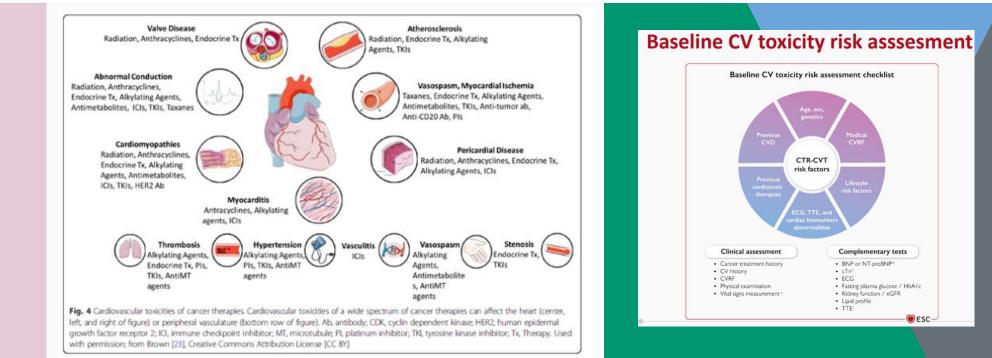


Kardiovaskuläre Spätfolgen der Onkologischen Therapie

Prof. Dr. med. Thomas Suter

Dr. med. Eva Strickler



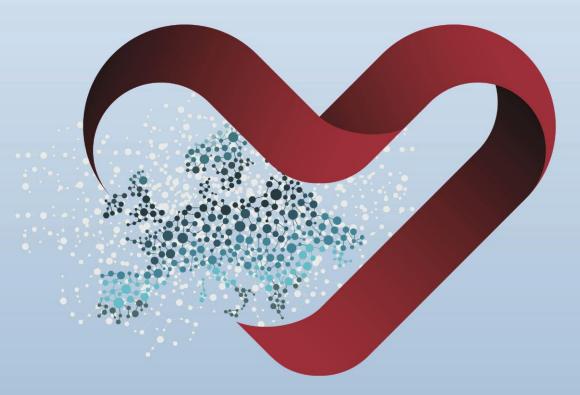
CARDIOTOX 24

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de Grupo de Cardio-Oncología







Cancer survivorship programs in 2024: fact or fiction

Thomas M. Suter MD, Bern Switzerland Lindenhofgruppe Bern

Department of Internal Medicine

No conflict of interest





Who is a Cancer Survivor?

- ...from the moment of diagnosis and for the balance of his or her life, regardless of the ultimate cause of death
- ...have survived breast cancer beyond 5 years without recurrence
- ...had a cancer diagnosis in the past, but he had completed treatment and he was disease-free for a minimum of 5 years
- ...have had a diagnosis of cancer for more than 5 years
- ...have had a cancer, and who are living, at any period after treatment, apparently free of recurrent or persistent cancer

GLOBAL CARDIO ONCOLOGY SUMMIT 2023

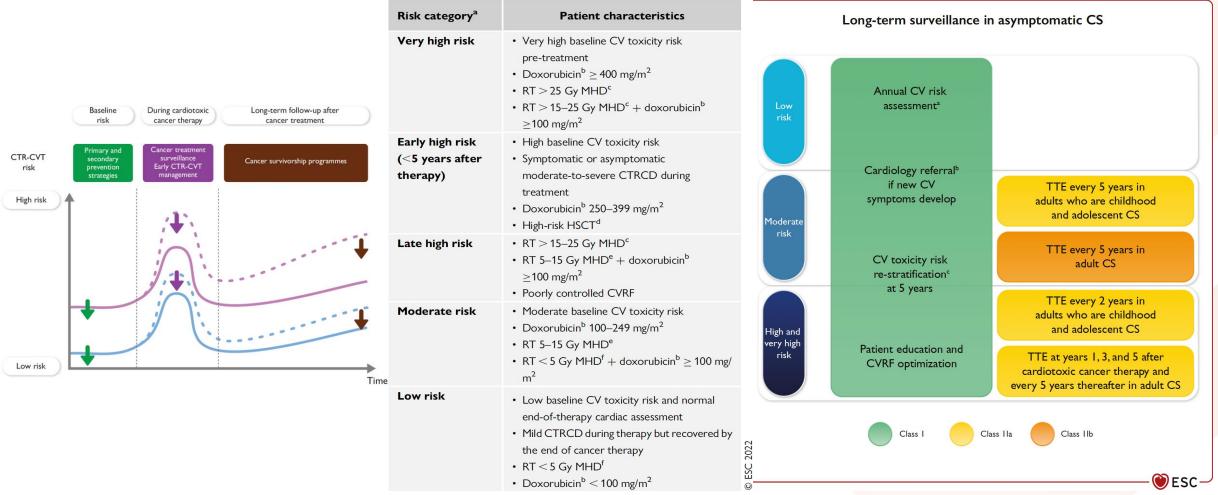
ADRID SEPTEMBER, 27.29"

National Coalition for Cancer Survivorship Marzorati C et al. *J Canc Educ* 2017: 32, 228–237





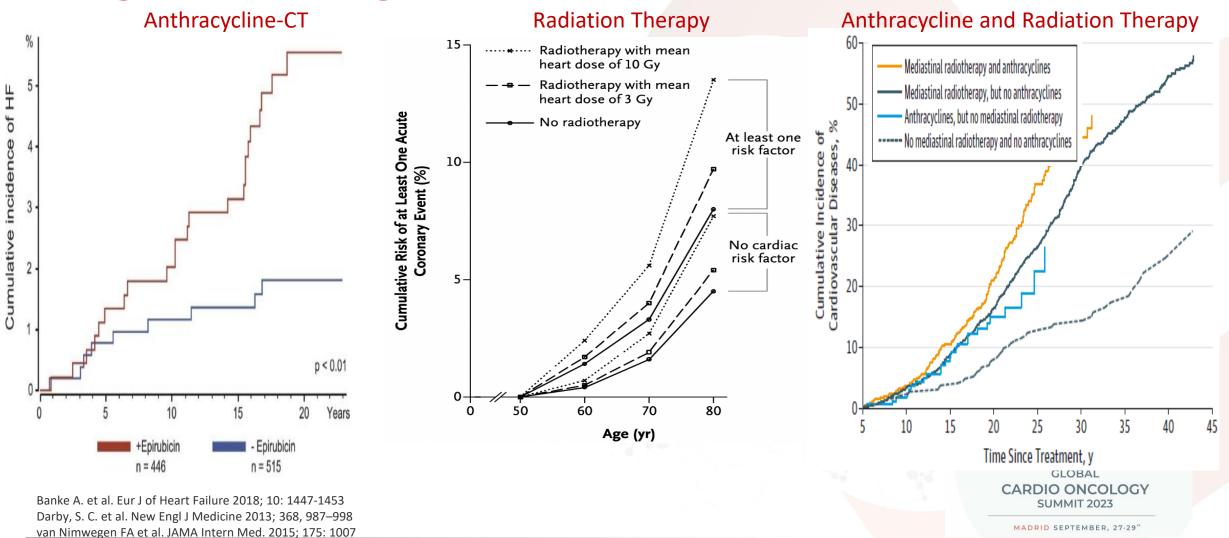
What do the Guidelines Tell us?







Long-Term Prognosis of Cancer Survivors



How to Organize a Survivorship Program? thomas.suter@lindenhofgruppe.ch





LV Dysfunction and Heart Failure



Overall heart failure



CV Adverse Events in Patients with Non-Hodgkin Lymphoma Treated with CHOP/R-CHOP

- 137 studies (21 211 patients)
- median follow-up 39.0 months [IQR 25.5–52.8])

	Screening	44				
	No	30		1.64% (0.82 to 2.65)		0.017*
	Yes	14		11·72% (3·00 to 24·53)		
ſ		45	$0.21(0.42 \pm 0.107)$			0.42†
	Age, years	45	0·31 (-0·42 to 1·07)		••	0.471
	<65 (young)	27		2·63% (0·88 to 5·05)		0.068*
	≥65 (old)	18		8·62% (2·77 to 16·89)		
	Old vs young				3·27 (2·54 to 4·20)	





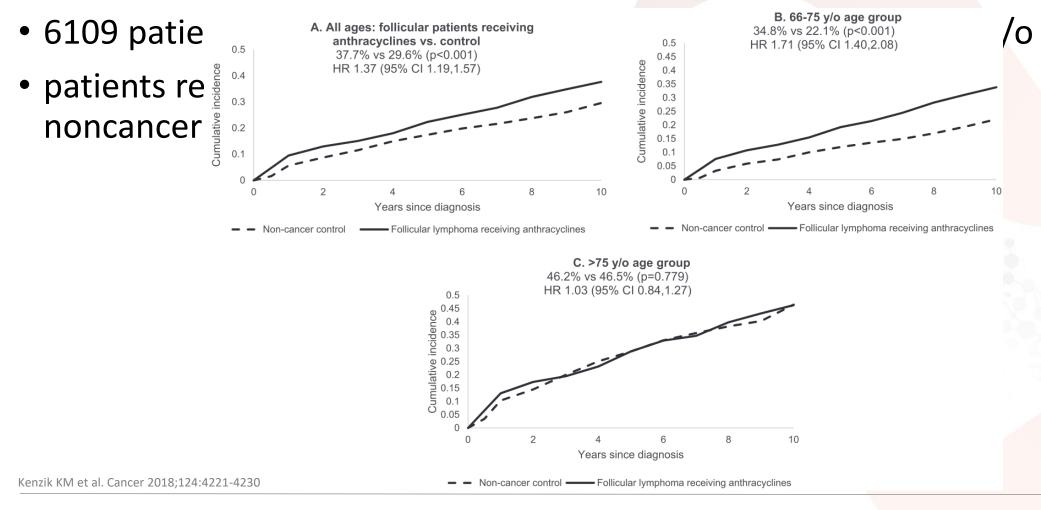
CV Adverse Events in Patients with Non-Hodgkin Lymphoma Treated with CHOP/R-CHOP

- ... considerable increase of reported heart failures with cardiac monitoring, indicates that this complication often remains undiagnosed...
- ...[*our data*]stresses the need for cardiac monitoring during and after chemotherapy...





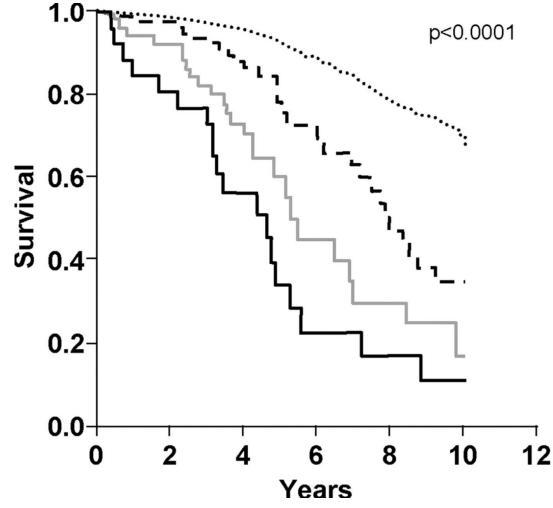
Congestive Heart Failure in Older Adults Diagnosed With Follicular Lymphoma







Prognosis of Asymptomatic Patients with LV Dysfunction



- ······ No ALVD
- – Mild ALVD
- LVEF >50% and no h/o **Osym**pt. LVSD (LVEF 40% to 50%)
- Mod/Sev ALVD
- Systolic CHF

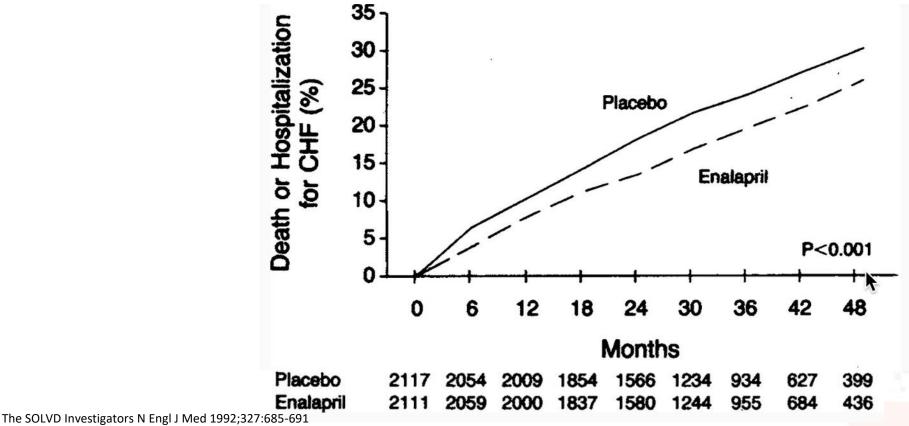
Wang TJ et al. Circulation. 2003; 108: 977–982





Treatment of asymptomatic patients with LV dysfunction

 Effect of Enalapril on Mortality and Development of Heart Failure in Asymptomatic Patients with Reduced Left Ventricular Ejection Fractions







Treatment of asymptomatic patients with LV dysfunction

Study	Patient Population (n)	Treatment	Average Duration, mo	Relative Mortality Risk Reduction	Sudden Death Risk Reduction	Death Due to Worsening HF Risk Reduction
ACE inhibitors						
SAVE ²¹	AMI and asymptomatic LVSD (2231)	Captopril vs placebo	42	19% (<i>P</i> =0.019)	No difference (<i>P</i> =NS)	36% (<i>P</i> =0.032)
SOLVD Prevention ¹⁷	Asymptomatic LVSD (4228)	Enalapril vs placebo	37.4	8% (<i>P</i> =NS)	No difference (<i>P</i> =NS)	20% [*] (<i>P</i> <0.001)
TRACE ^{22,23}	MI and LVSD (6676; 1749 randomized); Asymptomatic LVSD (542)	Trandolapril vs placebo	24–50	22% (<i>P</i> =0.001)	24% (P=0.03)	29% ⁺ (<i>P</i> =0.003)
β-blockers						
Retrospective analysis of SOLVD Prevention ²⁴	Asymptomatic LVSD (4228; 1015 patients taking β -blockers)	β-Blockers vs no β- blockers plus enalapril	37.4	23% (<i>P</i> <0.01)	28% [*] (P<0.05)	29% (<i>P</i> <0.05)
Post hoc analysis of SAVE $\frac{25}{2}$	Asymptomatic LVSD (2231; 789 patients taking β-blockers)	β-Blockers vs no β- blockers plus captopril	42	43% (<i>P</i> <0.001)	NR	32% ⁺ (P<0.001)
ANZ ²⁶	HF (415); asymptomatic LVSD (124)	Carvedilol vs placebo	19	36% [*] (<i>P</i> =0.02)	10% (<i>P</i> =NS)	8% (<i>P</i> =NS)
CAPRICORN ²⁷	Post-AMI LVSD (1959); asymptomatic LVSD (1023)	Carvedilol vs placebo (including ACE inhibitor)	15.6	23% (<i>P</i> =0.03)	26% (<i>P</i> =0.098)	40% (<i>P</i> =0.083)
ABRs						
VALIANT ²⁸	MI and LVSD, HF, or both (14 703) Asymptomatic LVSD (4099)	Valsartan, captopril, or both	24.7	No difference (<i>P</i> =NS)	NR	No difference (<i>P</i> =NS)
OPTIMAAL ²⁹ et al. Circulation 2006; 113, 24	AMI and symptomatic HF (5477); asymptomatic LVSD (1735)	Losartan vs captopril	32.4	13% Increase in risk with losartan (<i>P</i> =0.069)	19% Increase in risk with losartan (<i>P</i> =0.072)	NR





Guideline Recommendations and Levels of Evidence

ACE inhibitors

Class I	
	Use of ACE inhibitors in all patients with a recent or remote history of MI regardless of the presence of HF (Level of Evidence: A)
	Use of ACE inhibitors in patients with a reduced LVEF and no symptoms of HF, even if they have not experienced MI (Level of Evidence: A)
β-Blockers	
Class I	
	Use of β-blockers in all patients with a recent or remote history of MI regardless of the presence of HF (Level of Evidence: A)
	β-Blockers are indicated in all patients without a history of MI who have a reduced LVEF with no HF symptoms (Level of Evidence: C)
ARBs	
Class I	
	An ARB should be administered to post-MI patients without HF who are intolerant of ACE inhibitors and have a low LVEF (Level of Evidence: B)
Class I	a

ARBs can be beneficial in patients with low LVEF and no symptoms of HF who are intolerant of ACE inhibitors (Level of Evidence: C)





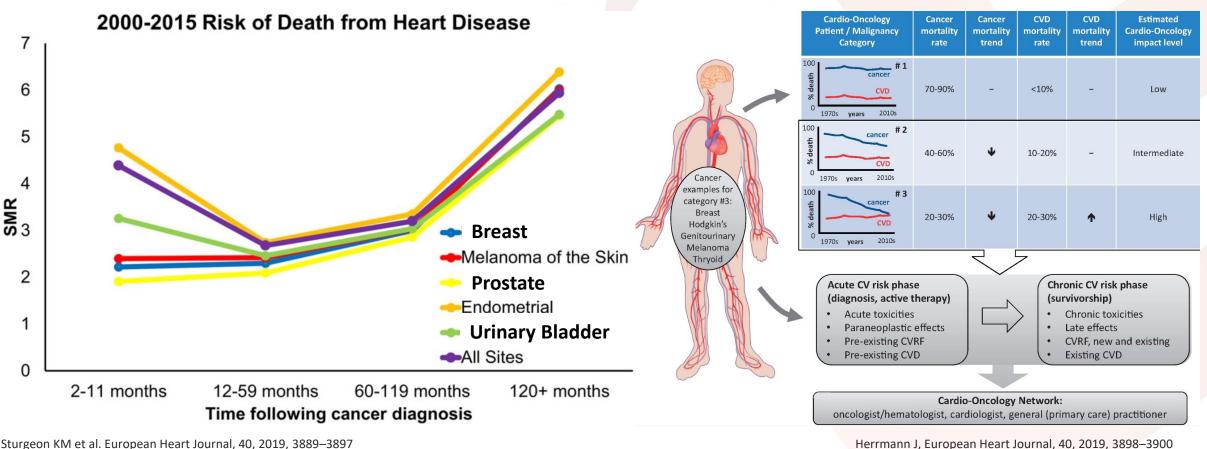
Coronary Artery Disease





Cancer Survivors are at Elevated Risk of Dying From CVD

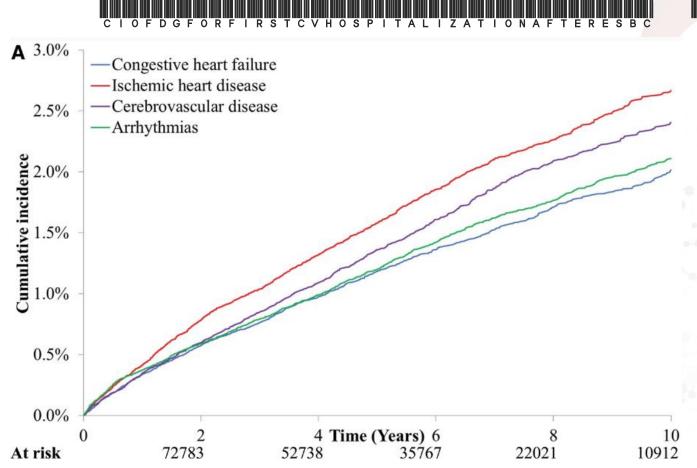
Cancer patients are at elevated risk of dying from CVDs compared to the general population ٠







CAD in Cancer Survivors



I N C R E A S E D R I **S K O F C A D I N C A N C E R S U R V I V O R S**

- All cancer survivors 1.3- to 3.6-fold increased risk
- Breast Cancer
- Prostate Cancer
- Urinary Bladder Cancer
- Hodgkins Disease
- Testicular Cancer

Gilchrist SC et al. Circulation 2019; 139: e 997 - 1012

Abdel-Qadir H. et al JNCI: Journal of the National Cancer Institute, Vol 111, 8, 2019, 854–862





SURVIVOR

35

50.9

Cancer Treatment Associated With CAD

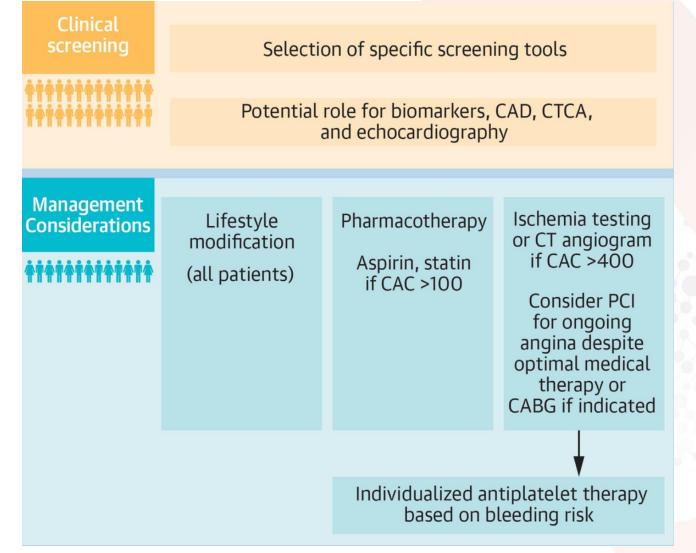
 ICI Nilotinib Ponatinib VEGFi Bleomycin Fluoropyrimidines Taxanes VEGFi 		R A D I A T I O N – A S S O C I A T E D R I S K O F C A D I N C A N C E R S
Accelerated atherosclerosis / Plaque rupture	 ICI Nilotinib Ponatinib 	CI of CAD in HL survivors treated between ages 36.5 and 5 40 = 25 Gy Mean Heart Dose (MHD) 20-24 Gy 35 = 15-20 Gy 1-14 Gy
Vasospasm	 Fluoropyrimidines Taxanes VEGFi 	H 30 - None
Coronary thrombosis	 Alkylating agents (cisplat, cycloph) Erlotinib ICI IMiD (lenalidomide, thalidomide) Monoclonal AB (VEGFi, anti-CD20) Nilotinib Platinum chemotherapy Ponatinib 	a 23 20 20 15 10 15 0 0 5 10 15 20 25 30 Time Since Treatment (years)
<i>Eur. Hear. J.</i> 43, 4229–4361 (2022)	• VEGFi	van Nimwegenen et al. JCO

van Nimwegenen et al. JCO 34, 3: 2015





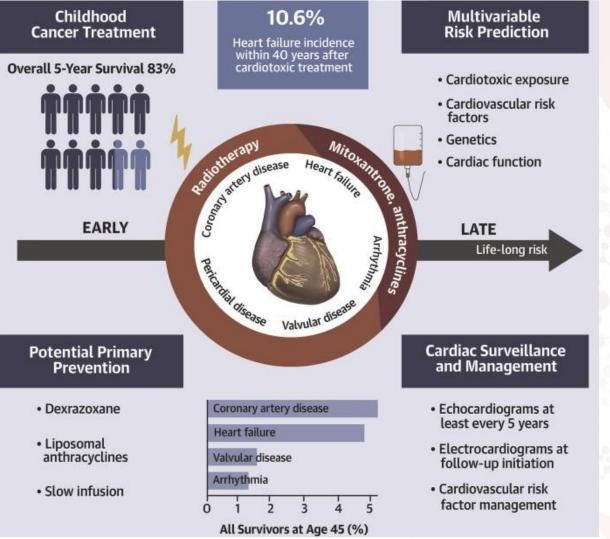
CAD in Cancer Survivors - Screening





CAD in Childhood Cancer Survivors - Screening

SOCIEDAD ESPAÑOLA DE Cardiología Clinica Grupo de Cardiología



Leerink, J.M. et al. J Am Coll Cardiol CardioOnc. 2020;2 (3):363-78.





Childhood cancer survivor: Who needs surveillance? Review IGHG

Cardiomyopathy:

Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group

Matthew J Ehrhardt*, Jan M Leerink*, Renée L Mulder, Annelies Mavinkurve-Groothuis, Wouter Kok, Anju Nohria, Paul C Nathan, Remy Merkx, Esmé de Baat, Ogechukwu A Asoguwa, Roderick Skinner, Hamish Wallace, E A M Lieke Feijer, Maalle de Ville de Goyet, Maya Prosad, Edit Bårdi, Vesna Pavasovic, Helena van der Pal, Brice Fresneau, Charlotte Demoor-Goldschmidt, Ulrike Hennewig, Julia Steinberger, Chris Plummer, Ming Hui Chen, Arco J Teske, Nadia Haddy, Elvira C van Dalen, Louis S Constine, Eric J Chow, Gill Levitt, Melissa M Hudson, Leontien C M Kremer†, Saro H Armenian†

Lancet Oncol 2023; 24: e108–20 Published Online February 14, 2023 https://doi.org/10.1016/ S1470-2045(23)00012-8 CAYA=childhood, adolescent and young adult Coronary artery disease

Review: Dr Elvira C van Dalen (Princess Máxima Center for Pediatric Oncology, NL) Systematic Review and Recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group Original Research

Coronary artery disease surveillance among childhood, adolescent and young adult cancer survivors: A systematic review and recommendations from the International Late Effects of Childhood Cancer Guideline Harmonization Group Eur J Cancer. 2021 Oct; 156:127-137. doi: 10.1016/j.ejca.2021.06.021





- 1. Who needs surveillance?
- 2. What surveillance modality should be used?
- 3. At what frequency and for how long surveillance be performed?

	Anthracycline (mg/m²)	Chest-directed radiotherapy (Gy)	Anthracycline (mg/m ²) + chest- directed radiotherapy (Gy)	ls screening recommended?	At what interval?		
High risk	≥250	≥30	≥100 and ≥15	Yes	2 years		
Moderate risk	100 to <250	15 to <30	NA	Maybe	5 years		
Low risk	>0 to <100	>0 to <15	NA	No	No screening		
NA=not applicable.							





Who needs surveillance?

	North American COG	Dutch COG	SIGN	UK CCSG	Concordance/ discordance
Anthracyclines	No	No	No	No	Concordance
Mitoxantrone	No	No	No	No	Concordance
RT exposing the heart	Yes	Yes	Yes	Yes	Concordance
Higher risk	RT dose ≥ 20 Gy to chest; TBI; combined with radiomimetic chemotherapy (e.g. doxorubicin, dactinomycin); combined with other cardiotoxic chemotherapy (anthracyclines, cyclophosphamide conditioning for HCT, amsacrine)	Not specified	≥30 Gy radiotherapy involving the heart; minimal protective cardiac blocking and younger age at irradiation	Not specified	Discordance
Highest Risk Factors	Anteriorly-weighted radiation fields; lack of subcarinal shielding; doses ≥ 30 Gy in patients who have received anthracyclines; doses ≥ 40 Gy in patients who have not received anthracyclines; longer time since treatment	Not specified	Not specified	Not specified	Discordance

Lancet Oncol 2023; 24: e108–20 Published Online February 14, 2023 https://doi.org/10.1016/S1470-2045(23)00012-8





What surveillance modality should be used?

	North American COG	Dutch COG	SIGN	UK CCSG	Concordance/ discordance
ECG	Yes	Yes	No	No	Discordance
Modifiable risk factors	Yes	Yes	Yes	Yes	Concordance

At what frequency and for how long should surveillance be performed?

	North American COG	Dutch COG	SIGN	UK CCSG	Concordance/ discordance
ECG	Baseline at entry LTFU, repeat as clinically indicated	Baseline at 5 years following diagnosis, repeat if clinical concerns	-	-	Discordance
Modifiable risk factors	Not mentioned for all modifiable risk factors, but if mentioned: dependent on specific risk factor	Not mentioned	Not mentioned	Not mentioned for all modifiable risk factors, but if mentioned: regularly all survivors	Discordance

Lancet Oncol 2023; 24: e108-20 Published Online February 14, 2023 https://doi.org/10.1016/ S1470-2045(23)00012-8



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SOCIEDAD ESPAÑOLA DE CARDIOLOGÍA	O	Asociación de Cardiología Clínica	Grupo de Cardio-Oncolog

	Echocardiography (3D or 2D LVEF)		Blood biomarkers				
High risk (anthracyclines ≥250 mg/m², chest-directed radiotherapy ≥30 Gy, or a combination of anthracyclines ≥100 mg/m² and chest-directed radiotherapy ≥15 Gy)	+ High risk of heart failure (>3·5 times) + Widely available, cheap, and cost- effective at 2-year intervals - Reasonable agreement with CMR*	 + High risk of heart failure (>3.5 times) + High reproducibility, cost-effective at 5-year intervals - Costs, availability, waiting times, interpretability by practitioners, and burden for survivors 	– Poor diagnostic value of biomarkers				
Moderate risk (anthracyclines 100–249 mg/m², or chest-directed radiotherapy 15–29 Gy, no combined treatment)	+ Risk of heart failure (>1·6 times) + Widely available, cheap, cost-effective at 5-year intervals – Reasonable agreement with CMR*	 + Risk of heart failure (>1.6 times) + High reproducibility, cost-effective at 10-year intervals - Costs, availability, waiting times, interpretability by practitioners, and burden for survivors 	– Poor diagnostic value of biomarkers				
Low risk (anthracyclines <100 mg/m ² and chest-directed radiotherapy <15 Gy) - No increased risk of heart failure		– No increased risk of heart failure	– No increased risk of heart failure				
 The balance between desirable and undesirable consequences is closely balanced or uncertain Desirable consequences clearly outweigh undesirable consequences in most settings Undesirable consequences clearly outweigh desirable consequences in most settings Desirable consequences probably outweigh undesirable consequences in most settings 							

Figure 3: Overall balance of benefits and harms of primary surveillance by risk group and modality

2D=two-dimensional. 3D=three-dimensional. LVEF=left-ventricular ejection fraction. CMR=cardiac magnetic resonance imaging. *2D in centres without experience with 3D or insufficient image quality. †Cost-effectiveness studies weighted for misclassification of echocardiography compared with CMR.

Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2023;24(3):e108- e120



Cardiomyopathy surveillance recommendations

General recommendation

CAYA cancer survivors treated with anthracyclines, chest RT, or both (high-quality evidence), and their health care providers should be aware of the risk of cardiomyopathy (strong recommendation).

Who needs cardiomyopathy surveillance?

Anthracyclines and/or mitoxantrone (as doxorubicin equivalent dose) alone

Cardiomyopathy surveillance is recommended for CAYA cancer survivors treated with high dose (≥250 mg/m²) anthracyclines (high-quality evidence, strong recommendation)

Cardiomyopathy surveillance is reasonable for CAYA cancer survivors treated with moderate dose $(\geq 100 \text{ to } < 250 \text{ mg/m}^2)$ anthracyclines (high-quality evidence, moderate recommendation).

Cardiomyopathy surveillance is not recommended for survivors treated with low dose (<100 mg/m²) anthracyclines (high-quality evidence, strong recommendation).

Chest-directed radiotherapy alone

Cardiomyopathy surveillance is recommended for CAYA cancer survivors treated with high dose (\geq 30 Gy) chest RT (high-quality evidence, strong recommendation).

Cardiomyopathy surveillance is reasonable for CAYA cancer survivors treated with moderate dose (>15 to <30 Gy) chest RT (high-quality evidence, moderate recommendation).

Cardiomyopathy surveillance is not recommended for CAYA cancer survivors treated with low dose (<15 Gy) chest RT with conventional fractionation (high-quality evidence, strong recommendation).

Anthracyclines and chest-directed radiotherapy

Cardiomyopathy surveillance is recommended for CAYA cancer survivors treated with moderate to high dose anthracyclines ($\geq 100 \text{ mg/m}^2$) and moderate to high dose chest RT ($\geq 15 \text{ Gy}$) (high-quality evidence, strong recommendation).

What surveillance modality should be used?

Left-ventricular ejection fraction measured with 2D or 3D echocardiography is recommended as the primary cardiomyopathy surveillance modality for assessment of left-ventricular systolic function in CAYA cancer survivors treated with anthracyclines or chest RT (moderate-quality evidence, strong recommendation).

Cardiac magnetic resonance imaging may be reasonable for cardiomyopathy surveillance in at-risk CAYA cancer survivors for whom echocardiography is not technically feasible or optimal (expert opinion, moderate recommendation).

Assessment of cardiac blood biomarkers (e.g., natriuretic peptides) in conjunction with imaging studies may be reasonable in instances where symptomatic cardiomyopathy is strongly suspected or

in CAYA cancer survivors who have borderline cardiac function during primary surveillance (expert opinion, moderate recommendation).

Assessment of cardiac blood biomarkers (e.g., natriuretic peptides and troponins) is not recommended as the only strategy for cardiomyopathy surveillance in at-risk CAYA survivors (low- to moderate-quality evidence, strong recommendation).

At what frequency should cardiomyopathy surveillance be performed?

High-risk CAYA cancer survivors

Cardiomyopathy surveillance is recommended for high-risk CAYA cancer survivors to begin no later than 2 years after completion of cardiotoxic therapy and continued every 2 years thereafter (moderate-quality evidence, strong recommendation).

Lifelong cardiomyopathy surveillance is reasonable for high-risk CAYA cancer survivors (expert opinion, moderate recommendation).

Moderate-risk CAYA cancer survivors

Cardiomyopathy surveillance is reasonable for moderate-risk CAYA survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis, and continue every 5 years thereafter (low-quality evidence, moderate recommendation).

Lifelong cardiomyopathy surveillance is reasonable for moderate-risk CAYA cancer survivors (expert opinion, moderate recommendation).

Systematic review and updated recommendations for cardiomyopathy surveillance for survivors of childhood, adolescent, and young adult cancer from the International Late Effects of Childhood Cancer Guideline Harmonization Group. Lancet Oncol. 2023;24(3):e108-e120

2022





Conclusion IGHG (CAYA, CM, CAD)

-The risk of CAD was increased among survivors who received radiotherapy exposing the heart, especially at doses ≥15 Gy (moderate-quality evidence)

-The guideline panel agreed that healthcare providers and CAYA cancer survivors treated with radiotherapy exposing the heart should be counselled about the increased risk for premature CAD.

-Evidence is insufficient to support primary screening, but monitoring and early management of modifiable cardiovascular risk factors are recommended

-Initiation and frequency of surveillance should be based on the intensity of treatment exposures, family history, and presence of co-morbidities but at least by age 40 years and at a minimum of every 5 years

-The main risk factors for cardiac disease in childhood cancer survivors are anthracyclines, mitoxantrone, and chestdirected radiotherapy dose (Cardiomyopathy)





Evidence for treatment with lipid lowering therapy (Adults)

Evidence use of statin for prevention of cardiotoxic effects of cancer therapies -Statins should be considered for primary prevention in adult patients with cancer at high and very high CV toxicity risk (IIa ESC Guideline Cardiooncologie, A.Lyon)

Evidence for primary prevention (cardiovascular, artherosclerotic disease)

- No RCT-Evidence, but cancer therapies and cancer are «risk-enhancers»
- No LDL-target value
- The general concept applies: the higher the CV risk, the lower the LDL target values and the stronger the indication for early, primary preventative statin therapy (10-year risk for heart disease or stroke > 7.5% (ACC/AHA heart risk calculator) should be treated appropriately with a statin





Evidence use of statin for prevention of cardiotoxic effects of cancer therapies (adults)?

-STOP-CA (JAMA 2023;330:528–536): Atorvastatin 40 mg vs Placebo bei 300 Patienten mit Lymphoma. Primärer Endpunkt (% von Patienten mit ≥10% LVEF-Reduktion): 22% vs. 9%, P=0.002

-**PREVENT** (NEJM Evid 2022;1:10. doi: 1024): Atorvastatin 40 mg vs Placebo bei 279 Pat. mit Brustkrebs oder Lymphoma unter Doxorubicin Behandlung. Primärer Endpunkt (LVEF nach 24 Monaten gemäss MRI): Kein signifikanter Unterschied

-**SPARE-HF** (Eur Heart J Cardiovasc Pharmacother 2023;9:515–525): Atorvastatin 40 mg vs. Placebo bei 112 Pat. unter Anthracycline Behandlung. Primärer Endpunkt (LVEF nach 4 Wochen und >10% LVEF-Reduktion): kein signifikanter Unterschied.

-Meta-Analysen: D'Amario D, J Cardiol 2023;391:131219. und Felix N, Eur J Intern Med 2024;126:43–48: signifikanter kardio-protektiver Effekt von Statinen



Bansal et al. Cardio-Oncology (2019) 5:18 https://doi.org/10.1186/s40959-019-0054-5

REVIEW



Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors

Neha Bansal¹, M. Jacob Adams², Sarju Ganatra^{3,4}, Steven D. Colan⁵, Sanjeev Aggarwal⁶, Rudolf Steiner⁷, Shahnawaz Amdani⁸, Emma R. Lipshultz^{9,10} and Steven E. Lipshultz^{11,12,13*}

Lipid lowering therapy in childhood cancer survivor

-study of >200 survivors from the Pediatric Long- Term Survivor Clinic at the University of Rochester found that their mean LDL-cholesterol concentration was higher than that of 70 healthy siblings (1) -long-term survivors of childhood cancer also have an increased incidence of dyslipidemia, hypercholesterolemia, and hypertriglyceridemia (2-4)

-" the benefits and risks remain unclear in the absence of any long-term studies in these Patients»

van Santen HM, Geskus RB, Raemaekers S, van Trotsenburg AS, Vulsma T, van der Pal HJ, et al. Changes in body mass index in long-term childhood cancer survivors. Cancer. 2015;121(23):4197–204.
 Felicetti F, D'Ascenzo F, Moretti C, Corrias A, Omede P, Marra WG, et al.Prevalence of cardiovascular risk factors in long-term survivors of childhood cancer: 16 years follow up from a prospective registry. Eur J Prev Cardiol. 2015;22(6):762–70.
 Talvensaari KK, Lanning M, Tapanainen P, Knip M. Long-term survivors of childhood cancer have an increased risk of manifesting the metabolic syndrome. J Clin Endocrinol Metab. 1996;81(8):3051–5.
 Gurney JG, Ness KK, Sibley SD, O'Leary M, Dengel DR, Lee JM, et al. Metabolic syndrome and growth hormone deficiency in adult survivors of childhood acute lymphoblastic leukemia. Cancer. 2006;107(6):1303–12.





Cancer survivorship programs in 2024: fact or fiction ?

- CV Mortality in Cancer Survivors Higher Than in Age-Maged General Population
 - Higher Rate of
 - Coronary Artery Disease
 - Cardiac Dysfunction / Heart Failure
 - Valvular Heart Disease
 - Arrhythmia
- High Rate of Asymptomatic CVD
 - Higher Morbidity and Mortality
 - Improved Prognosis with Treatment
- Cancer survivorship programs in 2024 Needed
- Differentiate Between Adulate and Childhood Cancer Suriviors