Summary of findings tables, grading of the evidence and detailed conclusions of evidence for cancer therapy-related cardiac dysfunction risk equivalence ratios for anthracycline and anthraquinone agents after childhood cancer treatment

Daunorubicin versus doxorubicin

Study	Number of partici-pants	Follow up	Anthracycline and/or anthraquinone agents and radiotherapy involving the heart	Events	Effect size	Risk of bias
Feijen 2019	28423 CCS	Median 20 years (range 5-40) after cancer diagnosis	Doxorubicin 34.8% Daunorubicin 18.0% Epirubicin 1.1% Idarubicin 1.1% Mitoxantrone 0.9% Treated with more than one type of anthracycline or anthraquinone 7.4% Treated with more than two types of anthracycline or anthraquinone 0.4% Radiotherapy involving the heart 21.2%	Heart failure defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; grade 3-5 Cumulative incidence of grade 3 to 5 cardiomyopathy by 40 years of age 3.4% (95% CI 3.1%-3.8%) Cardiomyopathy cases 399/28423 (1.4%) - Doxorubicin N=229 (56.2%) - Daunorubicin N=65	Daunorubicin to doxorubicin ratio: - <150mg/m^2: 0.8 - 150-299mg/m^2: 0.6 - ≥300mg/m^2: 0.5 Mean 0.6 (95% CI 0.4-1.0) Linear dose response model 0.5 (95% CI 0.4-0.7).	SB: unclear risk AB: low risk DB: unclear risk CF: low risk

GRADE assessment		
Study design	+4	Retrospective cohort study
Study limitations	-1	Few limitations: selection bias unclear risk; attrition bias low risk; detection bias unclear risk, confounding low risk
Consistency	0	Not applicable
Directness	0	Population and outcomes broadly generalizable
Precision	0	For risk of CTRCD for daunorubicin compared with doxorubicin: only one study has been identified, but with a large sample size, a large number of events and narrow confidence intervals
	-1	For exact equivalence ratio: some imprecision due to variation in point estimates based on dose and statistical model
Publication bias	0	Unlikely
Magnitude of effect	0	Not applicable
Dose response gradient	0	Not applicable
Plausible confounding	0	Not applicable

Quality of evidence	⊕⊕⊕⊖ MODERATE
Conclusion	Daunorubicin poses a lower risk of CTRCD after childhood cancer treatment compared with doxorubicin (1 study, 13763 participants, 294 events).
Quality of evidence	⊕⊕⊖⊖ LOW
Conclusion	On average, the risk of CTRCD after childhood cancer treatment with daunorubicin is 0.6 (95% CI 0.4-1.0; range of risk ratio 0.5-0.8 depending on dose category) times as high as after treatment with doxorubicin (1 study, 13763 participants, 294 events).

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; NCI CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; SB, selection bias

Mitoxantrone versus doxorubicin

Study	Number of participants	Follow up	Anthracycline and/or anthraquinone agents and radiotherapy involving the heart	Events	Effect size	Risk of bias
Feijen 2019	28423 CCS	Median 20 years (range 5-40) after cancer diagnosis	Doxorubicin 34.8% Daunorubicin 18.0% Epirubicin 1.1% Idarubicin 1.1% Mitoxantrone 0.9% Treated with more than one type of anthracycline or anthraquinone 7.4% Treated with more than two types of anthracycline or anthraquinone 0.4% Radiotherapy involving the heart 21.2%	Heart failure defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; grade 3-5 Cumulative incidence of grade 3 to 5 cardiomyopathy by 40 years of age 3.4% (95% CI 3.1%-3.8%) Cardiomyopathy cases 399/28423 (1.4%) - Doxorubicin N=229 (56.2%) - Mitoxantrone N=19	Mitoxantrone to doxorubicin ratio: - <150mg/m^2: 11.2 - 150-299mg/m^2: 4.0 - ≥300mg/m^2: 16.8 Mean 10.5 (95% CI 6.2-19.1) Linear dose response model 13.8 (95% CI 8.0-21.6)	SB: unclear risk AB: low risk DB: unclear risk CF: low risk
GRADE assessment						
Study design		+4		Retrospective cohort study		
Study limitations		-1		Few limitations: selection bias unclear risk; attrition bias low risk; detection bias unclear risk, confounding low risk		
Consistency		0		Not applicable		
Directness		0		Population and outcomes broadly generalizable		
Precision		0		For risk of CTRCD for mitoxantrone compared with doxorubicin: only one study has been identified, but with a large sample size, a large number of events and narrow confidence intervals		

	-1	For exact equivalence ratio: some imprecision due to variation in point estimates based on dose and statistical model
Publication bias	0	Unlikely
Magnitude of effect	0	Not applicable
Dose response gradient	0	Not applicable
Plausible confounding	0	Not applicable
Quality of evidence		⊕⊕⊕⊖ MODERATE
Conclusion		Mitoxantrone poses a higher risk of CTRCD after childhood cancer treatment compared with doxorubicin (1 study, 9595 participants, 248 events).
Quality of evidence		⊕⊕⊖⊖ LOW
Conclusion		On average, the risk of CTRCD after childhood cancer treatment with mitoxantrone is 10.5 (95% CI 6.2-19.1; range of risk ratio 4.0-16.8 depending on dose category) times as high as after treatment with doxorubicin (1 study, 9595 participants, 248 events).

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; NCI CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; SB, selection bias

Epirubicin versus doxorubicin

Study	Number of partici-pants	Follow up	Anthracycline and/or anthraquinone agents and radiotherapy involving the heart	Events	Effect size	Risk of bias
Feijen 2019	28423 CCS	Median 20 years (range 5-40) after cancer diagnosis	Doxorubicin 34.8% Daunorubicin 18.0% Epirubicin 1.1% Idarubicin 1.1% Mitoxantrone 0.9% Treated with more than one type of anthracycline or anthraquinone 7.4% Treated with more than two types of anthracycline or anthraquinone 0.4% Radiotherapy involving the heart 21.2%	Heart failure defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; grade 3-5 Cumulative incidence of grade 3 to 5 cardiomyopathy by 40 years of age 3.4% (95% CI 3.1%-3.8%) Cardiomyopathy cases 399/28423 (1.4%) - Doxorubicin N=229 (56.2%) - Epirubicin N=9	Epirubicin to doxorubicin ratio: - <150mg/m^2: 1.3 - 150-299mg/m^2: 0.6 - ≥300mg/m^2: 0.5 Mean 0.8 (95% CI 0.5-2.8) Linear dose response model 0.8 (95% CI 0.3-1.4)	SB: unclear risk AB: low risk DB: unclear risk CF: low risk

GRADE assessment		
Study design	+4	Retrospective cohort study
Study limitations	-1	Few limitations: selection bias unclear risk; attrition bias low risk; detection bias unclear risk, confounding low risk
Consistency	0	Not applicable
Directness	0	Population and outcomes broadly generalizable
Precision	-1	Only one study has been identified, with a large sample size and narrow confidence intervals, but with only a few events and non-significant results
Publication bias	0	Unlikely
Magnitude of effect	0	Not applicable
Dose response gradient	0	Not applicable
Plausible confounding	0	Not applicable
Quality of evidence		⨁⨁⨀⨀ LOW
Conclusion		On average, the risk of CTRCD after childhood cancer treatment with epirubicin is 0.8 (95% CI 0.3-1.4; range of risk ratio 0.5-1.3 depending on dose category) times as high as after treatment with doxorubicin. However, this estimate was not significant (1 study, 9630 participants, 238 events).

Abbreviations: AB, attrition bias; CCS, childhood cancer survivors; CF, confounding; DB, detection bias; NCI CTCAE, National Cancer Institute – Common Terminology Criteria for Adverse Events; SB, selection bias

Idarubicin versus doxorubicin

No eligible studies were identified, therefore the relative potency of idarubicin compared to doxorubicin is unclear.