Summary of findings tables, grading of the evidence and detailed conclusions of evidence cardiomyopathy surveillance

Working group 1: Who needs cardiomyopathy surveillance?

1. What is the exact anthracycline threshold dose for developing cardiomyopathy in CAYA cancer survivors, and does this differ by age at treatment or sex?
    a. Anthracycline threshold for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition Equivalent dose calculation	Risk factor estimates (95% confidence interval)	Risk of bias
1a Anthracycline threshold for developing symptomatic heart failure in CAYA cancer survivors **(n=19 studies)**	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271 -Doxorubicin equivalents (Feijen 2019/2015)[1]	Multivariable Cox regression -Anthracycline dose <250 mg/m2 versus none: HR 2.76 (1.93-3.97) -Anthracycline dose ≥250 mg/m2 versus none: HR 9.29 (6.01-14.37)	SB: high risk AB: high risk DB: unclear CF: low risk
	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=unknown -Doxorubicin equivalents (Feijen 2019/2015)[1]	Multivariable piecewise exponential models, RR Prediction timepoint (baseline): Age 20 / Age 35 -Anthracycline, mg/m2 (none=ref) <100: 1.09 (0.32-3.77) / 0 (-) 100-249: 3.67 (1.85-7.28) / 2.11 (0.46-9.76) ≥250: 11.54 (6.85-19.45) / 5.02 (2.09-12.06)	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-1	5845 survivors 47% ANT 22% RT	Median 19.9, range 5.0-50.4 years	-Heart failure (CTCAE grade 3-5), n=116 -Doxorubicin equivalents (Feijen 2019/2015)[1]	Multivariable Cox regression -Anthracycline dose studied with splines (p<0.001 for main effect) HRs from figure: 100 mg/m2 vs none: HR ± 3 150 mg/m2 vs none: HR ± 6 250 mg/m2 vs none: HR ± 12 300 mg.m2 vs none: HR ± 17 Exponential increase in risk up to 250 mg/m2, less steep increase in risk thereafter	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019	13,318 survivors 40% ANT 66% RT	Not reported, median ±23 years	-Heart transplantation, n=37, time to transplantation: median 17, IQR 13-26 years -Doxorubicin equivalents (Feijen 2019/2015)[1]	Multivariable Cox regression -Anthracycline dose, mg/m2 (none=ref) >0-150: HR 8.4 (2.2-32.6) >150-300: HR 5.0 (1.3-19.5) >300-450: HR 26.5 (9.9-71.0) >450: HR 94.2 (35.3-251.2)	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-2	28,423 survivors 35% DOX 18% DAU	Median 20, range 5-40 years	-Heart failure (CTCAE grade 3-5) before age 40, n=399	Multivariable Cox regression -Doxorubicin (none=reference) <150 mg/m2: HR 1.8 (1.2-2.6) 150-299 mg/m2: HR 4.6 (3.3-6.4)	SB: unclear AB: low risk DB: unclear CF: low risk

	1.1% EPI 1.1% IDA 0.9% Mitox 21% RT			≥300 mg/m2: HR 12.6 (9.8-16.3) -Daunorubicin (none=reference) <150 mg/m2: HR 1.4 (0.9-2.1) 150-299 mg/m2: HR 2.8 (1.7-4.5) ≥300 mg/m2: HR 6.0 (3.8-9.3) -Epirubicin (none=reference) <150 mg/m2: HR 1.9 (0.3-13.7) 150-299 mg/m2: HR 2.4 (0.6-9.9) ≥300 mg/m2: HR 6.0 (2.6-13.9) -Idarubicin: too few events -Mitoxantrone (none=reference) <150 mg/m2 : HR 4.2 (1.8-9.9) 150-299 mg/m2 : HR 4.2 (1.6-11.4) ≥300 mg/m2 : HR 48.3 (24.2-96.5)	
Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371 -Doxorubicin equivalents (Feijen 2019/2015)[1]	<u>Multivariable piecewise exponential model</u> -Cumulative anthracycline dose, mg/m2 1-249 vs. None: RR 2.9 (1.6-5.3) ≥ 250 vs. None: RR 6.5 (4.0-10.6)	SB: low risk AB: low risk DB: unclear CF: low risk
Mansouri 2019	239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7–26.9 Controls: 33.0, 27.2–39.0	-Clinically validated heart failure, n=239 -No dose conversion reported	<u>Conditional logistic regression</u> Anthracycline, mg/m2 0–250 vs. none: OR 3.4 (1.5–7.6) 250–360 vs. none: OR 11.4 (5.0–25.9) ≥360 vs. none: OR 15.0 (7.1–31.7)	SB: unclear AB: low risk DB: unclear CF: low risk
Chellapandian 2019	2053 ALL and AML 77% ANT 11% RT	10.4, range 5.9-16.0 years	-Heart failure, ALL n=32, AML n=20 -1*doxorubicin 1*daunorubicin, 0.67*epirubicin, 4*mitoxantrone, 5*idarubicin	<u>Multivariable Cox regression ALL cohort</u> -Anthracycline ≥250 vs <250 mg/m2: HR 3.04 (1.41-6.55) <u>Multivariable Cox regression AML cohort</u> -HR for anthracyclines ≥250 mg/m2 not available as all patients with heart failure were treated with doses ≥250mg/m2.	SB: low risk AB: low risk DB: unclear CF: low risk
Khanna 2019	7289 survivors 45% ANT 14% RT	Median 10, range 0-25 years	-Heart failure based on administration data algorithm, n=unknown (1.1% cumulative incidence at 10 years) -Dose conversion not reported	<u>Multivariable cox regression analysis:</u> -Doxorubicin equivalent ≥250 vs <250 mg/m2: HR 8.6 (4.5–16.6)	SB: low risk AB: low risk DB: unclear CF: low risk

Chow 2015	Survivors CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48 -daunorubicin*1.0; idarubicin*3.0; epirubicin*0.67; mitoxantrone*4.0	<u>Multivariable Poisson regression (model including chest RT dose)</u> -Anthracycline, mg/m2 <100 vs. None: RR 2.1 (0.8 to 5.9) 100-249 vs. None: RR 3.7 (2.3 to 5.9) ≥250 vs. None: RR 10.5 (7.7 to 14.4)	SB: unclear AB: unclear DB: unclear CF: low risk
Feijen 2015	15,851 survivors 32.5% DOX 14.7% DAU 17% RT	Median 17.3, range 5-35 years	-Heart failure (CTCAE grade 3-5) before age 40, n=271	<u>Multivariable Cox regression</u> -Doxorubicin (none=reference) ≥0.1 to <200 mg/m2: HR 2.80 (1.75 to 4.49) ≥200 to <300 mg/m2: HR 6.31 (4.11 to 9.69) ≥300 to <400 mg/m2: HR 13.19 (9.04 to 19.25) ≥400 mg/m2: HR 18.43 (12.82 to 26.50) -Daunorubicin (none=reference) ≥0.1 to <200 mg/m2: HR 1.09 (0.57 to 2.08) ≥200 to <300 mg/m2: HR 3.16 (1.16 to 8.61) ≥300 to <400 mg/m2: HR 4.33 (1.73 to 10.84) ≥400 mg/m2: HR 10.72 (5.13 to 22.42)	SB: unclear AB: low risk DB: unclear CF: low risk
van der Pal 2012	1362 survivors 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	-Heart failure (CTCAE grade 3-5), n=27 -Doxorubicin*1, daunorubicin*1, epirubicin*0.67	<u>Multivariable Cox regression (Model 1)</u> Anthracycline (per 100 mg/m2): HR 1.8 (1.5-2.3) <u>Multivariable Cox regression (Model 2)</u> Anthracyclines without RT vs no cardiotoxic therapy: HR 33.5 (4.4-254)	SB: low risk AB: low risk DB: unclear CF: low risk
Blanco 2012	Survivors: 170 cases ANT 91% RT 25% 317 controls 71% ANT 14% RT	Median, range Cases: 9.2, 0.1-35.1 Controls: 12.3, 0.4-40	-Clinically validated heart failure and/or LVEF ≤40% and/or FS≤28%, n=170 -Doxorubicin equivalents[2]	<u>Multivariable conditional logistic regression</u> -Anthracycline dose (reference = none) 1-100: OR 1.65 (0.5 to 5.6), not significant 101-150: OR 3.85 (1.1 to 13.9) 151-200: OR 3.69 (1.0 to 13.6) 201-250: OR 7.23 (2.3 to 22.5) 251-300: OR 23.5 (7.4 to 74.2) >300: OR 27.6 (9.3 to 82.1) P for trend p<0.001	SB: unclear AB: low risk DB: low risk CF: low risk
Armenian 2011	Lymphoma, leukemia and myeloma survivors 88 cases	Median 5.3, range 0.1-20.5 years	-Heart failure per AHA/ACC definition, n=88 -Dose calculation not reported	<u>Multivariable conditional logistic regression</u> Anthracycline Dose <150 mg/m2 (reference) 150-249: R 3.5, not significant 250-349: RR 9.9, p<0.01	SB: low risk AB: low risk DB: unclear CF: low risk

		218 controls 100% ANT RT unknown			>349: RR 19.8, p<0.01	
	Mulroney 2009	14,358 survivors 33% ANT 57% RT	Median 27.0, range 8-51 years	-Heart failure (CTCAE grade 3-5), n=248 -Doxorubicin*1, Daunorubicin*1, Idarubicin*3	Multivariable Cox regression Anthracycline dose (reference=none) <250 mg/m2: HR 2.4 (1.5-3.9) ≥250 mg/m2: HR 5.2 (3.6-7.4)	SB: low risk AB: low risk DB: unclear CF: low risk
	van Dalen 2006	830 survivors 100% ANT 21% RT	Median 8.5, range 0.01-28.4	-Heart failure, n=21 -Dose calculation not reported	Multivariable Cox regression Cumulative anthracycline ≥300 vs <300 mg/m2 RR: 7.78 (95% CI 1.76-34.27), p<0.01	SB: low risk AB: low risk DB: low risk CF: unclear
	Pein 2004	229 solid tumor survivors 100% ANT 55% RT	Mean 18 years	-Heart failure, FS<25%, EF<50%, or ESWS>100, n=89 -Most received doxorubicin, 2 received daunorubicin, no conversion score	Multivariable Cox regression (model 1) Cum anthracycline dose per 100mg/m2: RR 1.60 (1.22 – 2.09) Multivariable Cox regression (model 2) Cumulative anthracycline dose mg/m2 (1-150=reference) >150-250 mg/m2: 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)	SB: high risk AB: low risk DB: unclear CF: low risk
	Green 2001	Wilms tumor survivors Cases: 35 Controls: 137	Range ± 1-20 years	Heart failure, clinically validated, n=35 -Only doxorubicin	Multivariable conditional logistic regression (nested case-control) -Cumulative Doxorubicin dose (1-199 mg/m2=Reference) 200-299 mg/m2: RR 1.1 (0.3-5.1), not significant ≥300 mg/m2: RR 6.0 (1.5-24), p=0.01, p trend=0.002	SB: unclear AB: high risk DB: low risk CF: low risk
	Kremer 2002	Systematic review of 71 articles Searched: 1966-2000	Range across studies 0.9-7.3 years	Heart failure as reported by the authors	Risk with anthracycline dose in 5 out of 10 studies -Goorin (1981), N=382, >500 vs ≤500 mg/m2: RR 4.8 (1.6-14) -Dearth (1984), N=112, >400 vs ≤400 mg/m2: RR 26.1 (3.2-210) -Sallan (1984), N=379, maximal dose/wk ≥45 vs <45 mg/m2: RR 7.7 (2.1-28.1) -Godoy (1997), N=120, >300 mg/m2 vs ≤300 mg/m2: HR 1.5 (0.3-3.9) -Krischer (1997) ≥500 mg/m2 vs <500 mg/m2: RR 2.6 (1.1-6)	SB: high risk AB: unclear DB: high risk CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies, (nested) matched case-control studies and a systematic review
Study limitations:	0	Limitations: Selection bias high risk in 3/19, unclear in 6/19, low risk in 10/19; Attrition bias high risk in 2/19, unclear in 2/19, low risk in 15/19; Detection bias high risk in 2/19, unclear in 14/19, low risk in 3/19; Confounding high risk in 1/19, unclear in 1/19, low risk in 17/19.
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.
Publication bias:	0	Unlikely
Effect size:	+1	Large effect sizes

Dose-response:	+1	Clear evidence for a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Exponential increasing risk for symptomatic heart failure with increasing cumulative anthracycline dose in CAYA cancer survivors. Low risk: No significant effect of a cumulative anthracycline dose <100 mg/m2 vs. no anthracyclines on symptomatic heart failure in CAYA cancer survivors. Moderate risk: ≥3.7-fold increased risk of symptomatic heart failure in CAYA cancer survivors treated with a cumulative anthracycline dose of 100-249 mg/m2 vs, no anthracyclines. High risk: ≥5.2-fold increased risk of symptomatic heart failure in CAYA cancer survivors treated with a cumulative anthracycline dose ≥200 or ≥250 mg/m2 vs. no anthracyclines. (19 studies; 19 significant effect; >2812 events; 185,962 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

1: Doxorubucin equivalent doses according to Feijen et al. 2015 and 2019: Doxorubicin*1, Daunorubicin*0.45, Epirubicin*0.67, idarubicin*3.

2: Doxorubucin equivalent doses according to Lehman 2000: Doxorubicin*1, Daunorubicin*0.833, Epirubicin*0.67, Idarubicin*5.

Summary table: Risk for heart failure by anthracycline dose category with no anthracyclines as reference

Dose (mg/m^2) vs none	Mulrooney 2020	Chen 2020	Dietz 2019 heart tx	Feijen 2019-2 Doxorubicin	Bates 2019	Mansouri 2019	Chow 2015	Feijen 2015	Blanco 2012	Mulrooney 2009	Conclusion (range)
1-100		RR 1.09 (0.32-3.77)					RR 2.1 (0.8-5.9)		OR 1.65 (0.5-5.6)		Not significant
1-150			**HR 8.4 (2.2-32.6)**	**HR 1.8 (1.2-2.6)**							**1.8-8.4 fold**
1-199								**HR 2.8 (1.8-4.5)**			**2.8 fold**
101-150									**OR 3.85 (1.1-13.9)**		**3.9 fold**
151-200									**OR 3.69 (1.0-13.6)**		**3.7 fold**
1-249	**HR 2.76 (1.93-3.97)**				**RR 2.9 (1.6-5.3)**	**OR 3.4 (1.5-7.6)**				**HR 2.4 (1.5-3.9)**	**2.4-3.4 fold**
101-249		**3.67 (1.85-7.28)**					**RR 3.7 (2.3-5.9)**				**3.7 fold**
201-250									**OR 7.23 (2.3-22.5)**		**7.2 fold**
200-299								**HR 6.3 (4.1-9.7)**			**6.3 fold**

151-300			**HR 5.0 (1.3-19.5)**	**HR 4.6 (3.3-6.4)**						**4.6-5.0 fold**
251-300								**OR 23.5 (7.4-74.2)**		**23.5 fold**
250-360						**OR 11.4 (5.0-25.9)**				**11.4 fold**
≥250	**HR 9.29 (6.01-14.37)**	**11.54 (6.85-19.45)**			**RR 6.5 (4.0-10.6)**		**RR 10.5 (7.7-14.4)**		**HR 5.2 (3.6-7.4)**	**5.2-11.5 fold**
300-399								**HR 13.1 (9.0-19.3)**		**13.1 fold**
300-450			**HR 26.5 (9.9-71.0)**							**26.5 fold**
≥300				**HR 12.6 (9.8-16.3)**				**OR 27.6 (9.3-82.1)**		**12.6-27.6 fold**
≥360						**OR 15.0 (7.1-31.7)**				**15.0 fold**
≥400								**HR 18.4 (12.8-26.5)**		**18.4 fold**
≥450			**HR 94 (35-251)**							**94 fold**

Summary table: Risk for heart failure by anthracycline dose category with another dose category as the reference

Dose (mg/m^2)	Chellapandian 2019	Khanna 2019	Van der Pal 2012	Armenian 2011	Van Dalen 2006	Pein 2004	Green 2001	Kremer 2002
≥300 vs <300					**RR 7.78 (1.8-34.3)**			HR 1.5 (0.3-3.9)
≥250 vs <250	**HR 3.04 (1.41-6.55)**	**HR 8.6 (4.5-16.6)**						
150-249 vs <150				RR 3.5, p>0.05		RR 2.0 (0.4-9.5)		
250-349 vs <150				**RR 9.9, p<0.01**				
250-400 vs <150						RR 4.0 (0.95-17)		
>349 vs <150				**RR 19.8, p<0.01**				
>400 vs <150						RR 3.3 (0.8-14)		
200-299 vs 1-199							RR 1.1 (0.3-5.1)	
≥300 vs 1-199							**RR 5.0 (1.5-24)**	
>500 vs ≤500								**RR 4.8 (1.6-14); RR 2.6 (1.1-6)**
>400 vs ≤400								**RR 26.1 (3.2-210)**

Per 100 increase	**HR 1.8 (1.5-2.3)**	**RR 1.6 (1.2-2.1)**

b. Interaction anthracycline dose with sex for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition Equivalent dose calculation	Risk factor estimates (95% confidence interval)	Risk of bias
1b Interaction of anthracycline dose with sex and age at diagnosis for developing symptomatic heart failure in CAYA cancer survivors. **(n=1 study)**	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48 -daunorubicin*1.0; idarubicin*3.0; epirubicin*0.67; mitoxantrone*4.0	Multivariable Poisson regression (model including chest RT dose) -No interaction between anthracyclines and sex or age at diagnosis in exploratory analysis	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study
Study limitations:	0	No limitations
Consistency:	0	Not applicable (only 1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Only 1 study identified
Publication bias:	0	Unlikely
Effect size:	0	No large effect sizes
Dose-response:	0	No evidence of a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No evidence for an interaction of sex with anthracycline dose threshold for developing cardiomyopathy (1 study without a significant effect; 378 events; 22877 participants).

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

c. Interaction of anthracycline dose with age at diagnosis/treatment for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition Equivalent dose calculation	Risk factor estimates (95% confidence interval)	Risk of bias

1c Interaction of anthracycline dose with sex and age at diagnosis for developing symptomatic heart failure in CAYA cancer survivors. **(n=2 studies)**	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371 -Doxorubicin equivalents (Feijen 2019/2015)[1]	-Interaction of anthracycline dose with age at diagnosis 0 mg/m2 and ≤4 vs. >13 years: RR 1.3 (0.6 to 2.9) 0 mg/m2 and 4-13 vs. >13 years: RR 1.3 (0.8 to 2.2) 1-249 mg/m2 and ≤4 vs. >13 years: RR 2.1 (1.0 to 4.2) 1-249 mg/m2 and 4-13 vs. >13 years: RR 1.5 (0.8 to 2.8) ≥250 mg/m2 and ≤4 vs. >13 years: RR 4.6 (2.7 to 7.9) ≥250 mg/m2 and 4-13 vs. >13 years: RR 2.5 (1.7 to 3.8)	SB: low risk AB: low risk DB: unclear CF: low risk
	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48 -daunorubicin*1.0; idarubicin*3.0; epirubicin*0.67; mitoxantrone*4.0	Multivariable Poisson regression (model including chest RT dose) -No interaction between anthracyclines and sex or age at diagnosis in exploratory analysis	SB: unclear AB: unclear DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies
Study limitations:	-1	Some limitations: Selection bias unclear in 1/2, low risk in 1/2; Attrition bias unclear in 1/2, low risk in 1/2; Detection bias unclear in 2/2; Confounding low risk in 2/2.
Consistency:	-1	Inconsistency between 2 studies. One study did not find a significant interaction while the other study did find an interaction.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.
Publication bias:	0	Unlikely
Effect size:	0	No large effect sizes
Dose-response:	0	No evidence of a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Inconsistent evidence for an interaction between age at diagnosis and anthracycline dose for developing symptomatic heart failure. One study reported a lower anthracycline threshold with younger age at diagnosis (<4 years, 1-250 mg/m2) as compared to older patients (>13 years, ≥250 mg/m2) for developing heart failure (Bates 2019). However, the other study did not find a significant interaction between age at diagnosis and anthracycline dose (Chow 2015)(2 studies; 1 found a significant effect; 749 events; 47091 participants).

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

1: Doxorubucin equivalent doses according to Feijen et al. 2015 and 2019: Doxorubicin*1, Daunorubicin*0.45, Epirubicin*0.67, idarubicin*3.

d. Overall effect of age at diagnosis/treatment for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
1d Overall effect of age at diagnosis/treatment for developing symptomatic heart failure in CAYA cancer survivors **(n=11 studies)**	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=unknown	Multivariable piecewise exponential models, RR Prediction timepoint (baseline): Age 20 / Age 35 -Age at diagnosis (≥15 years=ref) <5: 0.84 (0.44-1.61) / 2.64 (0.31-22.69) 5-9: 1.44 (0.89-2.31) / 0.50 (0.07-3.90) 10-14: NA / 1.01 (0.44-2.35)	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-1	5845 survivors 47% ANT 22% RT	Median 19.9, range 5.0-50.4 years	-Heart failure (CTCAE grade 3-5), n=116	Multivariable Cox regression -Age at primary childhood diagnosis (per year): HR 0.8 (0.8-0.9)	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019	13,318 survivors 40% ANT 66% RT	Not reported, median ±23 years	-Heart transplantation, n=37, time to transplantation: median 17, IQR 13-26 years	Multivariable Cox regression -Age at diagnosis not significant (data not shown)	SB: low risk AB: low risk DB: unclear CF: low risk
	Chellapandian 2019	2053 ALL and AML 77% ANT 11% RT	10.4, range 5.9-16.0 years	-Heart failure, ALL n=32, AML n=20	Multivariable Cox regression ALL cohort -Age at cancer diagnosis <1 year vs ≥5 years HR 3.82 (1.09-13.31) -Age at cancer diagnosis 1-4 year vs ≥5 years HR 0.84 (0.38-1.85) Multivariable Cox regression AML cohort -Age at cancer diagnosis <1 year vs ≥5 years HR 0.93 (0.21-4.09) -Age at cancer diagnosis 1-4 year vs ≥5 years HR 0.47 (0.08-2.57)	SB: low risk AB: low risk DB: unclear CF: low risk
	Chow 2015	Survivors CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) -Age at diagnosis, years <5 vs. ≥15: RR 2.6 (1.6 to 4.1) 5-9 vs. ≥15: RR 1.9 (1.2 to 2.9) 10-14 vs. ≥15: RR 1.4 (1.0 to 2.0)	SB: unclear AB: unclear DB: unclear CF: low risk
	van der Pal 2012	1362 survivors 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	-Heart failure (CTCAE grade 3-5), n=27	Multivariable Cox regression Age at diagnosis (per year): HR 0.98 (0.90-1.07)	SB: low risk AB: low risk DB: unclear CF: low risk
	Blanco 2012	Survivors: 170 cases ANT 91% RT 25% 317 controls	Median, range Cases: 9.2, 0.1-35.1 Controls: 12.3, 0.4-40	-Clinically validated heart failure and/or LVEF ≤40% and/or FS≤28%, n=170	Multivariable conditional logistic regression -Age at diagnosis (per year): OR 0.99 (0.93 to 1.04)	SB: unclear AB: low risk DB: low risk CF: low risk

		71% ANT 14% RT				
	Mulroone y 2009	14,358 survivors 33% ANT 57% RT	Median 27.0, range 8-51 years	-Heart failure (CTCAE grade 3-5), n=248	Multivariable Cox regression Age at diagnosis (reference=15-20 years) 0-4 years: HR 3.9 (2.1-7.3), 5-9 years: HR 2.3 (1.3-4.0), 10-14 years: HR 1.2 ns.	SB: low risk AB: low risk DB: unclear CF: low risk
	van Dalen 2006	830 survivors 100% ANT 21% RT	Median 8.5, range 0.01-28.4	-Heart failure, n=21	Multivariable Cox regression RR of age at diagnosis was not significant and not reported	SB: low risk AB: low risk DB: low risk CF: unclear
	Pein 2004	229 solid tumor survivors 100% ANT 55% RT	Mean 18 years	-Heart failure, FS<25%, EF<50%, or ESWS>100, n=89	Multivariable Cox regression Age at first treatment <7 vs ≥8 years: RR 3.21 (1.63 – 6.34)	SB: high risk AB: low risk DB: unclear CF: low risk
	Kremer 2002	Systematic review of 71 articles Searched: 1966-2000	Range across studies 0.9-2487.3 years	Heart failure as reported by the authors	Age <4 years as predictor of CHF in 1 out of 10 studies: -Godoy (1997), N=69, RR = 11.7 (1.4-96.4)	SB: high risk AB: unclear DB: high risk CF: high risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies, matched case-control study and a systematic review				
Study limitations:	-1	Some limitations: Selection bias high risk in 1/11, unclear in 2/11, low risk in 7/11; Attrition bias high risk in 0/11, unclear in 2/11, low risk in 9/11; Detection bias high risk in 1/11, unclear in 8/11, low risk in 2/11; Confounding high risk in 1/11, unclear in 1/11, low risk in 9/11.				
Consistency:	-1	Some inconsistency: 5 studies showed a significant effect of age while 6 studies showed non-significant results				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊖⊖ LOW				
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors with a younger age at cancer diagnosis/treatment vs. older age (11 studies; 5 significant effect; >1138 events; 83971 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

Summary table: Risk for heart failure by age at cancer diagnosis/treatment

Age (years)	Chen 2020 Age 35	Feijen 2019-1	Dietz 2019	Chellapandian 2019 ALL	Chellapandian 2019 AML	Chow 2015	Van der Pal 2012	Blanco 2012	Mulrooney 2009	Van Dalen 2006	Pein 2004	Kremer 2002
0-4 vs ≥15	RR 2.64 (0.31-22.69)					**RR 2.6 (1.6-4.1)**			**HR 3.9 (2.1-7.3)**			
5-9 vs ≥15	RR 0.50 (0.07-3.90)					**RR 1.9 (1.2-2.9)**			**HR 2.3 (1.3-4.0)**			
10-14 vs ≥15	RR 1.01 (0.44-2.35)					RR 1.4 (1.0-2.0)			HR 1.2 ns			
<1 vs ≥5				**HR 3.82 (1.09-13.31)**	HR 0.93 (0.21-4.09)							
1-4 vs ≥5				HR 0.84 (0.38-1.85)	HR 0.47 (0.08-2.57)							
<7 vs ≥8											**RR 3.21 (1.63-6.34)**	
<4 vs ≥4												**RR 11.7 (1.4-96.4)**
Per year increase		HR 0.8 (0.8-0.9)	ns				HR 0.98 (0.90-1.07)	OR 0.99 (0.93-1.04)		ns		

e. Overall effect of sex for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
1e Overall effect sex for developing symptomatic heart failure in CAYA cancer survivors **(n=14 studies)**	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271	Multivariable Cox regression -Female vs male: HR 1.51 (1.10-2.06)	SB: high risk AB: high risk DB: unclear CF: low risk
	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=unknown	Multivariable piecewise exponential models, RR Prediction timepoint (baseline): Age 20 / Age 35 -Female vs male: 1.86 (1.23-2.82) / 1.47 (0.72-3.03)	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-1	5845 survivors 47% ANT	Median 19.9, range 5.0-50.4 years	-Heart failure (CTCAE grade 3-5), n=116	Multivariable Cox regression -Sex (reference=male): HR 0.9 (0.6-1.3)	SB: low risk AB: low risk DB: unclear

	22% RT				CF: low risk
Dietz 2019	13,318 survivors 40% ANT 66% RT	Not reported, median ±23 years	-Heart transplantation, n=37, time to transplantation: median 17, IQR 13-26 years	Multivariable Cox regression -Sex effect not significant (data not shown)	SB: low risk AB: low risk DB: unclear CF: low risk
Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	Multivariable piecewise exponential model -Female vs male: RR 1.4 (1.1-2.0)	SB: low risk AB: low risk DB: unclear CF: low risk
Chellapandian 2019	2053 ALL and AML 77% ANT 11% RT	10.4, range 5.9-16.0 years	-Heart failure, ALL n=32, AML n=20	Multivariable Cox regression ALL cohort -Female vs male gender HR 3.26 (1.49-7.14) Multivariable Cox regression AML cohort -Female gender HR 0.99 (not sign)	SB: low risk AB: low risk DB: unclear CF: low risk
Chow 2015	Survivors CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) -Female vs. male: RR 1.7 (1.3 to 2.1)	SB: unclear AB: unclear DB: unclear CF: low risk
van der Pal 2012	1362 survivors 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	-Heart failure (CTCAE grade 3-5), n=27	Multivariable Cox regression Sex (female vs male): HR 0.8 (0.4-1.8)	SB: low risk AB: low risk DB: unclear CF: low risk
Blanco 2012	Survivors: 170 cases ANT 91% RT 25% 317 controls 71% ANT 14% RT	Median, range Cases: 9.2, 0.1-35.1 Controls: 12.3, 0.4-40	-Clinically validated heart failure and/or LVEF ≤40% and/or FS≤28%, n=170	Multivariable conditional logistic regression -Sex (female vs male): OR 1.47 (0.9 to 2.4)	SB: unclear AB: low risk DB: low risk CF: low risk
Armenian 2011	Lymphoma, leukemia and myeloma survivors 88 cases 218 controls 100% ANT	Median 5.3, range 0.1-20.5 years	-Heart failure per AHA/ACC definition, n=88	Standardized incidence ratio (SIR) heart failure cases compared to matched controls -Female: SIR 7.05 (5.29-9.16) -Male: SIR 2.90 (2.04-4.00), confidence intervals do not overlap	SB: low risk AB: low risk DB: unclear CF: low risk

		RT unknown				
	Mulroone y 2009	14,358 survivors 33% ANT 57% RT	Median 27.0, range 8-51 years	-Heart failure (CTCAE grade 3-5), n=248	Multivariable Cox regression Female vs male: HR 1.4 (1.1-1.9)	SB: low risk AB: low risk DB: unclear CF: low risk
	van Dalen 2006	830 survivors 100% ANT 21% RT	Median 8.5, range 0.01-28.4	-Heart failure, n=21	Multivariable Cox regression RR of sex was not significant and not reported	SB: low risk AB: low risk DB: low risk CF: unclear
	Pein 2004	229 solid tumor survivors 100% ANT 55% RT	Mean 18 years	-Heart failure, FS<25%, EF<50%, or ESWS>100, n=89	Multivariable Cox regression Female vs male: RR 1.41 (0.8 – 2.6)	SB: high risk AB: low risk DB: unclear CF: low risk
	Green 2001	Wilms tumor survivors Cases: 35 Controls: 137	Range ± 1-20 years	Heart failure, clinically validated, n=35	Multivariable conditional logistic regression (nested case-control) -Female vs male: RR 3.5 (1.4-8.8)	SB: unclear AB: high risk DB: low risk CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies and matched case-control studies				
Study limitations:	0	Limitations: Selection bias high risk in 2/14, unclear in 3/14, low risk in 9/14; Attrition bias high risk in 2/14, unclear in 1/14, low risk in 11/14; Detection bias high risk in 0/14, unclear in 11/14, low risk in 3/14; Confounding high risk in 0/14, unclear in 1/14, low risk in 13/14.				
Consistency:	-1	Some inconsistency; 8 studies showed significant increased risk in females, the other studies showed no significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	Large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for symptomatic heart failure in female vs. male CAYA cancer survivors. (14 studies; 8 significant effect; 399 events; 59778 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

Summary table: Risk for heart failure by sex

Study	Risk estimate females vs males (95% CI)

Mulrooney 2020	**HR 1.51 (1.10-2.06)**
Chen 2020, age 20	**RR 1.86 (1.23-2.82)**
Chen 2020, age 35	RR 1.47 (0.72-3.03)
Feijen 2019-1	HR 0.9 (0.6-1.3)
Dietz 2019	ns
Bates 2019	**RR 1.4 (1.1-2.0)**
Chellapandian 2019 ALL	**HR 3.26 (1.49-7.14)**
Chellapandian 2019 AML	HR 0.99 (ns)
Chow 2015	**RR 1.7 (1.3-2.1)**
van der Pal 2012	HR 0.8 (0.4-1.8)
Blanco 2012	OR 1.47 (0.9-2.4)
Armenian 2011	**-Female: SIR 7.05 (5.29-9.16)** **-Male: SIR 2.90 (2.04-4.00)**
Mulrooney 2009	**HR 1.4 (1.1-1.9)**
van Dalen 2006	ns
Pein 2004	RR 1.41 (0.8-2.6)
Green 2001	**RR 3.5 (1.4-8.8)**

f. Anthracycline threshold for developing asymptomatic LV systolic dysfunction

PICO	Study	No. of participants	-Follow up (median/mean, range) yr	-Outcome definition -heart failure symptoms	Risk factor estimates (95% confidence interval)	Risk of bias
1f Anthracycline threshold for developing asymptomatic LV systolic dysfunction in CAYA cancer survivors **(n=19 studies)**	Slieker 2019	546 survivors 100% ANT 12% RT	Median 8.5, IQR 6.2-11.4 years	-Mean longitudinal strain Z score 4CH view -100% asymptomatic, 1.3% on meds	Multivariable linear regression: Cumulative anthracycline dose was not significantly associated with mean longitudinal strain Z score.	SB: unclear AB: low risk DB: unclear CF: low risk
	Nolan 2018	1807 survivors 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF -GLS -% asymptomatic not reported	Multivariable linear regression -Anthracycline dose, sex and age at diagnosis not significantly associated with GLS -Anthracycline dose significantly associated with lower 3D-LVEF (-1.51x10^-2; p<0.001)	SB: high risk AB: low risk DB: unclear CF: low risk
	Spewak 2017	853 survivors 95% ANT 28% RT	Median 7.5, range 2.4-19.9 years	At least one abnormal screening echo: LVEF <55% and/or FS <28%, n=37 -n=42 symptomatic	Multivariable logistic regression -Anthracycline, mg/m2 (100-199=reference) 200-299: OR 1.3 (0.5-3.4) ≥300: OR 3.1 (1.3-7.2)	SB: low risk AB: low risk DB: unclear CF: low risk
	Markman 2017	134 survivors 72% ANT	Mean 14 ± 7 years	-LV systolic dysfunction on echo (LVEF<55% or FS	Multivariable logistic regression -Anthracycline dose per 1 mg/m2: OR 1.001, p=0.054	SB: low risk AB: low risk

	21% RT		≥2SD below age normal), n=33 -42% of cases used ACEi		DB: unclear CF: low risk
Christiansen 2016	231 lymphoma ALL survivors 77% ANT 23% RT	Mean 21.9±8.0	-Peak |GLS| < -1.96SD of controls, sex-specific, n=74 (32%) -% asymptomatic not reported	-N=26 had LVEF<50% or FS<27% (females) or FS<25% (males) -N=14 had coronary artery disease, stroke, hypertension or diabetes <u>Multivariable logistic regression for abnormal GLS</u> Anthracycline >300 vs ≤300 mg/m2: OR 4.8 (1.7-14) p=0.003	SB: low risk AB: low risk DB: unclear CF: high risk
Yu 2016	134 survivors 100% ANT 39% RT	Median 15, range 2-39 years	-Echo LVEF, FS, GLS -GLS ≥-16%, n=31 -100% asymptomatic	<u>Multivariable linear and logistic regression</u> -Anthracycline dose was not significantly associated with abnormal GLS (≥-16%) or continuous LVEF, FS and GLS	SB: high risk AB: low risk DB: unclear CF: high risk
Mulrooney 2016	1853 survivors 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%, 4.7% newly identified during this evaluation) -nearly 100% asymptomatic	<u>Multivariable logistic regression</u> -Anthracycline dose ≥250 vs <250 mg/m2: OR 2.7 (1.1-6.9)	SB: high risk AB: low risk DB: unclear CF: low risk
Ramjaun 2015	333 survivors 92% ANT 39% RT	Median 15.8, range 5.0-47.9 years	-sustained LVEF <55% or FS <28% or valvular abnormalities, n=29 (8.7%) -% asymptomatic not reported	<u>Multivariable interval regression (time to first occurance of sustained echocardiographic abnormality)</u> -Negative coefficient indicates a shorter time to event -Anthracycline dose <250 mg/m2 vs none: -0.96 (-2.53, 0.61), p=0.23 ≥250 mg/m2 vs none: -2.10 (-3,72, -0.48), p=0.01	SB: low risk AB: low risk DB: unclear CF: high risk
Armstrong 2015	1820 survivors 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -Diastolic dysfunction ASE grade 1-3, n=158 (8.7%) -% asymptomatic not reported	<u>Multivariable poisson regression 3D LVEF<50%</u> -Anthracycline dose, mg/m2 (none=reference) 1-100: RR 1.74 (0.66 - 4.61) 101-200: RR 2.80 (1.24 - 6.31) 201-300: RR 3.80 (1.59 - 9.10) 301-400: RR 4.76 (2.16 - 10.50) >400: RR 7.71 (3.04 - 19.57) <u>Multivariable poisson regression GLS >2D</u> -Anthracycline dose, mg/m2 (none=reference) 1-100: RR 1.38 (1.05-1.82) 101-200: RR 1.16 (0.89-1.50) 201-300: RR 1.06 (0.78-1.45) 301-400: RR 1.72 (1.31-2.26) >400: RR 1.73 (1.19-2.50)	SB: high risk AB: low risk DB: unclear CF: low risk

Christiansen 2014	125 lymphoma 74% ANT 54% RT	Mean 20.4±8.6 years	-LVEF <50%, n=5 (4%) -FS <27% (F)/<25%(M), n=10 (8%) -Diastolic dysfunction -% asymptomatic not reported	Multivariable logistic regression for LV systolic dysfunction (including sex, diagnosis, age, age at Dx, RT and anthracycline treatment) -None significant (limited power)	SB: low risk AB: low risk DB: unclear CF: low risk
Armenian 2014	ALL, AML, lymphoma: 100 HR: ANT≥300 16% RT 50 LR: ANT<300 0% RT	Median, range HR:12.0, 2.6-37.9 LR: 13.2, 5.3-28.6	Abnormal LV end-systolic wall stress (>2SD normal). -100% asymptomatic **and LVEF>50%**	Multivariable logistic regression -HR (≥300 mg/m2) vs healthy control: OR 8.15 (P < 0.01) -LR (<300 mg/m2) vs healthy control: OR 2.13 (P=0.36). -Anthracycline dose, mg/m2 (none=reference), P = 0.01 (trend). 1–99: OR 1.43 (not significant); 100–299: OR 2.71; 300–399: OR 4.13; ≥400: OR 12.81	SB: low risk AB: low risk DB: low risk CF: low risk
Brouwer 2011	277 survivors 72% ANT 63% RT	Median 18.2, range 5.4-30.8 years	-FS<29%: n=100/274 (37%) -WMSI >1.00: n=39/267 (15%) -7 clinical heart failure and 17 on cardmeds	Multivariable logistic regression *FS<29%; OR* -Anthracycline dose ≥183 mg/m2 vs none: 2.18 (1.25-3.80) *WMSI >1.00; OR* -Anthracycline dose >183 mg/m2: 2.40 (1.10-5.25)	SB: low risk AB: low risk DB: unclear CF: low risk
Rathe 2010	80 ALL 100% ANT RT unknown	Median 8.2, range 1.1-30.6 years	-Echo LVEF -All asymptomatic	Multivariable linear regression analysis: ΔEF Anthracycline dose not significantly associated with EF decline (only patients treated with a cumulative dose <300 mg/m^2)	SB: high risk AB: low risk DB: unclear CF: low risk
van der Pal 2010	517 survivors 69% ANT 35% RT	Median 15.4, range 5.1-40.3 years	-Echo FS<30%, n=139 (27%) -7 had previous heart failure, all asymptomatic at present study	Multivariable logistic regression (FS<30%) -Anthracyclines, mg/m2 (1-150=reference) 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)	SB: low risk AB: low risk DB: low risk CF: low risk
Abosoudah 2010	469 survivors 100% ANT 34% RT	Median 3, range 1-10 years	-Abnormal echo: EF < 55% or FS < 28% or LVED z-score > 2.0 or LVPW z-score < −2.0 n=79 (16.8%) -% asymptomatic not reported	Median time from 1 year of therapy to abnormal echo 2.9, range 0.01-9.8 years Multivariable Cox regression -Anthracycline dose, mg/m2 (<200=reference) 200-300 HR 1.32 (0.61-2.85) NS >300 HR 3.00 (1.51-5.98)	SB: low risk AB: high risk DB: unclear CF: low risk
Hudson 2007	223 survivors 70% ANT 27% ANT+RT 2.7% RT	Median 9.0, range 3.0-18.0 years	-Screening echo: FS <28%, n=not reported -All asymptomatic	Multivariable logistic regression with univariable p<0.10 Anthracycline dose per 50 mg/m2: OR 1.19 (1.01-1.39) p=0.033	SB: high risk AB: low risk DB: low risk CF: low risk

	Paulides 2006	265 sarcoma 100% ANT 7% RT	Mean 3±1 years	-Subclinical FS<29% at least twice, n=16 -Heart failure, n=4	Multivariable linear and logistic regression -No significant risk factors among anthracycline dose, age at diagnosis, gender, mediastinal irradiation, and longer follow-up.	SB: high risk AB: unclear DB: unclear CF: unclear
	Sorensen 2003	101 ALL 97 Wilms 100% ANT RT unknown	Mean ± SD 1st evaluation: ALL 6.2 ±2.0 Wilms 6.7 ±3.7 2nd evaluation: ALL 10.3 ±2.1 Wilms 11.1 ±4.7	-Echo including FS	Multivariable linear regression (FS evaluation 2) Anthracycline dose per 100 mg: B -1.77 (-2.7, -0.9) Multivariable linear regression (difference FS evaluation 1-2) Anthracycline dose per 100 mg: B -1.48 (-2.4, -0.5)	SB: low risk AB: low risk DB: low risk CF: low risk
	Kremer 2002	25 articles included n=2563 Searched 1966-2001	Range across studies 0.1-23 years	Abnormal FS (<28 to <30%, 15 studies) or EF, VCFc, afterload (i.e., ESWS) or SVI	Significant risk factors for abnormal FS/EF in multivariable analysis ***Steinherz (1991) N=201, linear regression of FS*** Anth – median 450 (range 200-1275) -cumulative dose x length of follow-up: -0.9*10^{-3} FS decrease per 1 unit increase in cumulative dose x length of follow-up, p<0.05 -mediastinal radiation (yes/no): -3.04 lower FS, p<0.05 ***Silber (1993) N=150, logistic regression of EF<55%*** Anth – mean 307 (range 50-750) -anthracycline dose 400 vs 100 mg/m^2: OR 5.2 (1.9-14.1), p=0.001 -age at treatment 5 vs 18 years: OR 2.4 (1.0-5.4), p=0.05 -female vs male sex: OR 3.2 (1.6-6.6), p=0.001 ***Sorensen 1997, N=120, linear regression of FS*** -age at start of treatment: -0.24 lower FS per year ***Lipshultz (1995) N=87, linear regression of FS*** Anth- median 390 (range 224-550) -dosage in 3 weeks: -0.0543 standard deviation decrease in FS per 1 mg/m^2 increase, p=0.02 -cumulative dose: -0.0146 standard deviation decrease in FS per 1 mg/m^2 increase, p<0.001 -age at diagnosis: 0.0876 standard deviations increase in FS per year, p=0.02 ***Nysom (1998) N=189, linear regression analysis of FS*** Anth range 0-550 -significant non-linear association of higher cumulative dose with lower FS z score: FS z score=1.383+0.000123 x dose (mg/m^2) - 0.0000181 x dose^2. Significant lower FS at cumulative dose >280 mg/m^2.	SB: high risk AB: unclear DB: unclear CF: unclear
GRADE assessment:						
Study design:	+4	Retrospective cohort studies, matched case-control studies and a systematic review				

Study limitations:	-1	Some limitations: Selection bias high risk in 8/19, unclear in 1/19, low risk in 10/19; Attrition bias high risk in 1/19, unclear in 2/19, low risk in 16/19; Detection bias high risk in 0/19, unclear in 15/19, low risk in 4/19; Confounding high risk in 3/19, unclear in 2/19, low risk in 14/19.
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Some studies are underpowered to study risk factors and have wide confidence intervals (possibility of false negative results)
Publication bias:	0	Unlikely
Effect size:	+1	Large effect sizes for anthracycline dose
Dose-response:	+1	Clear evidence for a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increasing risk for asymptomatic LV systolic dysfunction with increasing cumulative anthracycline dose in CAYA cancer survivors (19 studies; 13 significant effect; 868 events; 100,015 participants). LVEF -Dose <100 mg/m2 vs none: no significant increased risk, RR range 1.43-1.74 (2 studies, 0 significant effect) -Dose 101-300 mg/m2 vs none: RR range 2.71-3.80 (2 studies, 2 found a significant effect) -Dose >300 mg/m2 vs none: RR range 4.13-12.81 (2 studies, 2 found a significant effect) Longitudinal strain -Dose <100 mg/m2 vs none: RR 1.38 (1 study, 1 found a significant effect) -Dose 101-300 mg/m2 vs none: RR range 1.06-1.16 (1 study, none found a significant effect) -Dose >300 mg/m2 vs none: RR range 1.72-1.73 (1 study, 1 found a significant effect)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

Summary table: Risk for asymptomatic LV dysfunction by anthracycline dose category with no anthracyclines as reference

Dose (mg/m2) vs none	Ramjaun 2015, sustained LVEF <55% or FS <28% or valvular abnormalities	Armenian 2014, ESWS >2SD (all LVEF>50%)	Armstrong 2015, 3D LVEF <50%	Armstrong 2015, GLS >2SD
1-100		OR 1.43 (not significant)	RR 1.74 (0.66 - 4.61)	**RR 1.38 (1.05-1.82)**
101-200			**RR 2.80 (1.24 - 6.31)**	RR 1.16 (0.89-1.50)
100-299		**OR 2.71 (p<0.05)**		
201-300			**RR 3.80 (1.59 - 9.10)**	RR 1.06 (0.78-1.45)
301-400		**OR 4.13 (p<0.05)**	**RR 4.76 (2.16 - 10.50)**	**RR 1.72 (1.31-2.26)**
>400		**OR 12.81 (p<0.05)**	**RR 7.71 (3.04 - 19.57)**	**RR 1.73 (1.19-2.50)**
<250	Time to outcome -0.96 (2.53, 0.61; p=0.23)			
≥250	**Time to outcome -2.10 (-3,72, -0.48; p=0.01)**			

g. Interaction anthracycline dose with sex and age at diagnosis/treatment for developing asymptomatic LV dysfunction

No studies

h. Overall effect of age at diagnosis/treatment for developing asymptomatic LV dysfunction

PICO	Study	No. of participants	-Follow up (median/mean, range) yr	-Outcome definition -heart failure symptoms	Risk factor estimates (95% confidence interval)	Risk of bias
1h Effect of age at diagnosis/treatment for developing asymptomatic LV systolic dysfunction in CAYA cancer survivors **(n= 16 studies)**	Slieker 2019	546 survivors 100% ANT 12% RT	Median 8.5, IQR 6.2-11.4 years	-Mean longitudinal strain Z score 4CH view -100% asymptomatic, 1.3% on meds	Multivariable linear regression: Age at diagnosis was not significantly associated with mean longitudinal strain Z score.	SB: unclear AB: low risk DB: unclear CF: low risk
	Nolan 2018	1807 survivors 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF -GLS -% asymptomatic not reported	Multivariable linear regression -Age at diagnosis not significantly associated with GLS	SB: high risk AB: low risk DB: unclear CF: low risk
	Spewak 2017	853 survivors 95% ANT 28% RT	Median 7.5, range 2.4-19.9 years	At least one abnormal screening echo: LVEF <55% and/or FS <28%, n=37 -n=42 symptomatic	Multivariable logistic regression -Age at diagnosis (<1 year=reference) 1-4 years: OR 1.3 (0.2-10.9), p>0.05 ≥5 years: OR 1.6 (0.2-12.3), p>0.05	SB: low risk AB: low risk DB: unclear CF: low risk
	Christiansen 2016	231 ALL AML 77% ANT 23% RT	Mean 21.9±8.0	-Peak |GLS| < -1.96SD of controls, sex-specific, n=74 (32%) -% asymptomatic not reported	Multivariable logistic regression for abnormal GLS Age at diagnosis not significant	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 survivors 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%, 4.7% newly identified during this evaluation) -nearly 100% asymptomatic	Multivariable logistic regression -Age at diagnosis (≥15 years=reference), p>0.05 for all 0-4 years: OR 0.5 (0.3–1.1) 5-9 years: OR 0.6 (0.3–1.2) 10-14 years: OR 0.9 (0.5–1.7)	SB: high risk AB: low risk DB: unclear CF: low risk
	Ramjaun 2015	333 survivors 92% ANT 39% RT	Median 15.8, range 5.0-47.9 years	-LVEF <55% or SF <28% or valvular abnormalities, n= -% asymptomatic not reported	Multivariable interval regression (time to first occurance of sustained echocardiographic abnormality) -Negative coefficient indicates a shorter time to event **-Age at diagnosis <5 vs ≥5 years: -0.72 (-1.37, -0.06), p=0.033**	SB: low risk AB: low risk DB: unclear CF: high risk
	Armstrong 2015	1820 survivors 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -Diastolic dysfunction ASE grade 1-3, n=158 (8.7%)	Multivariable poisson regression 3D LVEF<50% -Age at diagnosis (≥15 years=reference), p>0.05 for all 0-4 years: RR 0.66 (0.35 - 1.27) 5-9 years: RR 0.67 (0.36 - 1.25) 10-14 years: RR 1.02 (0.59 - 1.76)	SB: high risk AB: low risk DB: unclear CF: low risk

			-% asymptomatic not reported	Multivariable poisson regression GLS >2D -Age at diagnosis (≥15 years=reference), p>0.05 for all 0-4 years: RR 1.02 (0.82-1.27) 5-9 years: RR 0.92 (0.74-1.15) 10-14 years: RR 1.03 (0.83-1.24)	
Christiansen 2014	125 lymphoma 74% ANT 54% RT	Mean 20.4±8.6 years	-LVEF <50%, n=5 (4%) -FS <27% (F)/<25%(M), n=10 (8%) -Diastolic dysfunction -% asymptomatic not reported	Multivariable logistic regression for LV systolic dysfunction -covariates: sex, diagnosis, age, age at Dx, RT and anthracycline treatment -None significant (limited power)	SB: low risk AB: low risk DB: unclear CF: low risk
Brouwer 2011	277 survivors 72% ANT 63% RT	Median 18.2, range 5.4-30.8 years	-FS<29%: n=100/274 (37%) -WMSI >1.00: n=39/267 (15%) -7 clinical heart failure and 17 on cardmeds	Multivariable logistic regression -Age at diagnosis not significantly associated with FS<29% or WMSI >1.00	SB: low risk AB: low risk DB: unclear CF: low risk
Rathe 2010	80 ALL 100% ANT RT unknown	Median 8.2, range 1.1-30.6 years	-Echo LVEF -All asymptomatic	Multivariable linear regression analysis: ΔEF Age at diagnosis not significantly associated with EF decline (in patients treated with a cumulative dose <300 mg/m2)	SB: high risk AB: low risk DB: unclear CF: low risk
van der Pal 2010	517 survivors 69% ANT 35% RT	Median 15.4, range 5.1-40.3 years	-Echo FS<30%, n=139 (27%) -7 had previous heart failure, all asymptomatic at present study	Multivariable logistic regression (FS<30%) **-Age at diagnosis (≥15=referent), P for trend 0.049** 0-4 years OR 2.94 (1.08-8.02) NS 5-9 years OR 1.64 (0.67-4.01) 10-14 years OR 1.45 (0.64 to 3.28)	SB: low risk AB: low risk DB: low risk CF: low risk
Abosoudah 2010	469 survivors 100% ANT 34% RT	Median 3, range 1-10 years	-Abnormal echo: EF < 55% or FS < 28% or LVED z-score > 2.0 or LVPW z-score < −2.0 n=79 (16.8%) -% asymptomatic not reported	Multivariable Cox proportional hazard model -Age at treatment, years (>5=reference) <1 HR 1.16 (0.30-4.48) **1-4 1.89 (1.08-3.31)**	SB: low risk AB: high risk DB: unclear CF: low risk
Hudson 2007	223 survivors 70% ANT 27% ANT+RT 2.7% RT	Median 9.0, range 3.0-18.0 years	-Screening echo: FS <28% -All asymptomatic	Multivariable logistic regression with univariable p<0.10 **Age at diagnosis ≥5 vs <5 years: OR 2.41 (0.9-6.4), p=0.08**	SB: high risk AB: low risk DB: low risk CF: low risk
Paulides 2006	265 sarcoma 100% ANT	Mean 3±1 years	-Subclinical FS<29% at least twice, n=16	Multivariable linear and logistic regression	SB: high risk AB: unclear

		7% RT		-Heart failure, n=4	-No significant risk factors among anthracycline dose, age at diagnosis, gender, mediastinal irradiation, and longer follow-up.	DB: unclear CF: unclear
	Sorensen 2003	101 ALL 97 Wilms 100% ANT RT unknown	Mean ± SD 1st evaluation: ALL 6.2 ±2.0 Wilms 6.7 ±3.7 2nd evaluation: ALL 10.3 ±2.1 Wilms 11.1 ±4.7	-Echo including FS	Multivariable linear regression (FS evaluation 2) Age treatment/year: B -0.03 (-0.39, 0.07), p>0.05 Multivariable linear regression (difference FS evaluation 1-2) Age treatment/years: B 0.18 (-0.09, 0.45), p>0.05	SB: low risk AB: low risk DB: low risk CF: low risk
	Kremer 2002	25 articles included n=2563 Searched 1966-2001	Range across studies 0.1-23 years	Abnormal FS (<28 to <30%, 15 studies) or EF, VCFc, afterload (i.e., ESWS) or SVI	Significant risk factors for abnormal FS/EF in multivariable analysis ***Silber (1993) N=150, logistic regression of EF<55%*** -age at treatment 5 vs 18 years: OR 2.4 (1.0-5.4), p=0.05 ***Sorensen 1997, N=120, linear regression of FS*** -age at start of treatment: -0.24 lower FS per year ***Lipshultz (1995) N=87, linear regression of FS*** -age at diagnosis: 0.0876 standard deviations increase in FS per year, p=0.02	SB: high risk AB: unclear DB: unclear CF: unclear
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 7/16, unclear in 1/16, low risk in 8/16; Attrition bias high risk in 1/16, unclear in 2/16, low risk in 13/16; Detection bias high risk in 0/19, unclear in 13/16, low risk in 3/16; Confounding high risk in 2/16, unclear in 2/16, low risk in 12/16.				
Consistency:	-1	Some inconsistency: only 5 studies showed a significantly higher risk for children treated at a younger age, while 11 studies did not show a significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	Large studies and confidence intervals are not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊖⊖ LOW				
Conclusion:		No significant effect of age at cancer diagnosis/treatment for developing asymptomatic LV dysfunction (16 studies; 11 non-significant effect; 5 significant effect younger age; ; >704 events; 9954 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

i. Overall effect of sex for developing asymptomatic LV dysfunction

PICO	Study	No. of participants	-Follow up (median/mean, range) yr	-Outcome definition -heart failure symptoms	Risk factor estimates (95% confidence interval)	Risk of bias

1i Effect of sex for developing asymptomatic LV systolic dysfunction in CAYA cancer survivors **(n=17 studies)**	Slieker 2019	546 survivors 100% ANT 12% RT	Median 8.5, IQR 6.2-11.4 years	-Mean longitudinal strain Z score 4CH view -100% asymptomatic, 1.3% on meds	<u>Multivariable linear regression:</u> Sex not significantly associated with mean longitudinal strain Z score.	SB: unclear AB: low risk DB: unclear CF: low risk
	Nolan 2018	1807 survivors 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF -GLS -% asymptomatic not reported	<u>Multivariable linear regression</u> -Sex not significantly associated with GLS	SB: high risk AB: low risk DB: unclear CF: low risk
	Spewak 2017	853 survivors 95% ANT 28% RT	Median 7.5, range 2.4-19.9 years	At least one abnormal screening echo: LVEF <55% and/or FS <28%, n=37 -n=42 symptomatic	<u>Multivariable logistic regression</u> -Female vs male: OR 0.5 (0.2-1.1), p>0.05	SB: low risk AB: low risk DB: unclear CF: low risk
	Markman 2017	134 survivors 72% ANT 21% RT	Mean 14 ± 7 years	-LV systolic dysfunction on echo (LVEF<55% or FS ≥2SD below age normal), n=33 -42% of cases used ACEi	<u>Multivariable logistic regression</u> -Male vs female: OR 1.027, p=0.53	SB: low risk AB: low risk DB: unclear CF: low risk
	Christiansen 2016	231 ALL AML 77% ANT 23% RT	Mean 21.9±8.0	-Peak |GLS| < -1.96SD of controls, sex-specific, n=74 (32%) -% asymptomatic not reported	<u>Multivariable logistic regression for impaired GLS</u> Sex not significant	SB: low risk AB: low risk DB: unclear CF: high risk
	Yu 2016	134 survivors 100% ANT 39% RT	Median 15, range 2-39 years	-Echo LVEF, FS, GLS -GLS ≥-16%, n= -100% asymptomatic	-Sex was not significantly associated with abnormal GLS (≥-16%) or LVEF, FS and GLS as continuous variables in multivariable models.	SB: high risk AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 survivors 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%, 4.7% newly identified during this evaluation) -nearly 100% asymptomatic	<u>Multivariable logistic regression</u> **-Male vs female: OR 1.9 (1.1-1.3)**	SB: high risk AB: low risk DB: unclear CF: low risk
	Armstrong 2015	1820 survivors 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -Diastolic dysfunction ASE grade 1-3, n=158 (8.7%) -% asymptomatic not reported	<u>Multivariable poisson regression 3D LVEF<50%</u> **-Female vs male: RR 0.54 (0.36-0.83)** <u>Multivariable poisson regression GLS >2D</u> **-Female vs male: RR 1.55 (1.34-1.79)**	SB: high risk AB: low risk DB: unclear CF: low risk

Christiansen 2014	125 lymphoma survivors 74% ANT 54% RT	Mean 20.4±8.6 years	-LVEF <50%, n=5 (4%) -FS <27% (F)/<25%(M), n=10 (8%) -Diastolic dysfunction -% asymptomatic not reported	Multivariable logistic regression for LV systolic dysfunction -Covariates: sex, diagnosis, age, age at Dx, RT and anthracycline treatment -None significant (limited power)	SB: low risk AB: low risk DB: unclear CF: low risk
Brouwer 2011	277 survivors 72% ANT 63% RT	Median 18.2, range 5.4-30.8 years	-FS<29%: n=100/274 (37%) -WMSI >1.00: n=39/267 (15%) -7 clinical heart failure and 17 on cardmeds	Multivariable logistic regression -Sex not significantly associated with FS<29% or WMSI >1.00	SB: low risk AB: low risk DB: unclear CF: low risk
Rathe 2010	80 ALL 100% ANT RT unknown	Median 8.2, range 1.1-30.6 years	-Echo LVEF -All asymptomatic	Multivariable linear regression analysis: ΔEF Sex not significantly associated with EF decline (in patients treated with a cumulative dose <300 mg/m2)	SB: high risk AB: low risk DB: unclear CF: low risk
van der Pal 2010	517 survivors 69% ANT 35% RT	Median 15.4, range 5.1-40.3 years	-Echo FS<30%, n=139 (27%) -7 had previous heart failure, all asymptomatic at present study	Multivariable logistic regression (FS<30%) -Male vs female: OR 0.73 (0.47-1.13)	SB: low risk AB: low risk DB: low risk CF: low risk
Abosoudah 2010	469 survivors 100% ANT 34% RT	Median 3, range 1-10 years	-Abnormal echo: EF < 55% or FS < 28% or LVED z-score > 2.0 or LVPW z-score < −2.0 n=79 (16.8%) -% asymptomatic not reported	Multivariable Cox proportional hazard model **-Female vs male HR 1.65 (1.04-2.62)**	SB: low risk AB: high risk DB: unclear CF: low risk
Hudson 2007	223 survivors 70% ANT 27% ANT+RT 2.7% RT	Median 9.0, range 3.0-18.0 years	-Screening echo: FS <28% -All asymptomatic	Multivariable logistic regression with univariable p<0.10 Sex not significant in univariable analysis and therefore not taken forward to the multivariable model	SB: high risk AB: low risk DB: low risk CF: low risk
Paulides 2006	265 sarcoma survivors 100% ANT 7% RT	Mean 3±1 years	-Subclinical FS<29% at least twice, n=16 -Heart failure, n=4	Multivariable linear and logistic regression -No significant risk factors among anthracycline dose, age at diagnosis, sex, mediastinal irradiation, and longer follow-up.	SB: high risk AB: unclear DB: unclear CF: unclear
Sorensen 2003	101 ALL 97 Wilms 100% ANT	Mean ± SD 1st evaluation: ALL 6.2 ±2.0	-Echo including FS	Multivariable linear regression (FS evaluation 2) Female vs Male: B -0.73 (-2.07, 0.60) Multivariable linear regression (difference FS evaluation 1-2)	SB: low risk AB: low risk DB: low risk

		RT unknown	Wilms 6.7 ±3.7 2nd evaluation: ALL 10.3 ±2.1 Wilms 11.1 ±4.7		Female vs Male: B -1.38 (-2.78, 0.03)	CF: low risk
	Kremer 2002	25 articles included n=2563 Searched 1966-2001	Range across studies 0.1-23 years	Abnormal FS (<28 to <30%, 15 studies) or EF, VCFc, afterload (i.e., ESWS) or SVI	Significant risk factors for abnormal FS/EF in multivariable analysis *Silber (1993) N=150, logistic regression of EF<55%* **-female vs male sex: OR 3.2 (1.6-6.6), p=0.001**	SB: high risk AB: unclear DB: unclear CF: unclear
GRADE assessment:						
Study design:	+4	Retrospective cohort studies, matched case-control studies and a systematic review				
Study limitations:	-1	Some limitations: Selection bias high risk in 8/17, unclear in 1/17, low risk in 8/17; Attrition bias high risk in 1/17, unclear in 2/17, low risk in 14/17; Detection bias high risk in 0/19, unclear in 15/19, low risk in 4/19; Confounding high risk in 3/19, unclear in 2/19, low risk in 14/19.				
Consistency:	-1	Results are inconsistent, 2 studies found a significant higher risk for females, whereas 2 other studies found a higher risk for males; 13 studies showed non-significant effects.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	Large studies and confidence intervals are not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		No significant effect of sex for developing asymptomatic LV dysfunction (17 studies; 13 non-significant effect; 2 significant effect males; 2 significant effect females; >704 events; 9954 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

2. What is the exact radiotherapy (including TBI) threshold (including dose and volume) for developing cardiomyopathy in CAYA cancer survivors, and does this differ by age at treatment or sex?
    a. Radiotherapy dose threshold for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Dose calculation	Risk factor estimates (95% confidence interval)	Risk of bias
2a Radiotherapy dose threshold for developing symptomatic	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271	-Dose reconstruction using phantoms[1]	Multivariable Cox regression -Mean heart dose, Gray (ref=none) 1-15 HR 0.74 (0.54-1.03) 15.1-34.99 HR 1.56 (1.05-2.33) ≥35 HR 3.95 (2.87-5.43)	SB: high risk AB: high risk DB: unclear CF: low risk

heart failure in CAYA cancer survivors **(n=15 studies)**	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=unknown	-Dose reconstruction using phantoms[1]	<u>Multivariable piecewise exponential models</u> Prediction timepoint (baseline): Age 20 / Age 35 -Chest RT, Gray (none=ref) <5: RR 1.36 (0.64-2.85) / 0 (-) 5-14: RR 1.43 (0.55-3.70) / 0 (-) 15-34: RR 2.56 (1.43-4.57) / 1.11 (0.23-5.25) ≥35: RR 6.76 (3.89-11.76) / 6.30 (2.47-16.09)	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-1	5845 survivors 47% ANT 22% RT	Median 19.9, range 5.0-50.4 years	-Heart failure (CTCAE grade 3-5), n=116	-Max prescribed dose of the largest field involving the heart + TBI>20 Gy	<u>Multivariable Cox regression</u> -Chest RT (none=ref) Potential (yes/no): HR 1.0 (0.4–2.0) Involving the heart <20 Gy: HR 2.0 (1.1–3.6) Involving the heart ≥20 Gy: HR 2.1 (1.1–4.0)	SB: low risk AB: low risk DB: unclear CF: low risk
	Dietz 2019	13,318 survivors 40% ANT 66% RT	Not reported, median ±23 years	-Heart transplantation, n=37	-RT doses abstracted from medical records	<u>Multivariable Cox regression</u> -Mean heart dose, Gray (none=ref) >0-10: HR 2.2 (1.0-4.8), p=0.050 >10-20: HR 1.9 (0.5-7.3), p=0.33 >20-30: HR 6.1 (1.8-20.6), p=0.0035 >30: HR 19.7 (7.1-54.2), p<0.0001	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-2	28,423 survivors 35% DOX 18% DAU 1.1% EPI 1.1% IDA 0.9% Mitox 21% RT	Median 20, range 5-40 years	-Heart failure (CTCAE grade 3-5) before age 40, n=399	-Field-specific maximum total doses -Chest fields included abdominal RT above diaphragm or thorax in the field	<u>Multivariable Cox regression</u> -Chest RT dose 15-34.9 Gy vs none HR 2.1 (1.6-2.8) ≥35 Gy vs none HR 3.5 (2.5-4.8)	SB: unclear AB: low risk DB: unclear CF: low risk
	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	-Dose reconstruction using phantoms[1] -Volumes	<u>Multivariable piecewise exponential model</u> *Mean cardiac RT dose, Gy* 0.1-9.9 vs. None: RR 0.7 (0.5 to 1.0) 10-19.9 vs. None: RR 1.7 (1.1 to 2.7) 20-29.9 vs. None: RR 2.9 (1.9 to 4.6) ≥ 30 vs. None: RR 6.7 (4.6 to 9.9)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mansouri 2019	Survivors: 239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7–26.9 Controls: 33.0, 27.2–39.0	-Clinically validated heart failure, n=239	-Dose reconstruction using phantoms[2] -Volumes	<u>Conditional logistic regression, OR (95% CI)</u> *-Mean heart dose in Gy (no RT, no ANT=ref)* 0-5: OR 0.7 (0.2-2.0) 5-15: OR 2.0 (0.6-6.3) 15-30: OR 5.2 (1.9-13.8) ≥30: OR 20.6 (7.6-55.3)	SB: unclear AB: low risk DB: unclear CF: low risk

Niska 2018	Systematic review of 20 cohort studies	Range of median 2 to 28 years	Cardiac death (1 study) Heart failure (3 studies)	Not reported	<u>Tukenova 2010 n=4122, cardiovascular death n=32 (not only heart failure related)</u> Mean heart dose, Gray (none=reference) <1: RR 3.0 (0.3-28.0) 1-4.9: RR 2.5 (0.2-41.5) 5-14.9: RR 12.5 (1.4-116.1) ≥15: RR 25.1 (3.0-209.5) -Chow 2015, Mulrooney 2009, van der Pal 2012 are elsewhere in table -Overall doses ≥15 Gray substantially increased risk for valvular disease and heart failure	SB: unclear AB: unclear DB: unclear CF: unclear
Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	-Dose reconstruction using phantoms[1]	<u>Multivariable Poisson regression (model including chest RT dosimetry)</u> < 5 vs. None: RR 0.9 (0.5 to 1.6) 5-14 vs. None: RR 1.6 (1.0 to 2.7) 15-34 vs. None: RR 3.1 (2.2 to 4.5) ≥ 35 vs. None: RR 10.5 (7.2 to 15.4)	SB: unclear AB: unclear DB: unclear CF: low risk
van der Pal 2012	1362 survivors 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	-Heart failure (CTCAE grade 3-5), n=27	-Equivalent dose in 2-Gray fractions (EQD2)	<u>Multivariable Cox regression (Model 1)</u> ChestRT (EQD2 per 10 Gy): HR 1.4 (1.1-2.0) <u>Multivariable Cox regression (Model 2)</u> ANT + chest RT (Yes vs. No): HR 55.9 (6.6-470)	SB: low risk AB: low risk DB: unclear CF: low risk
Mulroone y 2009	14,358 survivors 33% ANT 57% RT	Median 27.0, range 8-51 years	-Heart failure (CTCAE grade 3-5), n=248	-Phantom reconstruction including scatter	<u>Multivariable Cox regression</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	SB: low risk AB: low risk DB: unclear CF: low risk
Guldner 2006	447 survivors 100% ANT 55% RT	Mean 18 years	-Heart failure, n=24	-Mean heart dose in Gray	<u>Multivariable logistic regression</u> Dose-dependent increase in HF and cardiac disease risk by radiation dose: increase in relative risk of 19% (95% CI: 2% to 50%) per 1 Gray.	SB: high risk AB: low risk DB: unclear CF: low risk
Van der Pal 2005	Systematic review of 10 studies	Range across studies 1-29 years.	-All cardiac events (heart failure, myocardial infarction)	-Inclusion criterium: radiotherapy involving the heart region	<u>Multivariable regression from 1 case-control study</u> Lung RT per 10 Gy: RR 1.6 (1.1-2.7) Left abd per 10 Gy: RR 1.8 (1.1-2.7) Right abd. 10 Gy: RR 0.94 (0.66-1.3)	SB: low risk AB: unclear DB: high risk CF: low risk

	Pein 2004	229 survivors 100% ANT 55% RT	Mean 18 years	-Heart failure, FS<25%, EF<50%, or ESWS>100, n=89	-Mean dose to six anatomical sites in the heart.	Multivariable Cox regression, RR (95% CI) 0 No chest RT (Ref) >0-5 Gy: RR 1.63 (0.82-3.26) >5-20 Gy: RR 6.48 (2.76-15.20) >20 Gy: RR 4.40 (1.11-17.48)	SB: high risk AB: low risk DB: unclear CF: low risk
	Green 2001	Cases: 35 Controls: 137	Range ± 1-20 years	Heart failure, clinically validated, n=35	-Doses to abdomen and lung determined within 6-month intervals from medical records	Multivariable conditional logistic regression (nested case-control) -Lung RT (none=reference) 10-19.99 Gray: RR 1.5 (0.6-3.9) p=0.39 ≥ 20 Gray: RR 4.3 (0.8-24) p=0.1, p trend=0.12 -Abdominal radiation (none or right sided=reference) Left sided: RR 4.0 (1.4-11.6), p=0.01	SB: unclear AB: high risk DB: low risk CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies, matched case-control studies and systematic reviews
Study limitations:	-1	Some limitations: Selection bias high risk in 3/15, unclear in 5/15, low risk in 7/15; Attrition bias high risk in 2/15, unclear in 3/15, low risk in 10/15; Detection bias high risk in 1/15, unclear in 13/15, low risk in 1/15; Confounding high risk in 0/15, unclear in 1/15, low risk in 14/15.
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals not wide.
Publication bias:	0	Unlikely
Effect size:	+1	Large effect sizes
Dose-response:	+1	Clear evidence for a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊕ HIGH
Conclusion:		Exponential increasing risk for symptomatic heart failure with increasing radiation dose exposing the heart region in CAYA cancer survivors. Low risk: No significant effect of a radiotherapy dose <15 Gy exposing the heart region vs. no radiotherapy on symptomatic heart failure in CAYA cancer survivors. Moderate risk: ≥1.6-fold increased risk of symptomatic heart failure in CAYA cancer survivors treated with a radiotherapy dose 15-30 Gy exposing the heart region vs. no radiotherapy. High risk: ≥3.5-fold increased risk of symptomatic heart failure in CAYA cancer survivors treated with a radiotherapy dose ≥30 or ≥35 Gy exposing the heart region vs. no radiotherapy. (15 studies; 14 significant effect; >2234 events; >158531 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; Gy, Gray; SB, selection bias.

1: Phantom based dose reconstructions: Stovall M, Weathers R, Kasper C, et al: Dose reconstruction for therapeutic and diagnostic radiation exposures: Use in epidemiological studies. Radiat Res 166: 141-157, 2006

2: Phantom based dose recontructions: Veres C, Allodji RS, Llanas D, Vu Bezin J, Chavaudra J, Mège JP, Lefkopoulos D, Quiniou E, Deutsh E, de Vathaire F, Diallo I. Retrospective reconstructions of active bone marrow dose-volume histograms. Int J Radiat Oncol Biol Phys 2014;90:1216 – 1224

Summary table: Radiotherapy dose threshold for developing symptomatic heart failure

Radiotherapy dose (Gray) vs none	Mulrooney 2020	Chen 2020, age 20	Feijen 2019-1	Dietz 2019	Feijen 2019-2	Bates 2019	Mansouri 2019	Niska 2018 also non-HF related	Chow 2015	Vd Pal 2012	Mulrooney 2009	Guldner 2006	Vd Pal 2005	Pein 2004	Green 2001, lung RT	Conclusion (range)
<1								RR 3.0 (0.3-28.0)								Not significant
1-5		RR 1.36 (0.64-2.85)					OR 0.7 (0.2-2.0)	RR 2.5 (0.2-41.5)	RR 0.9 (0.5 to 1.6)		HR 0.9 (0.6-1.4)			RR 1.63 (0.82-3.26)		Not significant
1-10				HR 2.2 (1.0-4.8)		RR 0.7 (0.5 to 1.0)										Not significant
1-15	HR 0.74 (0.54-1.03)															Not significant
1-19			**HR 2.0 (1.1-3.6)**													**2.0 fold**
5-14		RR 1.43 (0.55-3.70)					OR 2.0 (0.6-6.3)	**RR 12.5 (1.4-116.1)**	RR 1.6 (1.0 to 2.7)		HR 1.3 (0.7-2.5)					Not significant for heart failure; 12.5 fold for cardiac events including non-HF related
>5-20														**RR 6.48 (2.76-15.20)**		**6.5 fold**
>10-20				HR 1.9 (0.5-7.3)		**RR 1.7 (1.1 to 2.7)**									RR 1.5 (0.6-3.9)	**Not significant to 1.7 fold**
15-30							**OR 5.2 (1.9-13.8)**									**5.2 fold**

>15-34	**HR 1.56 (1.05-2.33)**	**RR 2.56 (1.43-4.57)**		**HR 2.1 (1.6-2.8)**				**RR 3.1 (2.2 to 4.5)**	**HR 2.2 (1.4-3.5)**					**1.6-3.1 fold**
≥15						**RR 25.1 (3.0-209.5)**								**25.1 fold**
>20-30				**HR 6.1 (1.8-20.6)**	**RR 2.9 (1.9 to 4.6)**									**2.9-6.1 fold**
≥20			**HR 2.1 (1.1–4.0)**									**RR 4.40 (1.11-17.48)**	RR 4.3 (0.8-24)	**2.1-4.4 fold**
>30				**HR 19.7 (7.1-54.2)**	**RR 6.7 (4.6 to 9.9)**	**OR 20.6 (7.6-55.3)**								**6.7-19.7 fold**
≥35	**HR 3.95 (2.87-5.43)**	**RR 6.76 (3.89-11.76)**		**HR 3.5 (2.5-4.8)**				**RR 10.5 (7.2 to 15.4)**	**HR 4.5 (2.8-7.2)**					**3.5-6.8 fold**
Per 1 Gray										**RR 1.19 (1.02-1.50)**				**1.19 fold**
Per 10 Gray							**HR 1.4 (1.1-2.0)**				**RR 1.6 (1.1-2.7)**			**1.4-1.6 fold**

b. Radiotherapy volume threshold for developing symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Dose calculation	Risk factor estimates (95% confidence interval)	Risk of bias
2b Radiotherapy volume threshold for developing	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	-Dose reconstruction using phantoms[1] -Volumes	Multivariable piecewise exponential model *Volume of heart receiving 5 Gray when volume receiving 20 Gray = 0% (no RT=ref)* 0%: RR 0.6 (0.5 to 0.9) 0.1-49.9%: RR 0.7 (0.3 to 1.8)	SB: low risk AB: low risk DB: unclear CF: low risk

symptomatic heart failure in CAYA cancer survivors **(n=2 studies)**						≥ 50%: RR 1.3 (0.8 to 2.2) *Volume of heart receiving >20 Gy (no RT=ref)* 0%: RR 0.8 (0.6 to 1.0) **0.1-29.9%: RR 2.3 (1.1 to 4.8)** **30-79.9%: RR 3.4 (2.1 to 5.6)** **≥ 80%: RR 4.5 (3.2 to 6.2)**	
	Mansouri 2019	Survivors: 239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7–26.9 Controls: 33.0, 27.2–39.0	-Clinically validated heart failure, n=239	-Dose reconstruction using phantoms[2] -Volumes	Conditional logistic regression, OR (95% CI) *-Volume of the heart (%) receiving ≥30 Gy (no RT, no ANT=ref)* <10%: 1.9 (0.7–5.5) **10–50%: 5.5 (2.1–14.1)** **≥50%: 17 (7.6–38.0)** *-Volume of the left ventricle (%) receiving ≥30 (no RT, no ANT=ref)* **0–10%: 3.6 (1.3–10.1)** **10–50%: 6.6 (2.8–15.4)** **≥50%: 24.6 (10.3–58.7)**	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort study and a matched case-control study
Study limitations:	-1	Some limitations: Selection bias unclear in 1/2, low risk in 1/2; Attrition bias low risk in 2/2; Detection bias unclear in 2/2; Confounding low risk in 2/2.
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals not wide.
Publication bias:	0	Unlikely
Effect size:	+1	Large effect sizes
Dose-response:	+1	Clear evidence for a dose-response relationship
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increasing risk for symptomatic heart failure with larger volumes of the heart exposed to >20 Gray in CAYA cancer survivors. There is not enough evidence to identify volume thresholds for developing symptomatic heart failure. (2 studies; 2 significant effect; 610 events; 25495 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

1: Phantom based dose reconstructions: Stovall M, Weathers R, Kasper C, et al: Dose reconstruction for therapeutic and diagnostic radiation exposures: Use in epidemiological studies. Radiat Res 166: 141-157, 2006

2: Phantom based dose recontructions: Veres C, Allodji RS, Llanas D, Vu Bezin J, Chavaudra J, Mège JP, Lefkopoulos D, Quiniou E, Deutsh E, de Vathaire F, Diallo I. Retrospective reconstructions of active bone marrow dose-volume histograms. Int J Radiat Oncol Biol Phys 2014;90:1216 – 1224

c. Interaction of radiotherapy dose/volume with sex and age at diagnosis/treatment for developing symptomatic heart failure or asymptomatic LV dysfunction

No studies

d. Radiotherapy dose threshold for developing asymptomatic LV dysfunction

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% asymptomatic	Dose and volume calculation	Risk factor estimates (95% confidence interval)	Risk of bias
2d Radiotherapy dose threshold for developing asymptomatic LV dysfunction in CAYA cancer survivors **(n=6 studies)**	Spewak 2017	853 survivors 95% ANT 28% RT	Median 7.5, range 2.4-19.9 years	At least one abnormal screening echo: LVEF <55% and/or FS <28%, n=37 -n=42 symptomatic	-Doses abstracted from medical records	Multivariable logistic regression -Chest RT dose, Gray (none=reference) <30: OR 1.2 (0.5-2.9), NS ≥30: OR 2.5 (0.9-7.1), NS	SB: low risk AB: low risk DB: unclear CF: low risk
	Markman 2017	134 survivors 72% ANT 21% RT	Mean 14 ± 7 years	LV systolic dysfunction on echo (LVEF<55% or FS ≥ 2SD below age normal), n=33	-Mediastinal RT, dose calculation not reported	Multivariable logistic regression **Mediastinal RT per 1 Gray: OR 1.002, p=0.027** -42% of cases used ACE-I	SB: low risk AB: low risk DB: unclear CF: low risk
	Mulroone y 2016	1853 survivors 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%, 4.7% newly identified during this evaluation) -nearly 100% asymptomatic	-Mean dose reconstruction using phantoms[1]	Multivariable logistic regression -mean heart dose ≤15 Gray vs none: OR 1.1 (0.5–2.2) **>15 Gray vs none: OR 1.9 (1.1-3.7)**	SB: high risk AB: low risk DB: unclear CF: low risk
	Armstron g 2015	1820 survivors 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -Diastolic dysfunction ASE grade 1-3, n=158 (8.7%) -% asymptomatic not reported	-Mean dose reconstruction using phantoms[1]	Multivariable poisson regression 3D LVEF<50% -Chest RT dose, Gray (none=reference) 1-19.9: RR 1.24 (0.70-2.22) **20-29.9: RR 1.86 (1.00-3.45), p<0.05** **≥30: RR 7.99 (3.88-16.48)** Multivariable poisson regression GLS >2D -Chest RT dose, Gray (none=reference) **1-19.9: RR 1.38 (1.14-1.66)** **20-29.9: RR 1.65 (1.31-2.08)** **≥30: RR 2.39 (1.79-3.18)**	SB: high risk AB: low risk DB: unclear CF: low risk
	Christians en 2014	125 lymphoma survivors 74% ANT 54% RT	Mean 20.4±8.6 years	-LVEF <50%, n=5 (4%) -FS <27% (F)/<25%(M), n=10 (8%) -Diastolic dysfunction -% asymptomatic not reported	-Total radiation dose to the mediastinum.	Multivariable logistic regression for LV systolic dysfunction Covariates: sex, diagnosis, age, age at Dx, RT and anthracycline treatment) -None significant (limited power)	SB: low risk AB: low risk DB: unclear CF: low risk
	van der Pal 2010	517 survivors 69% ANT 35% RT	Median 15.4, range 5.1-40.3 years	-Echo FS<30%, n=139 (27%)	-Doses abstracted from medical records, dose	Multivariable logistic regression (FS<30%) No Radiotherapy (Ref), OR **Thorax: 3.49 (1.6-7.6)**	SB: low risk AB: low risk DB: low risk

			-7 had previous heart failure, all asymptomatic at present study	calculation not reported	**Abdomen: 2.66 (1.0-7.05)** Spine: 0.64 (0.23-1.74) TBI: 0.53 (0.10-2.87)	CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 2/6, low risk in 4/6; Attrition bias low risk in 6/6; Detection bias unclear in 5/6, low risk in 1/6; Confounding low risk in 6/6.				
Consistency:	0	No important inconsistency				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide. One study that did not find an association was underpowered (10 events).				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	+1	Clear evidence for a dose-response relationship				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊕ HIGH				
Conclusion:		Increasing risk for asymptomatic LV dysfunction with increasing radiation dose exposing the heart region in CAYA cancer survivors. (6 studies; 4 significant effect; 448 events; 5302 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

1: Phantom based dose reconstructions: Stovall M, Weathers R, Kasper C, et al: Dose reconstruction for therapeutic and diagnostic radiation exposures: Use in epidemiological studies. Radiat Res 166: 141-157, 2006

e. Radiotherapy volume threshold for developing asymptomatic LV dysfunction

No studies

3. What is the additional risk of cardiomyopathy in CAYA cancer survivors treated with radiotherapy (including dose and volume) exposing the heart combined with other cardiotoxic chemotherapy (i.e., anthracyclines, cyclophosphamide, amsacrine, dactinomycin)?

a. Symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Dose and volume calculation	Risk factor estimates (95% confidence interval)	Risk of bias
3a Additional risk with cardiotoxic chemotherapy for developing symptomatic heart failure in CAYA cancer	Feijen 2019-1	5845 survivors 47% ANT 22% RT	Median 19.9, range 5.0-50.4 years	-Heart failure (CTCAE grade 3-5), n=116	-Max prescribed dose of the largest field involving the heart + TBI>20 Gy	Multivariable Cox regression -No significant interaction between anthracycline dose and radiotherapy involving the heart dose identified -HRs not reported	SB: low risk AB: low risk DB: unclear CF: low risk
	Feijen 2019-2	28,423 survivors 35% DOX	Median 20, range 5-40 years	-Heart failure (CTCAE grade 3-5)	-Field-specific maximum total doses	Multivariable Cox regression -No interaction between chest RT and doxorubicin (P = .39), daunorubicin (P = .69) or mitoxantrone (P = .97)	SB: unclear AB: low risk DB: unclear

survivors treated with radiotherapy **(n=7 studies)**		18% DAU 1.1% EPI 1.1% IDA 0.9% Mitox 21% RT		before age 40, n=399	-Chest fields included abdominal RT above diaphragm or thorax in the field	-HRs not reported	CF: low risk
	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	-Dose reconstruction using phantoms[1] -Volumes	<u>Multivariable piecewise exponential model</u> -Association of anthracycline dose with rate of cardiac disease was not modified by cardiac RT dose (data not shown)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mansouri 2019	Survivors: 239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7–26.9 Controls: 33.0, 27.2–39.0	-Clinically validated heart failure, n=239	-Dose reconstruction using phantoms[2] -Volumes	<u>Conditional logistic regression, OR (95% CI)</u> *-Mean heart dose in Gy (no RT, no ANT=ref)* 0-5 + no ANT: 0.7 (0.2-2.0) 5-15 + no ANT: 2.0 (0.6-6.3) **15-30 + no ANT: 5.2 (1.9-13.8)** **≥30 + no ANT: 20.6 (7.6-55.3)** **0 + ANT: 11.3 (4.7–27.0)** **0–5 + ANT: 21.5 (8.8–52.6)** **5–15 + ANT: 23.8 (7.6–75.0)** **15–30 + ANT: 54.4 (19.3–153)** **≥30 + ANT: 24.6 (7.2–84.1)** -Significant interaction of radiation dose with anthracyclines (yes/no)	SB: unclear AB: low risk DB: unclear CF: low risk
	van der Pal 2012	1362 survivors 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	-Heart failure (CTCAE grade 3-5), n=27	-Equivalent dose in 2-Gray fractions (EQD2)	<u>Multivariable Cox regression (mutually exclusive model)</u> Anthracyclines only (Yes/No) HR 33.5 (4.4-254) Radiotherapy only (Yes vs. No) HR 6.6 (0.6-73) **Anthracyclines+Radiotherapy (Yes vs. No) HR 55.9 (6.6-470)**	SB: low risk AB: low risk DB: unclear CF: low risk
	Aleman 2007	1474 Hodgkin lymphoma RT only 28% RT+chemo 38%	Median 18.7 yrs (28 669 person-years for cohort)	Heart failure, n=52	-84% of RT included the mediastinum	<u>Multivariable Cox regression (Mediastinal RT only=Ref)</u> Med. RT + CT, no anthracycline: RR 1.3 (0.79-2.24) **Med. RT + CT, anthracycline: RR 2.81 (1.44-5.49)**	SB: low risk AB: low risk DB: unclear CF: low risk
	Pein 2004	229 solid tumor 100% ANT 55% RT	Mean 18 years	-Heart failure, FS<25%, EF<50%, or ESWS>100, n=89	-Mean dose to six anatomical sites in the heart.	<u>Multivariable Cox regression, RR (95% CI)</u> <250 mg of adriamycin + < 5Gy to the heart (ref) **+ ≥ 5Gy to the heart 4.9 (1.3 –18.0)** ≥ 250 mg of adriamycin **+ < 5Gy to the heart 5.1 (1.8 –14.5)** **+ ≥ 5Gy to the heart 6.6 (2.1 –20.6)**	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:							
<u>Study design:</u>	+4	Retrospective cohort studies and a matched case control study					

Study limitations:	0	Limitations: Selection bias high risk in 1/7, unclear in 2/7, low risk in 4/7; Attrition bias low risk in 7/7; Detection bias high risk in 1/7, unclear in 6/7; Confounding low risk in 7/7.
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals not wide.
Publication bias:	0	Unlikely
Effect size:	+1	Large effect sizes
Dose-response:	0	Dose-response relationship in 2 studies but need to be confirmed
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Increased risk for symptomatic heart failure after exposure to both anthracyclines and radiotherapy exposing the heart region as compared to either treatment alone in CAYA cancer survivors. (7 studies; 4 significant effect; 922 events; 38,614 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

b. Asymptomatic LV systolic dysfunction
No studies

4. What is the risk for developing cardiomyopathy in CAYA cancer survivors who received dexrazoxane?
Evidence from the IGHG dexrazoxane guideline was used.

5. What is the risk of developing cardiomyopathy in CAYA cancer survivors who have modifiable risk factors and were treated with cardiotoxic cancer therapies?
   a. Risk of symptomatic heart failure associated with diabetes

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
5a Risk of symptomatic heart failure associated with diabetes in CAYA cancer survivors **(n=8 studies)**	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271	Multivariable Cox regression **-Diabetes: HR 2.66 (1.67-4.25)**	SB: high risk AB: high risk DB: unclear CF: low risk
	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=not reported	Multivariable piecewise exponential models Prediction timepoint (baseline): Age 20 / Age 35 -Diabetes: RR 3.78 (0.91-15.73) / 3.35 (0.75-14.95)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mansouri 2019	Survivors: 239 cases	Median, range	-Clinically validated heart failure, n=239	Modifiable CV risk factors studied in 117 cases and 353 controls. Conditional logistic regression	SB: unclear AB: high risk

		72% ANT 73% RT 1042 controls 35% ANT 62% RT	Cases: 19.7, 13.7-26.9 Controls: 33.0, 27.2-39.0		-Diabetes before HF diagnosis: OR 0.7 (0.1-3.6)	DB: unclear CF: low risk
	Khanna 2019	7289 survivors 45% ANT 14% RT	Median 10, range 0-25 years	-Heart failure based on administration data algorithm, n=not reported	Multivariable Cox regression analysis: **-Diabetes: HR 4.3 (1.8-10.7)**	SB: low risk AB: low risk DB: unclear CF: low risk
	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) -Diabetes: RR <1.3 -Exact estimates, p-values/ 95% confidence intervals not reported -No significant improvement in AUC when added to prediction model at 5-years from cancer diagnosis	SB: unclear AB: unclear DB: unclear CF: low risk
	Armstrong 2013	CCSS 10724	Median 25.6, range 7.4-39.3 years	Heart failure (CTCAE grade 3-5) at age 45 n=not reported, cumulative incidence 4.8%	Survivors exposed to chest RT - **Diabetes RR 5.7 (1.3-24.3)** Survivors exposed to anthracyclines - **Diabetes RR 4.3 (1.0-17.8)**	SB: high risk AB: low risk DB: unclear CF: low risk
	Armenian 2011	Lymphoma, ALL, multiple myeloma: 88 cases 218 controls 100% ANT RT unknown	Median 5.3, range 0.1-20.5 years	-Heart failure per AHA/ACC definition, n=88	Multivariable conditional logistic regression, OR (95% CI) (no CV risk factor and no HD-anthracycline=ref) *Model 1: CV risk factor alone and anthracycline <250 mg/m2* Diabetes: 6.2 (0.86-43.82) *Model 3: CV risk factor and anthracycline ≥250 mg/m2* **Diabetes: 26.8 (4.34-165.2)**	SB: low risk AB: low risk DB: unclear CF: low risk
	Aleman 2007	1474 Hodgkin lymphoma RT only 28% RT+chemo 38%	Median 18.7 yrs (28 669 person-years for cohort)	Heart failure, n=52	Multivariable Cox regression **Diabetes mellitus: HR 4.45 (2.54-7.81)**	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies and matched case-control studies
Study limitations:	-1	Some limitations: Selection bias high risk in 2/8, unclear in 2/8, low risk in 4/8; Attrition bias high risk in 2/8, unclear in 1/8, low risk in 5/8; Detection bias unclear in 8/8; Confounding low risk in 8/8.
Consistency:	0	No important inconsistency: 5 studies showed a significant increased risk of diabetes and 3 studies showed non-significant effects.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.
Publication bias:	0	Unlikely

Effect size:	0	No large effect sizes
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors with diabetes (8 studies; 5 significant effect; >1028 events; 89956 participants).

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

b. Risk of symptomatic heart failure associated with dyslipidemia

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
5b Risk of symptomatic heart failure associated with dyslipidemia in CAYA cancer survivors **(n=6 studies)**	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271	Multivariable Cox regression **-Dyslipidemia: HR 2.32 (1.53-3.52)**	SB: high risk AB: high risk DB: unclear CF: low risk
	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=not reported	Multivariable piecewise exponential models Prediction timepoint (baseline): Age 20 / Age 35 -Dyslipidemia: RR 2.94 (0.67-12.84) / 0 (-)	SB: low risk AB: low risk DB: unclear CF: low risk
	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) -Dyslipidemia: RR <1.3 -Exact estimates, p-values/ 95% confidence intervals not reported -No significant improvement in AUC when added to prediction model at 5-years from cancer diagnosis	SB: unclear AB: unclear DB: unclear CF: low risk
	Armstrong 2013	CCSS 10724	Median 25.6, range 7.4-39.3 years	Heart failure (CTCAE grade 3-5) at age 45 n=not reported, cumulative incidence 4.8%	Survivors exposed to chest RT - Dyslipidemia RR 1.1 (ns) Survivors exposed to anthracyclines - Dyslipidemia RR 1.1 (ns)	SB: high risk AB: low risk DB: unclear CF: low risk
	Armenian 2011	Lymphoma, ALL, multiple myeloma: 88 cases 218 controls 100% ANT RT unknown	Median 5.3, range 0.1-20.5 years	-Heart failure per AHA/ACC definition, n=88	Multivariable conditional logistic regression, OR (95% CI) (no CV risk factor and no HD-anthracycline=ref) *Model 1: CV risk factor alone and anthracycline <250 mg/m2* Dyslipidemia: 2.7 (0.56-13.40) *Model 3: CV risk factor and anthracycline ≥250 mg/m2* **Dyslipidemia: 5.4 (1.53-18.95)**	SB: low risk AB: low risk DB: unclear CF: low risk

	Aleman 2007	1474 Hodgkin lymphoma RT only 28% RT+chemo 38%	Median 18.7 yrs (28 669 person-years for cohort)	Heart failure, n=52	Multivariable Cox regression Hypercholesterolemia: HR 1.48 (0.85-2.58)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies and matched case-control studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 2/6, unclear in 1/6, low risk in 3/6; Attrition bias high risk in 1/6, unclear in 1/6, low risk in 4/8; Detection bias unclear in 6/6; Confounding low risk in 6/6.				
Consistency:	0	No important inconsistency: 2 studies showed a significant increased risk and 4 studies showed non-significant effects.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors with dyslipidemia (6 studies; 2 significant effect; >789 events; 81386 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

c. Risk of symptomatic heart failure associated with obesity

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
5c Risk of symptomatic heart failure associated with obesity in CAYA cancer survivors **(n=3 studies)**	Mansouri 2019	Survivors: 239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7-26.9 Controls: 33.0, 27.2-39.0	-Clinically validated heart failure, n=239	Modifiable CV risk factors studied in 117 cases and 353 controls. Conditional logistic regression -Obesity (BMI ≥30 kg/m2): OR 1.1 (0.4-3.1)	SB: unclear AB: high risk DB: unclear CF: low risk
	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) **-Obesity (BMI ≥30 kg/m2): RR 1.3-1.9** -Exact estimates, p-values/ 95% confidence intervals not reported -No significant improvement in AUC when added to prediction model at 5-years from cancer diagnosis	SB: unclear AB: unclear DB: unclear CF: low risk

	Armstrong 2013	CCSS 10724	Median 25.6, range 7.4-39.3 years	Heart failure (CTCAE grade 3-5) at age 45 n=not reported, cumulative incidence 4.8%	Survivors exposed to chest RT -Obesity, BMI>=30: RR 0.9 (ns) Survivors exposed to anthracyclines -Obesity: RR 1.6 (ns)	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-2	Some limitations: Selection bias high in 1/3, unclear in 2/3; Attrition bias high risk in 1/3, unclear in 1/3, low in 1/3; Detection bias unclear in 3/3; Confounding low risk in 3/3.				
Consistency:	0	No important inconsistency: 1 study showed a significant increased risk and 2 studies showed a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect size				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊖⊖ LOW				
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors with obesity (BMI ≥30 kg/m^2) (3 studies; 1 significant effect; 617 events; 34882 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

d. Risk of symptomatic heart failure associated with hypertension

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
5d Risk of symptomatic heart failure associated with hypertension in CAYA cancer survivors **(n=7 studies)**	Mulrooney 2020	23,462 survivors 51% ANT 54% RT	>5 years, median 20.5, range 7.0-39.3 years	Heart failure (CTCAE grade 3-5), n=271	Multivariable Cox regression **-Hypertension: HR 4.93 (3.61-6.72)**	SB: high risk AB: high risk DB: unclear CF: low risk
	Chen 2020	22,543 survivors 43-52% ANT 31-50% RT	Range 5 to >30 years	Heart failure (CTCAE grade 3-5) by age 50, n=not reported	Multivariable piecewise exponential models Prediction timepoint (baseline): Age 20 / Age 35 **-Hypertension: RR 5.66 (2.54-12.61)** / 1.44 (0.33-6.22)	SB: low risk AB: low risk DB: unclear CF: low risk
	Khanna 2019	7289 survivors 45% ANT 14% RT	Median 10, range 0-25 years	-Heart failure based on administration data algorithm, n=not reported	Multivariable Cox regression analysis: **-Hypertension: HR 3.1 (1.3-7.9)**	SB: low risk AB: low risk DB: unclear CF: low risk

	Chow 2015	CCSS: 13060 SJLIFE: 1695 EKZ: 1362 NWTS: 6760	Median, range CCSS: 24, 5-39 SJLIFE: unknown EKZ: 23, 5-45 NWTS: unknown	-Heart failure (CTCAE grade 3-5) before age 40 CCSS: n=285 SJLIFE: n=19 EKZ: n=26 NWTS: n=48	Multivariable Poisson regression (model including chest RT dose) **-Hypertension: RR 2.0-2.9** -Exact estimates, p-values/ 95% confidence intervals not reported -No significant improvement in AUC when added to prediction model at 5-years from cancer diagnosis	SB: unclear AB: unclear DB: unclear CF: low risk
	Armstrong 2013	CCSS 10724	Median 25.6, range 7.4-39.3 years	Heart failure (CTCAE grade 3-5) at age 45 n=not reported, cumulative incidence 4.8%	Survivors exposed to chest RT **-Hypertension RR 19.4 (11.4-33.1)** Survivors exposed to anthracyclines **-Hypertension RR 12.4 (7.6-20.1)**	SB: high risk AB: low risk DB: unclear CF: low risk
	Armenian 2011	Lymphoma, ALL, multiple myeloma: 88 cases 218 controls 100% ANT RT unknown	Median 5.3, range 0.1-20.5 years	-Heart failure per AHA/ACC definition, n=88	Multivariable conditional logistic regression, OR (95% CI) (no CV risk factor and no HD-anthracycline=ref) *Model 1: CV risk factor alone and anthracycline <250 mg/m2* Hypertension: 3.5 (0.88-14.01) *Model 3: CV risk factor and anthracycline ≥250 mg/m2* **Hypertension: 35.3 (8.30-150.18)**	SB: low risk AB: low risk DB: unclear CF: low risk
	Aleman 2007	1474 Hodgkin lymphoma RT only 28% RT+chemo 38%	Median 18.7 yrs (28 669 person-years for cohort)	Heart failure, n=52	Multivariable Cox regression Hypertension: HR 1.07 (0.59-1.94)	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies and matched case-control studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 2/7, unclear in 1/7, low risk in 4/7; Attrition bias high risk in 1/7, unclear in 1/7, low risk in 5/7; Detection bias unclear in 7/7; Confounding low risk in 7/7.				
Consistency:	0	No important inconsistency: 6 studies showed a significant increased risk and 1 study showed a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	+1	Large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⨁⨁⨁⨁ HIGH				
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors with hypertension (7 studies; 6 significant effect; >411 events; 65798 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

e. Risk of symptomatic heart failure associated with smoking

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
5e Risk of symptomatic heart failure associated with hypertension in CAYA cancer survivors **(n=3 studies)**	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	Multivariable piecewise exponential model -Smoking: RR 1.0 (0.7-1.3)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mansouri 2019	Survivors: 239 cases 72% ANT 73% RT 1042 controls 35% ANT 62% RT	Median, range Cases: 19.7, 13.7-26.9 Controls: 33.0, 27.2-39.0	-Clinically validated heart failure, n=239	Modifiable CV risk factors studied in 117 cases and 353 controls. Conditional logistic regression -Smoking at the time of HF diagnosis: OR 0.8 (0.4-1.5)	SB: unclear AB: high risk DB: unclear CF: low risk
	Aleman 2007	1474 Hodgkin lymphoma RT only 28% RT+chemo 38%	Median 18.7 yrs (28 669 person-years for cohort)	Heart failure, n=52	Multivariable Cox regression **Recent smoking: HR 1.96 (1.16-3.30)**	SB: low risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies and matched case-control studies				
Study limitations:	-1	Some limitations: Selection bias unclear in 1/3, low risk in 2/3; Attrition bias high risk in 1/3, low risk in 2/3; Detection bias unclear in 3/3; Confounding low risk in 3/3.				
Consistency:	0	No important inconsistency: 1 study showed a significant increased risk and 2 studies showed a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for symptomatic heart failure in CAYA cancer survivors who smoke (3 studies; 1 significant effect; 662 events; 226969 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

f. Risk of asymptomatic LV dysfunction associated with diabetes

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% Asymptomatic	Risk factor estimates (95% confidence interval)	Risk of bias
5f Risk of asymptomatic LV dysfunction associated with diabetes in CAYA cancer survivors **(n=4 studies)**	Nolan 2018	1807 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF<50%, n=unknown -GLS >2SD, n=unknown -% asymptomatic not reported	Logistic regression 3D LVEF <50% -Insulin resistance: NS (data not shown) Logistic regression GLS >2D age, sex normal values **-Insulin resistance: OR 1.72 (1.30 to 2.27), p < 0.001**	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulroone y 2016	1853 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%) -nearly 100% asymptomatic	Multivariable logistic regression, LVEF<50% -diabetes: OR 2.0 (0.9-4.2)	SB: high risk AB: low risk DB: unclear CF: low risk
	Armstron g 2015	1820 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -% asymptomatic not reported	Multivariable poisson regression 3D LVEF<50% -Metabolic syndrome: RR 1.07 (0.74-1.53) -Fasting glucose ≥100 mg/dl: RR 1.02 (0.75-1.39) Multivariable poisson regression GLS >2D **-Metabolic syndrome: RR 1.94 (1.66-2.28)** **-Fasting glucose ≥100 mg/dl: RR 1.37 (1.19-1.59)**	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 3/3; Attrition bias low risk in 3/3; Detection bias unclear in 3/3; Confounding low risk in 4/4.				
Consistency:	0	No important inconsistency; 2 studies found a significant increased risk and 1 study found a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for asymptomatic LV dysfunction in CAYA cancer survivors with diabetes (3 studies; 2 significant effect; >224 events; 5480 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

g. Risk of asymptomatic LV dysfunction associated with dyslipidemia

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% Asymptomatic	Risk factor estimates (95% confidence interval)	Risk of bias

5g Risk of asymptomatic LV dysfunction associated with dyslipidemia in CAYA cancer survivors **(n=2 studies)**	Mulroone y 2016	1853 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%) -nearly 100% asymptomatic	<u>Multivariable logistic regression, LVEF<50%</u> -dyslipidemia: OR 1.0 (0.6-1.7)	SB: high risk AB: low risk DB: unclear CF: low risk
	Armstron g 2015	1820 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -% asymptomatic not reported	<u>Multivariable poisson regression 3D LVEF<50%</u> -Triglyc ≥150 mg/dl: RR 1.01 (0.70-1.44) -Low HDL: RR 1.01 (0.74-1.38) <u>Multivariable poisson regression GLS >2D</u> **-Triglycerides ≥150 mg/dl: RR 1.65 (1.40-1.95)** **-Low HDL: RR 1.40 (1.23-1.59)**	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
<u>Study design:</u>	+4	Retrospective cohort studies
<u>Study limitations:</u>	-1	Some limitations: Selection bias high risk in 2/2; Attrition bias low risk in 2/2; Detection bias unclear in 2/2; Confounding low risk in 2/2.
<u>Consistency:</u>	0	No important inconsistency
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	-1	Some imprecision, for effect dyslipidemia on GLS as only one study performed.
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	No large effect sizes
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Increased risk for abnormal global longitudinal strain (GLS >2SD from normal) in CAYA cancer survivors with dyslipidemia. (1 study; 1 significant effect; 118 events; 1853 participants) No significant effect of dyslipidemia on the risk for abnormal LVEF (<50%) in CAYA cancer survivors (2 studies; 2 non-significant effect; 224 events; 3673 participants)

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

h. <u>Risk of asymptomatic LV dysfunction associated with obesity</u>

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% Asymptomatic	Risk factor estimates (95% confidence interval)	Risk of bias
5h Risk of asymptomatic LV dysfunction associated with obesity in CAYA	Nolan 2018	1807 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF, n=unknown -GLS, n=unknown -% asymptomatic not reported	<u>Logistic regression 3D LVEF <50%</u> -Obesity: NS (data not shown) <u>Logistic regression GLS >2D age, sex normal values</u> **-Obesity: OR 1.59 (1.19 to 2.13), p < 0.002**	SB: high risk AB: low risk DB: unclear CF: low risk

cancer survivors **(n=3 studies)**	Mulroone y 2016	1853 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%) -nearly 100% asymptomatic	Multivariable logistic regression, LVEF<50% -BMI, kg/m2 (<25=ref) 25-29: OR 1.0 (0.5-1.9) ≥30: 1.2 (0.6-2.3)	SB: high risk AB: low risk DB: unclear CF: low risk
	Armstron g 2015	1820 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -% asymptomatic not reported	Multivariable poisson regression 3D LVEF<50% -Metabolic syndrome: RR 1.07 (0.74-1.53) -Abdominal obesity: RR 1.34 (0.99-1.82) Multivariable poisson regression GLS >2D **-Metabolic syndrome: RR 1.94 (1.66-2.28)** **-Abdominal obesity: RR 1.73 (1.48-2.01)**	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 3/3; Attrition bias low risk in 3/3; Detection bias unclear in 3/3; Confounding low risk in 4/4.				
Consistency:	0	No important inconsistency; 2 studies found a significant increased risk and 1 study found a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for abnormal global longitudinal strain (GLS) in CAYA cancer survivors with obesity. (2 studies; 2 significant effect; >579 events; 3627 participants) No significant effect of obesity on the risk for abnormal LVEF in CAYA cancer survivors with (3 studies; 3 non-significant effect; >224 events; 5480 participants).				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

i. Risk of asymptomatic LV dysfunction associated with hypertension

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% Asymptomatic	Risk factor estimates (95% confidence interval)	Risk of bias
5i Risk of asymptomatic LV dysfunction associated with hypertension in	Nolan 2018	1807 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF -GLS -% asymptomatic not reported	Logistic regression 3D LVEF <50% **-Hypertension: OR 1.82 (1.25 to 2.63), p < 0.002** Logistic regression GLS >2D age, sex normal values -Hypertension: NS (data not shown)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulroone y 2016	1853 82% ANT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%)	Multivariable logistic regression, LVEF<50% **-Hypertension OR 3.0 (1.7-5.2)**	SB: high risk AB: low risk

CAYA cancer survivors		43% RT		-nearly 100% asymptomatic		DB: unclear CF: low risk
(n=3 studies)	Armstrong 2015	1820 83% ANT 41% RT	Median 22.6, range 10.4-48.3 years	-3D LVEF <50%, n=106 (5.8%) -GLS >2SD, n=579 (31.8%) -% asymptomatic not reported	Multivariable poisson regression 3D LVEF<50% **-Hypertension: RR 1.44 (1.22-1.70)** Multivariable poisson regression GLS >2D **-Hypertension: RR 1.48 (1.33-1.65)**	SB: high risk AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias high risk in 3/3; Attrition bias low risk in 3/3; Detection bias unclear in 3/3; Confounding low risk in 4/4.				
Consistency:	0	No important inconsistency; 2 studies found a significant increased risk and 1 study found a non-significant effect.				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.				
Publication bias:	0	Unlikely				
Effect size:	0	No large effect sizes				
Dose-response:	0	Not applicable				
Plausible confounding:	0	No plausible confounding				
Quality of evidence:		⊕⊕⊕⊖ MODERATE				
Conclusion:		Increased risk for asymptomatic LV dysfunction in CAYA cancer survivors with hypertension (3 studies; 3 significant effect; >224 events; 5480 participants)				

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

j. Risk of asymptomatic LV dysfunction associated with smoking

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition -% Asymptomatic	Risk factor estimates (95% confidence interval)	Risk of bias
5j Risk of asymptomatic LV dysfunction associated with smoking in CAYA cancer survivors **(n=4 studies)**	Nolan 2018	1807 58% ANT 17% RT	Median 23, range 10-48 years	-3D LVEF -GLS -% asymptomatic not reported	Logistic regression 3D LVEF <50% -Smoking: NS (data not shown) Logistic regression GLS >2D age, sex normal values -Smoking: NS (data not shown)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulroney 2016	1853 82% ANT 43% RT	Median 22.6, range 10-48 years	Echo LVEF<50%, n=118 (7.4%) -nearly 100% asymptomatic	Multivariable logistic regression, LVEF<50% -ever-smoker: OR 0.9 (0.5-1.5)	SB: high risk AB: low risk DB: unclear CF: low risk
	Hudson 2007	223 70% ANT 27% ANT+RT	Median 9.0, range 3.0-18.0 years	-Screening echo: FS <28%, n=37 (13.6%) -All asymptomatic	Multivariable logistic regression with univariable p<0.10, FS<28% -smoking not significant	SB: high risk AB: low risk DB: low risk

		2.7% RT	CF: low risk
GRADE assessment:			
Study design:	+4	Retrospective cohort studies	
Study limitations:	-1	Some limitations: Selection bias high risk in 3/3; Attrition bias low risk in 3/3; Detection bias unclear in 2/3, low risk in 1/3; Confounding low risk in 4/4.	
Consistency:	0	No important inconsistency; 2 studies found a significant increased risk and 1 study found a non-significant effect.	
Directness:	0	Results are direct, population and outcomes broadly generalizable	
Precision:	0	No important imprecision, large sample sizes and most confidence intervals were not wide.	
Publication bias:	0	Unlikely	
Effect size:	0	No large effect sizes	
Dose-response:	0	Not applicable	
Plausible confounding:	0	No plausible confounding	
Quality of evidence:		⊕⊕⊕⊖ MODERATE	
Conclusion:		No significant effect of smoking on the risk for asymptomatic LV dysfunction in CAYA cancer survivors (3 studies; 3 non-significant effect; >155 events; 3883 participants)	

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction, SB, selection bias.

6. What is the relative potency of individual anthracycline or anthraquinone agents with respect to risk of cardiomyopathy in CAYA cancer survivors?
    a. Symptomatic heart failure

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
6a Relative risk of cardiomyopathy in CAYA cancer survivors with different anthracycline derivatives **(n= 2 studies)**	Feijen 2019-2	28,423 35% DOX 18% DAU 1.1% EPI 1.1% IDA 0.9% Mitox 21% RT	Median 20, range 5-40 years	-Heart failure (CTCAE grade 3-5) before age 40, n=399	Equivalents compared to doxorubicin Ratio of HRs / linear dose response model -Daunorubicin: 0.6 (95% CI 0.4-1.0) / 0.5 (95% CI 0.4-0.7) -Epirubicin: 0.8 (95% CI 0.5-2.8) / 0.8 (95% CI 0.3-1.4) -Idarubicin: too few events -Mitoxantrone: 10.5 (6.2-19.1) / 13.8 (95% CI 8.0-21.6), nonlinearity beyond ≥300mg/m2 doxorubicin / ≥75 mg/m2 mitoxantrone.	SB: unclear AB: low risk DB: unclear CF: low risk
	Feijen 2015	15,851 32.5% DOX 14.7% DAU 17% RT	Median 17.3, range 5-35 years	-Heart failure (CTCAE grade 3-5) before age 40, n=271	Equivalence ratio of daunorubicin compared to doxorubicin -Average ratio of HRs: 0.45 (95% CI, 0.23 to 0.73). -Linear dose-response model: HR 0.49 (95% CI, 0.28 to 0.70).	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:						
Study design:	+4	Retrospective cohort studies				
Study limitations:	-1	Some limitations: Selection bias unclear in 2/2; Attrition bias low risk in 2/2; Detection bias unclear in 2/2; Confounding low risk in 2/2.				
Consistency:	0	No important inconsistency				
Directness:	0	Results are direct, population and outcomes broadly generalizable				
Precision:	0	Confidence intervals for the relative potencies are wide and cross 1; and regarding epirubicin, idarubicin and mitoxantrone only 1 study included				

Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		With respect to risk of symptomatic heart failure in CAYA cancer survivors: -Daunorubicin is 0.5-0.6 times as potent compared to doxorubicin with a 95% confidence interval of 0.4-1.0 (2 studies; 670 events; 44274 participants). -Epirubicin is 0.8 times as potent compared to doxorubicin with a 95% confidence interval of 0.3-2.8 (1 study; 399 events; 28423 participants). -Mitoxantrone is 10.5-13.8 times as potent compared to doxorubicin with a 95% confidence interval of 6.2-21.6. There is a non-linear relationship (i.e., higher conversion score) with mitoxantrone doses ≥75 mg/m2 (1 study; 399 events; 28423 participants). - Idarubicin potency is unclear (1 study; 399 events; 28423 participants).

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CCSS, childhood cancer survivor study; CF, confounding; DB, detection bias; SB, selection bias.

b. Asymptomatic LV dysfunction
No studies

7. What is the risk of developing peri/postpartum cardiomyopathy in pregnant female CAYA cancer survivors treated with cardiotoxic cancer therapies?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
7 Risk of cardiomyopathy in pregnant CAYA cancer survivors treated with cardiotoxic therapies **(n=1 meta-analysis of 6 studies)**	Nolan 2020	Systematic review of 6 studies (n=1137) 67% ANT RT unknown	Median 25, range 5-48 years	During or within 12 months after delivery either: 1) LV systolic dysfunction (reduction LVEF or FS, 4 studies) Or 2) Clinical heart failure (3 studies) N=33 (2.9%)	-Outcome: n= 33/1,137 (2.9%), of whom n=17 (52%) had a history of cancer therapeutics related cardiac dysfunction (CTRCD) before pregnancy. -Inverse variance weighted incidence of CTRCD with fixed effect model: 1.7% (95% CI 0.9-2.7%); -if history CTRCD: 28% (95% CI 15-44%); -no history of CTRCD: 0.24% (95% CI 0-0.81%). -Previous CTRCD versus no previous CTRCD: OR 47 (95% CI 18-126)	SB: unclear AB: unclear DB: unclear CF: high risk

GRADE assessment:		
Study design:	+4	Retrospective cohort studies and a systematic review of cohort studies
Study limitations:	-2	Limitations: Selection bias high risk in 2/4, unclear in 1/4, low risk in 1/4; Attrition bias unclear in 1/4, low risk in 3/4; Detection bias unclear in 4/4; Confounding high risk in 1/4, unclear or NA in 3/4.
Consistency:	0	No important inconsistency

Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, moderate sample sizes and limited number of events. However, the limited number of events underlines the low risk associated with pregnancy in those with no cardiomyopathy before pregnancy.
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Small increased risk for cardiomyopathy (LV systolic dysfunction and/or clinical heart failure) during pregnancy in CAYA cancer survivors treated with cardiotoxic cancer therapies without a history of cardiomyopathy prior to pregnancy (pooled incidence: 0.24%, 95% CI 0-0.81%). Increased risk for cardiomyopathy during pregnancy in CAYA cancer survivors treated with cardiotoxic cancer therapies with a history of cardiomyopathy prior to pregnancy (pooled incidence: 28%, 95% CI 15-44%) (1 meta-analysis of 6 studies; 33 events; 1137 participants).

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, confounding; DB, detection bias; LVEF=left ventricular ejection fraction, SB, selection bias.

8. Are genetic variants associated with increased and/or decreased risk of cardiomyopathy in CAYA cancer survivors treated with cardiotoxic cancer therapies?

Overview of studies

PICO	Study	No. of participants	Follow up (median/mean, range) yr	-Outcome definition	Risk factor estimates (95% confidence interval)	Risk of bias
8 Genetic variants and risk of cardiomyopathy in CAYA cancer survivors treated with cardiotoxic therapies **(n=1 systematic review and 4 additional studies)**	**Systematic review**					
	Aminkeng 2016	Systematic review and guideline recommendations based on studies in children and adults	Range of median follow-up in the 3 studies in which genes with +++ evidence were identified: 6.5-22.0 years	-Anthracycline cardiotoxicity as defined by the authors of each study. -Modified CTCAE ≥ grade 2 in the 3 studies in which genes with strong evidence were identified	Genes replicated at least twice and large effect sizes (OR >3 or <0.3) (+++ evidence, level B – moderate recommendation to test in patients treated with doxorubicin or daunorubicin) **-RARG rs2229774, 3 pediatric oncology cohorts[1] (n=458, 73 events)** **OR range in pediatric cohorts: 4.1-7.0, p-value 4.1*10-8 - 4.2*10^{-3}** Sensitivity: 45.7% (30.9-61) Specificity: 86.3% (81.8-90) Positive post-test probability: 55.1% Negative post-test probability: 18.9% PPV: 34.4% (22.7-47.7) NPV: 90.9% (86.9-94.1) **-SLC28A3 rs7853758, 3 pediatric oncology cohorts[2,3] (n=521, 124 events)** **OR range in pediatric cohorts: 0.29-0.46, p-value 0.0071-0.058** Sensitivity: 17.4% (7.8-31.4) Specificity: 64.6 (58.8-70.1)	Grading per genetic variant

				Positive post-test probability: 15.4% Negative post-test probability: 32.1% PPV: 7.2% (3.2-13.7) NPV: 83.2% (77.7-87.8) **-UGT1A6 rs17863783, 3 pediatric oncology cohorts[2,3] (n=521, 124 events)** **OR range in pediatric cohorts: 4.0-7.98, p-value 0.0062-0.075** Sensitivity: 15.2% (6.3-28.9) Specificity: 96.2% (93.3-98.1) Positive post-test probability: 59.8% Negative post-test probability: 24.6% PPV: 38.9% (17.3-64.3) NPV: 87.8% (83.7-91.2) <u>Genes not replicated at least twice and/or small effect size (++/+ evidence, no recommendation to test)</u> ABCC1, ABCC2, ABCC5, ABCB1, ABCB4, CBR3, RAC2, NCF4, CYBA, GSTP1, CAT, SULT2B1, POR, HAS3, SLC22A7, SCL22A17, HFE and NOS3	
Original studies not included in the systematic review					
Singh 2020	Survivors: 75 cases 92 controls 100% ANT	Cases: median 6.0, range 1.3-11.6 years Controls: 12.0, range 7.4-17.2 years	Heart failure according to AHA criteria Cases: mean LVEF 39.4%, mean FS 22.2%, n=75 Controls: mean LVEF 65.9, mean FS 36.7%	<u>Multivariable conditional logistic regression (95% CI)</u> -GSTM1 null vs positive: OR 2.7 (1.3-5.9) p=0.007 -No replication performed	Grading per genetic variant
Sagi 2018	680 ALL and osteosarcoma 100% ANT	During up to >15 years after therapy	FS ≤28% during follow-up, n=20	<u>Multivariable regression (p-values FDR adjusted)</u> *Genetic variants, not replicated:* -ABCC2 rs3740066 GG: lower FS at 5–10 years after treatment (p = 7.11E-04, OR not reported) -CYP3A5 rs4646450 TT: p = 5.60E-03; OR = 6.94 (1.76–27.39) -NQO1 rs1043470 rare T allele: lower FS at 5–10 years after treatment (p = 5.82E-03, OR not reported) -SLC22A6 rs6591722 AA: lower FS at 5–10 years after treatment (p = 1.71E-03, OR not reported) *Genetic variants, in conflict with previous studies:* **-SLC28A3 rs7853758 AA (12% in cases, 1% in controls): p = 6.50x10^{-3}; OR = 11.56 (1.98-67.45)** -Opposite effect direction compared to Visscher 2012 and 2013[2,3]	Grading per genetic variant

	Hildebrandt 2017	Survivors: 46 cases 82 controls 100% ANT	Cases: mean 21.2±11.2 years Controls: mean 15.7±7.6 years	-LVEF 45-50% + symptoms +/- cardiac medications or -LVEF <45% and/or FS ≤25% n=46	-12 variants previously associated with an increased risk of hypertension were tested Multivariable logistic regression, no replication performed -PLCE1 rs932764: OR 0.36 (0.18-0.76) p=0.0068 -ATP2B1 rs17249754: OR 0.26 (0.07-0.96) p=0.040	Grading per genetic variant
	Wang 2016	Discovery: 112 cases 219 controls Replication: 54 cases	Cases: Median 9.4, range 0.1-35.1 years. Controls: median 12.9, range 1.4-41 years	-Symptoms/signs of heart failure and/or LVEF ≤40%/FS ≤28% Discovery: n=112 Replication: n=54	Discovery: multivariable logistic regression -CELF4 (rs1786814) GG versus GA/AA: OR = 2.26 (1.2-4.0). -CELF4 (rs1786814) GG and anthracycline dose >300 mg/m2 versus GA/AA and anthracycline dose <=300 mg/m2: OR 10.16 (3.8-27.3) -CELF4 gene*anthracycline dose interaction reached multiple testing corrected significance: P = 1.14 * 10^25 Replication in 54 cases -CELF4*anthracycline dose interaction was replicated: OR 5.09 (1.0-25.2) for being in the >300mg/m2 group	Grading per genetic variant

Abbreviations: 95% CI, 95% confidence interval; AB, attrition bias; CAYA, childhood, adolescent and young adult; CF, CTCAE confounding; DB, detection bias; SB, selection bias; SNP, single nucleotide polymorphism.

Overview of genetic variants studied in CAYA cancer survivors

Genetic variant (references of original studies)	Study cohorts (D=discovery, R=replication)	Outcome definition	Effect size	p-value	Level of evidence CPNDS*	Level of evidence pharmacogenetics database#	Comments
Genetic variants included in systematic review Aminkeng et al. 2016 [4]							
RARG rs2229774[1]	D: 32 cases, 248 controls R1: 22 cases, 76 controls R2: 19 cases, 61 controls	CTCAE ≥grade 2	OR range 4.1-7.0	Range 4.1*10-8 - 4.2*10^{-3}	Moderate (+++)	Low (level 3)	Replicated twice, significant effect in all studied cohorts
UGT1A6 rs17863783[2,3]	D: 38 cases, 118 controls R1: 40 cases, 148 controls R2: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 4.0-8.0	Range 0.0062-0.075	Moderate (+++)	Unsupported (level 4)	Replicated once, significant effect in 2 of 3 cohorts
SLC28A3 rs7853758[2,3,5]	D: 38 cases, 118 controls R1: 40 cases, 148 controls	CTCAE ≥grade 2 or FS<28%	Risk decreasing effect: OR range 0.29-0.46 Risk increasing effect: OR 11.56	Risk decreasing effect: range 0.0071-0.058 Risk increasing effect: 6.50x10^{-3}	Low (++) [downgraded from moderate to	Low (level 3)	Replicated twice but opposite effect direction in a more recent study

	R2: 46 cases, 131 controls R3: 20 cases, 660 controls				low with updated evidence since 2016]		
SLC22A17 rs4982753[6]	D: 78 cases, 257 controls R1: 44 cases, 141 controls	CTCAE ≥grade 2	OR range 0.39-0.52	Range 0.0071-0.0078	Low (++)	Not reported	Replicated once
SLC22A7 rs4149178[6]	D: 78 cases, 257 controls R1: 44 cases, 141 controls	CTCAE ≥grade 2	OR range 0.39-0.41	Range 0.0034-0.047	Low (++)	Not reported	Replicated once
ABCC1 rs3743527[1,2,7]	D: 235 patients R1: 78 cases, 266 controls R2: 32 cases, 248 controls	Change in FS, CTCAE ≥grade 2	D: lower FS in patients with mutation R: OR range 0.65-0.92	D: 0.001 R: range 0.24-0.70	Low (++)	Not reported	No successful replication, significant effect in 1 of 3 cohorts
ABCC1 rs246221[1,2,7]	D: 235 patients R1: 78 cases, 266 controls R2: 32 cases, 248 controls	Change in FS, CTCAE ≥grade 2	D: lower FS in patients with mutation R: OR range 1.1-1.2	D: 0.027 R: range 0.37-0.68	Low (++)	Not reported	No successful replication, significant effect in 1 of 3 cohorts
ABCC1 rs4148350[2,3]	D: 78 cases, 266 controls R: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 1.29-3.44	Range 0.0012-0.61	Low (++)	Unsupported (level 4)	No successful replication
ABCC1 rs246214[8]	D: 130 cases, 194 controls R: 76 patients (children+adults)	AHA criteria	NA	0.014-0.071	Low (++)	-	No successful replication
ABCC2 rs8187694[9]	D: 78 cases, 266 controls	CTCAE ≥grade 2	OR 1.06	0.90	Low (++)	Not reported	Not significant in 1 study
ABCC2 rs8187710[1]	D: 77 cases, 178 controls R1: 32 cases, 248 controls	AHA criteria, CTCAE ≥grade 2	OR range 4.3-5.2	0.02 in both studies	Low (++)	Low (level 3)	Replicated once
ABCC5 rs7627754[10]	D: 251 patients R1: 32 patients	Change in FS/EF	Mean of 8–12% reduction in EF (P = 0.0001, replication p=0.03) and FS (P = 0.001, replication p=0.04).		Low (++)	Not reported	Replicated, no clinical endpoint

ABCB1 rs2235047[9,11]	D: 78 cases, 266 controls R: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 1.34-2.92	Range 0.0087-0.56	Low (++)	Unsupported (level 4)	No successful replication
ABCB4 rs1149222[9,11]	D: 78 cases, 266 controls R: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 0.89-1.87	Range 0.0054-0.69	Low (++)	Unsupported (level 4)	No successful replication
ABCB4 rs4148808[9,11]	D: 78 cases, 266 controls R: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 1.41-1.86	Range 0.0093-0.33	Low (++)	Unsupported (level 4)	No successful replication
CBR rs1056892[1,9,12,13]	D: 30 cases, 115 controls R1: 170 cases, 317 controls R2: 78 cases, 266 controls R3: 77 cases, 178 controls R4: 32 cases, 248 controls R5: 185 patients	Self-reported HF, CTCAE ≥grade 2, AHA criteria, percentage decrease in EF	OR range 0.85-8.16	Range 0.02-0.88	Low (++)	Low (level 3)	Replicated once, no successful replication in 4 other studies
CYBA rs4673[1,9]	D: 78 cases, 266 controls R1: 32 cases, 248 controls R2: 77 cases, 178 controls R3: 60 patients	CTCAE ≥grade 2, AHA criteria	OR range 0.91-1.29	Range 0.63-0.81	Low (++)	Low (level 3)	No association in pediatric cancer cohorts
RAC2 rs13058338[1,9,14]	D: 78 cases, 266 controls R1: 32 cases, 248 controls R2: 77 cases, 178 controls R3: 60 patients	CTCAE ≥grade 2, AHA criteria	OR range 0.68-2.61	Range 0.02-0.28	Low (++)	Low (level 3)	No successful replication, significant effect in 1 of 4 studies
NCF4 rs1883112[9]	D: 78 cases, 266 controls	CTCAE ≥grade 2, AHA criteria	OR range 1.06-1.10	Range 0.76-0.88	Low (++)	Low (level 3)	No association in pediatric cancer cohorts

	R1: 77 cases, 178 controls R2: 60 patients						
GSTP1 rs1695[1,9]	D: 60 patients R1: 78 cases, 266 controls R2: 32 cases, 248 controls R3	CTCAE ≥grade 2	OR range 0.97-9.4	Range 0.008-0.88	Low (++)	Low (level 3)	No successful replication, significant effect in 1 of 3 studies
CAT rs10836235[1]	D: 76 patients R: 32 cases, 248 controls	NA, CTCAE ≥grade 2	OR range 0.28-0.70	Range 0.02-0.46	Very low (+)	Low (level 3)	No successful replication
SULT2B1 rs10426377[9,11]	D: 38 cases, 118 controls R1: 40 cases, 148 controls R2: 46 cases, 131 controls	CTCAE ≥grade 2	OR range 0.35-0.72	Range 0.0019-0.30	Low (++)	Unsupported (level 4)	No successful replication
HAS3 rs2232228[1,8]	D: 93 cases, 194 controls R1: 76 cases, no controls R2: 32 cases, 248 controls	AHA criteria, CTCAE ≥grade 2	D: Overall AA vs GG OR 1.8, p=0.2 AA and dose >250mg/m2 vs GG with dose ≤250mg/m2 OR 8.9, p=0.04 R1: OR of AA carriers for being in the dose >250 mg/m2 group as compared to GG carriers: 4.5, p=0.04 R2 (no dose interaction tested): OR 0.67, p=0.18		Low (++)	Low (level 3)	SNP-anthracycline dose interaction P=5.3x10-7
HNMT rs17583889[1,9,11]	D: 38 cases, 118 controls R1: 40 cases, 148 controls R2: 46 cases, 131 controls R3: 32 cases, 248 controls	CTCAE ≥grade 2	OR range 1.14-3.67	Range $3.4*10^{-4}$ – 0.69	Low (++)	Unsupported (level 4)	Replicated once, significant effect in 2 of 4 cohorts tested
HFE rs1799945[1,15]	D: 77 cases, 178 controls R1: 172 patients R: 32 cases, 248 controls	AHA criteria, blood biomarkers for cardiac injury, CTCAE ≥grade 2	OR range 0.84-2.58, no association with troponins and NT-proBNP during treatment	Range 0.03-0.99	Low (++)	Not reported	No successful replication, significant effect in 1 of 3 studies

HFE rs1800562[15]	D: 172 patients R: 77 cases, 178 controls	Blood biomarkers for cardiac injury, CTCAE ≥grade 2	D: OR for multiple troponin elevations during treatment: 6.79, p=0.015 R: OR for CTCAE ≥grade 2: 0.30, p=0.28		Low (++)	Not reported	No significant effect for CTCAE graded cardiomyopathy in long-term survivors
POR rs2868177[1]	D: 32 cases, 248 controls	CTCAE ≥grade 2	OR 2.1	0.016	Very low (+)	Not reported	Single study
POR rs13240755[1,9]	D: 38 cases, 118 controls R1: 40 cases, 148 controls R2: 32 cases, 248 controls	CTCAE ≥grade 2	OR range 1.0-2.0	Range 0.033-0.93	Very low (+)	Not reported	No successful replication, significant effect in 1 of 3 cohorts
POR rs4732513[1,9]	D: 38 cases, 118 controls R1: 40 cases, 148 controls R2: 32 cases, 248 controls	CTCAE ≥grade 2	OR range 1.1-1.9	Range 0.041-0.84	Very low (+)	Not reported	No successful replication, significant effect in 1 of 3 cohorts
NOS3 rs1799983[1,10]	D: 251 patients R1: 44 patients R2: 32 cases, 248 controls	Difference in EF, CTCAE ≥grade 2	D: protective effect on EF, p=0.02; R: underpowered; R2: OR 0.69, p=0.33		Very low (+)	Low (level 3)	No successful replication, significant effect in 1 of 3 cohorts
Genetic variants not included in systematic review Aminkeng et al. 2016							
GSTM1 null[16]	D: 75 cases, 92 controls	AHA criteria	OR 2.7	0.007	Low (++)	Low (level 3)	Single study, functional validation performed
ABCC2 rs3740066[5]	D: 20 cases, 660 controls	FS ≤28%	Lower FS at 5–10 years after treatment	7.11E-04	Very low (+)	Low (level 3)	Single study
CYP3A5 rs4646450[5]	D: 20 cases, 660 controls	FS ≤28%	OR 6.94	5.60E-03	Low (++)	Not reported	Single study with large effect size
NQO1 rs1043470[5]	D: 20 cases, 660 controls	FS ≤28%	Lower FS at 5–10 years after treatment	5.82E-03	Very low (+)	Not reported	Single study
SLC22A6 rs6591722[5]	D: 20 cases, 660 controls	FS ≤28%	Lower FS at 5–10 years after treatment	1.71E-03	Very low (+)	Not reported	Single study
PLCE1 rs932764[17]	D: 46 cases, 82 controls	EF 45-50% with symptoms or	OR 0.36	0.0068	Very low (+)	Not reported	Single study

		EF <45%/ FS ≤25%					
ATP2B1 rs17249754[17]	D: 46 cases, 82 controls	EF 45-50% with symptoms or EF <45%/ FS ≤25%	OR 0.26	0.040	Very low (+)	Not reported	Single study
CELF4 rs1786814[18]	D: 112 cases, 219 controls R: 54 cases	Heart failure or EF ≤40%/FS ≤28%	-GG versus GA/AA: OR = 2.26 (1.2-4.0). -GG and anthracycline dose >300 mg/m2 versus GA/AA and anthracycline dose <=300 mg/m2: OR 10.16 (3.8-27.3) -Gene*anthracycline dose interaction P = $1.14*10^{-25}$ -CELF4*anthracycline dose interaction was replicated: OR 5.09 (1.0-25.2) for being in the >300mg/m2 group		Low (++)	Not reported	Gene*dose interaction successfully replicated once in the same study

*CPNDS (Canadian Pharmacogenomics Network for Drug Safety) grading was adopted from the systematic review from Aminkeng et al. 2016. The level of evidence of genes of which new evidence was published after 2016 were graded by the IGHG guideline panel. # obtained from www.pharmgkb.org on June 24th 2021. Abbreviations: D=discovery, OR=odds ratio, R=replication.

***Methods to grade the level of evidence of genetic variants**

Canadian Pharmacogenomics Network for Drug Safety (CPNDS, www.pharmgkb.org/page/cpnds)

GRADE	RESULTS	DESCRIPTION
High (++++)	Consistent, generalizable	Strong general conclusions can be drawn that are unlikely to change based on further research
Moderate (+++)	Consistent, but limited quantity, quality or generalizability	Evidence allows general conclusions, but with reduced confidence; further research is likely to have an important impact on confidence in conclusions
Low (++)	Inconsistent or insufficient quantity/quality, encouraging	No general conclusions can be drawn or conclusions are likely to change based on further research, but current evidence is encouraging
Very low (+)	Inconsistent or insufficient quantity/quality, discouraging	No conclusions can be drawn or conclusions are likely to change based on future studies, and current evidence is discouraging

Pharmacogenetics database (www.pharmgkb.org)

LEVEL OF EVIDENCE	STANDARD SCORING RANGE#	DESCRIPTION
High (1A)	≥80	Level 1A clinical annotations describe variant-drug combinations that have variant-specific prescribing guidance available in a current clinical guideline annotation or an FDA-approved drug label annotation. Annotations of drug labels or clinical guidelines must give prescribing guidance for specific variants (e.g. CYP2C9*3, HLA-B*57:01) or provide mapping from defined allele functions to diplotypes and phenotypes to be used as supporting evidence for a level 1A clinical annotation. Level 1A clinical annotations must also be supported by at least one publication in addition to a clinical guideline or drug label with variant-specific prescribing guidance.

High (1B)	25 - 79.9375	Level 1B clinical annotations describe variant-drug combinations with a high level of evidence supporting the association but no variant-specific prescribing guidance in an annotated clinical guideline or FDA drug label. Level 1B clinical annotations must be supported by at least two independent publications.
Moderate (2A)	8 - 24.9375 and variant in a Tier 1 VIP	Variants in Level 2A clinical annotations are found in PharmGKB's Tier 1 Very Important Pharmacogenes (VIPs). These variants are in known pharmacogenes, implying causation of drug phenotype is more likely. These clinical annotations describe variant-drug combinations with a moderate level of evidence supporting the association. For example, the association may be found in multiple cohorts, but there may be a minority of studies that do not support the majority assertion. Level 2A clinical annotations must be supported by at least two independent publications.
Moderate (2B)	8 - 24.9375	Variants in Level 2B clinical annotations are **not** in PharmGKB's Tier 1 VIPs. These clinical annotations describe variant-drug combinations with a moderate level of evidence supporting the association. For example, the association may be found in multiple cohorts, but there may be a minority of studies that do not support the majority assertion. Level 2B clinical annotations must be supported by at least two independent publications.
Low (3)	0 - 7.9375	Level 3 clinical annotations describe variant-drug combinations with a low level of evidence supporting the association. This association may be based on a single study annotated in PharmGKB, or there may be several studies that failed to replicate the association. The annotation may also be based on preliminary evidence (e.g., a case report, non-significant study, or in vitro, molecular, or functional assay evidence), resulting in a lower calculated score.
Unsupported (4)	< 0	Level 4 clinical annotations describe variant-drug combinations where the total score is negative and the evidence does not support an association between the variant and the drug phenotype.

#Scores are generated by the website based on 1) phenotype category (studies with clinically relevant outcomes), 2) p-value, 3) cohort size, 4) effect size, 5A) study type and 5B) inconsistencies between studies (www.pharmgkb.org/page/varAnnScoring).

9. Are there new childhood cancer treatments associated with cardiomyopathy in CAYA cancer survivors?
   No studies

References of genetic variants

1. Aminkeng F, Bhavsar AP, Visscher H, et al. A coding variant in RARG confers susceptibility to anthracycline-induced cardiotoxicity in childhood cancer. *Nat Genet* 2015; **47**(9): 1079-84.
2. Visscher H, Ross CJ, Rassekh SR, et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol* 2012; **30**(13): 1422-8.
3. Visscher H, Ross CJ, Rassekh SR, et al. Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. *Pediatr Blood Cancer* 2013; **60**(8): 1375-81.
4. Aminkeng F, Ross CJ, Rassekh SR, et al. Recommendations for genetic testing to reduce the incidence of anthracycline-induced cardiotoxicity. *Br J Clin Pharmacol* 2016; **82**(3): 683-95.
5. Sági JC, Egyed B, Kelemen A, et al. Possible roles of genetic variations in chemotherapy related cardiotoxicity in pediatric acute lymphoblastic leukemia and osteosarcoma. *BMC Cancer* 2018; **18**(1).
6. Visscher H, Rassekh SR, Sandor GS, et al. Genetic variants in SLC22A17 and SLC22A7 are associated with anthracycline-induced cardiotoxicity in children. *Pharmacogenomics* 2015; **16**(10): 1065-76.
7. Semsei AF, Erdelyi DJ, Ungvari I, et al. ABCC1 polymorphisms in anthracycline-induced cardiotoxicity in childhood acute lymphoblastic leukaemia. *Cell biology international* 2012; **36**(1): 79-86.
8. Wang X, Liu W, Sun CL, et al. Hyaluronan synthase 3 variant and anthracycline-related cardiomyopathy: a report from the children's oncology group. *J Clin Oncol* 2014; **32**(7): 647-53.
9. Visscher H, Ross CJ, Rassekh SR, et al. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol* 2012; **30**(13): 1422-8.

10. Krajinovic M, Elbared J, Drouin S, et al. Polymorphisms of ABCC5 and NOS3 genes influence doxorubicin cardiotoxicity in survivors of childhood acute lymphoblastic leukemia. *Pharmacogenomics J* 2016; **16**(6): 530-5.
11. Visscher H, Ross CJ, Rassekh SR, et al. Validation of variants in SLC28A3 and UGT1A6 as genetic markers predictive of anthracycline-induced cardiotoxicity in children. *Pediatr Blood Cancer* 2013; **60**(8): 1375-81.
12. Blanco JG, Sun CL, Landier W, et al. Anthracycline-related cardiomyopathy after childhood cancer: role of polymorphisms in carbonyl reductase genes--a report from the Children's Oncology Group. *J Clin Oncol* 2012; **30**(13): 1415-21.
13. Blanco JG, Leisenring WM, Gonzalez-Covarrubias VM, et al. Genetic polymorphisms in the carbonyl reductase 3 gene CBR3 and the NAD(P)H:quinone oxidoreductase 1 gene NQO1 in patients who developed anthracycline-related congestive heart failure after childhood cancer. *Cancer* 2008; **112**(12): 2789-95.
14. Windsor RE, Strauss SJ, Kallis C, Wood NE, Whelan JS. Germline genetic polymorphisms may influence chemotherapy response and disease outcome in osteosarcoma: a pilot study. *Cancer* 2012; **118**(7): 1856-67.
15. Lipshultz SE, Lipsitz SR, Kutok JL, et al. Impact of hemochromatosis gene mutations on cardiac status in doxorubicin-treated survivors of childhood high-risk leukemia. *Cancer* 2013; **119**(19): 3555-62.
16. Singh P, Wang X, Hageman L, et al. Association of GSTM1 null variant with anthracycline-related cardiomyopathy after childhood cancer-A Children's Oncology Group ALTE03N1 report. *Cancer* 2020; **126**(17): 4051-8.
17. Hildebrandt MAT, Reyes M, Wu X, et al. Hypertension Susceptibility Loci are Associated with Anthracycline-related Cardiotoxicity in Long-term Childhood Cancer Survivors. *Scientific Reports* 2017; **7**(1): 9698.
18. Wang X, Sun CL, Quiñones-Lombraña A, et al. CELF4 Variant and Anthracycline-Related Cardiomyopathy: A Children's Oncology Group Genome-Wide Association Study. *J Clin Oncol* 2016; **34**(8): 863-70.

Working group 2: What surveillance modalitity should be used?

1. What is the agreement of left ventricular ejection fraction measured with echocardiography as compared to cardiac MRI in CAYA cancer survivors?

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
1. Agreement of LVEF measured with echo as compared to CMR. **(n=3 studies)**	Ylänen 2014	71 survivors 63 ANT only 8 ANT+RT 71 healthy controls	Median 7, range 5-18 years	-FS <28%: 0/71 (0%) -3D LVEF <50%: 7/71 (10%) and in 6/58 with CMR (10%)	-CMR LVEF <55% 45/58 (50%)	<u>Bland altman analysis 3D LVEF - CMR LVEF (from figure)</u> Mean difference: 7% (lower for CMR) Lower limit [-1.96 SD]: -9% Upper limit [+1.96 SD]: 21% 1.96 SD=12% <u>Correlation 3D LVEF with CMR LVEF</u> r=0.189, p=0.155	SB: low risk IB: unclear RB: unclear VB: unclear AB: low risk
	Shah 2017	50 survivors 100% ANT 38% RT	Median 10.8, range 5-21.6 years from treatment	Echo -M-mode LVEF <53% -2D LVEF <53% -3D LVEF <53% CMR	CMR LVEF <53% n=4 (8%)	<u>Bland altman analysis</u> -M mode LVEF – CMR LVEF: mean 5.5% (lower for CMR), SD=6.3%, 1.96SD=12.3%, SE=0.89% -2D LVEF – CMR LVEF: mean 1.8% (lower for CMR), SD=5.5%, 1.96SD=10.8%, SE=0.78% -3D LVEF – CMR LVEF: mean 1.9% (lower for CMR), SD=5.3%, 1.96SD=10.4%, SE=0.78% <u>Correlations</u> -M mode LVEF – CMR LVEF: 0.17, P=0.265 -2D LVEF – CMR LVEF: 0.44, p=0.001 -3D LVEF – CMR LVEF: 0.24, p=0.12	SB: unclear IB: unclear RB: unclear VB: low risk AB: low risk
	Armstrong 2012	134 survivors	Median 27.8, range 18.4-38.3 years	Echo LVEF <50% -3D n=22 (19.3%) -2D Biplane n=6 (5.3%) -Apical 4CH n=8 (7%) -Teichholz n=24 (21.1%)	CMR LVEF <50% n=16 (14%)	<u>Correlation between CMR and echo LVEF</u> -Teichholz/M mode LVEF, *r* = 0.29 -Apical 4CH LVEF, *r* = 0.34 -2D biplane LVEF, *r* = 0.39 -3D LVEF, *r* = 0.37. <u>Bland-Altman analysis (±1.96 SD)</u> -CMR-Teichholz M-mode LVEF: mean -3.1% (−28.3% to 22.1%), 1.96SD=25.2% (lower LVEF with CMR)	SB: high risk IB: low risk RB: low risk VB: low risk AB: low risk

		-CMR - 2D apical 4CH LVEF: mean −5.4% (−22.1% to 11.4%), 1.96SD=16.8% (lower LVEF with CMR) -CMR - 2D biplane: mean −5.2% (−19.0% to 8.69%), 1.96SD=13.8% (lower LVEF with CMR) -CMR - 3D LVEF: mean 1.1% (−11.8% to 14.0%), 1.96SD=12.9% (higher LVEF with CMR)
GRADE assessment:		
Study design:	+4	Cohort studies
Study limitations:	-1	Some limitations: Selection bias high in 1/3, unclear in 1/3, low in 1/3; Index test and reference test bias unclear in 2/3, low in 1/3; Verification bias low in 2/3, unclear in 1/3; Attrition bias low in 3/3.
Consistency:	0	Sensitivity and PPV consistently low; specificity and NPV consistently high. Outcome definitions were slightly different between studies (CMR LVEF<50%, CMR LVEF<53% and CMR LVEF<55% were considered abnormal in the included studies)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Sample sizes of individual studies are small, but in total 255 patients included. Confidence intervals not reported in most but are not wide in 1/3 studies.
Publication bias:	0	Unlikely
Effect size:	0	Not applicable to diagnostic values
Dose-response:	0	Not applicable to diagnostic values
Plausible confounding:	0	Not applicable to diagnostic values
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		The mean difference in LVEF measured with M-mode echocardiography and CMR ranges from 3.1% to 5.5% lower for CMR (1.96SD range: 12.3-25.2%) The mean difference in LVEF measured with 2D echocardiography and CMR ranges from 1.8% to 5.4% lower for CMR (1.96SD range: 10.8-13.8%) The mean difference in LVEF measured with 3D echocardiography and CMR ranges from 1.1% higher for CMR to 7% lower for CMR (1.96SD range: 10.4-12.9%) (3 studies; 255 participants; 81 events).

Abbreviations: 3D=3-dimensional; AB=attrition bias; ALVD=asymptomatic left ventricular dysfunction; ANT=anthracyclines; CAYA=childhood, adolescent and young adult; CMR=cardiac magnetic resonance imaging; echo=echocardiography; FS=fractional shortening; IB=index test bias; LVEF=left ventricular ejection fraction; RB=reference test bias; RT=radiotherapy to the chest region; SB=selection bias; VB=verification bias.

2. What is the agreement of left ventricular ejection fraction measured with 2-dimensional echocardiography as compared to 3-dimensional echocardiography in CAYA cancer survivors?

No studies were identified in CAYA cancer survivors.
Summary of evidence from guidelines in the **general population.**

GUIDELINE	EVIDENCE	STRENGTH	LEVEL OF EVIDENCE
EACVI / ASE CARDIAC CHAMBER QUANTIFICATION WITH ECHOCARDIOGRAPHY 2015[1]	The guideline refers to a meta-analysis from Dorosz et al 2012 of 9 articles[2]: <u>Bland Altman analysis compared to CMR</u> -2D echocardiography – CMR LVEF: mean pooled difference/bias 0.1%, 2SD 13.9% -3D echocardiography – CMR LVEF: mean pooled difference/bias 0.0%, 2SD 9.2% -Difference in bias of 2D and 3D LVEF compared to CMR was not statistically significant (p=0.42) -Difference in variance of 2D and 3D LVEF compared to CMR was statistically significant (p<0.001)	Not graded	Not graded

Abbreviations: 2D=2-dimensional, 3D=3 dimensional, CMR=cardiac magnetic resonance imaging, LVEF=left ventricular ejection fraction, SD=standard deviation.

1: Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiogr. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

2: Dorosz JL, Lezotte DC, Weitzenkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;59(20):1799-1808. doi:10.1016/j.jacc.2012.01.037

3. What is the recommended modality to measure LV systolic function and what are the thresholds for abnormal?

No studies were identified in CAYA cancer survivors.
Summary of evidence from guidelines in the **general population.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
EACVI / ASE CARDIAC CHAMBER QUANTIFICATION WITH	-LV systolic function should be routinely assessed using 2D or 3D echocardiography by calculating EF from EDV and ESV. -LV size (EDV and ESV) should be routinely assessed on 2D echocardiography by calculating volumes using the biplane method of disks summation technique. In laboratories with	Not graded	Not graded

ECHOCARDIOGRAPHY 2015[1]	experience in 3D echocardiography, 3D measurement and reporting of LV volumes is recommended when feasible depending on image quality. -LVEFs of <52% for men and <54% for women are suggestive of abnormal LV systolic function.

Abbreviations: 2D=2-dimensional, 3D=3 dimensional, CMR=cardiac magnetic resonance imaging, LVEF=left ventricular ejection fraction, SD=standard deviation.

1: Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi:10.1016/j.echo.2014.10.003

4. What is the diagnostic value of serum biomarkers (ANP, BNP, troponin T, troponin I, or NT-pro-BNP) as compared to a control surveillance modality (i.e., either echocardiography, radionuclide angiography, or MRI) in CAYA cancer survivors for detecting asymptomatic cardiomyopathy?

N-terminal pro B-type natriuretic peptide (NT-proBNP)

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
2a. Diagnostic value of NT-proBNP for detecting ALVD on echo/MRI/radionuclide angiography. **(n=10 studies)**	Dixon 2020	1213 survivors, 736 cardiotoxic treatment, 8.6% previous CMP	Median 26.4, IQR 19.9-33.8 years	-NT-proBNP: sex and age normal values[$] (n=273, 22.5%)	Echo -3D LVEF<53% (n=171, 16.4%) -GLS >2SD above sex, age and vendor specific means[@] (n=425, 39.8%) -Diastolic dysfunction according to ASE^ (n=222, 22.1%)	-Patients with grade 3-4 cardiomyopathy were excluded for calculation of diagnostic values NT-proBNP to detect 3D LVEF <53% on echo Sensitivity: 23% (95%CI 17-29) Specificity: 82% (95%CI 80-85) Positive predictive value: 20% (15-26%) Negative predictive value: 85% (82-87%) NT-proBNP to detect abnormal GLS on echo Sensitivity: 22% (95%CI 18-26) Specificity: 83% (95%CI 80-86) Positive predictive value: 47% (95%CI 40-54) Negative predictive value: 62% (95%CI 59-65) NT-proBNP to detect diastolic dysfunction on echo Sensitivity: 26% (95%CI 20-32) Specificity: 84% (95%CI 81-86) Positive predictive value: 31% (95%CI 24-38) Negative predictive value: 80% (95%CI 77-83)	SB: low risk IB: low risk RB: low risk VB: low risk AB: low risk

					-Comparable results when limited to survivors exposed to cardiotoxic treatments	
	Corella 2018	57 asymptomatic survivors 72% ANT 14% RT	Mean 16.9 ± 4.0 years	-NT-proBNP -No normal values reported	-Echo 2D LVEF, males <52%, females <54% (n=4, 7%) -Echo GLS	-Higher NT-ProBNP associated with lower 2D LVEF (r = −0.49, p < 0.05) and higher/worse GLS (R = 0.61, p < 0.05). -Abnormal NT-proBNP compared to 2D LVEF <52% in males and <54% in females (NB cut-off for abnormal NT-proBNP not reported): Sensitivity: 100% Specificity: 81.4%.	SB: high risk IB: unclear RB: unclear VB: unclear AB: low risk
	Shah 2017	50 asymptomatic survivors 100% ANT 38% RT	Median 10.8, range 5-21.6 from treatment	-NT-proBNP >300 ng/L (n=1, 2%)	CMR LVEF <53% (n=4, 8%)	<u>1 patient with elevated NT-proBNP >300 ng/L had normal LVEF on CMR (LVEF>=53%, normal troponin I)</u> Sensitivity: 0% (95%CI 0-23) Specificity: 98% (95%CI 98-100) Positive predictive value: 0% (NA) Negative predictive value: 92% (95%CI 92-94)	SB: low risk IB: unclear RB: unclear VB: low risk AB: low risk
	Ylänen 2015*	76 asymptomatic survivors 100% ANT 13% RT	Median 9.0, range 5.4-18.4 years	-NT-proBNP >63 ng/L females: >116 ng/L, children[+] (n=4, 5.3%)	-FS <28% (n=2, 2.6%) -3D LVEF <50% (n=10/75, 13.3%) -CMR LVEF <55% or LVED or LVES volumes >2SD from normal (n=49/62, 79%)	<u>NT-proBNP to detect 3D LVEF<50% on echo</u> Sensitivity: 20% (95% CI 4-56) Specificity: 97% (95%CI 88-99) Positive predictive value: 50% (95%CI 9-91) Negative predictive value: 89% (95%CI 78-95) <u>NT-proBNP to detect LVEF<55% on MRI (in n=62)</u> Sensitivity: 8.2% (95%CI 3.4-8.2) Specificity: 100% (95%CI 82.1-100) Positive predictive value: 100% (95%CI 41.7-100) Negative predictive value: 22.4% (95%CI 18.4-22.2)	SB: high risk IB: unclear RB: unclear VB: unclear AB: low risk for echo, high risk for CMR
	Pourier 2015*	64 asymptomatic survivors 100% ANT RT unknown	Median 8.3, range 4.5-34.1 years	-NT-proBNP Age and sex normal values[$,+] (n=5, 7.8%)	Echo 2D LVEF <55% (n=7, 10.9%)	<u>NT-proBNP to detect 2D LVEF <55% on echo</u> Sensitivity: 14% (95%CI 1-58) Specificity: 93% (95%CI 83-98) Positive predictive value: 20% (95%CI 1-70) Negative predictive value: 90% (95%CI 79-96)	SB: low risk IB: unclear RB: unclear VB: low risk AB: low risk
	Sherief 2012	50 asymptomatic survivors 100% ANT	Median 3.75, range 1.5-6 years	-NT-proBNP, age-dependent reference values[#] (n=10, 20%)	Echo 2D LVEF <55% or LVFS <29% (n=8, 16%)	<u>NT-proBNP to detect LVEF<55% or LVFS<29% on echo</u> Data to calculate diagnostic values not provided Higher NT-proBNP levels associated with worse FS, LVEDS, LVEDD, abnormal TDI and with higher anthracycline dose.	SB: unclear IB: unclear RB: unclear VB: unclear

		RT unknown				AB: low risk
	Mladosievicova 2012*	36 asymptomatic survivors 100% ANT 0% RT	Median 11, range 5-22 years from therapy	-NT-proBNP, males >75 ng/L, females >105 ng/L (n=4, 11.1%)	Echo 2D LVEF <50% (n=0, 0%)	NT-proBNP to detect LVEF <50% on echo Sensitivity: NA Specificity: 89% (95% CI 89-89%) Positive predictive value: 0% (95% CI 0-0%) Negative predictive value: 100% (95% CI 100-100%)	SB: unclear IB: unclear RB: unclear VB: low risk AB: low risk
	Brouwer 2011*	227 survivors (7 clinical HF, 17 on meds) 72% ANT 63% RT	Median 18.2, range 5.4-30.8 years	-NT-pro-BNP >125 ng/L (n=32, 12.2%)	Echo: -LVFS <29% (n=97, 37%) -WMSI >1.00 (n=38, 14.5%)	NT-proBNP to detect LVFS<29% on echo 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: 64.8% (95% CI 62.4 to 67.1) Agreement between tests: 165/262 (63.0%) NT-proBNP to detect WMSI >1.00 on echo 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: 216/262 (82.4%)	SB: low risk IB: unclear RB: unclear VB: unclear AB: low risk
	Krawczuk-Rybak 2011	44 asymptomatic survivors 100% ANT 16% RT	Mean 5.91, range 1.6-13.8 years	NT-pro-BNP >115 ng/L (n=6, 13.6%)	Echo indexed stroke volume < 40 ml/m² (n=16, 36.4%)	NT-proBNP to detect stroke volume <40 ml/m2 on echo 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: 26/44 (59.1%).	SB: unclear IB: unclear RB: unclear VB: unclear AB: low risk
	Mavinkurve-Groothuis 2009*	122 asymptomatic survivors 100% ANT 6% RT	Median 13.8, range 5-28.7 years	-NT-pro-BNP, males >84.6 ng/L, females >152.2 ng/L children age dependent# (n=16, 13.1%)	Echo 2D -2D LVEF <55% (n=9, 7.4%) -LVFS <29% (n=4, 3.3%)	NT-proBNP to detect 2D LVEF <55% on echo 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) Negative predictive value: 93.4% (95% CI 91.8 to 96.3) Agreement: NT-proBNP: 101/122 (82.8%).	SB: unclear IB: low risk RB: low risk VB: low risk AB: low risk

		-Diagnostic value of NT-proBNP to detect LVFS<29% could not be calculated with numbers provided
GRADE assessment:		
Study design:	+4	Cohort studies
Study limitations:	-1	Some limitations: Selection bias low in 4/10, high in 2/10, unclear in 4/10; Index test and reference test bias low in 2/10, unclear in 8/10; Verification bias low in 5/10, unclear in 5/10; Attrition bias low in 10/10 for comparison with echo; Attrition bias low in 9/10 and high in 1/10 for comparison with CMR.
Consistency:	0	Diagnostic values are consistent across studies. Although, biomarker cut-off values for abnormal and outcome definitions of reference test (echo/MRI) were different across studies, diagnostic values were fairly consistent.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Large number of studies and number of patients included. Confidence intervals are small in the larger studies included.
Publication bias:	0	Unlikely
Effect size:	0	Not applicable to diagnostic values
Dose-response:	0	Not applicable to diagnostic values
Plausible confounding:	0	Not applicable to diagnostic values
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		The sensitivity of NT-proBNP (cut-off range 63-300 ng/l) to detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is low (ranging from 8%-100%) as compared to echocardiogram or cardiac magnetic resonance imaging. When one study that did not report the NT-proBNP cut-off for abnormal is excluded the sensitivity is very low (ranging from 8%-32%). The specificity of NT-proBNP (cut-off range 63-300 ng/l) to detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is high (ranging from 81%-100%) as compared to echocardiogram or cardiac magnetic resonance imaging. (10 studies, 1939 participants, 326 ALVD events).

Abbreviations: AB=attrition bias; ALVD=asymptomatic left ventricular dysfunction; ANT=anthracyclines; CAYA=childhood, adolescent and young adult; CI=confidence interval; echo=echocardiography; GLS=global longitudinal strain; IB=index test bias; MRI=magnetic resonance imaging; RB=reference test bias; RT=radiotherapy to the chest region; SB=selection bias; VB=verification bias, WMSI=wall motion score index.

* Included in systematic review of Leerink et al. 2019 (Leerink JM, Verkleij SJ, Feijen EAM, et al. Biomarkers to diagnose ventricular dysfunction in childhood cancer survivors: a systematic review. *Heart*. 2019;105(3):210-216.)

Albers et al. N-Terminal pro-brain natriuretic peptide: normal ranges in the pediatric population, Clinical Chemistry and Laboratory Medicine, vol. 44, no. 1, pp. 80–85, 2006.

$ Fradley et al. Reference limits for N-terminal- pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). Am J Cardiol 2011;108:1341–1345.

^ Nagueh et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321-1360.

@ Takigiku et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J*. 2012;76:2623-2632.

+ Nir et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. *Pediatr Cardiol*. 2009

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP)

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
2b. Diagnostic value of ANP and BNP for detecting ALVD on echo/MRI/radionuclide angiography. **(n= 1 study)**	Hayakawa 2001	34 asymptomatic survivors 100% ANT 0% RT	At least one month of therapy Age range 0.7-21.7 years	-ANP >26 pg/ml and BNP >13 pg/ml (i.e., >mean +2SD of 19 healthy controls) (n=6, 17.6%)	Echo LVEF <60% or LVSF <30% or regional wall dyskinesis, hypokynesis or akinesis (n=8, 23.5%)	ANP >26 pg/ml and BNP >13 pg/ml to detect LV dysfunction on echo 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: 30/34 (88.2%)	SB: low risk IB: unclear RB: unclear VB: low risk AB: low risk

GRADE assessment:		
Study design:	+4	Cohort study
Study limitations:	0	Selection bias low risk; Index test and reference test bias unclear; Verification bias low risk; Attrition bias low risk.
Consistency:	0	Not applicable (1 study)
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision: only 1 study performed with a small sample size
Publication bias:	0	Unlikely
Effect size:	0	Not applicable to diagnostic values
Dose-response:	0	Not applicable to diagnostic values
Plausible confounding:	0	Not applicable to diagnostic values
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		The sensitivity of atrial natriuretic peptide (ANP; cut-off 26 pg/ml) and brain natriuretic peptide (BNP; cutoff 13 pg/ml) to detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is moderate (63%) as compared to echocardiogram. The specificity of atrial natriuretic peptide (ANP; cut-off 26 pg/ml) and brain natriuretic peptide (BNP; cutoff 13 pg/ml) to detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is high (96%) as compared to echocardiogram. (1 study, 34 participants, 8 ALVD events).

Abbreviations: AB=attrition bias; ALVD=asymptomatic left ventricular dysfunction; ANT=anthracyclines; CAYA=childhood, adolescent and young adult; CI=confidence interval; echo=echocardiography; GLS=global longitudinal strain; IB=index test bias; MRI=magnetic resonance imaging; RB=reference test bias; RT=radiotherapy to the chest region; SB=selection bias; VB=verification bias, WMSI=wall motion score index.

Troponins (troponin T and troponin I)

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
2c. Diagnostic value of troponins for detecting ALVD on echo/MRI/radionuclide angiography. **(n=9 studies)**	Dixon 2020	1213 survivors, 736 cardiotoxic treatment, 8.6% previous CMP	Median 26.4, IQR 19.9-33.8 years	-Troponin T >0.01 ng/mL (n=5, 0.4%)	Echo -3D LVEF<53% (n=171, 16.4%)	-2/5 with abnormal troponin T had LVEF<53% on echo (both also had an abnormal NT-proBNP)	SB: low risk IB: low risk RB: low risk VB: low risk AB: low risk
	Corella 2018	57 asymptomatic survivors 72% ANT 14% RT	Mean 16.9 ± 4.0 years	-Troponin T -No normal values reported	-Echo 2D LVEF, males <52%, females <54% (n=4, 7%) -Echo GLS	-None had troponin T elevations	SB: high risk IB: unclear RB: unclear VB: unclear AB: low risk
	Shah 2017	50 asymptomatic survivors 100% ANT 38% RT	Median 10.8, range 5-21.6 from treatment	-Troponin-I >0.03 ng/mL (n=1, 2%)	CMR LVEF <53% (n=4, 8%)	1 patient with elevated troponin I >0.03 ng/mL had normal LVEF on CMR (LVEF>=53%, normal NT-proBNP) Sensitivity: 0% (95%CI 0-23) Specificity: 98% (95%CI 98-100) Positive predictive value: 0% (NA) Negative predictive value: 92% (95%CI 92-94)	SB: low risk IB: unclear RB: unclear VB: low risk AB: low risk
	Ylänen 2015*	76 asymptomatic survivors 100% ANT 13% RT	Median 9.0, range 5.4-18.4 years	-Troponin T >0.03 ng/mL (n=0) -High-sensitive troponin T >0.014 ng/mL (n=0) -Troponin I >0.0095 ng/mL (n=0) -autoantibodies to troponin T >100 counts (n=4, 5.3%)	-FS <28% (n=2, 2.6%) -3D LVEF <50% (n=10/75, 13.3%) -CMR LVEF <55% or LVED or LVES volumes >2SD from normal (n=49/62, 79%)	Troponins to detect 3D LVEF<50% on echo -cTnT, hs-cTnT, troponin I were normal in all -none of 4 with abnormal autoantibodies to troponin T had 3D LVEF <50%.	SB: high risk IB: unclear RB: unclear VB: unclear AB: low risk for echo, high risk for CMR
	Pourier 2015*	64 asymptomatic survivors 100% ANT RT unknown	Median 8.3, range 4.5-34.1 years	Hs-troponin T (Hs-cTnT >0.0135 ng/mL (n=0, 0%)	Echo 2D LVEF <55% (n=7, 10.9%)	Hs-troponinT -Not detected in any of the participants	SB: low risk IB: unclear RB: unclear VB: low risk AB: low risk

	Sherief 2012	50 asymptomatic survivors 100% ANT RT unknown	Median 3.75, range 1.5-6 years	-Troponin T >0.010 ng/ml (n=0, 0%).	Echo 2D LVEF <55% or LVFS <29% (n=8, 16%)	<u>Troponin T to detect LVEF<55% or LVFS<29% on echo</u> Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NA Negative predictive value: 84% (95% CI 84 to 84) Agreement between tests: 42/50 (84%)	SB: unclear IB: unclear RB: unclear VB: unclear AB: low risk
	Mavinkurve-Groothuis 2009*	122 asymptomatic survivors 100% ANT 6% RT	Median 13.8, range 5-28.7 years	-Troponin T ≥0.010 ng/ml (n=0%, 0%)	Echo 2D -2D LVEF <55% (n=9, 7.4%) -LVFS <29% (n=4, 3.3%)	<u>Troponin T to detect 2D LVEF <55% on echo</u> Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NA Negative predictive value: 92.6% (95% CI 92.6 to 92.6) Agreement: 113/122 (92.6%) <u>Troponin T to detect LVFS <29% on echo</u> Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NA Negative predictive value: 96.7% (95% CI 96.7 to 96.7) Agreement: 118/122 (96.7%)	SB: unclear IB: low risk RB: low risk VB: low risk AB: low risk
	Soker 2005	31 survivors 100% ANT RT unknown	Mean 9.39, range 1 to 42 months from anthracyclines	Troponin I ≥0.50 ng/ml (n=0, 0%)	Echo -LVEF <60% and LVFS <30% (n=4, 12.9%)	<u>Troponin I ≥0.50 ng/ml to detect LVEF <60% and LVFS <30% on echo</u> Sensitivity: 0% (95% CI 0 to 0) Specificity: 100% (95% CI 100 to 100) Positive predictive value: NA Negative predictive value: 87.1% (95% CI 87.1 to 87.1) Agreement: 27/31 (87.1%)	SB: unclear IB: unclear RB: unclear VB: low risk AB: low risk
	Kismet 2004*	24 asymptomatic survivors 100% ANT 17% RT	Median 12 months, range 1-168	Troponin T ≥0.010 ng/ml (n=3, 12.5%)	Echo -LVEF <55% and LVFS <29% (n=2, 8.3%)	<u>Troponin T ≥0.010 ng/ml detect LVEF <55% and LVFS <29% on echo</u> 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: 21/24 (87.5%)	SB: unclear IB: unclear RB: unclear VB: low risk AB: low risk
GRADE assessment:							

Study design:	+4	Cohort studies
Study limitations:	-1	Selection bias low in 3/9, unclear in 4/9 high in 2/9; Index test and reference test bias low risk in 2/9, unclear in 7/9; Verification bias low in 6/9, unclear in 3/9; Attrition bias low in 9/9 for comparison with echo; Attrition bias low in 8/9 and high in 1/9 for comparison with CMR.
Consistency:	0	Diagnostic values are consistent across studies. Although, biomarker cut-off values for abnormal and outcome definitions of reference test (echo/MRI) were different across studies, diagnostic values were fairly consistent.
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	Large number of studies and number of patients included. Confidence intervals are small in the larger studies included.
Publication bias:	0	Unlikely
Effect size:	0	Not applicable to diagnostic values
Dose-response:	0	Not applicable to diagnostic values
Plausible confounding:	0	Not applicable to diagnostic values
Quality of evidence:		⨁⨁⨁⨀ MODERATE
Conclusion:		The prevalence of abnormal cardiac (high-sensitive) troponin T (cut-off range 0.010-0.014 ng/mL) and I (cut-off range 0.0095-0.500 ng/mL) is low (range 0-12.5%) in CAYA cancer survivors >1 year after cancer treatment. The sensitivity of cardiac (high-sensitive) troponin T and troponin I detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is low (ranging from 0-50%) as compared to echocardiogram or cardiac magnetic resonance imaging. The specificity of cardiac (high-sensitive) troponin T and I to detect asymptomatic LV systolic dysfunction in CAYA cancer survivors is high (ranging from 91-100%) as compared to echocardiogram or cardiac magnetic resonance imaging. (9 studies, 1687 participants, 219 ALVD events).

Abbreviations: AB=attrition bias; ALVD=asymptomatic left ventricular dysfunction; ANT=anthracyclines; CAYA=childhood, adolescent and young adult; CI=confidence interval; echo=echocardiography; GLS=global longitudinal strain; IB=index test bias; MRI=magnetic resonance imaging; RB=reference test bias; RT=radiotherapy to the chest region; SB=selection bias; VB=verification bias, WMSI=wall motion score index.

* Included in systematic review of Leerink et al. 2019 (Leerink JM, Verkleij SJ, Feijen EAM, et al. Biomarkers to diagnose ventricular dysfunction in childhood cancer survivors: a systematic review. *Heart*. 2019;105(3):210-216.)

Albers et al. N-Terminal pro-brain natriuretic peptide: normal ranges in the pediatric population, Clinical Chemistry and Laboratory Medicine, vol. 44, no. 1, pp. 80–85, 2006.

$ Fradley et al. Reference limits for N-terminal- pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). Am J Cardiol 2011;108:1341–1345.

^ Nagueh et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17:1321-1360.

@ Takigiku et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J*. 2012;76:2623-2632.

+ Nir et al. NT-pro-B-type natriuretic peptide in infants and children: reference values based on combined data from four studies. *Pediatr Cardiol*. 2009

5. What is the cost-benefit ratio (both to patient and health care provider) of different surveillance strategies (including frequencies) in CAYA cancer survivors in different risk groups for cardiomyopathy?

Echocardiography

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
3a. Cost benefit of echo in CAYA cancer survivors **(n=3 studies)**	Ehrhardt 2020	Simulation using data from 24297 in CCSS and 3010 in SJLIFE	CCSS: median 21.1, range 5-39.3 years SJLIFE: median 27.2, range 11-53.2 years	Echo surveillance according to IGHG guideline	Heart failure Cost-effectiveness (QUALY)	40 year and lifetime HF risk -IGHG High: 9.9% and 36.7% -IGHG Mod: 4.5 and 24.7% -IGHG Low: 2.2% and 16.9% Preferred screening strategy -IGHG High: 2-year ($77,880/QALY gained) -IGHG Mod: 5-year ($94,580/QALY gained) -IGHG Low: none (all >$175,000/QALY gained) Delay in HF onset and reduction in HF deaths and for preferred strategy compared to no screening -IGHG High: 1.7 years and 196 -IGHG Mod: 0.9 years and 70 -IGHG Low: - Sensitivity analyses showed stability of results for high- and low-risk across several model parameters (e.g., treatment efficacy), but much variability for the moderate-risk group.	SB: unclear AB: unclear CF: low
	Wong 2014	Simulation using data from 4635 in CCSS	Median 20 years (range not reported)	Surveillance according to COG guidelines with: -2D-Echo LVEF, assumed sensitivity = 75% and specificity = 90% compared to MUGA -CMR LVEF (to confirm abnormal echo finding)	Heart failure Cost-effectiveness (QUALY)	<u>COG Guidelines overall</u> 1. Increased life expectancy by 6.1 months 2. Increased QALY by 1.6 moths 3. Reduced HF risk at 30 years after cancer by 18% 4. $61,500 per QALY gained <u>Simulations in 12 risk groups based on anthracycline dose, chest RT and age at diagnosis</u> Increasing screening intervals from 1 to 2 years, 2 to 5 years, and 5 to 10 years retained 80% benefit with half the cost ($33,200/QUALY gained)	SB: low risk AB: low risk CF: low

	Yeh 2014	Simulation using data from CCSS	Not reported	-2D echo surveillance at 1, 2, 5 and 10-year intervals. Assumed sensitivity = 25% and specificity = 99% compared to CMR	Heart failure Cost-effectiveness (QUALY)	1. For anthracycline exposure < 250 mg/m2 – no screening with echo was most cost-effective (QALY gained for every 10 years $104,400 exceeds cut-off value of $100,000) 2. For anthracycline ≥ 250 mg/m2 – screening every 2 years with echo was most cost-effective ($83,600/QALY gained)	SB: low risk AB: low risk CF: low

GRADE assessment:	**IGHG low risk group (anthracyclines <100 mg/m2 and/or chest-RT <15 Gray)**	**IGHG moderate risk group (anthracyclines 100-249 mg/m2 or chest-RT 15-34 Gray)**	**IGHG high risk group (anthracyclines ³250 mg/m2, chest RT ³35 Gray or combined treatment)**
Study design:	+4 Simulation studies based on data from cohort studies	+4 Simulation studies based on data from cohort studies	+4 Simulation studies based on data from cohort studies
Study limitations:	0 Selection bias low in 2/3 studies, unclear in 1/3 studies; attrition bias low in 2/3 studies, unclear in 1/3 studies.	0 Selection bias low in 2/3 studies, unclear in 1/3 studies; attrition bias low in 2/3 studies, unclear in 1/3 studies.	0 Selection bias low in 2/3 studies, unclear in 1/3 studies; attrition bias low in 2/3 studies, unclear in 1/3 studies.
Consistency:	0 No important inconsistency. 2/3 studies reported that echo surveillance in low-risk survivors treated with low doses of anthracyclines is not cost-effective.	0 No important inconsistency. None of the studies reports strong results on surveillance frequency in this risk group.	0 No important inconsistency. All studies reported that echo surveillance in high-risk survivors treated with high doses of anthracyclines is cost-effective.
Directness:	-1 Effectiveness of heart failure medications to treat asymptomatic LV dysfunction was obtained from the general population.	-1 Effectiveness of heart failure medications to treat asymptomatic LV dysfunction was obtained from the general population.	-1 Effectiveness of heart failure medications to treat asymptomatic LV dysfunction was obtained from the general population.
Precision:	0 Results remained the same in sensitivity analysis.	-1 Results were sensitive the changes in input variables.	0 Results remained the same in sensitivity analysis.
Publication bias:	0 Unlikely	0 Unlikely	0 Unlikely
Effect size:	0 Not applicable to simulation studies	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Dose-response:	0 Not applicable to simulation studies	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Plausible confounding:	0 Not applicable to simulation studies	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Quality of evidence:	⊕⊕⊕⊖ MODERATE	⊕⊕⊖⊖ LOW	⊕⊕⊕⊖ MODERATE
Conclusion:	-Echo surveillance is not cost-effective in low-risk CAYA cancer survivors treated with anthracyclines <100 mg/m2 and/or chest-RT <15 Gy. (3 simulation studies).	-Echo surveillance may be cost-effective at 5-year intervals in moderate-risk CAYA cancer survivors treated with anthracyclines 100-249 mg/m2 or chest-RT 15-34 Gy. (2 simulation studies).	-Echo surveillance is cost-effective at 2-year intervals in high-risk CAYA cancer survivors treated with anthracyclines ³250 mg/m2, chest RT ³35 Gy or a combination. (3 simulation studies).

Abbreviations: AB=attrition bias; CAYA=childhood, adolescent and young adult; CMR=cardiac magnetic resonance imaging; echo=echocardiography; IB=index test bias; RB=reference test bias; SB=selection bias; VB=verification bias; QUALY=quality-adjusted life year.

Cardiac magnetic resonance imaging (CMR)

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Diagnostic tests	Outcome definition	Diagnostic values Agreement between the tests	Risk of bias
3b. Cost benefit of CMR in CAYA cancer survivors **(n=1 study)**	Yeh 2014	Simulation using data from CCSS	Not reported	-CMR surveillance at 1, 2, 5 and 10-year intervals.	Heart failure Cost-effectiveness (QUALY)	CMR more cost-effective as a screening strategy than echo: -For anthracyclines < 250 mg/m2 – every 10 years ($78,000/QALY gained) -For anthracyclines ≥ 250 mg/m2- every 5 years ($89,800/QALY gained)	SB: low risk AB: low risk DB: high CF: low

GRADE assessment:	**Low to moderate risk group (anthracyclines <250 mg/m2)**	**High risk group (anthracyclines ≥250 mg/m2)**
Study design:	+4 Simulation studies based on data from cohort studies	+4 Simulation studies based on data from cohort studies
Study limitations:	0	0
Consistency:	0	0
Directness:	-1 Effectiveness of heart failure medications to treat asymptomatic LV dysfunction was obtained from the general population.	-1 Effectiveness of heart failure medications to treat asymptomatic LV dysfunction was obtained from the general population.
Precision:	-1 Some imprecision, only one study performed; Results remained the same in sensitivity analysis.	-1 Some imprecision, only one study performed; Results remained the same in sensitivity analysis.
Publication bias:	0 Unlikely	0 Unlikely
Effect size:	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Dose-response:	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Plausible confounding:	0 Not applicable to simulation studies	0 Not applicable to simulation studies
Quality of evidence:	⊕⊕⊖⊖ LOW	⊕⊕⊖⊖ LOW
Conclusion:	CMR surveillance may be cost-effective at 10-year intervals in low- to moderate-risk CAYA cancer survivors treated with anthracyclines <250mg/m2. (1 simulation study)	CMR surveillance is cost-effective at 5-year intervals in high-risk CAYA cancer survivors treated with anthracycline ³250mg/m2. (1 simulation study)

6. What is the diagnostic value of exercise stress echocardiography compared to diastolic function assessment by echocardiography for detecting asymptomatic restrictive cardiomyopathy in CAYA cancer survivors treated with cardiac radiation?
   No studies identified

Working group 3: At what frequency should cardiomyopathy surveillance be performed?

1. What is the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors treated with anthracyclines?

Asymptomatic

No studies address this question.

Symptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Time to cardiomyopathy	Risk of bias
Latency to onset of asymptomatic cardiomyopathy in CAYA cancer survivors treated with anthracyclines **(n= 1 study)**	Getz 2018	1022 AML 100% ANT 0% RT	Median (range) 6.6y (0-9.8) for patients alive at last contact. Echos with each chemo course	LV systolic dysfunction CTCAE grade ≥>2 (FS<24% or LVEF<50% or reported in CRF) CTCAE v3.0 Grade 2: EF<50-40% or SF<24-15% Grade 3: EF<40-20% or SF<15% Grade 4: EF <20% Grade 5: death related to LVSD	-n=124 (cumulative incidence=12%) developed LV systolic dysfunction within 5-years follow-up -n=88 (71%) occurred during on-protocol therapy, n=26 (29%) were first documented during off-protocol follow-up (25% infection-associated); n=9 (7.3%) were grade 4, n=2 (1.6%) grade 5 -Median time to cardiotoxicity: 4.3 months (IQR 3.1-5.9).	SB: low risk AB: high risk DB: unclear

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies, randomized-controlled trial
Study limitations:	-1	Limitations: Selection bias low in 1/1; Attrition bias high in 1/1; Detection bias unclear in 1/1
Consistency:	0	Not applicable, only one study
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-1	Only 1 study identified
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding

Quality of evidence:	⊕⊕⊖⊖ LOW
Conclusion:	There is an asymptomatic reduction in cardiac function occurring at a median of 4.3 months from AML diagnosis (1 study; 124 events; 1022 participants).

2. What is the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors treated with radiotherapy involving the heart?
   No studies address this question.

3. What is the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors treated with anthracyclines and/or radiotherapy involving the heart?

Symptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Time to cardiomyopathy	Risk of bias
Latency to onset of symptomatic cardiomyopathy in CAYA cancer survivors treated with anthracyclines **(n=2 studies)**	van der Pal 2012*	1362 33.6% ANT 11.6% RT	≥5 years Median 22.2, range 5.0-44.5 years	Validated symptomatic cardiac events (CE) Grading: CTCAE v 3.0 grade 3-5	-n=50 CEs; n=27 with congestive heart failure -Median time to first CE: 18.6, range 5.0-35.7 years -6 had heart failure during cancer treatment and recovered. 5/6 developed heart failure again at 5.1-19.6 years from cancer diagnosis.	SB: low risk AB: low risk DB: unclear
	van Dalen 2006*	830 100% ANT 21% RT	Any survivor Median 8.5, range 0.01-28.4 years	Anthracycline-induced CHF (A-CHF), not attributable to other known causes, such as direct medical effects of the tumor, septic shock, valvular disease or renal failure (CHF defined as presence of dyspnea, pulmonary edema, peripheral edema, and/or exercise intolerance treated with anticongestive tx)	n=20 cases of A-CHF -Cumulative incidence of A-CHF: 2.5% (21 patients; 95% CI 1.6-3.8%). -Mean time between the first dose of anthracyclines and A-CHF: 3.7 years (median 0.84 years; range 0.1-20.9 years).	SB: low risk AB: low risk DB: low risk

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	0	Limitations: Selection bias low in 2/2, Attrition bias low in 2/2; Detection bias low in 1/2, unclear in 1/2
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	-1	Some imprecision, only 2 studies with few cardiac events
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Median time from cardiotoxic exposure to onset of symptomatic cardiac events ranged from 0.84 to 18.6 years from cancer diagnosis, ranging from minimum 0.1 to maximum 35.7 years (2 studies, 47 events, 2192 patients).

*Overlap in cohorts

Asymptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Time to cardiomyopathy	Risk of bias
Latency to onset of asymptomatic cardiomyopathy in CAYA cancer survivors treated with anthracyclines and RT **(n= 6 studies)**	Border 2020	50 cases 50 controls 100% ANT 42-44% RT	≥1 year from end of initial cancer therapy Mean 5.4±5.0 for cases, 6.2 ±4.4 years for controls to last echo Median 5 echos (cases), 4 (controls)	Cases: FS≤28% or LVEF≤50% at 2 occasions Matched controls: FS≥30% and LVEF≥55%	-n=50 cases Follow-up from cancer to first abnormal echo: - <2 years 34%, 2-9 years 34%, 10+ years 32% - Mean time from cancer diagnosis to cardiomyopathy index time point was 6.4±5.3 years	SB: high risk AB: low risk DB: low risk
	Markman 2017	134 72% ANT 21% RT	Mean 14 ± 7 years All had ≥1 echo, unclear how many had multiple	LV systolic dysfunction on echo (LVEF<55% or FS ≥ 2SD below age normal)	-n=33 (24%) with LV dysfunction, 8 occurring during cancer treatment -Mean time to LV dysfunction: 3.7 ± 4.7 years from completion of therapy	SB: low risk AB: low risk DB: unclear
	Spewak 2017	853 95% ANT 28% RT	≥ 2 years, median 7.5, range 2.4-19.9 years Mean echos 2.0, range 1-11 51% had >1 echo	LV systolic dysfunction on echo (LVEF <55% and/or FS <28%) -Patients with pre-existing cardiotoxicity or abnormal ech before, during, or <2 years from treatment were excluded	-n=37 (4.3%) with LV systolic dysfunction -Median time to first occurrence of LV systolic dysfunction: 6.5 years (range 2.9–14.6 years)	SB: low risk AB: low risk DB: unclear
	Ramjaun 2015	333 92% ANT 39% RT	Median 15.8, range 5.0-47.9 years	-Echo abnormalities (LVEF<55% or FS<28% or >trivial valvular abn)	-n=49 (14.7%) with ≥1 echo abnormality -Median time to first abnormal echocardiogram: 11.7, range 1.8-42.0 years post-treatment	SB: low risk AB: low risk DB: unclear

		Mean # echos 2.86, SD 2.10	Median interval between echos 2.2, 0.1-19.4 years		- 20-year prob of abnormal echo was 20%, steadily climbing to that point -Time to first abnormal echo in those with sustained echo abnormalities not reported - No echo abnormalities noted in first 20 years for those treated with thoracic RT and no anthracyclines	
	Abosouda h 2010	469 100% ANT 34% RT	Median 3, range 1-10 years Echos off therapy - median 2, range 1-10, mean 2.2, SD 1.5	Abnormal echo: EF < 55% or FS < 28% or LVED z-score > 2.0 or LVPW z-score < −2.0	n=79 (16.8%) with abnormal echo Median (range) time from 1 year off therapy to abnormal echo 2.9 (0.01-9.8) years	SB: low risk AB: high risk DB: unclear
	Creutzig 2007	Eligible: N=1207 Late Cartox evaluated: N=885 early N=547 late (45%) 76% of echo evaluations done within first 5yrs ANT 100% RT 100% (px CNS)	BFM98: 3.6ys (0.8-7.0) BFM93: 7.5ys (1.1-11) Median F/up late cartox: 5.3 (0.8-11.5)	Subclinical cardiotoxicity - FS <30% on echo Clinical cardiotoxicity - signs and symptoms of heart failure in the absence of known causes such as sepsis Early if <1 year after completion of first line therapy Late occurred >1 year after the end of first line therapy	Late clinical or subclinical cardiotoxicity: -16/547, cumulative incidence 5% +/- 1 % (includes 4 that had early cardiotoxicity) Late subclinical cardiotoxicity: -7/547 - Decreased FS occurred after 2.7-7.5 years from diagnosis	SB: low risk AB: high risk DB: unclear

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low in 5/6, high in 1/6; Attrition bias low in 4/6, high in 2/6; Detection bias low in 1/6, unclear in 5/6
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large number of participants and events
Publication bias:	0	Unlikely

Effect size:	0	Not applicable
Dose-response:	0	Evidence of dose response relationship noted in only 1/10 studies
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		Abnormal cardiac function measured by echocardiogram occurred between 1 and 42 years from cardiotoxic exposure or cancer diagnosis. (6 studies; 264 events; 19,821 participants)

4. What is the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors who received dexrazoxane during anthracycline treatment?
   No studies address this question.

5. Do early changes in cardiac function (e.g., transient drop in EF) impact the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors?

Symptomatic
No studies address this question.

Asymptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Estimate (95% CI)	Risk of bias
Impact of early changes in cardiac function on latency to asymptomatic cardiomyopathy in CAYA cancer survivors **(n= 1 study)**	Leerink 2021	Derivation: 299 80% ANT 35% RT Validation: 218 88 % ANT 32 % RT	At first echo: -Derivation: median 16.7 (IQR 11.8-23.2) -Validation: 17.0 (IQR 13.0-21.7) - Median (range) follow-up echos per patient: derivation 5 (3-6), validation 3 (2-4) - Median (range) derivation 2.3 (2-2.7)	LV systolic dysfunction (LVEF<40%) Derivation n=11 Validation n=7	-Midrange EF at baseline in n=41 (13.7%) and n=12 (5.5%) of derivation and validation cohorts, respectively - n=11/299 cases of LVEF<40% after baseline follow-up echo Cumulative LVEF<40% incidence 10-years from initial EF - First LVEF 40-49% = 11.0% vs. ≥50% = 2.6% (p=0.012) Time to LV<40 - In survivors with LV<40, median time from first echo to LV<40 was 7.2 (1.2-12.2) years and did not significantly differ between those with LVEF ≥ 50% (median 6.6, IQR 4.7 to 7.7 years) and LVEF 40-49% (median 7.2, IQR 3.3 to 8.9 years), p = 0.085	SB: high risk AB: low risk DB: unclear

		and validation 1.9 (1.6-2.5) per 5 years
GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias high in 1/1; Attrition bias low in 1/1; Detection bias unclear in 1/1
Consistency:	0	Not applicable, only 1 study reports no difference in onset of EF <40 from time of baseline echo regardless of baseline EF 40-49% or ≥50%
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	-2	Important imprecision, only one study and few events
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		There is no significant difference in latency to onset of late echocardiogram abnormalities in those with mid-range ejection fractions at previous echo compared to those with normal ejection fractions at previous echo. (1 study; 18 events; 299 participants in derivation cohort, 218 in validation cohort)

6. Do early changes in cardiac function (e.g., transient drop in EF) predict late asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors?

Symptomatic

No studies

Asymptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Estimate (95% CI)	Risk of bias
Impact of early changes in cardiac function on prediction of asymptomatic cardiomyopathy in CAYA cancer survivors	Leerink 2021	Derivation: 299 80% ANT 35% RT Validation: 218 88 % ANT 32 % RT	At first echo: -Derivation: median 16.7 (IQR 11.8-23.2) -Validation: 17.0 (IQR 13.0-21.7) - Median (range) follow-up echos per patient: derivation 5	LV systolic dysfunction (LVEF<40%) Derivation n=11 Validation n=7	-Midrange EF at baseline in n=41 (13.7%) and n=12 (5.5%) of derivation and validation cohorts, respectively Cumulative LVEF<40% incidence 10-years from initial EF - First LVEF 40-49% = 11.0% vs. ≥50% = 2.6% (p=0.012) Multivariable models adjusted for anthracycline and chest-direct radiation	SB: high risk AB: low risk DB: unclear CB: high risk

(n= 5 studies)			(3-6), validation 3 (2-4) - Median (range) derivation 2.3 (2-2.7) and validation 1.9 (1.6-2.5) per 5 years		- Midrange baseline EF (40-49%) was associated with a higher risk of EF<40% at follow-up compared to baseline EF ≥50% (HR 7.8, 95% CI: 2.1-29.5)	
	Temming 2011	124 and 86 (late assessment) Only AML ANT (100%, presumed) RT (6%)	Median 7.3 (0-21.7)	Subclinical cardiotoxicity - FS <28% on 2D echo Clinical cardiotoxicity - clinical features of heart failure in the absence of known causes such as sepsis, but not strictly by AHA classification Early if <1 year after completion of first line therapy Late occurred or persisted >1 year after the end of first line therapy	15 of 86 individuals had late cardiotoxicity - 17.4% (10.9-26.8%) -5/67 (7.5%) developed subclinical late toxicity, 4 resolved, 1 remained borderline at last follow-up (FS 27%) -3/67 (4.5% [1.5-12.4%]) developed clinical late toxicity after frontline treatment alone -2/19 had late subclinical toxicity after relapse -5/19 had clinical cardiotoxicity after relapse Median time to cardiotoxicity after start of treatment -Early: 0.77 (0.32-1.89) years -Overall: 1.75 yrs (0.6-8.3) years -Early cardiotoxicity was a strong predictor of late cardiotoxicity (OR = 9.18, 95% CI: 2.10-40.11, p<0.005), adjusting for age at treatment, sex, and treatment intensity	SB: low risk AB: high risk DB: unclear CB: low risk
	Abosouda h 2011	469 100% ANT 34% RT	Median 3, range 1-10 years from 1 year after completion of therapy Echos >1 year off therapy - median 2, range 1-10, mean 2.2, SD 1.5	Abnormal echo ≥1 of: EF < 55%, FS < 28%, LVED z-score > 2.0, AND/OR LVPW z-score < −2.0	-n=79 (16.8%) with abnormal screening echo during follow-up -Median time from 1 year off therapy to abnormal echo 2.9, range 0.01-9.8 years -41/48 (85.4%) with a follow-up echo had persistent abnormalities - Adjusting for sex, RT, age at treatment, and cumulative ANT dose, abnormal echo during therapy was not significantly associated with increased risk of abnormal screening echo during follow-up (HR 1.39, 95% CI: 0.83 - 2.29).	SB: high risk AB: high risk DB: unclear CB: low risk
	Creutzig 2007	Eligible: N=1207 Late Cartox evaluated: N=885 early N=547 late (45%)	BFM98: 3.6ys (0.8-7.0) BFM93: 7.5ys (1.1-11) Median F/up late cartox: 5.3 (0.8-11.5)	Subclinical cardiotoxicity - FS <30% on echo Clinical cardiotoxicity - signs and symptoms of heart failure in the absence of known causes such as sepsis	Late clinical or subclinical cardiotoxicity: -16/547, cumulative incidence 5% +/- 1 % (includes 4 that had early cardiotoxicity) Late subclinical cardiotoxicity: -7/547	SB: low risk AB: high risk DB: unclear CB: low risk

		76% of echo evaluations done within first 5yrs ANT 100% RT 100% (px CNS)		<u>Early</u> if <1 year after completion of first line therapy <u>Late</u> occurred >1 year after the end of first line therapy	- Decreased FS occurred after 2.7-7.5 years from diagnosis <u>Cox Regression:</u> -Only early cardiotoxicity was a predictor of late cardiotoxicity (p<0.03) in the de novo AML group, adjusting for age, sex, FAB classification	
	Lipshultz 2005	287 ALL 100% ANT 0% RT	Median 11.8, range 8.3-15 years All >1 echo, but not reported otherwise	Longitudinal echo parameters (z-scores) LV contractility (stress velocity index), LVEDD, LVPW thickness, LV mass, LVFS, LV end systolic wall stress, thickness-dimen ratio	-n=11 with early CHF, 5 that persisted long-term -Mean z-score for FS and end-diastolic dimension at completion of therapy predicted z-score for FS and end-diastolic dimension at late follow-up (p<0.001). No report of adjustment. <u>Mean end of therapy FS z-score:</u> <-2 was associated with mean z-score <-2 mean 11 years later -2 to +1 associated with z-score -0.67 - >1 associated with z-score 0.3 <u>Mean end of therapy EDD z-score</u> <0 associated with mean z-score -0.96 >0 associated with mean z-score 0.41	SB: high risk AB: low risk DB: low risk CB: high risk

GRADE assessment:		
<u>Study design:</u>	+4	Longitudinal cohort studies
<u>Study limitations:</u>	-2	Limitations: Selection bias low in 2/5, high in 3/5; Attrition bias low in 2/5, high in 3/5; Detection bias low in 1/5, unclear in 4/5; Confounding bias low in 3/5, high in 2/5
<u>Consistency:</u>	0	No important inconsistency, 1 study reports no difference in onset, 5/6 studies report an increased risk of late cardiotoxicity in those with early abnormalities.
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable
<u>Precision:</u>	0	No important imprecision, large sample size and long follow-up period
<u>Publication bias:</u>	0	Unlikely
<u>Effect size:</u>	0	Not applicable
<u>Dose-response:</u>	0	Not applicable
<u>Plausible confounding:</u>	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW

Conclusion:	Early echocardiogram abnormalities are associated with increased risk of late echocardiogram abnormalities and/or cardiomyopathy. (5 studies; 4 studies significant effect; 139 events; 2,566 participants)

7. Is the latency to onset of asymptomatic/symptomatic cardiomyopathy different in low-, moderate-, and high-risk survivors?

Symptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Estimate (95% CI)	Risk of bias
Is latency to onset of symptomatic cardiomyopathy different in low-, moderate-, and high-risk survivors? (n= 2 studies)	Ehrhardt 2020	24,297 (CCSS) 3,010 (SJLIFE) 53% ANT 60% RT	CCSS: median 21.1, range 5-39.3 years SJLIFE: median 27.2, range 11-53.2 years	Simulated HF risk	Average age of HF onset without screening IGHG Low-risk: 66.4 years IGHG Moderate-risk: 61.8 years IGHG High-risk: 55.9 years	SB: unclear AB: unclear DB: unclear
	Yeh 2014	Published data only	Not reported	Simulated systolic HF risk	Average age at systolic CHF onset without screening <250 mg/m2: 58.2 years ≥250 mg/m2: 53.8 years	SB: low risk AB: unclear DB: unclear

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-2	Limitations: Selection bias (low in 1/2, unclear in 1/2); Attrition bias (unclear in 2/2); Detection bias (unclear in 2/2)
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable
Precision:	0	No important imprecision, large sample size and long follow-up period
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⨁⨁⊖⊖ LOW
Conclusion:		There is a dose-dependent decrease in age at onset of heart failure in CAYA cancer survivors exposed to higher doses of anthracyclines and/or chest-directed radiation. (2/2 studies; majority simulated events; 27,307 participants)

Asymptomatic

No studies report this.

8. Are different anthracyclines and/or anthraquinones associated with different latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors?
   No studies report this.

9. Does the risk for development of asymptomatic/symptomatic cardiomyopathy change over time in CAYA cancer survivors?

Asymptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Estimate (95% CI)	Risk of bias
Does the risk for asymptomatic cardiomyopathy change over time? **(n= 4 studies)**	Ramjaun 2015	333 92% ANT 39% RT Mean # echos 2.86, SD 2.10	Median 15.8, range 5.0-47.9 years Median interval between echos 2.2, 0.1-19.4 years	-Echo abnormalities (LVEF<55% or FS<28% or >trivial valvular abnormalities)	-n=49 (14.7%) with ≥1 echo abnormality - 20-year prob of abnormal echo was 20%, steadily climbing to that point -Sustained abnormal echo (confirmed at subsequent echo): n=29 (8.7%) -≥250mg/m2: Consistent increase in sustained echo abnormalities, higher in those treated at <5 years of age -<250mg/m2: Plateau in incidence of sustained echo abnormalities at 15 years post-therapy. -<250 mg/m2 and treated ≥5 years old: Plateau in incidence of sustained echo abnormalities at 10 years post-therapy.	SB: low risk AB: low risk DB: unclear CF: high risk
	Border 2020	50 cases 50 controls 100% ANT 42-44% RT	≥1 year from end of initial cancer therapy Mean 5.4±5.0 for cases, 6.2 ±4.4 years for controls to last echo Median 5 echos (cases), 4 (controls)	Cases: FS≤28% or LVEF≤50% at 2 occasions Matched controls: FS≥30% and LVEF≥55%	n=50 cases Differences, derived by least square means (95% CI) by time prior to index time point 2D FS, % ≥6 years: 4.0 (1.2-6.7), p=0.005 4 to <6 years: 3.1 (0.7-5.5), p=0.013 2 to <4 years: 2.8 (0.7-4.8), p=0.008 Index timepoint: 8.4 (6.7-10.1), p<0.001 Biplane EF, % ≥6 years: 2.8 (-3.2-8.8), p=0.364 4 to <6 years: 2.8 (-1.4-7.0), p=0.194	SB: high risk AB: low risk DB: low risk CF: low risk

					2 to <4 years: 4.8 (1.5-8.1), p=0.006 Index timepoint: 12.4 (9.8-15.0), p<0.001	
	Pourier 2020	ALL-survivors (n=41) Healthy controls n=70, age matched	Median 9.7 (range 7.9-12.6) after diagnosis	Subclinical cancer therapeutics related cardiac dysfunction (CTRCD): - Adults: Relative reduction of 15% in GLS (global longitudinal strain) compared with baseline Children: Relative reduction of 10% in GLS (global longitudinal strain) compared with baseline - Reduction of > 10% in LVEF	N=22 with GLS reduction of ≥10% -No further decrease in LVSF and LVEF at 1-year after end of treatment (T2) through >5 years (T3) **-T3 vs T0: Relative reduction of 10% in GLS over total time in 54% (≥ 15% reduction in 40%) despite preserved LVEF (<=10% LVEF decrease).** -All myocardial strain parameters decreased during anthracycline treatment and at late follow-up (T3 vs T2) (global longitudinal strain rate and global circumferential strain rate p < 0.001) -T3: Lower FS, GLS and GLS rate values in survivors compared to healthy controls (GLS p < 0.001 and GLSR p=0.008). LVEF and GCS were not different.	SB: high AB: low risk DB: unclear CF: unclear
	Wong, 2014	N=4635 childhood cancer survivors	Median f/u: 20 years within CCSS. Model estimates lifetime risk	ALVD	Cumulative incidence of ALVD increased across all risk groups as age increased in both men and women	SB: low risk AB: low risk DB: high risk CF: low risk

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low risk in 3/4, high in 1/4, unclear in 0/4; Attrition bias low in 4/4; Detection bias low in 1/4, high in 1/4, unclear in 2/4; Confounding bias low in 2/4, high in 1/4, unclear in 1/4
Consistency:	0	No important inconsistency
Directness:	-1	Ramjaun 2015 also included more than trivial valvular abnormalities as the outcome.
Precision:	-1	Some important imprecision (relatively few studies and events, unclear of clinical significance of the effect size)
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		The risk of asymptomatic cardiomyopathy increased over time in CAYA cancer survivors, especially after higher doses of anthracyclines.

	(4 studies; 121 events; 5059 participants) The risk of asymptomatic cardiomyopathy reached a plateau in CAYA cancer survivors treated with <250 mg/m2 anthracyclines. (1 study; 49 events; 333 participants)

Symptomatic

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Outcome	Estimate (95% CI)	Risk of bias
Does the risk for symptomatic cardiomyopathy change over time? **(n= 14 studies)**	Mulroney 2009	14,358 survivors 33% ANT 57% RT	Median 27.0, range 8-51 years	-Grade 3-4 CHF by survey	N=248 cases of HF or cardiomyopathy Estimated cumulative incidence of HF from figures: 0.5% at 10 years since diagnosis 1.5% at 20 years since diagnosis 5% at 30 years since diagnosis	SB: low risk AB: low risk DB: unclear CF: low risk
	Bates 2019	24,214 survivors 50% ANT 52% RT	Median 20.3, range 5.0-39.3 years	-Heart failure (CTCAE grade 3-5), n=371	n=371 with heart failure Estimated cumulative incidence of HF from supplemental figure: Female - 4% at 10 years - 14% at 20 years - 31% at 30 years Male - 2% at 10 years - 9% at 20 years - 20% at 30 years	SB: low risk AB: low risk DB: unclear CF: low risk
	Khanna 2019	7,289 45% ANT 14% RT	Median 10, range 0-25 years	Congestive heart failure based on administration data algorithm	N=203 cardiac events, but number of CHF cases not reported Cumulative incidence of heart failure: -10 years from diagnosis: 1.1% (95%CI 0.8-1.4%) -15 years from diagnosis: 1.8% (95%CI 1.4-2.3%)	SB: low risk AB: low risk DB: unclear CF: low risk
	Chellapandian 2019	2,053 survivors of ALL and AML 77% ANT 11% RT	0-24 years after diagnosis, no median reported	CHF according to ICD9 and 10 codes ALL n=32, AML n=20	ALL: 14/32 CHF events (43.8%) within 3 years from cancer diagnosis AML: 9/20 CHF events within 0.5 years from cancer diagnosis Cumulative incidence (95% CI) of CHF AML ○ 2.9% (1.4-5.3) at 6 months ○ 5.8% (3.6-8.9) at 3 years	SB: low risk AB: low risk DB: unclear CF: low risk

				○ 6.9% (4.4-10.1) at 5 years ○ 7.5% (4.8-10.9) at 10 years ○ 8.2% (5.3-11.9) at 15 years ALL ○ 0.4% (0.2-0.8) at 6 months ○ 0.9% (0.5-1.8) at 3 years ○ 1.2% (0.8-1.9) at 5 years ○ 1.7% (1.1-2.5) at 10 years ○ 2.4% (1.6-3.5) at 15 years	
Chow 2015	CCSS: 13,060 SJLIFE: 1,695 EKZ: 1,362 NWTS: 6,760 37.4%/59.2%/41.5%/50.8% ANT 25.9%/29.5%/15.9%/43.4% RT	<u>Years after diagnosis, median (range)</u> CCSS: 24 (5-39) SJLIFE: not reported EKZ: 23 (5-45) NWTS: not reported	Heart failure CTCAE version 4.03 or version 3 (EKZ)	CHF events: 285 (CCSS), 19 (SJLIFE), 26 (EKZ), 48 (NWTS); 10 with history of heart transplant All cohorts observed dose dependent increases in cumulative incidence of HF over time. "Low-risk" survivors based on prediction models had minimal to no increase in cumulative incidence over time.	SB: low risk AB: unclear DB: unclear CF: low risk
Dietz 2019	13,318 survivors 40% ANT 66% RT	<u>Not reported, median ±23 years</u>	-Heart transplantation, n=37, time to transplantation: median 17, IQR 13-26 years	62 survivors had end stage HF awaiting transplant Cumulative incidence of waiting on heart transplant list for end-stage HF ±0.07% at 10 years after cancer diagnosis ±0.21% at 20 years ±0.35% at 30 years 0.49% at 35 years (95% CI 0.36-0.62) ±0.55% at 40 years Cumulative incidence of having received a heart transplant for end-stage HF ±0.07% at 10 years ±0.14% at 20 years	SB: low risk AB: low risk DB: unclear CF: low risk

				±0.21% at 30 years 0.30 at 35 years (95% CI 0.20-0.40) ±0.35% at 40 years	
Ehrhardt 2020	24,297 CCSS and 3,010 SJLIFE survivors used to inform risk for simulation model	Follow-up, median (range) CCSS 21.1 (5-39.3) SJLIFE 27.2 (11-53.2)	ALVD HF risk at age 40 years and lifetime	HF cumulative incidence (95% CI) at age 40 years and lifetime, no screening: IGHG low risk: 2.2% (0.8-3.8) and 16.9% (11.2-23.8) IGHG moderate risk: 4.5% (2.3-6.2) and 24.7 (17.3-33.5) IGHG high risk: 9.9% (8.7-11.1) and 36.7% (27.5-42.4)	SB: unclear AB: unclear DB: high risk CF: unclear
Getz 2018	1,022 AML 100% ANT 0% RT	Median (range) 6.6y (0-9.8) for patients alive at last contact. Echos with each chemo course	LV systolic dysfunction CTCAE grade ≥>2 (FS<24% or LVEF<50% or reported in CRF) CTCAE v3.0 Grade 2: EF<50-40% or SF<24-15% Grade 3: EF<40-20% or SF<15% Grade 4: EF <20% Grade 5: death related to LVSD	-n=124 (cumulative incidence=12%) developed LV systolic dysfunction within 5-years follow-up -n=88 (71%) occurred during on-protocol therapy, n=26 (29%) were first documented during off-protocol follow-up (25% infection-associated); n=9 (7.3%) were grade 4, n=2 (1.6%) grade 5 Cumulative frequency of incident cardiotoxicity Induction I: 1.5% Induction II: 2.1% Intensification I: 3.8% Intensification II: 6.3% Intensification III: 8.1% HSCT: 8.6% 6-month follow-up: 10.9% 12-month follow-up: 11.5% 18-month follow-up: 11.9% 2-year follow-up: 11.9% 3-year follow-up: 11.9% 4-year follow-up: 11.9% 5-year follow-up: 12.1%	SB: low risk AB: high risk DB: unclear CF: high risk
Mansouri 2019	N=1281 cases and controls,	Median Cases: 19.7 [range 13.7–26.9] years.	HF graded according to the Common Terminology Criteria for	239 cases of HF Cumulative incidence of HF	SB: low risk AB: low risk DB: unclear

	HF cases=239 *Anth: Cases n (%) & controls n (%)* 172 (72.0) & 362 (34.7) Radiation to the heart: *Mean dose,* Cases: median 12.3 (0.004–49.1) Gy Controls: median 2.1 (0.005–45.3) Gy	<u>Controls: 33.0 (range 27.2–39.0) years</u>	Adverse Events (CTCAE version 4.03) HF was identified according to the Framingham criteria (11) by the presence of at least two major symptoms or one major and two minor symptoms.	30 years = 2.5% (95% CI 2.1–2.9%) 50 years = 5.7% (95% CI 5.0–6.6%)	CF: low risk
Chen 2020	N=22,543	<u>Follow-up</u> Various, depending on prediction timepoint. Range 5->30 years Duration of follow up in the 20y cohort was 10-19y in 35% and 20-29y in 51%. In the 35y cohort: 20-29y in 53% and >30y in 40%	<u>Outcome definitions</u> Only heart failure reported in this table CTCAE grade 3-5	<u>CI of HF (prediction baseline at age 20, 25, 30, 35)</u> (risk score based on prediction model including sex, age at diagnosis, anthracycline dose, chest RT dose, hypertension, diabetes dyslipidemia) *10-year follow-up:* Siblings: 0.03%-0.2% Moderate risk (score <5): 0.4%-1.3% High risk (score >=5): 2.7%-6.3% *By age 50 years:* Siblings: 0.4%-0.6% Moderate risk (score <5): 1.4%-2.4% High risk (score >=5): 9.7%-11.8%	SB: low risk AB: low risk DB: unclear CF: low risk
Mulroone y 2020	n= 35,649 (46.3% female) Analyzed: n= 23 462	Median follow-up time ranged from 11.0 years (diagnosis in the 1990s) to 29.5 years (diagnosis	Participants completed a baseline questionnaire and up to four follow-up surveys.	-140 had cardiac event prior to cohort entry - 271 HF events	SB: high risk AB: high risk DB: unclear CF: low risk

			in the 1970s).	Outcome definitions all reported cardiac conditions of CTCAE grades 3-5, including heart failure.	-Cumulative incidence of heart failure at 15 years from cancer diagnosis was significantly lower in the 1990s (0.54%) compared with the 1970s (0.69%) (P=0.01) and the 1980s (0.74%) (P=0.01) (fig 2). Cumulative incidence at 10, 15, and 20 years since cancer diagnosis (15 year reported, remainder estimated from figures) 1970's – 0.3%, 0.7%, 1.2% 1980's – 0.3%, 0.8%, 1.2% 1990's – 0.2%, 0.5%, 0.9%	
	Visscher 2012	*Development:* 156 CCS from Canada *Replication:* 188 CCS from Canada and 96 CCS from the EKZ.	*Canada development* Cases 6.5, 0.1-21.2 Controls 7.8, 5-17.9 *Canada replication* Cases 7.4, 0.2-20.7 Controls 9.2, 5-18.6 *EKZ replication* Cases 20.2, 7.4-27.9 Controls 15.4, 5.1-29.8	Anthracycline induced cardiotoxicity cases: FS≤26% and/or CTCAE grade ≥3 (symptomatic events requiring intervention, Htx or fatal events).	Discovery n=38, Replication n=48 with anthracycline-related cardiotoxicity The incidence of anthracycline-induced cardiotoxicity in the high-risk group was highest in the first year and continued to increase over time. In the intermediate-risk group, a similar pattern is observed but less pronounced. The low-risk group experienced very little cardiotoxicity over time.	SB: unclear AB: high risk DB: unclear CF: low risk
	Wong, 2014	N=4,635 childhood cancer survivors	Median f/u: 20 years within CCSS. Model estimates lifetime risk	Heart failure	Cumulative incidence of HF increased across all risk groups as age increased in both men and women	SB: low risk AB: low risk DB: high risk CF: low risk
	Yeh 2014	Published data only	Not reported	Simulated systolic HF risk	Cumulative incidence of CHF increased over time from diagnosis.	SB: low risk AB: unclear DB: unclear CF: unclear

GRADE assessment:		
Study design:	+4	Longitudinal cohort studies
Study limitations:	-1	Limitations: Selection bias low risk in 11/14, high in 1/14, unclear in 2/14; Attrition bias low 8/14, high in 3/14, unclear in 3/14; Detection bias low in 0/14, high in 2/14, unclear in 12/14; Confounding bias low risk in low in 11/14, high in 1/14, unclear in 2/14
Consistency:	0	No important inconsistency
Directness:	0	Results are direct, population and outcomes broadly generalizable

Precision:	0	Moderate sample size and long follow-up period
Publication bias:	0	Unlikely
Effect size:	0	Not applicable
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion		The risk of heart failure increased over time in CAYA cancer survivors treated with higher anthracycline and/or chest-directed radiotherapy doses. (14 studies; 1802 events; 175944 participants)

10. What is the latency to onset of asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors with genetic variants associated with increased and/or decreased risk for anthracycline- or radiation-induced cardiomyopathy?
    No studies report this.

Working group 4: What should be done when abnormalities are identified?

Overview of included study and systematic review in CAYA cancer survivors

1. Silber JH, Cnaan A, Clark BJ, et al. Enalapril to prevent cardiac function decline in long-term survivors of pediatric cancer exposed to anthracyclines. J Clin Oncol. 2004;22(5):820-828. doi:10.1200/JCO.2004.06.022
2. Cheuk DK, Sieswerda E, van Dalen EC, Postma A, Kremer LC. Medical interventions for treating anthracycline-induced symptomatic and asymptomatic cardiotoxicity during and after treatment for childhood cancer. Cochrane Database Syst Rev. 2016;(8):CD008011. Published 2016 Aug 23. doi:10.1002/14651858.CD008011.pub3

Overview of included clinical practice guidelines in the general population

Guideline	Strength of recommendation	Level of evidence
Guidelines in cancer survivors (CAYA and adult)		
AHA scientific statement on cardiovascular toxicities in CAYA cancer survivors 2013	Not reported	Not reported
ESC position paper on cardiovascular toxicity 2016	Not reported	Not reported
Guidelines in the general population in children		
ISHLT heart failure guideline 2014	Class I: Procedure or treatment should be performed/administered. Class IIa: It is reasonable to perform procedure/administer treatment. Class IIb: Procedure/treatment may be considered. Class III: No benefit or harm of procedure/treatment	Level A: Data derived from multiple randomized clinical trials or meta-analyses. Level B: Data derived from a single randomized clinical trial or non-randomized studies. Level C: Consensus opinion of the experts, case studies or standard of care.
Guidelines in the general population in adults		
AHA/ACC/HFSA heart failure guidelines 2013 and update 2017	Class I: Procedure or treatment should be performed/administered. Class IIa: It is reasonable to perform procedure/administer treatment. Class IIb: Procedure/treatment may be considered. Class III: No benefit or harm of procedure/treatment	Level A: Data derived from multiple randomized clinical trials or meta-analyses. Level B: Data derived from a single randomized clinical trial or non-randomized studies. Level C: Consensus opinion of the experts, case studies or standard of care.
ESC heart failure guideline 2016 and update 2021	Class I: Evidence and/or general agreement that a given procedure/therapy is useful and effective.	Level A: Data derived from multiple randomized clinical trials or meta-analyses.

	Class IIa: Conflicting evidence. Weight of evidence/opinion is in favor of its usefulness/efficacy. Class IIb: Conflicting evidence. Usefulness/efficacy is less well established by evidence/opinion. Class III: Evidence or general agreement that a procedure/therapy is not useful/effective, and in some cases may be harmful.	Level B: Data derived from a single randomized clinical trial or large non-randomized studies. Level C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.
NICE 2018 heart failure guideline	EXCLUDED (no recommendations in asymptomatic patients)	
SIGN 2016 heart failure guideline	Strong: For 'strong' recommendations on interventions that 'should' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For 'strong' recommendations on interventions that 'should not' be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more harm than good. Conditional: For 'conditional' recommendations on interventions that should be 'considered', the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.	1++: High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias 1+: Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias 1-: Meta-analyses, systematic reviews, or RCTs with a high risk of bias 2++: High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal 2+: Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal 2-: Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3: Non-analytic studies, eg case reports, case series 4: Expert opinion
Malaysian heart failure guideline 2019	Class I: Conditions for which there is evidence and/or general agreement that a given procedure/therapy is beneficial, useful and/or effective. Class IIa: Conflicting evidence. Weight of evidence/opinion is in favor of its usefulness/efficacy. Class IIb: Conflicting evidence. Usefulness/efficacy is less well established by evidence/opinion.	Level A: Data derived from multiple randomized clinical trials or meta-analyses. Level B: Data derived from a single randomized clinical trial or non-randomized studies. Level C: Consensus opinion of the experts, case studies or standard of care.

	Class III: Conditions for which there is evidence and/or general agreement that a procedure/therapy is not useful/effective and in some cases may be harmful.	
Canadian heart failure guideline 2017 and 2020	According to GRADE Strong: Benefits >>> risk & harms Moderate: Benefits > or = risk & harms Recommendation not to do: No benefit/potential harm	High: Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise). Moderate: Evidence from studies or systematic reviews with few important limitations. Low to very low: Evidence from studies with serious flaws, only expert opinion or, or standards of care.
Japanese heart failure guideline 2017	Class I: Evidence and/or general agreement that a given procedure/therapy is useful and effective. Class IIa: Conflicting evidence. Weight of evidence/opinion is in favor of its usefulness/efficacy. Class IIb: Conflicting evidence. Usefulness/efficacy is less well established by evidence/opinion. Class III: Evidence or general agreement that a procedure/therapy is not useful/effective, and in some cases may be harmful.	Level A: Data derived from multiple randomized clinical trials or meta-analyses. Level B: Data derived from a single randomized clinical trial or large non-randomized studies. Level C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

1. What is considered an abnormality for treatment (and at what threshold) in asymptomatic CAYA cancer survivors (with the background knowledge of the ESC and AHA heart failure guidelines in which the focus lies on 2D and 3D LVEF)?

Summary of guidelines including recommendations in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	This group has decided to consider **the lower limit of normal of LVEF in echocardiography as 50%**, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer.	Not graded	Not graded
	If **LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%),** ACE inhibitors (or ARBs) in combination with beta-blockers are recommended to prevent further LV dysfunction or the development of symptomatic heart failure, unless contraindicated, as these patients are at high risk of developing heart failure.[1]	Not graded	Not graded
	ACE inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or **asymptomatic cardiac dysfunction** unless contraindicated.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	No recommendations	NA	NA

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, LVEF=left ventricular ejection fraction.

1 ESC position paper: it is unclear if this recommendation is for patients on active cancer treatment or also for patients during follow-up after cancer treatment.

Summary of guidelines including recommendations in the **general population** in **children**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ISHLT 2014	No recommendations	NA	NA

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016	ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF (LV systolic dysfunction defined as **LVEF<40%).**	Class I: strong	B: moderate
ESC 2021	No recommendations		
AHA/ACC/HFSA 2013 AND 2017	Stage B (structural heart disease but without signs or symptoms of HF): ACE inhibitors should be used in all patients with a reduced EF to prevent HF (reduced EF defined as a **LVEF≤40%)**	Class I: strong	A: high
	Stage B: Beta blockers should be used in all patients with a reduced EF to prevent HF (reduced EF defined as a **LVEF<=40%)**	Class I: strong	C: low
MALAYSIAN HF GUIDELINE 2019	No recommendations	NA	NA
CANADIAN HF GUIDELINE 2017 AND 2020	We recommend an angiotensin-converting enzyme (ACE) inhibitor (ACEi) be used in all asymptomatic patients with a **LVEF<35%**	Strong	Moderate
	We recommend that beta-blockers should be considered in all asymptomatic patients with a **LVEF<40%**	Strong	Moderate
JAPANESE HF GUIDELINE 2017	ACE-I: Use in all patients (including asymptomatic patients) with left ventricular systolic dysfunction (**defined as LVEF<40%**) unless contraindicated. ARB: Use in patients intolerable to ACE inhibitors.	Class I: strong	A: high
	Beta-blocker: Use in asymptomatic patients with left ventricular systolic dysfunction (**defined as LVEF<40%**).	Class IIa: moderate	B: moderate
SIGN 2016	Patients with heart failure with reduced ejection fraction **(LVEF≤40%)** of all NYHA functional classes, should be given angiotensin-converting enzyme inhibitors.	Strong	1++: High

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association.

Recommendations: What is considered an abnormality for treatment?

Overall conclusions of recommendations in existing clinical practice guidelines in <u>cancer survivors</u> (CAYA and adult)	
Treatment with heart failure medications is recommended in asymptomatic pediatric and adult cancer survivors with a LVEF decrease of >10% to a value below 50%	1 position paper
Overall conclusions of recommendations in existing clinical practice guidelines in <u>children</u>	
No recommendations in children in the general population identified.	NA

Overall conclusions of recommendations in existing clinical practice guidelines in adults	
In adults with asymptomatic LVEF<=40% an ACE inhibitor is recommended (strong recommendation, moderate to high level of evidence).	Evidence based guidelines
In adults with asymptomatic LVEF<=40% a beta-blocker is recommended (strong recommendation, low to moderate level of evidence).	Evidence based guidelines

LVEF < 40%

2. What is considered an additional abnormality for treatment (and at what threshold) in CAYA cancer survivors with asymptomatic LVEF<40% (i.e., myocardial strain, shortening fraction, left ventricular diameter)?

Summary of guidelines including recommendations in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	Currently there is no evidence to guide specific cardioprotection if early signs of subclinical myocardial dysfunction are detected during echocardiography-based GLS surveillance.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	No recommendations on additional echocardiographic abnormalities to consider for treatment	NA	NA

Abbreviations: GLS=global longitudinal strain, LVEF=left ventricular ejection fraction.

Summary of guidelines including recommendations in the **general population** in **children**.
No recommendations

Summary of guidelines including recommendations in the **general population** in **adults**.
No recommendations

Recommendations: What is considered an additional abnormality for treatment in CAYA cancer survivors with asymptomatic LVEF<40%?

Overall conclusions of recommendations in existing clinical practice guidelines in cancer survivors (CAYA and adult)	
No evidence to initiate preventive treatments based on abnormalities in global longitudinal strain during echocardiographic surveillance.	1 position paper
Overall conclusions of recommendations in existing clinical practice guidelines in children and adults	
No recommendations	NA

3. What is the efficacy of treatments* in CAYA cancer survivors with asymptomatic LV dysfunction with LVEF<40%?

Summary of guidelines including recommendation in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), **ACE inhibitors (or ARBs) in combination with beta-blockers** are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high risk of developing HF.	Not graded	Not graded
	ACE inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	**Angiotensin-converting enzyme inhibitors and beta-blockers** can improve ejection fraction and decrease ventricular dilation in adults with LV dysfunction. These agents have been recommended for treatment of survivors at risk for ventricular dysfunction. However, a single 2004 multicenter, randomized, placebo-controlled trial of asymptomatic children with LV dysfunction after anthracycline therapy (Silber et al. 2004) found that enalapril did not affect the clinical status of survivors and had no long- lasting effect on ventricular remodeling. Thus, no data support the use of enalapril to prevent progression of LV dysfunction in asymptomatic patients. Beta-Blockade has not been studied in asymptomatic survivors with ventricular dysfunction.	Not graded	Not graded

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, LVEF=left ventricular ejection fraction.

Summary of guidelines including recommendations in the **general population** in **children**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ISHLT 2014	For the treatment of asymptomatic left ventricular dysfunction (HF Stage B), **ACE inhibitors** should be routinely used unless there is a specific contraindication.	Class I: strong	B: moderate
	Following adult HF guidelines, it is reasonable to consider **β-blockers** in asymptomatic children with systemic LV systolic dysfunction. Therapy should start at a small dose and slowly up-titrate.	Class IIa: moderate	B: moderate
	Similar to adults, **angiotensin receptor blockers** are generally reserved for those children with systemic ventricular systolic dysfunction who would benefit from renin-angiotensin-aldosterone– system blockade but are intolerant of ACE inhibitors.	Class IIa: moderate	C: low
	Digoxin is not recommended for children with asymptomatic LV dysfunction because no survival benefit was seen with digoxin in adults with HF and low EF.	Class I: strong	C: low

Abbreviations: ACE=Angiotensin converting enzyme, LV=left ventricular, HF=heart failure

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016	**ACE-I** is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF (LV systolic dysfunction defined as LVEF<40%).	Class I: strong/high effectiveness	B: moderate

	Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.	Class I: strong/high effectiveness	B: moderate
ESC 2021	No recommendations		
AHA/ACC/HFSA 2013 AND 2017	Stage B (structural heart disease but without signs or symptoms of HF): **ACE inhibitors** should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of myocardial infarction.	Class I: strong/ high effectiveness	A: high
	Stage B: **Beta blockers** should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI	Class I: strong/ high effectiveness	C: low
	Stage B: In all patients with a recent or remote history of myocardial infarction or acute coronary syndrome and reduced EF, evidence-based **beta blockers** should be used to reduce mortality.	Class I: strong	B: moderate
	Stage B: In patients with a history of MI and reduced EF, **ACE inhibitors or ARBs** should be used to prevent HF		
MALAYSIAN HF GUIDELINE 2019	No recommendations	NA	NA
CANADIAN HF GUIDELINE 2017 AND 2020	We recommend an **ACE inhibitor** be used in all asymptomatic patients with an LVEF < 35%	Strong	Moderate
	We recommend that **beta-blockers** should be considered in all asymptomatic patients with an LVEF < 40%	Strong	Moderate
	We recommend that in ACE-intolerant patients, an **angiotensin receptor blocker (ARB)** be considered for reduction of the risk of developing HF in patients with evidence of vascular disease or diabetes with end organ damage	Strong	High
JAPANESE HF GUIDELINE 2017	**ACE-I:** Use in all patients (including asymptomatic patients) with left ventricular systolic dysfunction (defined as LVEF<40%) unless contraindicated. **ARB**: Use in patients intolerable to ACE inhibitors.	Class I: strong	A: high
	Beta-blocker: Use in asymptomatic patients with left ventricular systolic dysfunction (defined as LVEF<40%).	Class IIa: moderate	B: moderate
SIGN 2016	Patients with heart failure with reduced ejection fraction (LVEF≤40%) of all NYHA functional classes, should be given **angiotensin-converting enzyme inhibitors.**	Strong	1++: high

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, HF=heart failure, LVEF=left ventricular ejection fraction, MI=myocardial infarction, NYHA=New York Heart Association.

Recommendations: What is the efficacy of treatments in CAYA cancer survivors with asymptomatic LVEF<40%?

Overall conclusions of recommendations in existing clinical practice guidelines in cancer survivors (CAYA and adult)

ACE-inhibitors and beta-blockers are effective in pediatric and adult cancer survivors with an asymptomatic decrease in LVEF of >10% to a value below 50% (not graded).	1 position paper, not graded
Overall conclusions of recommendations in existing clinical practice guidelines in <u>children</u>	
ACE inhibitors are effective for improving cardiac function in children with asymptomatic LVEF<40% (strong recommendation, moderate level of evidence).	Evidence based guideline
Beta-blockers are effective for improving cardiac function in children with asymptomatic LVEF<40% (moderate recommendation, moderate level of evidence).	Evidence based guideline
Angiotensin II receptor blockers are effective for improving cardiac function in children with asymptomatic LVEF<40% who are intolerant to ACE inhibitors (moderate recommendation, low level of evidence)	Evidence based guideline
Digoxin is not effective in children with asymptomatic LVEF<40% (strong recommendation, low level of evidence).	Evidence based guideline
Overall conclusions of recommendations in existing clinical practice guidelines in <u>adults</u>	
ACE inhibitors are effective for preventing heart failure in individuals with asymptomatic LVEF<40% (range <35% to ≤40%) (strong recommendation, moderate to high level of evidence).	Evidence based guidelines
Beta-blockers are effective for: 1) preventing heart failure in all individuals with asymptomatic LVEF<40% (strong recommendation, low level of evidence). 2) preventing heart failure in all individuals with asymptomatic LVEF<40% (range <35% to ≤40%) and a history of myocardial infarction (strong recommendation, moderate level of evidence).	Evidence based guidelines
Angiotensin II receptor blockers are effective for preventing heart failure in individuals with asymptomatic LVEF<40% (range <35% to ≤40%) and a history of myocardial infarction of vascular disease who are intolerant to ACE inhibitors	Evidence based guidelines

4. Were CAYA cancer survivors included in studies used for the ESC and AHA heart failure guideline recommendations for treatment of asymptomatic LV dysfunction with LVEF<40% and were subgroup analyses performed for CAYA cancer survivors?

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 AND 2021	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA
AHA/ACC/HFSA 2013 AND 2017	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA

Abbreviations: CAYA=childhood and young adult.

LVEF 40-upper limit of normal

5. What is considered an additional abnormality for treatment (and at what threshold) in CAYA cancer survivors with asymptomatic LVEF 40%-upper limit of normal (i.e., myocardial strain, shortening fraction, left ventricular diameter)?

Summary of guidelines including recommendations in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	Currently there is no evidence to guide specific cardioprotection if early signs of subclinical myocardial dysfunction are detected during echocardiography-based GLS surveillance.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	No recommendations on additional echocardiographic abnormalities to consider for treatment	NA	NA

Abbreviations: GLS=global longitudinal strain

Summary of guidelines including recommendations in the **general population** in **children**.
No recommendations

Summary of guidelines including recommendations in the **general population** in **adults**.
No recommendations

Recommendations: What is considered an additional abnormality for treatment in CAYA cancer survivors with asymptomatic LVEF 40% - upper limit of normal?

Overall conclusions of recommendations in existing clinical practice guidelines in cancer survivors (CAYA and adult)	
No evidence to initiate preventive treatments based on abnormalities in global longitudinal strain during echocardiographic surveillance.	1 position paper
Overall conclusions of recommendations in existing clinical practice guidelines in children and adults	
No recommendations	NA

6. What is the efficacy of treatments* <u>in CAYA cancer survivors</u> with asymptomatic LV dysfunction with LVEF 40%-upper limit of normal?

Summary of original studies in CAYA cancer survivors

PICO	Study	No. of participants	Follow up (median/mean, range) yr	Intervention	Outcome definition	Risk estimates (95% confidence interval)	Risk of bias
Efficacy of treatments in CAYA cancer survivors with LVEF<40% (n= 1 study)	Silber 2004	135 CCS with asymptomatic LV dysfunction (FS≤29% or 10% decrease, GNA EF≤55%, ergometry maximal cardiac index ≤7.4 L/min/m2, ECG QTC≥440ms) at >=2 years after anthracycline treatment. Patients on medication or with heart failure were excluded. Enalapril n=69 Placebo n=66	Median 2.8 years, range 2 weeks – 6.1 years	Enalapril uptitrated to max 0.15 mg/kg/day vs placebo	LV dysfunction defined as: -FS<= 29% -10% FS decrease -Gated nuclear angiography LVEF <=55% -10% decrease in LVEF with -Peak exercise maximal cardiac index (MCI) <=7.4 L/min/m2 -ECG QTc >=440 ms Enalapril n=1 Placebo n=6 Mean LVEF at baseline: Enalapril: 59±7% Placebo: 58±7%	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. **Subgroup analyses** in patients with baseline **FS <=28% or EF <=55%** (n = 58) produced similar results (data not shown) **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).	SB: low risk AB: unclear PB: low risk DB: low risk CF: low risk

GRADE assessment:		
<u>Study design:</u>	+4	RCT
<u>Study limitations:</u>	0	Limitations: Selection bias low risk; Attrition bias unclear; Performance bias low risk; Detection bias low risk; Confounding low risk.
<u>Consistency:</u>	0	NA
<u>Directness:</u>	0	Results are direct, population and outcomes broadly generalizable

Precision:	-2	Only 1 study with a limited samples size, underpowered for clinical heart failure due to a very limited number of events (n=7).
Publication bias:	0	Unlikely
Effect size:	0	No large effect size
Dose-response:	0	No dose response
Plausible confounding:	0	No plausible confounding
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Enalapril was not significantly associated with overall survival, mortality due to heart failure, development of clinical heart failure and quality of life in childhood cancer survivors with asymptomatic LV dysfunction more than 2 years after treatment with anthracyclines, as compared to placebo. In a post-hoc analysis, enalapril improved LV afterload determined with LVESWS in the first year of treatment but not afterwards in childhood cancer survivors more than 2 years after treatment with anthracyclines, as compared to placebo. No significant improvements in other echocardiographic parameters including FS was found. Enalapril increased the risk of dizziness or hypotension and fatigue in childhood cancer survivors more than 2 years after treatment with anthracyclines, as compared to placebo. (1 study; 7 events; 135 participants)

Summary of guidelines including recommendations in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	If LVEF decreases >10% to a value below the lower limit of normal (considered as an LVEF <50%), **ACE inhibitors (or ARBs) in combination with beta-blockers** are recommended to prevent further LV dysfunction or the development of symptomatic HF, unless contraindicated, as these patients are at high risk of developing HF.	Not graded	Not graded
	ACE inhibitors (or ARBs) and beta-blockers are recommended in patients with symptomatic HF or asymptomatic cardiac dysfunction unless contraindicated.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	**Angiotensin-converting enzyme inhibitors and β-blockers** can improve ejection fraction and decrease ventricular dilation in adults with LV dysfunction. These agents have been recommended for treatment of survivors at risk for ventricular dysfunction. However, a single 2004 multicenter, randomized, placebo-controlled trial of asymptomatic children with LV dysfunction after anthracycline therapy (Silber et al. 2004) found that enalapril did not affect the clinical status of survivors and had no long- lasting effect on ventricular remodeling. Thus, no data support the use of enalapril to prevent progression of LV dysfunction in asymptomatic patients. β-Blockade has not been studied in asymptomatic survivors with ventricular dysfunction.	Not graded	Not graded

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, HF=heart failure, LVEF=left ventricular ejection fraction.

Summary of guidelines including recommendations in the **general population** in **children**.

No recommendations

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 AND 2021	No recommendations (preventive interventions in patients without LV dysfunction are discussed below, question 10)	NA	NA
AHA/ACC/HFSA 2013 AND 2017	Stage B: Blood pressure should be controlled to prevent symptomatic HF.	Class I: strong	A: high
MALAYSIAN HF GUIDELINE 2019	Individuals with myocardial dysfunction but who do not as yet have signs and symptoms of HF: Treat the underlying cause wherever possible and prevent progression to symptomatic HF by guideline directed therapy.	Class I: strong	C: low
CANADIAN HF GUIDELINE 2017 AND 2020	No recommendations	NA	NA
JAPANESE HF GUIDELINE 2017	No recommendations		
SIGN 2016	No recommendations	NA	NA

Abbreviations: ACE=angiotensin converting enzyme, HF=heart failure, LVEF=left ventricular ejection fraction.

Recommendations: What is the efficacy of treatments in CAYA cancer survivors with asymptomatic LVEF 40-49%?

Overall conclusions of recommendations in existing clinical practice guidelines in cancer survivors (CAYA and adult)	
ACE-inhibitors and beta-blockers are effective in pediatric and adult cancer survivors with an asymptomatic decrease in LVEF of >10% to a value below 50% (not graded).	1 position paper, not graded
Overall conclusions of recommendations in existing clinical practice guidelines in children	
No recommendations	NA
Overall conclusions of recommendations in existing clinical practice guidelines in adults	
Treating hypertension is effective for preventing heart failure in individuals with hypertension and asymptomatic LV dysfunction (strong recommendation, high level of evidence)	Evidence based guidelines

7. Were CAYA cancer survivors included in studies used for the ESC and AHA heart failure recommendations for pharmacological treatment, ICD/ CRTD and rehabilitation programs for asymptomatic LV dysfunction LVEF 40%-the upper limit of normal.

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 AND 2021	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA
AHA/ACC/HFSA 2013 AND 2017	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA

Abbreviations: CAYA=childhood and young adult.

Normal LV systolic function (LVEF≥52% for males and LVEF≥54% for females)

8. What is considered an abnormality (and at what threshold) for preventive treatments (i.e., myocardial strain, shortening fraction, left ventricular diameter) in CAYA cancer survivors with normal LV systolic function?

Summary of guidelines including recommendation in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	Currently there is no evidence to guide specific cardioprotection if early signs of subclinical myocardial dysfunction are detected during echocardiography-based GLS surveillance.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	No recommendations on additional echocardiographic abnormalities to consider for treatment	NA	NA

Abbreviations: GLS=global longitudinal strain.

Summary of guidelines including recommendations in the **general population** in **children**.
No recommendations

Summary of guidelines including recommendations in the **general population** in **adults**.
No recommendations

9. Can risk stratifying methods (and at what threshold) be applied for decision to use preventive treatments (risk groups as defined by working group 1)?

Summary of guidelines including recommendation in **CAYA and adult cancer survivors.**
No recommendations

Summary of guidelines including recommendations in the **general population** in **children**.

No recommendations

Summary of guidelines including recommendations in the **general population** in **adults**.
No recommendations

10. What is the efficacy of physical activity and preventive lifestyle interventions in CAYA cancer survivors with normal LV systolic function who received potentially cardiotoxic therapies for prevention of LV dysfunction or heart failure?**

Summary of guidelines including recommendation in **CAYA and adult cancer survivors.**

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 POSITION PAPER	Positive health-promoting behavior, including lifestyle factors (healthy diet, smoking cessation, regular exercise, weight control) should be strongly advised. In particular, aerobic exercise is considered a promising non-pharmacological strategy to prevent and/or treat chemotherapy-induced cardiotoxicity.	Not graded	Not graded
AHA 2013 SCIENTIFIC STATEMENT	The same behavior changes for adults at risk for heart failure are recommended for children: smoking cessation, limiting or stopping alcohol or illicit drug use, treating hypertension, and controlling metabolic syndrome. No studies have tested medical therapies to prevent heart failure in survivors of childhood cancer.	Not graded	Not graded

Abbreviations:

Summary of guidelines including recommendations in the **general population** in **children**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ISHLT 2014 (PATIENTS WITHOUT HF)	The presence of obesity in pediatric patients with heart disease should prompt specific evaluation for metabolic syndrome and all other cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and liver disease.	Class I: strong	A: high
	An intensive, multidisciplinary weight-reduction program and management of other identifiable risk factors should be initiated in pediatric patients with metabolic syndrome.	Class I: strong	B: moderate
	No recommendations on exercise training in children with asymptomatic LV dysfunction.	NA	NA

Abbreviations: HF=heart failure

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 AND 2021	Treatment of **hypertension** is recommended to prevent or delay the onset of HF, and to prevent HF hospitalizations.	Class I: strong	A: high
	Counselling against **sedentary habit, obesity, cigarette smoking, and alcohol abuse** is recommended to prevent or delay the onset of HF.	Class I: strong	C: low

	Treatment with statins is recommended in patients at high risk of CV disease or with CV disease in order to prevent or delay the onset of HF, and to prevent HF hospitalizations.	Class I: strong	A: high
	Treating other risk factors of HF (e.g., **obesity, dysglycaemia**) should be considered in order to prevent or delay the onset of HF	Class IIa: moderate	C: low
	ACE-I should be considered in patients with stable coronary artery disease even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.	Class IIa: moderate	A: high
ESC 2021	SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, sotagliflozin) are recommended in patients with diabetes at high risk of CV disease or with CV disease in order to prevent HF hospitalizations.	Class I: strong	A: high
AHA/ACC/HFSA 2013 AND 2017	Stage A: **Hypertension and lipid disorders** should be controlled in accordance with contemporary guidelines to lower the risk of HF	Class I: strong	A: high
	Stage A: Other conditions that may lead to or contribute to HF, such as **obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents**, should be controlled or avoided.	Class I: strong	C: low
	In all patients with a recent or remote history of MI, **statins** should be used to prevent symptomatic HF and cardiovascular events.	Class I: strong	A: high
MALAYSIAN HF GUIDELINE 2019	Individuals who are at high risk of developing HF/coronary artery disease but who do not as yet have structural heart disease: Treating **hypertension** to target levels.	I: strong	A: high
	Diabetes - Optimize glycemic control. Poor glycemic control has been shown to increase the risk of HF.	IIa: moderate	B: moderate
	Healthy lifestyle - A normal body weight, absence of smoking, regular exercise, and consumption of fruits and vegetables were individually and jointly associated with a lower lifetime risk of HF.	I: strong	B: moderate
	Smoking cessation	I: strong	B: moderate
	Regular **exercise**	I: strong	B: moderate
	Maintain ideal body weight	I: strong	B: moderate
	Curbing **alcohol** consumption	I: strong	C: low
	Treating **lipids** to goal in all individuals with established cardiovascular disease to reduce mortality	I: strong	A: high
	SGLT2 in patients with diabetes	IIa: moderate	A: high
CANADIAN HF GUIDELINE 2017 AND 2020	We recommend that an **ACE inhibitor** should be prescribed in established effective doses to reduce the risk of developing HF in patients with evidence of vascular disease or diabetes with end organ damage.	Strong	High
	We recommend that in ACE-intolerant patients, an **ARB** should be considered for reduction of the risk of developing HF in patients with evidence of vascular disease or diabetes with end organ damage.	Strong	High
	We recommend that health professionals caring for **overweight or obese** individuals should educate them about the increased risk of HF.	Strong	Moderate
	We recommend **physical activity** to reduce the risk of developing HF in all individuals.	Strong	Moderate

	We recommend that most patients should have their **blood pressure** (BP) controlled to < 140/90 mm Hg; those with diabetes or at high risk for cardiovascular events should be treated to a systolic BP of < 130 mm Hg to reduce the risk of developing HF.	Strong	Moderate
	We recommend that **diabetes** should be treated according to the Canadian Diabetes Association's national guidelines to achieve optimal control of blood glucose levels.	Strong	Moderate
	We recommend **SGLT2 inhibitors**, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce the risk of HF hospitalization and death.	Strong	High
	We recommend **SGLT2 inhibitors**, such as dapagliflozin be used in patients with type 2 diabetes aged > 50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of HF.	Strong	High
	We recommend **SGLT2 inhibitors,** such as canagliflozin, be used in patients aged > 30 years with type 2 diabetes, and macroalbumineric renal disease, to reduce the risk of HF hospitalization and progression of renal disease.	Strong	High
JAPANESE HF GUIDELINE 2017	Treatment of **hypertension** including low-salt diet and weight reduction.	Class I: strong	A: high
	General lifestyle modifications through **weight reduction** and increased **physical activity**	Class I: strong	A: high
	Smoking cessation	Class I: strong	C: low
	Alcoholic control	Class IIa: moderate	C: low
	Physical activity and exercise habits	Class I: strong	B: moderate
	Thiazide diuretics in patients with hypertension to prevent heart failure.	Class I: strong	A: high
	Treatment with **SGLT2 inhibitors** in patients with type 2 diabetes mellitus and a history of cardiovascular disease	Class I: strong	A: high
	ACE inhibitors in patients with coronary artery disease	Class I: strong	A: high
SIGN 2016	No recommendations	NA	NA

Abbreviations: ACE=angiotensin converting enzyme, ARB=angiotensin receptor blockers, HF=heart failure, LVEF=left ventricular ejection fraction, SGLT2=sodium-glucose cotransporter-2 inhibitors.

Recommendations: What is the efficacy of physical activity and preventive lifestyle interventions in CAYA cancer survivors with normal LV systolic function?

Overall conclusions of recommendations in existing clinical practice guidelines in <u>cancer survivors</u> (CAYA and adult)	
Positive health-promoting behavior, including lifestyle factors (healthy diet, smoking cessation, regular exercise, weight control), treating hypertension and controlling metabolic syndrome is effective for preventing heart failure in pediatric and adult cancer survivors with normal left ventricular systolic function (not graded)	2 position papers (not graded)
Overall conclusions of recommendations in existing clinical practice guidelines in <u>children</u>	
In children with obesity, specific evaluation for metabolic syndrome and all other cardiovascular risk factors, including hypertension, dyslipidemia, insulin resistance, and liver disease is recommended (strong recommendation, high level of evidence).	Evidence based guideline
In children with metabolic syndrome, an intensive, multidisciplinary weight-reduction program and management of other identifiable risk factors is recommended (strong recommendation, moderate level of evidence).	Evidence based guideline
Overall conclusions of recommendations in existing clinical practice guidelines in <u>adults</u>	
Physical activity is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
Treating hypertension is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
Treating lipid disorders is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
Treating diabetes type II is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
SGLT2 inhibitors are effective for preventing heart failure in individuals with normal left ventricular function and with diabetes at high risk of cardiovascular disease or with cardiovascular disease	Evidence based guidelines
Treating obesity is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
Smoking cessation is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
Reducing excessive alcohol intake is effective for preventing heart failure in individuals with normal left ventricular function	Evidence based guidelines
ACE inhibitors or angiotensin II receptor blockers are effective for preventing heart failure in individuals with coronary artery disease, atherosclerotic vascular disease, diabetes and/or hypertension and normal left ventricular function	Evidence based guidelines

11. Were CAYA cancer survivors included in studies used for the ESC and AHA heart failure guideline recommendations for preventive therapies?

Summary of guidelines including recommendations in the **general population** in **adults**.

GUIDELINE	RECOMMENDATION	STRENGTH	LEVEL OF EVIDENCE
ESC 2016 AND 2021	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA
AHA/ACC/HFSA 2013 AND 2017	No asymptomatic CAYA cancer survivors were reported to be included (Supplementary Table 1)	NA	NA

Abbreviations: CAYA=childhood and young adult.

*Treatments include ACE-inhibitors, ARBs, ARNI, beta-blockers, MRA, ivabradine, hydralazine/nitrate, digoxin, diuretics, ICD/CRTD, rehabilitation programs.
**e.g., interventions for hypertension, dyslipidemia, obesity and diabetes mellitus, smoking advice, salt restriction

Working group 4 summary of findings supplementary table 1. List of studies used to formulate recommendations in the ESC and AHA heart failure guidelines and whether CAYA cancer survivors were included.

Trial	Patients	Intervention(s)	Control	Main results	CAYA cancer survivors included?
HFrEF					
CONSENSUS 1987	NYHA IV HFrEF, mainly ischemic	Enalapril	Placebo	Reduction in mortality	Not reported, no exclusion criterium
SOLVD-treatment 1991	HFrEF patients with LVEF<35%, mainly ischemic, hypertensive	Enalapril	Placebo	Reduction in mortality, HF incidence and HF hospitalizations	Not reported, no exclusion criterium
MERIT-HF 1999, 2000	HFrEF, NYHA II-IV, LVEF<40%, age 40-80	Metoprolol CR	Placebo	Reduction in mortality, HF hospitalizations	Not reported, no exclusion criterium
Packer 1996	HFrEF with LVEF <35%	Carvedilol	Placebo	Reduction in mortality and CV hospitalizations	Not reported, no exclusion criterium
COPERNICUS 2001, 2002	Severe HFrEF with symptoms at rest or minimal exertion, LVEF <25%	Carvedilol	Placebo	Reduction in mortalitity and HF hospitalizations and duration	Not reported, no exclusion criterium

CIBIS-II 1999	Stable HFrEF, aged 18-80, LVEF <35%, NYHA III/IV	Bisoprolol	Placebo	Reduction in mortality	Not reported, no exclusion criterium
CIBIS-III 2005	HFrEF with LVEF <35%, NYHA II/III, age >=65	Bisoprolol as first medication for 6 months followerd by combination	Enalapril as first medication for 6 months followerd by combination	Initiation with bisoprolol was as efficacious and safe as initiation with enalapril	Not reported, no exclusion criterium
RALES 1999	severe HFrEF, NYHA IV, LVEF < 35%, ischemic and non-ischemic	Spironolactone	Placebo	Reduction in mortality and CV hospitalizations	Not reported, no exclusion criterium
COMET 2003	HFrEF, NYHA II-IV, LVEF<35%	Carvedilol	Metoprolol	Carvedilol superior to metoprolol in reducing mortality	Not reported, no exclusion criterium
EMPHASIS-HF 2011	HFrEF, NYHA II, LVEF <35%, age >=55	Eplerenon	Placebo	Reduction in CV mortality and HF hospitalizations	Not reported, no exclusion criterium
CHARM-Alternative 2003	HFrEF, LVEF <40%, intolerance for ACEi, age >=18	Candesartan	Placebo	Reduction in CV death or hospitalization	Yes, 6 pts (1%) with cancer history, unknown whether adult or CAYA, unknown chemotherapy-induced
CHARM-Added 2003	HFrEF, LVEF <40%, taking ACEi, age >=18	Candesartan	Placebo	Reduction in CV death or hospitalization	Yes, 6 pts (1%) with cancer history, unknown whether adult or CAYA, unknown chemotherapy-induced
ValHeFT	HFrEF, age >18, NYHA II-IV, LVEF <40% and dilatation	Valsartan	Placebo	Reduction in mortality and symptoms	Not reported, no exclusion criterium
PARADIGM-HF	HFrEF, NYHA II-IV, LVEF<40%, age >=18	ARNI	Enalapril	reduction in mortality and HF hospitalizations	Not reported, exclusion criterium when diagnosed with cancer within 1 year prior to visit 1

ERMPEROR-reduced	HFrEF, LVEF<40% and elevated NT-proBNP, age >=18, NYHA II-IV	Empaglifozin	Placebo	Reduction in CV mortality and HF hospitalizations regardless of diabetes	Not reported, exclusion criterium when diagnosed with cancer within 1 year prior to visit 1
ALVD					
SOLVD prevention 1992 and extended follow-up in 2003	ALVD with LVEF<35%, mainly ischemic, hypertensive	Enalapril	Placebo	HF incidence, HF hospitalizations	Not reported, no exclusion criterium
CAPRICORN 2001	MI patients with LVEF<=40%. Also, symptomatic patients included.	Carvedilol	Placebo	No difference in primary endpoint all-cause mortality or hospitalizations. Reduction in all-cause mortality.	Not reported, no exclusion criterium
Modifiable CV risk factors					
SPRINT 2015	Hypertension (systolic BP >130 mmHg), age >50	Target systolic BP <120 mmHg	Target systolic BP <140 mmHg	Target systolic BP <120 resulted in lower fatal and non-fatal CV events	Not reported, no exclusion criterium
HOPE (Heart Outcomes Prevention Evaluation) study 2000	9297 high-risk patients (55 years of age or older) who had evidence of vascular disease (CAD, PAD, stroke) or diabetes plus one other cardiovascular risk factor (hypertension, dyslipidemia, smoking, microalbuminuria)	Ramipril	Placebo	Reduction in death, myocardial infarction, and stroke	Not reported, no exclusion criterium

Systolic Hypertension in the Elderly Program (SHEP) 1997	4736 persons aged 60 years and older with systolic blood pressure between 160- and 219-mm Hg and diastolic blood pressure below 90 mm Hg	step 1: chlorthalidone (12.5-25 mg), step 2: atenolol (25-50 mg)	Placebo	Reduction in HF	Not reported, no exclusion criterium, but patients were >60, unlikely that CAYA cancer survivors were included
Hypertension in the Very Elderly Trial (HYVET) 2008	3845 patients from Europe, China, Australasia, and Tunisia who were 80 years of age or older and had a sustained systolic blood pressure of 160 mm Hg or more	diuretic indapamide (sustained release, 1.5 mg) and if neccesary perindopril (2 or 4 mg) to reach target blood pressure of 150/80 mm Hg	Placebo	Reduction in CV events and HF	Not reported, no exclusion criterium, but patients were >80, unlikely that CAYA cancer survivors were included
Sciaretta et al. Meta-analysis. Antihypertensive Treatment and Development of Heart Failure in Hypertension 2011	RCTs including 223,313 patients with hypertension	All medications to treat hypertension: diuretics, ACE-I etc.	Placebo	Diuretics and ACE-I were most effective in prevention of HF in hypertensive patients. BB and Ca antagonists were less effective	Not reported, no exclusion criterium
Pandey et al. Dose-Response Relationship Between Physical Activity and Risk of Heart Failure: A Meta-Analysis 2015	meta-analysis of trials including patient > age 18 that reported association of baseline physical activity and incident HF	Risk factor: baseline physical activity (metabolic equivalent [MET]-min/wk)	None	Inverse dose-response relationship between PA and HF risk	Not reported, no exclusion criterium

STOP-HF randomized trial	RCT in 1374 participants with cardiovascular risk factors (mean age, 64.8 [SD, 10.2] years) recruited from 39 primary care practices	Screening with BNP testing (50 pg/mL or higher underwent echocardiography and collaborative care between their primary care physician and specialist cardiovascular service)	Usual care	BNP-based screening and collaborative care reduced the combined rates of LV systolic dysfunction, diastolic dysfunction, and heart failure.	Not reported, no exclusion criterium (only those with life expectancy <1 year)
Dagenais et al. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. 2006	29,805 patients in HOPE, EUROPE and PEACE RCTs that studied the effect of ACE inhibitors in stable vascular disease patients without LV dysfunction or heart failure	ACE-I	Placebo	ACE inhibitors reduce serious vascular events in patients with atherosclerosis without known evidence of LVSD or heart failure	Not reported, no exclusion criterium
PEACE Trial	8290 stable CAD pts with normal or slightly reduced left ventricular function (mean LVEF 58% ±9, mean age 64 years ±8).	ACE-I	Placebo	No reduction in primary endpoint. Reduction in HF hospitalizations or death	Not reported, no exclusion criterium

EUROPA study 2003	12218 low risk patients with stable coronary heart disease and no apparent heart failure. Mean age 60 years ±9	Perindopril	Placebo	Reduction in cardiovascular death, myocardial infarction, or cardiac arrest and secondary endpoint: HF	Not reported, no exclusion criterium
PONTIAC (NT-proBNP selected prevention of cardiac events in a population of diabetic patients without a history of cardiac disease)	300 patients with type 2 diabetes, elevated NT-proBNP (>125 pg/ml) but free of cardiac disease, mean age 67 years ± 9	The "intensified" group was additionally treated at a cardiac outpatient clinic for the up-titration of renin-angiotensin system (RAS) antagonists and beta-blockers	The "control" group was cared for at 4 diabetes care units	Reduction CV hospitalizations or death	Not reported, no exclusion criterium, active malignancies were excluded