Evidence tables for cancer therapy-related cardiac dysfunction risk equivalence ratios for anthracycline and anthraquinone agents after childhood cancer treatment

Feijen et al.: Equivalence ratio for daunorubicin to doxorubicin in relation to late heart failure in survivors of childhood cancer. J Clin Oncol, 2015; 33(32):3774-3780				
Study design Treatment era Follow-up	Participants	Treatment	Main outcomes	Additional remarks Risk of bias
<u>Study design</u> Cohort study (EKZ/AMC, NWTS, CCSS, SJLIFE cohorts) <u>Treatment era</u> 1963-2002 (either treatment or diagnosis of primary cancer) <u>Follow-up</u> Median 17.3 years (range 5-35) after cohort entry	<u>Type and number of participants</u> Childhood cancer survivors (≥5 years after diagnosis); N=15851 <u>Diagnosis</u> - Acute lymphoblastic leukemia N=4561 (29.5%) - Other leukemia N=535 (3.5%) - Hodgkin lymphoma N=1978 (12.5%) - Other lymphoma N=1190 (7.5%) - Brain tumor N=1941 (12.3%) - Neuroblastoma N=966 (6.1%) - Kidney tumor N=1713 (10.8%) - Soft tissue sarcoma 1351 (8.5%) - Bone tumor N=1245 (7.9%) - Other malignant neoplasm N=335 (2.1%) <u>Age at cancer diagnosis</u> Median 6.7 years (range 0.0-24.8) <u>Age at follow-up</u> Median 30.5 years (range 5.6 to 40.0) <u>Gender</u> - Male N=8347 (52.8%) - Female N=7468 (47.2%)	<u>Chemotherapy</u> *Anthracyclines* **Doxorubicin** N=5144 (32.5%); median dose 255mg/m^2 (IQR 144-365) **Daunorubicin** N=2243 (14.2%); median dose 111mg/m^2 (IQR 91-271) **Epirubicin** N=135 (0.9%); median dose 300mg/m^2 (IQR 200-420) **Idarubicin** N=18 (0.1%); median dose 20mg/m^2 (IQR 11-36) *Anthraquinones* **Mitoxantrone** N=44 (0.3%); median dose 34.6mg/m^2 (IQR 12-50) N=742 (4.7%) were treated with more than one type of anthracycline <u>Radiotherapy involving the heart</u>	<u>Outcome definitions</u> Heart failure according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; grade 3-5 Cardiomyopathy cases restricted to those occurring after cohort entry and by 40 years of age EKZ/AMC and SJLIFE cohorts N=3044/15851 (19.2%) *'heart failure occurrence was ascertained by means of medical records, death certificates, and prospective clinical cardiac assessments.'* NWTS cohort N=364/15851 (2.3%) *'heart failure occurrence was ascertained by using medical records, if possible, which were supplemented with death certificates.'* CCSS cohort N=12407/15851 (78.4%) *'relied on patient and/or family self-reports, if corroborated by concurrent use of appropriate cardiac medications, that were supplemented by death certificates.'*	<u>Additional remarks</u> Cohort overlap with Feijen et al., 2019 *'If a survivor of childhood cancer developed a second malignant neoplasm before surviving for 5 years, the patient was excluded from the analysis (in the EKZ/AMC, NWTS, and SJLIFE cohorts) or the treatment was taken into account (in CCSS).'* *'To incorporate the NWTS data with other cohort data, members of the NWTS subcohort were weighted by the subcohort sampling probability'* <u>Risk of bias</u> *Selection bias* Unclear risk (the original cohort of survivors is not reported) *Attrition bias* Low risk (outcome assessed for whole study group) *Detection bias*

	<u>Controls</u> Not applicable <u>Cardiovascular risk factors</u> Not reported	Direct chest radiotherapy N=4044 (25.6%); median dose 30Gy (IQR 20-38) <u>Hematopoietic stem cell transplantation</u> Not reported	<u>Results</u> Patients with heart failure available for analysis N=375 Exclusions for heart failure analysis N=104 (N=48 second malignancy before heart failure, N=56 heart failure occurrence after age 40 years) Heart failure occurrences included in analysis N=271 - **Doxorubicin** N=185 (68.1%) - **Daunorubicin** N=18 (7.0%) - **Doxorubicin and daunorubicin** N=11 (4.0%) - Either **epirubicin or mitoxantrone with or without doxorubicin** N=4 (1.1%) - Only chest radiotherapy N=37 (13.7%) - No known potential cardiotoxic treatment N=16 (5.9%) Cumulative incidence of heart failure at the age of 40 years 3.2% (95% CI 2.8%-3.7%) <u>Multivariable analyses</u> *'Because of the limited number of individuals who received epirubicin, idarubicin, or mitoxantrone, we examined only the relationships for doxorubicin and daunorubicin.'* *'Adjusted for sex, age at diagnosis, chest radiotherapy dose, and exposure to another anthracycline besides doxorubicin or daunorubicin, such as epirubicin, idarubicin, or mitoxantrone. It was also stratified by cohort.'*	Unclear risk (blinding of outcome assessors to anthracycline or anthraquinone treatment not reported) *Confounding* Low risk (all important prognostic factors adequately taken into account)

			Daunorubicin: HR (95% CI), patient with no daunorubicin as referent - ≤0.1 to <200mg/m^2: 1.09 (0.57-2.08) - ≥200 to <300mg/m^2: 3.16 (1.16-8.61) - ≥300 to <400mg/m^2: 4.33 (1.73-10.84) - ≥400mg/m^2: 10.72 (5.13-22.42) **Doxorubicin**: HR (95% CI), patient with no doxorubicin as referent - ≤0.1 to <200mg/m^2: 2.80 (1.75-4.49) - ≥200 to <300mg/m^2: 6.31 (4.11-9.69) - ≥300 to <400mg/m^2: 13.19 (9.04-19.25) - ≥400mg/m^2: 18.43 (12.82-26.50) **Daunorubicin to doxorubicin ratio** (95% CI): - ≤0.1 to <200mg/m^2: 0.39 (0.04-0.78) - ≥200 to <300mg/m^2: 0.50 (0.00-1.12) - ≥300 to <400mg/m^2: 0.33 (0.03-0.62) - ≥400mg/m^2: 0.58 (0.09-1.12) Mean 0.45 (0.23-0.73) Linear dose response model: Risk = exp(ΣαX) [1 + 0.033 doxorubicin dose + 0.016 daunorubicin dose]. Akaike information criterion: 4398.6 *'no evidence of an interaction between chest radiotherapy and either doxorubicin (*P*=0.09) or daunorubicin (*P*=0.73)'* *'In our dose-response analysis, the linear, linear-spline, and linear-exponential models all seemed to have a*	

			better fit (ie, lower Akaike information criterion) than the log-linear model. Because these models had similar log-likelihood values according to the excess relative risk of heart failure, we estimated a daunorubicin-to-doxorubicin ratio of 0.49 (95% CI, 0.28 to 0.70) by using the simplest model (ie, linear). This result was similar to the ratios derived by using Cox models that were based on dose increments of 100 mg/m^2'	

CCSS, Childhood Cancer Survivor Study; EKZ/AMC, Emma Children's Hospital/Academic Medical Center cohort; NTWS, National Wilms Tumor Study; SJLIFE, St Jude Lifetime study

Feijen et al.: Derivation of anthracycline and anthraquinone equivalence ratios to doxorubicin for late-onset cardiotoxicity. JAMA Oncol, 2019; 5(6):864-871				
Study design Treatment era Follow-up	Participants	Treatment	Main outcomes	Additional remarks Risk of bias
<u>Study design</u> Cohort study (CCSS, DCOG-LATER, SJLIFE cohorts) <u>Treatment era</u> 1962-2005 (either treatment or diagnosis of primary cancer) <u>Follow-up</u> Median 20 years (range 5-40) after cancer diagnosis	<u>Type and number of participants</u> Childhood cancer survivors (≥5 years); N=28423 <u>Diagnosis</u> - Leukemia N=8740 (36.3%) - Lymphoma N=5477 (17.7%) - Brain tumor N=4843 (15.7%) - Neuroblastoma N=2023 (6.6%) - Kidney tumor N=2547 (8.3%) - Soft tissue sarcoma N=2006 (6.5%) - Bone tumor 2151 (7.0%) - Other malignant neoplasm 636 (2.1%) <u>Age at cancer diagnosis</u> Median 6.1 years (range 0-22.7) <u>Age at follow-up</u> Median 27.5 years (range 5.1-40.0) <u>Gender</u> - Male N=15208 (53.6%) - Female N=13215 (46.4%) <u>Controls</u> Not applicable <u>Cardiovascular risk factors</u> Not reported	<u>Chemotherapy</u> *Anthracyclines* **Doxorubicin** N=9330 (34.8%); median dose 181mg/m^2 (IQR 119-320) **Daunorubicin** N=4433 (18.0%); median dose 120mg/m^2 (IQR 99-208) **Epirubicin** N=300 (1.1%); median dose 300mg/m^2 (IQR 240-400) **Idarubicin** N=241 (1.1%); median dose 36mg/m^2 (IQR 20-40) *Anthraquinones* **Mitoxantrone** N=265 (0.9%); median dose 40mg/m^2 (IQR 26-72) N=1857 (7.4%) were treated with more than one type of anthracycline or anthraquinone N=87 (0.4%) were treated with more than two types of anthracycline or anthraquinone	<u>Outcome definitions</u> Heart failure according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03; grade 3-5 Cardiomyopathy cases restricted to those occurring after cohort entry and by 40 years of age CCSS cohort N=20367 *'relied on patient or family self-report if corroborated by concurrent use of appropriate cardiac medications, supplemented by death certificates'* DCOG-LATER and SJLIFE cohorts N=8056 *'ascertained cardiomyopathy using medical records, death certificates, and prospective clinical assessment'* <u>Results</u> Cardiomyopathy cases N=399/28423 (1.4%) - **Doxorubicin** N=229 (56.2%) - **Daunorubicin** N=65 - **Epirubicin** N=9 - **Idarubicin** N=5 - **Mitoxantrone** N=19 - Only chest radiotherapy N=45 - No known potential cardiotoxic treatment N=44	<u>Additional remarks</u> Cohort overlap with Feijen et al., 2015 *'If a childhood cancer survivor developed a subsequent cancer before achieving survival for 5 (CCSS and DCOG-LATER) or 10 (SJLIFE) years, the patients was either excluded from the analysis (DCOG-LATER) or the treatment was taken into account (CCSS and SJLIFE).'* *'Percentages may not match numbers because percentages reflect weighting used in the CCSS [subcohort] for patients with acute lymphoblastic leukemia; reported median values and IQR also reflect weighting'* <u>Risk of bias</u> *Selection bias* Unclear risk (the original cohort of survivors is not reported) *Attrition bias* Low risk (outcome assessed for whole study group) *Detection bias*

		<u>Radiotherapy involving the heart</u> Chest radiotherapy N=6240 (21.2%); median dose 25Gy (IQR 15-36) *'Chest fields included any abdominal fields that extended to the lower part of the chest (ie, above the diapraghm) and also fields that included the thorax (eg, shoulders, ribs or supraclavicular areas), even if the central chest was not a target.'* <u>Hematopoietic stem cell transplantation</u> Not reported	Cumulative incidence of grade 3 to 5 cardiomyopathy by 40 years of age 3.4% (95% CI 3.1%-3.8%) <u>Multivariable analyses</u> '*to facilitate comparability on the same therapeutically administered dose scale (in units of milligrams per square meter) as doxorubicin, we multiplied idarubicin and mitoxantrone doses by a factor of 5 and 4, respectively'* *'models were adjusted for sex, age at diagnosis, exposure to any other anthracycline or mitoxantrone besides the 2 being compared, and stratified by cohort'* *'patient without exposure to the given anthracycline or anthraquinone as referent'* **Daunorubicin**: HR (95% CI) - <150mg/m^2: 1.4 (0.9-2.1) - 150-299mg/m^2: 2.8 (1.7-4.5) - ≥300mg/m^2: 6.0 (3.8-9.3) **Doxorubicin**: HR (95% CI) - <150mg/m^2: 1.8 (1.2-2.6) - 150-299mg/m^2: 4.6 (3.3-6.4) - ≥300mg/m^2: 12.6 (9.8-16.3) **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)	Unclear risk (blinding of outcome assessors to anthracycline or anthraquinone treatment not reported) *Confounding* Low risk (all important prognostic factors adequately taken into account)

			Linear dose response model 0.5 (95% CI 0.4-0.7) Linear dose response model: Risk = exp(ΣαX) [1 + 0.02963 doxorubicin dose + 0.01571 daunorubicin dose] Akaike information criterion: 6098.8 Log-likelihood deviance: 6072.8 '*The performance of the linear and linear exponential dose-response models was fairly similar in terms of Akaike information criterion and log-likelihood values and appeared to be a better fit than the log-linear model.*' **Epirubicin**: HR (95% CI) - <150mg/m^2: 1.9 (0.3-13.7) - 150-299mg/m^2: 2.4 (0.6-9.9) - ≥300mg/m^2: 6.0 (2.6-13.9) **Doxorubicin**: HR (95% CI) - <150mg/m^2: 1.5 (0.99-2.2) - 150-299mg/m^2: 4.2 (3.1-5.7) - ≥300mg/m^2: 11.3 (8.8-14.4) **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) Linear dose response model: Risk = exp(ΣαX) [1 + 0.02203 doxorubicin dose + 0.01685 epirubicin dose]	

			Akaike information criterion: 6235.8 Log-likelihood deviance: 6209.8 '*The linear dose-response model performed better than the less parsimonious log-linear model, whereas the linear exponential model was not estimable.*' **Idarubicin**: HR (95% CI) - <150mg/m^2: 0 - 150-299mg/m^2: 3.8 (1.5-9.5) - ≥300mg/m^2: 0 **Doxorubicin**: HR (95% CI) - <150mg/m^2: 1.4 (0.9-2.1) - 150-299mg/m^2: 4.1 (3.0-5.7) - ≥300mg/m^2: 11.1 (8.6-14.1) **Idarubicin to doxorubicin ratio**: - <150mg/m^2: 0 - 150-299mg/m^2: 0.9 - ≥300mg/m^2: 0 Mean and linear dose response model not estimable **Mitoxantrone**: HR (95% CI) - <150mg/m^2: 4.2 (1.8-9.9) - 150-299mg/m^2: 4.2 (1.6-11.4) - ≥300mg/m^2: 48.3 (24.2-96.5) **Doxorubicin**: HR (95% CI) - <150mg/m^2: 1.5 (1.0-2.3) - 150-299mg/m^2: 4.4 (3.2-6.0) - ≥300mg/m^2: 11.6 (9.1-15.0) **Mitoxantrone to doxorubicin ratio**: - <150mg/m^2: 2.8 - 150-299mg/m^2: 1.0 - ≥300mg/m^2: 4.2	

			Mean 10.5 (95% CI 6.2-19.1) Linear dose response model: Risk = exp(ΣαX) [1 + 0.02313 doxorubicin dose + 0.07966 mitoxantrone dose] Akaike information criterion 6192.0 Log-likelihood deviance: 6166.0 '*Whereas the mitoxantrone to doxorubicin linear dose-response model suggested a ratio of 13.8 (95% CI, 8.0-21.6), there was evidence for nonlinearity beyond the dose category of 300mg/m^2 or more because the exponential term for both drugs was significant in an alternative linear exponential model (*P*<.05). However, even when the analysis was restricted to doxorubicin doses of less than 300mg/m^2 and mitoxantrone doses of less than 75mg/m^2, the linear dose-response ratio remained high albeit imprecise at 8.1 (95% CI, 0.5-16.1).*' *'no evidence of an interaction between chest radiotherapy and doxorubicin (*P*=0.39), daunorubicin (*P*=0.69) or mitoxantrone (*P*=0.97)'*	

CCSS, Childhood Cancer Survivor Study; DCOG-LATER, Dutch Children's Oncology Group's LATER study; SJLIFE, St Jude Lifetime study