Conclusions of evidence for cardiomyopathy surveillance for CAYA cancer survivors

Who needs cardiomyopathy surveillance?		
Risk factors for symptomatic heart failure (HF) and asymptomatic left ventricular dysfunction (ALVD) in CAYA cancer survivors		
	Symptomatic HF (range of RR/HR/OR)	**ALVD (range of RR/HR/OR)**
Treatment factors		
Higher anthracycline dose	↑ ⊕⊕⊕⊕ HIGH[1-3,5,13-21,23,24,51,58,73,74]	↑ ⊕⊕⊕⊕ HIGH[25-27,37,53-56,75-85]
1-99 mg/m² vs. none	=[14,16,17]	LVEF =[27,85]; GLS ↑ 1·4-fold[27]
100-249 mg/m² vs. none	↑ 3·7 to 3·9-fold[14,17]	-
100-299 mg/m² vs. none	-	LVEF ↑ 2·7 to 3·8-fold[14,85]; GLS =[27]
≥250 mg/m² vs. none	↑ 5·2 to 94·0-fold[1,3,13-20]	-
≥300 mg/m² vs. none	-	LVEF ↑ 4·1 to 12·8-fold[14,85]; GLS ↑ 1·7-fold[27]
Higher chest RT dose	↑ ⊕⊕⊕⊕ HIGH[1-3,5,14-16,18-21,73,86-88]	↑ ⊕⊕⊕⊕ HIGH[26,27,53,54,82,84]
1-14 Gy vs. none	=[1,3,14-16,18,20,21,88]	No thresholds can be defined
15-30/34 Gy vs. none	↑ 1·6 to 6·1-fold[1,3,14-16,18-20]	No thresholds can be defined
≥30/35 Gy vs. none	↑ 3·5 to 19·7-fold[1,3,14-16,18-20]	No thresholds can be defined
Larger volume of the heart exposed to RT	↑ ⊕⊕⊕⊕ HIGH[15,18]	No studies
Anthracyclines + chest RT vs. treatment with either alone	↑ ⊕⊕⊕⊕ HIGH[2,5,15,18,19,21,22]	No studies
Interaction of female sex with anthracycline dose	= ⊕⊖⊖⊖ VERY LOW[16]	No studies
Interaction of younger age at diagnosis with anthracycline dose	↑ ⊕⊕⊖⊖ LOW[15,16]	No studies
Interaction of sex and age at diagnosis with chest RT dose	No studies	No studies
Relative potency of anthracycline analogues	⊕⊕⊕⊖ MODERATE[13,19]	No studies
Daunorubicin vs. doxorubicin	↓ 0·5 to 0·6-fold	No studies
Epirubicin vs. doxorubicin	↓ 0·8-fold	No studies
Mitoxantrone vs. doxorubicin	↑ 10·5 to 13·8-fold	No studies
Idarubicin vs. doxorubicin	Unclear	No studies
Dexrazoxane (from IGHG dexrazoxane guideline)	Children RCTs: ↓ pooled RR 0·20 (95% CI 0·01-4·19), not significant ⊕⊕⊖⊖ LOW (3 pediatric RCTs) Adult RCTs: ↓ pooled RR 0·22 (95% CI 0·11-0·43), ⊕⊕⊖⊖ LOW (7 adult RCTs)	Children RCT: ↓ for HF and ALVD combined: RR 0·33 (95% CI 0·13-0·85) ⊕⊕⊖⊖ LOW (1 pediatric RCT) Adult RCTs: ↓ for HF and ALVD combined: RR 0·37 (95% CI 0·24-0·56) ⊕⊕⊕⊖ MODERATE (3 adult RCTs)

New childhood cancer treatments	No studies	No studies	
Host factors			
Female sex	↑ ⊕⊕⊕⊖ MODERATE[1-3,5,14-17,20,21,23,51,58,73]	= ⊕⊕⊕⊖ MODERATE[25-27,37,53,54,56,75-84]	
Younger age at diagnosis	↑ ⊕⊕⊖⊖ LOW[2,3,5,14,16,17,20,21,51,58,74]	= ⊕⊕⊖⊖ LOW[25-27,37,54-56,75-80,82-84]	
Pregnancy, no previous cardiomyopathy	= Incidence 0·24% (95% CI 0-0·81%) ⊕⊕⊖⊖ LOW[28]		
Pregnancy, previous cardiomyopathy	↑ Incidence 28% 95% (CI 15-44%) ⊕⊕⊖⊖ LOW[28]		
Traditional CVRF			
Diabetes	↑ ⊕⊕⊕⊖ MODERATE[1,14,16,18,22-24]	↑ ⊕⊕⊕⊖ MODERATE[25-27]	
Dyslipidemia	↑ ⊕⊕⊕⊖ MODERATE[1,14,16,22,23]	↑ ⊕⊕⊖⊖ LOW[26,27]	
Obesity	↑ ⊕⊕⊖⊖ LOW[16,18]	↑ ⊕⊕⊕⊖ MODERATE[25-27]	
Hypertension	↑ ⊕⊕⊕⊕ HIGH[1,14,16,22-24]	↑ ⊕⊕⊕⊖ MODERATE[25-27]	
Smoking	↑ ⊕⊕⊕⊖ MODERATE[15,18,22]	= ⊕⊕⊕⊖ MODERATE[25,26,75]	
Genetic variants with moderate level of evidence	**Effect size**	**CPNDS level of evidence**	**PharmGKB level of evidence**
RARG (retinoic acid receptor gamma) rs2229774	↑ OR 4·1-7·0[29,89]	Moderate (+++)	Low (level 3)
UGT1A6 (UDP-glucosyltransferase A1) rs17863783	↑ OR 4·0-8·0[30,31,89]	Moderate (+++)	Unsupported (level 4)
What surveillance modality should be used?			
Agreement between modalities and diagnostic values			
	Outcome	**Quality of evidence**	
Agreement M-mode echocardiography and cardiac magnetic resonance imaging (CMR) LVEF	Mean difference 3·1% to 5·5% lower for CMR (1·96SD range: 12·3-25·2%)	⊕⊕⊕⊖ MODERATE[32-34]	
Agreement 2D echocardiography and CMR LVEF	Mean difference 1·8% to 5·4% lower for CMR (1·96SD range: 10·8-13·8%)	⊕⊕⊕⊖ MODERATE[32-34]	
Agreement 3D echocardiography and CMR LVEF	Mean difference 1·1% higher for CMR to 7% lower for CMR (1·96SD range: 10·4-12·9%)	⊕⊕⊕⊖ MODERATE[32-34]	
Agreement 2D and 3D echocardiography LVEF	No studies in CAYA cancer survivors. <u>Evidence in the general population</u>[35,93] Bland Altman analysis: -2D echocardiography - CMR LVEF: mean pooled difference/bias 0·1%, 2 standard deviations 13·9% -3D echocardiography - CMR LVEF: mean pooled difference/bias 0·0%, 2 standard deviations 9·2%	Not graded	

	-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)	
What is the recommended modality to measure LV systolic function and what are the thresholds for abnormal?	No studies in CAYA cancer survivors. <u>Evidence in the general population</u>[93] -LV systolic function should be assessed with 2D or 3D echocardiography by calculating LVEF from EDV and ESV. -EDV and ESV should be assessed on 2D echocardiography using the biplane method. In laboratories with 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.	Not graded
N-terminal pro B-type natriuretic peptide (NT-proBNP) as compared to echocardiography or CMR	-Low sensitivity (8%-100%). 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%). -High specificity (81%-100%)	⊕⊕⊕⊖ MODERATE[33,36,38-45,83]
Atrial natriuretic peptide or brain natriuretic peptide as compared to echocardiography	Moderate sensitivity (63%), high specificity (96%)	⊕⊕⊖⊖ LOW[47]
Troponin T and I as compared to echocardiography or CMR	Low sensitivity (0-50%), high specificity (91-100%)	⊕⊕⊕⊖ MODERATE[33,36,38-41,44-46,90]
Exercise stress echocardiography compared to diastolic function assessment by echocardiography for detecting asymptomatic restrictive cardiomyopathy in CAYA cancer survivors treated with cardiac RT	Unknown	No studies
At what frequency should cardiomyopathy surveillance be performed?		
Latency to onset of and risk over time for asymptomatic/symptomatic cardiomyopathy in CAYA cancer survivors		
	Symptomatic HF	**Asymptomatic LV dysfunction**
Anthracyclines	No studies	Median 4·3 months ⊕⊕⊖⊖ LOW[59]

Chest RT	No studies	No studies
Anthracyclines and chest RT	Range 0·1-35·7 years ⊕⊕⊕⊖ MODERATE[5,51]	Range 1-42 years ⊕⊕⊕⊖ MODERATE[52-57]
Anthracyclines and dexrazoxane	No studies	No studies
Impact of early changes on latency	No studies	= ⊕⊖⊖⊖ VERY LOW[71]
Do early changes predict late changes	No studies	↑ ⊕⊕⊖⊖ LOW[56,57,71,72,91]
Difference in latency in low-, moderate-, and high-risk survivors	Decrease in age at onset of HF with higher anthracycline and/or chest-directed RT dose ⊕⊕⊕⊖ MODERATE[48,50]	
Different anthracycline derivatives	No studies	No studies
Does risk change over time	Cumulative incidences: ↑ at higher anthracycline doses ⊕⊕⊕⊖ MODERATE[1,3,14-16,18,20,24,30,48-51,58,59]	↑ at higher anthracycline doses Plateaus at doses <250 mg/m^2 ⊕⊖⊖⊖ VERY LOW[49,52,55,60]
Genetic variants	No studies	No studies
Cost-benefit ratio of surveillance strategies (including frequencies) in CAYA cancer survivors in different risk groups for cardiomyopathy		
		Quality of evidence
Echo surveillance is not cost-effective in low-risk CAYA cancer survivors treated with anthracyclines <100 mg/m^2 and/or chest-RT <15 Gy		⊕⊕⊕⊖ MODERATE[48-50]
Echo surveillance may be cost-effective at 5-year intervals in moderate-risk CAYA cancer survivors treated with anthracyclines 100-249 mg/m^2 or chest-RT 15-34 Gy		⊕⊕⊖⊖ LOW[48-50]
Echo surveillance is cost-effective at 2-year intervals in high-risk CAYA cancer survivors treated with anthracyclines ≥250 mg/m^2, chest RT ≥35 Gy, or a combination		⊕⊕⊕⊖ MODERATE[48-50]
CMR surveillance may be cost-effective at 10-year intervals in low- to moderate-risk CAYA cancer survivors treated with anthracyclines <250 mg/m^2		⊕⊕⊖⊖ LOW[48]
CMR surveillance is cost-effective at 5-year intervals in high-risk CAYA cancer survivors treated with anthracyclines ≥250mg/m^2		⊕⊕⊖⊖ LOW[48]
What should be done when abnormalities are identified?		
Effectiveness of medical interventions *in CAYA cancer survivors* with ALVD to prevent HF		
		Quality of evidence
Unclear if ACE inhibitors are effective for improving cardiac function or preventing HF in CAYA cancer survivors with ALVD*		⊕⊕⊖⊖ LOW[61,96]
Unknown if beta-blockers are effective for improving cardiac function or preventing HF in CAYA cancer survivors with ALVD		No evidence from RCTs
Unknown if angiotensin II receptor blocker are effective for improving cardiac function or preventing HF in CAYA cancer survivors with ALVD who are intolerant to ACE inhibitors		No evidence from RCTs
Effectiveness of medical interventions *in the general population* with ALVD to prevent HF		
		Quality of evidence from evidence-based guidelines**

ACE inhibitors are effective for preventing HF in individuals with asymptomatic LVEF<40% (range <35% to ≤40%)	MODERATE[62-64] to HIGH[65-67]
Beta-blockers are effective for preventing HF in individuals with asymptomatic LVEF<40% (range <35% to ≤40%)	LOW in all patients[65]; MODERATE in patients with a previous myocardial infarction[62-66]
Angiotensin II receptor blockers are effective for preventing HF 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	LOW in all patients[64]; HIGH in patients with myocardial infarction or vascular disease[62,65,66]
Treating hypertension is effective for preventing HF in individuals with hypertension and asymptomatic LV dysfunction	HIGH[65]
Use of risk stratifying methods for the decision to use preventive treatments *in CAYA cancer survivors*	
	Quality of evidence
Unknown if risk stratification methods, such as risk groups defined by the IGHG, can be used to guide preventive treatments	No studies
Effectiveness of physical activity and (lifestyle) interventions to prevent HF *in CAYA cancer survivors* who received cardiotoxic cancer treatments and have normal left ventricular (LV) function	
	Quality of evidence
Unknown if physical activity and lifestyle interventions are effective for preventing HF in CAYA cancer survivors with normal LV function	No studies
Effectiveness of physical activity and lifestyle interventions to prevent HF *in other populations* with normal LV function	
	Quality of evidence from evidence-based guidelines**
Physical activity is effective for preventing HF in individuals with normal LV function	LOW[63] to MODERATE[62,66,68]
Treating hypertension is effective for preventing HF in individuals with normal LV function	MODERATE[62] to HIGH[63,65,66,68]
Treating lipid disorders is effective for preventing HF in individuals with normal LV function	LOW in all patients[65]; HIGH in patients with or at high-risk of cardiovascular disease[63,65,68]
Treating diabetes type II is effective for preventing HF in individuals with normal LV function	LOW[63,65] to MODERATE[62,64,68]
SGLT2 inhibitors are effective for preventing HF in individuals with normal LV function and with diabetes at high-risk of cardiovascular disease or with cardiovascular disease	HIGH[62,63,66,68-70,92]
Treating obesity is effective for preventing HF in individuals with normal LV function	LOW[63,65] to MODERATE[64,68]
Smoking cessation is effective for preventing HF in individuals with normal LV function	LOW[63,65,66] to MODERATE[68]
Reducing excessive alcohol intake is effective for preventing HF in individuals with normal LV function	LOW[63,65,67,68]
ACE inhibitors or angiotensin II receptor blockers are effective for preventing HF in individuals with coronary artery disease, atherosclerotic vascular disease, diabetes and/or hypertension, and normal LV function	HIGH[62,63,65,66]
*Silber et al. 2004.[61] In this trial, ALVD was defined as FS ≤29%, ≥10% decrease in FS, gated nuclear angiography EF≤55%, maximal cardiac index ≤7·4 mL/min/m^2 at peak exercise or ECG QTC ≥440ms at some time after anthracycline treatment. **Level of evidence adopted from evidence-based guidelines in the general population.	

Abbreviations: 2D=two-dimensional; 3D=three-dimensional; ACE=angiotensin converting enzyme; ALVD=asymptomatic left ventricular dysfunction; CAYA=childhood, adolescent, and young adult; CI=confidence interval; CMR= cardiac magnetic resonance imaging; CPNDS= Canadian Pharmacogenomics Network for Drug Safety; CVRF=cardiovascular risk factors; ECG=electrocardiogram; EDV= end-diastolic volume; EF=ejection fracture; ESV= end-systolic volume; FS=fractional shortening; GLS= global longitudinal strain; Gy=Gray; HF=heart failure; HR=hazard ratio; IGHG= International Late Effects of Childhood Cancer Guideline Harmonization Group; <=less than; ≤=less than or equal to; LV= left ventricular; LVEF=left ventricular ejection fraction; mL/min/m^2=milliliters per minute per body square meter; mg/m^2=milligrams per square meter; ≥=greater than or equal to; NT-proBNP; OR=odds ratio; %=percent; P=probability; QTC=corrected QT interval; RARG= retinoic acid receptor-γ; RCT= randomized controlled trial; RR=risk ratio; RT= chest-directed radiotherapy; SGLT2= sodium-glucose co-transporter 2; SNP=single nucleotide polymorphism; vs=versus.
Legend: =, no effect; ⬆, higher risk; ⬇, lower risk