSIS OF CONGESTIVE HEART FAILURE INCIDENCE

Eight RCTs reported the number of patients with CHF. Of the 621 patients allocated to dexrazoxane 9 developed CHF. Of the 627 patients not allocated to dexrazoxane, 64 developed CHF. Meta-analysis of the 8 RCTs showed that the odds of CHF was 79% lower in the dexrazoxane allocated patients compared with patients not allocated dexrazoxane (OR=0.21, 95% CI 0.13 – 0.34 p=0.0000) and this increase was statistically significant (see Figure 10).There was no significant heterogeneity between trials (I^2= 0.0%, p=0.635).

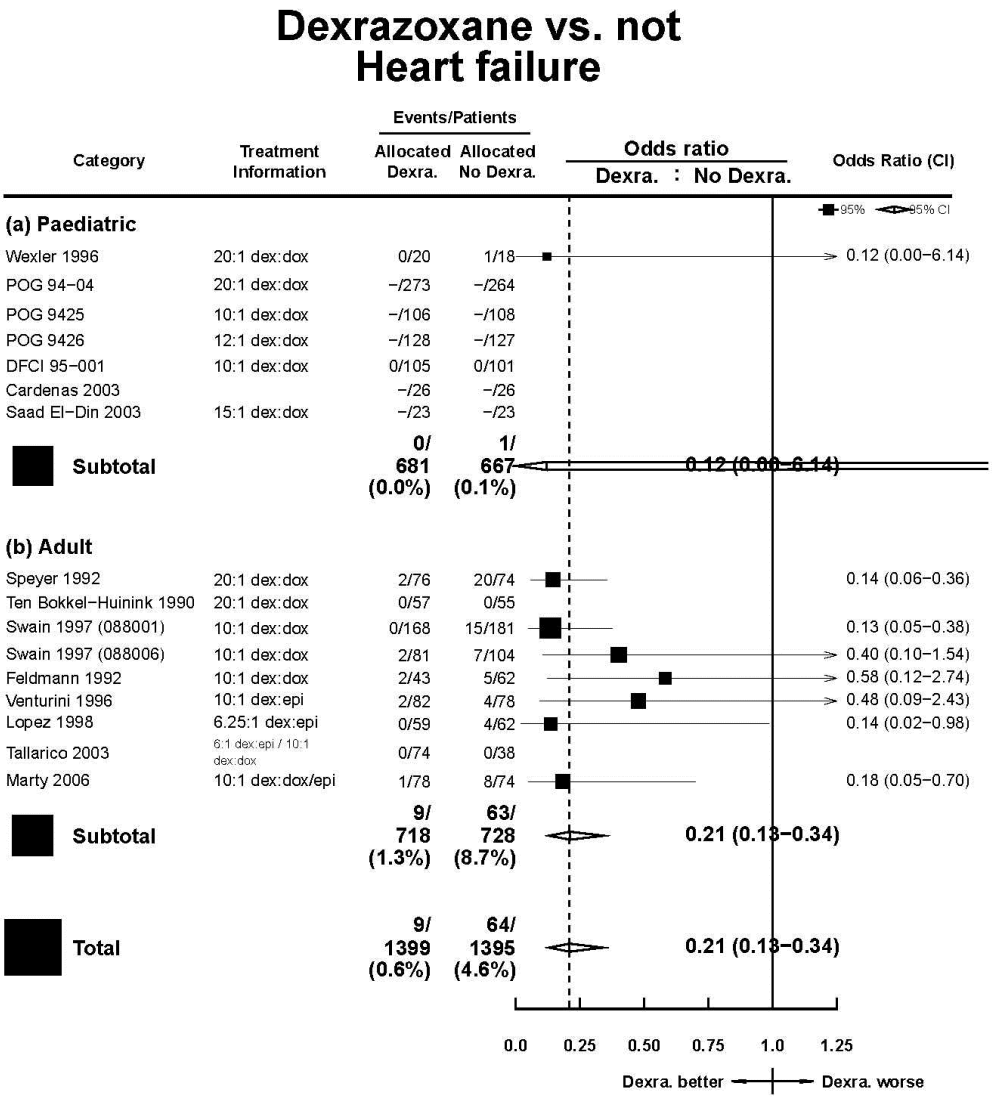


FIGURE 11 CONGESTIVE HEART FAILURE IN TRIALS OF DEXRAZOXANE VS NOT

8.5.2 META-ANALYSIS OF ANY CARDIOTOXICITY

Thirteen RCTs reported cardiac outcomes other than CHF. Outcomes included unspecified cardiotoxicity, total number of cardiotoxicity events in the trial, drop in LVEF, treatment discontinuation for cardiotoxicity, and scarring on myocardial perfusion studies. RCT publications did not specify when cardiotoxicity events occurred, so they may have occurred in the acute, early or late phase. There were 83

cardiotoxicity events in 1399 dexrazoxane-allocated patients and 238 cardiotoxicity events in 1395 patients not allocated dexrazoxane. Meta-analysis of the 13 RCTs showed that the odds of any cardiotoxicity was 71% lower in patients allocated to dexrazoxane compared with patients not allocated dexrazoxane (OR=0.29, 95% CI 0.22 to 0.37, p=0.000), and this increase was statistically significant (see Figure 11). There was no significant heterogeneity between trials (I^2=0.0, p=0.481).

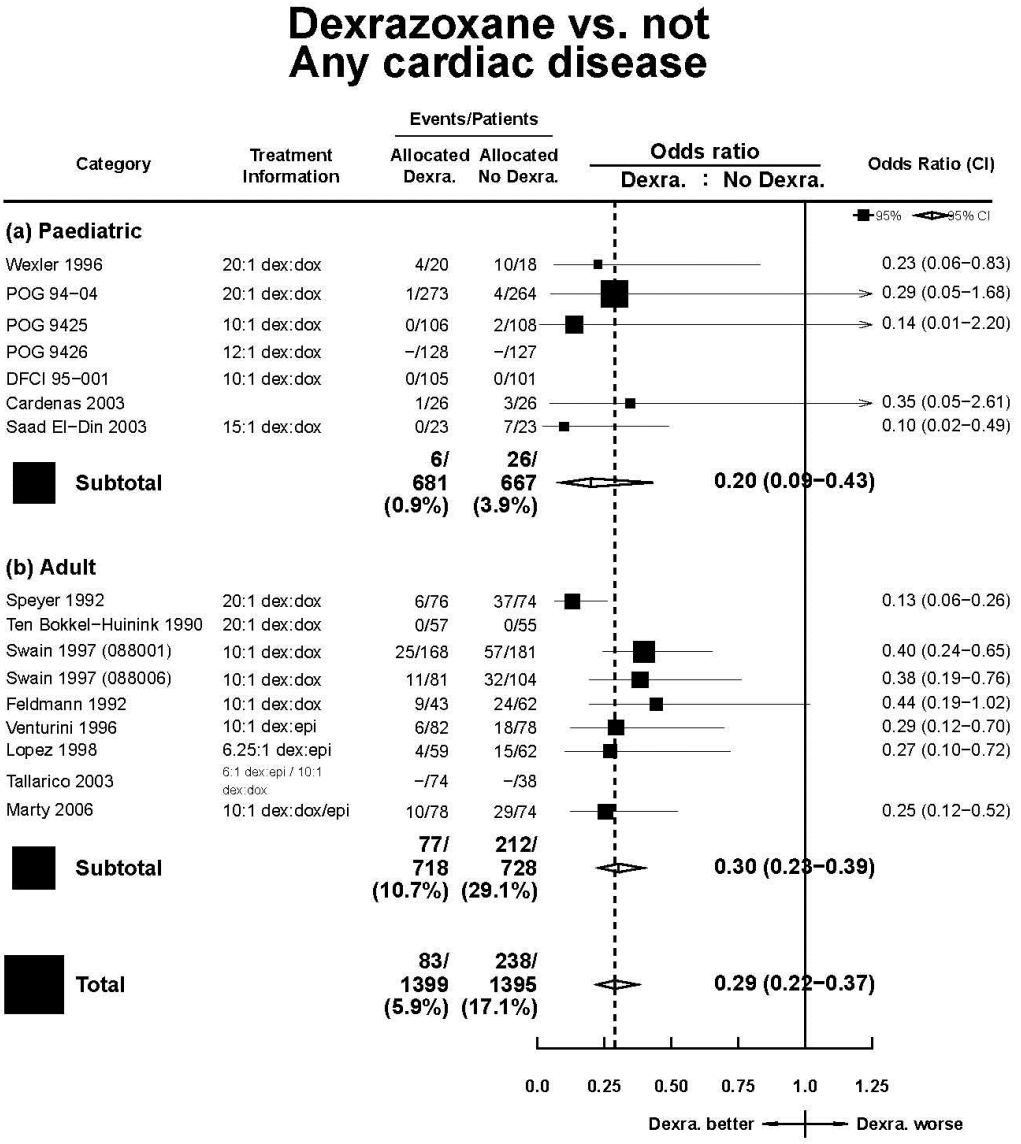


FIGURE 12 ANY CARDIOTOXICITY IN TRIALS OF DEXRAZOXANE VS NOT

8.6 INDIVIDUAL PATIENT DATA META-ANALYSIS

Principal investigators (PI) for each of the included dexrazoxane trials were contacted by email in March 2013. Four of the 8 paediatric RCTs (POG9404, POG9425, POG9426, and DFCI 95-001), including 1291 of the 1443 patients were managed by the Children's Oncology Group (COG). Shortly after contact was made with COG, they received funding for a long-term follow-up study of patients in the four dexrazoxane RCTs they manage. Individual patient data from these four RCTs would thus not be available within the timeframe of this thesis. In addition, discussions with the principal investigator of the two largest adult dexrazoxane RCTs, which included 1008 of the 1898 adult patients, revealed that the original data collected during these RCTs no longer existed. One of these RCTs was the trial that had raised concerns about tumour response rates. As data on more than half the patients ever randomised in dexrazoxane RCTs was unavailable, it was felt that little could be gained by pursing an IPD meta-analysis of dexrazoxane RCTs. As such, the IPD meta-analyses of dexrazoxane trials were abandoned. The published-data meta-analysis of cardiotoxicity in dexrazoxane RCTs described in section 8.4.4 above was then undertaken.

8.7 DISCUSSION

This analysis found much lower risk of both CHF and any cardiotoxicity in anthracycline-treated patients who were allocated dexrazoxane compared with those who were not allocated dexrazoxane. The reduction in cardiotoxicity risk when dexrazoxane was added to anthracycline regimen found in this study confirms the

risk reductions found in other published-data meta-analyses of dexrazoxane RCTs. Clearly dexrazoxane does provide cardioprotection while patients are receiving treatment with anthracyclines.

While an IPD meta-analysis had been planned, it was not possible as the data from several key RCTs were not available. This is problematic as one of the RCTs for which individual patient data no longer exists is the study which found reduced tumour response rates in dexrazoxane-allocated patients. One of the ongoing concerns regarding dexrazoxane is the potential for interference with tumour response to chemotherapy. A re-analysis of this RCT, alongside other RCTs in adults, would have allowed exploration of this phenomenon, and investigation of confounding factors that may have contributed to reduced tumour response rates.

The present meta-analysis of published data included more randomised trials of dexrazoxane than in previous meta-analyses. It confirms what had been previously found, that dexrazoxane reduces the risk of congestive heart failure and of other cardiotoxicity events in anthracycline-allocated patients. In spite of the clear cardioprotective effect of dexrazoxane, it is not widely used. It is hoped that current work on the TOP2 mechanisms of both anthracycline clinical effectiveness and dexrazoxane cardioprotection will help to allay concerns about its use. As the number of anthracycline-treated cancer survivors increases, strategies that prevent anthracycline cardiac damage, as well as treat its consequences will be needed.

CHAPTER 9 DISCUSSION AND CONCLUSIONS

9.1 DISCUSSION

Cancer is one of the most common diseases across the world. In the UK, cancer mortality rates are falling but cancer incidence rates are rising. Current estimates suggest that approximately 50% of adults will survive at least 10 years after a diagnosis of cancer[1, 2], and about 80% of children will survive at least 5 years.[4] Anthracycline chemotherapy has made a substantial contribution to improvements in survival in many cancers. However, as the number of cancer survivors increases, it becomes ever more important to understand the long-term side effects of cancer treatments. One of the most serious side-effects is cardiac toxicity, and anthracyclines are particularly implicated in this.

The broad aim of this thesis was to investigate risk of cardiac death in randomised trials of anthracycline vs. not. This was done, firstly by investigating methodological issues that have hampered past efforts to ascertain the magnitude of the risk. Under-reporting of cardiac outcomes, and limited indexing of harm outcomes by citation databases, led to difficulties in identifying relevant RCTs. Therefore an extensive search was undertaken that did not rely on publication of the harm outcome in question. Exclusion of confounded RCTs reduces the amount of information available on cardiac outcomes, and does not allow investigation of the effect of non-anthracycline drugs on anthracycline cardiotoxicity. So confounded trials were included in these analyses and a method was devised for categorising them according to the predicted effect of confounder drugs on the risk estimates generated by the meta-analysis.

Chapter 1 reviewed existing literature on anthracycline cardiotoxicity. It showed that anthracyclines are used to treat many cancers, and that they contribute to cancer

survival but that they also carry the risk of cardiotoxicity. Anthracycline cardiotoxicity can occur while the patient is on treatment, but also may not occur until months or years later. Anthracycline cardiotoxicity is characterised by drops in left ventricular ejection fraction, cardiomyopathy, congestive heart failure and the possibility of cardiac death.[17, 18] The Multiple-Hit hypothesis suggests that, while anthracyclines damage the heart, additional stressors can influence the course of the disease. Risk factors that increase the risk of anthracycline cardiotoxicity include cumulative anthracycline dose, age, genetic factors, exposure to other cardiotoxic treatments, pre-existing heart disease and other cardiac risk factors.[28] The mechanism for anthracycline cardiotoxicity is still not fully understood. It is thought that both damage by free radicals and the interruption of DNA repair mechanisms that are mediated by topoisomerase enzymes contribute to anthracycline cardiotoxicity.[25]

The risk of anthracycline cardiotoxicity has been investigated in several observational studies. Von Hoff et al. (1979)[32] and Swain et al. (1997)[42] both found dose response relationships such that the risk of congestive heart failure rises rapidly after a cumulative doxorubicin dose (or equivalent of other anthracyclines) of about 400 mg/m^2. Many of the patients included in these studies had cancers with poor prognosis who survived for less than five years after diagnosis. This gives little information about the risk of anthracycline cardiotoxicity over the long term.

Cohort studies of adult survivors of childhood cancer show higher risk of congestive heart failure in those treated in childhood with anthracyclines compared to those treated without anthracyclines, and they also show increased risk of death not only from congestive heart failure but also from other cardiac causes.[47, 49] Cohort studies

that involve cardiac imaging of anthracycline-treated adult survivors of childhood cancer, show abnormalities in heart function on echocardiography that are chronic and progressive.[21]

Previous meta-analyses of published data, although limited in the number of randomised trials included, show increased risk of congestive heart failure and cardiac death in anthracycline-allocated patients compared to patients not allocated anthracycline.[54] The only previous individual patient data meta-analysis of cardiac death in randomised anthracycline trials was carried out by the EBCTCG[16]. It showed that the risk of cardiac death was increased in women randomised to anthracyclines compared to women randomised to other chemotherapy and also in women randomised to anthracycline compared to women randomised to no chemotherapy. In order to better establish the both the magnitude and time dependence of cardiac mortality risk, IPD meta-analyses in patients with other cancers are needed.

Chapter 2 discussed the motivations for this study. Combining data from a small number of trials, as previous published-data meta-analyses have done, has resulted in analyses that include too few patients to detect true differences between trial arms. It is also possible that these analyses are biased due to including only trials that publish cardiac outcomes, which are a very small subset of the anthracycline trials that have ever been done and are unlikely to be a representative sample. Many more trials may have collected data on cardiac outcomes and could contribute data to cardiotoxicity analyses.

In addition, knowledge of the risk of anthracycline cardiotoxicity may lead to the cardiac health of anthracycline-treated patients being more closely monitored than that of patients treated without anthracyclines. If this is the case, then data on non-

fatal cardiac outcomes may not be as systematically collected in patients treated without anthracyclines compared to anthracycline-treated patients. This means that risk estimates of heart disease incidence based on meta-analyses of randomised trials of anthracyclines versus no anthracyclines may be inherently biased. In order to address this issue, it was decided to undertake analyses of cardiac death, which should be less subject to these biases.

In **Chapter 3** a search for randomised trials of anthracycline to treat cancer was undertaken. The initial version of this search, which included terms for anthracyclines, cardiac outcomes and randomised trials, found a large number of trials, but many of these were small, including less than 100 patients per trial arm, and/or with median survival of less than 12 months. Small trials may contain a limited number of cardiac deaths, as will trials with short survival. To assess the completeness of the initial trial search, the results were compared to the trial list maintained by the Early Breast Cancer Trialists' Collaborative Group, which can be considered a complete list of all randomised treatment trials in this patient population. This revealed that only 40% of the anthracycline vs not trials on the EBCTCG trial list were found by the trial search. When the search was run without cardiotoxicity terms it found 87% of the early breast cancer trials that fit the eligibility criteria for this study. The early breast cancer trials that were still not found by the search had either never been published, or had not yet published their results. The search for trials demonstrated that many relevant anthracycline vs not trials did not publish cardiac event data, so that they could not be found by a search including cardiac terms. This provides evidence of under-reporting of cardiac

outcome data in anthracycline trials, and highlights the need for meta-analyses using searches not hampered by under-reporting.

Chapter 4 outlined a method by which trials with multiple differences between trial arms may be included in meta-analyses. Many meta-analyses exclude such trials because there may be some confounding. Where there is a single difference between trial arms, significant differences in outcomes can usually be attributed directly to the intervention under investigation. However, this limits the number of trials able to be included and may exclude many events that could be informative. By including trials with multiple differences between trial arms, the number of events is increased, and evidence is gained on the effect of the confounding drugs on the outcome. The procedure for including confounded trials in meta-analyses is as follows. First, evidence on the effect of each individual drug or treatment on the outcome under investigation is reviewed. Second, the likely effect of any confounder drugs on the risk estimate for each trial is considered. Trials that include confounders that will probably affect the risk estimate in similar ways are grouped together in the analysis, regardless of the individual drugs concerned. Risk estimates can be compared between the unconfounded and confounded groups. If any differences found are in the directions predicted, it is then possible to establish the effect of confounder drugs and suggest further analyses that might be undertaken.

In order to evaluate the assertions made in Chapter 4, a published data meta-analysis was undertaken in **Chapter 5**. Thirty-two of the 171 trials found by the trial search had published cardiac death data in enough detail to allow data extraction. Following the process described in Chapter 4, 8 trials were categorised as unconfounded. Of the confounded studies, 12 were positively confounded, 6 were negatively confounded

and 6 were of unknown confounding. If confounder drugs do affect the risk of anthracycline-related cardiac mortality, the risk estimate for positively confounded trials would be larger than that for the unconfounded trials, and the risk estimate for negatively confounded trials would be smaller. In the meta-analysis of the 32 trials, when all trials were considered together, the overall risk of cardiac death was significantly higher in anthracycline-allocated patients compared to those not allocated anthracyclines, suggesting this is a true difference. When the different confounding group were considered separately, there was a 50% increased risk of cardiac death in anthracycline-allocated patients compared to patients not allocated anthracyclines in the unconfounded group. This difference was not statistically significant likely due to the small number of cardiac deaths in these trials, and resulting low statistical power. Analyses of the confounded groups did not reveal any statistically significant differences between confounding categories, and any apparent differences in risk may be explained by the median cumulative anthracycline dose in each category. The negatively confounded group, which also had the lowest median cumulative anthracycline dose, also had the smallest odds ratio. When the trials were grouped according to cumulative dose, the risk of cardiac death was only increased in the higher dose group, with no statistically significant difference in risk of cardiac death in the lower dose group. This is consistent with the dose response graphs produced by Von Hoff[32] and Swain[42] that show the risk of congestive heart failure in anthracycline treated patients rises rapidly after about 400 mg/m^2.

The magnitude of the increases in risk of cardiac death in anthracycline allocated patients in the analyses conducted by the Early Breast Cancer Trialists' Collaborative Group was similar to the overall increase found in the present meta-analysis when all

confounding groups were combined. The EBCTCG analyses included a mix of confounded and unconfounded trials, and exclude some anthracycline vs not trials for which they hold data. It would be of interest to analyse data from all of the eligible EBCTCG trials categorised according to the presence of confounding drugs, to determine if confounder drugs affect risk of cardiac death in that dataset. It would also be of interest to analyse a different outcome using the confounding process described here, to determine if the method is applicable to other outcomes.

Despite an increase in risk of cardiac death in patients allocated to anthracycline, the absolute risk of cardiac death is small. Only 1% of patients included in the trials in this analysis died of cardiac causes. This is likely an underestimate of the long-term risk of cardiac death as follow-up was less than 10 years for the majority of trials in this analysis. Long term follow-up of childhood cancer survivors show increased risk of cardiac death 20 or more years after chemotherapy.[5, 6, 47, 49, 199] There is a similarly increased risk of death from second malignancies in patients who received chemotherapy for childhood cancer. However, although there is a small increase in risk of late cardiac mortality, there are also clear benefits to their use. The EBCTCG breast cancer overviews showed that there is an absolute reduction in breast cancer mortality of about 6% in women allocated to anthracyclines compared to women who receive no chemotherapy. In addition, there is evidence that anthracyclines contribute to overall survival in soft tissue sarcoma,[200] lymphoma,[201] leukaemia, [202]and are still a mainstay of treatment in many other types of cancer. Thus while there is clearly some risk of treatment with anthracyclines, these are outweighed by the benefits of treatment.

Chapter 6 further examined the impact of reporting bias in randomised anthracycline trials. All 171 trials found by the searches described in Chapter 3 were eligible to have the risk of outcome reporting bias assessed, provided that they had been published as a full paper, 133 trials met this criteria. This assessment revealed that only 33% of the trials had fully reported cardiac morbidity data, and a similarly small proportion (27%) had fully published cardiac mortality data. Of those trials that had not fully published cardiac outcomes, 51% were deemed to be at high risk of outcome reporting bias for cardiac morbidity and 35% were judged to be at high risk of outcome reporting bias for cardiac mortality. It is likely that outcome reporting bias was under-estimated in this study. There were many different cardiac endpoints reported with little consistency between trials. Thus there may have been cardiac events that were not reported in trials that were classified as low risk of outcome reporting bias. Additionally, a study has low risk of outcome reporting bias if there are no events. Many of the trials assessed may have had no events, especially if they were small and the follow-up was short. This is compounded by cardiotoxicity data collection that takes place only while the patient is receiving treatment, but ceases after this. Thus many events may have been missed in these trials.

Analysis of factors that might predict the risk of outcome reporting bias was conducted. It showed that, for cardiac morbidity, as the number of patients included in the trial increased, the risk of outcome reporting bias decreased. This result was expected as smaller trials are less likely to observe events for relatively uncommon outcomes such as anthracycline cardiotoxicity, and are thus at higher risk of reporting bias than larger trials with more events. A different pattern was found for risk of cardiac mortality ORB. This analysis revealed that the year of first trial

publication was associated with the risk of outcome reporting bias such that trials that had first published more recently at were at higher risk of ORB than those that had published earlier. This was not expected. Reporting guidelines for harm outcomes have become more stringent over time thus one would expect more recently published trials to have reduced risk of outcome reporting bias.

The results of both Chapter 3 and Chapter 6 demonstrate that cardiac outcomes are under-reported, and that existing published-data meta-analyses may be more likely to include trials with biased outcomes. As such, the results of meta-analyses of cardiac outcomes using published data may not accurately reflect the true extent of the risk. In order to obtain a more accurate estimate of cardiac risk, more data on cardiac events is needed. There is likely much more data on cardiac deaths in anthracycline trials than has already been published. As such, there is clear need to extend the inclusion criteria for cardiotoxicity meta-analyses, and to conduct meta-analyses that avoid the biases described above.

The findings of this thesis have wider implications, beyond meta-analyses of cardiotoxicity in anthracycline trials. It is likely that similar issues affect reporting of other toxic outcomes in randomised trials. Chapter 3 showed that for a meta-analysis of a toxic outcome (in this case cardiotoxicity), searches including that outcome find a very low proportion of the relevant trials. The trials that are found by such a search are those that include the term in their title, abstract or keywords. However, many trials may report the outcome, without including it in the title or abstract. For the meta-analysis carried out in Chapter 5, almost one third (n=10) of the 32 trials that published cardiac outcomes, were not found by a search that included cardiac terms. This shows that much relevant data may be missed by using a search of this nature.

This, combined with the high risk of outcome reporting bias for harms, suggests that future meta-analyses of harms may be better served by conducting searches that do not limit by publication of the harm in question.

A further aim of this thesis was to commence the process of an individual patient data meta-analysis as described in **Chapter 7**. The first steps in this process, and a very preliminary analysis, were undertaken. Investigators for the 60 most recently published of the non-early-breast-cancer trials found by the trial search were contacted in March 2013. By June 2015, data had been received from 12 trials, including 6788 patients. Of these only 4 were unconfounded, and the rest were a mix of the other confounded groups. Meta-analyses of mortality before relapse or recurrence of cancer, and of cardiac mortality before recurrence were not statistically significant, and no effect of confounding was seen. It is hoped that a more thorough investigation of the effect of confounding on death before recurrence, and particularly of cardiac death before recurrence, will be possible in future when data from a larger number of trials has been collated. In the present analysis the effect of anthracyclines was not statistically significant, and the confidence intervals were wide, due to the small number of deaths before recurrence that occurred. Meta-analysis of cardiac death before recurrence was similarly underpowered, and the pattern of results did not show any clinically significant differences. With the limited data available, it was not possible to construct survival curves for cardiac mortality. Future research collating data from a larger number of trials would be desirable, to increase statistical power, and allow construction of survival curves. It is important to establish the time course of anthracycline cardiotoxicity, to determine whether most of the risk occurs early, or if it continues and increases over time. It would also

be of interest to investigate cardiac deaths in data from anthracycline trials included in the EBCTCG overviews of breast cancer treatment.

One final topic investigated in this thesis was the possibility of cardioprotection by the use of additional drugs during anthracycline chemotherapy. Anthracyclines damage the heart through the action of free radicals and probably by interference with topoisomerase-mediated DNA repair. The most studied cardioprotectant is dexrazoxane. Dexrazoxane is clearly cardioprotective, as shown in several published data meta-analyses[56, 63, 66]. However, there are ongoing concerns over the potential for dexrazoxane to interfere with tumour response rates and to increase the risk of second malignancies. An individual patient data meta-analysis of randomised trials of dexrazoxane versus not was proposed, as discussed in **Chapter 8**. The IPD meta-analysis was not possible as investigation revealed that data from several key trials were not available. A new meta-analysis of published data, however, was undertaken, which confirmed the results of prior meta-analyses. The risk of congestive heart failure was 79% lower in dexrazoxane-allocated patients than in patients not allocated dexrazoxane. Analysis of any cardiotoxicity similarly showed that dexrazoxane-allocated patients were at lower risk than those not allocated dexrazoxane. Should individual patient data become available, it would be of great interest to pursue an analysis of risk of both second malignancies, and of tumour response rates in the trials of dexrazoxane.

9.2 SUMMARY AND CLINICAL IMPLICATIONS

This thesis found increased risk of cardiac death in patients randomised to anthracyclines compared to those not randomised to anthracycline. It also found that

trial search strategies for meta-analyses of harms that include harm terms may miss up to 60% of the relevant trials and up to one third of the trials that have published relevant data. There was also a high risk of outcome reporting bias for cardiac outcomes found in many of the trials assessed in this thesis. This suggests that the results of previous published data meta-analyses may be biased as they include only trials that publish cardiac outcomes, and/or are found by searches that include cardiac terms. In order to increase the amount of information about cardiac outcomes in meta-analyses of cardiotoxicity, a method for including trials where there were multiple differences between treatment arms was developed Anthracyclines are frequently used in multi-drug chemotherapy regimens, thus increasing knowledge about the cardiotoxic effect of other drugs in combination with anthracyclines is important. The results of the published-data and individual patient data meta-analyses conducted in this thesis demonstrate that it is possible to include confounded trials in a meta-analysis. Future work will focus on whether the process for including confounded trials in meta-analyses described in this thesis is applicable to other harms, and other drugs.

Anthracyclines are used in the treatment of many cancers, and contribute to increasing cancer survival rates. In order that anthracyclines continue to be used and to help save lives, clinicians need better estimates of the magnitude of the cardiac risk and of the time dependence of that risk. This thesis has produced a new estimate of the risk of cardiac death in anthracycline-allocated patients that clinicians can use to inform their treatment decisions.

There is a clear need for the process of individual patient data meta-analysis to continue, to better elucidate the risk, risk factors and time course of anthracycline cardiotoxicity.

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CHAPTER 10 APPENDICES

10.1 APPENDIX A.1 SEARCH STRATEGIES FOR THE INITIAL TRIAL SEARCH

10.1.1 INITIAL TRIAL SEARCH - MEDLINE SEARCH STRATEGY

1. exp Anthracyclines/
2. anthracyclin*.mp.
3. exp Doxorubicin/
4. adriamyc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. adriablastin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. adriablastin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. adriablast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. adriblast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. doxorubicin hydrochloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. hydrochloride, doxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. doxorubic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. adriamycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
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156. placebo.ab.
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158. randomly.ab.
159. trial.ti.
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162. 160 not 161
163. 152 and 162
164. exp Heart/
165. exp Cardiomyopathies/
166. exp Heart Diseases/
167. exp Heart Failure/
168. exp Ventricular Dysfunction/
169. exp Coronary Disease/
170. exp Echocardiography, Three-Dimensional/ or exp Echocardiography, Doppler/ or exp Echocardiography, Four-Dimensional/ or exp Echocardiography/ or exp Echocardiography, Doppler, Pulsed/ or exp Echocardiography, Transesophageal/ or exp Echocardiography, Doppler, Color/ or exp Echocardiography, Stress/
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172. exp Ventricular Function, Left/
173. exp Radionuclide Imaging/

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215. 163 and 214

10.1.2 INITIAL TRIAL SEARCH - EMBASE SEARCH STRATEGY

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13. randomized controlled trial/
14. single blind procedure/
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196. radionuclide angiography.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
197. radionuclide ventriculography.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
198. ventriculography, radionuclide.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

199. gated blood-pool imaging.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
200. blood pool scintigraphy.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
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209. LVEF.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
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215. left ventricular dysfunction.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
216. exp heart left ventricle failure/
217. exp heart right ventricle failure/
218. right ventricular dysfunction.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
219. congestive heart failure.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
220. exp congestive heart failure/
221. exp congestive cardiomyopathy/ or exp cardiomyopathy/ or exp restrictive cardiomyopathy/
222. exp cardiotoxicity/
223. exp heart disease/
224. 165 or 166 or 167 or 168 or 169 or 170 or 171 or 172 or 173 or 174 or 175 or 176 or 177 or 178 or 179 or 180 or 181 or 182 or 183 or 184 or 185 or 186 or 187 or 188 or 189 or 190 or 191 or 192 or 193 or 194 or 195 or 196 or 197 or 198 or 199 or 200 or 201 or 202 or 203 or 204 or 205 or 206 or 207 or 208 or 209 or 210 or 211 or 212 or 213 or 214 or 215 or 216 or 217 or 218 or 219 or 220 or 221 or 222 or 223
225. 164 and 224
226. 15 and 225

10.2 APPENDIX A.2 SEARCH STRATEGIES FOR THE REVISED TRIAL SEARCH

10.2.1 REVISED TRIAL SEARCH - MEDLINE SEARCH STRATEGY

1. exp Anthracyclines/
2. anthracyclin*.mp.
3. exp Doxorubicin/
4. adriamyc*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. adriablastin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. adriablastin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
7. adriablast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. adriblast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. doxorubicin hydrochloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. hydrochloride, doxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
11. doxorubic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. adriamycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. hydroxydaunomycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. 14-hydroxydaunomycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
15. 14-hydroxydaunorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. hydroxydaunorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17. doxil.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18. caelyx.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19. doxil.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
20. rubex.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
21. myocet.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. thermodox.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

23. DOX-SL.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. DOX SL.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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26. adriacin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
27. adiblastine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
28. farmablast*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
29. liposomal doxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
30. doxorubicin, liposomal.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
31. adrim.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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36. axibin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
37. dicladox.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
38. doxocris.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
39. ribodoxo.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
40. 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. exp Epirubicin/
42. ellence.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
43. 4'epiadriamycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
44. 4' epiadriamycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
45. 4' epidoxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

46. 4'-epidoxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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48. 4' epi doxorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
49. 4'-epi-adriamycin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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52. epirubicin hydrochloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
53. hydrochloride, epirubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
54. farmorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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107. daunorubicin hydrochloride.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
108. hydrochloride, daunorubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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125. valrubicin.mp.
126. valstar.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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128. trifluoroacetyldoxorubicin-14-valerate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
129. exp Aclarubicin/
130. aclarubicin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
131. aclarubic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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134. valtaxin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
135. 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134
136. exp Mitoxantrone/
137. mito*antrone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
138. novantron*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

139. domitrone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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147. bluxantrone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
148. mitoxgen.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
149. misostol.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
150. mitrone.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
151. 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 or 149 or 150
152. 1 or 2 or 40 or 74 or 94 or 124 or 135 or 151
153. randomized controlled trial.pt.
154. controlled clinical trial.pt.
155. randomized.ab.
156. placebo.ab.
157. clinical trials as topic.sh.
158. randomly.ab.
159. trial.ti.
160. 153 or 154 or 155 or 156 or 157 or 158 or 159
161. exp animals/ not humans.sh.
162. 160 not 161
163. 152 and 162

10.2.2 REVISED TRIAL SEARCH - EMBASE SEARCH STATEGY

1. exp anthracycline/ or anthracyclinone derivative/ (13381)
2. exp anthracycline derivative/ (5403)
3. exp anthracycline antibiotic agent/ (177513)
4. anthracyclin*.mp. (26471)
5. exp doxorubicin/ (135702)
6. adriamyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (23783)
7. adriablastin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (289)
8. adriablastin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (117)
9. adriablast*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (289)
10. adriblast*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1080)
11. doxorubicin hydrochloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (651)
12. hydrochloride, doxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (6)
13. doxorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (138791)
14. adriamycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (23452)
15. hydroxydaunomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (47)
16. 14-hydroxydaunomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (8)
17. 14-hydroxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
18. hydroxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (201)
19. doxil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1772)
20. caelyx.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1029)
21. doxil.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1772)
22. rubex.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (62)
23. myocet.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (462)
24. thermodox.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (54)
25. DOX-SL.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (19)
26. DOX SL.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (19)
27. DOXSL.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
28. adriacin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (138)
29. adiblastine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
30. farmablast*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
31. liposomal doxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2132)
32. doxorubicin, liposomal.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (34)

33. adrim.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (5)
34. adrim*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (43)
35. adricept.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
36. adricin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
37. adrosal.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
38. axibin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
39. dicladox.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
40. doxocris.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
41. ribodoxo.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
42. exp epirubicin/ (21353)
43. ellence.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (139)
44. 4'epiadriamycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (5)
45. 4' epiadriamycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (33)
46. 4' epidoxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (156)
47. 4'-epidoxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (156)
48. 4'epidoxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (13)
49. 4' epi doxorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (101)
50. 4'-epi-adriamycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (47)
51. 4' epi DXR.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
52. epirubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (21747)
53. epirubicin hydrochloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (83)
54. hydrochloride, epirubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
55. farmorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (427)
56. pharmorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (116)
57. farmorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (510)
58. IMI-28.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
59. IMI28.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
60. IMI 28.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
61. NSC256942.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
62. NCS-256942.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
63. epirubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (21808)
64. epiadriamyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (55)

65. epidoxorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (396)
66. epi-adriamyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (63)
67. epi-doxorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (119)
68. ridorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
69. epi-DX.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (15)
70. pidorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
71. anthracin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (36)
72. dinarin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
73. bioepicyna.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
74. epidoxo.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
75. exp idarubicin/ (7641)
76. 4-demethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (163)
77. 4 demethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (163)
78. IMI 30.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (14)
79. IMI30.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
80. IMI-30.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (14)
81. idarubicin hydrochloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (21)
82. hydrochloride, idarubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
83. idarubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (7760)
84. NSC 256439.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (6)
85. NSC-256439.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (6)
86. idarubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (7810)
87. 4 desmethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
88. 4-desmethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
89. idamyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (57)
90. idaralem.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
91. zavedos.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (127)
92. demethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (171)
93. desmethoxydaunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
94. exp daunorubicin/ (23602)
95. daunorubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (24516)
96. dauno-rubidomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2)

97. dauno-rubidomycine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
98. dauno-rubidomyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2)
99. dauno rubidomyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2)
100. rubidomycin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (152)
101. rubidomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (140)
102. rubomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (298)
103. daunomycin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2273)
104. cerubidine.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (273)
105. daunoblastin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (158)
106. daunorubicin hydrochloride.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (42)
107. hydrochloride, daunorubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
108. rubidomyc*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (152)
109. NSC-82151.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (84)
110. NSC 82151.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (84)
111. NSC82151.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
112. daunoxome.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (575)
113. dauno*ome.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (580)
114. daunosom*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (6)
115. daunocin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
116. cerubidin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (97)
117. maxidauno.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
118. cerubidin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (370)
119. donobin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
120. daunorrubicin*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (13)
121. daunarubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
122. daunamycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2)
123. valrubicin.mp. (367)
124. exp valrubicin/ (366)
125. valstar.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (30)
126. trifluoroacetyladriamycin-14-valerate.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (62)
127. trifluoroacetyldoxorubicin-14-valerate.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (9)
128. exp Aclarubicin/ (1748)
129. aclarubicin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1784)

130. aclarubic*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1786)
131. aclacinomycin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (808)
132. aclacin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
133. valtaxin.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
134. exp mitoxantrone/ (18821)
135. mito*antrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (19206)
136. novantron*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1002)
137. domitrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
138. ebexantron.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
139. mitroxone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
140. oncotron.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
141. oncotrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
142. onkotrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (11)
143. onkotron*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (11)
144. santrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
145. bluxantrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
146. mitoxgen.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
147. misostol.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (0)
148. mitrone.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1)
149. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113 or 114 or 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139 or 140 or 141 or 142 or 143 or 144 or 145 or 146 or 147 or 148 (191969)
150. random$.mp. (1008637)
151. factorial$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (46070)
152. crossover$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (65698)
153. cross-over$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (22177)
154. placebo$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (328661)
155. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (181400)
156. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (26051)
157. assign$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (238999)
158. allocat$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (94897)

159. volunteer$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (186859)
160. crossover procedure/ (38713)
161. double blind procedure/ (115395)
162. randomized controlled trial/ (343187)
163. single blind procedure/ (18183)
164. 150 or 151 or 152 or 153 or 154 or 155 or 156 or 157 or 158 or 159 or 160 or 161 or 162 or 163 (1594831)
165. 149 and 164 (20487)

10.3 APPENDIX A.3 DEXRAZOXANE SEARCH STRATEGY

1. exp Razoxane/
2. dexrazox*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. cardiox*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. zinecard.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. dextrorazox*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. eucardio*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. ICRF-187.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. ICRF187.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. ICRF 187.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. ADR 529.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. ADR-529.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. ADR529.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. piperazinedion*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. dyzoxan*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15. desrazox*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
16. razoxan*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
17. dioxopiperazin*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

10.4 APPENDIX B.1 TRIAL DESCRIPTIONS FOR ALL INCLUDED TRIALS

Abbreviations used in this Appendix

5-FU – 5-fluorouracil
ALL – acute lymphoblastic leukaemia
AML – acute myeloid leukaemia
BCS – breast conserving surgery
CHF – congestive heart failure
CLL – chronic lymphocytic leukaemia
Daun – daunorubicin
Dox – doxorubicin
Epi – epirubicin
ER – oestrogen receptor
FIGO – International Federation of Gynecology and Obstetrics
HER2 – human epidermal growth factor receptor-2
Ida – Idarubicin
IHD – ischemic heart disease
LipDox – liposomal doxorubicin
LVEF – left ventricular ejection fraction / ejection fraction
MI – myocardial infarction
Mitox – mitoxantrone
nm – not mentioned
PR – progesterone receptor
unk – unknown

Risk of Bias items

A – random sequence generation

B - allocation concealment

C – blinding of participants and personnel

D – blinding of outcome assessment

E – Incomplete outcome data

F – other bias

Randomised trials of anthracycline vs not

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0332 FLOT-4[193] Pauligk (2010) (2010 – ongoing)	Gastric cancer ≥18 years No prior chemotherapy No cardiomyopathy, CHF LVEF >50% required	590	nm	Median age 62 years 78% male	Epirubicin (A) Cisplatin (T) 5-FU (T) *vs* Docetaxel (T) 5-FU (T) Leucovorin (N) Oxaliplatin (N)	Unknown	No	Not assessable	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0054 SUCCESS-C[194] Ortmann (2011) 2009 - ongoing	Breast cancer Female ≥18 years	3547	nm	nm	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Docetaxel (T) *vs* Docetaxel (T) Cyclophosphamide (T)	Positive	No	Not assessable	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0326 ICE II[195] Von Minckwitz (2010) 2009 - ongoing	Breast cancer ≥65 years	400	nm	nm	Epirubicin (A) Cyclophosphamide (T) *vs* Paclitaxel (T) Capecitabine (T)	Unknown	No	Not assessable	Epi 360 mg/m	U	U	U	U	U	U
ANTH0327 WSG Plan B[196] Gluz (2010) 2009 - ongoing	Breast cancer Female 18-75 years High risk No prior chemotherapy No prior radiotherapy	2448	nm	nm	Epirubicin (A) Cyclophosphamide (T) Docetaxel (T) *vs* Cyclophosphamide (T) Docetaxel (T)	Unconfounded	Yes	Not assessable	Epi 360 mg/m^2	U	U	U	U	U	U
ANTH0274 BRIGHT[197] Flinn (2014) (2009 – ongoing)	Non Hodgkin Lymphoma Mantle cell lymphoma ≥18 years Measurable disease No prior chemotherapy No prior radiotherapy	447	nm	Median age 59 (25 – 86) 60% male Balanced at baseline	Doxorubicin (A) Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Rituximab (T) Bendamustine (N)	Positive	Yes	Morbidity – T1 Mortality - Full	Dox 300 – 400 mg/m^2	U	U	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0320 ADMIRE unpublished 2009 - ongoing	CLL ≥18 years Binet stage B, C No prior treatment for CLL No CHF, unstable angina or severe EF impairment	218	unk	unk	Mitoxantrone (A) Fludarabine (T) Cyclophosphamide (T) Rituximab (T) *vs* Fludarabine (T) Cyclophosphamide (T) Rituximab (T)	Unconfounded	No	Not assessable	Mitox 36 mg/m^2	U	U	U	U	U	U
ANTH0331 ARCTIC[198] Hillmen (2013) 2009 - 2012	CLL ≥18 years Binet B,C No prior treatment for CLL	206	nm	Median age 63 (36 – 80) 67.5% male Balanced at baseline	Mitoxantrone (A) Cyclophosphamide (T) Rituximab (T) *vs* Fludarabine (T) Cyclophosphamide (T) Rituximab (T)	Unconfounded	No	Not assessable	Mitox 36 mg/m^2	U	U	U	U	U	U
ANTH0304 Neocent unpublished 2008 - ongoing	Breast cancer Female 18-70 years ER +ve Postmenopausal No CHF, MI, hypertension, arrhythmia, unstable angina	756	unk	unk	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) *vs* Letrozole (N)	Positive	No	Not assessable	Epi 600 mg/m^2	U	U	U	U	U	U
ANTH0330 PLRG4[199] Walewski (2013) 2007 - 2011	Indolent lymphoma ≥18 years Stage II-IV No prior chemotherapy No prior radiotherapy	250	nm	Median age 56 (21 – 85) 56% female	Doxorubicin (A) Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T)	Unconfounded	No	Not assessable	Dox 150 – 400 mg/m^2	U	U	U	U	U	U
ANTH0236 ACCEDE[200] Stone (2011) 2007 – UNK	AML ≥18 years	420	nm	Arms balanced at baseline	Daunorubicin (A) Cytarabine (T) *vs* Amonafide L-malate (N) Cytarabine (T)	Unconfounded	No	Not assessable	Daun 135 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0051 MINDACT[201] Rutgers (2010) 2006 -ongoing	Breast cancer Female ≥18 years No prior chemotherapy Radiotherapy mandatory for BCS Normal LVEF No CHF, MI, hypertension, arrhythmia, angina, valvular heart disease	6600	unk	unk	Doxorubicin (A) (or Epi) Cyclophosphamide (T) 5-FU (T) Methotrexate (T) if E-CMF *vs* Docetaxel (T) Capecitabine (T)	Unknown	No	Not assessable	Dox 360 mg/m^2 or Epi 600 mg/m^2	U	U	U	U	U	U
ANTH0240 FOLL05[202] Federico (2013) 2006 - 2010	Follicular lymphoma 18 – 75 years Stage II-IV No prior treatment LVEF >50% No history of severe cardiac disease	534	nm	Median age 56/56/54 (31-75) 52% male 63% had stage IV disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Rituximab (T) *vs* Mitoxantrone (A) Fludarabine (T) Rituximab (T) *vs* Cyclophosphamide (T) Vincristine (T) Prednisone (T) Rituximab (T)	Unconfounded 1 v 3 Unknown 2 v 3	Yes	Morbidity – Full Mortality – R2	Dox 400 mg/m^2 Or Mitox 80 mg/m^2	U	L	L	L	U	U
ANTH0096 IFM 2005-01[203] Harousseau (2010) 2005 - 2008	Multiple myeloma 18-65 years	482	nm	Median age 57.1 years 55% male	*1 Induction* Doxorubicin (A) Vincristine (T) Dexamethasone (T) *2 above + consolidation* Dexamethasone (T) Cyclophosphamide (T) Etoposide (T) Cisplatin (T) *vs* *3 Induction* Bortezomib (T) Dexamethasone (T) *4 above + consolidation* Dexamethasone (T) Cyclophosphamide (T) Etoposide (T) Cisplatin (T)	unknown 1 v 3 1 v 4 2 v 3 2 v 4	Yes	Morbidity – Full Mortality – S1	Dox 144 mg/m^2	U	L	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0227 PETHEMA GEM 2005[204] Bladé (2005) 2006 - 2009	Multiple myeloma <65 years Measurable disease MI, CHF, arrhythmia, angina, ischemia conduction abnormalities excluded	390	35.2 months	Median age 56 years 53% male Balanced at baseline	Doxorubicin (A) Vincristine (T) Carmustine (N) Dexamethasone (T) Cyclophosphamide (T) Melphalan (T) Prednisone (T) Bortezomib (T) *vs* Thalidomide (T) Dexamethasone (T) vs Thalidomide (T) Dexamethasone (T) Bortezomib (T)	Unknown 1 v 2 1 v 3	No	Morbidity – T1 Mortality – S1	Dox 80 mg/m	U	L	U	U	U	U
ANTH0223 Kluin-Nelemans (2011)[205] 2004 - 2010	Mantle cell lymphoma ≥60 years Stage II-IV Measurable disease No prior chemotherapy No prior radiotherapy	560	37 months	Median age 70 years (60 – 87) 70% male 81% had stage IV disease	Doxorubicin (A) Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Rituximab (T) Cyclophosphamide (T) Fludarabine (T)	Unknown	Yes	Morbidity – R2 Mortality - Full	Dox 400 mg/m^2	L	L	L	L	L	U
ANTH0222 Rummel (2013)[206] 2003 - 2008	Mantle cell lymphoma ≥18 years No prior treatment Severe cardiac disease, inadequate cardiac function, severe functional defects of heart all excluded	550	45 months	Median age 63/64 (31-83) 73% had stage IV disease	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Rituximab (T) *vs* Bendamustine (N) Rituximab (T)	Positive	Yes	Morbidity – Full Mortality – T1	Dox 300 mg/m^2	U	L	L	L	U	U
ANTH0014 MITO-2[207] Pignata (2006) 2003-UNK	Ovarian cancer Female ≤75 years Stage Ic-IV No prior chemotherapy No prior MI or arrhythmia No prior atrioventricular block	395	40 months	Median age 57 (21 - 77) 81% were stage III-IV Baseline characteristics balanced	Liposomal doxorubicin (A) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Negative	Yes	Morbidity – Full Mortality – T1	LipDox 180 mg/m^2	L	L	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0218 GOG 209[208] Miller (2012) 2003 - 2009	Endometrial carcinoma Female ≥18 years Stage III-IV No prior chemotherapy Prior radiotherapy allowed LVEF at least 50% MI, CHF. Conduction abnormalities, complete heart block, uncontrolled angina all excluded	1381	nm	nm	Doxorubicin (A) Cisplatin (T) Paclitaxel (T) *vs* Paclitaxel (T) Carboplatin (N)	Positive	Yes	Not assessable	Dox 315 mg/m^2	U	U	L	L	U	U
ANTH0229 CALGB 80101[209] Fuchs (2011) 2003 - 2009	Gastric cancer ≥18 years No metastatic disease No prior treatment CHF, MI, arrhythmia, unstable angina, heart disease that limits activity all excluded	546	nm	Balanced at baseline	Epirubicin (A) Cisplatin (T) 5-FU (T) Radiotherapy (T) *vs* 5-FU (T) Leucovorin (N) Radiotherapy (T)	Positive	No	Not assessable	Epi 130 mg/m^2	U	U	U	U	U	U
ANTH0214 Myeloma IX[210] Morgan (2012) 2003 - 2007	Multiple myeloma ≥18 years No prior chemotherapy Prior radiotherapy allowed	1111	nm	Median age 59 (31-78) 62% male Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Dexamethasone (T) *vs* Cyclophosphamide (T) Thalidomide (T) Dexamethasone (T)	Unknown	No	Morbidity – T1 Mortality – T1	Dox 216 mg/m^2	L	L	L	L	U	U
ANTH0295 CALGB 40101[211] Shulman (2012) 2002 - 2008	Breast cancer Female	3173	5.3 years	59% age ≥ 50 years 64% Er +ve 94% node –ve 48% premenopausal	Doxorubicin (A) Cyclophosphamide (T) *vs* Paclitaxel (T)	Unknown	No	Not assessable	Dox 240 – 360 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0053 BCIRG 006[212] Slamon (2006) 2001 - 2004	Breast cancer Female 18-70 years HER2 +ve Normal LVEF No prior anthracycline Other chemo allowed No prior radiotherapy No CHF, MI, arrhythmia, angina, valvular heart disease, cardiomegaly, ventricular hypertrophy	3222	65 months	53% aged <50 years Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Docetaxel (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Docetaxel (T) Trastuzumab (T) *vs* Docetaxel (T) Cisplatin (T) Trastuzumab (T)	Unknown 1 v 3 2 v 3	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m^2	L	L	L	L	L	U
ANTH0064 CALGB 49907[213] Muss (2009) 2001 - 2006	Breast cancer Female ≥65 years No prior chemotherapy	633	9 years	2/3 were ≥70 years 70% were node +ve Balanced at baseline except for slight imbalance in tumour size.	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Capecitabine (T)	Unknown	No	Morbidity – T1 Mortality – S1	Dox 240 mg.m^2	U	U	U	U	U	U
ANTH0216 GOG182 – ICON5[214] Bookman (2006) 2001 - 2004	Ovarian cancer Female Stage III-IV No prior anthracycline Prior radiotherapy allowed	4312	3.7 years	Median age 57.7-59.5 FIGO stage III 83.7-86.7	Liposomal doxorubicin (A) Carboplatin (N) Paclitaxel (T) *vs* Carboplatin (N) Paclitaxel (T) *vs* Topotecan (N) Carboplatin (N) Paclitaxel (T) *vs* Gemcitabine (T) Carboplatin (N) Paclitaxel (T)	Unconfounded 1 v 2 1 v 3 1 v 4 Unknown 1 v 5	No	Morbidity – R1 Mortality – T2	Lip Dox 120 mg/m^2	L	U	L	L	U	U
ANTH0098 Mellqvist (2008)[215] 2001 - 2003	Multiple myeloma <65 years	314	22 months	Median age 56/57 Balanced at baseline	Doxorubicin (A) Vincristine (T) Dexamethasone (T) *vs* Cyclophosphamide (T) Dexamethasone (T)	Unknown	Yes	Morbidity – Full Mortality - Full	Dox 432 mg/m^2	U	U	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0158 SIOP-WT-2001[216] Pritchard-Jones (2011) 2001 - UNK	Wilm's Tumor Stage II-III 6mths-18yrs No prior chemotherapy No prior radiotherapy	583	39 months	58% had stage II disease	Doxorubicin (A) Vincristine (T) Actinomycin D (N) *vs* Vincristine (T) Actinomycin D (N)	Unconfounded	No	Not assessable	Dox 250 mg/m^2	U	U	U	U	U	U
ANTH0056 N-SAS-BC02[217] Watanabe (2009) 2000 - 2006	Breast cancer Female <70 years Node +ve Stage I-IIIa No prior chemotherapy	1060	nm	Mean age 42.5	Doxorubicin (A) Cyclophosphamide (T) Paclitaxel (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Docetaxel (T) *vs* Paclitaxel (T) *vs* Docetaxel (T)	Positive 1 v 3 2 v 4 Unknown 2 v 3 1 v 4	No	Not assessable	Dox 240 mg/m^2	U	U	U	U	U	U
ANTH0318 WSG AGO MAMMA EC-DOC[218] Braun (2009) 2000 - 2005	Breast cancer Female 18-65 years Node +ve	2012	unk	Median age 51 71% ER +ve	Epirubicin (A) Cyclophosphamide (T) Docetaxel (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unknown	No	Not assessable	Epi 360 mg/m^2	U	U	U	U	U	U
ANTH0002 TAX327[219] Tannock (2004) 2000 - 2002	Prostate cancer Male Metastatic disease No prior chemotherapy Prior radiotherapy allowed Normal cardiac function Metastatic disease	1006	20.8 months	Median age 68(36 - 92) 40% had measurable soft tissue lesions	Mitoxantrone (A) Prednisone (T) *vs* Docetaxel qw (T) Prednisone (T) *vs* Docetaxel q3w (T) Prednisone (T)	Negative	Yes	Morbidity – Full Mortality – T2	Mitox 144 mg/m^2	L	L	L	L	U	U
ANTH0003 SWOG S9921[220] Dorff (2011) 2000 - 2007	Prostate cancer Male ≥18	983	nm	Median age 60.7 (40-82)	Mitoxantrone (A) Prednisone (T) Goserelin (T) Bicalutamide (N) *vs* Goserelin (T) Bicalutamide (N)	Positive	Yes	Morbidity – P3 Mortality – S1	Mitox 72 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0017 Aravantinos (2008)[221] 1999 - 2004	Ovarian cancer Female FIGO stage IIc, III, IV No prior chemotherapy CHF, abnormal LVEF, previous MI, arrhythmia, acute coronary disease all excluded	469	57.5 months	Median age 59/60 (22-82.5) 67% had stage III disease	Doxorubicin (A) Paclitaxel (T) Cisplatin (T) *vs* Paclitaxel (T) Carboplatin (N)	Positive	Yes	Morbidity – Full Mortality – S1	Dox 240 mg/m^2	U	U	L	L	L	U
ANTH0215 Kristensen (2005)[222] 1999 - 2001	Ovarian cancer Female ≥18 years FIGO stage IIB-IV No prior chemotherapy No prior radiotherapy No prior CHF, MI, arrhythmia Normal LVEF required	887	61 months	Median age 57 (25 – 80) 73% had stage IIIc-IV disease Balanced at baseline	Epirubicin (A) Paclitaxel (T) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Epi 450 mg/m^2	L	L	L	L	U	U
ANTH0065 Semiglazov (2007)[223] 1998 - UNK	Breast cancer Female Prior radiotherapy allowed	239	68 months	nm	Doxorubicin (A) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Thiotepa(N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Thiotepa (N) Tamoxifen (N)	Negative 1 v 2 1 v 3 Positive 1 v 4	No	Not assessable	Dox 500 mg/m^2	U	U	U	U	U	U
ANTH0210 PALG CLL2[224] 1998 - 2003	CLL >18 years Progressive disease No prior chemotherapy No prior radiotherapy	508	112 months	Median age 61 years (28-81) 60% male Balanced at baseline	Mitoxantrone (A) Cladribine (N) Cyclophosphamide (T) *vs* Cladribine (N) Cyclophosphamide (T) *vs* Cladribine (N)	Unconfounded 1 v 2 Positive 1 v 3	Yes	Morbidity – T1 Mortality - Full	Mitox 60 mg/m^2	U	L	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0221 Cascinu (2007)[225] 1998 - 2003	Gastric cancer Adequate cardiac function	400	54 months	Median age 58/59 64% male	Epirubicin (A) Cisplatin (T) 5-FU (T) Leucovorin (N) Glutathione (N) *vs* 5-FU (T) Leucovorin (N)	Positive	No	Morbidity – T1 Mortality – S2	Epi 28 mg/m	L	U	L	L	U	U
ANTH0212 SIOPEL-3[226] 1998 - 2006	Hepatoblastoma <16 years No prior treatment	254	46 months	Median age 13.5 months 61% male	Doxorubicin (A) Cisplatin (T) *vs* Cisplatin (T)	Unconfounded	Yes	Morbidity – Full Mortality – T1	Dox 300 mg/m^2	L	L	L	L	L	U
ANTH0045 IBIS-03[227] 1997 - 2004	Breast cancer Female ≤70 years Node +ve	1066	69 months	Median age 52 (26-70) 47% premenopausal 47% node +ve Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* *Reverse order of administration* Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – Full Mortality – S1	Epi 400 mg/m^2	L	L	U	U	L	U
ANTH0049 Trial 97-35[228] Jones (2006) 1997 - 1999	Breast cancer Female 18-75 years	1016	7 years	Median age 51/52 (27-77) Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) *vs* Docetaxel (T) Cyclophosphamide (T)	Negative	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m^2	U	L	L	L	U	U
ANTH0315 GMB1 unpublished 1997 - 2000	Breast cancer Female	450	unk	unk	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	No	Not assessable	Epi	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0316 Chrisanthar (2011)[229] 1997 - 2003	Breast cancer Female 18-70 years Stage II	223	nm	Median age 51 (25-70) 56% ER +ve	Epirubicin (A) *vs* Paclitaxel (T)	Negative	No	Morbidity – T2 Mortality – T2	Epi 360 mg/m^2	U	U	U	U	U	U
ANTH0018 Fruscio (2008)[230] 1997 - 2000	Ovarian cancer Female ≥18 years FIGO stage II-IV No prior chemotherapy No prior radiotherapy No prior CHF and arrhythmia	209	82 months	Median age 52 (24-73) 85% had stage IIIc-IV disease Baseline characteristics balanced	Paclitaxel (T) Cisplatin (T) Epirubicin (A) *vs* Paclitaxel (T) Cisplatin (T) Ifosfamide (T)	Negative	Yes	Morbidity – Full Mortality – T2	Epi 480 mg/m^2	U	L	L	L	U	U
ANTH0232 AGO-OVAR[231] Du Bois (2006) 1997 - 2000	Ovarian cancer Female ≥18 years FIGO stage IIB-IV No prior chemotherapy No prior radiotherapy No prior CHF, MI, arrhythmia Normal LVEF required	1282	54 months	Median age 59 (21 –79) 72% had stage IIIc-IV disease Balanced at baseline	Epirubicin (A) Paclitaxel (T) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Epi 360 mg/m^2	L	L	L	L	U	U
ANTH0033 NEAT[232] Earl (2008) (1996 – 2001)	Breast cancer Female No prior chemotherapy No prior radiotherapy	2027	7.4 years	Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – T2 Mortality – T1	Epi 400 mg/m^2	U	L	L	L	L	U
ANTH0046[233] Kimura (2010) 1996 - 2000	Breast cancer Female ≤60 years Stage I-IIIa Node +ve No prior chemotherapy No prior radiotherapy No serious cardiac disease	294	nm	61% premenopausal 68% stage II 54% ER +ve Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	No	Morbidity – T1 Mortality – T1	Epi 360 mg/m^2	L	L	L	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0288 GOCSI MAM2[234] Lombardi (2001) 1996 - 2001	Breast cancer Female ≤70 years Tumour >1cm	1079	26 months	48% were ER +ve 56% were node +ve	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	No	Not assessable	Epi 440 mg/m^2	U	U	U	U	U	U
ANTH0324 ABCSG Study IX Jakesz (2003)[235] 1996 - 2005	Breast cancer Female	439	nm	unk	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Tamoxifen (N) *vs* Tamoxifen (N)	Positive	n/a	Not assessable	Epi 240 mg/m^2	U	U	U	U	U	U
ANTH0325 BR9601[236] Poole (2006) 1996 - 2001	Breast cancer Female	374	7.4 years	49% <50 years 46% postmenopausal	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – T2 Mortality - Full	Epi 400 mg/m^2	L	L	U	U	U	U
ANTH0122 GOIM 9602[237] De Vita (2007) 1996 - 2001	Gastric cancer <70 years Stage Ib, II, IIIa, IIIb Cardiac dysfunction excluded	228	60 months	Median age 63/62 (39-70) 57% male	Epirubicin (A) Leucovorin (N) 5-FU (T) Etoposide (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality – T2	Epi 360 mg/m^2	U	U	U	U	L	U
ANTH0001 DM95-321[238] Millikan (2008) 1996 - 2003	Prostate cancer Male No prior chemotherapy Prior radiotherapy allowed CHF, ischemia, transient ischemic attack, all excluded	306	nm	Median age 58/59 (37-80)	Doxorubicin (A) Ketoconazole (N) Vinblastine (T) Estramustine (T) Hydrocortisone (T) Androgen ablation (T) *vs* Androgen ablation (T)	Positive	Yes	Morbidity – Full Mortality – S1	Dox 180 mg/m^2	L	U	L	L	H	U
ANTH0267 Zinzani (2000)[239] 1995 - 1998	Mantle cell lymphoma 18 – 65 years Stage II-IV	208	19 months (6 – 38)	Median age 54 years 54% male 72% had stage IV disease Comparable at baseline	Idarubicin (A) Fludarabine (T) *vs* Fludarabine (T)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Ida 72 mg/m^2	U	U	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0016 ICON 3[240] ICON (2002) 1995 - 1998	Ovarian cancer Female No prior chemotherapy No prior radiotherapy	653	51 months	Median age 58.9 63% had stage II-IV disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Cisplatin (T) *vs* Carboplatin (N) Paclitaxel (T)	Unknown	No	Morbidity – S1 Mortality – T2	Dox 300 mg/m^2	L	L	U	U	U	U
ANTH0120 Kulig (2010)[241] 1995 - 1999	Gastric cancer >18 years No prior treatment	309	37 months	Median age 61/64 (58-67)	Doxorubicin (A) Cisplatin (T) Etoposide (T) *vs* Observation (N)	Positive	Yes	Morbidity – R3 Mortality – R3	Dox 120 mg/m^2	L	L	L	L	H	U
ANTH0121 Di Costanzo (2008)[242] (1995 – 2000)	Gastric cancer ≤75 years Stage IB, II A-B, IV No prior chemotherapy No prior radiotherapy No abnormal cardiac function	258	5.6 years	Median age 59 (18 – 73) 60.5% had stage III-IV disease	Epirubicin (A) Cisplatin (T) 5-FU (T) Leucovorin (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality – R3	Epi 120 mg/m^2	L	L	H	H	U	U
ANTH0217 EORTC 62931[243] Woll (2012) 1995 - 2003	Soft tissue sarcoma 16 – 70 years No prior chemotherapy No cardiac disorders, or angina, or MI, or CHF	351	7.99 years (7.31-8.61)	Median age 49 (17.3-71.4) 55% male Balanced at baseline	Doxorubicin (A) Ifosfamide (T) Mesna (N) Lenograstim (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 375 mg/m^2	L	L	U	U	U	U
ANTH0219 MMT95[244] Oberlin (2012) 1995 - 2003	Soft tissue sarcoma or rhabdomyosarcoma 6months – 18years Stage I-II No prior chemotherapy No prior radiotherapy	457	8.6 years (0-14.2 years)	59% male 53% aged 3-10 years 63% stage II	Epirubicin (A) Carboplatin (N) Vincristine (T) Ifosfamide (T) Actinomycin D (N) Etoposide (T) *vs* Vincristine (T) Ifosfamide (N) Actinomycin D (N)	Positive	Yes	Morbidity – P3 Mortality – S1	Epi 450 mg/m^2	U	L	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0306 GOIRC SANG 2B R1 unpublished 1994 - 2000	Breast cancer Female	489	unk	unk	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N)	Positive	No	Not assessable	Epi	U	U	U	U	U	U
ANTH0241 HD6[245] Meyer (2005) 1994 - 2002	Hodgkin lymphoma ≥16 years Stage IA-IIA Cardiac dysfunction excluded	405	4.2 years	Median age 35/36.7 55% male 66% had stage IIA disease	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Radiotherapy (T)	Unknown	Yes	Morbidity – Full Mortality - Full	Dox 200-300 mg/m^2	L	L	L	L	U	U
ANTH0235 Aviles (2008)[246] 1994 - 2001	T-cell lymphoma 18 – 70 years Normal cardiac function	217	nm	Median age 52 75% male 95% had stage II-IV disease Baseline characteristics balanced	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Cyclophosphamide (T) Methotrexate(T) Etoposide(T) Dexamethasone (T) Leucovorin (N)	Unknown	No	Morbidity – T1 Mortality – Full	Dox 300 mg/m^2	U	H	U	U	U	U
ANTH0226 Susuma (2008)[247] 1994 - 2000	Endometrial cancer Female <75 years FIGO Ic-IIIc No prior treatment	475	59.5 months	Mean age 59 Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Cisplatin (T) *vs* Radiotherapy (N)	Positive	No	Morbidity – S1 Mortality – S1	Dox 120 mg/m^2	U	L	U	U	H	U
ANTH0073 MAGIC[248] Cunningham (2006) 1994 - 2002	Gastric cancer No prior chemotherapy No prior radiotherapy Uncontrolled cardiac disease excluded	503	49 months	Median age 62 (23-85) 79% male Balanced at baseline	Epirubicin (A) Cisplatin (T) 5-FU (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – T1 Mortality – S2	Epi 300 mg/m^2	L	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0150 SFOP OS94[249] Le Deley (2007) 1994 - 2001	Osteosarcoma <20 years No prior chemotherapy No prior radiotherapy	234	77 months	Median age 13.2 years (3.1-19.5) 56% male	Doxorubicin (A) Methotrexate (T) Leucovorin (N) *vs* Methotrexate (T) Leucovorin (N) Etoposide (T) Ifosfamide (T)	Negative	Yes	Morbidity – R3 Mortality – T2	Dox 145 mg/m^2	L	L	L	L	U	U
ANTH0132 AUO-AB 05/95[250] Lehmann (2005) 1994 - 2000	Bladder cancer 18-70 years Stage pT3a – 4a Prior intravesical chemotherapy allowed	335	3 years	Median age 60.5years (59.6 – 61.4) 78.6% male 56.6% node positive Balanced at baseline	Epirubicin (A) Methotrexate (T) Vinblastine (T) Cisplatin (T) *vs* Methotrexate (T) Cisplatin (T)	Positive	Yes	Morbidity – P1 Mortality – S1	Epi 90 mg/m^2	U	U	U	U	L	U
ANTH0145 GHSD-HD7[251] Engert (2007) 1994 - 1998	Hodgkin lymphoma 16-75 years No prior chemotherapy No prior radiotherapy Impaired heart excluded	650	87 months	Median age 36 years (16 – 75) 53% had stage IIa disease 61% male Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Extended field Radiotherapy (T) *vs* Extended field radiotherapy (T)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 100 mg/m^2	U	L	U	U	L	U
ANTH0139 NHL VIII[252] Taylor (2006) (1993 – 2000)	Non Hodgkin lymphoma ≥18 years No prior chemotherapy Prior radiotherapy for local disease allowed No prior MI No severe CHF	200	58 months	65% had stage IV disease	Idarubicin (A) Chlorambucil (N) Dexamethasone (T) *vs* Chlorambucil (N) Dexamethasone (T)	Unconfounded	No	Morbidity – T1 Mortality – T1	Ida	U	U	L	L	U	U
ANTH0083 EORTC-GELA H8[253] Fermé (2007) (1993 – 1999)	Hodgkin lymphoma 15-70 years Stage I-II No severe cardiac disease	1583	92 months	Median age 30 (15-50) Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Mechlorethamine (N) Vincristine (T) Procarbazine (N) Prednisone (T) *vs* STNI radiotherapy (T)	Unknown	Yes	Morbidity – R2 Mortality – S1	Dox 105 mg/m^2	U	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0307 ABC Trial[254] Bliss (2007) 1992 - 2000	Breast cancer Female No prior chemotherapy	2277	6.4 years	Mean age 53.5 62% >50 years 57% node +ve Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – T2 Mortality - Full	Dox 240 mg/m^2	L	L	U	U	U	U
ANTH0271 SWOG 9133[255] Press (2001) 1992 - 2000	Hodgkin lymphoma >16 years Stage I-II No prior chemotherapy No prior radiotherapy	348	3.3 years	Median age 32 (17-85) 54% male Balanced at baseline	Doxorubicin (A) Vinblastine (T) Radiotherapy (T) *vs* Radiotherapy (T)	Positive	Yes	Morbidity – Full Mortality - Full	Dox 150 mg/m^2	L	U	L	L	L	U
ANTH0019 GOG 122[256] Randall (2006) 1992 - 2000	Endometrial cancer Female FIGO stage III-IV Normal LVEF	422	nm	70% had stage IIIc-IV disease Balanced at baseline	Doxorubicin (A) Cisplatin (T) *vs* Radiotherapy (N)	Positive	Yes	Morbidity – P3 Mortality – Full	Dox 420 mg/m^2	L	L	U	U	U	U
ANTH0237 ITMO[257] Bajetta (2002) 1992 - 1997	Gastric cancer <70 years No metastatic disease	274	80 months	Median age 57 (23-70) 64% male	Doxorubicin (A) Etoposide (T) Cisplatin (T) 5-FU (T) Leucovorin (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – T1 Mortality – Full	Dox 80 mg/m^2	L	L	H	U	U	U
ANTH0035 NSABP B-23[258] Fisher (2001) 1991 - 1998	Breast cancer Female Node –ve ER -ve	2008	5 years	98% were ER-ve 55% were aged ≤49 years	Doxorubicin (A) Cyclophosphamide (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N)	Negative 1 v 3 1 v 4 2 v 3 2 v 4	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m^2	L	U	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0040 FASG 07[259] Namer (2006) 1991 - 1998	Breast cancer Female 51-64 years Node +ve ER +ve PR +ve Postmenopausal No history of cardiac disease	335	89 months	Median age 58 (44-65) 99% ER +ve	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Tamoxifen (N) Radiotherapy (T) *vs* Tamoxifen (N) Radiotherapy (T)	Positive	No	Not assessable	Epi 300 mg/m^2	U	U	L	U	U	U
ANTH0068 FASG 08[260] Fargeot (2004) 1991 - 2001	Breast cancer Female ≥65 years Node +ve Postmenopausal LVEF ≥ 50% No cardiac dysfunction No history of cardiac disease No prior chemotherapy No prior radiotherapy	338	72 months	Median age 69 (65-85) 78% ER and/or PR +ve Balanced at baseline	Epirubicin (A) Tamoxifen (N) *vs* Tamoxifen (N)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Epi 540 mg/m^2	U	U	U	U	U	U
ANTH0287 GOCSI MAM1[261] (De Placido (2008) 1991 - 1997	Breast cancer Female Premenopausal Node +ve	466	72 months	Median age 44 (20-52) 79% ER+ve or unknown 44% had ≥4 +ve nodes	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Goserelin (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Goserelin (T) Tamoxifen (N)	Unconfounded 1 v 3 2 v 4 Negative 1 v 4 Positive 2 v 3	No	Morbidity – T1 Mortality – T2	Dox 300 mg/m^2	L	L	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0015 ICON 2[262] ICON (1998) 1991 - 1996	Ovarian cancer Female No prior chemotherapy No prior radiotherapy	1526	35 months	76.8% had stage II-IV disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Cisplatin (T) *vs* Carboplatin (N)	Positive	Yes	Morbidity – P3 Mortality – S2	Dox 300 mg/m^2	L	L	L	L	L	U
ANTH0259 Kondo (2000)[263] 1991 - UNK	Gastric cancer Node +ve	333	nm	No significant differences in prognostic factors	Doxorubicin (A) Tegafur (T) *vs* Cisplatin (T) Tegafur (T) *vs* Mitomycin C (T) Tegafur (T)	Negative 1v2 1v3	No	Morbidity – S2 Mortality – S2	Dox 150 mg/m^2	U	U	U	U	U	U
ANTH0042 GOIRC SANG2[264] Colozza (2002) 1990 - 1994	Breast cancer Female 18-70 years ER-ve Node-ve Or Node +ve (≤9 nodes) Normal LVEF Normal ECG Normal cardiac function	348	8 years	Median age 50 (30-70) 52% premenopausal 77% node +ve	Epirubicin (A) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – Full Mortality - Full	Epi 480 mg/m^2	L	L	U	U	U	U
ANTH0058 DBCG 89d[265] Ejlertsen (2007) 1990 - 1998	Breast cancer Female	1224	10 years	67% aged <50 73% Premenopausal 71% node +ve Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Epirubicin (A) Cyclophosphamide (T) 5-FU (T) Pamidronate (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Pamidronate (N)	Negative	Yes	Morbidity – P3 Mortality - Full	Epi 540 mg/m^2	L	L	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH067 FASG 06[266] Roche (2006) 1990 - 1998	Breast cancer Female <50 years Node +ve ER +ve PR +ve premenopausal	333	83 months	Median age 44 (28-51) 90% ER +ve Balanced at baseline	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) *vs* Triptorelin (T) Tamoxifen (N)	Unknown	No	Not assessable	Epi 300 mg/m^2	L	L	U	U	U	U
ANTH0303 C/6/89[267] Marty (2004) 1990 – 2000	Breast cancer Female	950	100 months	nm	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	No	Not assessable	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0305 GOIRC SANG1[268] Cocconi (2002) 1990 - 1995	Breast cancer Female <70 years Stage I-II Adequate heart function	251	116 months	Median age 52/51.5 (27-73)	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Positive	No	Morbidity – T1 Mortality – T2	Epi 320 mg/m^2	U	L	L	L	U	U
ANTH0211 Maggi (2006)[269] 1990 - 1997	Endometrial cancer Female FIGO stage Ic G3, IIa-bG3 No prior radiotherapy No serious cardiopathy	345	95.5 months	Median age 63/62 64% had stage III disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Cisplatin (T) *vs* Radiotherapy (N)	Positive	No	Morbidity – S1 Mortality – T2	Dox 225 mg/m^2	U	L	U	U	L	U
ANTH0094 CLL90[270] Leporrier (2001) 1990 - 1998	CLL <75 years Stage B, C No prior treatment	938	70 months	Median age 62/60/62 (53-67) Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Prednisone (T) *vs* Fludarabine (T)	Unknown 1 v 3 2 v 3	Yes	Morbidity – Full Mortality – S1	Dox 150 - 300 mg/m^2	U	L	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0269 Chang (2002)[271] 1990 - 1993	Gastric cancer Stage IB, II, IIIA, IIIB	416	91 months	Median age 53 (21-75) 71% male 57% had stage III disease Balanced at baseline	Doxorubicin (A) 5-FU (T) Mitomycin C (T) *vs* 5-FU (T) Mitomycin C (T) *vs* 5-FU (T)	Unconfounded 2 v 3 1 v 3	Yes	Morbidity – T1 Mortality – R2	Dox 360 mg/m^2	L	L	L	L	L	U
ANTH0097 Bologna 90[272] Cavo (1992) 1990 - 1994	Multiple myeloma <80 years No prior treatment Severed heart disease excluded	527	31.5 months	52% male Balanced at baseline	Doxorubicin (A) Vincristine (T) Dexamethasone (T) Melphalan (T) Prednisone (T) *vs* Mitoxantrone (A) Vincristine (T) Dexamethasone (T) Melphalan (T) Prednisone (T) *vs* Melphalan (T) Prednisone (T)	Positive 1 v 3 2 v 3	Yes	Morbidity – Full Mortality – T2	Dox 144 mg/m^2 or Mitox 48 mg/m^2	L	L	L	L	U	U
ANTH0031 SWOG 8814[273] Albain (2009) (1989 – 1995)	Breast cancer Female ER +ve PR +ve Normal LVEF	1558	8.94 years	Median age 60/60.7/61.8	Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) Tamoxifen (N) *vs* Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) Tamoxifen (N) *vs* Tamoxifen (N)	Positive 1 v 2 2 v 3	Yes	Morbidity – Full Mortality – S1	Dox 300 mg/m^2	L	L	L	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0032 SWOG S8897[274] Hutchins (2005) (1989 – 1993)	Breast cancer Female Node -ve	2690	nm	Median age 48	Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N)	Negative 1 v 3 2 v 4 1 v 4 2 v 3	Yes	Morbidity – Full Mortality – S1	Dox	L	L	U	U	U	U
ANTH0044 NCIC MA5[275] Levine (1998) 1989 - 1993	Breast cancer Female Node +ve Premenopausal No prior chemotherapy No prior radiotherapy No history of cardiac disease	716	10 years	84% aged <50 years Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – Full Mortality – R3	Epi 720 mg/m^2	U	L	L	L	U	U
ANTH0300 Arriagada (2005)[276] 1989 - 1996	Breast cancer Female ≤69 years Node –ve No prior MI No CHF	1151	9 years	73% postmenopausal 55% node -ve Balanced at baseline	Doxorubicin (or Epi) (A) 5-FU (T) Cyclophosphamide (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – T2 Mortality – T2	Dox 300 mg/m^2 Or Epi 300 mg/m^2	L	L	U	U	U	U
ANTH0309 HE1092[277] Fountzilas (2004) 1989 - 1998	Breast cancer Female ≥18 years No prior chemotherapy No prior radiotherapy	459	5 years	Age range 24-83 Balanced at baseline	Mitoxantrone (A) Cyclophosphamide (T) 5-FU (T) Buserelin (T) Tamoxifen (N) *vs* Tamoxifen (N)	Positive	No	Morbidity – R3 Mortality – T2	Mitox	U	H	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0311 Paradiso (2001)[278] 1989 - 1994	Breast cancer Female ≤70 years Node –ve No history of heart disease	248	70 months	Median age 53/52/52	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – R3 Mortality – s!	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0314 Yasumura (1998)[279] 1989 - 1992	Breast cancer Female <75 years Node +ve No prior chemotherapy No prior radiotherapy	681	nm	Balanced at baseline	Epirubicin (A) 5-FU (T) Tamoxifen (N) *vs* 5-FU (T) Tamoxifen (N)	Unconfounded	Yes	Not assessable	Epi 120 mg/m^2	U	U	U	U	U	U
ANTH0333 Hiddemann (1994)[280] (1989 – 1996)	Non Hodgkin lymphoma 18-75 years Stage II-IV No prior chemotherapy No prior radiotherapy Normal cardiac function	246	nm	Median age 54 (28 – 77) 52% male	Mitoxantrone (A) Prednimustine (N) *vs* Cyclophosphamide (T) Vincristine (T) Prednisone (T)	Negative	Yes	Morbidity – P3 Mortality – T2	Mitox	U	L	L	U	U	U
ANTH0244 Tattersall (1995)[281] 1989 - 1993	Cervical cancer Female Stage IIb-Iva 30 – 75 years No prior treatment No history of significant cardiac disease	260	1.3 years	Mean age 47/52 (26-75)	Epirubicin (A) Cisplatin (T) Radiotherapy (N) *vs* Radiotherapy (N)	Positive	No	Morbidity – S1 Mortality – T2	Epi 330 mg/m^2	U	L	U	U	U	U
ANTH0159 VUMCA1 Cvitkovic (1996)[282] 1989 - 1993	Nasopharyngeal carcinoma 15-70 years Normal cardiac function	339	49 months	Mean age 43 years 75% male Balanced at baseline	Epirubicin (A) Bleomycin (T) Cisplatin (T) Radiotherapy (N) *vs* Radiotherapy (N)	Positive	Yes	Morbidity – R3 Mortality – T1	Epi 210 mg/m^2	L	L	L	L	U	U
ANTH0263 Chua (1998)[283] 1989 - 1993	Nasopharyngeal carcinoma Stage III-IV Normal ECG No prior chemotherapy No prior radiotherapy No prior cardiovascular disease	334	30 months	73% male 74% stage III	Epirubicin (A) Cisplatin (T) Radiotherapy (N) *vs* Radiotherapy (N)	Positive	No	Morbidity – T1 Mortality – T1	Epi 120 mg/m^2	L	L	U	U	H	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0039 FASG 03 Hery (2006)[284] 1988 - 1994	Breast cancer Female 18-64 years Node –ve ER poor PR poor >4cm tumour	328	114 months	nm	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Radiotherapy (T) *vs* Radiotherapy (T)	Positive	No	Not assessable	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0043 Piccart (2001)[285] 1988 - 1996	Breast cancer Female ≤70years Node +ve Normal LVEF No prior chemotherapy No prior radiotherapy	777	4 years	Median age 49 (25-70)	Epirubicin (A) Cyclophosphamide (T) *vs* Epirubicin (high dose) (A) Cyclophosphamide (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative 1 v 3 2 v 3	Yes	Morbidity – Full Mortality – T2	Epi 480 mg/m^2 Or Epi 800 mg/m^2	L	L	U	U	H	U
ANTH0069 Wils (1999)[286] 1988 - 1995	Breast cancer Female <75 years Node +ve Postmenopausal No prior chemotherapy No prior MI or CHF No history of cardiac disease	604	5.7 years	Median age 59/60 (39-75)	Epirubicin (A) Tamoxifen (N) *vs* Tamoxifen (N)	Unconfounded	Yes	Morbidity – Full Mortality – T1	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0313 Petit (2003)[287] 1988 - 1990	Breast cancer Female ≤65 years No prior chemotherapy No prior radiotherapy	578	6.1 years	Median age premenopausal – 44 years postmenopausal – 62 years 74% were ER +ve Balanced at baseline	Mitoxantrone (A) *vs* No chemotherapy (N)	Unconfounded	No	Morbidity – R3 Mortality – T2	Mitox 14 mg.m^2	L	L	H	U	U	U
ANTH0238 EORTC H7[288] Noordijk (2006) 1988 - 1993	Hodgkin lymphoma 15-70 years Stage I-II	722	9 years	Median age 28 years (15-49)	Epirubicin (A) Bleomycin (T) Vinblastine (T) Prednisone (T) *vs* STNI radiotherapy (T)	Unknown	No	Morbidity – T2 Mortality – S1	Epi 420 mg/m^2	U	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0258 Peest (1995)[289] 1988 - 1991	Multiple myeloma Stage III	204	nm	55% male	Doxorubicin (A) Vincristine (T) Carmustine (N) Melphalan (T) Dexamethasone (T) *vs* Melphalan (T) Prednisone (T)	Positive	No	Morbidity – S1 Mortality – S1	Dox UNK	U	U	U	U	U	U
ANTH0071 GEICAM 8701[290] Martin (2003) 1987 - 1991	Breast cancer Female 18-72 years Stage I-IIIa No history of significant cardiac disease (MI arrhythmia, cardiac insufficiency)	985	77.7 months	65% aged >50 years 66% postmenopausal 85% no prior radiotherapy Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – Full Mortality – T2	Dox 300 mg/m^2	U	U	L	L	U	U
ANTH0310 PRONACAM 87 Chacon (1995)[291] 1987 - 1993	Breast cancer Female Node +ve	322	nm	nm	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Prednisone (T) *vs* *longer* Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Prednisone (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Positive	No	Not assessable	Epi 250 mg/m^2 Or 360 mg/m^2	U	U	U	U	U	U
ANTH0268 Wong (1999)[292] 1987 - 1993	Cervical cancer Female Stage II-III No history of CHF, IHD, myocarditis or valvular disease	220	66 months	Age range 34 – 65 years Pts in chemo arm younger than pts in radiotherapy arm	Epirubicin (A) Radiotherapy (N) *vs* Radiotherapy (N)	Unconfounded	Yes	Morbidity – T1 Mortality – T2	Epi 450 mg/m^2	U	H	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0261 IGCI CLL-02[293] Jaksic (1997) 1987 - 1993	CLL ≤75 years No history of cardiomyopathy or abnormal cardiac examination	228	37 months	61 years 62% male Balanced at baseline except for Rai stage and Binet stage	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Prednisone (T) *vs* Chlorambucil (N)	Positive	Yes	Morbidity – Full Mortality – T2	Dox 150 – 300 mg/m^2	U	U	L	L	L	U
ANTH0224 S8710 Crawford (1990)[294] 1987 - 1998	Bladder cancer No metastatic disease no prior radiotherapy	317	8.7 years	Median age 63 (39-84) 82% male Balanced at baseline	Doxorubicin (A) Methotrexate (T) Vinblastine (T) Cisplatin (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – Full Mortality – T2	Dox 90 mg/m^2	L	L	U	U	U	U
ANTH0038 FASG 02[295] Gerard (1993) 1986 - 1990	Breast cancer Female 50-70 years Postmenopausal Node +ve	776	37 months	Median age 60 (49-70) 58% were ER +ve	Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Radiotherapy (T) vs Epirubicin (A) 5-FU (T) Cyclophosphamide (T) Radiotherapy (T) Tamoxifen (N) vs Radiotherapy (T) *vs* Radiotherapy (T) Tamoxifen (N)	Positive 1 v 3 2 v 4 2 v 3 1 v 4	No	Not assessable	Epi 300 mg/m^2	U	U	U	U	U	U
ANTH0063 EORTC 10854[296] Clahsen (1994) 1986 - 1991	Breast cancer Female < 70 years	2795	11 years	56.8% were aged >50 years 54.1% were node –ve	Doxorubicin (A) 5-FU (T) Cyclophosphamide (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – St Mortality – T2	Dox 50 mg/m^2	U	U	U	U	U	U
ANTH0285 NSABC BR-02-83[297] Chaitchik (1989) 1983 - 1985	Breast cancer Female Stage II Node +ve	203	58 months	nm	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Positive	No	Not assessable	Dox 200 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0292 GABG 3C unpublished 1986 - 1992	Breast cancer Female	288	unk	unk	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N)	Negative	n/a	Not assessable	Epi 360 mg/m^2	U	U	U	U	U	U
ANTH0308 Fountzilas (1996)[298] 1986 - 1992	Breast cancer Female ≥18 years No prior chemotherapy No prior radiotherapy	392	51 months	Median age 50/51 (22-77) 52% were premenopausal 54% were ER +ve	Mitoxantrone (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – T1 Mortality - Full	Mitox 60 mg/m^2	L	L	L	L	U	U
ANTH0312 Galligioni (1998)[299] 1986 - 1991	Breast cancer Female Node +ve premenopausal	207	nm	Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	No	Not assessable	Epi 480 mg/m^2	U	U	U	U	U	U
ANTH0296 Semiglazov (1998)[300] 1985 - 1990	Breast cancer Female	349	68.8 months	nm	Doxorubicin (A) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Tamoxifen (N)	Negative 1 v 2 Unconfounded 1 v 3	Yes	Morbidity – Full Mortality – T2	Dox 500 mg/m^2	U	U	U	U	U	U
ANTH0298 Mauriac (1992)[301] 1985 - 1993	Breast cancer Female <3cm tumour	390	59 months	Mean age 51 (30-69)	Epirubicin (A) Mitomycin C (T) Methotrexate (T) Thiotepa (N) Vincristine (T) Vindesine (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unknown	No	Morbidity – T1 Mortality – T2	Epi 150 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0299 Bedognetti (2011)[302] 1985 - 1992	Breast cancer Female ≤65 years Node –ve Stage I No prior chemotherapy No prior radiotherapy	431	12.3 years	Median age 49/51 (28-65)	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* No chemotherapy (N)	Positive	No	Not assessable	Epi 60 mg/m^2	U	L	U	U	U	U
ANTH0321 unpublished 1985 - 1988	Breast cancer Female	607	unk	unk	Epirubicin (A) Cyclophosphamide (T) *vs* No chemotherapy (N)	Positive	No	Not assessable	Epi unk	U	U	U	U	U	U
ANTH0075 CLL85[303] Binet (1994) 1985 - 1990	CLL Binet stage B	287	29 months	Median age 61years 77% male Comparable groups at baseline except more frequent involvement of spleen in CHOP pts	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Prednisone (T) *vs* Chlorambucil (N) Prednisone (T)	Positive	No	Morbidity – S2 Mortality – T2	Dox 250 mg/m^2	U	L	U	U	U	U
ANTH0074 Bladé (1993)[304] 1985 - 1989	Multiple myeloma CHF and arrhythmia excluded	501	nm	Median age 65 64% had stage III disease	Doxorubicin (A) Vincristine (T) Carmustine (N) Prednisone (T) Cyclophosphamide (T) Melphalan (T) *vs* Melphalan (T) Prednisone (T)	Positive	No	Morbidity – T2 Mortality – T2	Dox 120 mg/m^2	U	U	U	U	U	U
ANTH0225 Nordic Cystectomy Trial 1 Rintala (1993)[305] 1985 - 1989	Bladder cancer T1 – T4 No prior chemotherapy No prior radiotherapy	325	Mean 18 months (1 – 74 months)	Median age 64 years 75% male	Doxorubicin (A) Cisplatin (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – R2 Mortality – S1	Dox 60 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0059 ABCSG Trial 3 Ploner (2003)[306] 1984 - 1991	Breast cancer Female ER –ve PR –ve Node +ve	263	100 months	53% aged >50 50% postmenopausal	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Positive	No	Morbidity – S1 Mortality – T2	Dox 50 mg/m^2	L	L	L	L	U	U
ANTH0279 SWOG 8313[307] Budd (1995) 1984 - 1996	Breast cancer Female Node +ve Stage II-IIIa	628	nm	Median age 51/50 (22-77)	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Prednisone (T)	Negative	Yes	Morbidity – T1 Mortality - Full	Dox 200 mg.m^2	L	L	U	U	U	U
ANTH0281 ABCSG Trial 1[308] Jakesz (1998) 1984 - 1991	Breast cancer Female <70 years ER –ve PR -ve	307	7 years	46% postmenopausal 29% had prior radiotherapy	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* No chemotherapy (N)	Positive	No	Morbidity – R3 Mortality – S2	Dox 20 mg/m^2	U	U	U	U	U	U
ANTH0282 ABCSG Trial 2[309] Sevelda (1993) 1984 - 1990	Breast cancer Female 18-70 years Premenopausal No prior chemotherapy No prior radiotherapy	260	4 years	50% were premenopausal Balanced at baseline	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N) *vs* Tamoxifen (N)	Positive	No	Morbidity – S2 Mortality – S2	Dox 20 mg/m^2	U	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0283 ABCSG Trial 4[309] Sevelda (1993) 1984 - 1990	Breast cancer Female 18-70 years Postmenopausal No prior chemotherapy No prior radiotherapy	338	7.5 years	50% were premenopausal 70% were aged ≤50 years Balanced at baseline	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N) *vs* Tamoxifen (N) *vs* No treatment (N)	Positive 1 v 2 1 v 3	No	Morbidity – S2 Mortality – S2	Dox 20 mg/m^2	U	L	U	U	U	U
ANTH0286 GUN3[310] De Placido (1995) 1984 - 1991	Breast cancer Female ≤75 years Premenopausal Stage II - III	220	48 months	70% ≤70 years 72% postmenopausal	Epirubicin (A) Vincristine (T) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Positive	No	Morbidity – T1 Mortality – T2	Epi 450 mg/m^2	L	L	U	U	U	U
ANTH0289 NSABP B-15[311] Fisher (1990) 1984 - 1988	Breast cancer Female Node +ve	2338	11 years	79% were ≤49 years 46% were ER -ve	Doxorubicin (A) Cyclophosphamide (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded 2 v 3 Negative 1 v 3	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m^2	L	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A B C D E F
ANTH0290 NSABP B-16[312] Fisher (1990) 1984 - 1989	Breast cancer Female Node +ve	1296	11 years	56% were aged >60 years 19% were ER -ve	Doxorubicin (A) Cyclophosphamide (T) Tamoxifen (N) *vs* Doxorubicin (A) Melphalan (T) 5-FU (T) Tamoxifen (N) *vs* Melphalan (T) 5-FU (T) Tamoxifen (N) *vs* Tamoxifen (N)	Unconfounded 2 v 3 Positive 1 v 4 2 v 4 Unknown 1 v 3	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m^2	L U U U U U
ANTH0302 C/2/84[313] Wils (1993) 1984 - 1992	Breast cancer Female Node +ve Premenopausal No prior chemotherapy No history of cardiac disease	759	100 months	Median age 55 (23-57)	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – Full Mortality - Full	Epi 300 mg/m^2	L L L L L U
ANTH0249 Radford (1995)[314] 1984 - 1992	Hodgkin lymphoma 16-70 years Stage I-II (bulky disease) or Stage III-IV	423	4.5 years (0 – 9)	Median age 29.5 (15.2 – 68.8 years) 61% male Balanced at baseline	Doxorubicin (A) Chlorambucil (N) Vinblastine (T) Procarbazine (N) Prednisolone (T) Etoposide (T) Vincristine (T) *vs* Mustine (N) Vinblastine (T) Procarbazine (N) Prednisolone (T)	Unknown	Yes	Morbidity – T2 Mortality - Full	Dox 400 mg/m^2	U U L L L U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0034 GROCTA-1[315] Boccardo (1990) 1983 - 1987	Breast cancer Female 35-65 years ER +ve No prior chemotherapy	510	21 years	53% were postmenopausal Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N) *vs* Tamoxifen (N)	Positive 2 v 3 1 v 3	Yes	Morbidity – Full Mortality – S1	Epi 300 mg/m^2	L	L	U	U	U	U
ANTH0072 Levine (1988)[316] 1983 - 1987	Breast cancer Female <70 years Stage II Node +ve No prior chemotherapy No prior radiotherapy No cardiac disease	436	20 months	Mean age 52 years 55.8% ER +ve	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Prednisone (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Prednisone (T)	Unconfounded	No	Morbidity – T1 Mortality – T2	Dox 160 mg/m^2	U	U	U	U	U	U
ANTH0301 unpublished 1983 - 1989	Breast cancer Female	213	unk	unk	Doxorubicin (A) Cyclophosphamide (T) *Vs* No chemotherapy (N)	Positive	n/a	Not assessable	Dox 90 mg/m^2	U	U	U	U	U	U
ANTH0323 SECSG BRE83 307R[317] Carpenter (1994) 1983 - 1990	Breast cancer Female Node +ve	528	5 years	nm	Doxorubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	No	Not assessable	Dox 270 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0234 Aviles (1998)[318] 1983 – 1988	Hodgkin lymphoma Stage I or II Bulky disease	327	11.4 years (6.3 – 16.5)	Mean age 40 (18 – 76) 55% female 71% had stage II disease Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Radiotherapy (T) *vs* Radiotherapy (T)	Unknown	No	Morbidity – T1 Mortality – T2	Dox 240 mg/m^2	U	U	U	U	U	U
ANTH0084 CCG-503[319] Sposto (2001) 1983 - 1990	Non Hodgkin lymphoma <21 years	284	nm	69% male	*Induction* Daunorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Methotrexate (T) Cytarabine (T) *Maintenance* Cyclophosphamide (T) Vincristine (T) Methotrexate (T) Prednisone (T) *vs* *Induction* Daunorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Methotrexate (T) Cytarabine (T) *Maintenance* Cyclophosphamide (T) Vincristine (T) Methotrexate (T) Prednisone (T)	Unconfounded	Yes	Morbidity – R1 Mortality – P3	Daun 350 mg/m^2	U	U	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0252 M83 Boccadoro (1991)[320] 1983 - 1986	Multiple myeloma	304	42.6 months (0.3 – 75.7)	Balanced at baseline	Doxorubicin (A) Vincristine (T) Carmustine (N) Prednisone (T) *alternating* Vincristine (T) Melphalan (T) Cyclophosphamide (T) Prednisone (T) *vs* Melphalan (T) Prednisone (T)	Positive	No	Morbidity – S2 Mortality – T2	Dox 180 mg/m^2	U	U	L	L	U	U
ANTH0293 EST-5181[321] Tormey (1992) 1982 - 1987	Breast cancer Female Premenopausal ≤5cm tumour Node +ve No recent MI	658	5.1 years	Median age 44/42 63% were ER +ve	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Prednisone (T) Tamoxifen (N) Halotestin N) Thiotepa (N) Vinblastine (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Prednisone (T) Tamoxifen (N)	Positive	No	Morbidity – S1 Mortality – P3	Dox	L	L	U	U	U	U
ANTH0230 EORTC H6U[322] Carde (1993) 1982 - 1988	Hodgkin lymphoma 15-60 years Stage I-II	578	64 months (6-107)	Mean age 31 (15-65) 50% male	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Mechlorethamine (N) Vincristine (T) Procarbazine (N) Prednisone (T)	Unknown	Yes	Morbidity – R2 Mortality - Full	Dox 150 mg/m^2	U	U	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0093 Kimby (1991)[323] 1982 - 1988	CLL or Non Hodgkin lymphoma Stage III-IV No prior chemotherapy Cardiac disease excluded	259	All patients followed at least 57 months	Mean age 64.1 years 58% male 85%had stage IV disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Chlorambucil (N) Prednisone (T)	Positive	Yes	Morbidity – Full Mortality - Full	Dox 400 mg/m^2	U	U	L	L	L	U
ANTH0257 Vth MRC Myelomatosis Trial[324] MacLennan (1992) 1982 - 1986	Multiple Myeloma <75 years No prior chemotherapy Prior radiotherapy allowed	644	5 years 4 months	unk	Doxorubicin (A) Carmustine (N) Cyclophosphamide (T) Melphalan (T) *vs* Melphalan (T)	Positive	Yes	Morbidity – T1 Mortality - Full	Dox 360 mg/m	U	L	L	L	L	U
ANTH0060 Protocol 8005[325] Moliterni (1991) 1981 - 1990	Breast cancer Female ≤70 years No prior chemotherapy Radiotherapy allowed after BCS	558	61 months	Median age 47 (23-68) 25% were ER –ve Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – T1 Mortality – T2	Dox 300 mg/m^2	U	L	L	L	U	U
ANTH0061 NSABP B-11 Wolmark (1985)[326] 1981 - 1984	Breast cancer Female Node +ve ER -ve	707	11 years	56% were aged ≤49 years 72% were ER -ve	Doxorubicin (A) 5-FU (T) Melphalan (T) *Vs* 5-FU (T) Melphalan (T)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 300 mg/m^2	U	U	U	U	U	U
ANTH0062 NSABP B-12 Wolmark (1985)[326] 1981 - 1984	Breast cancer Female Node +ve ER +ve	1106	6 years	35% were aged ≤60 years 88% were ER +ve	Doxorubicin (A) 5-FU (T) Melphalan (T) Tamoxifen (N) *vs* 5-FU (T) Melphalan (T) Tamoxifen (N)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 300 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0233 Aviles (1996)[327] (1981 – 1991)	Non Hodgkin lymphoma Stage I	316	6.8 years	Median age 55 (21 – 77) 51% male Balanced at baseline	Doxorubicin (or Epi) (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) *vs* Doxorubicin (or Epi) (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) Radiotherapy (T) *vs* Radiotherapy (T)	Unknown 1 v 3 Positive 2 v 3	No	Morbidity – S1 Mortality – T2	Dox 300 mg/m^2 or Epi 420 mg/m^2	U	H	U	U	U	U
ANTH0255 GOG 52[328] Omura (1989) 1981 - 1985	Ovarian cancer Female Adult No prior chemotherapy No prior radiotherapy	415	nm	Age range 19 – 80 Reasonable distribution of characteristics at baseline	Doxorubicin (A) Cisplatin (T) Cyclophosphamide (T) *vs* Cisplatin (T) Cyclophosphamide (T)	Unconfounded	Yes	Morbidity – R2 Mortality – T2	Dox 400 mg/m^2	U	U	L	L	U	U
ANTH0277 Bertelsen (1987)[329] 1981- 1984	Ovarian cancer Female <70 years FIGO stage III_IV No prior chemotherapy No prior radiotherapy	276	Range 28-56 months	Median age 55/59 77% had stage III disease	Doxorubicin (A) Cyclophosphamide (T) Cisplatin (T) *vs* Cyclophosphamide (T) Cisplatin (T)	Unconfounded	No	Morbidity – R2 Mortality – T2	Dox 480 mg/m^2	U	U	L	L	U	U
ANTH0248 Coombes (1990)[330] 1981 - 1984	Gastric cancer No history of cardiac disorder No prior CHF	330	68 months	58% male Well balanced at baseline	Doxorubicin (A) 5-FU (T) Mitomycin C (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity - T1 Mortality - Full	Dox 360 mg/m^2	U	L	U	U	H	U
ANTH0231 Scandinavian Sarcoma Group Protocol 1[331] Alvegard (1989) 1981 - 1986	Soft tissue sarcoma ≥15 years Grade III or IV No prior chemotherapy No prior radiotherapy	240	nm	Median age 56 years (15 – 73) 54% male	Doxorubicin (A) *vs* No chemotherapy (N)	Unconfounded	No	Morbidity –S2 Mortality – T2	Dox 540 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0294 CALGB 8082[332] Perloff (1986) 1980 - 1985	Breast cancer Female <76 years Node +ve Stage II	744	11.5 years	Median age 52 years 41% premenopausal	Doxorubicin (A) Vinblastine (T) Thiotepa(N) Halotestin (N) Fluoxymesterone (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine T) Prednisone (T)	Unknown	No	Morbidity – T2 Mortality - T2	Dox	U	U	U	U	U	U
ANTH0250 CALGB 7951 Peterson (2003)[333] 1980 - 1985	Indolent follicular lymphoma Adult Stage III-IV Cardiac function must allow safe use of doxorubicin	234	10 years	Median age 55 (22 - 82) 52.5% female 72% had stage IV disease	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) *vs* Cyclophosphamide (T)	Positive	Yes	Morbidity – Full Mortality – S1	Dox 450 mg/m^2	U	U	L	L	L	U
ANTH0253 UKALL VIII[334] Eden (1991) 1980 - 1984	ALL 0-14 years	630	nm	53% male	Daunorubicin (A) Chemotherapy *vs* Same chemotherapy No daunorubicin	Unconfounded	No	Morbidity – S2 Mortality – T1	Daun 90 mg/m^2	U	U	L	L	L	U
ANTH0262 UKALL IX[335] Durrant (1993) 1980 - 1985	ALL ≥14 years No prior chemotherapy No prior radiotherapy	281	nm	38% aged <20 35% aged 20-39 55% male	Daunorubicin (A) Chemotherapy *vs* Same chemotherapy different doses	Unconfounded	No	Morbidity – S2 Mortality – T1	Daun 135 mg/m^2	U	L	L	L	U	U
ANTH0119 EORTC 40813[336] Lise (1988) 1980 - 1989	Gastric cancer <71 years Stage II-III No prior chemotherapy No prior radiotherapy	326	78 months	61% male Balanced at baseline	Doxorubicin (A) 5-FU (T) Mitomycin C (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 560 mg/m^2	U	U	H	H	U	U
ANTH0080 DCLSG ALLV[337] van der Does-van den Berg (1987) 1979 - 1982	ALL 0-15years	240	64 months (34 – 87 months)	50.4% Male 73.6% c-ALL	Chemotherapy Daunorubicin (A) *vs* Same chemotherapy No daunorubicin	Unconfounded	Yes (in a subset of patients)	Morbidity – P3 Mortality – T1	Daun 100 mg/m^2	U	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0156 NWTS – 3[338] D'Angio (1989) 1979 - 1985	Wilm's Tumor <16 years Stage II, III No prior chemotherapy No prior radiotherapy	560	Ongoing long-term follow up (30+ years)	Balanced at baseline	Doxorubicin (A) Actinomycin D (N) Vincristine (T) *vs* Actinomycin D (N) Vincristine (T)	Unconfounded	Yes	Morbidity – P3 Mortality – T2	Dox 300 mg/m^2	U	U	L	L	L	U
ANTH0335 Rossi (1988)[339] 1979 - 1983	Nasopharyngeal carcinoma <70 years No prior chemotherapy No prior radiotherapy	229	42 months	Median age 49 68% male Well balanced at baseline	Doxorubicin (A) Vincristine (T) Cyclophosphamide (T) Radiotherapy (N) *vs* Radiotherapy (N)	Positive	No	Morbidity – T1 Mortality – S1	Dox 240 – 480 mg/m^2	U	L	U	U	U	U
ANTH0291 ONCOFRANCE 1[340] Misset (1996) 1978 - 1981	Breast cancer Female 18-75 years Node +ve No prior chemotherapy Prior radiotherapy allowed	251	16 years	Mean age 50 55% had radiotherapy Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – P1 Mortality – T2	Dox 360 mg/m^2	L	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0251 LSA-LS[341] Anderson (1983) (1977 – 1979)	Non Hodgkin lymphoma <18 years	234	4 years	75% male	*Induction* Daunorubicin (A) Cyclophosphamide (T) Vincristine (T) Methotrexate (T) Prednisone (T) *Consolidation* Cytarabine (T) Thioguanine (N) Asparaginase (N) Methotrexate (T) Carmustine (N) *Maintenance* Thioguanine (N) Cyclophosphamide (T) Hydroxyurea (N) Daunorubicin (A) Methotrexate (T) Carmustine (N) Cytarabine (T) Vincristine (T) *vs* *Induction* Cyclophosphamide (T) Vincristine (T) Methotrexate (T) Prednisone (T) *Maintenance* Cyclophosphamide (T) Vincristine (T) Methotrexate (T) Prednisone (T)	Unknown	No	Morbidity – T1 Mortality – T1	Daun 300 mg/m2	L	L	L	L	H	U
ANTH0334 Gams (1985)[342] 1977 - 1971	Lymphoma No prior chemotherapy Local radiotherapy allowed	368	nm	Evaluability rates comparable between arms	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Carmustine (N) Cyclophosphamide (T) Vincristine (T) Prednisone (T)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Dox 400 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0243 EORTC 62771[343] Bramwell (1994) 1977 - 1988	Soft tissue sarcoma 15-70 years No prior chemotherapy No prior radiotherapy No heart disease	468	80 months	Median age 44/42 (15-70) Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Dacarbazine (N) *vs* No chemotherapy (T)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 400 mg/m^2	L	L	U	U	U	U
ANTH0280 BR30001[344] Morrison (1989) 1976 - 1984	Breast cancer Female Node +ve	568	7 years	57% aged >50 years 50% ER +ve	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Leucovorin (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality – T2	Dox 400 mg/m^2	L	L	U	U	L	U
ANTH0254 Gams (1986)[345] 1975 - 1981	Hodgkin lymphoma Stage IIIB or IV No prior chemotherapy Prior radiotherapy allowed	270	nm	79% male	Doxorubicin (A) Dacarbazine (N) Bleomycin (T) *Alternating* Carmustine (N) Cyclophosphamide (T) Vinblastine (T) Procarbazine (N) Prednisone (T) Bleomycin (T) *vs* Cyclophosphamide (T) Vinblastine (T) Procarbazine (N) Prednisone (T) Bleomycin (T)	Positive	Yes	Morbidity – Full Mortality – T2	Dox 180 mg/m^2	U	U	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0256 CCG-141[346] Miller (1983) 1975 - 1977	ALL <20 years No prior anthracycline No prior radiotherapy	306	nm	57% male 89% white ethnicity	Doxorubicin (A) Prednisone (T) Vincristine (T) Cyclophosphamide (T) Asparaginase (N) Mercaptopurine (N) Methotrexate (T) Cytarabine (T) *vs* Prednisone (T) Vincristine (T) Methotrexate (T) Mercaptopurine (N) Asparaginase (N)	Positive	No	Morbidity – S2 Mortality – S2	Dox 280 mg/m^2	U	L	L	L	U	U
ANTH0081 Sweetnam (1986)[347] 1975 - 1981	Osteosarcoma <40 years Prior radiotherapy allowed	235	26-94 months	57% male	Doxorubicin (A) Vincristine (T) Methotrexate (T) *vs* Vincristine (T) Methotrexate (T)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 540 mg/m^2	U	U	U	U	U	U
ANTH0157 NWTS – 2[348] D'Angio (1981) 1975 - 1978	Wilm's Tumor <16	268	Ongoing long term follow-up (30+ years)	Balanced at baseline	Doxorubicin (A) Actinomycin D (N) Vincristine (T) *vs* Actinomycin D (N) Vincristine (T)	Unconfounded	Yes	Morbidity – S1 Mortality - Full	Dox 300 mg/m^2	U	U	L	L	L	U
ANTH0245 Santoro (1987)[349] 1974 - 1982	Hodgkin lymphoma Stage IIB, IIIA, IIIB	236	84 months	Median age 31 (13 – 69) 54% male	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Radiotherapy (T) *vs* Mechlorethamine (N) Vincristine (N) Procarbazine (N) Prednisone (T) Radiotherapy (T)	Unknown	Yes	Morbidity – P3 Mortality - Full	Dox 600 mg/m^2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0266 SWOG 7406[350] Jones (1983) 1974 - 1978	Hodgkin lymphoma Recurrent or advanced disease No prior chemotherapy	316	47 months	Most prognostic factors balanced	Doxorubicin (A) Nitrogen mustard (N) Bleomycin (T) Procarbazine (N) Prednisone (T) *vs* Nitrogen mustard (N) Vincristine (T) Bleomycin (T) Procarbazine (N) Prednisone (T)	Unconfounded	Yes	Morbidity – Full Mortality – S1	Dox 300 mg/m^2	U	U	L	L	L	U
ANTH0078 SWOG 7426[351] Jones (1983) 1974 - 1977	Non Hodgkin lymphoma Stage III-IV No prior chemotherapy Prior radiotherapy allowed	652	nm	Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) BCG (N) *vs* Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T)	Unconfounded 1 v 3 Negative 2 v 3	Yes	Morbidity – R3 Mortality – T2	Dox 400 mg/m^2	U	U	U	U	U	U
ANTH0085 ALGB 6801[352] Halazun (1974) 1968 - 1971	Acute lymphoblastic leukaemia <20 No prior chemotherapy No prior radiotherapy	514	nm	nm	Chemotherapy Daunorubicin (A) *vs* same chemotherapy no daunorubicin	Unconfounded	Yes	Morbidity – Full Mortality - Full	Daun 360 – 1260 mg/m^2	U	U	U	U	U	U

10.5 APPENDIX B.2 TRIAL DESCRIPTIONS FOR TRIALS IN THE PUBLISHED-DATA META-ANALYSES

Abbreviations used in this Appendix

5-FU – 5-fluorouracil
ALL – acute lymphoblastic leukaemia
CHF – congestive heart failure
CLL – chronic lymphocytic leukaemia
Daun – daunorubicin
Dox – doxorubicin
Epi – epirubicin
ER – oestrogen receptor
FIGO – International Federation of Gynecology and Obstetrics
HER2 – human epidermal growth factor receptor-2
LVEF – left ventricular ejection fraction / ejection fraction
MI – myocardial infarction
Mitox – mitoxantrone
nm – not mentioned
PR – progesterone receptor
unk – unknown

Risk of Bias items

A – random sequence generation

B - allocation concealment

C – blinding of participants and personnel

D – blinding of outcome assessment

E – Incomplete outcome data

F – other bias

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0279 SWOG 8313[307] Budd (1995) 1984 - 1996	Breast cancer Female Node +ve Stage II-IIIa	628	nm	Median age 51/50 (22-77)	Doxorubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Vincristine (T) Prednisone (T)	Negative	Yes	Morbidity – T1 Mortality - Full	Dox 200 mg.m^2	L	L	U	U	U	U
ANTH0308 Fountzilas (1996)[298] 1986 - 1992	Breast cancer Female ≥18 years No prior chemotherapy No prior radiotherapy	392	51 months	Median age 50/51 (22-77) 52% were premenopausal 54% were ER +ve	Mitoxantrone (A) Cyclophosphamide (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – T1 Mortality - Full	Mitox 60 mg/m2	L	L	L	L	U	U
ANTH0042 GOIRC SANG2[264] Colozza (2002) 1990 - 1994	Breast cancer Female 18-70 years ER-ve Node-ve Or Node +ve (≤9 nodes) Normal LVEF Normal ECG Normal cardiac function	348	8 years	Median age 50 (30-70) 52% premenopausal 77% node +ve	Epirubicin (A) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Negative	Yes	Morbidity – Full Mortality - Full	Epi 480 mg/m2	L	L	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0058 DBCG 89d[265] Ejlertsen (2007) 1990 - 1998	Breast cancer Female	1224	10 years	67% aged <50 73% Premenopausal 71% node +ve Balanced at baseline	Epirubicin (A) Cyclophosphamide (T) 5-FU (T) *vs* Epirubicin (A) Cyclophosphamide (T) 5-FU (T) Pamidronate (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Pamidronate (N)	Negative	Yes	Morbidity – P3 Mortality - Full	Epi 540 mg/m2	L	L	L	L	L	U
ANTH0035 NSABP B-23[258] Fisher (2001) 1991 - 1998	Breast cancer Female Node –ve ER -ve	2008	5 years	98% were ER-ve 55% were aged ≤49 years	Doxorubicin (A) Cyclophosphamide (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Tamoxifen (N) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T) Tamoxifen (N)	Negative 1 v 3 2 v 4 1 v 4 2 v 3	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m2	L	U	U	U	L	U
ANTH0049 Trial 97-35[228] Jones (2006) 1997 - 1999	Breast cancer Female 18-75 years	1016	7 years	Median age 51/52 (27-77) Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) *vs* Docetaxel (T) Cyclophosphamide (T)	Negative	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m2	U	L	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0085 ALGB 6801[352] Halazun (1974) 1968 - 1971	ALL <20 No prior chemotherapy No prior radiotherapy	514	nm	nm	Chemotherapy Daunorubicin (A) *vs* same chemotherapy no daunorubicin	Unconfounded	Yes	Morbidity – Full Mortality - Full	Daun 360 – 1260 mg/m2	U	U	U	U	U	U
ANTH0157 NWTS – 2[348] D'Angio (1981) 1975 - 1978	Wilm's Tumor <16	268	Ongoing long-term follow-up (30+ years)	Balanced at baseline	Doxorubicin (A) Actinomycin D (N) Vincristine (T) *vs* Actinomycin D (N) Vincristine (T)	Unconfounded	Yes	Morbidity – S1 Mortality - Full	Dox 300 mg/m2	U	U	L	L	L	U
ANTH0081 Sweetnam (1986)[347] 1975 - 1981	Osteosarcoma <40 years Prior radiotherapy allowed	235	26-94 months	57% male	Doxorubicin (A) Vincristine (T) Methotrexate (T) *vs* Vincristine (T) Methotrexate (T)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 540 mg/m2	U	U	U	U	U	U
ANTH0061 NSABP B-11 Wolmark (1985)[326] 1981 - 1984	Breast cancer Female Node +ve ER -ve	707	11 years	56% were aged ≤49 years 72% were ER -ve	Doxorubicin (A) 5-FU (T) Melphalan (T) *Vs* 5-FU (T) Melphalan (T)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 300 mg/m2	U	U	U	U	U	U
ANTH0062 NSABP B-12 Wolmark (1985)[326] 1981 - 1984	Breast cancer Female Node +ve ER +ve	1106	6 years	35% were aged ≤60 years 88% were ER +ve	Doxorubicin (A) 5-FU (T) Melphalan (T) Tamoxifen (N) *vs* 5-FU (T) Melphalan (T) Tamoxifen (N)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Dox 300 mg/m2	U	U	U	U	U	U
ANTH0257 Vth MRC Myelomatosis Trial[324] MacLennan (1992) 1982 - 1986	Multiple Myeloma <75 years No prior chemotherapy Prior radiotherapy allowed	644	5 years 4 months	unk	Doxorubicin (A) Carmustine (N) Cyclophosphamide (T) Melphalan (T) *vs* Melphalan (T)	Positive	Yes	Morbidity – T1 Mortality - Full	Dox 360 mg/m	U	L	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0068 FASG 08[260] Fargeot (2004) 1991 - 2001	Breast cancer Female ≥65 years Node +ve Postmenopausal LVEF ≥ 50% No cardiac dysfunction No history of cardiac disease No prior chemotherapy No prior radiotherapy	338	72 months	Median age 69 (65-85) 78% ER and/or PR +ve Balanced at baseline	Epirubicin (A) Tamoxifen (N) *vs* Tamoxifen (N)	Unconfounded	Yes	Morbidity – Full Mortality - Full	Epi 540 mg/m2	U	U	U	U	U	U
ANTH0325 BR9601[236] Poole (2006) 1996 - 2001	Breast cancer Female	374	7.4 years	49% <50 years 46% postmenopausal	Epirubicin (A) Cyclophosphamide (T) Methotrexate (T) 5-FU (T) *vs* Cyclophosphamide (T) Methotrexate (T) 5-FU (T)	Unconfounded	Yes	Morbidity – T2 Mortality - Full	Epi 400 mg/m2	L	L	U	U	U	U
ANTH0210 PALG CLL2[224] Robak (2006) 1998 - 2003	CLL >18 years Progressive disease No prior chemotherapy No prior radiotherapy	508	112 months	Median age 61 years (28-81) 60% male Balanced at baseline	Mitoxantrone (A) Cladribine (N) Cyclophosphamide (T) *vs* Cladribine (N) Cyclophosphamide (T) *vs* Cladribine (N)	Unconfounded 1 v 2 Positive 1 v 3	Yes	Morbidity – T1 Mortality - Full	Mitox 60 mg/m2	U	L	L	L	U	U
ANTH0243 EORTC 62771[343] Bramwell (1994) 1977 - 1988	Soft tissue sarcoma 15-70 years No prior chemotherapy No prior radiotherapy No heart disease	468	80 months	Median age 44/42 (15-70) Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Dacarbazine (N) *vs* No chemotherapy (T)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 400 mg/m2	L	L	U	U	U	U
ANTH0119 EORTC 40813[336] Lise (1988) 1980 - 1989	Gastric cancer <71 years Stage II-III No prior chemotherapy No prior radiotherapy	326	78 months	61% male Balanced at baseline	Doxorubicin (A) 5-FU (T) Mitomycin C (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 560 mg/m2	U	U	H	H	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0248 Coombes (1990)[330] 1981 - 1984	Gastric cancer No history of cardiac disorder No prior CHF	330	68 months	58% male Well balanced at baseline	Doxorubicin (A) 5-FU (T) Mitomycin C (T) *vs* No chemotherapy (N)	Positive	Yes	Morbidity - T1 Mortality - Full	Dox 360 mg/m2	U	L	U	U	H	U
ANTH0093 Kimby (1991)[323] 1982 - 1988	CLL or Non Hodgkin lymphoma Stage III-IV No prior chemotherapy Cardiac disease excluded	259	All patients followed at least 57 months	Mean age 64.1 years 58% male 85%had stage IV disease Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Chlorambucil (N) Prednisone (T)	Positive	Yes	Morbidity – Full Mortality - Full	Dox 400 mg/m2	U	U	L	L	L	U
ANTH0237 ITMO[257] Bajetta (2002) 1992 - 1997	Gastric cancer <70 years No metastatic disease	274	80 months	Median age 57 (23-70) 64% male	Doxorubicin (A) Etoposide (T) Cisplatin (T) 5-FU (T) Leucovorin (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – T1 Mortality – Full	Dox 80 mg/m2	L	L	H	U	U	U
ANTH0271 SWOG 9133[255] Press (2001) 1992 - 2000	Hodgkin lymphoma >16 years Stage I-II No prior chemotherapy No prior radiotherapy	348	3.3 years	Median age 32 years (17-85) 54% male Balanced at baseline	Doxorubicin (A) Vinblastine (T) Radiotherapy (T) *vs* Radiotherapy (T)	Positive	Yes	Morbidity – Full Mortality - Full	Dox 150 mg/m2	L	U	L	L	L	U
ANTH0019 GOG 122[256] Randall (2006) 1992 - 2000	Endometrial cancer Female FIGO stage III-IV Normal LVEF	422	nm	70% had stage IIIc-IV disease Balanced at baseline	Doxorubicin (A) Cisplatin (T) *vs* Radiotherapy (N)	Positive	Yes	Morbidity – P3 Mortality – Full	Dox 420 mg/m2	L	L	U	U	U	U
ANTH0145 GHSD-HD7[251] Engert (2007) 1994 - 1998	Hodgkin lymphoma 16-75 years No prior chemotherapy No prior radiotherapy Impaired heart excluded	650	87 months	Median age 36 years (16 – 75) 53% had stage IIa disease 61% male Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Extended field Radiotherapy (T) *vs* Extended field radiotherapy (T)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 100 mg/m2	U	L	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0217 EORTC 62931[243] Woll (2012) 1995 - 2003	Soft tissue sarcoma 16 – 70 years No prior chemotherapy No cardiac disorders, or angina, or MI, or CHF	351	7.99 years (7.31-8.61)	Median age 49.1/49.2)17.3-71.4) 55% male Balanced at baseline	Doxorubicin (A) Ifosfamide (T) Mesna (N) Lenograstim (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 375 mg/m2	L	L	U	U	U	U
ANTH0098 Mellqvist (2008)[215] 2001 - 2003	Multiple myeloma <65 years	314	22 months	Median age 56/57 Balanced at baseline	Doxorubicin (A) Vincristine (T) Dexamethasone (T) *vs* Cyclophosphamide (T) Dexamethasone (T)	Unknown	Yes	Morbidity – Full Mortality - Full	Dox 432 mg/m2	U	U	L	L	U	U
ANTH0274 BRIGHT[197] Flinn (2014) (2009 – ongoing)	Non Hodgkin Lymphoma Mantle cell lymphoma ≥18 years Measurable disease No prior chemotherapy No prior radiotherapy	447	nm	Median age 59 (25 – 86) 60% male Balanced at baseline	Doxorubicin (A) Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Rituximab (T) Bendamustine (N)	Positive	Yes	Morbidity – T1 Mortality - Full	Dox 300 – 400 mg/m2	U	U	L	L	L	U
ANTH0245 Bonadonna (1991)[349] 1974 - 1982	Hodgkin lymphoma Stage IIB, IIIA, IIIB	236	84 months	Median age 31 years (13 – 69) 54% male	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Radiotherapy (T) *vs* Mechlorethamine (N) Vincristine (N) Procarbazine (T) Prednisone (T) Radiotherapy (T)	Unknown	Yes	Morbidity – P3 Mortality - Full	Dox 600 mg/m2	U	U	U	U	U	U
ANTH0230 EORTC H6U[322] Carde (1993) 1982 - 1988	Hodgkin lymphoma 15-60 years Stage I-II	578	64 months (6-107)	Mean age 31 years (15-65) 50% male	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Mechlorethamine (N) Vincristine (T) Procarbazine (N) Prednisone (T)	Unknown	Yes	Morbidity – R2 Mortality - Full	Dox 150 mg/m2	U	U	L	L	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P - cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0249 Radford (1995)[314] 1984 - 1992	Hodgkin lymphoma 16-70 years Stage I-II (bulky disease) or Stage III-IV	423	4.5 years (0 – 9)	29.5 years (15.2 – 68.8) 61% male Balanced at baseline	Doxorubicin (A) Chlorambucil (N) Vinblastine (T) Procarbazine (N) Prednisolone (T) Etoposide (T) Vincristine (T) *vs* Mustine (N) Vinblastine (T) Procarbazine (N) Prednisolone (T)	Positive	Yes	Morbidity – T2 Mortality - Full	Dox 400 mg/m2	U	U	L	L	L	U
ANTH0241 HD6[245] Meyer (2005) 1994 - 2002	Hodgkin lymphoma ≥16 years Stage IA-IIA Cardiac dysfunction excluded	405	4.2 years	Median age 35/36.7 55% male 66% had stage IIA disease	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Radiotherapy (T)	Unknown	Yes	Morbidity – Full Mortality - Full	Dox 100-150 mg/m2	L	L	L	L	U	U
ANTH0053 BCIRG 006[212] Slamon (2011) 2001 - 2004	Breast cancer Female 18-70 years HER2 +ve Normal LVEF No prior anthracycline Other chemo allowed No prior radiotherapy No CHF, MI, arrhythmia, angina, valvular heart disease, cardiomegaly, ventricular hypertrophy	3222	65 months	53% aged <50 years Balanced at baseline	Doxorubicin (A) Cyclophosphamide (T) Docetaxel (T) *vs* Doxorubicin (A) Cyclophosphamide (T) Docetaxel (T) Trastuzumab (T) *vs* Docetaxel (T) Cisplatin (T) Trastuzumab (T)	Unknown 1 v 3 2 v 3	Yes	Morbidity – Full Mortality - Full	Dox 240 mg/m2	L	L	L	L	L	U
ANTH0223 Kluin-Nelemans (2011)[205] 2004 - 2010	Mantle cell lymphoma ≥60 years Stage II-IV Measurable disease No prior chemotherapy No prior radiotherapy	560	37 months	Median age 70 years (60 – 87) 70% male 81% had stage IV disease	Doxorubicin (A) Rituximab (T) Cyclophosphamide (T) Vincristine (T) Prednisone (T) *vs* Rituximab (T) Cyclophosphamide (T) Fludarabine (T)	Unknown	Yes	Morbidity – R2 Mortality - Full	Dox 400 mg/m2	L	L	L	L	L	U

10.6 APPENDIX B.3 TRIAL DESCRIPTIONS FOR TRIALS IN THE INDIVIDUAL PATIENT DATA META-ANALYSES

Abbreviations used in this Appendix

5-FU – 5-fluorouracil
CHF – congestive heart failure
Dox – doxorubicin
Epi – epirubicin
FIGO – International Federation of Gynecology and Obstetrics
LipDox – liposomal doxorubicin
LVEF – left ventricular ejection fraction / ejection fraction
MI – myocardial infarction
Mitox – mitoxantrone
nm – not mentioned
unk – unknown

Risk of Bias items

A – random sequence generation

B - allocation concealment

C – blinding of participants and personnel

D – blinding of outcome assessment

E – Incomplete outcome data

F – other bias

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P – cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0018 Fruscio (2008)[230] 1997 - 2000	Ovarian cancer Female ≥18 years FIGO stage II-IV No prior chemotherapy No prior radiotherapy No prior CHF and arrhythmia	209	82 months	Median age 52 (24-73) 85% had stage IIIc-IV disease Baseline characteristics balanced	Paclitaxel (T) Cisplatin (T) Epirubicin (A) *vs* Paclitaxel (T) Cisplatin (T) Ifosfamide (T)	Negative	Yes	Morbidity – Full Mortality – T2	Epi 480 mg/m^2	U	L	L	L	U	U
ANTH0002 TAX327[219] Tannock (2004) 2000 - 2002	Prostate cancer Male Metastatic disease No prior chemotherapy Prior radiotherapy allowed Normal cardiac function Metastatic disease	1006	20.8 months	Median age 68(36 - 92) 40% had measurable soft tissue lesions	Mitoxantrone (A) Prednisone (T) *vs* Docetaxel qw (T) Prednisone (T) *vs* Docetaxel q3w (T) Prednisone (T)	Negative	Yes	Morbidity – Full Mortality – T2	Mitox 144 mg/m2	L	L	L	L	U	U
ANTH0014 MITO-2[207] Pignata (2006) 2003-UNK	Ovarian cancer Female ≤75 years Stage Ic-IV No prior chemotherapy No prior MI or arrhythmia No prior atrioventricular block	395	40 months	Median age 57 (21 - 77) 81% were stage III-IV Baseline characteristics balanced	Liposomal doxorubicin (A) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Negative	Yes	Morbidity – Full Mortality – T1	LipDox 180 mg/m2	L	L	L	L	L	U
ANTH0156 NWTS – 3[338] D'Angio (1989) 1979 - 1985	Wilm's Tumor <16 years Stage II, III No prior chemotherapy No prior radiotherapy	560	Ongoing long-term follow up (30+ years)	Balanced at baseline	Doxorubicin (A) Actinomycin D (N) Vincristine (T) *vs* Actinomycin D (N) Vincristine (T)	Unconfounded	Yes	Morbidity – P3 Mortality – T2	Dox 300 mg/m2	U	U	L	L	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P – cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0157 NWTS – 2[348] D'Angio (1981) 1975 - 1978	Wilm's Tumor <16	268	Ongoing long term follow-up (30+ years)	Balanced at baseline	Doxorubicin (A) Actinomycin D (N) Vincristine (T) *vs* Actinomycin D (N) Vincristine (T)	Unconfounded	Yes	Morbidity – S1 Mortality - Full	Dox 300 mg/m2	U	U	L	L	L	U
ANTH0232 AGO-OVAR[231] Du Bois (2006) 1997 - 2000	Ovarian cancer Female ≥18 years FIGO stage IIB-IV No prior chemotherapy No prior radiotherapy No prior CHF, MI, arrhythmia Normal LVEF required	1282	54 months	Median age 59 (21 –79) 72% had stage IIIc-IV disease Balanced at baseline	Epirubicin (A) Paclitaxel (T) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Epi 360 mg/m2	L	L	L	L	U	U
ANTH0215 Kristensen (2005)[222] 1999 - 2001	Ovarian cancer Female ≥18 years FIGO stage IIB-IV No prior chemotherapy No prior radiotherapy No prior CHF, MI, arrhythmia Normal LVEF required	887	61 months	Median age 57 (25 – 80) 73% had stage IIIc-IV disease Balanced at baseline	Epirubicin (A) Paclitaxel (T) Carboplatin (N) *vs* Paclitaxel (T) Carboplatin (N)	Unconfounded	Yes	Morbidity – Full Mortality – T2	Epi 450 mg/m2	L	L	L	L	U	U
ANTH0145 GHSD-HD7[251] Engert (2007) 1994 - 1998	Hodgkin lymphoma 16-75 years No prior chemotherapy No prior radiotherapy Impaired heart excluded	650	87 months	Median age 36 years (16 – 75) 53% had stage IIa disease 61% male Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Extended field Radiotherapy (T) *vs* Extended field radiotherapy (T)	Positive	Yes	Morbidity – R3 Mortality - Full	Dox 100 mg/m2	U	L	U	U	L	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P – cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk A	B	C	D	E	F
ANTH0121 Di Costanzo (2008)[242] (1995 – 2000)	Gastric cancer ≤75 years Stage IB, II A-B, IV No prior chemotherapy No prior radiotherapy No abnormal cardiac function	258	5.6 years	Median age 59 years (18 – 73) 60.5% had stage III-IV disease	Epirubicin (A) Cisplatin (T) 5-FU (T) Leucovorin (N) *vs* No chemotherapy (N)	Positive	Yes	Morbidity – R3 Mortality – R3	Epi 120 mg/m2	L	L	H	H	U	U
ANTH0233 Aviles (1996)[327] (1981 – 1991)	Non Hodgkin lymphoma Stage I	316	6.8 years	Median age 55 (21 – 77) 51% male Balanced at baseline	Doxorubicin (or Epi) (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) *vs* Doxorubicin (or Epi) (A) Cyclophosphamide (T) Vincristine (T) Prednisone (T) Bleomycin (T) Radiotherapy (T) *vs* Radiotherapy (T)	Unknown	No	Morbidity – S1 Mortality – T2	Dox 300 mg/m2 or Epi 420 mg/m2	U	H	U	U	U	U
ANTH0234 Aviles (1998)[318] 1983 – 1988	Hodgkin lymphoma Stage I or II Bulky disease	327	11.4 years (6.3 – 16.5)	Mean age 40 (18 – 76) 55% female 71% had stage II disease Balanced at baseline	Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) *vs* Doxorubicin (A) Bleomycin (T) Vinblastine (T) Dacarbazine (N) Radiotherapy (T) *vs* Radiotherapy (T)	Unknown	No	Morbidity – T1 Mortality – T2	Dox 240 mg/m2	U	U	U	U	U	U

Trial (Recruitment dates)	Eligibility criteria	Number of patients	Median follow-up	Patient characteristics	Comparison A – anthracycline T – cardiotoxic N – no known cardiotoxicity P – cardioprotective	Confounding category	Cardiac outcomes reported	Outcome reporting bias	Cumulative anthracycline dose	Risk of bias L – low risk H – high risk U – unclear risk					
										A	B	C	D	E	F
ANTH0235 Aviles (2008)[246] 1994 - 2001	T-cell lymphoma 18 – 70 years Normal cardiac function	217	nm	Median age 52 75% male 95% had stage II-IV disease Baseline characteristics balanced	Doxorubicin (A) Cyclophosphamide(T) Vincristine (T) Prednisone (T) *vs* Cyclophosphamide (T) Methotrexate(T) Etoposide(T) Dexamethasone (T) Leucovorin (N)	Unknown	No	Morbidity – T1 Mortality – Full	Dox 300 mg/m2	U	H	U	U	U	U

10.7 APPENDIX C.1 ORBIT I CLASSIFICATION CODES

Orbit I classification codes

Classification	Description	Level of reporting	Risk of bias*
Clear that the outcome was measured and analysed			
A	Trial report states that outcome was analysed by only reports that result was not significant (typically stating P>0.05)	Partial	High risk
B	Trial report states that outcome was analysed by only reports that result was significant (typically stating P<0.05)	Partial	No risk
C	Trial report states that outcome was analysed but insufficient data were presented for the trial to be included in meta-analysis or to be considered to be fully tabulated	Partial	Low risk
D	Trial report states that outcome was analysed by no results reported	None	High risk
Clear that the outcome was measured			
E	Clear that outcome was measured but not necessarily analysed. Judgement says likely to have been analysed but not reported because of non-significant results	None	High risk
F	Clear that the outcome was measured but not necessarily analysed. Judgement says unlikely to have been analysed but not reported because of non-significant results	None	Low risk
Unclear whether outcome was measured			
G	Not mentioned but clinical judgement says likely to have been measured and analysed but not reported on the basis of non-significant results	None	High risk
H	Not mentioned but clinical judgement says unlikely to have been measured at all	None	Low risk
Clear that the outcome was not measured			
I	Clear that outcome was not measured	N/A	No risk

*Risk of bias arising from the lack of inclusion of non-significant results when a trial was excluded from a meta-analysis or not fully reported in a review because the data were unavailable.

10.8 APPENDIX C.2 ORBIT II CLASSIFICATION CODES WITH DECISION CRITERIA

ORBIT II classifications codes with decision criteria for cardiac mortality and cardiac morbidity

Classification	Guidelines / Examples
Explicit the specific harm outcome was measured and compared across treatment groups	
P1	*States outcome analysed but reported only that p-value > 0.*05 **Cardiac Morbidity:** A statement such as "There was no significant difference in CHF between anthracycline treated and control patients" or "Cardiotoxicity was not recorded any more often in anthracycline than control patients" **Cardiac Mortality**: A statement such as "There were similar numbers of cardiac deaths in control and anthracycline treated patients" **It's clear that CHF/cardiotoxicity/cardiac deaths were recorded, and that the data were looked at, but there were no differences between treatment groups**
P2	*States outcome analysed but reported only that p-value <0.05* Example **Cardiac morbidity:** A statement such as "The results of the analysis showed that there were significantly (p<0.05) more cardiac events in the anthracycline treated group than the control group." **Cardiac mortality:** A statement such as " There were significantly more (p<0.05) cardiac deaths in anthracycline patients **It's clear that cardiotoxicity / non-cancer causes of death were recorded, and that the data were looked at, and there was a significant difference between treatment groups.**
P3	*Insufficient reporting for meta-analysis/full tabulation* In order to obtain a P3 classification, it must be clear that the data were analysed, with some results presented other than just the significance level of the treatment comparison. This would include when • for binary data (common for harms), percentage data is given for all groups but either the numerator or denominator is unclear • the results are reported graphically only and accurate data extraction is not possible • no measure of variance/precision is presented (e.g. an odds ratio or relative risk reported without a confidence interval, standard error or precise p-value)
Explicit specific harm outcome was measured, but not compared across treatment groups	
Q	*Clear that outcome was measured and clear outcome not compared* It is likely that a Q classification will occur rarely. In terms of a classification based on the report, this would have to be explicitly stated e.g. **"Cardiac events were recorded but were not compared across groups**".

Explicit specific harm outcome was measured, not clear whether compared or not across treatment groups	
R1	*Clear that outcome was measured but no results reported* An R1 classification is awarded when it states in any part of the study report that the review harm outcome will be measured or recorded but then no results on the review harm outcome are provided in any of the study publications. **Cardiac Morbidity:** In the methods section of the research article (or an easily accessible full study protocol) it states that cardiac status is assessed at baseline and in follow-up, but no cardiac events were reported. For example a statement such as "LVEF was measured before cycle 3, at the end of treatment, and at each follow-up visit." **Clear from the methods section that 'LVEF' was measured. Data on 'LVEF' was not reported in the results section or mentioned in the discussion.** **Cardiac Mortality:** In the methods section it states that specific cause of death was recorded, but only cancer deaths are reported.
R2	*Result reported globally across all groups* **Cardiac Morbidity – Failure to complete (due to adverse events)**: "Across all treatment groups, 16 patients discontinued due to cardiotoxicity." "The most common side effect necessitating a change or cessation in therapy was LVEF reduction. A drop in LVEF occurred in 28 of the 217 patients in the trial" **It is clear from the results that cardiac events were recorded, but only the total number of events in the trial are reported, not the number of events per trial arm.** **Cardiac Mortality** – "3 patients died of congestive heart failure during the trial" **It is clear from the results that specific causes of death were recorded, but only the total number of cardiac deaths in the trial are reported, not the number of cardiac deaths per trial arm.**
R3	*Result reported from some groups only* **Cardiac Morbidity*:** An R3 classification would be given if it is clear that cardiac events were collected in only one arm, for instance a trial where one arm is treated with chemotherapy and the other arm receives no treatment. "The most frequently reported AEs in chemotherapy patients were nausea and vomiting (33.7%), alopecia (36.7%), and congestive heart failure (1.5%)." * Clinical consideration may need to be made about known harms for comparator groups. For example, it may be clear that the harm 'pain at injection site' may not be observed in the comparator group if the comparator does not involve a vaccination. Another example would be surgical infections, if the comparator group did not involve a surgical intervention. In this situation full reporting may be considered if harm data were reported in full for all groups where the harm outcome could be measured. **An R3 classification may be possible in a trial of chemotherapy vs no treatment, where toxicity is recorded only in the chemotherapy arm, and not collected in the no treatment arm.** **Cardiac Mortality:** It is highly unlikely that an R3 classification would be given. Survival is an outcome in many, if not all, cancer trials. **It is unlikely that non cancer deaths would be recorded in one trial arm and not others.**

Specific harm outcome not explicitly mentioned, likely measured and likely compared across treatment groups	
S1	*Pooled AEs reported (some of which may be the specific harm outcome)* Examples: **Cardiac morbidity** – "Overall, there were adverse events in 82 of the 130 anthracycline treated patients, and 58 of the 128 control patients." **In this example the total number of adverse events is specified for each trial arm and the number of patients per arm is specified. Some of these adverse events may be cardiac events but this detail is not specified in the study reports.** **Cardiac mortality** – "10 patients died before recurrence in the AC group, 6 patients died before recurrence in the CMF group" **In this example deaths before recurrence are non-cancer deaths. It specifies the number per arm but not specific causes of death, which could include some cardiac deaths.**
S2	*No harms mentioned/reported (not even pooled AEs), clinical judgement says likely measured* To award a S2 classification, clinical expertise in the field of interest will often be required. This would include the following situations. • Routine practice suggests the harm outcome would have been measured (e.g. biochemical disturbances in major surgery trials) • Based on the methodology for data collection, it is likely that the harm could have been measured (e.g. the methods suggest that the relevant laboratory tests were carried out to measure the specific review harm outcomes) • The majority of other included studies in the review reported data on the specific review harm outcomes **An S2 classification could also be awarded if an adverse event grading scheme (which would have included cardiac events) was specified in the methods section, but no toxicity or adverse events were reported in the publications.**
Specific harm outcome not explicitly mentioned, likely measured (no events)	
T1	*Specific harm not mentioned but all other specific harms fully reported* For a T1 classification, all specific harms should have been clearly reported (in full) in the text and/or a table in the study report. If the review harm outcome is not listed then judgment would suggest that there were no events for the specific review harm outcome of interest. NOTE: Be careful that the specific harms that are listed are not based on reporting thresholds, e.g. specific harms reported only if observed in >=5% patients. For example, "No other adverse event occurred with an incidence of greater than 5%". If this is the case then there may be missing data (not necessarily no events) on the specific review harm outcome that went unreported as the number of events did not meet this specified threshold. In this situation an alternative classification should be sought. **Cardiac Morbidity – There is a toxicity table, or description of toxicities, and all mentioned toxicities are fully reported, but no cardiac events are listed.** **Cardiac Mortality** – non cancer causes of death are fully reported, but no cardiac deaths are mentioned

	No description of specific harms, likely to be no events (consider similar studies) A T2 should be used if it is likely that the specific review harm outcome was measured in the study but it is probable that the non-reporting was a result of there being no events. A judgment could be made, if perhaps, a similar study (of similar size) reported on no events for the specific review harm outcome.
T2	**Cardiac morbidity** – clinical judgement suggests that adverse events would have been collected, but no adverse events are reported. There is no mention of adverse event grading or collection of toxicities in the methods section of the paper. **Cardiac Mortality** – clinical judgment suggests that specific cause of death would have been collected, but non-cancer deaths are not mentioned in the paper. There is no mention of how cause of death was recorded in the methods section of the paper.

Specific harm outcome not explicitly mentioned, unlikely measured	
U	*No harms mentioned/reported (not even pooled AEs), clinical judgement says unlikely measured* To award a U classification, clinical expertise in the field of interest will often be required. This would include the following situations. • Follow-up appears to be too short to measure the specific review harm outcome of interest, e.g. harm outcome is percentage emergency department re-representations but data collection was completed on patient discharge. • Data collection methods used in the study would suggest the specific review harm outcome was not measured (e.g. if the harm involved a laboratory marker that was not performed in the study) • Outcome measurements used in the study were not appropriate for the specific review harm outcome (e.g. the review required an objective measure whereas the study reported on subjective measures). A similar judgment can be made for validated and invalidated measurement scales used. • Specific review harm outcome would not have been routinely collected; a) at the time the study was conducted, b) the specific setting (e.g. a harm may have been collected if the patient underwent major surgery but not minor surgery), c) the country where the trial was undertaken. **A U classification is possible of clinical judgement suggests that at the time the study was conducted, it is unlikely that adverse events were collected routinely.** **This classification is also possible if clinical judgement suggests that at the time the study was conducted, it is unlikely that specific cause of death was recorded. An example would be cause of death recorded as "cancer/toxicity/other/unknown".**
Explicit the specific harm outcome was not measured	
V	*Report clearly specifies the data on the specific harm of interest was not measured* For a V classification there must be clear evidence that the review specific review harm outcome was not measured. <u>Examples:</u> **Single primary harm outcome – Total amount of postoperative chest tube drainage:** "This study was solely designed to examine blood product use among a large sample of patients. ***No information was obtained*** about preoperative renal function, ***post-operative chest tube drainage***, hemodynamics, hematological indices, or the need for surgical re-exploration" **Single primary harm outcome – Pain at vaccination site (classified as non-serious):** "Non-serious AEs were not collected" **The report specifically states that adverse events were not recorded, or that specific cause of death was not recorded. This is unlikely in chemotherapy trials.**

10.9 APPENDIX D VARIABLE LIST

CCCG Variables for Trials Carried Out in Cancer Patients

Use your own codes and tell us what they mean. If you use standard codes, e.g. ICD, TNM, CTCAE etc., tell us which revision you are using.

A. Patient demographics

1. ID number (*anonymised)*
2. Date of birth or age at diagnosis
3. Sex
4. Cancer diagnosis conferring trial eligibility
5. Date of cancer diagnosis
6. Stage of malignancy (or risk group for leukemias)
7. Did your group's analyses exclude this patient? (e*.g., A few trial patients may have been randomised in error, otherwise ineligible, lost with no follow-up, unevaluable or have withdrawn consent. (1=no known reason for exclusion, 2=yes [specify main reason(s) for exclusion, if known])*

B. Treatment (for current disease episode)

8. Date of randomisation
9. Randomly allocated treatment
10. If known: Agents and cumulative doses received of each randomised anti-cancer systemic therapy *(list all agents and doses)*
11. If known: Did the patient receive radiotherapy? (*If yes, where known please state sites irradiated, radiotherapy technique, radiotherapy dose and fractionation)*
12. If known: Other trial protocol therapies received? (*if yes, list agents if known)*
13. If known: Has the patient previously been treated for cancer (*if yes specify prior treatment where known*)

D. Outcome

14. Relapse, Recurrence or Progression (*did the patient have a relapse, recurrence or progression of their cancer, if yes specify date, also specify site of recurrence where relevant)*
15. Patient known to have died? *(yes or no)*
16. Date of death, if dead, otherwise date last known to be alive
17. Cause of death
18. If available: second malignancies and dates (*Give all diagnoses and date(s))*

If any variable is not available or not applicable, please omit it and just send the variables for which you have data

Using your own codes, please extract from your dataset the variables that correspond most closely to the items listed. Please provide one record for each patient ever randomised (including any patient who was randomised and then was later categorised as ineligible, withdrawn, unevaluable, lost or "protocol deviant" – but please tell us in question 7 which patients your group's preferred analyses would exclude, and why).

If any variable is not available or not applicable, please omit it and just send the variables for which you have data. If you have any of the requested variables in your records only in a form that would require substantial additional work to supply (e.g. computerisation, or manual coding), please omit them for now, but in your cover document please tell us of their existence.

- Please send your data in a separate CSV file or Excel spreadsheet for each separate trial, if possible.

- Please send a cover document giving all your coding conventions (including format for dates).

- Please send your data to: cccg@ctsu.ox.ac.uk with your research group's name (and/or the CCCG number for your trial) and the name you usually use for referring to the trial in the subject line.

This study has approval from the Oxford Tropical Research Ethics Committee of the University of Oxford (OXTREC ref 500-12). All data supplied to the secretariat will be held securely and treated confidentially, in accordance with UK Medical Research Council data security policies.

If you have any questions about this data request, please contact the CCCG secretariat on cccg@ctsu.ox.ac.uk.

CHAPTER 11 APPENDIX REFERENCES

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