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 participants	Follow up		Anthracycline a anthraquinone radiotherapy in heart	agents and	Events	Effect size	Risk of bias	
Feijen 2019	28423 CCS	Median 20 (range 5-4 cancer dia	0) after	Doxorubicin 34. Daunorubicin 18 Epirubicin 1.1% Idarubicin 1.1% Mitoxantrone 0 Treated with mo type of anthracy anthraquinone 1 Treated with mo types of anthracy anthraquinone 0 Radiotherapy in heart 21.2%	9.9% ore than one ycline or 7.4% ore than two cycline or 0.4%	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/m²: 0.8 - 150-299mg/m²: 0.6 - ≥300mg/m²: 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	
	assessment		_						
Study d			+4		Retrospective cohort study				
Study limitations -1				Few limitations: selection bias unclear risk; attrition bias low risk; detection bias unclear risk, confounding low risk					
Consiste	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 equivalent statistical mode	alence ratio: some imprecision due to variation in poel	oint estimates based on d	ose and	
Publication bias 0				Unlikely					
Magnitude of effect 0				Not applicable					
Dose response gradient 0				Not applicable					
Plausible confounding 0			<u> </u>	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	$\oplus \oplus \ominus \ominus$ 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	28423 CCS	Median 20 years (range 5-	Doxorubicin 34.8%	Heart failure defined	Mitoxantrone	SB:	
2019		40) after cancer diagnosis	Daunorubicin 18.0%	according to National	to doxorubicin	unclear	
			Epirubicin 1.1%	Cancer Institute	<u>ratio</u> :	risk	
			Idarubicin 1.1%	Common Terminology	- <150mg/m <sup>2</sup> :	AB: low	
			Mitoxantrone 0.9%	Criteria for Adverse	11.2	risk	
			Treated with more than one type of anthracycline or	Events (NCI CTCAE),	- 150-	DB:	
			anthraquinone 7.4%	version 4.03; grade 3-	299mg/m <sup>2</sup> : 4.0	unclear	
			Treated with more than two types of anthracycline or	5	- ≥300mg/m <sup>2</sup> :	risk	
			anthraquinone 0.4%		16.8	CF: low	
			Radiotherapy involving the heart 21.2%	Cumulative incidence	Mean 10.5	risk	
				of grade 3 to 5	(95% CI 6.2-		
				cardiomyopathy by 40	19.1)		
				years of age 3.4%	Linear dose		
				(95% CI 3.1%-3.8%)	response		
					model 13.8		
				Cardiomyopathy	(95% CI 8.0-		
				cases 399/28423	21.6)		
				(1.4%) - Doxorubicin N=229			
				(56.2%)			
				- Mitoxantrone N=19			
GRADE	assessment			- IVIILOXAIILIOIIE IV-13			
Study d		+4		Retrospective cohort study			
Study li	mitations	-1		Few limitations: selection bias unclear risk;			
			attrition bias low risk; detection bias unclear risk,				
				confounding low risk			
Consistency		0	Not applicable				
Directn	Directness 0			Population and outcomes broadly generalizable			
Precisio	on	0			For risk of CTRCD for mitoxantrone compared with		
				doxorubicin: only one s	tudy has been ide	ntified,	
				but with a large sample	size, a large numb	per of	
				events and narrow conf	fidence intervals		

	-1	For exact equivalence ratio: some imprecision due		
	-1	·		
		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		$\oplus \oplus \ominus \ominus$ 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 participants	Follow up		Anthracycline and anthraquinone and anthraquinone and	agents and	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/m²: 1.3 - 150-299mg/m²: 0.6 - ≥300mg/m²: 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	
	assessment								
Study de			+4		Retrospective cohort study				
Study lin	Study limitations -1				Few limitations: selection bias unclear risk; attrition bias low risk; detection bias unclear risk, confounding low risk				
Consiste	Consistency 0				Not applicable				
Directne	ess		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					
Publicati	ion bias		0		Unlikely				
Magnitu	Magnitude of effect 0				Not applicable				
Dose response gradient 0				Not applicable					
Plausible confounding 0					Not applicable				
Quality of evidence					$\oplus \oplus \ominus \ominus$ 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.