Who needs surveillance?

1. What is the evidence behind the conversion score for different derivates for anthracyclines (including mitoxantrone)					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362)		<u>Conversion score:</u> Doxorubicin : 1.0 Daunorubicin: 1.0 Epirubicin: 0.67	Refs: Mertens (2008): late mortality Le Deley (2003): SMN after solid CA Perez (1991): Breast CA (epi vs.dox)
Mulrooney[2] 2009	Retrospective cohort 1970-1986 27.0 yrs (8-51)	5-yr Survivors (N=14, 358) Siblings (N=3899)		<u>Conversion score:</u> Doxorubicin = Daunorubicin Idarubicin = 3x doxorubicin	Conversion score based on a review paper recommendations (Pai Nahata 2000)
Blanco[3] 2012	Case-Control 1966-2008 Cases: 9.2 (0.1-35.1) Controls: 12.3 (0.4-40)	Case (CHF) – N=170 Control (none) – N=317		<u>Conversion score:</u> <u>COG LTFU Guidelines</u> Doxorubicin: 1.0 Doxorubicin: 1.0 Daunorubicin: 0.75 Daunorubicin: 0.83 Epirubicin: 0.75 Epirubicin: 0.67 Idarubicin: 3 Idarubicin: 5 Mitoxantrone: 3 Mitoxantrone: 4	Conversion score based on: Lehmann (2000), which is based on sited review literature with 1 in vivo model of acute toxicity
Temming[4] 2011	Retrospective cohort N=124, 86 1987-2004 7.3 yrs (0-21.7)	124/158 available for Cardiotox analysis 86 data for late cardiotox		AML 10 and 12 trials Anthracyclines: Dauno and Mitox (1:5 conversion) 550-610 mg/m2	Anthracycline dose range similar across AML 10 and 12, unable to assess dose-association No discussion on conversion factor
Creutzig[5] 2007	Retrospective cohort 1993-2003 BFM98: 3.6ys (0.8-7.0) BFM93: 7.5ys (1.1-11)	Eligible: N=1207 Late Cartox eval: N=547 (45%) 76% of echo w/in first 5yrs		AML BFM 93 98 Dauno : Ida 1:5 Dauno : Mitox 1:5	
van Dalen[6] 2010	Systematic review Meta-analysis 1966-2009 RCT's: children, adults	Different anthracycline derivatives	Dox Epi Lipo-Dox	Epi vs. Dox (5 RCTs) = 1036 pts R=0.36, NS Lipo- vs. Dox (2 RCTs) = 521 pts Clinical: RR=0.2 (0.02-0.75) Subclinical: RR=0.38 (0.24-0.59)	For *other* possible combinations of different anthracycline derivatives, only 1 RCT or no RCT was identified Inconclusive evidence for children

Le Deley[7] 2003	Case-control 1980-1999	Secondary leukemias after treatment of solid ca in childhood		Doxorubicin 50 mg/m2 = 75 mg/m2 epirubicin 60 mg/m2 dauno 12.5 mg/m2 mitox	Conversion based on leukemogenic potential of anthracyclines - NO ref for basis of anthracycline dose calculation
Neri[8] 1989	Observational ?Tx era: 1980's	Doxorubicin N=9 Epirubicin N=13 <u>Authors propose:</u> - Epi less concentrated in heart - Epi inhibits less of the Na/Ca exchange in heart sarcomeres - Epi produces less oxidative mitochondrial damage than dox	Dox 60 mg/m2 (Max 540) Vs. Epi 60 mg/m2 (Max 720)	Blood biomarker measurements, Echo's Epirubicin less CK-MB elevation VO2 changes: Dox vs. Epi: 44% vs. 13% reduction Incidence of CHF: Dox vs. Epi: 67% vs. 23% Conclusion: "Epi-related cardiotoxicity 40% less than that produced by doxorubicin.."	Small numbers, not controlled for risk factors, older treatment era Non-random assignment Breast CA, non-pediatric Acute cardiotoxicity

2. What is the risk of (a)symptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors of TBI that is above and beyond the risk due to pre-HCT anthracycline and chest radiation?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Uderzo[9] 2007	Prospective cohort 1994-1997 5 yrs.	N= 162, Age: 0-18 y.o. at HCT	Allogeneic HCT 67% anthracyclines 58% TBI 80% HCT for malignancy	Decline in FS over time <u>Univariate:</u> TBI alone, p=0.04 TBI + Anthracyclines, p=0.004 <u>Multivariate</u> No association with TBI and FS decline	In addition, no differences seen by gender or age at HCT. TBI fractionated (12Gy) in nearly all except 2.
Lonnerholm[10] 1999	Prospective cohort 1985-1996 1-10 years (median 5)	N= 45, Age: 1.2-16.2 at dx	Autologous HCT 53% TBI Pre-HCT anthr: 150-450	Standard echo: 1y-, 3y- and 5- post LVDD/SD, EF, FS No difference in LV dimensions by TBI No discussion of anthracycline dose and changes in LV parameters	
Eames[11] 1997	Cross-sectional 1994-1995 Mean f-up 4.1 yrs	N=63 Age: 2y-32 y at partic.	Allo HCT: 82% Auto HCT: 18% TBI: 65% HD-Cy: 95% Anth: 63.5% Anth dose: 308 (60-450)	Comprehensive cardiac echo: NYHA grading of all participants Normal FS (>=29%): 98% No regression analysis for risk factors for abn EF/FS TBI (fractionated or not) NOT predictive of cardiotoxicity	Selection bias 22% of HCT population included Treadmill exercise testing Abnormal: 48.4%
Armenian[12] 2011	Retrospective cohort 1970-1986 CCSS 1974-1998 BMTSS CCSS: 16 yrs (+/-5) BMTSS: 13 yrs (+/-5.6)	Heme malign <u>CCSS: N=7207</u> Age: 8.9 yrs at dx 25 yrs at partic. <u>BMTSS: N=145</u> Age: 10.9 yrs at dx 24 yrs at partic. <u>Sibling N=4020</u> Age: 26. yrs at partic.	<u>BMTSS</u> Chemo + TBI: 76.6% Autologous HCT: 28% Anthracycline: None - 8.3% 1-249 – 50.3% >=250 – 41.4% Chest Radiation: 5.5% <u>CCSS</u> Anthracycline: None – 61.0% 1-249 – 19.3% >=250 – 19.7% Chest radiation: 23.1%	CTCAE graded chronic health conditions <u>Grade 3-5 cardiac disease</u> Multivariate regression adjusting for: Age, gender, race, insurance, treatment era, time from dx, diagnosis, chest radiation, anthracycline dose BMTSS vs. siblings: RR 12.7 p<0.01 BMTSS vs. CCSS: RR 0.5, p=NS	After adjusting for pre-HCT treatment-related exposures, no differences in CV outcomes seen, Sub-analysis of specific HCT-related exposures (TBI, HD Cytoxan) did not reveal a difference

Armenian 2008[13]	Case-control 1981-2003 6.4 yrs (1.3-22.1)	1+year survivors Allo and auto HCT Case (CHF): 60 Control: 166 Age 43 yrs (+/- 13)	Mean Anthracycline: 261 vs. 171 mg/m2 Chest XRT: 10% vs. 8% TBI: 65.0% vs. 65.7% HD-Cy: 75.0% vs. 75.3%	Clinical CHF per AHA/ACC def. Anthracyclines as the only treatment-related predictor of post-HCT CHF. TBI, HD-Cy not significant in univariate or multivariate models.	Mostly adults, only included late-occurring events.
Armenian 2011[14]	Retrospective cohort Nested case-control 1988-2002 5.3 yrs (0.1-20.5 yrs)	Autologous HCT Cohort: N= 1244 CHF: N=88 peds + adults 7200 person-yrs	TBI (12 Gy Frax): 59.2% (60% vs. 59%) HD-CY: 85.9% (87% vs. 86%) Anthracycline mg/m2: 309 vs. 237, p<0.01	Clinical CHF per AHA/ACC def. <u>Multivariate Condit. regression:</u> Female: RR 2.4, p<0.01 Lymphoma dx: 1.5, p=0.05 Age: RR↑ wth age TBI, HD-Cy NOT associated with risk	Pre-HCT anthracycline dose, and post-HCT CV risk factors, gender, most significant predictors of post-HCT risk. CI of CHF 15% at 15 yrs in female lymphoma survivors.
Chow[15] 2011	Retrospective cohort 1985-2006	2+year survivors Allo and auto HCT N=1491 Gen pop (by age) matching N=4352	Autologous: 43.7% Allogeneic: 56.3% TBI: 76.7% HD-Cy: 48.1%	CV outcomes, ICD-9 coding, hospital records: MI, DCM, CHF, stroke, other vascular dz. <u>Multivariate regression Risk of DCM, CHF:</u> Post HCT relapse: RR 1.9 (1.1-3.3) TBI: RR 1.0 (0.6-1.8) Allo HCT: 0.8 (0.5-1.4)	No anthracycline in models Hosp ICD-9 codes, not validated outcomes Post-HCT CV risk factors as significant predictors of DCM or CHF.
Tichelli[16] 2008	Retrospective cohort 1990-1995 9 yrs (1-16 yrs)	1+-year survivors Allogeneic HCT Adult HCT N=548	Hem. Malign: 85% TBI: 58%	<u>Limited to clinically validated arterial events</u> TBI: 70% (arterial dz), 57% (no dz), NS Multivariate model: Older age at HCT and CVRFs as the only independent predictors of dz.	No anthracycline in models Post-HCT risk factors as predictors of post-HCT CV outcomes

3. What is the risk for different anthracycline doses for developing (a)symptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Clinical Cardiotoxity and anthracycline dose					
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362) Age at Dx: 5.9 (0-18)	Anthracyclines: 33.6% Cardiac XRT: 19.5% Anth+XRT: 7.9% Median Anth: 250 (25-775)	Symptomatic cardiac events (CE) Grading: CTCAE v 3.0 50 CEs in 42 CS (CHF in 27/50) Median time to event: 18.6 yrs <u>Multivariate regression (Model 1)</u> Anthracycline (per 100 mg/m2) HR 1.8 (1.5-2.3) <u>Multivariate regression (Model 2)</u> Anthracycline (Yes/No) vs. no cardiotoxic therapy HR 33.5 (4.4-254)	Clinically validated outcomes Long follow-up, large cohort
Blanco[3] 2012	Case-Control 1966-2008 Cases: 9.2 (0.1-35.1) Controls: 12.3 (0.4-40)	Case (CHF) – N=170 Control (none) – N=317 Matching criteria: Diagnosis Year of Dx (+/-5 yrs) Race/ethnicity Follow-up (controls)	<u>Cases vs. controls:</u> Anthracyclines 291 vs. 168, p<0.01 Chest XRT 25% vs. 14%, p<0.01	Clinically validated DCM, CHF <u>Multivariate (CHF):</u> Referent group – no anthracycline P for trend p<0.001; Odds Ratios 1-100: 1.65 101-150: 3.85 151-200: 3.69 201-250: 7.23 251-300: 23.5 >300: 27.6	Genetic susceptibility Matching based on diagnosis Differences in mean anthracycline dose between Ca-Co's
Temming[4] 2011	Retrospective cohort 1987-2004 7.3 yrs (0-21.7)	124/158 available for Cardiotox analysis 86 data for late cardiotox Age at Dx: 2.9 (0.1-12.9)	AML 10 and 12 trials Anthracyclines: Dauno and Mitox (1:5 conversion) 550-610 mg/m2	Subclinical cardiotox (SF<28%) Clinical CHF per AHA Anthracycline dose-relationship not determined	Not a very wide distribution of age due to Dx., likely reason for no anth-dose association
Armenian[14] 2011	Retrospective cohort Nested case-control 1988-2002 5.3 yrs (0.1-20.5 yrs)	Autologous HCT Cohort: N= 1244 CHF: N=88 peds + adults 7200 person-yrs Clinical CHF per AHA/ACC def.	<u>Regression:</u> Anthr Dose <150 (ref) 150-249: RR 3.5 250-349: RR 9.9, >349: RR 19.8, <0.01	<u>CV Risk factors and HD (≥250 Anth)</u> No HTN, No HD-Anth: Ref HTN, no HD-Anth: 3.5 (NS) HTN + HD Anth: 35.3, <0.01	No Diab, No HD-Anth: Ref Diab, no HD-Anth: 5.1, <0.01 Diab + HD Anth: 26.8, <0.01

Rathe[17] 2010	Prospective cohort 1986-2000 8.2 yrs (1.1-30.6)	1-yr survivors ALL N=116, 36 excluded Screening echo: At Diagnosis 2yrs after completion 5-year intervals	Median age at Dx: 4.0 yrs (0.8-13.4) Median age at f/up: 13.o yrs (2.0-30.5) Median anth dose: 250 mg/m2 (120-300)	1 patient with EF<55% None with clinical CHF Evidence of cardiac remodelling over time, but no symptoms. No association with gender, age.	Looking specifically at cardiotoxicity at lower doses of anthracyclines (<300)
Mulrooney[2] 2009	Retrospective cohort 1970-1986 27.0 yrs (8-51)	5-yr Survivors (N=14, 358) Age at Dx: 0-4 yrs: 40.1% 5-9 yrs: 22.3% 10-14 yrs: 20.3% 15-20 yrs: 17.3% Siblings (N=3899)	Anthracyclines: 33.1% No Cardiac XRT: 29% <5 Gy: 34% 5-15 Gy: 5.8% 15-35Gy: 9.7% >=35Gy: 6.9%	Self-reported CV outcomes Graded per CTCAE v. 3.0 CHF (N=248) – HR 5.9 (3.4-9.6) <u>Multivariate (CHF):</u> Anthracycline vs. none <250 mg/m2 – HR 2.4 (1.5-3.9) >=250 mg/m2 – HR 5.2 (3.6-7.4)	Self-reported Large sample size Long-term follow-up
Creutzig[5] 2007	Retrospective cohort 1993-2003 BFM98: 3.6ys (0.8-7.0) BFM93: 7.5ys (1.1-11) Median F/up late cartox: 5.3 (0.8-11.5)	Eligible: N=1207 Late Cartox evaluated: N=547 (45%) 76% of echo evaluations done within first 5yrs	AML BFM 93 and 98 Dauno : Ida – 1:5 Dauno : Mitox – 1:5 Anth dose: B 93: 300-400 mg/m2 B 98: 420-450 mg/m2	CI of late cardiotoxicity: 5% +/1 % (includes subset with early cardiotoxicity) No difference by randomization: Dauno vs. Ida <u>Cox Regression:</u> <u>Age, early crtox, FAB</u> Early cartox only predictor of late	Early and late cardiotoxicity. Study summary only presents data on *late* cardiotoxicity. Sig. #'s lost to follow-up Homogeneous pop: Age Anthracycline dose
van Dalen[18] 2006	Retrospective cohort 1976-2001 8.5 yrs (0.01-28.4) F/up on prev 2001 *JCO* study	830 Children treated with anthracyclines Age at Anth exposure: <2 - 9.2% 2-6 – 30.9% 7-11 – 27% 12-16 – 30.2% >16 – 2.7%	Anthracyclines: Mean – 288 (15-900) Chest XRT: 21.2% Mitoxantrone: Any 4.1%	CI and risk factors for A-CHF <u>Univariate (CHF):</u> Cumulative anthracycline ≥300 RR: 8.66 (2.01-37.35), p<0.01 <u>Multivariate (CHF):</u> Cumulative anthracycline ≥300 RR: 7.78 (1.76-34.27), p<0.01	Not limited to long-term survivors
Pein[19] 2004	Retrospective cohort 1968-1982 18 yrs	Original cohort: 447 218 (48.8%) not evaluated 229 (51.2%) echo's	Anthracycline: 344 mg/m2 (40-600) Radiotherapy: 245 (55%)	Cardiac abnormality: <u>Multivariate regression</u> Cardiac failure, FS<25, EF<50, or ESWS>100	High proportion with XRT exposure. Potential survival bias due to participation rate

		15+year survivors Age at treatment: 6.2 yrs (0-21)		Cumulative anthracycline: 1-150 (Ref) >150-250: RR 2.0 (0.44-9.5) >250-400: RR 4.0 (0.95-17) >400: RR 3.3 (0.78-14) P<0.001 (trend)	XRT included in regression model
Green[20] 2001	Retrospective cohort Case-Control Through 1998	NWTS 1-4 Cohort 1: 1-4 received dox N=2,843 Cohort 2: 1-3, dox as part of salvage only N=228	Anthracyclines Chest XRT – mostly due to lung XRT	CI and risk factors for CHF <u>Nested Case-Control Multivariate</u> Cumulative Doxorubicin: 1-199 mg/m2 (Referent) 200-299 mg/m2: 1.1 (0.3-5.1), NS ≥300 mg/m2: 6.0 (1.5-24), p=0.01	Homogeneous population due to diagnosis, the vast majority were exposed before 7 yo
Kremer[21] 2002	Review of Frequency and Risk Factors of anthracycline-induced *clinical* heart failure Medline search: 1966-2000	71 articles reviewed Limitations in many studies evaluated: Missing info Lack of RF analysis Non-rep. populations	Assess RR of possible Risk factors in 10 studies	<u>Univariate (CHF):</u> Risk with anthracycline dose in 5 out of 10 studies <u>Goorin (1981), N=382</u> ≤500 mg/m2 (Ref) >500 mg/m2: RR 4.8 (1.6-14) <u>Dearth (1984), N=112</u> ≤400 mg/m2 (Ref) >400 mg/m2: RR 26.1 (3.2-210) <u>Sallan (1984), N=379</u> Maximal dose/wk <45 mg/m2 (Ref) Maximal dose/wk ≥45 mg/m2 RR: 7.7 (2.1-28.1) <u>Godoy (1997), N=120</u> ≤300 mg/m2 (Ref) >300 mg/m2 – HR 1.5 (0.3-3.9), NS <u>Krischer (1997)</u> <500 mg/m2 (Ref) ≥500 mg/m2: RR 2.6 (1.1-6)	Multivariate regression showed type of anthracycline and maximal dose of anthracycline within 1 week were independent predictors of frequency of CHF.

Subclinical Cardiotoxicity and anthracycline dose (Abnormal EF, SF)					
Brouwer[22] 2011	Cross-sectional 1976-1999 17.7 years	5-yr survivors 401 eligible 277 (69%) participated 8 (3%) on cardiac meds for CHF/ renal	Anthracycline Median: 183 (50-600) Radiation 63%??	<u>Multivariate Logistic Regression SF<29%</u> Anthracycline ≥183 mg/m2: OR 2.2, 1.25-3.8, p<0.01 Mediast RT: 3.0, 1.4-6.7, p<0.01 TBI: 1.9, 0.6-5.6	Good participation rates Comprehensive echo screen Long term follow-up Handful with clinical HF included in analysis
van der Pal[23] 2010	Prospective cohort -Survivorship clinic 1966-1997 15.4 yrs (5.1-4.3)	5-yr survivors 735 anthracycline-treated 601 Eligible for study 525 Had echocardiogram Age at Dx: 8.9 (0.1-17.8)	Anthracycline: Med – 250 (33-720) Chest XRT: 36.4%	Asymptomatic cardiac dysf. Graded per CTCAE LVSF as primary outcome (1st echo) <u>Multivariate regression (SF<30%):</u> 1-150 mg/m2 (Ref) 151-300: OR 3.98 (1.58-10.01) 301-450: OR 7.77 (2.85-21.22) >450: OR 10.58 (3.35-33.40)	
Abosoudah[24] 2010	Prospective cohort -Survivorship clinic 1995-2003 3.0 yrs (1-10)	4-year survivors 896 anthracycline-treated 603 eligible for study 469 >=1 screening echo Age at Dx: 7.7 (SD 4.6)	Anthracycline: Mean – 205 (114.7) Chest XRT: 34%	Screening echo per COG LTFU Guidelines *Not limited to abn EF/FS* <u>Multivariate regression:</u> <200 mg/m2 (Ref) 200-300: HR 1.32 (0.61-2.85) >300: HR 3.0 (1.51-5.98)	Time to first abnormal echocardiogram Unclear for transients Screening frequency driven by age and *anthracycline dose*, so unclear implication
Hudson[25] 2007	Cross-sectional 9.0 (3.0-18.0)	223 anthracycline-treated Vs. 55 – not at risk Age at Dx: 5.5 (0-23.6)	Anthracycline (AR) Med: 202 (25-510) Chest XRT: 29% Anth + XRT: 26.9%	Screening echo. LVSF, Wall stress <u>Multivariate regression (SF<28%):</u> Anthracycline dose 50 unit increase: 1.19 (1.01-1.39)	Asymptomatic One time-point
Paulides[26] 2006	Prospective cohort 1992-2004 3 yrs (+/-1 yr)	LESS - sarcoma 1066 non-relapse cohort 564 excluded 502 eligible 265 with echo	Anthracycline: Mean – 290 +/-91 Chest XRT: 6.8%	Subclinical FS<29% x 2 Clinical CHF – per AHA 4/265 Clinical CHF 16/265 subclinical DCM	- Clinical and subclinical DCM - Low participation rate - Homogeneous cohort, similar age, so not as clear

		Age at tx: 13 +/5 yrs		No regression analyses	- Short follow-up - Similar to several other low-yield studies
Lipshultz[27] 2005	Prospective cohort DF consortium: 72 - 85-01 11.8 years	ALL survivors N=115 Serial echos N=499	Median anth: 352 mg/m2 (45-550)	Fig 2, dose-breakdown of FS Z-score: Clear delineation between <300 mg/m2, 300-400 mg/m2, >400	No multivariate regression analysis
Sorensen[28] 2003	Prospective cohort 1970-1990 6.2-6.7 years from Dx	ALL survivors – N=101 Age dx: 4.8 +/-2.7 Wilm;s – N=83 Age dx: 4.1 +/-2.3 2 Echo's mean 4 years apart.	Anthracycline: ALL – 180 +/-73 WT – 301 +/-78	Comprehensive echo. Intermediate indices + FS <u>Multivariate linear regression</u> FS timepoint 2: Dose x 100 mg: B -1.77 (-2.7, -0.9) Diff FS (time 1-2): Dose x 100 mg: B -1.48 (-2.4, -0.5)	Homogeneous populations: ALL and Wilm's Essentially comparing high dose vs. low-dose anthracycline with no heterogeneity in age
Kremer[29] 2002	Review of Frequency and Risk Factors of anthracycline-induced sub*clinical* cardiotoxicity Medline: 1966-2001 >50 children/study	58 articles reviewed Limitations in many: Missing info Non-rep. populations Non-original research Validity evaluated in 25 studies 10 studies with RF analyses 6 studies which defined an abnormal SF with validity score>5	<u>Risk Factor analysis:</u> Steinherz (1991) Lipshutz (1991) Silber (1993) Sorensen (1995) Lipshultz (1995) Pihkala (1996) Sorensen (1997) Nysom (1998) Lanzarini (2000) Bossi (2001)	4 Studies with anthracyline dose as predictor *(limited to FS or EF abn)* Risk Factor analysis: <u>Steinherz (1991) N=201:</u> Anth – median 450 (200-1275) >cumulative dose x f/up <u>Silber (1993) N=150:</u> Anth – mean 307 (50-750) >anthracycline dose <u>Lipshultz (1995) N=87:</u> Anth- median 390 (224-550) >dosage in w3 wks x diagnosis >cumulative dose <u>Nysom (1998) N=189:</u> Anth range 0-550 >cumulative dose	6 with validity score >5 Frequency of abnormal SF <300 mg/m2 (0-15.2%) >300 mg/m2 (15.5%-27.8%)

4. What is the risk for different cardiac RT doses for developing (a)symptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors?					
Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Clinical cardiotoxicity and radiation dose					
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362) Age at Dx: 5.9 (0-18)	Anthracyclines: 33.6% Anth+XRT: 7.9% Median Anth: 250 mg/m2 (25-775) Cardiac irradiation: None (80.4%) Any (19.5%) Localization of XRT: Thorax (31.6%) Abdomen (24.4%) Spine (33.5%) TBI (10.5%) Cardiac XRT (EQD2): Thorax: 24 (9.5-88.5) Abd: 26.9 (3.7-57) Spine: 30.14 (8-50) TBI: 15.8 (14-21.6)	Symptomatic cardiac events (CE) Grading: CTCAE v 3.0 50 CEs in 42 CS (CHF in 27/50) Median time to event: 18.6 yrs <u>CI of CHF:</u> Radiotherapy only: 0.7% at 30-yrs XRT + Anth: 7.9% at 30yrs <u>Multivariate regression (Model 1)</u> Radiotherapy (per 10 Gy) HR 1.4 (1.1-2.0) <u>Multivariate regression (Model 2)</u> Radiotherapy (Yes vs. No) HR 6.6 (0.6-73), p=0.13 Anth + Radiotherapy (Yes vs. No) HR 55.9 (6.6-470), p<0.001	Clinically validated outcomes Long follow-up, large cohort <u>XRT dose conversion:</u> Fractions of 2 Gy (EQD2) – includes both fractionation size and total dose <u>Model 2</u> removes mutually exclusive cardiotoxic treatments. Radiotherapy alone not significant for CHF, but is predictive of other cardiac events
Schellong[30] 2010	Prospective cohort 1978-1995 15.1 yrs (3.1-29.4)	Hodgkin lymphoma: All pts. treated on German HD-78 to HD90 studies XRT field/dose reduction Uniform anth. dose Age at Dx:12.8 (2.5-17.9) Cardiac screening	1132 eligible survivors Anthracyclines: 160mg/m2 *everyone* <u>Mediastinal XRT:</u> Median 25Gy (8-50) Mediast RT (MedRT) ≥36 Gy: 248 (21.9%)	Cardiac grading per ACC/AHA 50/1132 (4.4%) w/ cardiac dz <u>14/1132 (1.2%) w/myocardial dz.</u> 10/14 (71%) – MedRD-36 3/14 – MedRD20-30 <u>25-yr CI of non-valvular cards dz</u> ≥36 Gy: 4%, 30 Gy: 9%, 25 Gy: 4%, 20 Gy: 5%, None: 3%; p=0.2	Low prevalence/ incidence of myocardial disease likely due to low dose of anthracycline. Large study, long f/up, XRT is the only modified cardiotoxic exposure Unable to look at anth+XRT Non-valvular card dz includes CADz, valvular, conduction

		recs: Every 2-3 yrs up to 10 yrs Every 5 years thereafter In person +questionnaire	30 Gy: 133 (11.7%) 25 Gy: 282 (24.9%) 20 Gy: 171 (15.1%) None: 298 (26.3%)	Cox-regression: MedRD only predictor	Homogeneous patient pop (age)
Mulrooney[2] 2009	Retrospective cohort 1970-1986 27.0 yrs (8-51)	5-yr Survivors (N=14, 358) Age at Dx: 0-4 yrs: 40.1% 5-9 yrs: 22.3% 10-14 yrs: 20.3% 15-20 yrs: 17.3% Siblings (N=3899)	Anthracyclines: 33.1% No Cardiac XRT: 29% <5 Gy: 34% 5-15 Gy: 5.8% 15-35Gy: 9.7% >=35Gy: 6.9%	CV outcomes Graded per: CTCAE v. 3.0 CHF (N=248) – HR 5.9 (3.4-9.6) <u>Multivariate (CHF):</u> No cardiac radiation (Ref) <5 Gy: HR 0.9 (0.6-1.4) 5-15 Gy: HR 1.3 (0.7-2.5) 15-35Gy: HR 2.2 (1.4-3.5) ≥35Gy: HR (4.5 (2.8-7.2) Dose-dependent increase in cumulative incidence of CHF	Self-reported Large sample size Long-term follow-up Cardiac XRT dosimetry calculations (Stovall et al.) Significance emerges at 15-35Gy XRT data not mutually exclusive of anthracycline exposure.
Blanco[3] 2012	Case-Control 1966-2008	Case (CHF) – N=170 Control (none) – N=317 Matching criteria: Diagnosis Year of Dx (+/-5 yrs) Race/ethnicity Follow-up (controls)	<u>Cases vs. controls:</u> Anthracyclines 291 vs. 168, p<0.01 Chest XRT 25% vs. 14%, p<0.01	Clinically validated DCM, CHF Genetic susceptibility <u>Multivariate (CHF):</u> Chest radiation None (Ref) Any: OR 4.29 (1.9-9.6), p<0.001	Largest pop of clinically validated DCM, CHF XRT prevalence difference, but no info on dosimetry.
Aleman[31] 2007	Retrospective cohort 1965-1995 8.7 yrs (28 669 person-years for cohort)	5-year survivors of HL Age at treatment: <20 yo (21.3%) 20-35 yo (63.4%) >35 yo (15.3%) Age at f/up: <35 yo (16.6%) >55 yo (20.1%)	RT only 27.5% Chemo (CT) only 4.8% RT + CT, anth 29.5% RT + CT, no anth 38% Unknown 0.2% 17% recent smokers 10% HTN	Cumulative incidence of CHF 25y: No RT 0.4% Mediastinal RT only 6.8% Mediast RT + CT, no anth 4.9% Mediast RT + CT, anth 7.9% <u>Multivariate regression (CHF):</u> Model 2 Mediastinal RT only (Ref)	Large pop of adult lymphoma survivors (most <35 yo at Dx) Very long follow-up Critical role of cardiovascular risk factors Suggest that RT alone no inc. risk for CHF? Ref group is RT

			5% diabetes 8.5% Dyslipidemia	Med. RT + CT, no anthracycline: RR 1.3 (0.79-2.24) Med. RT + CT, anthracycline: RR 2.81 (1.44-5.49)	No dosimetry for cardiac XRT Includes older treatment era
van Dalen[18] 2006	Retrospective cohort 1976-2001 8.5 yrs (0.01-28.4) F/up on prev 2001 *JCO* study	830 Children treated with anthracyclines Age at Anth exposure: <2 - 9.2% 2-6 – 30.9% 7-11 – 27% 12-16 – 30.2% >16 – 2.7%	Anthracyclines: Mean – 288 (15-900) Chest XRT: Any 21.2% None 78.7% Unknown 0.1%	CI and risk factors for A-CHF <u>Univariate (CHF):</u> RT on heart: RR 0.67 (0.2-2.3), NS <u>Multivariate (CHF):</u> No association with chest RT reported.	Not limited to long-term survivors No XRT dosimetry reported
Guldner[32] 2006	Retrospective cohort Cross-sectional eval 1968-1985 5.4 yrs	447 eligible based on anthracycline exposure No XRT alone pop. 245 (N=55%) participated in study Age at Dx: 6.2 (0-21 yrs)	Anthracyclines: Median: 300 mg/m2 Entire cohort XRT heart dose: Mean 8.1 (15.6)	140 examined and healthy 24 with cardiac failure 65 with other cardiac disorders Heart radiation dose: Healthy vs. heart failure: 0.6 Gy vs. 17.8 Gy, p<0.001 Dose-dependent increase in HF risk by radiation dose	No XRT heart dosimetry, dosing estimated
Pein[19] 2004	Retrospective cohort 1968-1982 18 yrs	Original cohort: 447 218 (48.8%) not evaluated 229 (51.2%) echo's 15+year survivors Age at treatment: 6.2 yrs (0-21)	Anthracycline: 344 mg/m2 (40-600) Radiotherapy: 245 (55%) XRT dose to heart: Mean 6.7 Gy (0-91) Max 31.3 Gy (0-125)	Clear increase incidence w/time <u>Multivariate regression:</u> Cardiac failure, FS<25, EF<50, or ESWS>100 (not limited to CHF) Avg. XRT dose to heart, p<0.001 0 No XRT (Ref) >0-5 Gy: 1.63 (0.82-3.26) >5-20 Gy: 6.48 (2.76-15.20) >20 Gy: 4.40 (1.11-17.48)	High proportion treated with chest radiation Very long term follow-up One of the earlier studies to demonstrate dose-resposne with XRT
Adams[33] 2004	Cross-sectional 1970-1991 14.3 (5.9-27.5)	Hodgkin Lymphoma 24% participation rate Age at diagnosis:	Anthracycline: 4/48 (8.3%) Mediastinal XRT dose:	Comprehensive echo evaluation and stress testing No discussion of CHF	Very long-term follow-up One of few studies to evaluate XRT without anthracyclines

		Median 16.5 (6.3-25.0) Age at study visit: Median 31.9 (18-49)	Median 40 Gy (27-52)	Very few had systolic dysfunction Most with indices of diastolic dysfunction	Homogeneous population with not much variance in XRT dose Poor participation rate
Green[20] 2001	Retrospective cohort Case-Control Through 1998	NWTS 1-4 Cohort 1: 1-4 received dox N=2,843 Cohort 2: 1-3, dox as part of salvage only (N=228) Age at Dx: 80% <8 y.o.	Anthracyclines Chest XRT – mostly due to lung XRT	CI and risk factors for CHF Risk of CHF est. to increase by factor of 1.6 for every 10 Gy of lung XRT, 1.8 for every 10Gy of left abd. XRT (no effect for Right) <u>Multivariate regression (incl anth)</u> Lung XRT: None (Ref) 10-19.9 Gy: RR 1.5 (0.6-3.9), p-0.4 ≥20 Gy: 4.3 (0.8-24), p=0.1 L. Abd XRT: None or right (Ref) Left: RR 4.0 (1.4-11.6)	Homogeneous population due to diagnosis, the vast majority were exposed before 7 yo Results approach sig at high dose lung XRT
Van der Pal[34] 2005	Systematic review of risk of morbidity and mortality from cardiovascular disease for childhood cancer Lit Review: 1966-2002	Criteria for review: 1) Original report 2) English, Dutch, French, German 3) Study pop.: >50 pts. 4) Childhood CA: <=18 y. 5) XRT involving heart region 6) Outcome: Clinical cardiovascular event (CVE) or cardiovascular mortality	Many studies include arterial events (ie: MI) and CHF as CVE. <u>For CVE:</u> 9 studies selected based on validity and inclusion criteria. 8/9 studies, outcome well-defined 3/9 risk estimation well-defined and adequate	Relative Risk for CVE: Cardiac event, matched for anthracycline, time at risk, cohort <u>Continuous tx. Variables (RR):</u> Female/Male: 4.5, p<0.01 Anth, 100 mg/m2: 3.2, p<0.01 Lung RT, 10 Gy: 1.6, p=0.06 Left abd, 10 Gy: 1.8, p=0.02 Right abd. 10 Gy: 0.94, p=0.77 <u>Categorical tx. Variables (RR):</u> Female/Male: 3.7, p<0.01 Anth,>300 mg/m2: 5.0, p<0.02 Lung RT >20Gy: 3.1, p=0.21 Left abd. RT: 3.5, p=0.02	Older treatment eras For many, no clear delineation between RT-related systolic heart failure vs. CHF due to coronary artery disease, or MI alone. Dose-dependent Risk
Kremer[21] 2002	Review of Frequency and Risk Factors of <u>anthracycline-induced *clinical*</u> heart failure	71 articles reviewed Limitations in many: Missing info Lack of RF analysis Non-rep. populations	Assess RR of possible Risk factors in 10 studies	<u>Univariate (CHF):</u> Risk with XRT reported in 4 out of 10 studies (3 out of 4 significant) Gilladoga (1976) N=50	Review is driven by anthracycline exposure Few with XRT dose quantification and none with careful heart dosimetry

	Medline: 1966-2000			XRT to heart: RR 5.2 (1.6-16.8) Dearth (1984) N=116 XRT to heat: RR13.5 (3.4-53.3) Bu'Lock (1996) N=226 XRT to heart: 11.1 (3.7-33.5) Krischer (1997) N=6493 XRT to heart: RR 0.7 (0.3-1.9)	calculation
Subclinical cardiotoxicity and radiation (Abnormal EF, SF).					
Brouwer[22] 2011	Cross-sectional 1976-1999 17.7 years	5-yr survivors 401 eligible 277 (69%) participated 8 (3%) on cardiac meds for CHF/ renal	Anthracycline Median: 183 (50-600) Radiation 63%??	No breakdown by dose <u>Multivariate Logistic Regression SF<29%</u> Anthracycline ≥183: OR 2.2, 1.25-3.8, p<0.01 Mediast RT: 3.0, 1.4-6.7, p<0.01 TBI: 1.9, 0.6-5.6	Good participation rates Comprehensive echo screen Long term follow-up Handful with clinical HF included in analysis
van der Pal[23] 2010	Prospective cohort -Survivorship clinic 1966-1997 15.4 yrs (5.1-4.3)	5-yr survivors 735 anthracycline-treated 601 Eligible for study 525 Had echocardiogram Age at Dx: 8.9 (0.1-17.8)	Anthracycline: Med – 250 (33-720) Chest XRT: 36.4% Cumm. XRT dose: ≤30 Gy 10.8% >30 Gy 23.2%	Asymptomatic cardiac dysf. Graded per CTCAE LVSF as primary outcome (1st echo) <u>LVSF<30%</u> XRT ≤30 vs. >30 Gy: 12.5% vs. 31% <u>Multivariate regression (SF<30%):</u> No Radiotherapy (Ref) Odds Ratio Thorax: 3.49 (1.6-7.6) Abdomen: 2.66 (1.0-7.05) Spine: 0.64 (0.23-1.74) TBI: 0.53 (0.10-2.87)	

Abosoudah[24] 2011	Prospective cohort -Survivorship clinic 1995-2003 3.0 yrs (1-10)	4-year survivors 896 anthracycline-treated 603 eligible for study 469 >=1 screening echo Age at Dx: 7.7 (SD 4.6)	Anthracycline: Mean – 205 (114.7) Chest XRT: 34% No dose in model *Field involving heart*	Screening echo per COG LTFU Guidelines *Not limited to abn EF/FS* <u>Multivariate regression:</u> No radiation (Ref) RT to heart: HR 1.7 (1.1-2.8)	Time to first abnormal echocardiogram Screening frequency driven by age, anthracycline dose, and XRT so unclear implication
Hudson[25] 2007	Cross-sectional 9.0 (3.0-18.0)	223 anthracycline-treated Vs. 55 – not at risk Age at Dx: 5.5 (0-23.6)	Anthracycline (AR) Med: 202 (25-510) Anth + XRT: 26.9% Chest XRT: 2.7%	Screening echo. LVSF, Wall stress <u>Univariate regression (SF<28%):</u> No Cardiac RT (Ref) RT: OR 0.9 (0.4-2.05)	Asymptomatic One time-point No cardiac dose quantification
Kremer[29] 2002	Review of Frequency and Risk Factors of anthracycline-induced sub*clinical* cardiotoxicity Medline: 1966-2001 >50 children/study	58 articles reviewed Limitations in many: Missing info Non-rep. populations Non-original research <u>Validity evaluated in 25 studies</u> 10 studies w/RF analyses 6 studies which defined an abnormal SF with validity score>5	<u>Risk Factor analysis:</u> Steinherz (1991) Lipshutz (1991) Silber (1993) Sorensen (1995) Lipshultz (1995) Pihkala (1996) Sorensen (1997) Nysom (1998) Lanzarini (2000) Bossi (2001)	1 Study with chest radiation dose as predictor *(limited to FS or EF abn)* Risk Factor analysis: Steinherz (1991), N=201 >cumulative anth dose x f/up >mediastinal radiation No dose-effect calculations	Not all 10 studies had populations that would have received chest radiation (ie: ALL, AML)

5. What is the additional effect of age at treatment on developing (a)symptomatic cardiac systolic dysfunction					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Clinical cardiotoxicity and age					
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362) Age at Dx: 5.9 (0-18)	Anthracyclines: 33.6% Cardiac XRT: 19.5% Anth+XRT: 7.9% Median Anth: 250 (25-775)	Symptomatic cardiac events (CE) Grading: CTCAE v 3.0 50 CEs in 42 CS (CHF in 27/50) Median time to event: 18.6 yrs <u>Multivariate (CHF):</u> Age at Dx (per year): HR 0.98, NS	Clinically validated outcomes
Mulrooney[2] 2009	Retrospective cohort 1970-1986 27.0 yrs (8-51)	5-yr Survivors (N=14, 358) Age at Dx: 0-4 yrs: 40.1% 5-9 yrs: 22.3% 10-14 yrs: 20.3% 15-20 yrs: 17.3% Siblings (N=3899)	Anthracyclines: 33.1% No Cardiac XRT: 29% <5 Gy: 34% 5-15 Gy: 5.8% 15-35Gy: 9.7% >=35Gy: 6.9%	Self-reported CV outcomes Graded per CTCAE v. 3.0 CHF (N=248) – HR 5.9 (3.4-9.6) <u>Multivariate (CHF):</u> Age at Dx: 0-4 yrs – HR 3.9 (2.1-7.3) 5-9 yrs – HR 2.3 (1.3-4.0) 10-14 yrs – HR 1.2 (0.8-1.9) 15-20 yrs – Ref	Self-reported Large sample size Long-term follow-up
Blanco[3] 2012	Case-Control 1966-2008 Cases: 9.2 (0.1-35.1) Controls: 12.3 (0.4-40)	Case (CHF) – N=170 Control (none) – N=317 Matching criteria: Diagnosis Year of Dx (+/-5 yrs) Race/ethnicity Follow-up (controls)	<u>Cases vs. controls:</u> Anthracyclines 291 vs. 168, p<0.01 Chest XRT 25% vs. 14%, p<0.01	Clinically validated DCM, CHF Genetic susceptibility <u>Multivariate (CHF):</u> Age at dx (per year): 0.99, NS	Largest pop of clinically validated DCM, CHF Ca-Co matched on diagnosis, by default would have also matched on Age at diagnosis (exposure)

Temming[4] 2011	Retrospective cohort 1987-2004 7.3 yrs (0-21.7)	124/158 available for Cardiotox analysis 86 data for late cardiotox Age at Dx: 2.9 (0.1-12.9)	AML 10 and 12 trials Anthracyclines: Dauno and Mitox (1:5 conversion) 550-610 mg/m2	Subclinical cardiotox (SF<28%) Clinical CHF per AHA <u>Multivariate (CHF):</u> Age <4 yrs: 0.76 (0.20-2.94) Age >=4 (Ref)	Not a very wide distribution of age due to Dx.
Creutzig[5] 2007	Retrospective cohort 1993-2003 BFM98: 3.6ys (0.8-7.0) BFM93: 7.5ys (1.1-11) Median F/up late cartox: 5.3 (0.8-11.5)	Eligible: N=1207 Late Cartox evaluated: N=547 (45%) 76% of echo evaluations done within first 5yrs Age at diagnosis not provided, all <18 y.o.	AML BFM 93 and 98 Dauno : Ida – 1:5 Dauno : Mitox – 1:5 Anth dose: B 93: 300-400 mg/m2 B 98: 420-450 mg/m2	CI of late cardiotoxicity: 5% +/1 % (includes subset with early cardiotoxicity) No difference by randomization: Dauno vs. Ida <u>Cox Regression:</u> <u>Age, early cartox, FAB</u> Early cartox only predictor of late	Early and late cardiotoxicity. Study summary only presents data on *late* cardiotoxicity. Sig. #'s lost to follow-up Homogeneous pop: Age, Anthracycline dose ??Role of HCT
van Dalen[18] 2006	Retrospective cohort 1976-2001 8.5 yrs (0.01-28.4) F/up on prev 2001 *JCO* study	830 Children treated with anthracyclines Age at Anth exposure: <2 - 9.2% 2-6 – 30.9% 7-11 – 27% 12-16 – 30.2% >16 – 2.7%	Anthracyclines: Mean –288 (15-900) Chest XRT: 21.2% Mitoxantrone: Any 4.1%	CI and risk factors for A-CHF <u>Univariate (CHF):</u> Age <=2 yrs = RR 0.28 (0.04-2.1) <u>Multivariate (CHF):</u> No association with age	Not limited to long-term survivors
Pein[19] 2004	Retrospective cohort 1968-1982 18 yrs	Original cohort: 447 218 (48.8%) not evaluated 229 (51.2%) echo's 15+year survivors Age at treatment: 6.2 yrs (0-21)	Anthracycline: 344 mg/m2 (40-600) Radiotherapy: 245 (55%)	Clear increase CHD incidence over time <u>Univariate regression:</u> Cardiac failure, FS<25, EF<50, or ESWS>100 (not limited to clinical CHF) >=8 yrs (Ref) 0-7 years: RR 2.63 (0.87-7.96) P-Value 0.08??	High proportion treated with chest radiation Very long term follow-up No mention if age was significant in multivariate regression model
Green[20] 2001	Retrospective cohort Case-Control Through 1998	NWTS 1-4 Cohort 1: 1-4 received dox N=2,843 Cohort 2: 1-3, dox as part of salvage only (N=228) Age at Dx: 80% <8 y.o.	Anthracyclines Chest XRT – mostly due to lung XRT	CI and risk factors for CHF Age not included in multivariate model	Homogeneous population due to diagnosis, the vast majority were exposed before 7 yo

Kremer[21] 2002	Review of Frequency and Risk Factors of anthracycline-induced *clinical* heart failure Medline: 1966-2000	71 articles reviewed Limitations in many: Missing info Lack of RF analysis Non-rep. populations	Assess RR of possible Risk factors in 10 studies	1 out of 10 studies: Age <4 years as predictor of CHF Godoy (1997), N=69 RR = 11.7 (1.4-96.4)	Unclear If lack of association with age in the other 9 studies b/c age not evaluated or non-significant.
Subclinical cardiotoxicity and age (Abnormal EF, SF)					
van der Pal [23]2010	Prospective cohort -Survivorship clinic 1966-1997 15.4 yrs (5.1-4.3)	5-yr survivors 735 anthracycline-treated 601 Eligible for study 525 Had echocardiogram Age at Dx: 8.9 (0.1-17.8)	Anthracycline: Med – 250 (33-720) Chest XRT: 36.4%	Asymptomatic cardiac dysf. Graded per CTCAE LVSF as primary outcome (1st echo) <u>Multivariate regression (SF<30%):</u> Age at dx 0-5yr – OR 2.94 (1.08-8.02) >5-10 – OR 1.64 (0.67-4.01) >10-15 – (0.64-3.28) >15 – Ref	
Abosoudah[24] 2010	Prospective cohort -Survivorship clinic 1995-2003 3.0 yrs (1-10)	4-year survivors 896 anthracycline-treated 603 eligible for study 469 >=1 screening echo Age at Dx: 7.7 (SD 4.6)	Anthracycline: Mean – 205 (114.7) Chest XRT: 34%	Screening echo per COG LTFU Guidelines *Not limited to abn EF/FS* <u>Multivariate regression:</u> Age at tx: 1-4 yrs – 1.89 (1.1-3.3); Ref >=5	Time to first abnormal echocardiogram Unclear for transients Screening frequency driven by age, so unclear implication
Hudson[25] 2007	Cross-sectional 9.0 (3.0-18.0)	223 anthracycline-treated Vs. 55 – not at risk Age at Dx: 5.5 (0-23.6)	Anthracycline (AR) Med: 202 (25-510) Chest XRT: 29% Anth + XRT: 26.9%	Screening echo. LVSF, Wall stress <u>Multivariate regression (SF<28%):</u> Age at dx >=5 yrs – OR 2.41 (0.9-6.4), p0.08 <5 Ref	Asymptomatic One time-point
Paulides[26] 2006	Prospective cohort 1992-2004 3 yrs (+/-1 yr)	LESS - sarcoma 1066 non-relapse cohort 564 excluded (addt'l anth) Age at tx: 13 +/5 yrs	Anthracycline: Mean – 290 +/-91 Chest XRT: 6.8%	Subclinical FS<29% x 2 Clinical CHF – per AHA 4/265 Clinical CHF 16/265 subclinical DCM No regression analyses	Clinical and subclinical DCM Homogeneous cohort, similar age, so not as clear Short follow-up

Sorensen[28] 2003	Prospective cohort 1970-1990 6.2-6.7 years from Dx	ALL survivors – N=101 Age dx: 4.8 +/-2.7 Wilm;s – N=83 Age dx: 4.1 +/-2.3 2 Echo's mean 4 years apart.	Anthracycline: ALL – 180 +/-73 WT – 301 +/-78	Comprehensive echo. Intermediate indices + FS <u>Multivariate linear regression</u> FS at second timepoint (FS2) Age (yrs): -0.09 (-0.35, +0.16) Difference in FS over time Age (yrs): +0.18 (-0.09, +0.45)	Homogeneous populations: ALL and Wilm's Essentially comparing high dose vs. low-dose anthracycline with no heterogeneity in age
Kremer[29] 2002	Review of Frequency and Risk Factors of anthracycline-induced sub*clinical* cardiotoxicity Medline: 1966-2001 >50 children/study	58 articles reviewed Limitations in many: Missing info Non-rep. populations Non-original research Validity evaluated in 25 studies RF analyses in 10	Steinherz (1991) Lipshutz (1991) Silber (1993) Sorensen (1995) Lipshultz (1995) Pihkala (1996) Sorensen (1997) Nysom (1998) Lanzarini (2000) Bossi (2001)	<u>Studies with age as predictor</u> (limited to FS or EF abn) Silber 1993 - <age at tx Lipshultz 1995 - <age at dx Sorensen 1997 - >age at tx	Several studies with associations with age and other indices (ie: ESWS, SVI, wall thickness)

6. What is the risk of (a)symptomatic cardiac dysfunction in childhood and young adult cancer survivors treated with mitoxantrone?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Temming[4] 2011	Retrospective cohort N=124, 86 1987-2004 7.3 yrs (0-21.7)	124/158 available for Cardiotox analysis 86 data for late cardiotox Age at Dx: 2.9 (0.1-12.9)	AML 10 and 12 trials Anthracyclines: Dauno and Mitox (1:5 conversion) 550-610 mg/m2 Amsacrine 100 mg/m2 in AML 10/12	Late cardiotoxicity prevalence: 17.4% (10.9-26.8%) Non-relapse pts: 4.5% (1.5-12%) Time to CHF: 1.75 yrs (0.6-8.3) Unclear role of potentiating cardiotoxicity amsacrine Regression analysis does not include Mitox dose comparison	Not a very wide distribution of age due to Dx. Anthracycline dose range similar across AML 10 and 12, unable to assess dose-association
O'Brien[35] 2008	Prospective Cohort Down synd.: N=57 Vs. Non DS: N=565 1995-1999 Long-term f/up not clear (chart review)	Down syndrome 42% with CHDz Age at Dx <2y: 67% AML M7: 79% Daunorubicin 135 mg/m2 Mitox 80 mg/m2 Cumulative: 535 mg/m2 *5:1 conversion Mitox:Dauno* Study echo reqmt's while on study and at end of therapy	POG 9421 No Mitox randomization	Symptomatic CHF 10/57: 17.5% *Includes during and after tx* 5/10 with CHF had hx of CHDz 9/10 with sx's during therapy Anecdotal report of CHF 1.1% in non-DS cohort (not validated) <u>Historic DS studies:</u> POG 8821 (dauno 135 mg/m2): 5/34 – 15% CCG 2891 (dauno 350 mg/m2): 1% (vs. 2% without DS) BFM-93-98 (220-240 mg/m2) 2.7% early, 4% late CHF	Small numbers Disproportionate number with CHDz Nearly all events occurred while on tx Long-term follow-up for cardiac outcomes not complete Non DS population with low prevalence of CHF (Host vs. treatment vs. study methodology) Suggestion of high Cardiotox but likely due to combination of factors
Aviles[36] 2005	Randomized clinical trial ABVD (N=191) vs. EBVD (N=182) vs. MBVD (N=103) 1988-1996 11.5 yrs (7.5-14.8)	Hodgkin lymphoma III-IV Adults-onset Median age: 38.5-40.1 yrs. MBVD arm closed early due to low efficacy	A-Doxorubicin (400 mg/m2) E-Epirubicin (560 mg/m2) M-Mitoxantrone (160 mg/m2) No chest XRT	Clinical CHF and subclinical dz Clinical CHF: Mitox (17%), Epi (6%), Dox (9%) SMR for clinical cardiac event: Mitox: 67.8 (39.8-89.4) Epi: 19.4 (11.6-36.8) Dox: 46.4 (28.9-70.1)	Adult data, Stages III-IV HL 33-38% smokers Long term follow-up Unbalanced accrual due to early Mitox arm closure No multivariate regression Groups similar in characteristics

van Dalen[37] 2004	Systematic Review 17 studies included - 15 prospective - 2 retrospective 1960-2002	Krischer (1997) only study to assess risk factors - no inclusion of cum. Anthracycline dose - absence of CI reporting - non-standardized definitions for outcome - no risk factor, regression, analyses	*CI and risk factors for mitoxantrone-induced cardiotoxicity in children* Sympt. Cardiotox (16/17 articles): 0-6.7% (7/16 no symptomatic CHF) Asympt. Cardiotox (11/17 articles) 0-80% (2/11 no Cardiotox) <u>Risk Factor (Krischer):</u> Univariate analysis: Mitox >40 mg/m2 (RR 5.08, p<0.05) Multivariate analysis: Non-sig	Children treated with Mitox at risk, but difficult to quantify CI and risk factors due to methodologic limitations of studies. Difficult to find attribution to Mitox alone due to mixed use
Smith[38] 2010	Systematic Review and meta-analysis 55 RCTs Majority women with advanced breast CA 1988-2008	15 studies comparing anthracycline vs. Mitox - advanced breast ca, multiple myeloma, NHL, Hodgkin lymphoma	Meta-analysis: Clinical cardiotoxicity Mitoxantrone: OR 2.88 (1.29-6.44, p=0.01) Subclinical cardiotoxicity: OR 1.09 (0.74-1.61, p=0.67)	?Conversion scores of meta-analyses Adult population

7. What is the additional effect of radiotherapy on developing (a)symptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors treated with anthracyclines?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362) Age at Dx: 5.9 (0-18)	Anthracyclines: 33.6% Anth+XRT: 7.9% Median Anth: 250 mg/m2 (25-775) Cardiac irradiation: None (80.4%) Any (19.5%) Localization of XRT: Thorax (31.6%) Abdomen (24.4%) Spine (33.5%) TBI (10.5%) Cardiac XRT (EQD2): Thorax: 24 (9.5-88.5) Abd: 26.9 (3.7-57) Spine: 30.14 (8-50) TBI: 15.8 (14-21.6)	Symptomatic cardiac events (CE) Grading: CTCAE v 3.0 50 CEs in 42 CS (CHF in 27/50) Median time to event: 18.6 yrs <u>CI of CHF:</u> Radiotherapy only: 0.7% at 30-yrs **XRT + Anth: 7.9% at 30yrs** <u>Multivariate regression (Model 1)</u> Radiotherapy (per 10 Gy) HR 1.4 (1.1-2.0) <u>Multivariate regression (Model 2)</u> Radiotherapy (Yes vs. No) HR 6.6 (0.6-73), p=0.13 **Anth + Radiotherapy (Yes vs. No)** **HR 55.9 (6.6-470), p<0.001**	Clinically validated outcomes Long follow-up, large cohort <u>XRT dose conversion:</u> Fractions of 2 Gy (EQD2) – includes both fractionation size and total dose <u>Model 2</u> removes mutually exclusive cardiotoxic treatments. Radiotherapy alone not significant for CHF, but is predictive of other cardiac events
Aleman[31] 2007	Retrospective cohort 1965-1995 8.7 yrs (28 669 person-years for cohort)	5-year survivors of HL Age at treatment: <20 yo (21.3%) 20-35 yo (63.4%) >35 yo (15.3%) Age at f/up: <35 yo (16.6%) >55 yo (20.1%)	RT only 27.5% Chemo (CT) only 4.8% RT + CT, anth 29.5% RT + CT, no anth 38% Unknown 0.2% 17% recent smokers 10% HTN 5% diabetes 8.5% Dyslipidemia	Cumulative incidence of CHF 25y: No RT 0.4% Mediastinal RT only 6.8% Mediast RT + CT, no anth 4.9% **Mediast RT + CT, anth 7.9%** <u>Multivariate regression (CHF):</u> Model 2 Mediastinal RT only (Ref) Med. RT + CT, no anthracycline: RR 1.3 (0.79-2.24) **Med. RT + CT, anthracycline:** **RR 2.81 (1.44-5.49)**	Large pop of adult lymphoma survivors (most <35 yo at Dx) Very long follow-up Critical role of cardiovascular risk factors Suggest that RT alone no inc. risk for CHF? Ref group is RT Includes older treatment era

Pein[19] 2004 *Br J Ca*	Retrospective cohort 1968-1982 18 yrs	Original cohort: 447 218 (48.8%) not evaluated 229 (51.2%) echo's 15+year survivors Age at treatment: 6.2 yrs (0-21)	Anthracycline: 344 mg/m2 (40-600) Radiotherapy: 245 (55%) XRT dose to heart: Mean 6.7 Gy (0-91) Max 31.3 Gy (0-125)	Clear increase incidence w/time <u>Multivariate regression:</u> Cardiac failure, FS<25, EF<50, or ESWS>100 (not limited to CHF) **<250 mg/m2 Dox** <5Gy to the heart (Ref) ≥5 Gy: RR 4.9 (1.3-18) **≥250 mg/m2 Dox** <5Gy + <250 anth (Ref) <5Gy: RR 5.1 (1.8-14.5) ≥5 Gy: RR 6.6 (2.1-20.6)	High proportion treated with chest radiation Very long term follow-up One of the earlier studies to demonstrate dose-response with XRT Potential interaction with anthracycline, with highest risk among those exposed to HD-anth and XRT

What surveillance modality should be used?

1. What is the diagnostic value (i.e. sensitivity, specificity and/or inter-observer variability) of radionuclide angiography as compared to echocardiography (or vice versa) for screening of asymptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Addt'l remarks**
Postma[39] 1996	Single-center cohort study (the Netherlands). Treatment era: 1977-1990*. Years of follow-up since last doxorubicin dose: mean 8.7 years~ (range 2.3-14.1).	22 long-term survivors of a malignant bone tumour. 17 men/5 women; mean age at diagnosis tumour 15.8 years~ (range 10-21.3). Treatment based on Rosen's T5 and T10 protocols: doxorubicin median cumulative dose 360 mg/m² (range 225-550); cyclophosphamide median cumulative dose 4800 mg/m² (range 500-9600); no mediastinal irradiation*.	Two-dimensional M-mode and colour Doppler echocardiography (single observer to exclude interobserver variability); an abnormal test result was defined as LVSF<0.29 (n=6; prevalence 27.3%). Equilibrium gated radionuclide angiography (LVEF was calculated with a semi-automatic software program); an abnormal test result was defined as LVEF<55% (n=2; prevalence 9.1%). Time between tests: nm.	When the echocardiographic result is used as the reference standard^: Sensitivity: 16.7% (95% CI 0.9 to 32.4) Specificity: 93.8% (95% CI 87.8 to 99.7) Positive predictive value: 50% (95% CI 2.7 to 97.3) Negative predictive value: 75% (95% CI 70.3 to 79.7) Agreement between tests (i.e. either both abnormal or both normal): 16/22 (72.7%).	At time of testing clinical symptoms (fatigue and/or palpitations) were mentioned by 6 patients, of which 1 had physical signs of congestive heart failure*. Selection bias cannot be ruled out (31 out of 37 (84%) consecutive patients still alive at the time of this study: 3 lost to follow-up, 2 refused participation and 1 excluded because of pregnancy*). The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 22 patients had both tests.
Pihkala[40] 1994	Single-center cohort study (Finland). Treatment era: November 1974 through January 1992. Years of follow-up after transplant: Median 4.8 years (range 0.5 to 10.7).	30 bone marrow transplant survivors (20 allogeneic, 9 autologous and 1 peripheral blood stem cells) for ALL (n=9), AML (n=7), neuroblastoma (n=8), retinoblastoma (n=1) or aplastic anaemia (n=5).	Two-dimensional M-mode echocardiography (number of observers nm); an abnormal test result was defined contractility <-2SD (SD according to Colan) (n=4; prevalence 14.8%). ECG-gated radionuclide	When the echocardiographic result is used as the reference standard^: Sensitivity: 0% (95% CI 0.00 to 55.8) Specificity: 69.6% (95% CI 69.6 to 79.3) Positive predictive value: 0% (95% CI 0.00 to 31.9) Negative predictive value:	At time of testing none of the patients had symptomatic cardiac disease. Selection bias cannot be ruled out (30 out of 41 (73%) consecutive patients still alive at the time of this study: reasons for not participating nm). The risk of detection bias is

		15 men/15 women; mean age at transplant 8.1 years~ (range 1.1 to 16.4); median age at time of study 9 years (range 1 to 25). Treatment: High-dose therapy preparative for transplant: cyclophosphamide (n=4); cyclophosphamide and TBI (n=12); ara-C and TBI (n=3); ara-C, VP-16 and TBI (n=2); VP-16, cisplatin, melphalan and TBI (n=9). Mean TBI dose 1097CGy~ (range 970 to 1200); mean number of fractions 4.46 (range 1 to 6). Previous anthracyclines (n=25): cumulative dose unclear.	cineangiography (number of observers nm); an abnormal test result was defined as LVEF<50% (n=7; prevalence 25.9%). Time between tests: nm.	80% (95% CI 80.0 to 91.2) Agreement between tests (i.e. either both abnormal or both normal): 16/27 (59.3%).	unclear; nm if outcome assessors were blinded. Outcome/attrition bias cannot be ruled out (for 3 out of 30 participants (10%) no radionuclide cineangiography results were available).

LVSF: left ventricular shortening fraction; LVEF: left ventricular ejection fraction; nm: not mentioned; CI: confidence interval; N: number; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; TBI: total body irradiation

≠ In this study not only 22 childhood and young adult cancer survivors (i.e. tumor diagnosis ≤21 years) were included, but also 9 adult cancer survivors (i.e. tumor diagnosis ≥22 years). In this table only data for the childhood and young adult cancer survivors is included, unless otherwise stated.

* For all 31 patients combined.

^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard.

~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html).

[1] In the text of the article it was stated that the median cumulative dose was 140 mg/m² (range 90 to 450), while in the table the range was 60 to 400 mg/m² (median nm, mean 167 mg/m²~).

2. What is the diagnostic value (i.e. sensitivity and/or specificity) of biomarker ANP, BNP, NT-pro-BNP, troponin-T, and troponin-I to detect asymptomatic cardiac systolic dysfunction as measured by echocardiography in childhood and adult cancer survivors?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Addt'l remarks**
Krawczuk-Rybak[41] 2011	Single-center cohort study (Poland). Treatment era: Nm. Years of follow-up after treatment completion: mean 5.91 years (range 1.6 to 13.8).	44 childhood cancer survivors treated with anthracyclines (doxorubicin, daunorubicin) for ALL (n=37) or Hodgkin lymphoma (n=7). 30 males/ 14 females; mean age at diagnosis nm; mean age at study 14.7 years (range 6 to 23). Treatment: Cumulative anthracycline dose for ALL 180 to 540 mg/m²; for Hodgkin lymphoma 120 to 240 mg/m²; patients with Hodgkin lymphoma received 15 Gy of radiotherapy to the upper mediastinum (no information on number of fractions).	Doppler and colour flow visualization echocardiography; M-mode for heart structures and Teicholz method for contractility and LVEF (number of observers nm); an abnormal test result was defined as indexed stroke volume < 40 ml/m² (n=16; prevalence 36.4%). NT-pro-BNP; an abnormal test result was defined as > 115 ng/ml (n=6; prevalence 13.6%). Time between tests: nm.	When the echocardiographic result is used as the reference standard^: Sensitivity: 12.5% (95% CI 2.3 to 27.9) Specificity: 85.7% (95% CI 79.9 to 94.5) Positive predictive value: 33.3% (95% CI 6.1 to 74.4) Negative predictive value: 63.2% (95% CI 58.9 to 69.6) Agreement between tests (i.e. either both abnormal or both normal): 26/44 (59.1%).	Patients had no history of heart disease and no signs of cardiac failure. The risk of selection bias is unclear: not stated if all eligible patients or a random sample thereof were included. The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 44 patients had both tests.
Brouwer[22] 2011	Single-center cross-sectional study (the Netherlands). Treatment era: between 1976 and 1999; current tests between August 2004 and April 2007. Years of follow-up post-treatment: median 18.2 years	277 childhood cancer survivors ≥ 18 years treated with potential cardiotoxic therapy (i.e. anthracyclines, platinum analogues or radiotherapy on mediastinum (including mantle field, spine or total body) for leukemia (n=113), malignant lymphoma (n=56), sarcoma	2D echocardiography, colour flow mapping 2D guided M-mode blood pool and tissue velocity imaging (performed by a single skilled technician masked to treatment versus control group to exclude interobserver variability); an abnormal test result was defined as LVSF <	When the echocardiographic result of the LVSF is used as the reference standard^: Sensitivity: 16.5% (95% CI 10.9 to 22.1) Specificity: 90.3% (95% CI 87.0 to 93.6) Positive predictive value: 50% (95% CI 33.1 to 66.8) Negative predictive value:	Patients with current treatment for a relapse or secondary malignant disease or with mental incapacity were excluded. At time of study 263 out of 274 patients had NYHA class I and 11 out of 274 NYHA class II; for 3 patients no data mentioned. 17 out of 275 patients used

	(range 5.4 to 30.8).	(n=48), brain tumor (n=32), nephro/neuroblastoma (n=23) or germ cell tumor (n=5) and surviving at least 5 years after diagnosis. 155 males/122 females; median age at diagnosis 8.8 years (range 0 to 20.1); median age at cardiac evaluation 27.5 years (range 18.1 to 48.2). Treatment: Median cumulative anthracycline dose (doxorubicin, daunorubicin) 183 mg/m² (range 50-600); median dose of mediastinal radiotherapy 25 Gy (no information on number of fractions); no further information on treatment doses provided; all patients received anthracyclines, platinum analogues or radiotherapy as described above.	29% (n=97; prevalence 37%) or WMSI > 1.00 (n=38; prevalence 14.5%). NT-pro-BNP; an abnormal test result was defined as > 125 ng/ml (n=32; prevalence 12.2%). Time between tests: nm.	64.8% (95% CI 62.4 to 67.1) Agreement between tests (i.e. either both abnormal or both normal): 165/262 (63.0%). When the echocardiographic result of the WMSI is used as the reference standard^: Sensitivity: 31.6% (95% CI 19.2 to 45.1) Specificity: 91.1% (95% CI 89.0 to 93.4) Positive predictive value: 37.5% (95% CI 22.7 to 53.6) Negative predictive value: 88.7% (95% CI 86.6 to 90.9) Agreement between tests (i.e. either both abnormal or both normal): 216/262 (82.4%).	cardioactive medications (ACE-inhibitor, ß-blocker or diuretic); for 2 patients this was unknown; nm if all patients receiving medication did for cardiac causes. Selection bias cannot be ruled out (277 out of 401 eligible patients (69%) participated in this study). The risk of detection bias is low; the echocardiographic outcome assessor was blinded. Outcome/attrition bias cannot be ruled out (only for 262 out of 277 patients (95%) both test were available). The authors stated that the high prevalence of abnormal LVSF in apparently healthy sibling controls suggests (22%) the possibility of false-positive findings and challenges the appropriateness of LVSF as a reliable marker of systolic function in adults.
Mavinkurve-Groothuis[42] 2009	Single-center cohort study (the Netherlands). Treatment era: Nm (current study executed between May 2006 and October 2007). Median years of	122 long-term survivors of childhood cancer treated with anthracyclines for ALL (n=38), AML (n=8), ependymoma (n=1), Ewing sarcoma (n=6), hepatoblastoma (n=3), Hodgkin lymphoma (n=13), neuroblastoma (n=6),	Transthoracic M-mode echocardiography (performed by experienced echocardiographic technicians and supervised by 2 (pediatric) cardiologists who were unaware of the cumulative chemotherapy dose	When the echo result is used as the reference standard^: Sensitivity: 22.2% (95% CI 4.0 to 57.0) Specificity: 87.6% (95% CI 86.2 to 90.4) Positive predictive value: 12.5% (95% CI 2.3 to 32.1)	At time of testing none of the patients had symptomatic cardiac disease (defined as < NYHA class II) or a history of cardiovascular disease or chronic renal insufficiency. The risk of selection bias is unclear: all consecutive

	follow-up: 13.8 years (range 5 to 28.7).	NHL (n=30), oesteosarcoma (n=3), rhabdomyosarcoma (n=4) or Wilms tumor (n=10). 62 males/60 females; median age at diagnosis 5.7 years (range 0.03 to 14.4); median age at study 21 years (range 5 to 39.4 years). Treatment: Median cumulative anthracycline dose (doxorubicin and/or daunorubicin) 180 mg/m² (range 50-542); 7 patients also received mediastinal irradiation (no further information provided).	and levels of NT-pro-BNP); an abnormal test result was defined as LVEF < 55% (n=9; prevalence 7.4%). NT-pro-BNP; an abnormal test result was defined as males <10 pmol/L, females <18 pmol/L and for children age dependent reference values by Albers et al (n=16; prevalence 13.1%). Both tests were performed at the same time.	Negative predictive value: 93.4% (95% CI 91.8 to 96.3) Agreement between tests (i.e. either both abnormal or both normal): 101/122 (82.8%).	patients who visited the Late Effects Clinic during the study period were included, but it is not stated if those patients represented a random sample of the complete cohort of survivors. The risk of detection bias is low; echocardiographic outcome assessors were blinded. Low risk of outcome/attrition bias: all 122 patients had both tests.
Hayakawa[43] 2001	Single-center cohort study/cross-sectional study at time of first echocardiogram after treatment (Japan). Treatment era: January 1994 to January 1999. Years of follow-up after last anthracycline dose: at least 1 month.	34 childhood cancer patients (no further information on diagnoses provided) treated with anthracyclines who continued to be in complete remission. 18 males/ 16 females; mean age at diagnosis nm; mean age at study 11.5 years (range 0.7 to 21.7). Treatment: Mean cumulative doxorubicin dose 315 mg/m²; median 314 mg/m² (range 42 to 696).	Pulsed wave doppler and M-mode echocardiography (number of observers nm); an abnormal test result was defined as LVEF <60% or LVSF <30% and if abnormal regional wall motion such as dyskinesis, hypokynesis or akinesis was detected (n=8; prevalence 23.5%). ANP and BNP; an abnormal test result was defined as ANP > 26 pg/ml and BNP > 13 pg/ml (i.e. > mean + 2 SD of 19 healthy controls) (n=6; prevalence 17.6%*).	When the echocardiographic result is used as the reference standard*^: Sensitivity: 62.5% (95% CI 30.6 to 74.3) Specificity: 96.2% (95% CI 86.3 to 99.8) Positive predictive value: 83.3% (95% CI 40.8 to 99.1) Negative predictive value: 89.3% (95% CI 80.2 to 92.7) Agreement between tests (i.e. either both abnormal or both normal): 30/34 (88.2%).	Patients who received mediastinal radiotherapy, developed congestive heart failure or had other illness such as infection were excluded. The risk of selection bias is low: all 34 eligible patients were included. The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 34 patients had both tests.

			All tests were performed at the same time.		
Mavinkurve-Groothuis[42] 2009	Single-center cohort study (the Netherlands). Treatment era: nm (current study executed between May 2006 and October 2007). Median years of follow-up: 13.8 years (range 5 to 28.7).	122 long-term survivors of childhood cancer treated with anthracyclines for ALL (n=38), AML (n=8), ependymoma (n=1), Ewing sarcoma (n=6), hepatoblastoma (n=3), Hodgkin lymphoma (n=13), neuroblastoma (n=6), NHL (n=30), osteosarcoma (n=3), rhabdomyosarcoma (n=4) or Wilms tumor (n=10). 62 males/60 females; median age at diagnosis 5.7 years (range 0.03 to 14.4); median age at study 21 years (range 5 to 39.4 years). Treatment: Median cumulative anthracycline dose (doxorubicin and/or daunorubicin) 180 mg/m² (range 50-542); 7 patients also received mediastinal irradiation (no further information provided).	Transthoracic M-mode echocardiography (performed by experienced echocardiographic technicians and supervised by 2 (pediatric) cardiologists who were unaware of the cumulative chemotherapy dose and levels of cardiac troponin T); an abnormal test result was defined as LVEF < 55% (n=9; prevalence 7.4%) or as LVSF < 29% (n=4; prevalence 3.3%). Cardiac troponin T; an abnormal test result was defined as ≥ 0.010 ng/ml (n=0%; prevalence 0%) Both tests were performed at the same time.	When the echocardiographic result of the LVEF is used as the reference standard^: Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NaN Negative predictive value: 92.6% (95% CI 92.6 to 92.6) Agreement between tests (i.e. either both abnormal or both normal): 113/122 (92.6%). When the echocardiographic result of the LVSF is used as the reference standard^: Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NaN Negative predictive value: 96.7% (95% CI 96.7 to 96.7) Agreement between tests (i.e. either both abnormal or both normal): 118/122 (96.7%).	At time of testing none of the patients had symptomatic cardiac disease (defined as < NYHA class II) or a history of cardiovascular disease or chronic renal insufficiency. The risk of selection bias is unclear: all consecutive patients who visited the Late Effects Clinic during the study period were included, but it is not stated if those patients represented a random sample of the complete cohort of survivors. The risk of detection bias is low; echocardiographic outcome assessors were blinded. Low risk of outcome/attrition bias: all 122 patients had both tests.
Sherief[44] 2012	Single-center cohort study.	50 survivors of childhood acute leukemia (n=39 ALL;	Conventional echocardiography (no further information	When the echocardiographic result is used as the reference standard^:	At time of testing all survivors were asymptomatic (i.e. no signs

	Treatment era: nm. Mean years of follow-up: not completely clear from manuscript, but most likely 3.75 years (range 1.5 to 6).	n=11 AML) treated with anthracyclines. 30 males/20 females; mean age at diagnosis 8.4 years (range 3 to 15); mean age at evaluation 11.63 years (range 8 to 16). Treatment: n=18 cumulative anthracycline dose <150-300 mg/m²; n=32 cumulative anthracycline dose > 300 mg/m² (but elsewhere in the manuscript n=19 < 300mg/m² and n=31 > 300 mg/m² was mentioned).	provided; number of observers nm); an abnormal test result was defined as LVEF < 55% or a LVSF < 29% (n=8 subclinical cardiotoxicity in the form of increase of left ventricular dimension and EF; prevalence 16%). Cardiac troponin T; an abnormal test result was defined as > 0.010 ng/ml (n=0; prevalence 0%). Time between tests: Nm.	Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NaN Negative predictive value: 84% (95% CI 84 to 84) Agreement between tests (i.e. either both abnormal or both normal): 42/50 (84%).	and symptoms of cardiac impairment); patients with renal or hepatic impairment were excluded as were patients with a history of cardiac disease and hypertension. The risk of selection bias is unclear; not clear if these 50 patients were all eligible patients or a random sample thereof. The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 50 patients had both tests.
Kismet[45] 2004	Multi-center cohort study Treatment era: June 1982 to August 2000. Median time from last doxorubicin dose: 12 months (range 1 to 168).	24 childhood cancer patients who received doxorubicin for treatment of Hodgkin disease (n=4), rhabdomyosarcoma (n=4), Ewing sarcoma (n=3), osteosarcoma (n=3), malignant mesenchymal tumor (n=3). Wilms tumor (n=2), neuroblastoma (n=1), hepatoblastoma (n=1), clear cell sarcoma (n=1), malignant mesothelioma (n=1) and primitive neuroectodermal tumor (n=1). 14 males/10 females;	Two-dimensional, M-mode and Doppler echocardiography performed by pediatric cardiologists (number of observers nm); an abnormal test result was defined as LVEF < 55% and LVSF < 29% (n=2; prevalence 8.3%). Cardiac troponin T; an abnormal test result was defined as ≥ 0.010 ng/ml (n=3; prevalence 12.5%). Time between tests: within 24 hours.	When the echocardiographic result is used as the reference standard^: Sensitivity: 50% (95% CI 2.7 to 97.2) Specificity: 90.9% (95% CI 86.6 to 95.2) Positive predictive value: 33.3% (95% CI 1.8 to 64.8) Negative predictive value: 95.2% (95% CI 90.7 to 99.7) Agreement between tests (i.e. either both abnormal or both normal): 21/24 (87.5%).	None of the patients had clinical evidence of abnormal cardiac functions; patients with evidence of renal disease were excluded from the study. The risk of selection bias is unclear; not clear if these 24 patients were all eligible patients or a random sample thereof. The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 24 patients had both tests.

		median age at diagnosis nm; median age at study 14 years (range 3-31). Treatment: Median cumulative doxorubicin dose 480 mg/m² (range 400 to 840); 4 patients also received mediastinal irradiation (no further information provided).			
Soker[46] 2005	Single-center study Treatment era: October 2000 and December 2004. Mean follow-up after the last anthracycline dose 9.39 months (range 1 to 42).	31 childhood cancer patients who received doxorubicin for treatment of ALL (n=27), AML (n=2), Hodgkin disease (n=1), NHL (n=1). 14 males/17 females; median age at diagnosis nm; median age at study 8.16 years (range 4 to 15). Treatment: Median cumulative doxorubicin dose 240 mg/m² (range 30-600).	Two-dimensional, pulse-wave Doppler and M-mode echocardiography (performed by 1 experienced pediatric cardiologist); an abnormal test result was defined as LVEF < 60% and LVSF < 30% (n=4; prevalence 12.9%). Cardiac troponin I; an abnormal test result was defined as ≥ 0.50 ng/ml (n=0; prevalence 0%). Time between tests: performed simultaneously.	When the echocardiographic result is used as the reference standard^: Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NaN Negative predictive value: 87.1% (95% CI 87.1 to 87.1) Agreement between tests (i.e. either both abnormal or both normal): 27/31 (87.1%).	Two of the 4 patients with systolic dysfunction had clinical findings; patients who received mediastinal irradiation or had other illnesses such as infections were excluded. The risk of selection bias is unclear; not clear if these 31 patients were all eligible patients or a random sample thereof. The risk of detection bias is unclear; nm if outcome assessors were blinded. Low risk of outcome/attrition bias: all 31 patients had both tests.

Nm: not mentioned; ALL: acute lymphoblastic leukaemia; n: number; LVEF: left ventricular ejection fraction; CI: confidence interval; LVSF: left ventricular shortening fraction; WMSI: wall motion score index; NYHA: New York Heart Association; AML: acute myeloid leukaemia; NHL: non-Hodgkin lymphoma; NaN: not a number (data type)

^ Since echocardiography is most often used to assess cardiac function in clinical practice, we have chosen the echocardiographic results as reference standard

~ Calculated by the guideline developers based on information provided in the article (for the main outcomes we used the calculator on http://statpages.org/ctab2x2.html)

* It was unclear if both or only one of the two markers should have been abnormal for this definition

3. What is the diagnostic value (i.e. sensitivity and/or specificity) of biomarker ANP, BNP, NT-pro-BNP to detect asymptomatic cardiac systolic dysfunction as measured by echocardiography in *adult non-cancer populations*?					
First Author Year	**Study Design**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Addt'l remarks**
Hill[47] 2008	Systematic review of RCTs and observational studies (published between 1989 and February 2005). For screening studies general populations with no known symptomatic heart failure were included. 6 studies were addressing our question* (n=2 cross sectional study, n=4 cohort study).	Setting: population-based cohort study (n=1; males and females reported separately), GP sample (n=1), population samples (n=3), cohort with stable coronary artery disease (n=1). Sample size: range 293-2042 participants (1 study presented males (1470) en females (1707) separately: 3177 in total). Males: range 43-49.6% (n=3), results presented for males and females separately (46.3% males) (n=1), nm (n=2). Age: range mean age 58-75 years (n=3), >45 years (n=1), range 50-90 years (n=1), nm (n=1). Prevalence cardiac dysfunction: 1-16%.	Index test: BNP (n=5) or NT-pro-BNP (n=2)¶. Reference standard: LVSD based on LVEF (n=5) or a combination of LV mass, LVEF<50% and moderate to severe LVSD (LVEF<40%) (n=1). Time between tests: Nm. Cutoff points: BNP: range 21->115 pg/mL. NTproBNP: range >338-850 pg/mL. Reference test: LVEF range 35-55%.	BNP: Sensitivity: range 26-93% Specificity: range 47-89% NT-pro-BNP: Sensitivity: range 70-80% Specificity: range 63-85%	Risk of bias assessment of included studies: nm.

Ewald[48] 2008	Systematic review of prospective studies (published up to June 2005). 7 studies were addressing our question*.	Setting: population-based cohort studies (n=2; 1 study reporting males and females separately), GP samples (n=2), population samples (n=3). Sample size: range 203-1997 participants (1 study presented males (1470) and females (1707) separately: 3177 in total). Males: range 43-56% (n=6), results presented for males and females separately (46.3% males) (n=1). Median/average age: range 58-75 years. Prevalence cardiac dysfunction: 0.6-6.9%.	Index test: BNP (n=5) or NT-pro-BNP (n=3)¶. Reference standard: LVSD based on LVSF (n=1), LVEF (n=4), wall motion index (n=2). Time between tests: nm for each study separately, but it was stated that the quality of studies was generally adequate, except for 1 study with delays up to one year between both tests. Cutoff points: BNP: range 6.9-19.2 pM/L (n=4); >54.5 pg/ml (n=1). NTproBNP: range 37.7-48.9 pM/L (n=2), nm (n=1). Reference test: LVSF: 28% (n=1); LVEF: range 40-50% (n=4); wall motion index: >2 (n=1) and < 1.7 (equates LVEF < 40%) (n=1).	BNP: Sensitivity: range 55-90%~ Specificity: range 77-90%~ NT-pro-BNP: Sensitivity: range 76-92% Specificity: range 67-81%	Risk of bias assessment of included studies was based on (1) blinding of outcome assessor for other test result, (2) detailed description of methods and criteria for both tests, and (3) performance of both tests on same day. The quality of included studies was generally adequate, but in 1 study delays of up to 1 year occurred between the echocardiography and the peptide estimation (no further information provided); a sensitivity analysis taking into account the quality score was done, but not presented in the paper.
Wang[49] 2003	Systematic review of studies of patients with asymptomatic LVSD (published between 1975 and November 2002). 13 studies were addressing our question* (n=5 community based studies, n=6 referral series).	Setting: population-based cohort studies (n=3; 1 study reporting males and females separately), GP sample (n=1), population sample (n=1), referral series (not further specified) (n=6).	Index test¶: Community based: BNP (n=3), NT-ANP (n=2). Referral series: BNP (n=5), NT-ANP (n=1). Reference standard: Community based: LVSD based on LVSF (n=1), LVSF or mild or	Community based: BNP: Sensitivity: range 26-77% Specificity: range 84-89% NT-ANP: Sensitivity: range 43-86% Specificity: range 75-89% Referral series: BNP: Sensitivity: range 58-100%	Risk of bias assessment of included studies: nm.

		Sample size: Community based: range 126-1707 participants (1 study presented males (1470) and females (1707) separately: 3177 in total); Referral series: range 75-466 participants. Males: Community based: only men (n=1), results presented for males and females separately (46.3% males) (n=1), nm (n=3). Referral series: nm (n=6) Age: Nm. Prevalence cardiac dysfunction: Nm.	greater reduction in LVEF on visual estimation (n=1) or LVEF (n=3). Referral series: LVSD based on LVEF alone (n=4), LVEF in rest or exercise (n=1) or LVEF or wall-motion abnormalities (n=1) Time between tests: Nm. Cutoff points: Community based: BNP: range 17.9-34 ng/L. NT-ANP: range 398-800 pmol/L. Reference test: LVSF: range 0.28-0.29 (no further information provided on combination with LVEF reduction); LVEF: range 0.30-0.45. Referral series: BNP: range 13.8-87 ng/L. NT-ANP: 54 pmol/L. Reference test: LVEF: range 0.35-0.55 (LVEF at rest or during exercise: resting LVEF<0.45 or exercise LVEF<0.55; no further information provided on combination with wall motion abnormalities).	Specificity: range 58-81% NT-ANP: Sensitivity: 90% Specificity: 92%	

RCT: randomized controlled trial; n: number; nm: not mentioned; GP: general practitioner; LVSD: left ventricular systolic dysfunction; LVEF: left ventricular ejection fraction; LV: left ventricular; LVSF: left ventricular shortening fraction

* We only included studies that used a measure of asymptomatic cardiac systolic dysfunction as the reference standard. Studies comparing biomarkers with measures of diastolic dysfunction, a qualitative assessment, a clinical assessment or studies that did not report the reference test were excluded. We

included all studies reporting LVEF as a reference test, although in the different systematic reviews it was not reported if in the individual studies LVEF was measured by echocardiography or radionuclide angiography. Only studies for which sensitivity and/or specificity were available were eligible. Please note that there is overlap in included studies between the different systematic reviews.
Some studies presented results for different cutoff points for either one or both diagnostic tests and/or for males and females separately; we have included all available information in this evidence table
¶one study assessed both tests
~ For one of the included studies sensitivity and specificity were calculated by the guideline developers based on information provided in the systematic review
≠ Only results for the better performing biomarker (if applicable, i.e. either BNP or NT-ANP) were presented in the systematic review

4. What is the diagnostic value (i.e. sensitivity, specificity and/or inter-observer variability) of MRI as compared to echocardiography (or vice versa) for detection of asymptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors?

First Author Year	Study Design	Participants	Diagnostic tests	Main outcomes	Addt'l remarks
Armstrong[50] 2012	Single-center cohort study (USA). Treatment era: nm. Years of follow-up since cancer diagnosis: mean 27.7 years (range 18.4-38.3).	134 adult childhood cancer survivors (cancer diagnosed before age 21 years) treated with chest-directed radiotherapy and/or anthracyclines for ALL (n=44), Hodgkin's lymphoma (n=37), osteosarcoma (n=11), non-Hodgkin's lymphoma (n=8), AML (n=6), neuroblastoma (n=3), Ewing sarcoma (n=2). Wilms tumour (n=2) and soft tissue sarcoma (n=1). 47 men / 67 women; mean age at diagnosis tumour 10.5 years (range 0.02-19); mean age at time of study 38.3 years (range 22.7 -53.7). Treatment: Mean cumulative anthracycline dose 186 mg/m² (range 0-803); 97 patients	Cardiac magnetic resonance imaging (analysis was supervised and/or performed by a single investigator); an abnormal test result was defined as LVEF<50% (n=16; prevalence 14%). 3D as well as a 2D echocardiogram with Doppler and time-motion mode (M-mode) (analysis was performed by a single investigator); an abnormal test result was defined as LVEF<50% (n=22/prevalence 19.3% with 3D echocardiography; n=6/prevalence 5.3% with biplane 2D echocardiography; n=8/prevalence 7% with apical 4-Chamber 2D echocardiography and n=24/prevalence	Screening performance of echocardiography compared with cardiac magnetic resonance imaging (reference standard) for detection of an LVEF<50%: 3D echocardiography: Sensitivity 53% Specificity 86% Positive predictive value 36% Negative predictive value 92% Biplane 2D echocardiography: Sensitivity 25% Specificity 98% Positive predictive value 67% Negative predictive value 89% Apical 4-Chamber 2D echocardiography: Sensitivity 25% Specificity 96% Positive predictive value 50% Negative predictive value 89% Teichholz 2D echocardiography: Sensitivity 29% Specificity 79% Positive predictive value 17%	This study is an analysis of data from 5 pilot studies, convenience sampled from the larger St. Jude Lifetime Cohort Study (SJLIFE). Patients with an implanted medical device or a history of congenital heart disease were excluded. Of the 114 patients that completed the evaluation, 108 were previously undiagnosed with cardiomyopathy. Selection bias cannot be ruled out (692 survivors enrolled in the SJLIFE cohort were exposed to anthracyclines and/or chest radiotherapy of which 134 participated in the study). The risk of detection bias is unclear; nm if outcome assessors were blinded. Outcome/attrition bias cannot be ruled out (for 20 out of 134 survivors that agreed to participate (15%) cardiac magnetic

		received anthracyclines. 37 patients received chest-directed radiotherapy (n=16 1-30 Gy and n=21 > 30Gy; no information on number of fractions).	21.1% with Teichholz 2D echocardiography). Time between tests: within a 48-hour period.	Negative predictive value 88% Bland-Altman measures of agreement with cardiac magnetic resonance imaging: For 3D echocardiography (bias, 1%; Bland-Altman limits of agreement [± 1.96 standard deviation], −11.8% to 14.0%); For 2D echocardiography: 2D biplane (bias, −5.2%; −19.0% to 8.69%), 2D apical 4-chamber (bias, −5.4%; −22.1% to 11.4%), Teichholz M-mode (bias, −3.1%; −28.3% to 22.1%).	resonance imaging could not be completed*).

5. What is the cost-benefit ratio of screening for asymptomatic cardiac systolic dysfunction in childhood and young adult cancer survivors?					
First Author Year	**Study Design**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Addt'l remarks**
No studies identified					

6. What is the cost-benefit ratio of screening for asymptomatic cardiac systolic dysfunction in adult non-oncology populations?					
First Author Year	**Study Design**	**Participants**	**Diagnostic tests**	**Main outcomes**	**Addt'l remarks**
Heidenreich[51] 2004	Cost-benefit analysis using published data from community cohorts (gender-specific BNP test characteristics, prevalence of depressed LVEF) and randomized trials (benefit from treatment).	Men and women age 60 years with no history of heart failure (hypothetical cohorts). Prevalence of depressed LVEF: 3.5% in men; 0.45% in women.	Four screening strategies: 1) BNP testing and, if abnormal, echocardiography. Patients with an LVEF<40% are treated (ACE inhibitors) to prevent the development of heart failure. 2) BNP only, with treatment based on the results. 3) Echocardiography for all patients (treatment based on	Screening 1,000 asymptomatic patients with BNP followed by echocardiography in those with an abnormal test increased the lifetime cost of care (176,000 US dollars for men, 101,000 US dollars for women) and improved outcome (7.9 QALYs for men, 1.3 QALYs for women), resulting in a cost per QALY of 22,300 US dollars for men and 77,700 US dollars for women. The number of men needed to screen with BNP was 44 to identify one with depressed	Possible limitations as reported in the article: 1) the absence of data on the effect of ACE inhibitors in patients with no known cardiac disease. Patients in the used SOLVD prevention trial are likely to have a higher event rate and the effect of ACE inhibitors greater than for patients with unsuspected left ventricular dysfunction. However, if beta-blockers are shown to prevent heart failure then the potential value of screening might be underestimated.

			the results). 4) Not to screen for depressed left ventricular function. Threshold BNP: 21ng/dl for men; 34 ng/dl for women.	LVEF, 133 to gain one year of life, and 127 to gain one QALY. The number of women needed to screen with BNP was 278 to identify one with depressed LVEF, 909 to gain one year of life, and 769 to gain one QALY. Screening with BNP followed by echocardiography in those with an abnormal test was economically attractive for 60-year-old men and possibly for women. Screening all patients with echocardiography was expensive, and relying on BNP alone to decide treatment led to higher cost and worse outcome compared to the sequential BNP-echocardiography strategy. In general, screening with BNP followed by echocardiography is likely to be economically attractive for patient groups with at least a 1% prevalence of moderate or greater LV systolic dysfunction (i.e. increased outcome at a cost < 50,000 US dollars per QALY gained). Screening would not be attractive if a diagnosis of left ventricular dysfunction led to significant decreases in quality of life or income.	2) Although a quality-of-life decrement for patients receiving a positive test was accounted for, the repercussions of a diagnosis of LV dysfunction may be underestimated. In addition, there are financial consequences if the ability to obtain insurance and employment is limited. These issues will be most significant for young patients, where many positive test results will be false positives because of the low prevalence of disease. 3) Potential screening benefits of identifying diastolic dysfunction or significant valvular disease that may be found with BNP screening were not included. These patients may benefit from more aggressive treatment of hypertension or fluid overload. Including these benefits would make screening more economically attractive. A recent meta-analysis suggests that ACE inhibitors may be more effective for asymptomatic men than women with reduced LV function post myocardial infarction. If true for all patients with depressed EF, this would further support screening for men, but in women only at high-risk for heart disease.
BNP: B-type natriuretic peptide; LVEF: left ventricular ejection fraction; QALY: quality-adjusted life years.					

At what frequency should cardiomyopathy surveillance be performed?

1. Is there evidence for a difference in deterioration of cardiac systolic dysfunction between high or standard risk groups of childhood and young adult cancer survivors treated with anthracyclines and/or radiation involving the heart?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
No studies identified					

2. Does the risk of cardiac deterioration cease after a certain follow-up time?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
van der Pal[1] 2012	Retrospective cohort 1966-1996 22.2 yrs (5.0-44.5)	5-yr survivors (N=1362) Age at Dx: 5.9 (0-18)	Anthracyclines: 33.6% Anth+XRT: 7.9% Median Anth: 250 mg/m2 (25-775)	Symptomatic cardiac events (CE); Grading: CTCAE v 3.0 CI of CHF: Radiotherapy: 0.7% at 30-yrs XRT + Anth: 7.9% at 30yrs	Clinically validated outcomes Long follow-up, large cohort
Lipshutz[27] 2005	Observational prospective longitudinal cohort	115 survivors at a median of 11.8 (8.3-15) years off therapy	Median anthracycline 360 mg/m^2 (280-550), no radiation	5 late CHF, LV contractility fell significantly over time and was depressed at last f/u in those who received >300mg/m^2	With median f/u of 11.8 years, thinned ventricular wall by 6 years, depressed LV contractility by 12 years, depressed SF over time
Mulrooney[2] 2009	Prospective longitudinal cohort study – questionnaire based	14,358 survivors and 3,899 siblings	Mix of anthracycline treated/not treated	1.7% risk of CHF in survivors. Increasing incidence over time with no plateau. Longest follow-up was 30 years.	
Roodpeyma[52] 2008	Cross-sectional	58 survivors of pediatric cancer plus health controls	Various anthracyclines	SF/EF reduced in survivors compared with controls.	With a median follow-up of 9 years (5-22), significant association between length of follow-up and risk for abnormal SF/EF.
Pein[19] 2004	Cross-sectional	447 treated for solid tumor in single institution	Anthracyclines +/- radiation therapy	Risk for CHF increased without plateau over time. Increased risk with increasing dose.	Last case occurred at ~25 years from exposure
Sorensen[28] 2003	Prospective longitudinal cohort study	101 ALL survivors; 83 Wilms tumor survivors	Range of anthracyclines	Decreased contractility in both groups. Anthracycline dose most important risk factor.	Significant decrease in wall thickness and SF in Wilms tumor survivors in echocardiograms

					performed at a mean of 11.9 years and 16.3 years.
Van Dalen[18] 2006	Retrospective medical record review – cross sectional	830 children at a single institution	Mean cumulative anthracycline dose 299 mg/m^2	At a mean follow up of 8.5 years, 2.5% risk of CHF. Authors calculated 10% risk of CHF at 20-years after treatment in survivors treated with ≥300 mg/m^2	
Van der Pal[23] 2010	Retrospective medical record review and prospective cardiac screening (cross sectional)	525 survivors seen in an outpatient clinic with echocardiogram	361/525 received an anthracycline	At average age of assessment=23.1 (18.0-47.1) years, 27% had an abnormal LVSF (<30%). Risk greatest in those with >25 year follow up and anthracycline dose ≥450 mg/m^2	

3. Is there an increased risk of deterioration during puberty?

First Author Year	Study Design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Addt'l remarks
No studies identified					

4. Is there an increased risk of deterioration during pregnancy and delivery?

Author Year	Study Design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Addt'l remarks
Bar[53] 2003	Single centre cohort	37 females treated with anthracyclines b/w 1973-1982 who had a pregnancy between 1986-2003	Median doxorubicin 400 mg/m^2 (150-500)	No change in average FS through pregnancy. Among 8 women with FS<30%, pregnancy outcome was worse. More hospitalizations, ICU stays, induction. Two had admission for cardiac deterioration. Non-significant decrease in FS in women who started <30%	
Van Dalen 2006 *EJC*	Single centre prospective cohort study	206 females >17 y.o. who had survived >5 yrs after a childhood malignancy. 53 had delivered 1 or more children	Among 53, mean anthracycline 267 mg/m^2(60-552).	No peripartum CHF after 83 pregnancies in 53 women	Upper limit of 95% CI is 5.7%

What should be done when abnormalities are found? What are the limitations in physical activity?

1. What is the effect of treatment with ACE-inhibitors in childhood and young adult cancer survivors with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Silber[54] 2004	RCT (double-blinded) Unknown treatment era (probably end '70 – mid '90) Median (range) follow-up time was 2.80 years (2 weeks to 6.1 years).	135 childhood cancer survivors (aged 8.3 to 30.6 years, 78 males, at least 4 years from diagnosis and 2 years off treatment) with asymptomatic decline of cardiac function at some time after anthracycline exposure, detected with echocardiography, resting or exercise GNA, MCI at peak exercise and / or resting ECG. Median (range) time since cancer diagnosis 9 (4.2 to 22.3) years in the enalapril group and 9.6 (4.3 to 25.8) years in the placebo group	Oral enalapril once daily (n = 69) or oral placebo once daily (n = 66). Dosing of study medication was as follows: at start 0.05 mg/kg/day, escalation after 14 days to 0.10 mg/ kg/day and escalation at 3 months visit to 0.15 mg/kg/day if no side effects occurred.	Overall survival, mortality due to heart failure, development of **clinical heart failure and quality of life**: no (statistically) significant differences between treatment and control group. **Cardiac function:** a post-hoc analysis showed a decrease (i.e. improvement) in one measure (left ventricular end systolic wall stress (LVESWS): -8.62%change) compared with placebo (+1.66% change) in the first year of treatment (P = 0.036), but not afterwards. **Adverse events:** patients treated with enalapril had a higher risk of dizziness or hypotension (RR 7.17, 95% CI 1.71 to 30.17) and fatigue (Fisher's exact test, P = 0.013).	Median (range) follow-up time was 2.80 years (2 weeks to 6.1 years). Loss of follow-up was not mentioned. Since the authors did not present dichotomous outcomes, we were not able to define RRs for the outcome change in cardiac function; we therefore describe the outcomes as presented in the original study. The study had a low/moderate risk of selection bias, performance biasand detection bias. For most outcomes there was a low risk of attrition bias, but for some outcomes (the post-hoc analysis of LVESWS, other parameters of cardiac function (shortening fraction and stress-velocity index), the change in quality of life and the risk of adverse events) intention-to-treat analysis was not possible or it was unclear if follow-up was complete,leading to a possible risk of attrition bias for these other outcomes.

2. What is the effect of treatment with beta-blockers in childhood and young adult cancer survivors with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
No studies identified					A Cochrane systematic review assessed if a study on beta-blockers in children with heart failure included anthracycline-treated patients (Shaddy 2007)[55]: patients with anthracycline-induced cardiomyopathy were included in the trial, but it was not possible to separate the data of these patients from the data of all included patients.

3. What is the effect of other medical interventions in childhood and young adult cancer survivors with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
No studies identified					

4. What is the effect of treatment with ACE-inhibitors in *non-oncology populations* with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
SOLVD investigators[56] 1992	Double-blind, placebo-controlled RCT Mean: 37.4 (range: 14.6 – 62) months	4228 asymptomatic patients with EF <35%, and no medication for heart failure	Enalapril: *N*=2111 Placebo: *N*=2117	All-cause mortality: Enalapril: 313 (14.8%) Placebo: 334 (15.8%) Risk reduction: 8% (95% CI -8% to +21%) Clinical heart failure or all cause mortality: Enalapril: 630 (29.8%) Placebo: 818 (38.6%) Risk reduction: 29% (95% CI 21% to 36%)	Flather 2000: 74% of all SOLVD-patients (including another RCT with symptomatic patients) had a previous MI. Exner 1999: one third of the SOLVD prevention trial was in NYHA II EF was determined by echocardiography
Pfeffer[57] 1992	Double-blind, Placebo controlled RCT Mean: 42 (range: 24 – 60) months	2231 asymptomatic patients with EF ≤40%, 3 – 16 days after MI	Captopril: *N*=1115 Placebo: *N*=1116	**All-cause mortality:** Captopril: 20% versus placebo 25% (RR 19%, 3 – 32%, *P*=0.014) **Development of clinical heart failure:** Captopril: 11% versus placebo 16%, RR 37% (20-50%, *P*<0.001)	EF was determined by RNA
Jong[58] 2003	Cohort study after RCT 11.2 years (IQR: 10.3 – 12.1) since randomization	3581 patients of the SOLVD prevention trial (asymptomatic patients with EF <35%), treated previously with enalapril or placebo during a mean of 37.4 months, who survived the time of the trial	Enalapril group: *N*=1798 Placebo group: *N*=1783	**All-cause mortality:** Enalapril: 1074 (50.9%) Placebo: 1195 (56.4%) HR: 0.86 (95% CI 0.77 – 0.93) **Increased life expectancy (median)**: 9.2 months (95% CI 0 – 19.2 months)	Patients with a lower EF had more benefit of treatment EF was determined by echocardiography
Kober[59] 1995	Double-blind, Placebo controlled RCT 24 – 50 months clinical follow-up	1749 patients with an MI in the previous week and EF ≤35%	Trandopril: *N*=876 Placebo: *N*=873	**All-cause mortality:** Trandopril versus placebo: RR 0.78 (0.67 – 0.91) **Clinical heart failure:** Trandopril versus placebo: RR 0.71 (0.56 – 0.89)	41% of patients was in NYHA I EF was determined by echocardiography
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Angiotensin converting enzyme inhibitors can be useful to prevent HF	Stage A * with a history of atherosclerotic vascular	Perindopril Ramipril	Class of recommendation IIa Level of evidence A	

	in patients at high risk for developing HF	disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors			
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Angiotensin converting enzyme inhibitors should be used in patients with a reduced EF and no symptoms of HF, even if they have not experienced MI	Stage B*	Enalapril	Class of recommendation I Level of evidence A	
Dickstein[62] 2008 ESC Guideline	Recommendation to treat with beta-blockers based upon the patients enrolled in the RCTs	LVEF ≤40% Mild to severe symptoms (NYHA II–IV)** and patients with asymptomatic LV systolic dysfunction after MI	Bisoprolol Carvedilol Metoprolol succinate Nebivolol	Class of recommendation I Level of evidence A	CIBIS-II 1999 MERIT-HF 1999 & 2000 Packer 2001 COPERNICUS 2002 SENIORS 2005 BBEST 2001 COMET 2003

5. What is the effect of treatment with beta-blockers in *non-oncology populations* with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Dargie[63] 2001	Double-blind, placebo-controlled RCT 1.3 years clinical follow-up	1959 patients with MI 3-21 days before randomization, EF≤ 40% or wall-motion score index ≤ 1.3 and at least 24 hours on a stable dose of ACE-inhibitor treatment.	Carvedilol: *N*=975 Placebo: *N*=984	All-cause mortality: Carvedilol: 116 (12%) Placebo: 141 (15%) HR: 0.77 (0.60 – 0.98) Hospitalization for heart failure: Carvedilol: 118 (12%) Placebo: (138 (14%) HR 0.86 (0.67 – 1.09)	Eligible patients had LV dysfunction with or without heart failure, but patients with severe heart failure were excluded. EF was determined by echocardiography, RNA or ventriculography
Exner[64] 1999	Retrospective analysis of RCT Mean followup 35 months	4228 patients participating in the SOLVD prevention trial	Patients that used a beta blocker at the start of the trial, in addition to study medication: *N*=1015 (24%) Patients that did not use a beta blocker at the start of the trial, in addition to study medication: *N*=3213 (76%)	**All-cause mortality:** Using a beta blocker: IR 4.3/100 person-years No beta blocker: IR 5.6/100 person-years Multivariate model, using a beta blocker in addition to ACE inhibitor allocation: *** All-cause mortality**: RR 0.70 *** All-cause mortality or hospitalization for CHF:** RR 0.64 (0.49 – 0.83)	
Vantrimpont[65] 1997	Retrospective analysis of RCT Mean clinical follow-up of surviving patients: 42 months (+/-10 months)	2231 patients participating in the SAVE trial	Patients that used captopril at the start of the trial, in addition to study medication: *N*=789 (35%) Patients that did not use captopril at the start of the trial, in addition to study medication: *N*=1442 (65%)	**Cardiovascular mortality:** Captopril: 13.1% No captopril: 22.1% (RR 0.58, 0.43 – 0.79) **Severe heart failure:** Captopril: 16.5% No captopril: 22.6% (RR 0.68, 0.55 – 0.83) Multivariate model (including captopril use): *** CV mortality**: RR 0.70 *** Severe CHF**: RR 0.79	
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Beta-blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms	Stage B*		Class of recommendation I Level of evidence C	

6. What is the effect of other medical interventions in other groups of patients with asymptomatic cardiomyopathy?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Konstam[66] 2000	Double-blind, placebo-controlled RCT Median follow-up 555 days.	3152 patients aged 60 years or older with New York Heart Association class II–IV heart failure and LVEF ≤40%	losartan (n=1578) titrated to 50 mg once daily or captopril (n=1574) titrated to 50 mg three times daily	all-cause mortality: 11·7 *vs* 10·4% average annual mortality rate HR 1·13 [95·7% CI 0·95–1·35], p=0·16 sudden death or resuscitated arrests: 9·0 *vs* 7·3% HR 1·25 [95% CI 0·98–1·60], p=0·08	Significantly fewer patients in the losartan group (excluding those who died) discontinued study treatment because of adverse effects (9·7 *vs* 14·7%, p<0·001), including cough (0·3 *vs* 2·7%)
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Angiotensin II receptor blockers can be useful to prevent HF in patients at high risk for developing HF	Stage A* who have a history of atherosclerotic vascular disease, diabetes mellitus, or hypertension with associated cardiovascular risk factors	Angiotensin II receptor blockers	Class of recommendation IIa Level of evidence C	
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Angiotensin II receptor blockers can be beneficial in patients with low EF and no symptoms of HF who are intolerant of ACEIs.	Stage B*	Angiotensin II receptor blockers	Class of recommendation IIa Level of evidence C	
Hunt[60,61] AHA/ACC Guideline (2005 and 2009)	Placement of an ICD might be considered in patients without HF	Stage B* who have non-ischemic cardiomyopathy and an LVEF ≤30% who are in NYHA I with chronic optimal medical therapy and have a reasonable expectation of survival with good functional status for >1 year.	ICD	Class of recommendation IIb Level of evidence C	

Dickstein[62] 2008	Recommendation to treat with angiotensin receptor blockers (ARB) based upon the patients enrolled in the RCTs	LVEF ≤40% and either 1. as an alternative in patients with mild to severe symptoms (NYHA II–IV) who are intolerant of an ACE-I 2. or in patients with persistent symptoms (NYHA II–IV) despite treatment with an ACE-Inhibitor and beta-blocker	Candesartan Valsartan	Treatment reduces the risk of death from cardiovascular causes Class of recommendation I Level of evidence A 1. An ARB is recommended as an alternative in patients intolerant of an ACEI Class of recommendation IIa Level of evidence B 2. in patients with persistent symptoms (NYHA II–IV) despite treatment with an ACE-Inhibitor and beta-blocker Class of recommendation I Level of evidence B	Cohn 2001 CHARM-Added trial 2003 CHARM-Alternative trial 2003 Pfeffer 2003 OPTIMAAL trial 2002 McMurray 2004
Dickstein[67] 2010	Recommendation cardiac resynchronization therapy with defibrillator function in patients with heart failure in NYHA I/II	NYHA function class II LVEF ≤35%, QRS ≥150 ms, SR Optimal medical therapy	CRT preferentially by CRT-D is recommended to reduce morbidity or to prevent disease progression***	Class of recommendation I Level of evidence A	Abraham 2004 Moss 2009 Linde 2009 Daubert 2009

7. Is there evidence that exercise increases the risk of deterioration of cardiac systolic function in *childhood cancer survivors* who received potentially cardiotoxic therapies?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Huang[68] 2011	Systematic review. 15 studies identified including 4 RCTs	Mostly ALL patients during and after treatment	Different exercise training schedules	Different in all studies. Positive effects of physical training on organ system function, fatigue and physical well-being	However, the optimal intervention modality and the intensity, timing, and duration of the intervention are difficult to determine.

8. Is there evidence that exercise increases the risk of deterioration of cardiac systolic function in adult-onset cancer survivors and non-oncology at-risk populations?					
First Author Year	**Study Design Treatment era Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Addt'l remarks**
Schmitz[69] 2010	Guideline-expert opinion- American College of Sports Medicine	Only ADULT cancer studies reviewed		Physical activity is strongly recommended with the exception of activities resulting in rapid BP elevation (eg isometric exercise)	
Pellicia[70] 2006	Guideline-expert opinion- European Society of Cardiology			Recommendation is for physical activity in individuals with genetic susceptibility to CHF, but with normal systolic function.	
Dickstein[62] 2008	Guideline – review of published evidence, expert panel; European Society of Cardiology			Recommendations – Weight reduction should be considered in obese persons with heart failure In moderate to severe heart failure, weight reduction should not be recommended routinely	No supporting evidence supplied Level of evidence C

Maron[71] 2004	Consensus document; expert international panel of clinical cardiovascular specialists and molecular biologists; American Heart Association	Young people (<40 years age) with genetic cardiovascular diseases including hypertrophic cardiomyopathy but not specifically including dilated cardiomyopathy.	Not specifically considered. Considered recommendations for physical activity and recreational sports participation. Childhood cancer survivors (CCS) not included.	Recommendations: Can safely participate in most low or moderate-intensity recreational exercise Some activities should be avoided, eg burst exertion, extremely adverse environmental conditions, exercise programmes with systematic / progressive levels of exertion and aiming at higher levels of conditioning, intense isometric exertion, extreme sports, performance-enhancing substances	
Riegel[72] 2009	Review / scientific statement; expert panel; American Heart Association	Persons with heart failure	Not specifically considered. CCS not mentioned specifically.	Statements In moderate heart failure, exercise improves certain physiological parameters including V_{O2}max, ventilatory response, heart rate variability. Can also reduce depression. Effect on mortality not clear. Cites Pina et al 2003. Individually tailored exercise programme based on results of formal exercise testing may benefit patients with severe symptomatic LV dysfunction. Cites Fletcher et al 2001. Exercise is a beneficial adjunctive treatment in patients with current or prior heart failure symptoms and reduced LVEF. Cites Hunt et al 2005 (states this is level 1B evidence). Modest benefit in HF-Action RCT (Flynn et al, 2009, see below)	
Flynn[73] 2009	HF-Action Randomised controlled trial Randomised 2003-7 Median FU 2.5 years	2331 stable out-patients with heart failure (LVEF ≤35%) 82 centres in USA, Canada, France	Randomised to Usual care + aerobic exercise training (initially supervised, subsequently home-based) vs usual care +	At 3 months, usual care + exercise training group showed statistically greater improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ – a 23 item disease-	

			recommendation for regular physical activity. Usual care included optimal medical therapy.	specific questionnaire) score than usual care group. Improvement was maintained. Also modest but significant improvement in quality of life and non-significant reduction in all-cause mortality and hospitalisation in usual care + exercise training group.	
Piepoli[74] 2004	Meta-analysis (individual patient data) 1990-2002 Individual median F/U 5-75mths, overall 23mths	9 studies, total 395 training to 406 control 87% males, 59% with IHD, mean LVEF <28%, 73% on ACE inhibitors	All RCTs, usual care vs addition of exercise training (mostly supervised)	Outcome of mortality in favour of exercise – 0.65 (0.46-0.92) Outcome of death or admission to hospital also in favour of exercise – 0.72 (0.56-0.93)	Intensity generally set at 60-80% peak oxygen consumption. These trials are designed to be "safe" first and foremost. Question of whether differing aetiologies of systolic dysfunction/heart failure have differing responses to physical activity not yet answered.
Davies[75] 2010	Meta-analysis (publication data) 2001-Jan2008 Individual median F/U 5 mths-60mths. , overall 11mths	19 trials, total 3647 patients (HF-ACTION trial contributed 60%) Only one trial 57% femaies, others 72-100% male; age 58	All RCTs, usual care vs addition of exercise training (mostly supervised) Only 4 trials F/U longer than 12 mths.	All cause mortality <12 mth F/U outcome in favour of usual care – 1.03 (0.70-1.53), but >12mth F/U favoured exercise - 0.91 (0.78-1.06) All hospital admissions both < and >12 mths favoured exercise. HRQoL measurements also favoured exercise.	If HF-ACTION trial excluded, significant reduction longer-term mortality seen (0.62 (0.39-0.98). Issues of mix of endurance and resistance training starting to be addressed.

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