SUPPLEMENTARY APPENDIX

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A. Coronary artery disease guideline panel

The guideline development panel consisted of international representatives from the North American Children's Oncology Group (COG), Dutch Childhood Oncology Group (DCOG), United Kingdom Children's Cancer and Leukaemia Group (UKCCLG), Scottish Intercollegiate Guidelines Network (SIGN), and Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare), as well as experts from a range of medical specialties (pediatric, medical and radiation oncology; internal medicine; pediatrics; pediatric and adult cardiology; and epidemiology).

Name	Country	Area of expertise	Role
Core leadership group			
Daniel A. Mulrooney	USA	Pediatric oncology	Chair
Gill Levitt	UK	Pediatric oncology	Co-Chair
Elvira van Dalen	Netherlands	Systematic review and guideline development/ epidemiology/ Pediatric oncology	Coordinator
Renée Mulder	Netherlands	Guideline development/ Pediatric oncology	Advisor
Hamish Wallace	UK	Pediatric oncology	Advisor
Louis (Sandy) Constine	USA	Radiation oncology	Advisor
Roderick Skinner	UK	Pediatric oncology	Advisor
Melissa Hudson	USA	Pediatric oncology	Advisor
Leontien Kremer	Netherlands	Guideline development/ Pediatric oncology	Advisor
Expert panel			
Eugene Suh	USA	Pediatric oncology	WG member
Matthew Ehrhardt	USA	Pediatric oncology	WG member
Gregory Aune	USA	Pediatric oncology	WG member
Edit Bardi	Austria	Pediatric oncology	WG member
Bradley Benson	USA	Internal medicine/ pediatrics	WG member
Jutta Bergler-Klein	Austria	Cardiology	WG member
Ming Hui Chen	USA	(Pediatric) cardiology	WG member
Eva Frey	Austria	Pediatric oncology	WG member
Ulrike Hennewig	Germany	Pediatric oncology	WG member
Liane Lockwood	Australia	Pediatric oncology	WG member
Ulla Martinsson	Sweden	Radiation oncology	WG member
Monica Muraca	Italy	Pediatrics	WG member
Helena van der Pal	Netherlands	Medical oncology	WG member
Chris Plummer	UK	Cardiology	WG member
Katrin Scheinemann	Switzerland/ Canada	Pediatric oncology	WG member
Christina Schindera	Switzerland	Pediatric oncology	WG member
Emily Tonorezos	USA	Internal medicine	WG member

External reviewers		
Daniel Duprez	USA	Cardiology
Adam Glaser	UK	Pediatric oncology
Jason Schwartz	USA	Survivor representative
Zuzana Tomášiková	Switzerland	Survivor representative

B. Clinical questions*

Who needs surveillance?

1. What is the risk of CAD in childhood, adolescent and young adult cancer survivors exposed to chemotherapy alone?
    a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by chemotherapy dose (lower vs higher dose)?
    b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure to chemotherapy?
2. What is the risk of CAD in childhood, adolescent and young adult cancer survivors exposed to radiation alone?
    a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by radiotherapy dose (lower vs higher dose)?
    b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure to radiation?
3. What is risk of CAD in childhood, adolescent and young adult cancer survivors exposed to both chemotherapy and radiation therapy?
    a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by chemotherapy and radiation therapy dose (lower vs higher dose)?
    b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure (to chemotherapy and radiation therapy)?
    c. What is the risk of CAD in childhood, adolescent and young adult cancer survivors treated with stem cell transplant?
4. What is the added risk of cardiovascular risk factors (i.e. dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors etc) to CAD in childhood, adolescent and young adult cancer survivors?

What surveillance modality should be used?

1. What is the diagnostic value (i.e. sensitivity, specificity, positive predictive value and/or negative predictive value) of one possible surveillance modality as compared to another possible surveillance modality for surveillance of asymptomatic CAD in childhood, adolescent and young adult cancer survivors?

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

For this working group clinical questions depended on the available evidence identified in the surveillance modality should be used working group. No evidence in CAYA cancer survivors was available, so no clinical questions were developed.

What should be done when abnormalities are identified?

1. What is the evidence for treatment with lipid-lowering agents in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?
2. What is the evidence for treatment with anti-hypertensive agents in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?
3. What is the evidence for lifestyle modification in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?

**Looking at modifiable cardiovascular risk factors was a post-hoc decision:*

1. *Who needs surveillance for modifiable CVD risk factors?*
2. *When should surveillance for modifiable CVD risk factors be initiated and at what frequency?*
3. *What can be done when modifiable CVD risk factors have been identified?*

C. Search strategy

Search strategies were developed by Cochrane Childhood Cancer (www.childhoodcancer.cochrane.org) in collaboration with the guideline development panel, which suggested appropriate terms and confirmed the final search strategy. The search was performed in MEDLINE (through PubMed).

Search 1a: Childhood cancer + testis cancer + breast cancer	((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors)) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute) OR (leukemia, lymphocytic, acute*) OR (breast cancer OR breast cancers OR breast neoplasm OR breast neoplasms OR breast neoplasm*) OR (testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor*)
Search 1b: Children, adolescents, young adults	Infan* OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR young adult[mh] OR young adult
Search 2: Chemotherapy	Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap*
Search 3: Radiotherapy	Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations

Search 4: Hematopoietic stem cell transplant	Stem cell transplant[mh] OR stem-cell transplant OR stem cell transplant* OR stem cell transplantation OR bone marrow transplantation[mh] OR transplantation, conditioning[mh] OR hematopoietic stem cell transplantation[mh] OR reduced-intensity conditioning regimen OR myeloablative agonists[mh]
Search 5: Coronary artery disease	angina OR angina pectoris[mh] OR coronary artery disease OR coronary artery disease[mh] OR myocardial infarction OR myocardial infarction[mh] OR heart attack[tiab] OR heart arrest[mh] OR cardiac arrest OR ischemic heart disease OR ischaemic heart disease OR myocardial ischemia[mh] OR ischemic cardiomyopath* OR ischaemic cardiomyopath* OR coronary ischemia[tiab] OR atherosclerotic heart disease[tiab] OR (coronary AND (vasculopathy OR thrombosis OR occlusion[tiab] OR plaque[tiab] OR occlusive disease* OR atherosclerosis OR artery disease* OR atherosclerotic disease* OR artery calcification* OR angiogram OR angioplasty OR artery bypass OR arteriosclerosis OR aneurysm)) OR coronary angiography[mh] OR angioplasty, balloon, coronary[mh] OR coronary artery bypass[mh] OR coronary aneurysm[mh] OR (cardiac AND (atherosclerosis OR atherosclerotic*))
Search (1a AND 1b) AND (2 OR 3 OR 4) AND 5 **Filters: published since 1990; humans; English language**	

Additionally, reference lists of the guidelines and relevant review articles identified during the search were screened, as well as key papers known to the guideline panel.

D. In- and exclusion criteria

- **Study population:**
  - Childhood, adolescent and young adult cancer survivors
  - At least 75% diagnosed with cancer prior to age 35 years
    In case the article did not provide enough information to be certain about the age at cancer diagnosis and the percentage of patients aged less than 35 years, the IGHG core group decided that we should use "mean/median ≤ 25 years" as an indicator that at least 75% is diagnosed with cancer prior to age 35 years.
  - All patients (100%) should be off active cancer treatment with CAD assessment post completion of treatment
- **Outcomes:**
  - (Asymptomatic) coronary artery disease (CAD)
  - For Who needs surveillance: studies investigating a certain risk factor as included in the clinical question.
  - For What surveillance modality should be used: Studies investigating the diagnostic value of possible surveillance modalities for asymptomatic CAD as included in the clinical question.
  - For What should be done if abnormalities are identified: Studies investigating the effectiveness of a certain treatment on asymptomatic CAD as included in the clinical questions.
- **Types of studies:**
  - All study designs except case reports, case series and narrative reviews
  - Sample size at least N=20
  - For Who needs surveillance: only studies that controlled for important confounding factors (i.e. multivariable analysis if cohort study or matching/risk stratification if case-control study) were eligible for the evaluation of risk factors for CAD.
  - English language
  - Published from 1990 onwards

Studies including both eligible and non-eligible participants were included if results for the subgroup of eligible participants were described separately.

We run the search in MEDLINE on November 1, 2018 and updated this search on August 26, 2020. During this update only studies with relevant multivariable analyses were included.

Study selection was done by 2 independent guideline panel members. Discrepancies between panel members were resolved by discussion and if that was not possible by using third party arbitration by another member.

E. Grading system

E.1: Risk of bias criteria for included studies*

	Type of bias	Definition
Study group	Selection bias	*Is the study group representative of the underlying study population?* Low risk if: • the study group consisted of >75% of the original cohort of CAYA cancer survivors or: • it was a random sample with respect to the cancer treatment
Follow-up	Attrition bias	*Is the follow-up adequate?* Low risk if: the outcome was assessed for >75% of the study group
Outcome	Detection bias	*Are the outcome assessors blinded for important determinants related to the outcome?* Low risk if: the outcome assessors were blinded for important determinants related to the outcome
Risk estimation	Confounding	*Are the analyses adjusted for important confounding factors?* Low risk if: important prognostic factors (i.e. age, gender, co-treatment, follow-up) were taken adequately into account

**based on previously described checklists according to evidence-based medicine criteria:*
Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. Lancet 2002; 359(9303): 341-5.
Laupacis A, Wells G, Richardson WS, Tugwell P. Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. JAMA 1994; 272(3): 234-7.

Risk of bias assessment was done by 1 guideline panel member and checked by another member. Discrepancies between panel members were resolved by discussion and if that was not possible by using third party arbitration by another member.

E.2: Grading the quality of the body of evidence

Initial score based on type of evidence		
+4	Randomized controlled trials/systematic reviews of randomized controlled trials	
+2	Controlled clinical trials or observational evidence (e.g. cohort, case-control) for intervention questions	
+4	Observational evidence for etiologic, prognostic and diagnostic questions	
Factors decreasing quality of evidence	**Assessment**	**Effect on quality**
1. Study limitations	Risk of biased based on selection bias, attrition bias, detection bias and confounding	No problems: 0; Problem with 1 element: -1; Problem with 2 elements: -2; Problem with 3 or more elements: -3
2. Inconsistency	Degree of consistency of effect between or within studies	All/most studies show similar results: 0; Lack of agreement between studies (including statistical heterogeneity/conflicting results, e.g. effect sizes in different directions): -1
3. Indirectness	The generalizability of population and outcomes from each study to the population of interest	Population and outcomes broadly generalizable: 0; Problem with 1 element (population different from the defined inclusion criteria or outcomes different from the defined inclusion): -1; Problem with 2 elements: (population and outcomes): -2
4. Imprecision	The precision of the results	No important imprecision when studies include many patients and many events and thus have narrow confidence intervals: 0; Important imprecision when studies include relatively few patients and few events and thus have wide confidence intervals, or if the effect estimate and confidence intervals cross the clinical decision threshold, or if only one study has been identified: -1; Important imprecision (see -1) and if only one study has been identified: -2
5. Publication bias	If investigators fail to report studies and outcomes (typically those that show no effect)	Publication bias unlikely: 0; Risk of publication bias when for example published evidence is limited to industry funded trials: -1
Factors increasing quality of evidence	**Assessment**	**Effect on quality**
6. Magnitude of effect	-	Large magnitude of effect if all studies show significant effect sizes (point estimate) >2 or <0.5: +1; Very large magnitude of effect if all studies show significant effect sizes (point estimate) >5 or <0.2: +2

7. Dose response gradient	-	Evidence of clear relation with increases in the outcome with higher exposure levels across or within studies: +1
8. Plausible confounding	-	If adjustment for confounders would have increased the effect size: +1
Total score		
⊕⊕⊕⊕	High quality evidence (i.e. further research is unlikely to change the confidence in the estimate of effect)	
⊕⊕⊕⊖	Moderate quality evidence (i.e. further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate)	
⊕⊕⊖⊖	Low quality evidence (i.e. further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate)	
⊕⊖⊖⊖	Very low quality evidence (i.e. any estimate of effect is very uncertain)	

Mulder RL, Brown MC, Skinner R, Hudson MM, Kremer LCM. Handbook for guideline development; collaboration between International Guideline Harmonization Group, PanCare Guideline Group and Cochrane Childhood Cancer Group, 2019

The GRADE assessment was done by 1 guideline panel member and checked by another member. Discrepancies between panel members were resolved by discussion and if that was not possible by using third party arbitration by another member.

E.3: Criteria for grading the recommendations

Grade of Recommendation **Conclusions of evidence according to GRADE**	**Strong recommendation to do** Benefits >>> risk & harms	**Moderate recommendation to do** Benefits > or = risk & harms	**Recommendation not to do** No benefit / Potentially harm
High quality of evidence Consistent evidence from well performed and high quality studies or systematic reviews (low risk of bias, direct, consistent, precise).	Strong recommendation based on high quality evidence	Moderate recommendation based on high quality evidence	Recommendation not to do based on high quality evidence
Moderate quality of evidence Evidence from studies or systematic reviews with few important limitations.	Strong recommendation based on moderate quality evidence	Moderate recommendation based on moderate quality evidence	Recommendation not to do based on moderate quality evidence
Low to very low quality of evidence Evidence from studies with serious flaws, only expert opinion, or standards of care.	Strong recommendation based on expert opinion	Moderate recommendation based on (very) low quality evidence Diverging expert opinions	Recommendation not to do based on expert opinion
	Wording in recommendations:		
	… is recommended …	… is reasonable …	… is not recommended …

Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? Circulation. 2003; 107(23): 2979-86.

F. Evidence tables*

Who needs surveillance?				
Armstrong GT et al. Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 2013; 31(29): 3673-80.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (CCSS) Treatment era: Initial treatment between 1970-1986 Follow-up: Median 25.6 years (range 7.4-39.3) from cancer diagnosis.	N=10724 5-year (after diagnosis) survivors of childhood cancer; aged <21 years at diagnosis. Diagnosis: ALL N= 3237 (30.2%) AML N=280 (2.6%) Other leukemia N=78 (0.7%) Astrocytomas N=823 (7.7%) Medulloblastoma/PNET N=277 (2.6%) Other CNS tumors N=232 (2.2%) Hodgkin's lymphoma N=1368 (12.8%) Non-Hodgkin's lymphoma N=835 (7.8%) Wilms tumor N=1030 (9.6%) Neuroblastoma N=762 (7.1%) Soft tissue sarcoma N=935 (8.7%) Ewing sarcoma N=269 (2.5%) Osteosarcoma N=559 (5.2%)	Chemotherapy: N=3779 (35.2%) anthracyclines (for N=1011 anthracyclines yes/no not reported). Doses and other agents not reported. Irradiation: N=2532 (23.6%) chest-directed radiotherapy (for N=1134 chest-directed radiotherapy yes/no not reported). Doses and other radiotherapy locations not reported. Chemotherapy only: Not reported Irradiation only: Not reported	Diagnostic test used for CAD assessment: All participants completed a baseline questionnaire (1994 to 1999) that included demographics, personal/family medical history, and history of health conditions including cardiovascular outcomes. A surrogate (parent, spouse, next of kin) completed the baseline questionnaire for survivors who died more than 5 years after diagnosis, who were younger than age 18 or unable to complete the questionnaire. In addition, information on cardiovascular outcomes was collected on two subsequent follow-up questionnaires, most recently administered from 2007 to 2009.	Risk of bias: Selection bias: Unclear risk (study group consists of less than 75% (i.e. 51.8%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment) Attrition bias: Low risk (for the follow-up questionnaire follow-up is at least 67.6%, but for the first questionnaire it is complete) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding:

	Other bone tumors N=39 (0.4%) <u>Age at diagnosis:</u> < 5 years N=4408 (41.1%) 5-9.9 years N=2362 (22%) 10-14.9 years N=2149 (20%) 15-20.9 N=1805 (16.8%) <u>Proportion <age 35 at diagnosis:</u> 100% <u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Median age 33.7 years, range 11-58.9 years <u>Gender:</u> 5623 (52.4%) males; 5101 (47.6%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Patients with diabetes, hypertension, and dyslipidemia were defined as those who	<u>Chemotherapy and irradiation:</u> Not reported <u>Stem cell transplant:</u> Not reported	Study questionnaires included self-report of all prescribed medications taken regularly (consistently for > 1 month or for 30 days or more in 1 year) during the previous 2-year period. Cancer diagnosis and treatment data were abstracted from medical records. For assessment of cardiac mortality, the CCSS cohort was linked with the NDI to ascertain cardiac deaths. All cardiac events, as well as cardiovascular risk factors, were self-reported, without medical record confirmation. Survivors who completed the baseline questionnaire and at least one of two follow-up questionnaires or were subsequently deceased were considered eligible for longitudinal evaluation of cardiovascular risk factors and subsequent cardiac events. Survivors who developed a second malignant neoplasm or	Low risk (all important confounding factors have been taken into account) <u>Funding of the trial:</u> Supported by the National Cancer Institute, the American Lebanese-Syrian Associated Charities and the Cancer Center Support (CORE). *Possible overlap in study population of the different CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.* *This study has an additional decade of follow-up from the report of Mulrooney 2009.* *"We limited this analysis to severe, life-threatening, and fatal (grades 3 to 5) cardiac events substantiated by medical/surgical intervention, so that over-reporting is less likely. Further, only survivors and siblings reporting corroborating pharmacotherapy were considered to have*

	reported being diagnosed by a physician with the condition(s) and who reported taking specific medications prescribed for the treatment of the condition(s). Obesity was defined as a body mass index ≥ 30 kg/m^2 calculated from self-report of height and weight. For survivors younger than age 20 years, obesity was defined as a body mass index in the 95th percentile or above for age- and sex-specific distributions for US children. Diabetes mellitus: N=397 (3.7%) survivors; N=75 (2.4%) siblings Hypertension: N=1602 (14.9%) survivors; N=304 (9.6%) siblings Dyslipidemia: N=959 (8.9%) survivors; 190 (6%) siblings Obesity: 2308 (21.5%; not reported for N=91) survivors; 727 (23%; not reported for N=7) siblings Multiple (2 or more) cardiovascular risk factors: 1109 (10.3%; not reported for N=4) survivors; 248 (7.9%; not reported for N=1) siblings		late recurrence (5 or more years from diagnosis) of primary cancer before the baseline questionnaire were excluded from analysis because treatment information for these neoplasms was not uniformly obtained. <u>Timing of the diagnostic test:</u> The questionnaire was sent at least 5 years after cancer diagnosis; it was not clear if all CAD cases occurred after the end of treatment, but we gave this manuscript the benefit of the doubt and included it anyway. <u>Outcome definitions:</u> CAD defined as CTCAEv4.03 grade 3 (severe), 4 (life threatening) or grade 5 (fatal). <u>Occurrence of CAD:</u> CAD grade 3-5: N=184 (1.8%) in survivors; N=16 (0.5%) in siblings. ALL N= 18 (0.6%) AML N=3 (1.1%) Other leukemia N=3 (4%)	*hypertension, diabetes, or dyslipidemia."* *"…. survivors exposed to cardiotoxic therapy may be more likely to be monitored for cardiovascular function, representing a potential for surveillance bias."* *"It is likely that the length of exposure and follow-up may not have been sufficient to detect adverse effects of smoking in this young patient population."*

	With aging, the prevalence of cardiovascular risk factors increased among survivors and was statistically significantly greater than that for siblings at age 50 years for hypertension (40.2% vs 25.5%; P < .001) and dyslipidemia (23.0% vs 13.6%; P = .008). The prevalence of obesity was higher among siblings at age 50 (25.2% vs 31.3%; P = .02). The prevalence of diabetes at age 50 was 9% in survivors and 6% in siblings (P value not reported). Multiple cardiac risk factors at age 50 27% in survivors and 22% in siblings (P-value not reported). <u>Controls:</u> 3159 siblings of CCSS participants (random sample)		Astrocytomas N=3 (0.4%) Medulloblastoma N=4 (1.5%) Other CNS tumors N=2 (0.9%) Hodgkin's lymphoma N=109 (8.5%) Non-Hodgkin's lymphoma N=10 (1.2%) Wilms tumor N=5 (0.5%) Neuroblastoma N=5 (0.7%) Soft tissue sarcoma N=8 (0.9%) Ewing sarcoma N=5 (1.9%) Osteosarcoma N=8 (1.5%) Other bone tumors N=1 (2.6%) CAD grade 3: N=72 (0.7%) in survivors; N=5 (0.2%) in siblings CAD grade 4: N=87 (0.8%) in survivors; N=11 (0.3%) in siblings CAD grade 5: N=25 (0.2%) in survivors; N=0 in siblings Cumulative incidence of CAD by 45 years of age: 5.3% (95% CI 4.4%-6.1%) in survivors; 0.9% (95% CI 0.4-1.4%) in siblings. (Death, secondary malignant neoplasms and late recurrence (survivors only)	

			were taken as competing risk events) The cumulative incidence of CAD was associated with exposure to chest-directed radiotherapy (P<0.001). <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Multivariable Poisson regression models: Models included age, household income, and education as time-dependent variables and sex, race, smoking, chest-directed radiotherapy and anthracycline exposure. Number of risk factors and exposure to chest-directed radiotherapy: Results based on a single model that included the entire study population (rate ratio (95% CI)): N of risk factors: Four: 17.6 (5.3-58.3) P<0.001 Any 3: 13.7 (6.7-27.8) P<0.001 Any 2: 10.4 (6.1-17.7) P<0.001	

			Any 1: 4.0 (2.5-6.4) P<0.001 None: 1.0 Individual and combinations of risk factors after exposure to chest-directed radiotherapy: Results based on one model of the entire study population in which survivors with only one risk factor were separated into 4 groups (hypertension alone, dyslipidemia alone, diabetes alone, obesity alone); survivors with all other combinations or with no risk factors were included in the model but only selected risk estimates are displayed (rate ratio (95% CI)): Hypertension alone: 6.1 (3.4-11.2) P<0.001 Dyslipidemia alone: 4.7 (2.0-10.7) P<0.001 Diabetes alone: 2.7 (0.4-20.0) P=0.32 Obesity alone: 2.8 (1.5-5.3) P=0.001 Hypertension + dyslipidemia: 20.9 (11.1-39.4) P<0.001 Hypertension + diabetes: 23.5 (7.1-77.8) P<0.001	

			Hypertension + obesity: 5.8 (2.2-14.9) P<0.001 No risk factors: 1.0 Models adjusted for age, household income and education as time-dependent variables and sex, race, smoking, chest-directed radiotherapy and anthracycline exposure. Results for all risk factors were based on a single model that included the entire study population (chest-directed radiotherapy present, risk factor present, rate ratio (95% CI)): Hypertension: No No: 1.0 No Yes: 8.7 (4.8-15.8) Yes No: 5.3 (3.2-8.7) Yes Yes: 37.2 (22.2-62.3) RERI: 24.2 (11.8-39.7); statistically significant Dyslipidemia: No No: 1.0 No Yes: 5.0 (2.4-10.3) Yes No: 4.6 (3.0-6.9) Yes Yes: 25.0 (15.2-41.3) RERI: 16.4 (7.9-29.8); statistically significant	

			Diabetes: No No: 1.0 No Yes: 5.2 (2.2-12.5) Yes No: 5.1 (3.5-7.5) Yes Yes: 20.1 (10.6-38.4) RERI: 10.8 (0.0-28.6); not statistically significant Obesity: No No: 1.0 No Yes: 1.4 (0.7-2.6) Yes No: 4.6 (3.1-7.0) Yes Yes: 9.3 (5.6-15.5) RERI: 4.3 (0.9-8.7); statistically significant Multiple risk factors (2 or more) including Hypertension: No No: 1.0 No Yes: 7.9 (4.1-15.1) Yes No: 5.0 (3.3-7.7) Yes Yes: 39.8 (23.9-66.3) RERI: 27.9 (14.6-51.0); statistically significant Multiple (2 or more) risk factors excluding hypertension: No No: 1.0 No Yes: 0.0 (0.0-2.5) Yes No: 4.9 (3.4-7.0)	

			Yes Yes: 3.0 (0.4-21.6) RERI: -0.9 (-5.4 to 5.9); not statistically significant A RERI term statistically significantly greater than zero indicates that interaction between treatment and cardiovascular risk factor is more than additive. Smoking was not found to be associated with risk of a major cardiac event. Thus, although we adjusted for smoking in the risk factor analyses, specific risks for smoking are not presented. <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Chen MH et al. Blood pressure is associated with occult cardiovascular disease in prospectively studied Hodgkin lymphoma survivors after chest radiation. Leuk Lymphoma 2014; 55(11): 2477-83.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective multi-center cohort; cardiac screening from March 2004 to July 2008. Treatment era: 1970-2002 Follow-up: Median time since completion of radiotherapy 14.8 years (range 5.2-35.7 years)	N=182 adult asymptomatic long-term (more than 5 years post-treatment) survivors who received chest irradiation; aged 15 years or older at cancer diagnosis. Diagnosis: Hodgkin lymphoma Age at diagnosis: Median age at radiotherapy completion 28.6 years, range 13.1-55.6 Proportion <age 35 at diagnosis: 79% (144/182 survivors; based on additional information provided by first author) Proportion <age 21 at diagnosis: Not reported Age at testing/follow-up:	Chemotherapy: N=99 (54%): ABVD N=68 (69%) EVA N=8 (8%) MOPP N=29 (29%) Other N=5 (5%) History of anthracycline: N=76 (42%) Doses not reported. Irradiation: N=182 (100%) chest irradiation. Radiotherapy field: Mantle only N=83 (46%) Mantle and para-aortic N=83 (46%) Involved field N=13 (7%) Other N=3 (2%)	Diagnostic test used for CAD assessment: Cardiac screening included completion of study questionnaires, a clinic visit with a cardiologist, three direct measurements of BP by health care personnel, laboratory testing, and an exercise stress echocardiogram to assess ischemia. All echocardiographic findings were classified according to the guidelines established by the American Society of Echocardiography. Timing of the diagnostic test: At least 5 years post-treatment. Outcome definitions: CAD defined as the presence of ischemia on non-invasive imaging, which was confirmed	Risk of bias: Selection bias: Unclear risk (original cohort not reported and unclear if it is a random sample with respect to cancer treatment) Attrition bias: Low risk (182/210 (87%) survivors who signed informed consent completed cardiac screening) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Support from the Translational Fund for Research in Cardiology and Oncology, Department of Cardiology,

	Median age 43.2 years, range 21.3-65.3 years <u>Gender:</u> 73 (40%) males; 109 (60%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Traditional cardiovascular risk factors were ascertained prospectively via study questionnaire, physician visits and/or laboratory testing. Smoking history was categorized as >100 cigarettes in one's lifetime. Hyperglycemia was defined as fasting glucose levels >110 mg/dL, a history of diabetes or use of anti-hyperglycemic agents. Hypertension was defined as systolic BP 140 mmHg or higher, or diastolic BP 90 mmHg or higher; measured in accordance with JNC7 guidelines. Patients with a history of hypertension or use of anti-hypertensive	Whole heart N=24 (13%) Median dose to the mediastinum 3960 cGy (range 2550-5325 cGy). Prescribed radiation doses were normalized to the central axis. Because of reduced scattered dose from the lung blocks and greater separation at the level of the lower mediastinum, the lower mediastinum typically received approximately 7% lower than the prescribed dose. Other radiotherapy locations not reported. <u>Chemotherapy only:</u> N=0 <u>Irradiation only:</u> N=83 (46%) <u>Chemotherapy and irradiation:</u> N=99 (54%)	by coronary angiography (presence of 70% coronary stenosis). <u>Occurrence of CAD:</u> Obstructive CAD: N=8 (4.4%) ischemia on non-invasive testing and all confirmed to have obstructive CAD by angiography; all in asymptomatic survivors. <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	Boston Children's Hospital and the Swim-Across-America Foundation. *Possible overlap in study population with the Mauch 1995 and Galper 2011 studies.* *"The incidence of hypertensive patients in this asymptomatic cohort (26%) was higher than previously reported (9-14%). The higher prevalence is likely due to this study's direct ascertainment of BP as most other studies relied on medical records or patient questionnaires to determine whether a patient was hypertensive."* *"The study population was biased toward those with higher risk of CVD because longer-term survivors, by definition, were treated with older, outmoded radiotherapy techniques. Furthermore, even though the study cohort was similar in all demographics to the 28 patients who withdrew, the former received slightly higher radiotherapy doses (39.6 Gy vs. 37.2 Gy), and*

	agents were also classified as hypertensive. Physical inactivity was defined as exercise <3 days per week. Positive family history of premature cardiovascular disease was defined as atherosclerosis, heart attack or stroke before age 55 in male relatives or age 65 in female relatives. Overweight was defined as a BMI 25 kg/m^2 or higher but <30 kg/m^2 and obese as a BMI 30 kg/m^2 or higher. Hyperlipidemia was defined as a fasting total cholesterol 200 mg/dL or higher, low density lipoprotein 130 mg/dL or higher, high density lipoprotein 40 mg/dL or lower for men and 50 mg/dL or lower for women, or triglycerides >150 mg/dL. Hyperlipidemia was also defined as a history of elevated lipids or use of lipid-lowering medication. An elevated high sensitivity C-reactive protein hs-CRP was defined as >3 mg/dL. All laboratory testing was performed at a single center,	<u>Stem cell transplant:</u> Not reported		*therefore may be at higher risk for CVD."*

	in accordance with institutional guidelines. Positive family history of CVD N=55 (31%) History of smoking N=63 (35%) Hypertension N=48 (26%): N=24/48 (50%) had a prior diagnosis of hypertension and N=24/48 (50%) were classified as hypertensive based on elevated BP measurements. Elevated high sensitivity C-reactive protein N=64 (35%) Hyperlipidemia N=101 (55%) Physical inactivity N=79 (43%) Overweight or obese BMI N=103 (57%) Hyperglycemia N=8 (4%) N=147 (81%) at least one modifiable risk factor; 84 (46%) two or more. <u>Controls:</u> No			

Who needs surveillance?				
Constine LS et al. Cardiac function, perfusion, and morbidity in irradiated long-term survivors of Hodgkin's disease. Int J Radiat Oncol Biol Phys 1997; 39(4): 897-906.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center Treatment era: 1964-1994 Follow-up: Mean interval between radiation therapy and testing 9.1±7.5 years, median 6.1 years, range 1.1-29.1 years.	N=50 cancer survivors aged less than 50 years at the time of radiotherapy receiving care in the radiation oncology follow-up clinic with an interval of at least 1 year between completion of radiotherapy and cardiac evaluation. Diagnosis: Hodgkin's disease Age at diagnosis: Mean age at time of radiation therapy 26±8.6 years, median 25 years, range 10.2-46.1 years. Proportion <age 35 at diagnosis: Not reported (but more than 50%) Proportion <age 21 at diagnosis: Not reported	Chemotherapy: N=17 (34%): • N=6 BCVPP (35%) • N=2 MOPP (12%) • N=1 CVPP (6%) • N=1 CVPN (6%) • N=1 MOPP+CVPP (6%) • N=1 MOPP+MVPP (6%) • N=1 NOVP (6%) • N=2 ABVD (12%) • N=1 ABV/MOPP (6%) • N=1 CVP (6%) Doses not reported. Irradiation: N=50 (100%); all patients radiotherapy to part or all of the heart. Central cardiac doses were calculated with specific reference to	Thallium-201 or ^{99m}Tc-sestamibi myocardial perfusion scintigraphy (rest and exercise) Exercise tolerance testing (treadmill test) Timing of the diagnostic test: At least 1 year after completion of radiotherapy Outcome definitions: • Abnormalities on exercise tolerance testing: not further specified • Abnormalities on myocardial perfusion scintigraphy; not further specified • Clinical MI; not further specified Occurrence of CAD: All patients had Hodgkin's disease;	Risk of bias: Selection bias: Unclear risk (original cohort not reported so unclear if study group consisted of more than 75% of the original cohort or was a random sample with respect to the cancer treatment) Attrition bias: Low risk (for the different tests used in this study the outcome was assessed for more than 75% of the study group (range 76-100%)) Detection bias: Unclear risk (no information on blinding of outcome assessors provided for exercise testing and diagnosis of MI; for perfusion scintigrams it is stated that they were assessed without knowledge of clinical, electrocardiographic, or

	Age at testing/follow-up: Mean age at first cardiac evaluation 35.1±10.3 years, median 32.7 years, range 17.5-60.6 years (elsewhere in the manuscript 17.5-60.2 years). Gender: 18 males (36%); 32 females (64%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Survivors had no history of hypertension, angina pectoris or congestive heart failure prior to cancer diagnosis. No information on other risk factors reported, except the following information for the 2 patients with clinical MI: Obese and diabetes in both, family history of CAD in female survivor. Controls: No	blocking techniques and field sizes. All mantle field and 7 (14%) also mediastinal boost. Mean cardiac dose 35.1Gy (range 18.5-47.5Gy). In patients with partial LV blocking (N=12/24%): mean cardiac dose 37.2Gy (range 25.8-45.6Gy) In patients with full LV blocking (N=38/76%): mean cardiac dose 34.4Gy (range 18.5-47.5Gy). Chemotherapy only: N=0 Irradiation only: N=33 (66%) Chemotherapy and irradiation: N=17 (34%) Stem cell transplant: N=0	N=0 signs and symptoms of cardiac disease at time of testing: *Exercise tolerance testing:* • partial LV blocking: 9/10 (90%) normal stress ECG and 1/10 nondiagnostic exaggeration of baseline repolarization changes (10%) • Full LV blocking: 23/29 (79%) normal stress ECG and 6/29 (21%) nondiagnostic result. In total: 32/39 (82%) normal stress ECG and 7/39 (18%) nondiagnostic result (elsewhere in the manuscript it was stated that only 38 patients underwent this test). *Myocardial perfusion scintigraphy:* N=2/38 (5.3%) mild stress-induced ischemia (N=3/38 (8%) borderline normal result) *Clinical MI after non-invasive testing:* N=2 (4%) • 29-year old female irradiated at age 21 years	exercise performance data, but it is unclear if treatment was included in the clinical data) Confounding: Not applicable Funding of the trial: Not reported *Possible overlap with King 1996.* *"The prognostic value of exercise testing with myocardial SPECT perfusion imaging for the determination of future cardiac events is related to the pretest likelihood of the adverse outcome event rather than the symptomatic status of patients per se. The occurrence of anginal quality chest pain with exercise testing alone has limited prognostic value. We performed routine quantitative myocardial perfusion imaging to assess the extent and severityof stress-induced myocardial hypoperfusion, a*

			with cardiac dose of 45Gy; 6 cycles of CVPP. Eight years after radiotherapy angina and transient rise in cardiac enzymes and ECG changes suggestive of inferior MI, coronary angiography showed 70% stenosis of left anterior descending artery and high-grade stenosis of an obtuse marginal artery/moderate hypokinesis anterior wall; 3 years after the event no angina or stress-induced ischemia on myocardial perfusion imaging. • 56-year old male treated at age 26 years with cardiac dose of 45.6Gy; died of massive MI 3 years after cardiac evaluation; necropsy confirmed MI. <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable	*pattern closely linked to morbid ischemia event outcomes in patients without known CAD but who are found to be in low, intermediate, and high-risk categories of the Duke treadmill scoring system that combines exercise duration, symptomatic status, and ECG response of patients during treadmill testing. Furthermore, the use of exercise electrocardiography with SPECT myocardial perfusion imaging successfully identifies risk of future coronary events in a high-risk asymptomatic population of siblings of patients who have experienced morbid cardiac events."* *"While SPECT is a relatively sensitive and specific test to detect significant CAD, subcritical coronary lesions with luminal reductions of <50% may exist in our relatively young patient population and would not be expected to create clinically significant alteration of myocardial perfusion."*

			Results of univariable analyses: Not applicable	

Who needs surveillance?				
Galper SL et al. Clinically significant cardiac disease in patients with Hodgkin lymphoma treated with mediastinal irradiation. Blood 2011; 117(2): 412-8.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center Treatment era: 1969-1998 Follow-up: Median 14.7 years after radiotherapy ended, interquartile range 8.1-21 years.	N=1279 cancer survivors Diagnosis: Hodgkin's lymphoma Age at diagnosis: Median 25 years, range 3-93 years Proportion <age 35 at diagnosis: Not reported (64.2% <29 years) Proportion <age 21 at diagnosis: Not reported (28.2% <20 years) Age at testing/follow-up: Not reported Gender: 685 males (53.6%); 594 females (46.4%) Cardiovascular risk factors (like dyslipidemia, hypertension,	Chemotherapy: N=499 (39%) Not all agents and cumulative doses reported, but N=233 (46.7%) received doxorubicin Irradiation: N=1279 (100%) mediastinal radiotherapy: Median dose 40Gy, range 15-53Gy (midmediastinal dose was used to estimate dose to the heart) Exact location of irradiation: • Mantle alone n=393 (30.7%) • Mantle and para-aortic: n=713 (55.7%)	Diagnostic test used for CAD assessment: Hospital and physicians records Timing of the diagnostic test: Not reported Outcome definitions: Clinically significant CAD: a history of documented MI, CABG, PTCA with or without stenting or stenosis >75% of the diameter of the vessel on coronary angiography. Occurrence of CAD: All patients had Hodgkin's lymphoma; N=107 (8.4%) median of 15.8 years after radiotherapy; cumulative incidence rates at 5, 10, 15, 20 and 25 years were 1.1%, 2.4%, 5.2%, 9.4% and 13.6% (adjusted for competing risk of death).	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Not reported *Possible overlap in study population with the Chen 2014 and Mauch 1995 studies.* *It is not mentioned how the follow-up was performed; it is*

	obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Matched general population (diagnosis and procedure incidence data from the National Hospital Discharge Survey from 1979 to 2003 were accessed to estimate baseline age and sex stratified national utilization rates which were applied to the year 2000 United States population standard from census data to establish expected age and sex stratified incidence rates)	• Total nodal irradiation: n=122 (9.5%) • Involved field: n=51 (4%) Chemotherapy only: N=0 Irradiation only: N=780 (61%) Chemotherapy and irradiation: N=499 (39%) Stem cell transplant: Not reported	N=76 MI (N=7 survivors had 2 MIs, making a total of 83 MIs) N=63 CABG and/or PTCA SIR for CABG: 3.19 (95% CI 2.83 to 3.55) AER for CABG: 18.24 per 10000 person years/average of 0.18% per year SIR for PTCA: 1.55 (95% CI 1.39 to 1.71) AER for PTCA: 19.29 per 10000 person years/average of 0.19% per year 27 females (25.2%); 80 males (74.8%) • N=48 aged below 30 years at cancer diagnosis (44.9%) • N=16 aged below 20 years at cancer diagnosis (14.9%) • N=82 radiotherapy only (76.6%) • N=25 radiotherapy and chemotherapy (23.4%)	*possible that events have been missed.*

			Median radiotherapy dose 40Gy • N=3 doxorubicin (2.8%) <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Gustavsson A et al. Late cardiac effects after mantle radiotherapy in patients with Hodgkin's disease. Ann Oncol 1990; 1(5): 355-63.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center in 25 patients; in 1 patient who died as a result of a MI it was retrospective single-center Treatment era: 1967-1977 Follow-up: Median 15 years, range 4-20 years from completed treatment to study (with the exception of 1 patient who died of a MI at 4 years	N=26 cancer survivors aged 45 years or less and alive at time of study; excluded if chemotherapy was received. Diagnosis: Hodgkin's lymphoma Age at diagnosis: Median 24 years, range 6-33 years at time of mantle radiotherapy Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 35% (9/26 patients) Age at testing/follow-up: Median 38 years, range 21-45 years Gender:	Chemotherapy: N=0 Irradiation: N=26 (100%) mantle radiotherapy (same technique): dose range 35-43Gy (mean 40Gy) in the center of the heart (at a point one-third of the AP-distance in the inferior mediastinum) Chemotherapy only: N=0 Irradiation only: N=26 (100%) Chemotherapy and irradiation: N=0 Stem cell transplant: N=0	Diagnostic test used for CAD assessment: Clinical examination and ECG (at rest and exercise) followed by myocardial perfusion scintigraphy with 201-thallium during exercise, autopsy. Timing of the diagnostic test: At least 10 years after completed treatment (except 1 patient; see follow-up in first column) Outcome definitions: • Symptomatic MI; not further specified • Infarction pattern at ECG at rest and vector ECG; not further specified • Pathological ST-depression (followed by triple balloon angioplasty) on exercise ECG test • Chest pain on exercise ECG test	Risk of bias: Selection bias: Unclear risk (study group consists of less than 75% (i.e. 65%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment (all patients received mediastinal radiotherapy, but dose in the non-participating survivors not reported)) Attrition bias: Low risk (for the different test used in this study the outcome was assessed for more than 75% of the study group (range 88-100%)) Detection bias: Unclear risk (no information on blinding of outcome assessors provided)

after therapy, all patients had a follow-up of at least 10 years).	17 males (65%); 9 females (35%) <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> TSH was assessed and elevated (4-12U, normal is 0.3-3.8U) in 13/25 patients (52%) including the 2 alive patients with CAD. Other cardiovascular risk factors were only reported for some of the patients (of which most had more than 1): • 2 hypertension (during pregnancies in 1 female with fatal MI and in 1 male without CAD) • 2 (subclinical) hypothyroidism (including 1 male with abnormal exercise ECG, 1 male with MI and 1 male without CAD) • 1 hypercholesterolemia (1 male with abnormal exercise ECG) • 2 former smoker (1 male with abnormal exercise ECG, 1 male with MI)		• Abnormal stress myocardial scintigraphy; not further specified <u>Occurrence of CAD:</u> All patients had Hodgkin's lymphoma; *In total*: N=3/26 (12%) (2 (8%) symptomatic and 1 (4%) asymptomatic); total radiotherapy dose to the heart: 41.5Gy, 40Gy and 37.5Gy N=2/26 (8%) <u>*symptomatic MI*</u>: • 36 year old female died as a result of a MI 4 years after therapy, MI was confirmed at autopsy (this patient is not included in the cardiac tests reported hereafter); • 39 year old male (elsewhere in the manuscript 44 years is reported) with repeated MIs and angioplasties 14+ years after therapy (no family history of CAD). N=1/23 (4%) <u>*infarction pattern at ECG at rest and vector ECG*</u> (this is the male patient with	<u>Confounding:</u> Not applicable <u>Funding of the trial:</u> John and Augusta Persson Foundation for Scientific Medical Research and the Swedish Medical Research Council grant, AB Procordia Nova grant

	• 1 positive family history for CAD (1 male with abnormal exercise ECG) <u>Controls:</u> No		the symptomatic MI) (in 2 patients data was incomplete at analysis) N= 1/24 (4%) (36 year old male) <u>*pathological ST-depression (followed by triple balloon angioplasty) on exercise ECG test*</u> (1 patient was not subjected to the test for safety reasons in view of an abnormal resting ECG, not reported which patient) N=0/24 (0%) <u>*chest pain on exercise ECG test*</u> (1 patient was not subjected to the test for safety reasons in view of an abnormal resting ECG, not reported which patient) N= 2/23 (9%) <u>*abnormal stress myocardial scintigraphy*</u>: • 1 patient showed ischemia (this is the patient with pathological ST depression and balloon angioplasty mentioned above) • 1 interpreted as a scar or infarction 9/23 (39%) normal test results and 12/23 (52%) ambiguous results (i.e. mainly uneven	

			isotope uptake of a mottled type without distinct uptake defects and not fulfilling the usual criteria for CAD or MI) (1 patient was not subjected to the test for safety reasons in view of an abnormal resting ECG, not reported which patient; 1 patient with repeated MIs also not included) <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Hancock SL et al. Cardiac disease following treatment of Hodgkin's disease in children and adolescents. J Clin Oncol 1993; 11(7): 1208-15.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center Treatment era: January 1961-April 1991 Follow-up: Mean 10.3 years (start point not reported)	N= 635 CAYA cancer survivors aged less than 21 years at initial treatment Diagnosis: Hodgkin's disease Age at diagnosis: Mean age at treatment 15.4 years (range 2-20 years) Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Not reported Gender: 351 males (55%); 284 females (45%)	Chemotherapy: N=402 (63%): • ABVD±MOPP or PAVe: N=76 (19%) • MOPP N=225 (56%) • PAVe N=57 (14%) • ABVD or MOPP/ABVD N=6 (2%) • Other N=38 (agents not reported) (9%) Doses not reported. Chemotherapy and age at treatment: 0-4 years: 100% 5-9 years: 76.8% 10-14 years: 68.7% 15-20 years: 58.9% Irradiation: N=629 (99%) of which: • N=578 (92%) mediastinal	Diagnostic test used for CAD assessment: Individual records, computerized database and if 2 years elapsed since last contact health questionnaire to patients or parents and patient's referring and follow-up physicians; records pertaining to cardiac diseases or death were requested from other facilities if necessary. Timing of the diagnostic test: Not reported Outcome definitions: Fatal MI; not further specified Non-fatal MI; not further specified Angina pectoris requiring revascularization Occurrence of CAD: All patients had Hodgkin's disease;	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete CAD follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (only univariable analyses available) Funding of the trial: Not reported *Possible overlap with Hancock 1993 JAMA.*

	<u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Not reported <u>Controls:</u> Matched general population (annualized mortality rates for acute MI specific for race, age and sex obtained from the US decennial life-tables for 1979 to 1981)	radiotherapy (N=566 mantle fields; N=12 exact radiotherapy not mentioned) • N=51 (8%) irradiation but not mediastinal (limited-field) Only mediastinal radiotherapy doses provided (71% of patients received doses of 40Gy or greater to the mediastinum): 0Gy (N=57 (9%)): • 0-4 years at treatment N=3 • 5-9 years at treatment N=15 • 10-14 years at treatment N=21 • 15-20 years at treatment N=18 ≤15Gy (N=27 (4%)): • 0-4 years at treatment N=2 • 5-9 years at treatment N=6 • 10-14 years at treatment N=13	*<u>Fatal MI:</u>* N=7 (1.1%) (RR 41.5 (95% CI 18.1 to 82.1); AR 10.4 (excess cases per 10000 person years): • N=6 mediastinal radiotherapy only • N=1 both mediastinal radiotherapy and chemotherapy • N=1 survivor aged 10-14 years at treatment (>30 Gy and ≤44 Gy mediastinal dose) • N=6 survivors aged 15-20 years at treatment (N=4 >30 Gy and ≤44 Gy mediastinal dose and N=2 >44Gy mediastinal dose) Fatal MI occurred 6 to 22 years after therapy; average 14 years. *<u>Non-fatal MI:</u>* N=3 (0.5%) following mediastinal radiation doses of 44 to 45.1Gy at a mean interval from radiation of 12 years (range 6.2-19.8 years); N=2 (67%) patients required surgical intervention.	

		• 15-20 years at treatment N=6 >15 and ≤30Gy (N=69 (11%)): • 0-4 years at treatment N=4 • 5-9 years at treatment N=13 • 10-14 years at treatment N=38 • 15-20 years at treatment N=14 >30 and ≤44Gy (N=371 (58%)): • 0-4 years at treatment N=0 (0%) • 5-9 years at treatment N=21 (6%) • 10-14 years at treatment N=62 (17%) • 15-20 years at treatment N=288 (77%) >44Gy (N=111 (17%)): • 0-4 years at treatment N=0	Risk of fatal or non-fatal acute MI is 8.1% at 22 years after therapy. All fatal and non-fatal MI in patients treated with 42 to 45Gy to the mediastinum. *<u>Angina pectoris requiring revascularization:</u>* N=1 (0.2%) after mediastinal radiation dose of 44Gy. <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> For fatal MI: Gender: • Males: RR 35.6 (95% CI 13 to 79.1); AR 13.6 • Females: RR 70.4 (95% CI 11.7 to 233; AR 6.6 Treatment: • Radiation alone: RR 52.2 (95% CI 21.1 to 109); AR 18.7; P=0.6	

		• 5-9 years at treatment N=1 • 10-14 years at treatment N=13 • 15-20 years at treatment N=97 <u>Chemotherapy only:</u> N=6 (1%) <u>Irradiation only:</u> N=233 (37%) <u>Chemotherapy and irradiation:</u> N=396 (62%) <u>Stem cell transplant:</u> Not reported	• Chemotherapy plus radiation: RR 21.1 (95% CI 0 to 104.4); AR not reported; P=0.6 • No mediastinal radiation: - Treatment era: • More than 30 Gy to the mediastinum before 1971: RR 40 (95% CI 13 to 97) • More than 30 Gy to the mediastinum after 1971: RR 53 (95% CI 13 to 145) Years after Hodgkin's disease: • 0-4: - • 5-9: RR 111.1 (95% CI 18.4-367); AR 10.4 • 10-14: RR 25.4 (95% CI 0-125); AR not reported • 15-19: 50.6 (95% CI 12.6-138); AR 53.5 • ≥20: RR 23 (95% CI 0-114); AR not reported There are no clear trends in the latency of risk for death from acute MI with risk increasing within 10 years of irradiation and persisted throughout more than 20 years of follow-up.	

Who needs surveillance?				
Hancock SL et al. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 1993; 270(16): 1949-55.				
Study design Treatment era Follow-up	**Participants**	**Treatment**	**Diagnostic test Main outcomes**	**Additional remarks**
Study design: Retrospective single-center Treatment era: Not reported for the subgroup (but for the total study cohort: November 1960-December 1990) Follow-up: Not reported for the subgroup (but for the total study cohort: averaged 9.5 years; starting point not reported)	N= 1341 CAYA cancer survivors aged less than 30 years at treatment (which is a subgroup of the total study cohort presented in this study) Diagnosis: Hodgkin's lymphoma Age at diagnosis: • <10 years at treatment: n=65 (4.8%) • 10-19 years at treatment: n=479 (35.7%) • 20-29 years at treatment: n=797 (59.4%) Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: Not reported , but n=544 (40.6%) younger than 20 years at treatment	Chemotherapy: N=795 (59.3%) • <10 years at treatment: n=51 (78.5%) • 10-19 years at treatment: n=291 (60.8%) • 20-29 years at treatment: n=453 (56.8%) Agents and cumulative dose not reported Irradiation: Not reported for all locations, but mediastinal irradiation N=1237 (92.2%) • <10 years at treatment: n=47 (72.3%) • 10-19 years at treatment: n=442 (92.3%)	Diagnostic test used for CAD assessment: Letters and brief health questionnaires to patients and physicians. Autopsy reports and records pertaining to cardiac diseases or death. Timing of the diagnostic test: Not reported Outcome definitions: Death due to acute MI; not further specified Occurrence of CAD: All patients had Hodgkin's lymphoma; N=14 (1%) (ratio of observed to expected number of cases 52.4 (95% CI 0-259)): • N=0 (0%) < 10 years at treatment • N=6 (42.9%) 10-19 years at treatment	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (only univariable analyses available) Funding of the trial: In part by a National Institutes of Health grant *Possible overlap with Hancock 1993 JCO.*

	Age at testing/follow-up: Not reported Gender: Not reported Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Matched general population (annualized mortality rates for acute MI specific for race, age and gender obtained from the US Decennial Life Tables for 1979 to 1981)	• 20-29 years at treatment: n=748 (93.9%) 0-15 Gy n=43 (3.5%): • <10 years at treatment: n=8 • 10-19 years at treatment: n=18 • 20-29 years at treatment: n=17 >15-30 Gy n=83 (6.7%): • <10 years at treatment: n=17 • 10-19 years at treatment: n=51 • 20-29 years at treatment: n=15 >30-44 Gy n=863 (69.8%): • <10 years at treatment: n=21 • 10-19 years at treatment: n=294 • 20-29 years at treatment: n=548 >44 Gy N=248 (20.0%): • <10 years at treatment: n=1	• N=8 (57.1%) 20-29 years at treatment In 89 patients treated with radiation alone before 17 years of age: N=2 (ratio of observed to expected number of cases 214 (95% CI 36-709)) In 192 children (age not specified) treated with combined therapy: N=0 Risk factors assessed: Yes Results of multivariable analyses: Not applicable Results of univariable analyses: Effect of age at irradiation: <20 years: • Ratio of observed to expected number of cases 44.1 (95% CI 17.8-91.8) • AR 11.3 20-29 years: • Ratio of observed to expected number of cases 7.3 (95% CI 3.4-13.8) • AR 9.0	

		• 10-19 years at treatment: n=79 • 20-29 years at treatment: n=168 <u>Chemotherapy only:</u> Not reported <u>Irradiation only:</u> Not reported for all eligible patients; 89 (6.6%) patients treated with radiation alone before 17 years of age (mediastinal dose averaged 44.6 (±0.2) Gy). <u>Chemotherapy and irradiation:</u> Not reported for all eligible patients; 192 (14.3%) children (aged not defined) treated with combined therapy (mean mediastinal dose 32.9 (±0.9) Gy) <u>Stem cell transplant:</u> Not reported	Effect of time since radiation: < 10 years after radiation vs 10 years or more after radiation: • Irradiated < 20 years of age: Ratio of observed to expected number of cases 52 vs 41 • Irradiated from 20-29 years of age: Ratio of observed to expected number of cases 10.2 vs 5.4	

Who needs surveillance?				
Hull MC et al. Valvular dysfunction and carotid, subclavian, and coronary artery disease in survivors of hodgkin lymphoma treated with radiation therapy. JAMA 2003; 290(21): 2831-7.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center Treatment era: 1962-1998 Follow-up: Median 11.2 years, range 2.1-36.3 years (starting point not reported).	N=415 cancer survivors with a minimum of 2 years follow-up treated with radiotherapy to fields including a portion of the heart, carotid or subclavian arteries Diagnosis: Hodgkin's lymphoma Age at diagnosis: Median 25 years, range 4-75 years Proportion <age 35 at diagnosis: Not reported (but more than 50%) Proportion <age 21 at diagnosis: Not reported Age at testing/follow-up: Not reported	Chemotherapy: N=257 (62%) Not all agents and cumulative doses reported, but at least N=90 chemotherapy regimens included doxorubicin Irradiation: N=415 (100%) radiotherapy to fields including a portion of the heart, carotid or subclavian arteries; N=404 (97%) received cardiac radiotherapy Median mid-mediastinal dose 33Gy, range 10-47 Gy; median low-cervical dose 36Gy, range 13-76 Gy (mid-mediastinal dose, located near the base of the heart, was	Diagnostic test used for CAD assessment: Hospital and physicians records and through direct contact with the majority of patients or their families. Timing of the diagnostic test: Not reported Outcome definitions: A history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy. Occurrence of CAD: All patients had Hodgkin's lymphoma; N=42/404 survivors in cardiac radiotherapy group (10.4%) Median time to CAD 9 years after radiotherapy, range 1-32 years.	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (for 404/415 survivors (97%) data on CAD are provided) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (follow-up not taken into account in multivariable analysis) Funding of the trial: Not reported

	Gender: 251 males (60%); 164 females (40%) (but elsewhere in the manuscript it is stated to be 253 (61%) and 162 (39%) respectively) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Hypertension N=59/384 survivors with data Diabetes N=21/389 survivors with data Hypercholesterolemia N=90/264 survivors with data (total cholesterol ≥200 mg/dL/5.19 mmol/L) Family history of CAD N=94/311 survivors with data (at least 1 first-degree relative) Tobacco N=163/371 survivors with data Controls: Matched general population (procedure incidence data from the National Hospital Discharge Survey from 1999 were accessed to estimate a baseline age and sex stratified national	used to estimate dose to the coronary arteries and valves; low-cervical dose was used to estimate the dose delivered to the carotid and subclavian arteries) Location of irradiation: • Mantle alone n=54 (13%) • Mantle and subdiaphragmatic fields: n=339 (81%) • Primarily subdiaphragmatic treating only the inferior portion of the heart: n=11 (3%) • Involved field: n=11 (3%) Chemotherapy only: N=0 Irradiation only: N=158 (38%) Chemotherapy and irradiation: N=257 (62%)	Mid-mediastinal dose median 35 Gy, range 25-42Gy (elsewhere in the manuscript 36 (25-42) is reported). Median age at cancer diagnosis 34 years, range 16-67 years. 30 men; 12 women. At least 1 cardiac risk factor was present in all patients who developed CAD. Actuarial incidence of CAD: 3% at 5 years 6% at 10 years 10% at 20 years OER for CABG: 2.42 (95% CI 1.11 to 3.74) OER for percutaneous coronary intervention: 0.86 (95% CI 0.04 to 1.37) OER for total procedures 1.63 (95% CI 0.98 to 2.28) Risk factors assessed: Yes Results of multivariable analyses: Cox multiple regression analyses; results final model: *Patient-related variables:*	

	utilization rate for percutaneous intervention and CABG which were applied to the 1999 US population estimate obtained from the SEER database to establish an expected incidence of these procedures)	<u>Stem cell transplant:</u> Not reported	• Hypertension: HR 3.0 (95% CI 1.6 to 5.8) P=0.002 • Hypercholesterolemia: HR 3.0 (95% CI 1.2 to 7.4) P=0.02 • Older than median age at radiation therapy: HR 8.1 (95% CI 3.2 to 20.3) P=<0.001 • Male sex: HR 2.9 (95% CI 1.4 to 6.0) P=0.01 *Treatment-related variables:* • Greater than median total radiation therapy dose: HR 0.8 (95% CI 0.4 to 1.7) P=0.57 • Alternate vs daily mantle field: HR 1.3 (95% CI 0.6 to 2.7) P=0.49 • Mantle or subdiaphragmatic field vs matched mantle and subdiaphragmatic fields: HR 7.8 (95% CI 1.1 to 53.2) P=0.04 (previous irradiation technique used before 1990 that resulted in a 50% or more increase in total dose over a small section of cardiac tissue	

			was associated with the development of CAD) • Chemotherapy: HR 0.7 (95% CI 0.4 to 1.5) P=0.41 <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
King V et al. Symptomatic coronary artery disease after mantle irradiation for Hodgkin's disease. Int J Radiat Oncol Biol Phys 1996; 36(4): 881-9.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort Treatment era: Not reported for the subgroup (but for the total study cohort: treated 1954-1989) Follow-up: At least 3 years without evidence of disease activity	N= 114 cancer survivors treated with mediastinal irradiation (minimal a 3 year follow-up interval without evidence of disease activity) aged less than 21 years at treatment (which is a subgroup of the total study cohort presented in this study) Diagnosis: Hodgkin's disease Age at diagnosis: Aged < 21 years at treatment Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Not reported	Chemotherapy: Not reported Irradiation: N=114 (100%) mantle irradiation (included all of the cardiac volume except a part of the left ventricle); dose not reported Chemotherapy only: N=0 Irradiation only: Not reported Chemotherapy and irradiation: Not reported Stem cell transplant: Not reported	Diagnostic test used for CAD assessment: • MI was documented by history, ECG and/or cardiac enzymes. • Fatal MI was documented by these same criteria, but assisted by previous cardiac history, physician's assessment, autopsy results, and case review by a cardiologist. • Angina was determined if described by the patient or diagnosed by their physician. • All available information concerning the status of the coronary arteries was obtained for patients reporting a cardiac event (cardiac catheterization data and autopsy data). Timing of the diagnostic test: Not reported	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Supported by grant NIHT32ES07271 *Possible overlap with Constine 1997.*

	Gender: 61 males (54%); 53 females (46%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported, but all survivors with CAD had at least 1 risk factor: Smoking, male sex, hypercholesterolemia, obese, positive family history, hypertension, diabetes Used definitions: • moderate to high cholesterol level ≥ 200 mg/dl • present or previous tobacco use • BMI at or above the sex-specific 85th percentile for the US • systolic BP≥140 or diastolic BP≥90 • diabetes by medical history Controls: Annualized mortality rates of the US population were used to		Outcome definitions: • Fatal MI • Non-fatal MI • Angina For all options: see information at diagnostic test above; not further specified. Occurrence of CAD: All patients had Hodgkin's disease; Overall: N=5 (4.4%) Average age at radiotherapy 17.4 years Average age at CAD 30 years Average interval radiotherapy-CAD 12.6 years Mean prescribed dose 44.16 Gy with the coronary vessels receiving a dose between 42.03 and 45.29 Gy. Fatal MI: N=2 (1.8%): OER 38.2 (95% CI 0-91.1) • 1 male (1.6%) OER 22.3 (95% CI 0-65.9): died at age 26; 40 Gy mantle radiotherapy at age 20 as well as CVPP; current	

	adjust for 5-year age, sex, and race-specific incidence rates obtained from the US Department of Health and Human Services		smoker, elevated cholesterol; autopsy: CAD. • 1 female (1.9%) OER 133.8 (95% CI 0-396.2): died at age 26; 46.81 Gy to the coronary arteries at age 19 as well as CVVP; obese, hypercholesterolemia, current smoker (for 10 years); autopsy: old and new MI and occlusion of coronary arteries. Non-fatal MI: N=2 (1.8%): • 1 male aged 10 years at 46.18 Gy to coronary arteries and aged 24 years at CAD event, no known risk factors • 1 approximately 21 years at 41.02 Gy to coronary arteries and approximately 30 years at CAD event. Angina: N=1 (0.9%); approximately 18 years at radiotherapy and approximately 45 years at CAD	

			event; 52.43 Gy to coronary arteries <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Küpeli S et al. Evaluation of coronary artery disease by computed tomography angiography in patients treated for childhood Hodgkin's lymphoma. J Clin Oncol 2010; 28(6): 1025-30.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center Treatment era: Not reported; study period January 2007-December 2008 Follow-up: Time from cancer diagnosis to CTA for the whole study group range 2-31 years.	N= 119 childhood and adolescent cancer survivors aged less than 18 years at diagnosis and being in remission at least 2 years after completion of treatment; excluded from study if: pregnant/breast feeding, allergy against contrast material, renal impairment or diabetes mellitus, serious cardiac arrhythmias; none of the participants had any complaints related to the cardiovascular system. Diagnosis: Hodgkin's lymphoma Age at diagnosis: Mean 8.3 years, median 7 years, range 2-18 years Proportion <age 35 at diagnosis: 100%	Chemotherapy: N=119 (100%) Not all agents and cumulative doses reported, but N=92 (77.3%) received doxorubicin (mean cumulative dose in CAD group 150 mg/$m^{2;}$ mean cumulative dose in non-CAD group 145 mg/m^2) Irradiation: N=110 (92.4%) Location and dose not reported with the exception of mediastinal radiotherapy: N=59 (49.6%) received mediastinal irradiation (in CAD group: median dose 27.5Gy, mean dose 27.4 Gy, range 19.8-40Gy; in non-CAD	Diagnostic test used for CAD assessment: CTA Timing of the diagnostic test: At least 2 years after completion of treatment. Outcome definitions: Abnormalities on CTA; not further specified. Occurrence of CAD: All patients had Hodgkin's lymphoma; N=19 (16%) 1/19 CAD patients required a stent implantation; the others are in medical follow-up. Time from cancer diagnosis to CTA mean 14.1 years, median 10 years, range 5-31 years. Risk factors assessed: Yes	Risk of bias: Selection bias: Unclear risk (study group consists of 88.1% of patients coming for routine controls to the outpatient clinic, but the complete original cohort is not reported so unclear if study group consisted of more than 75% of the original cohort or was a random sample with respect to the cancer treatment) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (univariable analysis and follow-up and gender not

	Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Mean and median 20 years, range 6-43 years Gender: 86 males (72.3%); 33 females (27.7%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Reported for dyslipidemia, hypertension, obesity, smoking (see at univariable analyses) Controls: No	group: median 20Gy, median 22.6Gy, range 18-40Gy) Chemotherapy only: N=9 (7.6%) Irradiation only: N=0 Chemotherapy and irradiation: N=110 (92.4%) Stem cell transplant: Not reported	Results of multivariable analyses: Logistic regression: • Lipid profile: risk 2.620 (95% CI 0.698 to 9.825); P=0.153 • Current age: risk 1.048 (95% CI 0.960 to 1.144); P=0.297 • Mediastinal radiotherapy dose (Gy): Dose: P=0.03 ≤20: risk 1.739 (95% CI 0.449 to 6.740); P=0.423 >20: risk 6.817 (95% CI 1.612 to 28.820); P=0.009 • Nodular sclerosing histopathologic subtype: risk 0.957 (95% CI 0.259 to 3.540); P=0.948 Results of univariable analyses: (CAD group; non-CAD group; *no effect measures reported*) • Male sex (84%; 70%) P=0.2 • Mean age at diagnosis (8.6 years; 8.3 years) P=0.77 • Mean current age (23.7 years; 19.3 years) P=0.009 • Advanced stage of disease (36.8%; 41%) P=0.73	taken into account in multivariable analysis) Funding of the trial: Not reported

			• Nodular sclerosing histopathologic subtype (26.2%; 22%) P=0.154 • Receiving doxorubicin (73.7%; 78%) P=0.68 • Mean cumulative doxorubicin dose (150 mg/m^2; 145 mg/m^2) P=0.93 • Receiving mediastinal radiation (73.7%; 45%) P=0.02 • Median dose of mediastinal irradiation (27.5Gy; 20Gy) P=0.003 • Hypertension under control with medical treatment (15% (elsewhere in the manuscript 10.5% is reported); 0%) P=0.02 • Obesity (BMI >28kg/m^2) (10.5%; 1%) P=0.07 • Abnormal lipid profile (26%; 12%) P=0.15 • Mean CKMB level (3; 3.1) P=0.88 • Troponin T-level for all (<0.01; <0.01) P=1.0 • Mean BNP level (14.1; 12.8) P=0.68	

			• Echocardiographic abnormality (53%; 47%) P=0.67 • Smoking (10.5%; 7%) P=0.63 • Positive family history (5.3%; 6%) P=0.9 • Mean time from diagnosis to CTA (14.1 years; 10 years) P=0.04	

Who needs surveillance?				
Mulrooney DA et al. Cardiac outcomes in adult survivors of childhood cancer exposed to cardiotoxic therapy: a cross-sectional Study. Ann Intern Med 2016; 164(2): 93-101.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center cohort (SJLIFE); cross sectional analysis. Treatment era: Not specifically reported, but range before 1983 until 2003. Follow-up: Median time from diagnosis 22.6 years (range 10-48 years)	N=1853 adult (≥18 years) survivors of childhood cancer previously exposed to cardiotoxic therapies (anthracyclines and cardiac-directed radiation therapy) who have survived ≥10 years after diagnosis of childhood cancer and who have completed the initial/baseline health evaluation. Diagnosis: Leukemia N=763 (41.2%) Hodgkin's lymphoma N=313 (16.9%) Non-Hodgkin's lymphoma N=169 (9.1%) Sarcoma N=260 (14%) Wilms' tumor N=133 (7.2%) Neuroblastoma N=84 (4.5%) CNS tumor N=79 (4.3%) Germ cell tumors N=11 (0.6%) Liver cancer N=7 (0.4%) Retinoblastoma N=6 (0.3%)	Chemotherapy: N=not reported for chemotherapy in general Anthracyclines: • None N=332 (17.9%) • <100 mg/m^2 N=488 (26.3%) • 100-249 mg/m^2 N=647 (34.9%) • ≥250 mg/m^2 N=386 (20.8%) Anthracycline doses were converted to doxorubicin isotoxic equivalents by summing doxorubicin, daunorubicin (×0.83), epirubicin (×0.67), idarubicin (×5), and mitoxantrone (×4) doses.	Diagnostic test used for CAD assessment: Health questionnaire and medical evaluation according to the Children's Oncology Group's Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Assessments included a history and physical examination, and ECG and resting echocardiography. Information on medical events during and after therapy from medical records. Timing of the diagnostic test: Time after cancer diagnosis: • 10-20 years: N=671 (36.2%) • 20-30 years: N=753 (40.6%) • >30 years: N=429 (23.2%)	Risk of bias: Selection bias: High risk (study group consists of less than 75% (i.e. 61%) of patients included in the original cohort and was not a random sample with respect to cancer treatment) Attrition bias: Low risk (the exact number of survivors who had a CAD outcome assessment is unclear, but on different locations in the manuscript it varied between 86 and 100%) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding:

	Carcinoma N=19 (1%) Other N=9 (0.5%) <u>Age at diagnosis:</u> Median 8 years (range 0-24 years) at diagnosis <u>Proportion <age 35 at diagnosis:</u> 100% <u>Proportion <age 21 at diagnosis:</u> Not reported (but N=1516 (81.8%) younger than 15 years) <u>Age at testing/follow-up:</u> Median 31 years (range 18-60 years) at the time of study. <u>Gender:</u> 969 (52.3%) males; 884 females (47.7%) <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Present at the time of SJLIFE assessment: BMI:	<u>Irradiation:</u> N=not reported for radiotherapy in general Cardiac radiation: • None N=1050 (56.7%) • ≤1500cGy N=366 (19.8%) • >1500cGy N=411 (22.2%) • Unknown N=26 (1.4%) Scatter dose to the heart was estimated for each case, regardless of radiation site and target volume. Other radiotherapy locations and doses not reported. <u>Chemotherapy only:</u> N=not reported <u>Irradiation only:</u> N=not reported <u>Chemotherapy and irradiation:</u>	<u>Outcome definitions:</u> Coronary artery disease defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG; not further specified. <u>Occurrence of CAD:</u> Detected before SJLIFE N=29 (1.6%) Detected at SJLIFE by cardiovascular screening N=40 (2.2%) Total prevalence N=69 (3.8%) Age at detection: • 18-29 years N=7/791 (0.9%) • 30-39 years N=24/701 (3.4%) • ≥40 years N=38/361 (10.5%) Most findings were asymptomatic; 4 survivors reported intermittent chest pain, unclear if these were patients diagnosed with CAD. Cancer diagnosis of CAD patients not reported.	Low risk (all important confounding factors have been taken into account) <u>Funding of the trial:</u> Supported by the American Lebanese-Syrian Associated Charities and the National Cancer Institute. *Possible overlap with Mulrooney 2014 and Hudson 1998.* *"Medical records were not routinely obtained for persons who did not report a cardiac event, which may have biased our estimates."* *"Only survivors with a history of cardiotoxic therapies were studied, which limited the ability to generalize these findings and may have resulted in missed cardiac disease in survivors with other exposure histories."* *The attrition regarding echocardiography may lead to underestimation of CAD. However, wall motion abnormalities may be*

	Normal/underweight (<25 kg/m^2): N=717 (38.7%) Overweight (25-29 kg/m^2): N=525 (28.3%) Obese (≥30 kg/m^2): N=611 (33%) Smoker: Former: N=217 (11.7%) (smoked at least 100 cigarettes in their lifetime but not within the past month) Current: N=439 (23.7%) (within the past month) Never: N=1197 (64.6%) Physical activity: Active (>450 MET/minutes week (=metabolic equivalent): N=934 (50.4%) Inactive (≤450 MET/ minutes week): N=919 (49.6%) Physical activity was assessed by asking participants if they participated in "usual weekly vigorous activities for at least 10 minutes at a time such as: running, aerobics, wheelchair basketball, heavy yard work, or anything else that caused large increases in breathing or heart rate; or moderate activities for	N=not reported <u>Stem cell transplant:</u> Not reported	<u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Multivariable logistic model; estimates adjusted for all variables in the table: Sex Female OR 1.0 Male OR 1.7 (95% CI 0.9-3.2) Age at diagnosis (years) 0-4 OR 0.5 (95% CI 0.2-1.3) 5-9 OR 0.8 (95% CI 0.3-1.9) 10-14 OR 0.4 (95% CI 0.2-1.1) ≥ 15 OR 1.0 Age at SJLIFE Evaluation (years) 18-29 OR 1.0 30-39 OR 1.8 (95% CI 0.7-4.7) ≥ 40 OR 3.1 (95% CI 1.2-8.2) Anthracycline (mg/m^2) None OR 1.0	*heterogeneous in patients with cardiomyopathy, resulting in overdiagnosis too. Rest ECG is not very sensitive for ischemia.*

	at least 10 minutes such as: brisk walking, bicycling, gardening, manual operation of a wheelchair, or anything else that caused small increases in breathing or heart rate". The frequency of exercise sessions per week was multiplied by the duration of each session and weighted by the standardized classification of the energy expenditure in metabolic equivalents expressed as metabolic equivalent minutes/week (inactive ≤450). Risky drinking: No N=1132 (61.1%) Yes N=721 (38.9%) (defined as alcohol consumption of 5 drinks or more on 1 occasion or 15 drinks or more per week for men and consumption of 4 drinks or more on 1 occasion or 8 drinks or more per week for women) Hypertension: No N=1421 (76.7%) Yes N=432 (23.3%) (defined as receiving an antihypertensive agent or having a systolic blood pressure of 140 mm Hg or		< 250 OR 2.0 (95% CI 0.9-4.6) ≥ 250 OR 2.0 (95% CI 0.7-5.4) Average cardiac radiation dose (cGy) None OR 1.0 ≤ 1500 OR 2.2 (95% CI 0.7-7.1) > 1500 OR 10.5 (95% CI 4.2-26.3) <u>Results of univariable analyses:</u> Not applicable	

	greater or diastolic blood pressure of 90 mm Hg or greater) Diabetes: No N=1727 (93.2%) Yes N=126 (6.8%) (defined as receiving an oral hypoglycemic agent or insulin for diabetes or having a fasting blood glucose level of 6.99 mmol/L or greater (≥126 mg/dL) or glycosylated hemoglobin level of 6.5% or greater) Dyslipidemia: No N=706 (38.1%) Yes N=1147 (61.9%) (defined as receiving treatment for a lipid abnormality or having a low-density lipoprotein cholesterol level of 4.14 mmol/L or greater (≥160 mg/dL), high-density lipoprotein cholesterol level less than 1.04 mmol/L (<40 mg/dL) in men or less than 1.30 mmol/L (<50 mg/dL) in women, or triglyceride level greater than 1.70 mmol/L (>150 mg/dL)) Physical fitness (6-minute walk test):			

	Normal (≥490 m) N=1387 (74.9%) Impaired (<490 m) N=427 (23%) Unknown N=39 (2.1%) <u>Controls:</u> No			

Who needs surveillance?				
Mulrooney DA et al. Coronary artery disease detected by coronary computed tomography angiography in adult survivors of childhood Hodgkin lymphoma. Cancer 2014; 120(22): 3536-44.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center: convenience sample of survivors participating in the cohort (SJLIFE) Treatment era: Not reported Follow-up: Median time from initial cancer diagnosis to time of evaluation 24 years, range 17-39 years.	N= 31 asymptomatic adult childhood cancer survivors who were ≥15 years past Hodgkin diagnosis, aged ≤55 years and had received radiotherapy alone or multimodal therapy (radiotherapy and chemotherapy). Excluded if they had an implanted medical device, irregular cardiac rhythm, or were allergic to CT contrast; were unable to hold their breath for CT imaging or walk on a treadmill; or were pregnant. In addition, participants with a history of congenital heart disease, congestive heart failure, myocardial infarction, or coronary artery revascularization (percutaneous or surgical) were not included. Diagnosis:	Chemotherapy: N=18 (58%) Median anthracycline dose 191 mg/m^2 (range, 96-316 mg/m^2). Type of anthracycline not reported; other agents and doses not reported. Irradiation: N=31 (100%) chest radiotherapy: • N=13 (42%) radiotherapy alone: ≥30Gy • N=18 (58%) multimodal treatment: N=2 (11%): ≥30Gy N=13 (72%): 20 to 29Gy N=3 (17%): <20Gy (elsewhere in the manuscript N=2 ≥3 Gy	Diagnostic test used for CAD assessment: CCTA Twelve-lead ECG Treadmill testing Timing of the diagnostic test: At least 15 years after cancer diagnosis. Outcome definitions: CAD (obstructive and non-obstructive) detected by CCTA in asymptomatic survivors: obstructive CAD defined as ≥50% occlusion of the left main coronary artery or ≥70% occlusion of the left anterior descending artery, left circumflex artery or right coronary artery. Twelve-lead ECG: tracings were considered positive for CAD if coded a high likelihood of Q-wave MI	Risk of bias: Selection bias: Unclear risk (original cohort not reported so unclear if study group consisted of more than 75% of the original cohort or was a random sample with respect to the cancer treatment) Attrition bias: Low risk (for the different tests used in this study the outcome was assessed for more than 75% of the study group (range 97-100%)) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial:

	Hodgkin's lymphoma <u>Age at diagnosis:</u> Range birth-19 years <u>Proportion <age 35 at diagnosis:</u> 100% <u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Median age at the time of evaluation 40 years, range 26-55 years. <u>Gender:</u> 12 males (39%); 19 females (61%) <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> • Overweight (BMI 25-29): N=18 (58%) • Obesity (BMI ≥30): N=5 (16%) • Diabetes mellitus: N=1 (3%)	and N=16 20-29Gy is mentioned) <u>Chemotherapy only:</u> N=0 <u>Irradiation only:</u> N=13 (42%) <u>Chemotherapy and irradiation:</u> N=18 (58%) <u>Stem cell transplant:</u> Not reported	(Q-wave MI with major Q waves or Q-wave MI with moderate Q waves with ST-T abnormalities), a moderate likelihood of Q-wave MI (possible Q-wave MI with moderate Q-waves without ST-T abnormalities or possible Q-wave MI with minor Q-waves with ST-T abnormalities), or isolated ischemic abnormalities (ST abnormalities without Q-waves or T-wave abnormalities without Q-waves). Treadmill testing: observation of a J-point depression ≥1 mm with a horizontal or downsloping ST segment was considered to be positive for CAD. <u>Occurrence of CAD:</u> All patients had Hodgkin's lymphoma; <u>*CAD on CCTA:*</u> N=12 (39%) (39 coronary artery lesions of which 4 obstructive lesions)/no resting wall motion abnormalities: N=3 obstructive:	Cancer Center Support (CORE) Grant and the American Lebanese Syrian Associated Charities. *Possible overlap with Mulrooney 2016 and Hudson 1998.* *In the method and result sections no control population was mentioned, but in the discussion it was stated that survivors in the current study had a significantly higher burden of CAD (39%) than what has been reported among the similarly aged general population (8.5-11%).* *"Both obstructive and nonobstructive plaques have been associated with future adverse cardiovascular events. Alternatively, a lack of coronary plaque on CCTA is associated with a low probability of a future event (negative likelihood ratio, 0.008;* *95% CI, 0.0004-0.17)."* *"Given initial concerns regarding maximally stressing*

	• Hypertension (BP ≥140/90 mm Hg and/or treatment with an antihypertensive): N=7 (23%) • Dyslipidemia (any abnormality on a fasting lipid panel (total cholesterol >200 mg/dL, low-density lipoprotein cholesterol >130 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, and triglycerides >150 mg/dL) and/or treatment with a lipid-lowering agent): N=15 (48%) • Current smoker: N=6 (19%) • Past smoker: N=7 (23%) • Never smoked: N=18 (58%) The majority of patients were considered to be at low risk based on National Cholesterol Education Program Adult Treatment Panel III risk scoring for asymptomatic adults; only 1 patient would have met recommendations for coronary artery calcium screening. <u>Controls:</u> No (see additional remarks)		all were treated with radiotherapy only (dose range 35-39Gy); they subsequently underwent conventional angiography with confirmation of disease in all 3. Only 1 patient reported a history of angina. Two patients underwent surgical revascularization, and 2 subsequently died of cardiovascular disease (1 with and 1 without revascularization). Age at CAD diagnosis: 40 to 53 years; 2 females and 1 male. N=9 non-obstructive: N=5 treated with radiotherapy only and N=4 with multimodal therapy (cumulative anthracycline dose range 136-170 mg/m^2); radiotherapy dose range 19.2-38.5Gy; coronary angiography revealed only non-obstructive disease, although review of the images revealed a small vessel with coronary spasm during the procedure, potentially confounding the findings; none of these	*at-risk survivors of Hodgkin lymphoma, the current study did not use a Bruce Treadmill Test Protocol, thus potentially limiting the overall yield from treadmill stress testing."*

			patients had clinically evident CAD. Age at CAD diagnosis: 37 to 55 years; 4 females and 5 males; all alive. <u>*Resting ECG abnormalities:*</u> N=9 (29%); N=3 in patients with obstructive lesions on CCTA, N=4 in patients with non-obstructive lesions on CCTA and N=2 in patients without CCTA abnormalities. <u>*Treadmill abnormalities:*</u> N=1/30 (3%) survivors (1 of the tests was invalid) (with obstructive lesion on CCTA) Median age of patients with CAD was 40 years. <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Mulrooney DA et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 2009; 339: b4606.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (CCSS) Treatment era: Date of diagnosis 1970-1986 Follow-up: Median time since cohort entry (at least 5 years after cancer diagnosis) to most recent questionnaire 13 years, range 0-27 years, mean 20 years.	N=14358 adult survivors of childhood and adolescent cancer who have survived at least 5 years after treatment/diagnosis for/of childhood cancer; aged <21 years at diagnosis. Diagnosis: Leukemia N=4830 (33.6%) Brain cancer N=1876 (13.1%) Hodgkin's lymphoma N=1927 (13.4%) Non-Hodgkin's lymphoma N=1081 (7.5%) Kidney tumor N=1256 (8.7%) Neuroblastoma N=954 (6.6%) Soft tissue sarcoma N=1245 (8.7%) Bone cancer N=1189 (8.3%) Age at diagnosis: Median 6 years, range 0-20 years at diagnosis	Chemotherapy: N=10099 (70.3%) of which: Anthracycline (N=1838 (12.8%) unknown or missing data): • No anthracycline N=7385 (51.4%) • <250 mg/m^2 N=1931 (13.4%) • ≥250 mg/m^2 N=2834 (19.7%) Anthracycline dose was determined by the sum of doxorubicin, daunorubicin, and three times the idarubicin dose. Bleomycin (N=1838 (12.8%) unknown or missing data): • No N=11818 (82.3%) • Yes N=756 (5.3%)	Diagnostic test used for CAD assessment: At study enrolment, data were collected by questionnaire on demographic characteristics, current height and weight, and health habits, as well as medical conditions and surgical procedures occurring since diagnosis. A parent, spouse, or closest next of kin was contacted for those survivors known to have died more than five years after diagnosis. A follow-up questionnaire was administered to confirm previously reported conditions and to add data on new first events (N=10367 (72.2%)). Survivors who reported a cardiac complication and were still alive or, when possible, proxy relatives for dead survivors, were contacted by telephone and asked a series	Risk of bias: Selection bias: Unclear risk (study group consists of less than 75% (i.e. 69.6%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment) Attrition bias: Low risk (for the follow-up questionnaire follow-up is 72.2%, but for the first questionnaire it is complete) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk for analysis with sibling controls (age not taken into account in multivariable analysis); low risk for other

	Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Age at most recent questionnaire median 27 years, range 8-51 years Gender: 7713 (53.7%) males; 6645 females (46.3%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Smoking status was recorded but no results were reported. Controls: 3899 nearest-age living siblings of a random sample of participating survivors.	Cisplatin (N=1838 (12.8%) unknown or missing data): • No N=11836 (82.4%) • Yes N=738 (5.1%) Cyclophosphamide (N=1838 (12.8%) unknown or missing data): • No N=6880 (47.9%) • Yes N=5694 (39.7%) Vincristine (N=1838 (12.8%) unknown or missing data): • No N=3543 (24.7%) • Yes N=9031 (62.9%) Other agents and doses not reported. Irradiation: N=8521 (59.3%) Cardiac radiation dose (N=1838 (12.8%)	of questions to document disease specifics. Medical record validation of self-reported cardiac events was determined to be unfeasible. Timing of the diagnostic test: At least 5 years after cancer diagnosis Outcome definitions: First MI occurring more than 5 years after cancer diagnosis for survivors and five or more years after birth for siblings were included in the analysis; not further specified. Occurrence of CAD: N=101 (0.7%) in survivors; N=6 (0.2%) in siblings Rate per 10000 person years 2.8 (95% CI 2.4 to 3.3); age adjusted and predicted at median survivors' age of 20 years; too few events for stable age adjusted rate estimation among siblings In survivors the median age of onset of MI was 30 years (range 11-44 years); in siblings	analysis (all important confounding factors have been taken into account) Funding of the trial: Supported by the National Institutes of Health, the American Lebanese-Syrian Associated Charities, the Children's Cancer Research Fund and the National Cancer Institute. *Possible overlap in study population of the different CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.* *"…. potential for surveillance bias, given that a proportion of the study population had been exposed to known cardiotoxic substances and thus may have been under greater medical monitoring. Such bias would overestimate the risk of adverse cardiac outcomes. Previous reports, however, have found a poor knowledge of and little appropriate screening for late effects of*

		unknown or missing data): • No cardiac radiation N=4160 (29%) • <500 cGy N=4897 (34.1%) • 500 to <1500 cGy N=832 (5.8%) • 1500 to <3500 cGy N=1398 (9.7%) • ≥3500 cGy N=988 (6.9%) Treatment information was merged with measurements of scatter dose in tissue equivalent phantoms to estimate dose to the heart in cGy for each individual, regardless of primary tumor site and target volume. Other radiotherapy locations and doses not reported. <u>Chemotherapy only:</u> N=3090 (21.4%) <u>Irradiation only:</u>	median 31 years (range 18-40 years) The cumulative incidence of reported adverse cardiac events increased with time from diagnosis. There was no plateau in this relation, with the possible exception of myocardial infarction. Cancer diagnosis of CAD patients not reported. <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Compared with sibling control groups; adjusted for gender, race, household income, education, and tobacco use. The analysis accounted for within-family correlations: • All diagnoses HR 5.0 (95% CI 2.3 to 10.4) P<0.001 • Leukemia HR 3.3 (95% CI 1.2 to 8.6) P=0.018 • Brain tumor HR 6.1 (95% CI 2.3 to 16.2) P<0.001	*treatment among survivors of childhood cancer."* *"The accuracy of self-reported cardiac outcomes reflects an area of potential concern. On the other hand, the validity of self-reported long term events among cancer survivors has been found to be generally high, with 83% sensitivity and 98% specificity for MI."*

		N=1512 (10.5%) <u>Chemotherapy and irradiation:</u> N=7009 (48.8%) <u>Stem cell transplant:</u> Not reported *N=909 (6.3%) no chemotherapy or radiation therapy (surgery)* *N=1838 missing or unknown treatment (12.8%)*	• Hodgkin's lymphoma HR 12.2 (95% CI 5.2 to 28.2) P<0.001 • Non-Hodgkin's lymphoma HR 2.9 (95% CI 0.9 to 9.6) P=0.085 • Kidney tumor unable to estimate • Neuroblastoma HR 11.1 (95% CI 3.3 to 36.9) P<0.001 • Sarcoma HR 3.6 (95% CI 1.2 to 11.0) P=0.026 • Bone cancer HR 4.2 (95% CI 1.5 to 11.8) P=0.007 Cox proportional hazards model with age as the time scale; adjusted for all variables in the table as well as race, household income, education, tobacco use: • Gender: Male HR 1.0 (reference group) Female HR 0.6 (95% CI 0.4 to 0.9) P=0.014 • Age at diagnosis: 0-4 years HR 1.0 (95% CI 0.4 to 3.0) P=0.96 5-9 years HR 1.9 (95% CI 0.9 to 4.0) P=0.090	

			10-14 years HR 0.8 (95% CI 0.4 to 1.5) P=0.49 15-20 years HR 1.0 (reference group) • Treatment era: 1970-4 HR 1.0 (reference group) 1975-9 HR 2.1 (95% CI 1.2 to 3.8) P=0.010 1980-6 HR 2.2 (95% CI 1.1 to 4.3) P=0.023 • Average cardiac radiation dose (Test for trend (P value)-all outcomes (<0.001)): No cardiac radiation HR 1.0 (reference group) <500 cGy HR 0.7 (95% CI 0.4 to 1.4) P=0.36 500 to <1500 cGy HR 0.6 (95% CI 0.1 to 2.5) P=0.45 1500 to <3500 cGy HR 2.4 (95% CI 1.2 to 4.9) P=0.011 ≥3500 cGy HR 3.6 (95% CI 1.9 to 6.9) P<0.001 • Chemotherapy: Anthracycline v none (Test for trend (P value)-(0.8)): <250 mg/m^2 HR 1.3 (95% CI 0.6 to 2.8) P=0.50	

			≥250 mg/m^2 HR 1.1 (95% 0.5 to 2.1) P=0.87 Cisplatin v none Not included in model Vincristine v none HR 0.7 (95% CI 0.4 to 1.1) P=0.081 Bleomycin v none Not included in model Cyclophosphamide v none Not included in model <u>Results of univariable analyses:</u> Not reported	

Who needs surveillance?				
Reinders JG et al. Ischemic heart disease after mantlefield irradiation for Hodgkin's disease in long-term follow-up. Radiother Oncol 1999; 51(1): 35-42				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center Treatment era: Not reported for the subgroup (but for the whole study group: 1965-1980) Follow-up: Not reported for the subgroup (but for the total study cohort: median 14.2 years, range 0.7-26.2 years; starting point not reported)	N= 145 cancer survivors treated initially with radiotherapy alone (at least a mantle field technique) and a complete response after radiotherapy aged less than 30 years at treatment (which is a subgroup of the total study cohort presented in this study) Diagnosis: Hodgkin's disease Age at diagnosis: < 30 years (the youngest patient was 5 years old at radiotherapy) Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 36%	Chemotherapy: N=not reported (but in the whole study group some patients were treated with chemotherapy because of a relapse, for example with MOPP, ABV(D) and/or COPP; doses and other agents not reported) Irradiation: All patients mantle field; cardiac apex was always outside the treatment field. Dose not reported (but in the whole study group mean total dose in the mediastinum inferior 37.2 Gy (SD 2.9); the cardiac dose was approximated by the doses applied to the midplane of the	Diagnostic test used for CAD assessment: Medical records; for those patients with symptoms mentioned in the records that could potentially be of cardiac origin, but which could not be diagnosed, the general practitioner and/or medical specialists were consulted. Timing of the diagnostic test: Not reported Outcome definitions: • Fatal ischemic cardiac disease; not further specified • Hospital admission for ischemic heart disease; not further specified Occurrence of CAD: All patients had Hodgkin's disease; *Fatal ischemic cardiac disease:*	Risk of bias: Selection bias: In the worst-case scenario all 42 missing survivors are aged less than 30 years at diagnosis: low risk (study group consists of more than 75% (i.e. 77.5%) of patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Not reported

	Age at testing/follow-up: Not reported Gender: Not reported Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Expected incidence based on gender, age and calender period-specific data for the Dutch population, i.e. hospital admission rates for ischemic heart disease (obtained from the S.I.G., Health Care Information), and incidence rates for ischemic myocardial and sudden death (obtained from the National Office for Statistics in The Netherlands).	inferior part of the mediastinum, that is, at the level of the 10th thoracic vertebra) Chemotherapy only: N=0 Irradiation only: Not reported Chemotherapy and irradiation: Not reported Stem cell transplant: Not reported	N=2 (1.4%) SMR 11.0 (95% CI 1.3 to 40.2) ER 86 per 100000 person years. *Hospital admission for ischemic heart disease:* N=7 (4.8%) Observed/expected ratio 4.0 (95% CI 1.6 to 8.2) ER 834 per 100000 person years (some patients were not counted as hospital admission for ischemic heart disease as they were for example already hospitalized for a noncardiac reason or died at home; N for subgroup not reported). Youngest age at occurrence of ischemic event was 24.5 years. Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	

Who needs surveillance?				
Schellong G et al. Late valvular and other cardiac diseases after different doses of mediastinal radiotherapy for Hodgkin disease in children and adolescents: report from the longitudinal GPOH follow-up project of the German-Austrian DAL-HD studies. Pediatr Blood Cancer 2010; 55(6): 1145-52.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Longitudinal multi-center follow-up study Treatment era: Not reported, but eligible survivors were included in studies that were run between 1978- 1995 Follow-up: Median 15.1 years, range 3.1-29.4 years from beginning of treatment.	N= 1132 childhood cancer survivors in continuous first complete remission without ever being treated for a secondary malignancy Diagnosis: Hodgkin's disease Age at diagnosis: Median 12.8 years, range 2.5 to 17.9 years Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Median age at last information 27.9 years, range 8.7-44 years.	Chemotherapy: N=1126 (99.5%): • N=547 (48.6%): OPPA or OPA or OEPA • N=579 (51.4%) also received: COPP or COMP All survivors received doxorubicin with a cumulative dose of 160 mg/m^2; other doses not reported. Irradiation: N=not reported (doses and locations other than mediastinal not reported): • N=834 radiation to whole or part of the mediastinum (median MedRD 25 Gy, range 8-50 Gy;	Diagnostic test used for CAD assessment: Cardiac examinations (ECG) were performed as part of the regular longitudinal follow-up surveillance of the survivors. Information came from pediatric oncology departments at pediatric age; follow-up data collected by mailing questionnaires to the individual patients at 3-year intervals and in addition contacting the involved physicians in case of health problems at adult age. Timing of the diagnostic test: Recommended cardiac follow-up included ECG at 2-3 year intervals for the first 10 years and at 3-5 year intervals thereafter. Outcome definitions:	Risk of bias: Selection bias: Unclear risk (original cohort not reported so unclear if study group consisted of more than 75% of the original cohort or was a random sample with respect to the cancer treatment) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Deutsche Leukämie-Forschungshilfe, Dachverband,

	Gender: 660 males (58%); 472 females (42%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: No	location: (reduced) involved field ± adjacent fields) • N=248 (22%) MedRD 36 Gy (range 33.6-50) • N=133 (12%) MedRD 30 Gy (range 27.7-32) • N=282 (25%) MedRD 25 Gy (range 23-27) • N=171 (15%) MedRD 20 Gy (range 8-22.1) • N=298 (26%) MedRD 0 Gy Chemotherapy only: Not reported Irradiation only: N=6 (5.3%) Chemotherapy and irradiation: Not reported Stem cell transplant: Not reported	CAD; not further specified. Occurrence of CAD: All patients had Hodgkin's disease; N=14 CAD (1.2%) including 8 MIs MedRD 36 Gy: N=10/258 (4%) MedRD 30 Gy: N=2/133 (1.5%) MedRD 25 Gy: N=1/282 (0.4%) MedRD 20 Gy: N=1/171 (0.6%) MedRD 0 Gy: N=0/298 (0%) Interval between cancer diagnosis and beginning of CAD was not reported but the minimal interval in all survivors with heart disease (including non-CAD diagnoses) was 3 years. Age at diagnosis CAD was not reported but the minimal age for all survivors with heart disease was 15 years. Risk factors assessed: No Results of multivariable analyses: Not applicable	Bonn and Kinderkrebshilfe, Muenster.

			Results of univariable analyses: Not applicable	

Who needs surveillance?				
Strumberg D et al. Evaluation of long-term toxicity in patients after cisplatin-based chemotherapy for non-seminomatous testicular cancer. Ann Oncol 2002; 13(2): 229-36.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center Treatment era: Not reported for the study population, but they were a sample of all patients treated between 1977-1981 Follow-up: Median 15 years, range 13-17 years (start point not reported)	N=32 cancer survivors being in complete remission for at least 12 months Diagnosis: Non-seminomatous testicular germ-cell cancer Age at diagnosis: Median age at time of chemotherapy 25 years (range 17-42 years) Proportion <age 35 at diagnosis: Not reported (but more than 50%) Proportion <age 21 at diagnosis: Not reported Age at testing/follow-up: Median 40 years, range 30-59 years	Chemotherapy: N=32 (100%): • Cisplatin: median cumulative dose 407 mg/m^2, range 45-1200 • Doxorubicin: median cumulative dose 227 mg/m^2, range 58-480 • Bleomycin: median cumulative dose 296 mg/m^2, range 74-457 • Vinblastine: median cumulative dose 59 mg/m^2, range 12-245 In case of no response or relapse (N not reported) also: • Etoposide: median cumulative dose 443 mg/m^2, range 116-1756	Diagnostic test used for CAD assessment: Medical history based on standardized questionnaire SCL-90-R including questions related to heart function and exercise ECG Timing of the diagnostic test: Not reported Outcome definitions: Silent myocardial ischemia; not further specified MI; not further specified Episodes of angina; not further specified Occurrence of CAD: All patients had non-seminomatous testicular germ-cell cancer; *Silent myocardial ischemia:* N=0	Risk of bias: Selection bias: Unclear risk (study group consists of less than 75% (i.e. 58%) of patients included in the original cohort and unclear if it was a random sample with respect to the cancer treatment) Attrition bias: Low risk (complete CAD follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Not reported

	Gender: 32 males (100%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): 25/31 analyzed survivors (81%) elevated total serum cholesterol levels >200 mg/dl 12/31 analyzed survivors (39%) elevated levels of triglycerides (>200 mg/dl) 1 survivor (not reported how many patients were analyzed) apolipoprotein A1 levels elevated (cutoff point as recommended by the American National Education Program) 4 survivors (not reported how many patients were analyzed, but presented as 15% so presumably 26 or 27) levels for HDL-cholesterol <30 mg/dl 15/31 analyzed survivors (48%) BMI >=25 (=considered overweight)	• Ifosfamide: median cumulative dose 16200 mg/m^2, range 3100-59500 Irradiation: N=8 (25%) after chemotherapy, location and dose not reported Chemotherapy only: N=24 (75%) Irradiation only: N=0 Chemotherapy and irradiation: N=8 (25%) Stem cell transplant: Not reported	*MI:* N=1 (3%) (11 years after chemotherapy at age 46 years; smoking history) *Episodes of angina:* N=0 None of the 31 survivors without an MI received regular cardiac medication. Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	

	8/32 survivors (25%) diastolic arterial hypertension (>95 mmHg), systolic pressure was not altered compared with pretreatment measurements Positive smoking history: 18/32 survivors (56%) Taken together: approximately half of the survivors presented an unfavorable cardiovascular risk profile. <u>Controls:</u> No			

Who needs surveillance?				
Van den Belt-Dusebout et al. Long-term risk of cardiovascular disease in 5-year survivors of testicular cancer. J Clin Oncol 2006; 24(3): 467-75.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort Treatment era: Not reported for the subgroup(but for the total study cohort: treated from 1965-1995) Follow-up: Not reported for the subgroup (but for the total study group range 5-38.4 years, median 18.4 years	N= 919 CAYA 5-year cancer survivors aged less than 30 years at diagnosis (which is a subgroup of the total study cohort presented in this study) Diagnosis: Testicular cancer: Seminoma N=204 (22.2%) Non-seminoma N=715 (77.8%) Age at diagnosis: Less than 30 years Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: Not reported Age at testing/follow-up: Not reported	Chemotherapy: Not reported for the subgroup, but in the total study cohort some patients were treated with chemotherapy including bleomycin, cisplatin, etoposide, vinblastine, ifosfamide, dactinomycin and/or carboplatin; doses not reported. Irradiation: Not reported for the subgroup but in the total study cohort some patients received radiotherapy (including PAO, ipsilateral iliac lymph nodes, supraclavicular, lung and/or mediastinal); doses not reported.	Diagnostic test used for CAD assessment: From medical records and through questionnaires to general practitioners and attending physicians; uncertain cardiovascular diagnoses were verified through the patient's cardiologist. Timing of the diagnostic test: At least 5 years from cancer diagnosis Outcome definitions: MI occurring at least 5 years from cancer diagnosis; not further specified. Occurrence of CAD: All patients had testicular cancer: N=4 seminoma and N=15 non-seminoma; MI N=19 (2.1%)	Risk of bias: Selection bias: In the worst-case scenario all 173 excluded survivors (because no CVD data could be obtained) are aged less than 30 years at diagnosis: low risk (study group consists of more than 75% (i.e. 84.2%) of patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial:

after cancer diagnosis)	Gender: 919 (100%) males Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Recent smoking was assessed, but no data for the subgroup available. Controls: The Netherlands male population using age-, sex-, and calendar period–specific incidence rates for the period from 1972 through 2000 from the Continuous Morbidity Registration Nijmegen from several Netherlands GP practices.	Chemotherapy only: Not reported Irradiation only: Not reported Chemotherapy and irradiation: Not reported Stem cell transplant: No *No chemotherapy or radiotherapy (surgery only) not reported for subgroup.*	SIR 1.37 (95% CI 0.83-2.15) AER 4.2 per 10000 patient years Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	Supported by the Lance Armstrong Foundation and the Dutch Cancer Society

Who needs surveillance?				
Adams MJ et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol 2004; 22(15): 3139-48.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center cohort Treatment era: Diagnosed between 1-1-1970 and 1-6-1991 Follow-up: Median time since diagnosis 14.3 years, range 5.9-27.5 years; mean 15.5 years after radiotherapy	N= 48 cancer survivors treated during childhood or young adulthood and ≥5 years since diagnosis and were ≥18 years at time of study. Exclusion criteria: pregnant or contemplating pregnancy in near future, unable to perform stress exercise testing or had cardiovascular disease before therapy for Hodgkin's disease. Diagnosis: Hodgkin's disease Age at diagnosis: Median 16.5 years, range 6.3-25 years at diagnosis Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis:	Chemotherapy: N=21 (43.8%) of which N=4 (8.3%) received an anthracycline (cumulative dose and type of anthracycline not reported) Other agents and doses not reported. Irradiation: N=48 (100%) mediastinal radiotherapy (mantle irradiation). Total mediastinal dose: median 40 Gy, range 27-51.7 Gy N=42 36-44 Gy (87.5%) N=2 < 36 Gy (4.2%) N=4 >44 Gy (8.3%) Chemotherapy only: N=0	Diagnostic test used for CAD assessment: Resting ECG 24 hour ECG (Holter monitor) Exercise stress test Timing of the diagnostic test: At least 5 years after cancer diagnosis Outcome definitions: Resting ECG: not further specified 24 hour ECG (Holter monitor): not further specified Exercise stress test: consistent pattern of ischemic changes (as the references relating to this statement were for children and the study population is adult the outcome definition is not clear) Occurrence of CAD:	Risk of bias: Selection bias: High risk (study group consists of less than 75% (i.e. 18%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment, which would make an unclear risk; however, as only an extremely small number of eligible patients has been included we decided to judge the risk of bias to be high) Attrition bias: Low risk (for the different test used in this study the outcome was assessed for more than 75% of the study group (range 87.5-97.9%)) Detection bias: Low risk (outcome assessors were blinded to patients' medical history)

	Not reported (but only 3 patients older than 22 years) Age at testing/follow-up: Median age at study visit 31.9 years, range 18.7 to 49.5 years Gender: 23 males (48%); 25 (52%) females Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Current or past cigarette smoking N=13 (27%) Current cigarette smoking (in last 4 weeks) N=7 (14.5%) Controls: No	Irradiation only: N=27 (56.3%) Chemotherapy and irradiation: N=21 (43.8%) Stem cell transplant: Not reported	All patients had Hodgkin's disease; Resting ECG: N=1 (2.1%) previously undiagnosed MI; no survivor had specific signs of current ischemia at rest (0%) (47 survivors completed the test). 24 hour ECG: N=1 previously undiagnosed MI (same patient as above with ECG); no survivor had specific signs of current ischemia at rest (0%) (42 survivors completed the test) Exercise stress test: N=1 (2.2%) ischemia (46 survivors underwent the test) Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	Confounding: Not applicable Funding of the trial: Supported by the United States Food and Drug Administration, National Institutes of Health and Wilmot Cancer Research Fellowship of the James P Wilmot Foundation. Note that the previously undiagnosed MI could have occurred during treatment. *This manuscripts seems to only present significant results of univariable analyses and no specific data for CAD are presented.*

Who needs surveillance?				
Aleman BM et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007; 109(5): 1878-86.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort Treatment era: 1965-1995 Follow-up: Median follow-up time was 18.7 years (starting point not reported, but presumably after cancer diagnosis).	N= 1486 5-year cancer survivors diagnosed before age 41 years Diagnosis: Hodgkin's lymphoma Age at diagnosis: Median 25.7 years at start of treatment Proportion <age 35 at diagnosis: Not reported (but N=235 (16%) older than 35 years at start of treatment) Proportion <age 21 at diagnosis: N=314 (21%) < 21 years at start of treatment Age at testing/follow-up: Attained age at end of follow-up ranged from less than 35 years to more than 55 years.	Chemotherapy: N=1065 (72.3%): • N=435 anthracyclines (40.8%) • N=559 no anthracyclines (52.5%) • N=71 unclear if anthracyclines (6.7%) • MOPP N=255 (23.9%) • ABVD N=38 (3.6%) • MOPP/ABV N=189 (17.7%) • Other combined chemotherapies N=496 (46.6%) (among those combinations, including MOPP (n = 167), MOPP/ABV (n = 51), ABVD (n =	Diagnostic test used for CAD assessment: Data were collected directly from the medical records, through general practitioners and attending physicians. Questionnaires on specific cardiovascular diagnoses and risk factors were sent to the patients' general practitioners and/or the patients' last known attending physicians in case the information could not be obtained from the medical record. When there was ambiguous information on cardiovascular diseases, additional information was requested from the patient's cardiologist. Patients were not routinely screened for CVDs. Timing of the diagnostic test:	Risk of bias: Selection bias: Unclear risk (original cohort not reported and unclear if random sample with regard to cancer treatment) Attrition bias: Low risk (the outcome was assessed for more than 75% of the study group (99%)) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (univariable analysis and follow-up and gender not taken into account in multivariable analysis) Funding of the trial:

	Gender: 790 males (54%); 684 females (46%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Smoking was scored positive when the patient was smoking at the end of follow-up or had stopped smoking less than 1 year before the end of follow-up. Hypertension, hypercholesterolemia, and diabetes mellitus were scored positive when stated in the medical information or when treated. Data from oncology records and general practitioners, not from screening on cardiovascular risk factors: • Smoking (no mutually exclusive categories): Recent N=253 (17.2%) Ever N=675 (45.8%) Never N=541 (36.7%) Unknown N=258 (17.5%)	73), and EBVP (n = 43)) • Unknown N=87 (8.2%) Cumulative doses of anthracyclines were not reported, but it is expected to be below 280 mg/m^2 because treatment for Hodgkin lymphoma in both study centers usually consisted of maximally 8 cycles of MOPP/ABV. Other agents and doses not reported. Irradiation: N=1400 (95%) • Radiotherapy mediastinum N=1241 (84.2%) • PAO or inverted Y with spleen N=410 (27.8%) (N=372 received radiotherapy to the mediastinum, PAO (or inverted Y), and spleen)	At least 5 years after cancer diagnosis Outcome definitions: Coronary heart disease: • MI (ICD-9 code 410) • Angina (ICD-9 code 413) Occurring at least 5 years after cancer diagnosis (patients who were diagnosed with MI or angina pectoris before cancer diagnosis or within 5 years after cancer diagnosis were excluded) Occurrence of CAD: All patients had Hodgkin's lymphoma; In 1474 survivors with CAD data: *Combined diagnostic group:* Coronary heart disease (ICD-9 code 410 and 413; allowing both diagnoses per person; 51 patients had both diagnoses): N=233 (15.8%); SIR 4.0 (95% CI 3.5-4.6); AER 87.0 per 10000 person years; median interval 20.2 years (range 5.0-37.2) Coronary heart disease (ICD-9 codes 410 and 413; acute MI	Supported by the Dutch Cancer Society. Data reported in this table are for 1474 patients (99%) with outcome assessment. *"Possibly hypertension did not increase CVD risk because patients with Hodgkin's lymphoma diagnosed with hypertension were adequately treated whereas the reference group of patients without known hypertension may include undiagnosed hypertension".*

	• Hypertension: Yes N=147 (10.0%) No N=1292 (87.7%) Unknown N=35 (2.4%) • Diabetes mellitus: Yes N=73 (5.0%) No N=1381 (93.7%) Unknown N=20 (1.4%) • Hypercholesterolemia: Yes N=126 (8.5%) No N=1316 (89.3%) Unknown N=32 (2.2%) <u>Controls:</u> The Netherlands population, using age-, sex-, and calendar period–specific incidence rates for the period from 1972 through 2000 from the Continuous Morbidity Registration Nijmegen from several Dutch GP practices.	• PAO or inverted Y without spleen N=280 (19.0%) (N=240 received radiotherapy to both the mediastinum and the PAO (or inverted Y) without radiotherapy to the spleen) • No mediastinal radiotherapy N=153 • Unknown N=6 N=1241 mediastinal radiotherapy: • N=1093 (88%) mantlefield • N=52 (4%) mediastinum only • N=64 (5%) mediastinum + axillary • N=32 (3%) mediastinum + cervical N=153 no mediastinal radiotherapy: • N=64 below diaphragm only	and angina pectoris combined allowing only 1 event per person); N=182 (12.3%); SIR 3.2 (95% CI 2.7-3.7); AER 61.7; median interval 20.2 years (5.0-37.2) <u>*Specific heart diseases:*</u> Acute MI (ICD-9 code 410) N=102 (6.9%) (84 men and 18 women); SIR 3.6 (95% CI 2.9-4.4); AER 35.7; median interval 19.5 years (range 7.0-37.5) Angina pectoris (ICD-9 code 413) N=134 (9.1%) (86 men and 48 women); SIR 4.1 (95% CI 3.5-4.9); AER 49.6; median interval 20.7 years (range 5.1-37.2) There were 22 fatal MIs (22%); MI was non-fatal in 78% of the cases. The overall 30-year cumulative incidence in mediastinally irradiated patients, using the competitive risk method, was 12.9% for MI.	

		• N=33 below and above diaphragm • N=56 above diaphragm only Detailed information on radiation doses was not collected, but patients usually received 40 Gy when they were treated with radiotherapy only and 30 to 36 Gy when they also received chemotherapy. <u>Chemotherapy only:</u> N=71 (4.8%) <u>Irradiation only:</u> N=406 (27.5%) <u>Chemotherapy and irradiation:</u> N=994 (67.4%): • 559 radiotherapy and no anthracyclines (56.2%) • 435 radiotherapy and anthracyclines (43.8%)	SIR (95%CI); AER per 10000 patients per year: <u>*Myocardial infarction:*</u> Sex: • Men 4.2 (3.4-5.2) 60.7 • Women 2.1 (1.2-3.3) 9.4 Age at start of treatment: • No older than 20 years 5.4 (2.4-10.3); 15.0 • 21-25 years 5.9 (3.8-8.7); 39.7 • 26-30 years 4.1 (2.6-6.2); 40.4 • 31-35 years 2.7 (1.8-4.1); 40.7 • 36-40 years 2.6 (1.6-4.0); 51.8 Attained age (age of patients at diagnosis of a given cardiovascular event or at the end of follow-up): • Younger than 40 years 4.4 (2.3-7.5); 9.7 • 40-49 years 4.0 (2.9-5.4); 47.4 • At least 50 years 3.1 (2.3-4.2); 93.0 Treatment (radiotherapy includes all irradiated patients (n =1400); 3 patients with incomplete treatment data were excluded):	

		<u>Stem cell transplant:</u> Not reported *N=3 treatment unknown (0.2%)*	• Initial radiotherapy only 3.9 (2.7-5.4); 49.9 • Radiotherapy + chemotherapy, no anthracyclines 3.9 (2.9-5.1); 66.0 • Radiotherapy + chemotherapy, anthracyclines 3.5 (1.9-5.9); 23.6 • Initial chemotherapy only 1.0 (0.1-3.5); 7.4 Anthracycline-containing Chemotherapy: • No 3.5 (2.6-4.6); 37.7 • Yes 3.3 (1.8-5.5); 23.5 Follow-up interval: • 5-9 years 1.7 (0.7-3.6); 4.3 • 10-14 years 4.4 (2.8-6.5); 33.9 • 15-19 years 4.0 (2.5-5.9); 46.4 • 20-24 years 4.7 (3.1-7.0); 84.0 • At least 25 years 2.9 (1.8-4.4); 69.2 <u>*Angina Pectoris:*</u> Sex: • Men 3.7 (3.0-4.6); 59.4 • Women 5.2 (3.8-6.9); 39.1 Age at start of treatment:	

			• No older than 20 years 11.6 (7.0-17.9); 37.2 • 21-25 years 6.2 (4.2-8.8); 48.1 • 26-30 years 4.8 (3.2-6.9); 58.6 • 31-35 years 2.6 (1.7-3.9); 43.5 • 36-40 years 2.9 (1.9-4.2); 70.2 Attained age (age of patients at diagnosis of a given cardiovascular event or at the end of follow-up): • Younger than 40 years 6.0 (3.5-9.6); 13.7 • 40-49 years 3.8 (2.8-5.0); 53.8 • At least 50 years 4.1 (3.2-5.2); 159.4 Treatment (radiotherapy includes all irradiated patients (n =1400); 3 patients with incomplete treatment data were excluded): • Initial radiotherapy only 5.2 (3.9-6.7); 66.8 • Radiotherapy + chemotherapy, no anthracyclines 3.8 (2.9-5.0); 47.0 • Radiotherapy + chemotherapy,	

			anthracyclines 4.5 (2.7-6.9); 39.9 • Initial chemotherapy only 0.8 (0.1-2.9); -4.6 Anthracycline-containing chemotherapy: • No 3.5 (2.7-4.5); 43.3 • Yes 4.2 (2.6-6.5); 37.1 Follow-up interval: • 5-9 years 2.6 (1.3-4.5); 10.7 • 10-14 years 3.3 (2.0-5.1); 26.8 • 15-19 years 3.5 (2.2-5.1); 46.0 • 20-24 years 4.6 (3.1-6.5); 96.7 • At least 25 years 6.0 (4.4-8.0); 207.7 <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Multivariable Cox model analyses; treatment factors were adjusted for age at diagnosis, cardiovascular disease risk factors and recent smoking.	

			Model 1, no. of events MI 102: *Treatment, HR (95% CI):* • Mediastinal radiotherapy (yes vs no) 2.42 (1.12-5.24) • Anthracycline-containing chemotherapy (yes vs no) 0.90 (0.50-1.62) *Cardiovascular risk factors, HR (95% CI)* (patients were not screened for cardiovascular risk factors; data from medical records and general practitioners): • Recent smoking (yes vs no/unknown) 2.04 (1.29-3.23) • Hypertension (yes vs no/unknown) 0.52 (0.29-0.94) • Hypercholesterolemia (yes vs no/unknown) 4.12 (2.68-6.33) • Diabetes mellitus (yes vs no/unknown) 1.44 (0.73-2.83) *Model 1, AP no. of events 129* *Treatment, HR (95% CI):* • Mediastinal radiotherapy 4.85 (1.97-11.9)	

			• Anthracycline-containing chemotherapy (yes vs no) 1.49 (0.89-2.49) *Cardiovascular risk factors, HR (95% CI)* (patients were not screened for cardiovascular risk factors; data from medical records and general practitioners): • Recent smoking (yes vs no/unknown) 1.35 (0.85-2.16) • Hypertension (yes vs no/unknown) 0.90 (0.58-1.42) • Hypercholesterolemia (yes vs no/unknown) 4.55 (3.10-6.68) • Diabetes mellitus (yes vs no/unknown) 2.43 (1.45-4.09) *Model 2, MI no. of events 95 Treatment group, HR (95% CI)* (patients without mediastinal radiotherapy were excluded N=233; different number than presented elsewhere in the manuscript): • Mediastinal radiotherapy 1.00 • Mediastinal radiotherapy + chemotherapy, no	

			anthracyclines (N=283; different number than presented elsewhere in the manuscript) 1.17 (0.75-1.83) • Mediastinal radiotherapy + chemotherapy, anthracyclines (N=288; different number than presented elsewhere in the manuscript) 1.00 (0.52-1.94) *Model 2, AP no. of events 124 Treatment group, HR (95% CI)* (patients without mediastinal radiotherapy were excluded N=233; different number than presented elsewhere in the manuscript): • Mediastinal radiotherapy 1.00 • Mediastinal radiotherapy + chemotherapy, no anthracyclines (N=283; different number than presented elsewhere in the manuscript) 0.78 (0.53-1.15) • Mediastinal radiotherapy + chemotherapy, anthracyclines (N=288; different number than	

			presented elsewhere in the manuscript) 1.32 (0.76-2.30) <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Armstrong GT et al. Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study. J Clin Oncol 2009; 27(14): 2328-38.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
<u>Study design:</u> Retrospective multi-center cohort (CCSS) <u>Treatment era:</u> Diagnosed 1970-1986 <u>Follow-up:</u> More than 20 years of mean follow-up; range 5-34 years after diagnosis.	N= 20483 5-year (after diagnosis) survivors of childhood cancer <u>Diagnosis:</u> • Leukemia N=6755 (33%) • CNS tumors N=2821 (14%) • Non-Hodgkin's lymphoma N=1524 (7%) • Hodgkin's disease N=2717 (13%) • Kidney tumors N=1735 (8%) • Neuroblastoma N=1358 (7%) • Soft tissue sarcoma N=1838 (9%) • Bone tumors N=1735 (8%) <u>Age at diagnosis:</u> • 0-4 years: N=8181 (40%) • 5-9 years: N=4600 (22%) • 10-14 years: N=4142 (20%) • 15-20 years: N=3560 (17%) <u>Proportion <age 35 at diagnosis:</u>	<u>Chemotherapy:</u> No numbers of survivors provided. Anthracyclines: range 0-401+mg/m^2 Epipodophyllotoxin: range 0-4109+mg/m^2 Bleomycin: range 0-119+ mg/m^2 Alkylating agent score: range 0-5+ Other agents and doses not reported. <u>Irradiation:</u> No number of survivors provided, but radiotherapy was part of some treatments. Doses and locations not reported <u>Chemotherapy only:</u> Not reported	<u>Diagnostic test used for CAD assessment:</u> Names of all patients eligible for participation in the CCSS were included in a search for deaths using the NDI from 1979 to 2002. The NDI uses the ICD-9. For deaths that predated the NDI (i.e. 1975 to 1978), death certificates from states where deaths occurred were requested. Cause of death was determined from information provided by the NDI in addition to the information provided on death certificates. This was augmented by knowledge of the original cancer diagnosis as well as telephone interviews with parents of deceased CCSS participants. <u>Timing of the diagnostic test:</u> Not reported	<u>Risk of bias:</u> <u>Selection bias:</u> Unclear risk (original cohort not reported and unclear if random sample with regard to cancer treatment) <u>Attrition bias:</u> Low risk (complete follow-up) <u>Detection bias:</u> Unclear risk (no information on blinding of outcome assessors provided) <u>Confounding:</u> Not applicable <u>Funding of the trial:</u> Supported by the American Lebanese-Syrian Associated Charities and the National Cancer Institute *Possible overlap in study population of the different*

	100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Not reported Gender: 11322 males (55%); 9161 (45%) females Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Not for CAD	Irradiation only: Not reported Chemotherapy and irradiation: Not reported Stem cell transplant: Not reported *Not reported if all patients received chemotherapy and/or radiotherapy.*	Outcome definitions: Fatal ischemic heart disease (ICD-9 code 410-414) Occurrence of CAD: Cancer diagnosis of CAD patients not reported; N=44 (0.2 %): N=32 in males (73%) N=12 in females (27%) Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	*CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.*

Who needs surveillance?				
Castellino SM et al. Morbidity and mortality in long-term survivors of Hodgkin lymphoma: a report from the Childhood Cancer Survivor Study. Blood 2011; 117(6): 1806-16.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
<u>Study design:</u> Retrospective-prospective multi-center cohort (CCSS) <u>Treatment era:</u> Diagnosis 1970-1986 <u>Follow-up:</u> For N=1927 (CAD grade 3-5 analysis) median follow-up 23.8 years from diagnosis, range 16-33 years for those alive and median 16.1 years from	N= 2633 childhood cancer survivors who survived at least 5 years after diagnosis; aged < 21 years at diagnosis for the mortality analysis; N=1927 for the CAD grade 3-5 analysis. <u>Diagnosis:</u> Hodgkin's lymphoma <u>Age at diagnosis:</u> For N=1927 (CAD grade 3-5 analysis): median 14 years at diagnosis, range 2-20 years For N=2633 (mortality analysis): 0-9 years: N=476 (18%) 10-14 years: N=884 (34%) 15-21 years: N=1273 (48%) <u>Proportion <age 35 at diagnosis:</u> 100%	*Treatment data are reported for the 1927 survivors from the CAD grade 3-5 analysis.* <u>Chemotherapy:</u> N=1122 (58%); of N=1117 anthracycline status reported: N=689 no anthracycline N=428 anthracycline (but elsewhere in the manuscript it is reported N=1237 no anthracyclines, N=387 anthracyclines and N=303 missing data). N=781 received alkylating agents (N=606 no alkylating agents; N=540 missing data). Doses and other agents not reported.	<u>Diagnostic test used for CAD assessment:</u> The US NDI (followed up with a death certificate request); self-report questionnaires administered to the survivors or parent proxy (for subjects who had died or were ≤ 18 years of age). Questionnaires included questions on CAD diagnosed by a physician; subjects were asked to provide an age at first occurrence of the condition. <u>Timing of the diagnostic test:</u> At least 5 years after diagnosis <u>Outcome definitions:</u> Fatal ischemic heart disease CTCAEv3 grade 3-5 CAD (MI; angina or coronary heart	<u>Risk of bias:</u> <u>Selection bias:</u> Low risk for mortality analysis (study group consists of all eligible patients included in the original cohort); unclear risk for CAD grade 3-5 analysis (study group consists of less than 75% (i.e. 70.3%) of patients included in the original cohort; unclear if it was a random sample with respect to cancer treatment) <u>Attrition bias:</u> Low risk for mortality analysis (outcome assessed for more than 75% of the study group (98.3%)); low risk for CAD grade 3-5 analysis (outcome assessed for all eligible patients) <u>Detection bias:</u>

diagnosis, range 5-31.5 years for those deceased. For N=2633 (mortality analysis) not reported but at least 5 years from diagnosis.	<u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Not reported <u>Gender:</u> For N=2633 (mortality analysis): 1507 males (57%); 1126 females (43%) For N=1927 (CAD grade 3-5 analysis): 1049 (54%) males; 878 females (46%) <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Not reported <u>Controls:</u> For the mortality analysis: US resident cohort; an age, sex, and calendar year matched general population, based on US mortality rates from the National Center for Health Statistics.	<u>Irradiation:</u> N=1572 (82%) • Supradiaphragmatic, < 30 Gy N=156 • Supradiaphragmatic, ≥ 30 Gy N=406 • Infradiaphragmatic + supradiaphragmatic, < 30 Gy N=147; includes 49 patients with infradiaphragmatic sites only • Infradiaphragmatic + supradiaphragmatic, ≥ 30 Gy N=790; includes 49 patients with infradiaphragmatic sites only • Missing N=330 *(These numbers don't add up to 1572 irradiated patients).* <u>Chemotherapy only:</u> N=98 (5%) <u>Irradiation only:</u>	disease on anti–angina medication or requiring cardiac catheterization, angioplasty, or CABG). Events dated before cohort entry were included as prevalent at 5 years from diagnosis. <u>Occurrence of CAD:</u> All patients had Hodgkin's lymphoma; Fatal ischemic heart disease: N=37/2589 for whom cause of death available (1.4%) EAR 7.6 (95% CI 5.2-10.7) per 10000 person years SMR 16.5 (95% CI 11.6-22.8) By years after diagnosis: N=4 5-9 years after diagnosis (percentage not clear as N with available data not reported); EAR 3.1 (95% CI 0.8-7.9) N=20 10-19 years after diagnosis (percentage not clear as N with available data not reported); EAR 8.5 (95% CI 5.1-13.3) N=13 ≥20 years after diagnosis (percentage not clear as N	Unclear risk (no information on blinding of outcome assessors provided) <u>Confounding:</u> Not applicable <u>Funding of the trial:</u> Supported by National Institutes of Health and the American Lebanese-Syrian Associated Charities. *Possible overlap in study population of the different CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.*

		N=548 (28%) <u>Chemotherapy and irradiation:</u> N=1024 (53%) <u>Stem cell transplant:</u> Not reported *Treatment group data missing for N=257 (14%)*	with available data not reported); EAR 11.4 (95% CI 5.4-20.5) Grade 3-5 CAD: N=39 (2%) CAD requiring medication N=24 (1.2%) MI <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Fidler MM et al. Population-Based Long-Term Cardiac-Specific Mortality Among 34 489 Five-Year Survivors of Childhood Cancer in Great Britain. Circulation 2017; 135(10):951-963.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Population-based retrospective cohort (British Childhood Cancer Survivor Study) Treatment era: Diagnosed from 1940 to 2006 Follow-up: Mean follow-up from 5-year survival 18 years (range 0-68.7 years); mean 23 years from diagnosis	N=34489 5-year childhood cancer survivors. Diagnosis: CNS (excluding PNET) N=6970 (20.2%) CNS PNET N=1198 (3.5%) Leukemia (excluding AML) N=9493 (27.5%) AML N=981 (2.8%) Hodgkin lymphoma N=2234 (6.5%) Non-Hodgkin lymphoma N=1549 (4.5%) Neuroblastoma N=1535 (4.4%) Non-heritable retinoblastoma N=1006 (2.9%) Heritable retinoblastoma N=750 (2.2%) Wilms tumor N=1388 (4%) Bone sarcoma N=1195 (3.5%) Soft tissue sarcoma N=2147 (6.2%) Other N=3043 (8.8%) Not mentioned N=1000 (2.9%)	Chemotherapy: Not reported Irradiation: Not reported Chemotherapy only: Not reported Irradiation only: Not reported Chemotherapy and irradiation: Not reported Stem cell transplant: Not reported	Diagnostic test used for CAD assessment: Ascertainment of each survivor's vital status by collaboration with the Health and Social Care Information Center (England and Wales) and National Health Service Central Register (Scotland). For each death, an attempt was made to obtain the death certificate and underlying cause of death as coded by the Office of National Statistics (England and Wales) and National Records of Scotland (Scotland). Timing of the diagnostic test: Follow-up for cardiac mortality began at 5-year survival. Outcome definitions: Ischemic heart disease mortality (according to ICD-5	Risk of bias: Selection bias: Low risk (study group consists of almost all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (treatment not taken into account) Funding of the trial: Supported by Cancer Research UK; PanCareSurFup, European 7th Framework Programme, Medical Research Council, British Heart Foundation.

	<u>Age at diagnosis:</u> Mean 6.6 years; all <15 years <u>Proportion <age 35 at diagnosis:</u> 100% <u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Mean 29.6 years (range 5.5-85.6) <u>Gender:</u> 18939 (55%) males; 15550 (45%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Not reported <u>Controls:</u> Expected numbers were calculated by multiplying the person-years within each sex-, age- (quinquennial), and calendar year- (single year) specific stratum by the		to ICD-10, depending on calendar year of death) <u>Occurrence of CAD:</u> N=96 (0.28%) ischemic heart disease deaths. *Overall:* SMR 2.5 (95% CI 2-3.1); AER 0.9 (95% CI 0.6-1.2) *Sex:* • Male SMR 2.2 (95% CI 1.7-2.8); AER 1.1 (95% CI 0.7-1.6); EMR 1 (reference) • Female SMR 4.0 (95% CI 2.6-5.8); AER 0.7 (95% CI 0.3-1.0); EMR 0.7 (0.4-1.3) *First primary neoplasm type:* • CNS (excluding PNET) SMR 1.9 (95% CI 1.2-3.0); AER 0.8 (95% CI 0.1-1.5); EMR 1 (reference) • CNS PNET SMR 3.7 (95% CI 1.0-9.5); AER 1.6 (95% CI −0.5-3.7); EMR 1.7 (95% CI 0.3-12.5) • Leukemia (excluding AML) SMR 1.4 (95% CI 0.3-4.0); AER 0.1 (95% CI −0.2-0.3); EMR 0.2 (95% CI 0.0-4.4)	*Possible overlap with Feijen 2020* *"….. possible limitation of this study is that our classification of cardiac death relied on the underlying cause of death as listed on the death certificate, which has been previously shown to have imperfect accuracy. Although there is possible misclassification, it is more likely that we have underascertained cardiac deaths and thus underestimated the risk of cardiac death among childhood cancer survivors because these individuals are more likely to be coded as having a neoplastic-related death resulting from their previous medical history"*

	corresponding mortality rate for the population of England and Wales and then summing across the strata.		• AML SMR 4.3 (95% CI 0.1-24.0); AER 0.6 (95% CI −0.9-2.1); EMR 2.3 (95% CI 0.2-23.5) • Hodgkin lymphoma SMR 4.4 (95% CI 2.7-6.8); AER 3.6 (95% CI 1.6-5.7); EMR 3.6 (95% CI 1.3-9.8) • Non-Hodgkin lymphoma SMR 2.6 (95% CI 1.1-5.1); AER 1.6 (95% CI −0.2-3.4); EMR 2.1 (95% CI 0.6-7.1) • Neuroblastoma SMR 0.9 (95% CI 0.0-4.8); AER −0.1 (95% CI −0.7-0.6); EMR 0.5 (95% CI 0.0-9.1) • Non-heritable retinoblastoma SMR 0.9 (95% CI 0.1-3.4); AER −0.0 (95% CI −1.1-1.0); EMR 0.5 (95% CI 0.0-5.0) • Heritable retinoblastoma SMR 2.9 (95% CI 0.8-7.4); AER 1.3 (95% CI −0.6-3.2); EMR 1.5 (95% CI 0.2-9.9) • Wilms tumor SMR 5.3 (95% CI 2.7-9.5); AER 1.7 (95% CI 0.5-3.0); EMR 2.8 (95% CI 0.8-9.5) • Bone sarcoma SMR 2.1 (95% CI 0.7-4.9); AER 1.2 (95% CI −0.8-3.2); EMR 0.9 (95% CI 0.1-8.6)	

			• Soft tissue sarcoma SMR 1.9 (95% CI 0.8-4.0); AER 0.8 (95% CI −0.4-2.0); EMR 0.9 (95% CI 0.2-4.5) • Other SMR 2.6 (95% CI 1.2-4.8); AER 1.1 (95% CI −0.0-2.2); EMR 1.2 (95% CI 0.3-4.6) *Age at diagnosis:* • 0-4 years SMR 2.6 (95% CI 1.7-3.9); AER 0.6 (95% CI 0.2-0.9); EMR 1 (reference) • 5-9 years SMR 2.6 (95% CI 1.7-3.9); AER 0.9 (95% CI 0.3-1.5); EMR 1.0 (95% CI 0.4-2.8) • 10-14 years SMR 2.4 (95% CI 1.8-3.2); AER 1.6 (95% CI 0.8-2.4); EMR 1.0 (95% CI 0.3-2.7) Ptrend SMR 0.5110; AER/EMR 0.8914 *Treatment era:* • <1970 SMR 2.2 (95% CI 1.7-2.8); AER 2.4 (95% CI 1.3-3.6); EMR 1 (reference) • 1970-1979 SMR 3.6 (95% CI 2.4-5.4); AER 1.2 (95%	

			CI 0.5-1.8); EMR 1.0 (95% CI 0.4-2.2) • 1980-1989 SMR 2.9 (95% CI 1.1-6.2); AER 0.3 (95% CI −0.1-0.6); EMR 0.3 (95% CI 0.1-1.4) • 1990-2006 SMR 7.1 (95% CI 1.5-20.6); AER 0.1 (95% CI −0.0-0.3); EMR 0.4 (95% CI 0.1-2.0) Ptrend SMR 0.9171; AER/EMR 0.1098 *Attained age:* • 5-19 years SMR 8.0 (95% CI 0.2-44.6); AER 0.0 (95% CI −0.0-0.1); EMR 1 (reference) • 20-29 years SMR 10.0 (95% CI 5.2-17.5); AER 0.6 (95% CI 0.2-0.9); EMR 11.4 (95% CI 1.3-102.2) • 30-39 years SMR 3.4 (95% CI 2.0-5.3); AER 1.2 (95% CI 0.4-1.9); EMR 19.8 (95% CI 2.2-182.6) • 40-49 years SMR 2.0 (95% CI 1.3-2.9); AER 2.3 (95% CI 0.4-4.1); EMR 30.1 (95% CI 3.0-298.5) • 50-59 years SMR 2.0 (95% CI 1.3-3.0); AER 7.2 (95%	

			CI 1.6-12.7); EMR 93.2 (95% CI 9.1-949.8) • 60+ years SMR 2.3 (95% CI 1.3-3.8); AER 22.2 (95% CI 3.2-41.1); EMR 267.5 (95% CI 23.9-2992.9) Ptrend SMR 0.0344; AER/EMR <0.0001 (EMRs, and all P values were estimated with a multivariable Poisson regression model adjusted for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age) The cumulative mortality of ischemic heart disease increased steadily until ≈45 years of follow-up, at which point there was a steeper increase, ultimately reaching 3.8% at 65 years of follow-up since diagnosis (1.0% higher than expected). Causes of death other than cardiac disease were treated as competing risks. <u>Risk factors assessed:</u> Yes	

			<u>Results of multivariable analyses:</u> Multivariable Poisson regression model adjusted for sex, first primary neoplasm type, age at cancer diagnosis, treatment era and attained age (RR; 95% CI): *Sex:* • Male 1 (reference) • Female 1.9 (1.2-3.0) *First primary neoplasm type:* • CNS (excluding PNET) 1 (reference) • CNS PNET 1.9 (0.6-5.5) • Leukemia (excluding AML) 0.4 (0.1-1.5) • AML 1.7 (0.2-12.6) • Hodgkin lymphoma 2.4 (1.3-4.5) • Non-Hodgkin lymphoma 1.4 (0.6-3.3) • Neuroblastoma 0.4 (0.1-3.2) • Non-heritable retinoblastoma 0.5 (0.1-2.1) • Heritable retinoblastoma 1.4 (0.4-4.5) • Wilms tumor 2.2 (1.0-5.1)	

			• Bone sarcoma 1.1 (0.4-3.0) • Soft tissue sarcoma 1.0 (0.4-2.4) • Other 1.2 (0.6-2.6) *Age at diagnosis:* • 0-4 years 1 (reference) • 5-9 years 0.9 (0.5-1.8) • 10-14 years 0.8 (0.4-1.6) Ptrend 0.5110 *Treatment era:* • <1970 1 (reference) • 1970-1979 1.5 (0.9-2.6) • 1980-1989 0.8 (0.3-2.0) • 1990-2006 1.0 (0.3-3.8) Ptrend 0.9171 *Attained age:* • 5-19 years 1 (reference) • 20-29 years 1.3 (0.2-10.0) • 30-39 years 0.4 (0-3.1) • 40-49 years 0.2 (0-1.8) • 50-59 years 0.2 (0-2.0) • 60+ years 0.3 (0-2.6) Ptrend 0.0344 <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Green DM et al. Cancer and cardiac mortality among 15-year survivors of cancer diagnosed during childhood or adolescence. J Clin Oncol 1999; 17(10): 3207-15.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort Treatment era: Diagnosed 1960-1989 Follow-up: Median 23.39 years after diagnosis, mean 24.13±6.13 years, range 15.04 to 38.54 years.	N= 474 15-year (after diagnosis) survivors of childhood and adolescent cancer; included if previously untreated. Diagnosis: • ALL N=99 (21%) • Non-Hodgkin's lymphoma N=46 (10%) • Hodgkin's disease N=104 (22%) • Osteosarcoma N=26 (5%) • Neuroblastoma N=7 (2%) • CNS tumor N=26 (5%) • Other N=166 (35%) Age at diagnosis: Mean age at diagnosis 10.86±6.10 years Proportion <age 35 at diagnosis: 100%	Chemotherapy: N=352 (74%): N=221 (47%) alkylating agents N=79 (17%) doxorubicin Doses and other agents not reported Irradiation: N=270 (57%) Doses and locations not reported Chemotherapy only: N=153 (32%) Irradiation only: N=71 (15%) Chemotherapy and irradiation: N=199 (42%) Stem cell transplant: Not reported	Diagnostic test used for CAD assessment: Cause of death was determined from review of hospital records if death occurred at the study hospital; records were requested and obtained for all deaths that did not occur at the study hospital. Timing of the diagnostic test: Not reported Outcome definitions: Fatal acute MI (coded using ICD-9) Occurrence of CAD: N=3 (0.6%) All males (aged ≥10 years at cancer diagnosis); 2 of them received mediastinal radiotherapy (67%) (21Gy and 20.5Gy); CAD occurred 20.9 to	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Supported in part by Developmental Funds Award from the Roswell park Alliance Foundation and by the Cancer Research Education Training Program, National Cancer

	Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Mean age at follow-up 35±8.48 years Gender: 265 males (56%); 209 (44%) females Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Not for CAD	*N=51 no radiotherapy and/or chemotherapy (surgery only) (11%)*	27.6 years after cancer diagnosis. Cancer diagnosis of CAD patients not reported. Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	Institute, National Institutes of Health.

Who needs surveillance?				
Haddy N et al. Cardiac Diseases Following Childhood Cancer Treatment: Cohort Study. Circulation 2016;133(1):31-8.				
Study design Treatment era Follow-up	**Participants**	**Treatment**	**Diagnostic test Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (Euro2K, French patients only) Treatment era: Initial treatment between 1942 and 1985 Follow-up: Median 26 years (25th to 75th percentile 18-32) from first cancer diagnosis.	N=3162 5-year (after diagnosis) survivors of childhood cancer. Diagnosis: Nephroblastoma N=642 (20.3%) Neuroblastoma N=427 (13.5%) Hodgkin's disease N=218 (6.9%) Non-Hodgkin lymphoma N=342 (10.8%) Sarcoma N=599 (18.9%) CNS tumor N=447 (14.1%) Other N=487 (15.4%) Leukemia N=0 (0%) Age at diagnosis: Not reported Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis:	Chemotherapy: • Anthracyclines (=doxorubicin, daunorubicin, epirubicin): ○ No N=2165 (68.5%) ○ Yes N=997 (31.5%) All bolus infusions. Dose (mg/m^2): ○ None N=2165 (68.5%) ○ 1-250 N=297 (9.4%) ○ 250-360 N=302 (9.6%) ○ 360+ N=398 (12.6%) • Alkylating agents (=cyclophosphamide, procarbazine, lomustine, caryolysine,	Diagnostic test used for CAD assessment: CAD was identified from multiple sources: as reported by the patient in self-questionnaires, from medical records, from long-term follow-up of cancer survivors, from reimbursement databases, and from the national database of causes of death. The general practitioner or the cardiologist of all patients alive who had reported CAD was invited to complete a questionnaire confirming the diagnosis, specifying the date of onset, whether the validation criteria were met, and which drug and interventional treatment was given. A copy of medical results was asked for when appropriate.	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Low risk (all important confounding factors have been taken into account) Funding of the trial: Supported by the Institut National for Cancer (INCA), the Ligue Nationale Contre le Cancer (Equipe Labellisée Ligue 2008), the Fondation

	100% Age at testing/follow-up: Median age 31 years Gender: Not reported Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: No	ifosfamide, dacarbazine, etoposide, carmustine, cisplatin, busulfan, melphalan, thiotepa): ○ No N=1606 (50.8%) ○ Yes N=1556 (49.2%) Dose (moles/m^2): ○ None N=1606 (50.8%) ○ <19 N=515 (16.3%) ○ <39 N=526 (16.6%) ○ 39+ N=515 (16.3%) • Vinca alkaloids (=vincristine, vinblastine, vindesine, teniposide): ○ No N=1301 (41.1%) ○ Yes N=1861 (58.9%) Dose (moles/m^2) ○ None N=1301 (41.1%)	Deceased patients were considered to have had a CAD if the cause of death was myocardial infarction (ICD-9: 410–412; ICD-10: I21–I25) or angina pectoris (ICD-9: 413; ICD-10: I20). Timing of the diagnostic test: At least 5 years after the childhood cancer diagnosis. Outcome definitions: CAD diagnosed at least 5 years after childhood cancer diagnosis using criteria of the European Society of Cardiology and/or from the Framingham and PRIME studies: • *Myocardial infarction:* Elevation of cardiac enzymes (troponin) associated with retrosternal pain radiating into the neck, jaw and/or upper limbs for more than 20 minutes and/or abnormal ST segment on the ECG leading to myocardial necrosis (q wave). • *Unstable angina:* Retrosternal pain radiating to the arm, neck, jaw,	Force, the Program Hospitalier de Recherche Clinique (PHRC), the Agence Française de Sécurité Sanitaire et Produit de Santé (AFSSAPS), Electricité de France (EDF), the Pfizer Foundation for childhood and adolescent health, the PanCareSurFup Health FP7 (Contract N° 257505) and ProCardio Euratom FP7 (Contract N° 295823). *Possible overlap with Feijen 2020*

		○ <0.02 N=615 (19.4%) ○ <0.03 N=644 (20.4%) ○ >0.03 N=602 (19%) Chemotherapy combinations: • No or other drugs N=1.144 (36.2%) • Anthracycline alone N=1 (0.03%) • Alkylating agent alone N=106 (3.4%) • Vinca alkaloids alone N=356 (11.3%) • Anthracycline + Alkylating agent N=50 (1.6%) • Anthracycline + Vinca alkaloids N=105 (3.3%) • Alkylating agent + Vinca alkaloids N=559 (17.7%) • Anthracycline + Alkylating agent + Vinca alkaloids N=841 (26.6%) (Other=bleomycin, methotrexate, actinomycin-D,	intermittent (few minutes) or persisting for more than 20 minutes, and exacerbated by exercise and relieved by rest and/or by nitrates. Plus one of the following signs: - Abnormal ECG without necrosis - Elevation of cardiac enzymes • *Stable angina:* Pain with the three following characteristics: - In chest (tightness, irradiation possible in arms, neck, jaw, duration <10 minutes) - Caused by exertion or emotion - Relieved by rest and/or by nitrates Or pain with two of these three characteristics, associated with at least one of the four following signs: - Stenosis detected by angiography (> 50%) - Positive scintigraphy - Positive exercise testing - Modification of the resting ECG without necrosis	

		cytarabine, asparaginase, hydroxyurea, mercaptopurine, 6-thioguanine, carboplatin). <u>Irradiation:</u> N=2178 (68.9%) radiotherapy; mean dose radiation to the heart in all patients 7.5Gy (reconstructed). Doses and other radiotherapy locations not reported. <u>Chemotherapy only:</u> Not reported <u>Irradiation only:</u> Not reported <u>Chemotherapy and irradiation:</u> Not reported <u>Stem cell transplant:</u> Not reported	All confirmed CADs were graded according to the CTCAEv3: defined as grade 1 if asymptomatic, grade 2 if symptomatic but mild enough to remain untreated, and grade ≥3 if symptomatic and treated, life threatening, or having led to death. <u>Occurrence of CAD:</u> MI N=20 (0.6%); all grade ≥3 Angina N=12 (0.4%); N= 3 grade 1 or 2, N=9 grade ≥3 MI: Radiotherapy: N=19/20 (95%) Chemotherapy: N=16/20 (80%) Anthracyclines: N=4/20 (20%) Radiotherapy and anthracyclines: N=3/20 (15%) Angina: Radiotherapy: N=12/12 (100%) Chemotherapy: N=5/12 (42%) Anthracyclines: N=0/12 (0%) Radiotherapy and anthracyclines: 0/12 (0%)	

			The occurrence of CAD did not start at a younger age in patients treated with anthracycline than in other patients. <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Multivariable Cox proportional hazards regression model was used to evaluate the effects of the type of first cancer and of treatment on the risk of a first cardiac disease. Age at first cancer plus 5 years was used as the entry time and attained age as a timescale. Relative risk adjusted for age and year at diagnosis of cancer, gender, type of first cancer, chemotherapy and brachytherapy; N=29 grade ≥3 ischemic diseases (MI and angina combined): *Anthracycline no:* Cardiac radiation dose (Gy): • <1 (N=4): RR 1 (reference group)	

			• 1-15 (N=5): RR 1.8 (95% CI 0.5-7.0) • ≥15 (N=16): RR 6.3 (95% CI 1.8-21.3) *Anthracycline yes:* Cardiac radiation dose (Gy): • <1 (N=1): RR 0.8 (95% CI 0.07-8.0) • 1-15 (N=2): RR 6.4 (95% CI 1.0-39.6) • ≥15 (N=1): RR 2.3 (95% CI 0.2-22.6) <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Hudson MM et al. Increased mortality after successful treatment for Hodgkin's disease. J Clin Oncol 1998; 16(11): 3592-600.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center Treatment era: 1968-1990 Follow-up: Not reported for all 387 patients, but for the 316 survivors (82%) alive at April 1997 the median follow-up duration was 15.1 years from diagnosis, range 2.9 to 28.6 years	N=387 childhood cancer survivors Diagnosis: Hodgkin's disease Age at diagnosis: Median age at diagnosis 14.4 years; range 3-25.4 years Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: Not reported (but it was stated that only N=16 were >20 years at diagnosis) Age at testing/follow-up: Not reported Gender:	Chemotherapy: N=271 (70%): • N=55 (20%) CO±PP • N=131 (48%) COPP • N=85 (32%) COP(P)/ABVD Doses not reported. Irradiation: N=372 (96%) Exact location not reported, but N=109 (29%) involved field and N=263 (71%) extended field Dose: N=166 (45%) 35-44Gy N=206 (55%) 20Gy Chemotherapy only: N=15 (4%) Irradiation only: N=116 (30%)	Diagnostic test used for CAD assessment: Hospital records and if follow-up by local physician annual mail questionnaires; for patients who died at study hospital often included autopsy results available; for patients who died elsewhere death certificates were requested and cause of death verified with local physician or family, when available autopsy reports were also reviewed. Timing of the diagnostic test: Not reported Outcome definitions: Fatal MI; not further specified Occurrence of CAD: All patients had Hodgkin's disease;	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Supported in part by grants from the National Cancer Institute and by the American Lebanese Syrian Associated Charities.

(start point not reported).	222 males (57%); 165 females (43%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: No	Chemotherapy and irradiation: N=256 (66%) Stem cell transplant: Not reported	N=5 (1.3%) All male patients; age at diagnosis ranged from 4.6 to 17.4 years, age at MI from 24.4 to 41.7 years (median 34 years); all were treated with standard-dose extended field radiotherapy (35-37Gy), N=3 (60%) also received cyclophosphamide (median dose 16.7 g/m^2, range 15.3 to 19.7 g/m^2), vincristine and procarbazine (doses not reported); all MIs occurred at a median of 19.1 years (range 16.5 to 22.0 years) after diagnosis. Autopsy results in 2 patients showed severe coronary artery atherosclerosis. Risk factors assessed: No Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	*Possible overlap with Mulrooney 2016 and Mulrooney 2014.*

Who needs surveillance?				
Machann W et al. Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease. Int J Radiat Oncol Biol Phys 2011; 79(4): 1117-23.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Prospective single-center Treatment era: Not reported for the study population, but they were a sample of all patients treated 1978-1985 Follow-up: Median 24 years between start of mediastinal radiotherapy and cardiac MRI, range 20-28 years	N=31 long-term cancer survivors alive at time of study; excluded if cardiac pacemaker, claustrophobia or concern of interference of metal clips with MRI Diagnosis: Hodgkin's disease Age at diagnosis: Median age at radiotherapy 21 years (range 6-41 years) Proportion <age 35 at diagnosis: Not reported (but more than 50%) Proportion <age 21 at diagnosis: Not reported (but at least 50%) Age at testing/follow-up: Median 45 years, range 29 to 67 years at invitation for MRI	Chemotherapy: N=14 (45%) of which N=8 anthracyclines (57%). Further information on agents and doses not reported. Irradiation: N=31 (100%) mediastinal radiotherapy: • N=15 anterior mantle field (48%) • N=16 anterior mantle field + boost (52%) Total dose midmediastinum median 40.3 Gy (range 19.5-52Gy) Chemotherapy only: N=0 Irradiation only:	Diagnostic test used for CAD assessment: Cardiac MRI under rest and stress (using adenosine) Timing of the diagnostic test: At least 20 years after start radiotherapy Outcome definitions: • MI defined as typically ischemic enhancement in left ventricular myocardium ranging from small subendocardial to large transmural infarctions. • Perfusion deficit at rest; not further specified • Perfusion deficit at stress; not further specified Occurrence of CAD: All patients had Hodgkin's disease; *MI*: N=8/31 (26%)	Risk of bias: Selection bias: Unclear risk (study group consists of less than 75% (i.e. 66%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment (no statistically significant differences in treatment modalities and radiation dose between participating and non-participating survivors, but chemotherapy doses not reported)) Attrition bias: Low risk (for the different test used in this study the outcome was assessed for more than 75% of the study group (range 81 to 100%)) Detection bias:

	Gender: 18 males (58%), 13 females (42%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): • Diabetes N=0 • Hyperlipoproteinemia N=8/31 (26%) • Hypertension N=3/31 (10%) • Current smokers N=5/31 (16%) • Previous smokers N=2/31 (6%) • Cerebrovascular disease N=3/31 (10%) • CAD N=3/31 (10%) • Previous stent/PTCA N=2/31 (6%) • Family history of cardiac disease N=15/31 (48%) No definitions of the risk factors were provided. Controls: No	N=17 (55%) Chemotherapy and irradiation: N=14 (45%) Stem cell transplant: Not reported	*Rest perfusion*: N=19/31 (61%) (but 1/31 patients aborted the ongoing examination because of claustrophobia) *Stress perfusion*: N=18/25 (72%) *Any perfusion deficit*: N=21/31 (68%) Risk factors assessed: Yes Results of multivariable analyses: Not applicable Results of univariable analyses: P<0.01 was considered significant to correct for multiple comparisons. • Survivors with perfusion deficit median 40.6 Gy and without perfusion deficit 40.3Gy: not different (P>=0.01) • Survivors with any late enhancement median 41.4 Gy and without late enhancement 40.3Gy: not different (P>=0.01)	Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (only univariable analyses available) Funding of the trial: Not reported *Ten percent of the survivors were already diagnosed with CAD at the time of the cardiac MRI.* *"… the yet missing validation of the high prevalence of perfusion deficits in our series using cardiac catheterization."*

			• No clear pattern of increased doses to any relevant cardiac structure for the different types and localizations (specific coronary arteries) of cardiac pathology emerged. The only significant difference (P<0.01) was observed between perfusion deficit right circumflex artery and minimum dose to the right ventricle, however the group with pathology had lower doses here.	

Who needs surveillance?				
Materazzo et al. Clinical and subclinical cardiac late effects in pediatric Hodgkin's lymphoma survivors. Tumori 2017; 103(6):566-571.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort Treatment era: October 1979-February 1989 Follow-up: N=83: median 25 years (range 21.6-31.2 years) after completing treatment; N=53: extensive cardiac assessment a mean 21 years after diagnosis	N=83 consecutive 5-year survivors; subgroup of N=53 (64%) unselected asymptomatic survivors Diagnosis: Hodgkin lymphoma Age at diagnosis: Median 12 (range 2-16) years at start of treatment Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Not reported for N=83; for N=53: median 32 (24-41) years at stress echocardiography Gender:	Chemotherapy: N=83 ABVD (100%), 3 or 6 cycles. Cumulative doxorubicin dose: In N=83: 150 mg/m^2 N=45 (54%) and 300 mg/m^2 N=38 (46%) In N=53 subgroup: 150 mg/m^2 N=31 (58%) and 300 mg/m^2 N=22 (42%) No doses for other chemotherapeutic agents reported. Irradiation: N=83 (100%) limited field radiotherapy. Radiotherapy field: Involved sites plus contiguous areas.	Diagnostic test used for CAD assessment: During routine follow-up a specialist cardiac assessment was conducted at the discretion of the pediatric oncologist. For patients living far away and those who could not undergo or failed any routine tests detailed clinical information was collected by contacting them directly by phone or through their primary care physician. Cardiac assessment in subgroup: physical examination, ECG, resting and post-exercise echocardiograms (exercise: symptom-limited effort on a cycle ergometer according to modified Bruce protocol; ECG measured at each stage of the protocol). Timing of the diagnostic test:	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) for the clinical assessment; unclear risk for the cardiac assessment in the asymptomatic subgroup (study group consists of less than 75% (i.e. 64%) of patients included in the original cohort and it is unclear if it is a random sample with respect to cancer treatment) Attrition bias: Low risk (for both the complete cohort and the subgroup the outcome was assessed for all participants) Detection bias: Unclear risk (no information on blinding of outcome assessors provided)

	N=83: 58 (70%) males; 25 (30%) females N=53: 41 (77%) males; 12 (23%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Not reported <u>Controls:</u> No	• Involved sites: 35 Gy (if partial remission after 3 ABVD cycles; number of survivors not reported) or 30 Gy (if complete remission after 3 ABVD cycles; number of survivors not reported) • Contiguous areas: 25 Gy N=74 (89%) mediastinal radiotherapy. Other radiotherapy locations not reported. <u>Chemotherapy only:</u> N=0 <u>Irradiation only:</u> N=0 <u>Chemotherapy and irradiation:</u> N=83 (100%) <u>Stem cell transplant:</u> No	Not reported for N=83; for subgroup N=53 mean 21 years after diagnosis <u>Outcome definitions:</u> CTCAEv3.0 grade 3 or higher <u>Occurrence of CAD:</u> Acute MI: N=4/83 (5%) (all in males; 20-23 years after therapy; age at acute MI 32-37 years; all 300 mg/m^2 doxorubicin) Stable angina: N=1/83 (1%) (male; 22 years since therapy; age at angina 22 years; 150 mg/m^2 doxorubicin) None of the 53 asymptomatic survivors showed cardiac symptoms or significant ECG abnormalities during or after the stress echocardiogram. <u>Risk factors assessed:</u> No <u>Results of multivariable analyses:</u> Not applicable <u>Results of univariable analyses:</u>	<u>Confounding:</u> Not applicable <u>Funding of the trial:</u> No *Possible overlap with Feijen 2020*

			Not applicable	

Who needs surveillance?				
Mauch PM et al. Long-term survival in Hodgkin's disease relative impact of mortality, second tumors, infection, and cardiovascular disease. Cancer J Sci Am 1995; 1(1): 33-42.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Multi-center (likely retrospective) Treatment era: Patients were seen between April 1969-December 1988 Follow-up: Median follow-up for survivors 11 years (person years of observation) (started at the end of treatment)	N= 794 cancer survivors Diagnosis: Hodgkin's disease Age at diagnosis: Median age at treatment 24 years, range 3 to 69 years). Proportion <age 35 at diagnosis: Not reported (but more than 50%) Proportion <age 21 at diagnosis: Not reported (but N=153 (19%) aged ≤16 years at treatment) Age at testing/follow-up: Not reported Gender: 445 males (56%); 349 (44%) females	Chemotherapy: N=305 (38%) Initial chemotherapy (N=158 (20%)): N=139 MOPP (88%) N=10 ABVD (6%) N=3 MOPP/ABVD (2%) N=5 ChlVPP (3%) N=1 COPP (1%) Chemotherapy for first relapse (N=140 (18%): N=102 MOPP (73%) N=17 ABVD (12%) N=8 MOPP/ABVD (6%) N=5 EVA (4%) N=6 ChlVPP (4%) N=2 single agent chemotherapy (specific agents not reported) (1%) N=7 (0.9%) no chemotherapy initially and at first relapse, so	Diagnostic test used for CAD assessment: Not reported Timing of the diagnostic test: Not reported Outcome definitions: Documented fatal MI; not further specified Occurrence of CAD: All patients had Hodgkin's disease; N=10 (1.3%) (N=6 (60%) only radiotherapy; N=4 (40%) radiotherapy and chemotherapy) N=6/10 patients were aged 37 to 45 years at the time of fatal MI; no information on other 4 patients provided. Risk factors assessed: No	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Not applicable Funding of the trial: Not reported, but it is stated that "No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article".

	Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: Not for CAD	we assume after first relapse. Doses not reported. Irradiation: N=794 (100%): N=115 (15%) total nodal irradiation N=679 (85%) mantle and para-aortic field irradiation or smaller (elsewhere in the manuscript different numbers are presented) The doses to the mantle field ranged from 35 to 40 Gy with a boost to bulk disease for a total of 40 to 44 Gy; para-aortic and pelvic nodes were treated to 30 to 40 Gy. Chemotherapy only: N=0 Irradiation only: N=489 (62%)	Results of multivariable analyses: Not applicable Results of univariable analyses: Not applicable	*Possible overlap in study population with the Chen 2014 and Galper 2011 studies.*

		<u>Chemotherapy and irradiation:</u> N=305 (38%) <u>Stem cell transplant:</u> Not reported		

Who needs surveillance?				
Oeffinger KC et al. Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 2006; 355(15): 1572-82.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (CCSS) Treatment era: Not reported for survivors included in this study, but for all survivors in the CCSS date of diagnosis 1970-1986 Follow-up: Mean interval between cancer diagnosis and completion of questionnaire was 17.5±4.6	N= 10397 adult childhood cancer survivors who have survived at least 5 years after diagnosis; aged <21 years at diagnosis. Diagnosis: Leukemia N=3061 (29.5%) CNS tumor N=1322 (12.7%) Hodgkin's disease N=1876 (18%) Non-Hodgkin's lymphoma N=928 (8.9%) Wilm's tumor N=670 (6.5%) Neuroblastoma N=416 (4%) Soft tissue sarcoma N=991 (9.5%) Bone tumor N=1133 (10.9%) Age at diagnosis: Not reported but eligible if aged <21 years at diagnosis. Proportion <age 35 at diagnosis: 100%	Chemotherapy: Any chemotherapy: N=7012 (67.4%) Alkylating agent: N= 3982 (38.3%) Anthracycline: N=3161 (30.4%) Other chemotherapy: N=3418 (32.9%) Type of anthracycline not reported; other agents and doses not reported. Irradiation: Any radiation therapy: N=6469 (62.2%) Brain irradiation: N=2852 (27.4%) Chest irradiation: N=2266 (21.8%) Abdominal or pelvic irradiation: N=2259 (21.7%)	Diagnostic test used for CAD assessment: Written questionnaire regarding physical health conditions. Self-reported without external verification with the exception of death. Timing of the diagnostic test: At least 5 years after cancer diagnosis Outcome definitions: CAD (CTCAEv3) starting 5 years after the date of diagnosis of cancer (for both survivors and siblings): Grade 3=CAD on medication Grade 4=MI Grade 5=MI death Occurrence of CAD: *CAD grade 3 or 4:* In survivors: N =115 (1.11%) In siblings: N=6 (0.2%)	Risk of bias: Selection bias: Unclear risk (original cohort not reported so unclear if study group consisted of more than 75% of the original cohort or was a random sample with respect to the cancer treatment (similar type of cancer treatment in participants and non-participants but no doses reported)) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (follow-up not taken into account in multivariable analysis)

years, range 6-31 years.	<u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Age at interview mean 26.6±6.1 years, range 18-48 years. <u>Gender:</u> 5593 males (53.8%); 4804 females (46.2%) <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> • Diabetes (not on medication, on oral medication or on insulin): N=124 survivors (1.2%) and N=28 siblings (0.9%) • Hypertension (with or without medication): N=500 (4.8%) survivors and N=135 siblings (4.4%) • Lipid disorder unspecified: N=13 (0.1%) survivors and N=3 siblings (0.1%) <u>Controls:</u>	Dose not reported. <u>Chemotherapy only:</u> N=1784 (17%) <u>Irradiation only:</u> N=1241 (12%) <u>Chemotherapy and irradiation:</u> N=5228 (50%) <u>Stem cell transplant:</u> Not reported *N=626 (6%) no chemotherapy or radiation therapy* *N=1518 missing or unknown treatment (14.6%)*	• Grade 3: N=99 (1%) survivors and N=6 (0.2%) siblings; Leukemia N=23, CNS tumor N=6, Hodgkin's disease N=36, Non-Hodgkin's lymphoma N=3, Wilm's tumor N=3, neuroblastoma N=1, soft tissue sarcoma N=14, bone tumor N=13 • Grade 4: N=16 (0.2%) survivors and N=0 siblings; Leukemia N=1, Hodgkin's disease N=12, Non-Hodgkin's lymphoma N=1, soft tissue sarcoma N=1, bone tumor N=1 • Grade 5: N=19 (0.2%) survivors (not applicable for siblings); Leukemia N=1, Hodgkin's disease N=12, soft tissue sarcoma N=2, bone tumor N=4 <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u>	<u>Funding of the trial:</u> Supported by a grant from the Department of Health and Human Services; by the Children's Cancer Research Fund and by American Lebanese Syrian Associated Charities. *Possible overlap in study population of the different CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.* *Under-reporting as a result of self-reporting outcomes is possible.*

	3034 nearest-age living siblings of a random sample of participating survivors		Comparisons between survivors and siblings were adjusted for the age at enrollment, sex, and race or ethnic group. The analysis accounted for within-family correlations. None of the siblings had died (grade 5) of CAD. Therefore, the highest grade used in the analysis was grade 4. For deceased survivors, investigators used the maximum grade reported prior to death. For example, if a survivor died of CAD, a grade of 4 was applied rather than grade 5. CAD grade 3 or 4: RR 10.4 (95% CI 4.1-25.9) <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Van der Pal HJ et al. High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol 2012; 30(13): 1429-37.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective single-center cohort Treatment era: Diagnosed between 1-1-1966 and 1-1-1996 Follow-up: Median 22.5 years (elsewhere in the manuscript 22.2 years), range 5 to 44.5 years since primary cancer diagnosis	N=1362 5-year childhood cancer survivors Diagnosis: ALL N=302 (22.2%) ANLL N=30 (2.2%) Non-Hodgkin's disease N=167 (12.3%) Hodgkin's disease N=104 (7.6%) Nephroblastoma N=186 (13.7%) Soft tissue sarcoma N=131 (9.6%) Ewing sarcoma N=53 (3.9%) Osteosarcoma N=73 (5.4%) CNS tumor N=124 (9.1%) Neuroblastoma N=85 (6.2%) Germ cell tumor N=45 (3.3%) Other N=62 (4.5%) Age at diagnosis: 0-4 years: N=596 (43.7%) 5-9 years: N=378 (27.8%) 10-14 years: N=309 (22.7%) 15-18 years: N=79 (5.8%) Proportion <age 35 at diagnosis: 100%	Chemotherapy: N=1167 (85.7%), of which anthracyclines N=565 (48.4%); cumulative dose range 1->500 mg/m^2; dose unknown in N=15. Other agents and doses not reported for all survivors. Irradiation: N=597 (43.8%), of which cardiac irradiation N=266 (44.6%); unknown in 1 patient. Cardiac irradiation was defined as: • Thorax (=left lung, mantle field, and/or mediastinum) N=84, dose in EQD2 median 24.08, range 9.47-88.46 • Abdomen (=whole abdomen, left kidney,	Diagnostic test used for CAD assessment: Childhood Cancer Registry, medical records or general practitioners or attending physicians; all cardiac events were diagnosed by cardiologists and validated by a cardiologist. Timing of the diagnostic test: Time at risk started 5 years from diagnosis. Survivors who developed a cardiac event in the first 5 years after primary cancer diagnosis were eligible only if they had recovered (i.e. no symptoms of cardiac events or treatment) within the same 5 years. Survivors who did not recover within 5 years were excluded. Outcome definitions: Cardiac ischemia/infarction grade 3 or higher (i.e. symptomatic) according to the CTCAEv3	Risk of bias: Selection bias: Low risk (study group consists of all patients included in the original cohort) Attrition bias: Low risk (complete follow-up) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: High risk (only univariable analyses available) Funding of the trial: Foundation of Pediatric Cancer Research Amsterdam *Possible overlap with Feijen 2020*

	Proportion <age 21 at diagnosis: 100% Age at testing/follow-up: Median attained age 29.1 years, range 5.2 to 54.2 years Gender: 745 males (54.7%); 617 females (45.3%) Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors): Not reported Controls: No	inverted Y field, and/or PAO) N=65, dose in EQD2 median 26.9, range 3.73-57.19 • Spine N=89, dose in EQD2 median 30.14, range 8-50.11 • TBI N=28, dose in EQD2 median 15.75, range 14-21.60 Dose unknown in N=10 Chemotherapy only: N=658 (48.3%) Irradiation only: N=88 (6.5%) Chemotherapy and irradiation: N=509 (37.4%) Stem cell transplant: Not reported *N=107 no chemotherapy and/or radiotherapy (surgery only) (7.9%)* N=723 cardiotoxic therapy (=anthracyclines	diagnosed more than 5 years after primary cancer diagnosis Occurrence of CAD: N=6 (0.4%): N=3 grade 3 N=3 grade 4 N=0 grade 5 All survivors with CAD received cardiotoxic treatment (N=2 anthracyclines only, N=3 radiotherapy only and N=1 combination): N=3 anthracyclines (median cumulative dose 405 mg/m^2 (range 360-450) N=4 cardiac irradiation (median cumulative dose 38.7 EQD2 (range 16.6-39.6); n=3 thorax and n=1 abdomen N=0 ifosfamide N=0 cisplatin N=5 vincristine (no dose reported) N=3 cyclophosphamide; median cumulative dose 9.2g/m^2 (range 3.9-14.4) All showed stable disease with treatment; none had congenital heart disease.	

		and/or cardiac radiotherapy) (53.1%)	4 males; 2 females 2 Ewing sarcoma, 2 non-Hodgkin's disease, 1 Hodgkin's disease, 1 osteosarcoma Median age at diagnosis: 13.7 years (range 10.3-14.4) Median follow-up 22.4 years (range 18.7-35.7) Median attained age 36.5 years (range 33-46) Competing risk cumulative incidence with death from any cause or another cardiac event as competing risks: 10-year cause-specific cumulative incidence: 0% 20-year cause-specific cumulative incidence: 0.1% (95% CI 0 to 0.3%) 30-year cause-specific cumulative incidence: 0.8% (95% CI 0.1 to 1.4%) 40-year cause-specific cumulative incidence: 1.9% (95% CI 0 to 4.1%) <u>Risk factors assessed:</u> Yes <u>Results of multivariable analyses:</u> Not applicable	

			<u>Results of univariable analyses:</u> Competing risk cumulative incidence with death from any cause or another cardiac event as competing risks: 20-years: Cardiotoxic therapy no: 0% Cardiotoxic therapy yes: 0.2% (95% CI 0 to 0.7%) Radiotherapy (=cardiac irradiation and no anthracyclines with or without all other treatment) no: 0.2% (95% CI 0 to 0.3%) Radiotherapy yes: 0% 30-years: Cardiotoxic therapy no: 0% Cardiotoxic therapy yes: 1.6% (95% CI 0.2 to 3%) Radiotherapy (=cardiac irradiation and no anthracyclines with or without all other treatment) no: 0.3% (95% CI 0 to 0.8%) Radiotherapy yes: 2.2% (95% CI 0 to 4.7%) 40-years: Cardiotoxic therapy no: 0% Cardiotoxic therapy yes: 4.9% (95% CI 0 to 11.2%)	

			Radiotherapy (=cardiac irradiation and no anthracyclines with or without all other treatment) no: 0.3% (95% CI 0 to 0.8%) Radiotherapy yes: 6% (0 to 13.3%) Cardiotoxic therapy log-rank P=0.007 Radiotherapy log-rank P=0.01	

Who needs surveillance?				
Mulrooney DA et al. Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort. BMJ 2020; 368: l6794.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (CCSS) Treatment era: Years of diagnosis 1970-1999. Follow-up: Median 20.5 years (range 7.0-39.3) from diagnosis.	N=23462 5-year childhood cancer survivors; aged < 21 years at diagnosis. Diagnosis: ALL N=6127 (35.2%) AML N=852 (3.2%) Other leukemia N=302 (1.1%) Astrocytoma N=2589 (9.7%) Medulloblastoma N=994 (3.7%) Other brain tumor N=644 (2.4%) Hodgkin lymphoma N=2985 (11.2%) Non-Hodgkin lymphoma N=1919 (7.2%) Kidney tumor N=2130 (8.0%) Neuroblastoma N=1825 (6.8%) Soft tissue sarcoma N=1153 (4.3%) Osteosarcoma N=1187 (4.4%) Ewing sarcoma N=702 (2.6%) Other bone cancer N=53 (0.2%) Age at diagnosis:	Chemotherapy: N=17323 (73.8%) Anthracycline (mg/m2) in doxorubicin equivalents: None N=11145 (47.5%) <250 N=6190 (26.4%) ≥250 N=3415 (14.6%) Missing N=2712 (11.6%) Other doses and agents not reported. Irradiation: N=12059 (51.4%) Mean heart radiation dose (Gy): None N=9234 (39.4%) <15 N=8199 (34.9%) 15 to <35 N=2376 (10.1%) ≥35 N=1074 (4.6%)	Diagnostic test used for CAD assessment: Participants completed a baseline questionnaire and up to four follow-up surveys. Outcomes were self-reported and supplemented by data from the National Death Index. A multidisciplinary team reviewed and adjudicated all conditions graded and scored according to the CTCAE v4.03. Timing of the diagnostic test: At least 5 years after cancer diagnosis. Outcome definitions: CAD (including myocardial infarction or coronary revascularization) graded according to the	Risk of bias: Selection bias: High risk (number of survivors in original cohort with only rhabdomyosarcoma as a soft tissue sarcoma (adjusted in the expanded cohort) was not reported, but based on previous CCSS publications we judged this not to have influenced the percentage (67.2%) in such a way as to have resulted in at least 75% completeness) Attrition bias: Low risk (outcome assessed for the complete study group) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding:

	Median 6.1 years (range 0-20.9) <u>Proportion <age 35 at diagnosis:</u> 100% <u>Proportion <age 21 at diagnosis:</u> 100% <u>Age at testing/follow-up:</u> Median 27.7 years (range 8.2-58.3) <u>Gender:</u> 12588 (53.7%) males; 10874 (46.3%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors):</u> Participants were considered to have diabetes, dyslipidemia, or hypertension if they reported one of these conditions diagnosed by a physician and were taking drugs for the condition (grade 2 or higher). Smoking (ever or never)	Missing N=2579 (10.1%) The Department of Radiation Physics at MD Anderson Cancer Center estimated the mean dose of heart radiation by reconstructing individual radiation treatments on age specific computational phantoms. Other doses and radiotherapy locations not reported. <u>Chemotherapy only:</u> N=7230 (30.8%) <u>Irradiation only:</u> N=1966 (8.4%) <u>Chemotherapy and irradiation:</u> N=10093 (43.0%) <u>Stem cell transplant:</u> Not reported	CTCAE v4.03 criteria (grade 3-5). <u>Occurrence of CAD:</u> CAD grade 3-5: N=186 (0.79%); siblings N=4 (0.08%) 1970-1979 N=85; siblings N=0 1980-1989 N=71; siblings N=4 1990-1999 N=30; siblings N=0 Leukemia N=37: 1970-1979 N=13 1980-1989 N=14 1990-1999 N=10 CNS tumors N=12: 1970-1979 N=3 1980-1989 N=5 1990-1999 N=4 Hodgkin lymphoma N=85: 1970-1979 N=48 1980-1989 N=31 1990-1999 N=6 Non-Hodgkin lymphoma N=12: 1970-1979 N=4 1980-1989 N=5 1990-1999 N=3 Kidney tumor N=3: 1970-1979 N=2 1980-1989 N=0 1990-1999 N=1 Neuroblastoma N=8:	Either low or high risk depending on the analysis. <u>Funding of the trial:</u> "The Childhood Cancer Survivor Study is supported by the National Cancer Institute grant CA55727 (to GTA, principal investigator), the Cancer Center Support (CORE) grant (CA21765) to St Jude Children's Research Hospital (to CW Roberts, principal investigator) and the American Lebanese Syrian Associated Charities (ALSAC), Memphis, TN." *Possible overlap in study population of the different CCSS studies: Armstrong 2013, Mulrooney 2009, Armstrong 2009, Castellino 2011, Oeffinger 2006 and Mulrooney 2020.* *This study has an expanded cohort (years of diagnosis 1987-1999) from the other CCSS studies.*

	BMI was categorized as underweight (<18.5 weight (kg)/(height (m)^2), normal (18.5-24.9), overweight (25.0-29.9), or obese (≥30). BMI median (range) 24.6 (11.0-63.2); siblings 23.8 (11.2-60.8) P<0.001 Smoking: Never N=14435 (61.5%); siblings N=3109 (61.5%) Ever N=6654 (28.4%); siblings N=1674 (33.1%) Missing N=2374 (10.1%); siblings N=274 (5.4%) P<0.001 Diabetes mellitus: Yes N=687 (2.8%); siblings 94 (1.9%) No N=22775 (97.2%); siblings 4963 (98.1%) P<0.001 Dyslipidemia: Yes N=1578 (6.7%); siblings N=271 (5.4%) No N=21884 (93.3%); siblings N=4786 (94.6%) P=0.02 Hypertension: Yes N=2232 (9.5%); siblings N=437 (8.6%)	*N= 1867 (8.0%) surgery only* *N= 2306 (9.8%) missing data*	1970-1979 N=3 1980-1989 N=3 1990-1999 N=2 Soft tissue sarcoma N=5: 1970-1979 N=3 1980-1989 N=2 1990-1999 N=0 Bone cancer N=24: 1970-1979 N=9 1980-1989 N=11 1990-1999 N=4 20 year cumulative incidence (treating all cause death (except death due to the particular outcome analyzed) as a competing risk event): 1970s 0.38% (95% CI 0.26 to 0.54) 1980s 0.24% (95% CI 0.16 to 0.35) 1990s 0.19% (95% CI 0.12 to 0.33) Cumulative incidences: CAD 1970s vs 1980s P=0.02 CAD 1970s vs 1990s P=0.01 CAD 1980s vs 1980s P=0.17 <u>Risk factors assessed:</u> Yes	

	No N=21230 (90.5%); siblings N=4620 (91.4%) P=0.35 <u>Controls:</u> N=5057 siblings (random sample of siblings of participating survivors)		<u>Results of multivariable analyses:</u> HRs (95% CI) of CAD 20 years from diagnosis by treatment era (adjusted for age at diagnosis, race, and sex): All survivors 1970-79 1.0 1980-89 0.65 (0.45 to 0.92) 1990-99 0.53 (0.36 to 0.77) Leukemia: 1970-79 1.0 1980-89 0.69 (0.33 to 1.44) 1990-99 0.83 (0.31 to 2.22) CNS tumors: 1970-79 1.0 1980-89 0.80 (0.19 to 3.43) 1990-99 0.60 (0.12 to 2.88) Hodgkin lymphoma: 1970-79 1.0 1980-89 0.77 (0.40 to 1.45) 1990-99 0.44 (0.23 to 0.85) Non-Hodgkin lymphoma: 1970-79 1.0 1980-89 0.82 (0.25 to 2.75) 1990-99 0.86 (0.23 to 3.22) Kidney tumor: 1970-79 1.0 1980-89 not estimable owing to small cell size 1990-99 1.68 (0.11 to 24.71) Neuroblastoma: 1970-79 1.0	

			1980-89 0.64 (0.17 to 2.43) 1990-99 0.49 (0.05 to 4.46) Soft tissue sarcoma: 1970-79 1.0 1980-89 0.47 (0.13 to 1.68) 1990-99 not estimable owing to small cell size Bone cancer: 1970-79 1.0 1980-89 0.92 (0.38 to 2.24) 1990-99 0.53 (0.14 to 2.07) Multivariable analysis of CAD by treatment era and cardiovascular risk factors 20 years from diagnosis (estimates adjusted for race, age at diagnosis, body mass index, smoking, and exercise intensity (metabolic hours/week)) (HR (95% CI)): Sex: Male 1.0 Female 0.87 (0.62 to 1.23) Treatment era: 1970-79 1.0 1980-89 0.66 (0.42 to 1.02) 1990-99 0.63 (0.36 to 1.08) Mean heart dose (Gy): None 1.0 1-15 1.31 (0.88 to 1.96) 15.1-34.99 2.26 (1.32 to 3.84) ≥35 5.86 (3.69 to 9.28)	

			Anthracycline dose (mg/m^2): None 1.0 <250 1.42 (0.93 to 2.16) ≥250 1.77 (1.15 to 2.72) Comorbidities: Diabetes 1.55 (0.67 to 3.58) Dyslipidemia 3.49 (2.11 to 5.77) Hypertension 4.75 (3.37 to 6.69) HRs of CAD per five year treatment era (continuous variable) (HR (95% CI)); mediation analysis; Adjusted for demographics and modifiable risk factors 0.80 (0.71 to 0.91) Adjusted for demographics, modifiable risk factors, and cardiac radiation exposure 0.90 (0.78 to 1.05) Adjusted for demographics, modifiable risk factors, and anthracycline exposure 0.79 (0.69 to 0.91) Adjusted for demographics, modifiable risk factors, and cardiotoxic exposures 0.87 (0.74 to 1.03) *Demographics=age at diagnosis, sex, race, body mass index, smoking, exercise*	

			intensity (metabolic hours/week); modifiable risk factors=diabetes, dyslipidemia, and hypertension; cardiotoxic exposures=cardiac radiation and anthracycline. These results are consistent regardless of whether the model used time since diagnosis or attained age as its timescale; adjusted for age at diagnosis. Also mediation analysis: HRs (95% CI) for CAD, per five-year treatment eras, by diagnosis, with and without adjustment for cardio-toxic exposures (estimates adjusted for age at diagnosis, sex, race, BMI, smoking, exercise intensity (metabolic hours/week), and modifiable risk factors (diabetes, dyslipidemia, hypertension): Leukemia No 0.92 (0.65 – 1.31) Yes 0.89 (0.58 – 1.37) CNS tumors No 0.82 (0.57 – 1.18) Yes 0.85 (0.58 – 1.25)	

			Hodgkin lymphoma No 0.77 (0.66 – 0.89) Yes 0.87 (0.69 – 1.10) Non-Hodgkin lymphoma No 1.16 (0.79 – 1.71) Yes 1.05 (0.65 – 1.71) Kidney tumor No 0.75 (0.25 – 2.21) Yes not estimable owing to small cell size Neuroblastoma No 0.70 (0.34 – 1.43) Yes 0.82 (0.52 – 1.31) Soft tissue sarcoma No 0.51 (0.24 – 1.07) Yes 0.39 (0.14 – 1.08) Bone cancer No 0.91 (0.66 – 1.25) Yes 0.86 (0.60 – 1.23) All Survivors No 0.80 (0.71 – 0.91) Yes 0.87 (0.74 – 1.03) <u>Results of univariable analyses:</u> Not applicable	

Who needs surveillance?				
Feijen EA et al. Increased risk of cardiac ischemia in a Pan-European cohort of 36205 childhood cancer survivors: a PanCareSurFup study. Heart 2020; epub ahead of print.				
Study design **Treatment era** **Follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Study design: Retrospective multi-center cohort (PanCareSurFup study) Treatment era: Years of diagnosis 1940-2007. Follow-up: Median 23 years (range 5-72.5) after primary cancer diagnosis.	N=36205 ≥5 year (after diagnosis) childhood cancer survivors; aged <21 years at diagnosis. Diagnosis: Leukemia N=9775 (27.0%) Lymphoma N=5587 (15.4%) CNS tumor N=6836 (18.9%) Bone and soft tissue sarcoma 4270 (11.8%) Other tumor N=9737 (26.9%) Age at diagnosis: Median 5.8 years (IQR 2.7-11.0) Proportion <age 35 at diagnosis: 100% Proportion <age 21 at diagnosis: 100% Age at testing/follow-up:	Chemotherapy: N=19735 (54.5%) Doses and agents not reported. Irradiation: N=16733 (46.2%) Doses and radiotherapy locations not reported. Chemotherapy only: N=7812 (21.6%) Irradiation only: N=4810 (13.3%) Chemotherapy and irradiation: N=11923 (33.0%) Stem cell transplant: Not reported *N=4215 (11.7%) without*	Diagnostic test used for CAD assessment: Identification of symptomatic cardiac ischaemia cases using: linkage to population, hospital or regional-based databases (hospitalisations, medication use, GP visits) and questionnaires sent to survivors and GPs. All potential events were validated using information from medical records or treating physicians; an extraction and flow chart method was used to grade the cardiac ischaemia. Timing of the diagnostic test: Time at risk started 5 years after the first primary cancer diagnosis. Outcome definitions:	Risk of bias: Selection bias: Low risk (the original cohort after adjustment of inclusion criteria is unclear, but the study group consists of more than 75% (i.e. at least 78.1%) of patients included in the original cohort) Attrition bias: Low risk (outcome assessed for the complete study group) Detection bias: Unclear risk (no information on blinding of outcome assessors provided) Confounding: Low risk for model 1 and 3 (all important confounding factors have been taken into account);

	Median 29.7 years (range 5.1-79.8) <u>Gender:</u> 19883 (54.9%) males; 16322 (45.1%) females <u>Cardiovascular risk factors (like dyslipidemia, hypertension, obesity, physical activity, diabetes mellitus, smoking, genetic factors):</u> Not reported <u>Controls:</u> No (see additional remarks).	*treatment/surgery only* *N=7445 (20.6%) missing data*	Symptomatic cardiac ischaemia graded according to the CTCAEv3.0 criteria (grade 3–5). <u>Occurrence of CAD:</u> CAD grade 3-5: N=302 (0.83%). Grade 3: N=43 (14.2%) Grade 4: N=169 (60%) Grade 5: N=90 (29.8%) N=83 (27.5%) females; N=219 (72.5%) males Age at diagnosis (years) 0–4 N=67 (22.2%) 5–9 N=74 (24.5%) 10–14 N=149 (49.3%) ≥15 N=12 (4.0%) Median (IQR) 10.5 (5.4–13.3) Leukemia N=22 (7.3%) Lymphoma N=123 (40.7%) CNS tumor N=42 (13.9%) Bone and soft tissue sarcoma N=45 (14.9%) Other tumor N=70 (23.2%) Calendar year of diagnosis: <1980 N=240 (79.5%)	high risk for model 2 (co-treatment not taken into account). <u>Funding of the trial:</u> Supported by the European Union's Seventh Framework Programme for research, technological development and demonstration (Grant Agreement No. 257505; PanCareSurFup). An author was supported by grant funding from the Dutch Cancer Society. The Swiss Childhood Cancer Registry and the Swiss Childhood Cancer Survivor Study are supported by the Swiss Paediatric Oncology Group, the Swiss Cancer League (KLS-3412-02-2014, KLS-3886-02-2016), Swiss Cancer Research (KFS-02783-02-2011), the Swiss National Science Foundation (PDFMP3_141775), Kinderkrebshilfe Schweiz, the Federal Office of Public Health and the National Institute of Cancer Epidemiology and Registration. Slovenian Research Agency. The French Childhood Cancer Survivor

			1980–1989 N=53 (17.5%) ≥1990 N=9 (3.0%) Without treatment/surgery only N=36 (11.9%) Chemotherapy±surgery N=22 (7.3%) Radiotherapy±surgery N=122 (40.4%) Chemotherapy and radiotherapy±surgery N=91 (30.1%) Missing N=31 (10.3%) Attained age at end of follow-up (year) ≤20 N=8 (2.6%) 20–29 N=33 (10.9%) 30–39 N=73 (24.2%) 40–49 N=102 (33.8%) 50–59 N=63 (20.9%) ≥60 N=23 (7.6%) Median (range) 43.6 (14.6–73.3) Median follow-up after primary cancer diagnosis: 28.9 years (range 0.1–57.5) Median age at symptomatic cardiac ischaemia: 43.6 years	Cohort is supported by the French Society of Childhood Cancer (SFCE), ARC foundation with the Pop-HaRC and CHART projects, the French National Cancer Institute (INCA) with Programme Hospitalier de Recherche Clinique, the Pfizer Foundation for childhood and adolescent health, the Ligue Nationale Contre le Cancer (LNCC), the Institut de Recherche en Santé Publique (IRESP) and the French 'Agence Nationale Pour la Recherche Scientifique' (Hope-Epi Project). *Possible overlap in study population with Van der Pal 2012, Haddy 2016, Fidler 2017, Materazzo 2017.* *The average age at first myocardial infarction in the general population is 64.5 years for males and 70.4 years for females.* *No treatment or surgery only was considered as a proxy for the general population.*

			(range 14.6–73.3); 41 / 302 (13.6%) diagnosed < 30 years. Cases in survivors treated with radiotherapy/chemotherapy appeared earlier than in survivors without treatment/surgery only (15% vs 3% prior to age 30 years, respectively (p=0.04)). The first symptomatic cardiac ischaemia event in the no treatment/surgery only group occurred at 29.9 years, while the first event in the chemotherapy-treated and/or radiotherapy-treated group occurred at 14.5 years of age. Cumulative incidence (competing risk analyses): Attained age 10 years (% (95% CI)) • Overall 0.00% (0.00 to 0.00) • Sex Male 0.00% (0.00 to 0.00) Female 0.00% (0.00 to 0.00) • Treatment	*"When we focus on the first 30 years of age, there is no statistically significant difference between male and female CCS. However, after 30 years of age the risk of ischaemic heart disease in males increases steadily. Females treated with chemotherapy and/or radiotherapy seem to have the same risk as males treated without treatment/surgery only, again the difference did not reach statistical significance."* *"Potential limitations of this study are the variation between data providers in inclusion criteria and method of follow-up. We carried out a sensitivity analysis evaluating inclusion criteria (incidence year 1970–1986 and age at diagnosis <15 years), and showed no clear differences in results…. It is possible that identification of cardiac ischaemia cases were less optimal for some data providers, however we*

			No treatment/surgery only 0.00% (0.00 to 0.00) Chemotherapy and/or radiotherapy 0.00% (0.00 to 0.00) • Treatment and sex Male no treatment/surgery only 0.00% (0.00 to 0.00) Male chemotherapy and/or radiotherapy 0.00% (0.00 to 0.00) Female no treatment/surgery only 0.00% (0.00 to 0.00) Female chemotherapy and/or radiotherapy 0.00% (0.00 to 0.00) • Primary cancer groups Leukemia 0.00% (0.00 to 0.00) Lymphoma 0.00% (0.00 to 0.00) CNS tumor 0.00% (0.00 to 0.00) Bone and soft tissue sarcoma 0.00% (0.00 to 0.00) Oher tumor 0.00% (0.00 to 0.00) Attained age 20 years (% (95% CI))	*corrected for data provider in the multivariable model."*

			• Overall 0.02% (0.01 to 0.04) • Sex Male 0.01% (0.00 to 0.03) Female 0.04% (0.01 to 0.08) • Treatment No treatment/surgery only 0.00% (0.00 to 0.00) Chemotherapy and/or radiotherapy 0.04% (0.01 to 0.06) • Treatment and sex Male no treatment/surgery only 0.00% (0.00 to 0.00) Male chemotherapy and/or radiotherapy 0.02% (0.00 to 0.04) Female no treatment/surgery only 0.00% (0.00 to 0.00) Female chemotherapy and/or radiotherapy 0.06% (0.01 to 0.11) • Primary cancer groups Leukemia 0.02% (0.00 to 0.06) Lymphoma 0.06% (0.00 to 0.13) CNS tumor 0.00% (0.00 to 0.00)	

			Bone and soft tissue sarcoma 0.05% (0.00 to 0.13) Other tumor 0.01% (0.00 to 0.04) Attained age 30 years (% (95% CI)) • Overall 0.16% (0.11 to 0.21) • Sex Male 0.20% (0.13 to 0.28) Female 0.10% (0.05 to 0.16) • Treatment No treatment/surgery only 0.04% (0.00 to 0.11) Chemotherapy and/or radiotherapy 0.20% (0.13 to 0.26) • Treatment and sex Male no treatment/surgery only 0.00% (0.00 to 0.00) Male chemotherapy and/or radiotherapy 0.25% (0.15 to 0.35) Female no treatment/surgery only 0.07% (0.00 to 0.22) Female chemotherapy and/or radiotherapy 0.13% (0.05 to 0.21) • Primary cancer groups	

			Leukemia 0.15% (0.06 to 0.25) Lymphoma 0.38% (0.19 to 0.56) CNS tumor 0.04% (0.00 to 0.10) Bone and soft tissue sarcoma 0.20% (0.05 to 0.35) Other tumor 0.10% (0.02 to 0.18) Attained age 40 years (% (95% CI)) • Overall 0.71% (0.58 to 0.85) • Sex Male 0.98% (0.76 to 1.20) Female 0.40% (0.26 to 0.55) • Treatment No treatment/surgery only 0.45% (0.15 to 0.74) Chemotherapy and/or radiotherapy 0.77% (0.61 to 0.94) • Treatment and sex Male no treatment/surgery only 0.43% (0.01 to 0.85) Male chemotherapy and/or radiotherapy 1.06% (0.80 to 1.33)	

			Female no treatment/surgery only 0.47% (0.05 to 0.89) Female chemotherapy and/or radiotherapy 0.42% (0.25 to 0.59) • Primary cancer groups Leukemia 0.30% (0.11 to 0.49) Lymphoma 1.93% (1.39 to 2.46) CNS tumor 0.35% (0.16 to 0.55) Bone and soft tissue sarcoma 0.76% (0.38 to 1.13) Other tumor 0.51% (0.28 to 0.74) Attained age 50 years (% (95% CI)) • Overall 2.46% (2.08 to 2.84) • Sex Male 3.40% (2.80 to 4.01) Female 1.36% (0.95 to 1.77) • Treatment No treatment/surgery only 1.45% (0.78 to 2.11) Chemotherapy and/or radiotherapy 2.84% (2.34 to 3.34) • Treatment and sex	

			Male no treatment/surgery only 2.01% (0.90 to 3.13) Male chemotherapy and/or radiotherapy 3.77% (3.00 to 4.55) Female no treatment/surgery only 0.92% (0.17 to 1.66) Female chemotherapy and/or radiotherapy 1.65% (1.09 to 2.20) • Primary cancer groups Leukemia 1.58% (0.33 to 2.84) Lymphoma 5.79% (4.50 to 7.08) CNS tumor 0.98% (0.56 to 1.40) Bone and soft tissue sarcoma 2.20% (1.26 to 3.13) Other tumor 2.43% (1.66 to 3.20) Attained age 60 years (% (95% CI)) • Overall 5.39% (4.55 to 6.22) • Sex Male 7.09% (5.81 to 8.37) Female 3.39% (2.39 to 4.39) • Treatment	

			No treatment/surgery only 3.61% (2.14 to 5.08) Chemotherapy and/or radiotherapy 6.20% (5.09 to 7.31) • Treatment and sex Male no treatment/surgery only 5.53% (2.92 to 8.13) Male chemotherapy and/or radiotherapy 7.73% (6.11 to 9.35) Female no treatment/surgery only 1.74% (0.35 to 3.13) Female chemotherapy and/or radiotherapy.18% (2.76 to 5.61) • Primary cancer groups Leukemia 3.81% (0.49 to 7.13) Lymphoma 10.75% (8.22 to 13.28) CNS tumor 2.86% (1.81 to 3.90) Bone and soft tissue sarcoma 6.01% (3.62 to 8.40) Other tumor 4.82% (3.31 to 6.33) <u>Risk factors assessed:</u> Yes	

			<u>Results of multivariable analyses:</u> Multivariable Cox proportional hazards models with attained age as time scale; adjusted for sex, age at diagnosis, year of childhood cancer diagnosis and data provider. Model 1 (HR (95% CI)): • Age at primary childhood cancer diagnosis 1.0 (0.97 to 1.03) • Sex Male Ref Female 0.4 (0.3 to 0.6) • Treatment No treatment/surgery only Ref Chemotherapy and/or radiotherapy 2.1 (1.5 to 3.0) There was no significant interaction term between sex and treatment. Model 2 (HR (95% CI)): • Age at primary childhood cancer diagnosis 0.97 (0.93 to 0.99) (continuous variable; decreasing risk with increasing age)	

			• Sex Male Ref Female 0.5 (0.4 to 0.6) • Primary cancer diagnosis Leukemia Ref Lymphoma 3.4 (2.0 to 5.3) Central nervous system 0.9 (0.5 to 1.4) Bone and soft tissue sarcoma 1.5 (0.9 to 2.5) Other tumors 1.3 (0.8 to 2.1) Model 3 (HR (95% CI)): • Age at primary childhood cancer diagnosis 1.01 (0.98-1.04) • Sex Male Ref Female 0.5 (0.35-0.60) • Treatment group No treatment/ surgery only Ref Chemotherapy +/- surgery 1.6 (0.89-2.8) Radiotherapy +/- surgery 2.0 (1.4-2.9) Chemotherapy and radiotherapy +/- surgery 2.4 (1.6-3.7) <u>Results of univariable analyses:</u> Not applicable	

Footnotes:
*At treatment: chemotherapy and irradiation can include treatment other than chemotherapy and irradiation and in order to be able to assign patients to the chemotherapy only, irradiation only or chemotherapy and irradiation group information on all chemotherapy agents (not only anthracyclines) and all radiotherapy locations (not only cardiac) should have been available; in case of subgroups: information provided in the tables is for the subgroup only unless otherwise specified; range describes the minimum and maximum value.

Abbreviations:
CAD=coronary artery disease; CCSS=childhood cancer survivor study; ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; PNET=primitive neuroectodermal tumor; CNS=central nervous system; N=number; US=United States; NDI=National Death Index; CTCAEv4.03=Common Terminology Criteria for Adverse Events version 4.03; CI=confidence interval; RERI=relative excess risk due to interaction; BP=blood pressure; JNC7 guidelines=seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; BMI=body mass index; CVD=cardiovascular diseases; ABVD=doxorubicin, bleomycin, vinblastine, dacarbazine; EVA=doxorubicin, etoposide, vinblastine; MOPP=mechlorethamine, vincristine, procarbazine, prednisone; MI=myocardial infarction; BCVPP=carmustine, cyclophosphamide, vinblastine, procarbazine, prednisone; CVPP=cyclophosphamide, vinblastine, procarbazine, prednisone; CVPN=cyclophosphamide, vinblastine, prednisone, natulan; MVPP=mechlorethamine, vinblastine, procarbazine, prednisone; NOVP=novantrone/mitoxantrone, vincristine, vinblastine, prednisone; ABV=doxorubicin, bleomycin, vinblastine; CVP=cyclophosphamide, vincristine, prednisone; LV=left ventricular; ECG=electrocardiogram; CABG=coronary bypass graft surgery; PTCA=percutaneous transluminal coronary angioplasty; SIR=standardized incidence ratio; AER=absolute excess risk; TSH=thyroid stimulating hormone; CAYA=childhood, adolescent and young adult; PAVe=melphalan, vinblastine, procarbazine; RR=relative risk; AR=absolute risk; SEER= Surveillance, Epidemiology and End Results; OER=observed to expected ratio; HR=hazard ratio; ICD-*n*= International Classification of Diseases n^{th} revision; CTA=Computed tomography angiography; CKMB=creatinine kinase-myocardial band; BNP=brain natriuretic peptide; MET=metabolic equivalent; CT=computed tomography; CCTA=coronary computed tomography angiography; COPP= cyclophosphamide, vincristine, procarbazine, prednisone; SMR=standardized mortality ratio); ER=excess risk; OPPA=vincristine, prednisone, procarbazine, doxorubicin; OPA=vincristine, prednisone, doxorubicin; OEPA= vincristine, prednisone, etoposide, doxorubicin; COMP=cyclophosphamide, vincristine, methotrexate, prednisone; MedRD=mediastinal radiation dose; EBVP=epirubicine, bleomycin, vinblastine, prednisone; PAO=para-aortic lymph nodes; CTCAEv3=Common Terminology Criteria for Adverse Events version 3; EAR=excess absolute risk; CO±PP=cyclophosphamide and vincristine ± procarbazine and predinison; MRI=Magnetic Resonance Imaging; ChlVPP=chlorambucil, vinblastine, procarbazine and prednisone; ANLL= acute non-lymphoblastic leukemia; TBI=total body irradiation; EQD2=equivalent dose in 2GY fractions; EMR=excess mortality ratio; GP=general practitioner

G. Short overview of the CAD prevalence in included studies (n=32):

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Risk of bias
CAD	Constine 1997*	50 Hodgkin survivors	Mean 9.1±7.5 yr, median 6.1 yr, range 1.1-29.1 yr between radiotherapy and testing	Chemotherapy: 34% Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: 0%	0/38 or 0/39 (0%) partial or full LV blocking on exercise tolerance testing (including 7 non-diagnostic results) 2/38 (5.3%) mild stress-induced ischemia on thallium-201 or 99mTc-sestamibi myocardial perfusion scintigraphy 2/50 (4%) clinical MI (of which 1 fatal (2%))	SB: unclear AB: low risk DB: unclear
	Galper 2011~	1279 Hodgkin survivors	Median 14.7 yr, interquartile range 8.1-21 yr after radiotherapy ended	Chemotherapy: 39% Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: NM	107/1279 (8.4%) clinically significant CAD (i.e. a history of documented MI, CABG, PTCA with or without stenting or stenosis >75% of the diameter of the vessel on coronary angiography): 76 MI (7 survivors had 2 MIs, making a total of 83 MIs) 63 CABG and/or PTCA	SB: low risk AB: low risk DB: unclear
	Gustavsson 1990	26 Hodgkin survivors	Median 15 yr, range 4-20 yr from completed treatment to study (with the exception of 1 patient who died of a MI at 4 yr after therapy, all patients had a	Chemotherapy: 0% Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: 0%	In total 3/26 (12%) CAD: 2 (8%) symptomatic and 1 (4%) asymptomatic 2/26 (8%) symptomatic MI (of which 1 fatal (4%)) 1/23 (4%) infarction pattern at ECG at rest and vector ECG (this is a patient with symptomatic MI as mentioned above) 1/24 (4%) pathological ST-depression (followed by triple balloon angioplasty) on exercise ECG test 0/24 (0%) chest pain on exercise ECG test	SB: unclear AB: low risk DB: unclear

			follow-up of at least 10 yr)		2/23 (9%) abnormal 201-thallium stress myocardial: 1 scar or infarction and 1 ischemia (this is the patient with pathological ST depression and balloon angioplasty mentioned above)	
	Hancock 1993 JCO**	635 Hodgkin survivors	Mean 10.3 yr (start point not reported)	Chemotherapy: 63% Radiotherapy: 99% Cardiac irradiation: 91% Stem cell transplant: NM	7/635 (1.1%) fatal MI 3/635 (0.5%) non-fatal MI 1/635 (0.2%) angina pectoris requiring revascularization	SB: low risk AB: low risk DB: unclear
	Hancock 1993 JAMA**	1341 Hodgkin survivors	NM for eligible patients	Chemotherapy: 59.3% Radiotherapy: at least 92.2% Cardiac irradiation: 92.2% Stem cell transplant: NM	14/1341 (1%) death due to acute MI	SB: low risk AB: low risk DB: unclear
	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	SB: low risk AB: low risk DB: unclear
	King 1996*	114 Hodgkin survivors	At least 3 yr without evidence of disease activity	Chemotherapy: NM Radiotherapy: 100%	Overall 5/114 (4.4%) fatal MI, non-fatal MI or angina 2/114 (1.8%) fatal MI 2/114 (1.8%) non-fatal MI 1/114 (0.9%) angina	SB: low risk AB: low risk DB: unclear

				Cardiac irradiation: 100% Stem cell transplant: NM		
	Küpeli 2010	119 Hodgkin survivors	At least 2 yr from cancer diagnosis to CTA	Chemotherapy: 100% Radiotherapy: 92.4% Cardiac irradiation: 49.6% Stem cell transplant: NM	19/119 (16%) abnormalities on CTA	SB: unclear AB: low risk DB: unclear
	Mulrooney 2014[#]	31 Hodgkin survivors vs similarly aged general population	Median 24 yr, range 17-39 yr from initial cancer diagnosis to time of evaluation	Chemotherapy: 58% Radiotherapy: 100% Cardiac irradiation: max 100% Stem cell transplant: NM	12/31 (39%) CAD (3 obstructive and 9 non-obstructive) on CCTA; obstructive CAD defined as ≥50% occlusion of the left main coronary artery or ≥70% occlusion of the left anterior descending artery, left circumflex artery or right coronary artery. *In similarly aged general population: CAD 8.5-11%.* 9/31 (29%) resting 12-lead ECG abnormalities; tracings were considered positive for CAD if coded a high likelihood of Q-wave MI (Q-wave MI with major Q waves or Q-wave MI with moderate Q waves with ST-T abnormalities), a moderate likelihood of Q-wave MI (possible Q-wave MI with moderate Q-waves without ST-T abnormalities or possible Q-wave MI with minor Q-waves with ST-T abnormalities), or isolated ischemic abnormalities (ST abnormalities without Q-waves or T-wave abnormalities without Q-waves). (3 patients with obstructive lesions on CCTA, 4 patients with non-obstructive lesions on CCTA and 2 in patients without CCTA abnormalities). 1/30 (3%) treadmill abnormalities (i.e. observation of a J-point depression ≥1 mm with a horizontal or	SB: unclear AB: low risk DB: unclear

					downsloping ST segment was considered to be positive for CAD); patient with obstructive lesion on CCTA.	
	Reinders 1999	145 Hodgkin survivors	At least 0.7 yr (starting point not reported)	Chemotherapy: NM Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: NM	2/145 (1.4%) fatal ischemic cardiac disease 7/145 (4.8%) hospital admission for ischemic heart disease (some patients were not counted as hospital admission for ischemic heart disease as they were for example already hospitalized for a noncardiac reason or died at home; number NM).	SB: low risk AB: low risk DB: unclear
	Schellong 2010	1132 Hodgkin survivors	Median 15.1 yr, range 3.1-29.4 yr from beginning of treatment	Chemotherapy: 99.5% Radiotherapy: at least 73.6% Cardiac irradiation: 73.6% Stem cell transplant: NM	14/1132 CAD (1.2%) including 8 MIs	SB: unclear AB: low risk DB: unclear
	Adams 2004	48 Hodgkin survivors	Median time since diagnosis 14.3 yr, range 5.9-27.5 yr; mean 15.5 yr after radiotherapy	Chemotherapy: 43.8% Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: NM	1/47 (2.1%) previously undiagnosed MI on resting ECG 1/42 (2.4%) previously undiagnosed MI on 24 hour Holter-ECG (same patient as above with resting ECG) 1/46 (2.2%) ischemia on exercise stress test (i.e. consistent pattern of ischemic changes)	SB: high risk AB: low risk DB: low risk
	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but	Chemotherapy: 72.3% (of 1474 survivors)	Coronary heart disease occurring at least 5 yr after cancer diagnosis (ICD-9 code 410 and 413; allowing both diagnoses per person; 51 patients had both diagnoses): 233/1474 (15.8%)	SB: unclear AB: low risk DB: unclear

			presumably after cancer diagnosis)	Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	Coronary heart disease occurring at least 5 yr after cancer diagnosis (ICD-9 codes 410 and 413; acute MI and angina pectoris combined allowing only 1 event per person): 182/1474 (12.3%)	
					102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	
					22/1474 (1.5%) fatal MI occurring at least 5 yr after cancer diagnosis	
	Castellino 2011[§]	2633 Hodgkin survivors	At least 5 yr from diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: NM	37/2589 (1.4%) fatal ischemic heart disease	SB: low risk AB: low risk DB: unclear
		1927 Hodgkin survivors	Median 23.8 yr from diagnosis, range 16-33 yr for those alive and median 16.1 yr from diagnosis, range 5-31.5 yr for those deceased	Chemotherapy: 58% Radiotherapy: unclear Cardiac irradiation: unclear Stem cell transplant: NM	CTCAEv3 grade 3-5 CAD (i.e. MI; angina or coronary heart disease on anti–angina medication or requiring cardiac catheterization, angioplasty, or CABG): 39/1927 (2%) CAD requiring medication 24/1927 (1.2%) MI	SB: unclear AB: low risk DB: unclear
	Hudson 1998[#]	387 Hodgkin survivors	NM for all survivors; for 316 survivors alive median 15.1 yr from diagnosis, range 2.9 to 28.6	Chemotherapy: 70% Radiotherapy: 96% Cardiac irradiation: NM	5/387 (1.3%) fatal MI Autopsy results in 2 patients showed severe coronary artery atherosclerosis.	SB: low risk AB: low risk DB: unclear

			yr (start point not reported)	Stem cell transplant: NM		
	Machann 2011	31 Hodgkin survivors	Median 24 yr between start of mediastinal radiotherapy and cardiac MRI, range 20-28 yr	Chemotherapy: 45% Radiotherapy: 100% Cardiac irradiation: 100% Stem cell transplant: NM	8/31 (26%) MI defined as typically ischemic enhancement in left ventricular myocardium ranging from small subendocardial to large transmural infarctions on cardiac MRI under rest and stress (using adenosine). 19/31 (61%) perfusion deficit at rest on cardiac MRI (but 1/31 patients aborted the ongoing examination because of claustrophobia) 18/25 (72%) perfusion deficit at stress on cardiac MRI (using adenosine) Any perfusion deficit on cardiac MRI: 21/31 (68%)	SB: unclear AB: low risk DB: unclear
	Mauch 1995~	794 Hodgkin survivors	Median 11 yr (person yr of observation) started at the end of treatment	Chemotherapy: 38% Radiotherapy: 100% Cardiac irradiation: at least 85% Stem cell transplant: NM	10/794 (1.3%) documented fatal MI	SB: low risk AB: low risk DB: unclear
	Chen 2014~	182 Hodgkin survivors	Median 14.8 yr, range 5.2-35.7 yr since completion of radiotherapy	Chemotherapy: 54% Radiotherapy: 100% Cardiac irradiation: max 100% Stem cell transplant: NM	CAD defined as the presence of ischemia on non-invasive imaging, which was confirmed by coronary angiography (presence of 70% coronary stenosis): 8/182 (4.4%) obstructive CAD; all in asymptomatic survivors	SB: unclear AB: low risk DB: unclear
	Materazzo 2017###	83 Hodgkin survivors	Median 25 yr, range 21.6-31.2 yr after completing treatment; for 53	Chemotherapy: 100% Radiotherapy: 100%	Acute MI (CTCAEv3): 4/83 (5%) Stable angina (CTCAEv3): 1/83 (1%) Cardiac symptoms or significant ECG abnormalities during or after stress echocardiogram in asymptomatic survivors: 0/53 (0%)	SB: low risk all survivors; unclear for asymptomatic subgroup

			survivors with an extensive cardiac assessment mean 21 yr after diagnosis	Cardiac irradiation: 89% Stem cell transplant: 0%		AB: low risk DB: unclear
	Strumberg 2002	32 non-seminomatous testicular germ-cell cancer survivors	Median 15 yr, range 13-17 yr (start point not reported)	Chemotherapy: 100% Radiotherapy: 25% Cardiac irradiation: NM Stem cell transplant: NM	0/32 (0%) silent myocardial ischemia 1/32 (3%) MI 0/32 (0%) episodes of angina	SB: unclear AB: low risk DB: unclear
	Van den Belt-Dusebout 2006	919 testicular cancer survivors (seminoma and non-seminoma)	At least 5 yr after cancer diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: 0%	19/919 (2.1%) MI	SB: low risk AB: low risk DB: unclear
	Armstrong 2009[§]	20483 CCS	Mean > 20 yr; range 5-34 yr after diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: NM	44/20483 (0.2%) fatal ischemic heart disease (ICD-9 code 410-414)	SB: unclear AB: low risk DB: unclear
	Green 1999	474 CCS	Median 23.39 yr, mean 24.13±6.13 yr, range 15.04 to 38.54 yr after diagnosis	Chemotherapy: 74% Radiotherapy: 57% Cardiac irradiation: NM	3/474 (0.6%) fatal acute MI (coded using ICD-9)	SB: low risk AB: low risk DB: unclear

				Stem cell transplant: NM		
	Mulrooney 2009[§]	14358 CCS vs 3899 siblings	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis for survivors *6/3899 (0.2%) first MI occurring five or more yr after birth for siblings*	SB: unclear AB: low risk DB: unclear
	Mulrooney 2016[#]	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	SB: high risk AB: low risk DB: unclear
	Oeffinger 2006[§]	10397 CCS vs 3034 siblings	Mean 17.5±4.6 yr, range 6-31 yr interval between cancer diagnosis and completion of questionnaire	Chemotherapy: at least 67.4% Radiotherapy: at least 62.2% Cardiac irradiation: NM Stem cell transplant: NM	CAD (CTCAEv3) starting 5 yr after the date of diagnosis of cancer (for both survivors and siblings): Grade 3 (i.e. CAD on medication): 99/10397 (1%) survivors; *6/3034 (0.2%) siblings* Grade 4 (i.e. MI): 16/10397 (0.2%) survivors; *0/3034 (0%) siblings* Grade 5 (MI death): 19/10397 (0.2%) survivors (not applicable for siblings) *CAD grade 3 or 4 multivariable analyses survivors/siblings: RR 10.4 (95% CI 4.1-25.9)*	SB: unclear AB: low risk DB: unclear
	Van der Pal 2012[##]	1362 CCS	Median 22.5 or 22.2 yr, range 5 to 44.5 yr since	Chemotherapy: 85.7%	Cardiac ischemia/infarction grade 3 or higher (i.e. symptomatic) according to the CTCAEv3 diagnosed more than 5 yr after primary cancer diagnosis:	SB: low risk AB: low risk DB: unclear

			primary cancer diagnosis	Radiotherapy: 43.8% Cardiac irradiation: 19.5% (max. 19.6%) Stem cell transplant: NM	3/1362 (0.2%) grade 3 3/1362 (0.2%) grade 4 0/1362 (0%) grade 5	
	Armstrong 2013[§]	10724 CCS vs 3159 siblings	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5) survivors; *16/3159 (0.5%) siblings.* It was not clear if all CAD cases occurred after the end of treatment.	SB: unclear AB: low risk DB: unclear
	Fidler 2017^	34489 CCS	Mean 18 yr from 5-year survival, range 0-68.7 yr; mean 23 yr from diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: NM	96/34489 (0.28%) ischemic heart disease deaths (according to ICD-5 to ICD-10)	SB: low risk AB: low risk DB: unclear
	Haddy 2016[@]	3162 CCS	Median 26 yr, 25th to 75th percentile 18-32yr from first cancer diagnosis	Chemotherapy: more than 63.8% Radiotherapy: 68.9% Cardiac irradiation: NM Stem cell transplant: NM	CAD diagnosed at least 5 years after childhood cancer diagnosis using criteria of the European Society of Cardiology and/or from the Framingham and PRIME studies; all confirmed CADs were graded according to the CTCAEv3: 20/3162 (0.6%) MI; all grade ≥3 12/3162 (0.4%) angina; 3 grade 1 or 2, 9 grade ≥3	SB: low risk AB: low risk DB: unclear

	Mulrooney 2020[§]	23462 CCS vs 5057 siblings	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including myocardial infarction or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis; *siblings 4/5057 (0.08%)*	SB: high risk AB: low risk DB: unclear
	Feijen 2020[@, ^, ##, ###]	36205 CCS	Median 23 yr, range 5-72.5 yr after primary cancer diagnosis	Chemotherapy: at least 54.5% Radiotherapy: at least 46.2% Cardiac irradiation: NM Stem cell transplant: NM	302/36205 (0.83%) CAD (CTCAEv3.0 grade 3–5) starting 5 years after the first primary cancer diagnosis	SB: low risk AB: low risk DB: unclear

Abbreviations: yr, year(s); CAD, coronary artery disease; LV, left ventricular; vs, versus; CTA, computed tomography angiography; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; PTCA, percutaneous transluminal coronary angioplasty; ECG, electrocardiogram; ICD-*n*, International Classification of Diseases *n*th revision; CCS, childhood cancer survivors; CTCAEv3, Common Terminology Criteria for Adverse Events version 3; CTCAEv4.03, Common Terminology for Adverse Events version 4.03; CCTA, coronary computed tomography angiography; MRI, Magnetic Resonance Imaging; RR, relative risk; 95% CI, 95% confidence interval; SB, selection bias, AB, attrition bias; DB, detection bias.

*, **, #, §, ~, @, ^, ##, ###: possible overlap in included patients; range describes the minimum and maximum value

H. Summary of findings from included studies

Who needs surveillance?

1. What is the risk of CAD in childhood, adolescent and young adult cancer survivors exposed to chemotherapy alone?
a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by chemotherapy dose (lower vs higher dose)?
b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure to chemotherapy?

No studies identified investigating the risk of CAD in CAYA cancer survivors exposed to chemotherapy only.

2. What is the risk of CAD in childhood, adolescent and young adult cancer survivors exposed to radiation alone?
a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by radiotherapy dose (lower vs higher dose)?
b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure to radiation?

No studies identified investigating the risk of CAD in CAYA cancer survivors exposed to radiotherapy only.

3. What is risk of CAD in childhood, adolescent and young adult cancer survivors exposed to both chemotherapy and radiation therapy?
a. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by chemotherapy and radiation therapy dose (lower vs higher dose)?
b. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of exposure (to chemotherapy and radiation therapy)?
c. What is the risk of CAD in childhood, adolescent and young adult cancer survivors treated with stem cell transplant?

No studies identified investigating the risk of CAD in CAYA cancer survivors exposed to both chemotherapy and radiotherapy.

4. What is the added risk of cardiovascular risk factors (i.e. dyslipidemia, hypertension, obesity, inactivity, diabetes mellitus, smoking, genetic factors etc) to CAD in childhood, adolescent and young adult cancer survivors?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.1 Risk CAD with dyslipidemia in multivariable analyses (n= 5 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Hypercholesterolemia: HR 3.0 (95% CI 1.2 to 7.4) P=0.02	SB: low risk AB: low risk DB: unclear CF: high risk
	Küpeli 2010	119 Hodgkin survivors	At least 2 yr from cancer diagnosis to CTA	Chemotherapy: 100% Radiotherapy: 92.4% Cardiac irradiation: 49.6% Stem cell transplant: NM	19/119 (16%) abnormalities on CTA	Lipid profile: risk 2.620 (95% CI 0.698 to 9.825); P=0.153	SB: unclear AB: low risk DB: unclear CF: high risk
	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors)	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Hypercholesterolemia (yes vs no/unknown) HR 4.12 (95% CI 2.68-6.33)	SB: unclear AB: low risk DB: unclear CF: high risk

				Cardiac irradiation: max 89.6% Stem cell transplant: NM	134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Hypercholesterolemia (yes vs no/unknown) HR 4.55 (95% CI 3.10-6.68)	
	Armstrong 2013*	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	After exposure to chest-directed radiotherapy: Dyslipidemia alone: rate ratio 4.7 (95% CI 2.0-10.7) P<0.001 No risk factors: 1.0 Chest-directed radiotherapy present yes/no; dyslipidemia present yes/no: No No: 1.0 No Yes: rate ratio 5.0 (95% CI 2.4-10.3) Yes No: rate ratio 4.6 (95 CI 3.0-6.9) Yes Yes: rate ratio 25.0 (95% CI 15.2-41.3) RERI: 16.4 (95% CI 7.9-29.8); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7%	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Dyslipidemia: HR 3.49 (95% CI 2.11 to 5.77)	SB: high risk AB: low risk DB: unclear CF: low risk

		Stem cell transplant: NM
GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-2	Important limitations: selection bias 1/5 studies low risk, 1/5 studies high and 3/5 unclear risk; attrition bias 5/5 low risk, detection bias 5/5 unclear risk and confounding 3/5 high risk and 2/5 low risk
Consistency:	0	No important inconsistency; all studies show a higher risk of CAD with dyslipidemia (1 non-significant result)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events (wide confidence interval in only 20% of studies)
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in all studies
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999).
Quality of evidence:		⨁⨁⨁⊖ MODERATE
Conclusion:		Dyslipidemia increases the risk of CAD in CAYA cancer survivors (5 studies*, 36206 participants, 667 events, 5 multivariable analyses).

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CTA, computed tomography angiography; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; International Classification of Diseases 9th revision; HR, hazard ratio; 95% CI, 95% confidence interval; CCS, childhood cancer survivors; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03.

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.2 Risk CAD with hypertension in multivariable analyses (n= 3 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Hypertension: HR 3.0 (95% CI 1.6 to 5.8) P=0.002	SB: low risk AB: low risk DB: unclear CF: high risk
	Armstrong 2013*	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	After exposure to chest-directed radiotherapy: Hypertension alone: rate ratio 6.1 (95% CI 3.4-11.2) P<0.001 No risk factors: 1.0 Chest-directed radiotherapy present yes/no; hypertension present yes/no: No No: 1.0 No Yes: rate ratio 8.7 (95% CI 4.8-15.8) Yes No: rate ratio 5.3 (95% CI 3.2-8.7) Yes Yes: rate ratio 37.2 (95% CI 22.2-62.3) RERI: 24.2 (95% CI 11.8-39.7); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Hypertension: HR 4.75 (95% CI 3.37 to 6.69)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Important limitations: selection bias 1/3 studies low risk, 1/3 high risk and 1/3 studies unclear risk, attrition bias 3/3 low risk, detection bias 3/3 unclear risk and confounding 1/3 high risk and 2/3 low risk
Consistency:	0	No inconsistency; all studies show a significant effect of hypertension
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events (wide confidence intervals in only 33% of studies)
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect in all studies
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used. *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999). The study of Aleman 2007 stated "Possibly hypertension did not increase CVD risk because patients with HL diagnosed with hypertension were adequately treated whereas the reference group of patients without known hypertension may include undiagnosed hypertension". The guideline panel decided that antihypertensive treatment could have a possible confounding effect and therefore to exclude this study from the conclusions about hypertension.
Quality of evidence:		⨁⨁⨁⨁ HIGH
Conclusion:		Hypertension increases the risk of CAD in CAYA cancer survivors (3 studies*, 34601 participants, 412 events, 3 multivariable analyses).

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03.

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.3 Risk CAD with diabetes mellitus in multivariable analyses (n= 3 studies)	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Diabetes mellitus (yes vs no/unknown) HR 1.44 (95% CI 0.73-2.83)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Diabetes mellitus (yes vs no/unknown) HR 2.43 (95% CI 1.45-4.09)	
	Armstrong 2013*	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	After exposure to chest-directed radiotherapy: Diabetes alone: rate ratio 2.7 (95% CI 0.4-20.0) P=0.32 No risk factors: 1.0	SB: unclear AB: low risk DB: unclear CF: low risk
						Chest-directed radiotherapy present yes/no; diabetes present yes/no: No No: 1.0 No Yes: rate ratio 5.2 (95% CI 2.2-12.5) Yes No: rate ratio 5.1 (95% CI 3.5-7.5) Yes Yes: rate ratio 20.1 (95% CI 10.6-38.4) RERI: 10.8 (95% CI 0.0-28.6); not statistically significant	
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4%	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade	Diabetes: HR 1.55 (95% CI 0.67 to 3.58))	SB: high risk AB: low risk DB: unclear CF: low risk

			Cardiac irradiation: at least 49.7% Stem cell transplant: NM	3-5) occurring at least 5 years after cancer diagnosis
GRADE assessment:				
Study design:	+4	Observational studies		
Study limitations:	-1	Important limitations: selection bias 1/3 high risk and 2/3 studies unclear risk; attrition bias 3/3 low risk, detection bias 3/3 unclear risk and confounding 1/3 high risk and 2/3 low risk		
Consistency:	0	No important inconsistency; all studies show a higher risk of CAD with diabetes (1 study showed a significant effect on angina pectoris, and 1 study on CAD; other studies showed non-significant results)		
Directness:	0	Population and outcome definitions broadly generalizable		
Precision:	0	Some imprecision; large study populations and high number of events (wide confidence intervals in only 33% of the studies)		
Publication bias:	0	Unlikely		
Effect size:	0	No large magnitude of effect in all multivariable analyses		
Dose-response:	0	Unclear if dose-response relationship		
Plausible confounding:	0	No plausible confounding		
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999).		
Quality of evidence:		⨁⨁⨁⊖ MODERATE		
Conclusion:		Diabetes mellitus increases the risk of CAD in CAYA cancer survivors (3 studies*, 35672 participants, 606 events, 3 multivariable analyses)		

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; MI, myocardial infarction; ICD-9, International Classification of Diseases 9th revision; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03.

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.4 Risk CAD with recent smoking in multivariable analyses (n= 2 studies)	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Recent smoking (yes vs no/unknown) HR 2.04 (95% CI 1.29-3.23)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Recent smoking (yes vs no/unknown) HR 1.35 (95% CI 0.85-2.16)	
	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	After exposure to chest-directed radiotherapy: Smoking was not found to be associated with risk of a major cardiac event; specific risks not presented.	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:

Study design:	+4	Observational studies
Study limitations:	-2	Important limitations: selection bias 2/2 studies unclear risk; attrition bias 2/2 low risk, detection bias 2/2 unclear risk and confounding 1/2 high risk and 1/2 low risk
Consistency:	-1	Important inconsistency; 1 study showed a significant higher risk of acute MI with recent smoking and a non-significant higher risk of angina pectoris, and 1 study showed no higher risk of CAD with smoking (non-significant result, unclear in which direction)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all multivariable analyses
Dose-response:	0	Unclear if dose-response relationship

Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used; the guideline panel assumed that the direction of effect for the Armstrong 2013 study was a higher risk as smoking is unlikely to be protective for CAD.
Quality of evidence:		⨁⊖⊖⊖ VERY LOW
Conclusion:		(Recent) smoking increases the risk of CAD in CAYA cancer survivors (2 studies, 12210 participants, 420 events, 2 multivariable analyses).

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; MI, myocardial infarction; ICD-9, International Classification of Diseases 9th revision; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias, AB; attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03.

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.5 Risk CAD with obesity in multivariable analyses (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	After exposure to chest-directed radiotherapy: Obesity alone: rate ratio 2.8 (95% CI 1.5-5.3) P=0.001 No risk factors: 1.0 Chest-directed radiotherapy present yes/no; obesity present yes/no: No No: 1.0 No Yes: rate ratio 1.4 (95% CI 0.7-2.6) Yes No: rate ratio 4.6 (95% CI 3.1-7.0) Yes Yes: rate ratio 9.3 (95% CI 5.6-15.5) RERI: 4.3 (95% CI 0.9-8.7); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision; only 1 study included but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Obesity increases the risk of CAD in CAYA cancer survivors (1 study, 10724 participants, 184 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
4.6 Risk CAD with 1 or more cardiovascular risk factors in multivariable analyses (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	Four risk factors (hypertension, dyslipidemia, diabetes, obesity): rate ratio 17.6 (95% CI 5.3-58.3) P<0.001 Any 3 risk factors: rate ratio 13.7 (95% CI 6.7-27.8) P<0.001 Any 2 risk factors: rate ratio 10.4 (95% CI 6.1-17.7) P<0.001 Any 1 risk factor: rate ratio 4.0 (95% CI 2.5-6.4) P<0.001 None : 1.0	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-2	Important imprecision; only 1 study included and wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	+1	Dose-response relationship as there is an increase in risk with an increase in number of risk factors present
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		An increase in the number of cardiovascular risk factors (hypertension, dyslipidemia, diabetes, obesity) increases the risk of CAD in CAYA cancer survivors (1 study, 1486 participants, 236 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

5. What is the risk of CAD in childhood, adolescent and young adult cancer survivors treated with chemotherapy?

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.1 Risk CAD after chemotherapy in multivariable analysis (n= 2 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Chemotherapy: HR 0.7 (95% CI 0.4 to 1.5) P=0.41	SB: low risk AB: low risk DB: unclear CF: high risk
	Feijen 2020	36205 CCS	Median 23 yr, range 5-72.5 yr after primary cancer diagnosis	Chemotherapy: at least 54.5% Radiotherapy: at least 46.2% Cardiac irradiation: NM Stem cell transplant: NM	302/36205 (0.83%) CAD (CTCAEv3.0 grade 3–5) starting 5 years after the first primary cancer diagnosis	No treatment/surgery only Reference Chemotherapy +/- surgery HR 1.6 (95% CI 0.89-2.8)	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Important limitations: selection bias 2/2 studies low risk; attrition bias 2/2 low risk, detection bias 2/2 unclear risk and confounding 1/2 high risk and 1/2 low risk
Consistency:	0	No important inconsistency: the non-significant results show overlapping confidence intervals
Directness:	0	Population and outcome definition broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship

Plausible confounding:	0	No plausible confounding
Other considerations:		Different outcome definitions of CAD used
Quality of evidence:		⊕⊕⊕⊖ MODERATE
Conclusion:		No significant effect of chemotherapy on the risk of CAD in CAYA cancer survivors (2 studies, 36620 participants, 344 events, 2 multivariable analyses).

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; HR, hazard ratio; 95% CI, 95% confidence interval; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; CCS, childhood cancer survivors; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.2 Risk CAD after vincristine in multivariable analysis (n= 1 study)	Mulrooney 2009	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Vincristine vs none HR 0.7 (95% CI 0.4 to 1.1) P=0.081	SB: unclear AB: low risk DB: unclear CF: low risk
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk					
Consistency:	0	NA (1 study)					
Directness:	0	Population and outcome definition broadly generalizable					
Precision:	-1	Some imprecision; only 1 study included but narrow confidence interval					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding:	0	No plausible confounding					
Other considerations							
Quality of evidence:	⊕⊕⊖⊖ LOW						
Conclusion:	No significant effect of treatment with vincristine on the risk of CAD in CAYA cancer survivors (1 study, 14358 participants, 101 events, 1 multivariable analysis).						

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors, NM, not mentioned; NA, not applicable; MI, myocardial infarction; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.3 Risk CAD after anthracycline containing chemotherapy in multivariable analysis (n= 4 studies)	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Anthracycline (mg/m^2): None OR 1.0 < 250 OR 2.0 (95% CI 0.9-4.6) ≥ 250 OR 2.0 (95% CI 0.7-5.4)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2009*	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Anthracycline vs none (Test for trend (P value)-(0.8)): <250 mg/m^2 HR 1.3 (95% CI 0.6 to 2.8) P=0.50 ≥250 mg/m^2 HR 1.1 (95% 0.5 to 2.1) P=0.87	SB: unclear AB: low risk DB: unclear CF: low risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Anthracycline dose (mg/m^2): None HR 1.0 <250 HR 1.42 (95% CI 0.93 to 2.16) ≥250 HR 1.77 (95% CI 1.15 to 2.72)	SB: high risk AB: low risk DB: unclear CF: low risk

	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Anthracycline-containing chemotherapy (yes vs no) HR 0.90 (95% CI 0.50-1.62)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Anthracycline-containing chemotherapy (yes vs no) HR 1.49 (95% CI 0.89-2.49)	
GRADE assessment:							
Study design:	+4	Observational study					
Study limitations:	-1	Important limitations: selection bias 2/4 studies unclear risk and 2/4 high risk; attrition bias 4/4 low risk, detection bias 4/4 unclear risk, confounding 3/4 low risk and 1/4 high risk					
Consistency:	0	No inconsistency; almost all studies show (non-)significant effect of anthracycline containing chemotherapy					
Directness:	0	Population and outcome definition broadly generalizable					
Precision:	-1	Some imprecision; large study populations and high number of events; however, only one study showed a significant effect					
Publication bias:	0	Unlikely					
Effect size:	0	No large magnitude of effect					
Dose-response:	0	Unclear if dose-response relationship					
Plausible confounding:	0	No plausible confounding					
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999).					
Quality of evidence:		⊕⊕⊖⊖ LOW					
Conclusion:		No significant effect of anthracycline containing chemotherapy as compared to no anthracycline containing chemotherapy when cumulative anthracycline dose is not taken into account (4 studies*; 41159 participants, 592 events, 4 multivariable analyses)					

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; MI, myocardial infarction; ICD-9, International Classification of Diseases 9th revision; HR, hazard ratio; OR, odds ratio; 95% CI, 95% confidence interval; CCS, childhood cancer survivor; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; ECG, electrocardiogram; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.4 Risk CAD after different anthracycline doses in multivariable analysis (n= 3 studies)	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Anthracycline (mg/m^2): None OR 1.0 < 250 OR 2.0 (95% CI 0.9-4.6) ≥ 250 OR 2.0 (95% CI 0.7-5.4)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2009*	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Anthracycline vs none (Test for trend (P value)-(0.8)): <250 mg/m^2 HR 1.3 (95% CI 0.6 to 2.8) P=0.50 ≥250 mg/m^2 HR 1.1 (95% 0.5 to 2.1) P=0.87	SB: unclear AB: low risk DB: unclear CF: low risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Anthracycline dose (mg/m^2): None HR 1.0 <250 HR 1.42 (95% CI 0.93 to 2.16) ≥250 HR 1.77 (95% CI 1.15 to 2.72)	SB: high risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Important limitations: selection bias 1/3 studies unclear risk and 2/3 high risk; attrition bias 3/3 low risk, detection bias 3/3 unclear risk and confounding 3/3 low risk
Consistency:	0	No inconsistency; all studies show (non-)significant effect of anthracycline dose
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision; large study populations and high number of events; however, only one study showed a significant effect
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	No clear dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999).
Quality of evidence:		⨁⨁⨀⨀ LOW
Conclusion:		Anthracycline dose ≥250 mg/m^2 increases the risk of CAD in CAYA cancer survivors as compared to no anthracyclines (3 studies*, 39673 participants, 356 events, 3 multivariable analyses) No significant effect of treatment with anthracycline doses <250 mg/m2 on the risk of CAD in CAYA cancer survivors as compared to no anthracycline containing chemotherapy (3 studies*, 39673 participants, 356 events, 3 multivariable analyses)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors; NM, not mentioned; MI, myocardial infarction; ECG, electrocardiogram; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.5 Risk CAD after mediastinal radiotherapy + chemotherapy, no anthracyclines in multivariable analysis (n= 1 study)	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Mediastinal radiotherapy HR 1.00 Mediastinal radiotherapy + chemotherapy, no anthracyclines HR 1.17 (95% CI 0.75-1.83)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Mediastinal radiotherapy HR 1.00 Mediastinal radiotherapy + chemotherapy, no anthracyclines HR 0.78 (95% CI 0.53-1.15)	

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-2	Important limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 high risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision, only 1 study included but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:	⊕⊖⊖⊖ VERY LOW	

Conclusion:	No significant effect of treatment with mediastinal radiotherapy and chemotherapy (no anthracyclines) as compared to mediastinal radiotherapy only on the risk of CAD in CAYA cancer survivors (1 study, 1486 participants, 236 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; NA, not applicable; MI, myocardial infarction; ICD-9, International Classification of Diseases 9th revision; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
5.6 Risk CAD after mediastinal radiotherapy + chemotherapy, anthracyclines in multivariable analysis (n= 1 study)	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Mediastinal radiotherapy HR 1.00 Mediastinal radiotherapy + chemotherapy, anthracyclines HR 1.00 (95% CI 0.52-1.94)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Mediastinal radiotherapy HR 1.00 Mediastinal radiotherapy + chemotherapy, anthracyclines HR 1.32 (95% CI 0.76-2.30)	

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-2	Important limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 high risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision, only 1 study included but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊖⊖⊖ VERY LOW
Conclusion:		No significant effect of treatment with mediastinal radiotherapy and chemotherapy (including anthracyclines) as compared to mediastinal radiotherapy only on the risk of CAD in CAYA cancer survivors (1 study, 1486 participants, 236 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; NM, not mentioned; NA, not applicable; MI, myocardial infarction; ICD-9, International Classification of Diseases 9th revision; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

6. What is the risk of CAD in childhood, adolescent and young adult cancer survivors treated with radiotherapy?

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.1 Risk CAD after radiotherapy exposing the heart in multivariable analysis (n= 7 studies)	Küpeli 2010	119 Hodgkin survivors	At least 2 yr from cancer diagnosis to CTA	Chemotherapy: 100% Radiotherapy: 92.4% Cardiac irradiation: 49.6% Stem cell transplant: NM	19/119 (16%) abnormalities on CTA	Mediastinal radiotherapy dose (Gy): Dose: P=0.03 ≤20: risk 1.739 (95% CI 0.449 to 6.740); P=0.423 >20: risk 6.817 (95% CI 1.612 to 28.820); P=0.009	SB: unclear AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Average cardiac radiation dose (cGy): None OR 1.0 ≤ 1500 OR 2.2 (95% CI 0.7-7.1) > 1500 OR 10.5 (95% CI 4.2-26.3)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2009*	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Average cardiac radiation dose (Test for trend (P value)-all outcomes (<0.001)): No cardiac radiation HR 1.0 (reference group) <500 cGy HR 0.7 (95% CI 0.4 to 1.4) P=0.36 500 to <1500 cGy HR 0.6 (95% CI 0.1 to 2.5) P=0.45 1500 to <3500 cGy HR 2.4 (95% CI 1.2 to 4.9) P=0.011	SB: unclear AB: low risk DB: unclear CF: low risk

						≥3500 cGy HR 3.6 (95% CI 1.9 to 6.9) P<0.001	
	Haddy 2016	3162 CCS	Median 26 yr, 25th to 75th percentile 18-32yr from first cancer diagnosis.	Chemotherapy: more than 63.8% Radiotherapy: 68.9% Cardiac irradiation: NM Stem cell transplant: NM	CAD diagnosed at least 5 years after childhood cancer diagnosis using criteria of the European Society of Cardiology and/or from the Framingham and PRIME studies; all confirmed CADs were graded according to the CTCAEv3: 20/3162 (0.6%) MI; all grade ≥3 12/3162 (0.4%) angina; 3 grade 1 or 2, 9 grade ≥3	N=29 grade ≥3 ischemic diseases: Anthracycline no: Cardiac radiation dose (Gy): <1 (N=4): RR 1 (reference group) 1-15 (N=5): RR 1.8 (95% CI 0.5-7.0) ≥15 (N=16): RR 6.3 (95% CI 1.8-21.3) Anthracycline yes: Cardiac radiation dose (Gy): <1 (N=1): RR 0.8 (95% CI 0.07-8.0) 1-15 (N=2): RR 6.4 (95% CI 1.0-39.6) ≥15 (N=1): RR 2.3 (95% CI 0.2-22.6)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Mean heart dose (Gy): None HR 1.0 1-15 HR 1.31 (95% CI 0.88 to 1.96) 15.1-34.99 HR 2.26 (95% CI 1.32 to 3.84) ≥35 HR 5.86 (95% CI 3.69 to 9.28)	SB: high risk AB: low risk DB: unclear CF: low risk
	Feijen 2020	36205 CCS	Median 23 yr, range 5-72.5 yr after primary cancer diagnosis	Chemotherapy: at least 54.5% Radiotherapy: at least 46.2% Cardiac irradiation: NM	302/36205 (0.83%) CAD (CTCAEv3 grade 3–5) starting 5 years after the first primary cancer diagnosis	No treatment/surgery only Reference Radiotherapy +/- surgery HR 2.0 (95% CI 1.4-2.9) *Primary cancer diagnosis* *Leukemia Reference*	SB: low risk AB: low risk DB: unclear CF: low risk

				Stem cell transplant: NM		*Lymphoma HR 3.4 (95% CI 2.0 to 5.3)* *Central nervous system HR 0.9 (95% CI 0.5 to 1.4)* *Bone and soft tissue sarcoma HR 1.5 (95% CI 0.9 to 2.5)* *Other tumors HR 1.3 (95% CI 0.8 to 2.1)*	
	Aleman 2007	1486 Hodgkin survivors	Median 18.7 yr, at least 5 yr (starting point not reported, but presumably after cancer diagnosis)	Chemotherapy: 72.3% (of 1474 survivors) Radiotherapy: 95% (of 1474 survivors) Cardiac irradiation: max 89.6% Stem cell transplant: NM	102/1474 (6.9%) acute MI occurring at least 5 yr after cancer diagnosis (ICD-9 code 410)	Mediastinal radiotherapy (yes vs no) HR 2.42 (95% CI 1.12-5.24)	SB: unclear AB: low risk DB: unclear CF: high risk
					134/1474 (9%) angina pectoris occurring at least 5 yr after cancer diagnosis (ICD-9 code 413)	Mediastinal radiotherapy (yes vs no) HR 4.85 (95% CI 1.97-11.9)	

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	selection bias 2/7 study low risk, 3/7 unclear risk and 2/7 high risk; attrition bias 7/7 low risk; detection bias 7/7 unclear risk and confounding 5/7 low risk and 2/7 high risk
Consistency:	0	No inconsistency; all studies show a (non-)significant higher risk of CAD with radiotherapy exposing the heart
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision; large study populations and high number of events but wide confidence intervals in almost 50% of studies
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all multivariable analyses
Dose-response:	+1	Dose-response relationship in almost all multivariable analyses
Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999); in Feijen 2020 the exact location of radiotherapy was not specified, but based on primary cancer diagnosis and treatment era we assumed that many of the CCS did receive radiotherapy exposing the heart
Quality of evidence:		⊕⊕⊕⊖ MODERATE

Conclusion:	Radiotherapy exposing the heart increases the risk of CAD in CAYA cancer survivors (7 studies*, 80645 participants, 945 events, 7 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors; CTA, computed tomography angiography; NM, not mentioned; MI, myocardial infarction; ECG, electrocardiogram; OR, odds ratio; HR, hazard ratio; RR, relative risk; 95% CI, 95% confidence interval; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; CTCAEv3, Common Terminology Criteria for Adverse Events version 3; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.2 Risk CAD after different doses of radiotherapy exposing the heart in multivariable analysis (n= 6 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Mantle or subdiaphragmatic field vs matched mantle and subdiaphragmatic fields: HR 7.8 (95% CI 1.1 to 53.2) P=0.04 *(previous irradiation technique used before 1990 that resulted in a 50% or more increase in total dose over a small section of cardiac tissue was associated with the development of CAD)* Greater than median total radiation therapy dose: HR 0.8 (95% CI 0.4 to 1.7) P=0.57	SB: low risk AB: low risk DB: unclear CF: high risk
	Küpeli 2010	119 Hodgkin survivors	At least 2 yr from cancer diagnosis to CTA	Chemotherapy: 100% Radiotherapy: 92.4% Cardiac irradiation: 49.6% Stem cell transplant: NM	19/119 (16%) abnormalities on CTA	Mediastinal radiotherapy dose (Gy): Dose: P=0.03 ≤20: risk 1.739 (95% CI 0.449 to 6.740); P=0.423 >20: risk 6.817 (95% CI 1.612 to 28.820); P=0.009	SB: unclear AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Average cardiac radiation dose (cGy): None OR 1.0 ≤ 1500 OR 2.2 (95% CI 0.7-7.1) > 1500 OR 10.5 (95% CI 4.2-26.3)	SB: high risk AB: low risk DB: unclear CF: low risk

	Mulrooney 2009*	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Average cardiac radiation dose (Test for trend (P value)-all outcomes (<0.001)): No cardiac radiation HR 1.0 (reference group) <500 cGy HR 0.7 (95% CI 0.4 to 1.4) P=0.36 500 to <1500 cGy HR 0.6 (95% CI 0.1 to 2.5) P=0.45 1500 to <3500 cGy HR 2.4 (95% CI 1.2 to 4.9) P=0.011 ≥3500 cGy HR 3.6 (95% CI 1.9 to 6.9) P<0.001	SB: unclear AB: low risk DB: unclear CF: low risk
	Haddy 2016	3162 CCS	Median 26 yr, 25th to 75th percentile 18-32yr from first cancer diagnosis.	Chemotherapy: more than 63.8% Radiotherapy: 68.9% Cardiac irradiation: NM Stem cell transplant: NM	CAD diagnosed at least 5 years after childhood cancer diagnosis using criteria of the European Society of Cardiology and/or from the Framingham and PRIME studies; all confirmed CADs were graded according to the CTCAEv3: 20/3162 (0.6%) MI; all grade ≥3 12/3162 (0.4%) angina; 3 grade 1 or 2, 9 grade ≥3	N=29 grade ≥3 ischemic diseases: Anthracycline no: Cardiac radiation dose (Gy): <1 (N=4): RR 1 (reference group) 1-15 (N=5): RR 1.8 (95% CI 0.5-7.0) ≥15 (N=16): RR 6.3 (95% CI 1.8-21.3) Anthracycline yes: Cardiac radiation dose (Gy): <1 (N=1): RR 0.8 (95% CI 0.07-8.0) 1-15 (N=2): RR 6.4 (95% CI 1.0-39.6) ≥15 (N=1): RR 2.3 (95% CI 0.2-22.6)	SB: low risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7%	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5	Mean heart dose (Gy): None HR 1.0 1-15 HR 1.31 (95% CI 0.88 to 1.96) 15.1-34.99 HR 2.26 (95% CI 1.32 to 3.84) ≥35 HR 5.86 (95% CI 3.69 to 9.28)	SB: high risk AB: low risk DB: unclear CF: low risk

		Stem cell transplant: NM	years after cancer diagnosis
GRADE assessment:			
Study design:	+4	Observational studies	
Study limitations:	-1	Important limitations: selection bias 2/6 studies low risk, 2/6 unclear risk and 2/6 high risk; attrition bias 6/6 low risk, detection bias 6/6 unclear risk and confounding 4/6 low risk and 2/6 high risk	
Consistency:	0	No important inconsistency: most studies show significant effect of dose of radiotherapy exposing the heart, confidence intervals overlap	
Directness:	0	Population and outcome definitions broadly generalizable	
Precision:	-1	Some imprecision; large study populations and high number of events but wide confidence intervals in 67% of studies	
Publication bias:	0	Unlikely	
Effect size:	0	No large magnitude of effect in all multivariable analyses	
Dose-response:	+1	Dose-response relationship in almost all multivariable analyses	
Plausible confounding:	0	No plausible confounding	
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999).	
Quality of evidence:		⊕⊕⊕⊖ MODERATE	
Conclusion:		Higher doses of radiotherapy exposing the heart, especially doses of 15 Gy and higher, increase the risk of CAD in CAYA cancer survivors (6 studies*, 43369 participants, 449 events, 6 multivariable analyses)	

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors; CTA, computed tomography angiography; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; ECG, electrocardiogram; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; CTCAEv3, Common Terminology Criteria for Adverse Events version 3; RR, relative risk; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.3 Risk CAD after chest-directed radiotherapy and/or hypertension in multivariable analysis (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	Chest-directed radiotherapy present yes/no; hypertension present yes/no: No No: 1.0 No Yes: rate ratio 8.7 (95% CI 4.8-15.8) Yes No: rate ratio 5.3 (95% CI 3.2-8.7) Yes Yes: rate ratio 37.2 (95% CI 22.2-62.3) RERI: 24.2 (95% CI 11.8-39.7); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The interaction between chest-directed radiotherapy and hypertension is more than additive with regard to the increased risk of CAD in CAYA cancer survivors (1 study, 10724 participants, 184 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.4 Risk CAD after chest-directed radiotherapy and/or dyslipidemia in multivariable analysis (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	Chest-directed radiotherapy present yes/no; dyslipidemia present yes/no: No No: 1.0 No Yes: rate ratio 5.0 (95% CI 2.4-10.3) Yes No: rate ratio 4.6 (95 CI 3.0-6.9) Yes Yes: rate ratio 25.0 (95% CI 15.2-41.3) RERI: 16.4 (95% CI 7.9-29.8); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The interaction between chest-directed radiotherapy and dyslipidemia is more than additive with regard to the increased risk of CAD in CAYA cancer survivors (1 study, 10724 participants, 184 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.5 Risk CAD after chest-directed radiotherapy and/or diabetes in multivariable analysis (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	Chest-directed radiotherapy present yes/no; diabetes present yes/no: No No: 1.0 No Yes: rate ratio 5.2 (95% CI 2.2-12.5) Yes No: rate ratio 5.1 (95% CI 3.5-7.5) Yes Yes: rate ratio 20.1 (95% CI 10.6-38.4) RERI: 10.8 (95% CI 0.0-28.6); not statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-2	Important imprecision, only 1 study included with wide confidence intervals
Publication bias:	0	Unlikely
Effect size:	+1	Large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		No significant additive interaction between chest-directed radiotherapy and diabetes on the risk of CAD in CAYA cancer survivors (1 study, 10724 participants, 184 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
6.6 Risk CAD after chest-directed radiotherapy and/or obesity in multivariable analysis (n= 1 study)	Armstrong 2013	10724 CCS	Median 25.6 yr, range 7.4-39.3 yr from cancer diagnosis	Chemotherapy: at least 35.2% Radiotherapy: at least 23.6% Cardiac irradiation: NM (at least 23.6% chest-directed) Stem cell transplant: NM	184/10724 (1.8%) CAD (CTCAEv4.03 grade 3-5); it was not clear if all CAD cases occurred after the end of treatment	Chest-directed radiotherapy present yes/no; obesity present yes/no: No No: 1.0 No Yes: rate ratio 1.4 (95% CI 0.7-2.6) Yes No: rate ratio 4.6 (95% CI 3.1-7.0) Yes Yes: rate ratio 9.3 (95% CI 5.6-15.5) RERI: 4.3 (95% CI 0.9-8.7); statistically significant	SB: unclear AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational study
Study limitations:	-1	Some limitations: selection bias 1/1 study unclear risk; attrition bias 1/1 low risk, detection bias 1/1 unclear risk and confounding 1/1 low risk
Consistency:	0	NA (1 study)
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	-1	Some imprecision, only 1 study included but narrow confidence intervals
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding
Other considerations		
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		The interaction between chest-directed radiotherapy and obesity is more than additive with regard to the increased risk of CAD in CAYA cancer survivors (1 study, 10724 participants, 184 events, 1 multivariable analysis)

Footnote: range describes the minimum and maximum value

Abbreviations: yr, year(s); CAD, coronary artery disease; NM, not mentioned; 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CCS, childhood cancer survivors; RERI, relative excess risk due to interaction; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; NA, not applicable.

7. Does the risk of CAD in childhood, adolescent and young adult cancer survivors vary by gender or age of treatment exposure?

Outcome	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
7.1 Risk CAD by gender in multivariable analysis (n= 6 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Male sex: HR 2.9 (95% CI 1.4 to 6.0) P=0.01	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Female sex: OR 1.0 Male sex: OR 1.7 (95% CI 0.9-3.2)	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2009*	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max 71%)	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Male sex: HR 1.0 (reference group) Female sex: HR 0.6 (95% CI 0.4 to 0.9) P=0.014	SB: unclear AB: low risk DB: unclear CF: low risk

				Stem cell transplant: NM			
	Fidler 2017^	34489 CCS	Mean 18 yr from 5-year survival, range 0-68.7 yr; mean 23 yr from diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: NM	96/34489 (0.28%) ischemic heart disease deaths (according to ICD-5 to ICD-10)	Male RR 1 (reference) Female RR 1.9 (95% CI 1.2-3.0)	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulrooney 2020*	23462 CCS	Median 20.5 yr, range 7.0-39.3 yr from diagnosis	Chemotherapy: at least 73.8% Radiotherapy: at least 51.4% Cardiac irradiation: at least 49.7% Stem cell transplant: NM	186/23462 (0.79%) CAD (including MI or coronary revascularization; CTCAE v4.03 grade 3-5) occurring at least 5 years after cancer diagnosis	Male HR 1.0 Female HR 0.87 (95% CI 0.62-1.23)	SB: high risk AB: low risk DB: unclear CF: low risk
	Feijen 2020^	36205 CCS	Median 23 yr, range 5-72.5 yr after primary cancer diagnosis	Chemotherapy: at least 54.5% Radiotherapy: at least 46.2% Cardiac irradiation: NM Stem cell transplant: NM	302/36205 (0.83%) CAD (CTCAEv3.0 grade 3–5) starting 5 years after the first primary cancer diagnosis	Male (Reference) Female HR 0.5 (95% CI 0.35-0.60) *"When we focus on the first 30 years of age, there is no statistically significant difference between male and female CCS. However, after 30 years of age the risk of ischemic heart disease in males increases steadily. Females treated with chemotherapy and/or radiotherapy seem to have the same risk as males treated without treatment/surgery only, again the difference did not reach statistical significance."*	SB: low risk AB: low risk DB: unclear CF: low risk

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Important limitations: selection bias 3/6 studies low risk, 1/6 unclear risk and 2/6 high risk; attrition bias 6/6 low risk, detection bias 6/6 unclear risk and confounding 4/6 low risk and 2/6 high risk
Consistency:	-1	Some inconsistency; most studies show a higher risk of CAD in males or a lower risk of CAD in females (2 non-significant results), 1 study shows a significant higher risk of CAD in females
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	NA
Plausible confounding:	0	No plausible confounding
Other considerations		Different outcome definitions of CAD used; *Possible overlap in study populations; Mulrooney 2020 has an expanded cohort (years of diagnosis 1987-1999); ^Possible overlap in study populations.
Quality of evidence:		⊕⊕⊖⊖ LOW
Conclusion:		Male gender increases the risk of CAD in CAYA cancer survivors (6 studies*^, 110782 participants, 796 events, 6 multivariable analyses)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; ECG, electrocardiogram; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; CTCAEv3, Common Terminology Criteria for Adverse Events version 3; RR, relative risk; ICD-X, International Classification of Diseases Xth revision.

Subgroup	Study	No. of participants	Follow up (median/mean, range) yr	Treatment	Events	Effect size	Risk of bias
7.2 Risk CAD by age at diagnosis or treatment in multivariable analysis (n= 5 studies)	Hull 2003	415 Hodgkin survivors	Median 11.2 yr, range 2.1-36.3 yr (starting point not reported)	Chemotherapy: 62% Radiotherapy: 100% Cardiac irradiation: 97% Stem cell transplant: NM	42/404 survivors in cardiac radiotherapy group (10.4%) CAD (i.e. a history of documented MI, CABG, percutaneous coronary intervention, or >75% diameter stenosis on coronary angiography or autopsy)	Older than median age at radiation therapy: HR 8.1 (95% CI 3.2 to 20.3) P=<0.001	SB: low risk AB: low risk DB: unclear CF: high risk
	Mulrooney 2016	1853 CCS	Median 22.6 yr (range 10-48 yr) from diagnosis	Chemotherapy: at least 82% Radiotherapy: at least 42% Cardiac irradiation: at least 42% (max. 43.3%) Stem cell transplant: NM	69/1853 (3.8%) CAD defined as a history of MI, evidence of wall motion defect on echocardiography, or ischemia on ECG	Age at diagnosis (yr): 0-4 OR 0.5 (95% CI 0.2-1.3) 5-9 OR 0.8 (95% CI 0.3-1.9) 10-14 OR 0.4 (95% CI 0.2-1.1) ≥ 15 OR 1.0	SB: high risk AB: low risk DB: unclear CF: low risk
	Mulrooney 2009	14358 CCS	Median 13 yr, range 0-27 yr, mean 20 yr since cohort entry (at least 5 yr after cancer diagnosis)	Chemotherapy: 70.3% Radiotherapy: at least 59.3% (max 72.1%) Cardiac irradiation: at least 56.5% (max. 71%) Stem cell transplant: NM	101/14358 (0.7%) first MI occurring more than 5 yr after cancer diagnosis	Age at diagnosis: 0-4 yr HR 1.0 (95% CI 0.4 to 3.0) P=0.96 5-9 yr HR 1.9 (95% CI 0.9 to 4.0) P=0.090 10-14 yr HR 0.8 (95% CI 0.4 to 1.5) P=0.49 15-20 yr HR 1.0 (reference group)	SB: unclear AB: low risk DB: unclear CF: low risk

	Fidler 2017^	34489 CCS	Mean 18 yr from 5-year survival, range 0-68.7 yr; mean 23 yr from diagnosis	Chemotherapy: NM Radiotherapy: NM Cardiac irradiation: NM Stem cell transplant: NM	96/34489 (0.28%) ischemic heart disease deaths (according to ICD-5 to ICD-10)	Age at diagnosis: 0-4 years 1 (reference) 5-9 years RR 0.9 (95% CI 0.5-1.8) 10-14 years RR 0.8 (95% CI 0.4-1.6) Ptrend=0.5110	SB: low risk AB: low risk DB: unclear CF: high risk
	Feijen 2020^	36205 CCS	Median 23 yr, range 5-72.5 yr after primary cancer diagnosis	Chemotherapy: at least 54.5% Radiotherapy: at least 46.2% Cardiac irradiation: NM Stem cell transplant: NM	302/36205 (0.83%) CAD (CTCAEv3.0 grade 3–5) starting 5 years after the first primary cancer diagnosis	Age at primary childhood cancer diagnosis (continuous): HR 1.01 (95% CI 0.98-1.04) in the model with treatment groups Age at primary childhood cancer diagnosis (continuous; decreasing risk with increasing age): HR 0.97 (95% CI 0.93 to 0.99) in the model with cancer diagnosis	SB: low risk AB: low risk DB: unclear CF: low risk (treatment groups model) / high risk (cancer diagnosis model)

GRADE assessment:		
Study design:	+4	Observational studies
Study limitations:	-1	Important limitations: selection bias 3/5 studies low risk, 1/5 unclear risk and 1/5 high risk; attrition bias 5/5 low risk, detection bias 5/5 unclear risk and confounding in treatment groups model 3/5 low risk and 2/5 high risk / confounding in primary cancer diagnosis model 2/5 low risk and 3/5 high risk
Consistency:	0	No important inconsistency: confidence intervals overlap (1 study shows significant effect of older than mean age at treatment; 3 studies don't show a significant effect of age at diagnosis; in 1 study it depends on the used model (either significant effect for decreasing risk with increasing age at diagnosis or no significant effect))
Directness:	0	Population and outcome definitions broadly generalizable
Precision:	0	No important imprecision; large study populations and high number of events (wide confidence interval in only 20% of studies)
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect in all studies
Dose-response:	0	Unclear if dose-response relationship
Plausible confounding:	0	No plausible confounding

Other considerations	Different outcome definitions of CAD used; ^Possible overlap in study populations.
Quality of evidence:	⊕⊕⊕⊖ MODERATE
Conclusion:	Conflicting evidence for the effect of age at treatment on the risk of CAD in CAYA cancer survivors (5 studies^, 87320 participants, 610 events, 5 multivariable analyses)

Footnote: range describes the minimum and maximum value

Abbreviations: CAYA, childhood, adolescent and young adult; yr, year(s); CAD, coronary artery disease; CCS, childhood cancer survivors; NM, not mentioned; MI, myocardial infarction; CABG, coronary bypass graft surgery; ECG, electrocardiogram; OR, odds ratio; HR, hazard ratio; 95% CI, 95% confidence interval; SB, selection bias; AB, attrition bias; DB, detection bias; CF, confounding; CTCAEv4.03, Common Terminology Criteria for Adverse Events version 4.03; CTCAEv3, Common Terminology Criteria for Adverse Events version 3; RR, relative risk; ; ICD-X, International Classification of Diseases Xth revision.

What surveillance modality should be used?

1. What is the diagnostic value (i.e. sensitivity, specificity, positive predictive value and/or negative predictive value) of one possible surveillance modality as compared to another possible surveillance modality for surveillance of asymptomatic CAD in childhood, adolescent and young adult cancer survivors?

No studies identified investigating the diagnostic value of possible CAD surveillance modalities for asymptomatic CAD in CAYA cancer survivors.

What should be done when abnormalities are identified?

1. **What is the evidence for treatment with lipid-lowering agents in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?**

No studies identified investigating treatment with lipid-lowering agents in CAYA cancer survivors with asymptomatic CAD.

2. **What is the evidence for treatment with anti-hypertensive agents in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?**

No studies identified investigating treatment with anti-hypertensive agents in CAYA cancer survivors with asymptomatic CAD.

3. **What is the evidence for lifestyle modification in childhood, adolescent and young adult cancer survivors with asymptomatic CAD?**

No studies identified investigating lifestyle modification in CAYA cancer survivors with asymptomatic CAD.

H. Evidence regarding modifiable CVD risk factors in other populations

Guideline	Risk score	Definition of CVD risk	Start treatment with medication when CVD risk
Dutch guideline[1]	Adapted SCORE	10-year risk CVD and mortality	• 10-20%: when additional risk factors are identified and systolic blood pressure >140 mg and/or LDL >2.5 mmol/l • >20%: when systolic blood pressure >140 mg and/or LDL >2.5 mmol/l
European guideline[2]	SCORE	10-year risk fatal CVD	• >5% consider treatment (different cut off values for different risk scores)
UK guideline[3]	QRISK2	10-year risk CVD and mortality	• >10%: shared decision making based on expected risk reduction
USA guideline[4]	Pooled Cohort Equations	10-year risk CVD and mortality	• > 7.5%

CVD: cardiovascular disease

**These guidelines looked at CVD in general, not CAD specifically.*

1. Multidisciplinaire richtlijn Cardiovasculair risicomanagement, herziening 2011
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Eur Heart J 2016;37(29):2315-2381.
3. https://www.nice.org.uk/guidance/cg181
4. Goff DC, Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014; 129(25 Suppl 2): S49-73.

I. Evidence regarding timing of initiation and frequency of screening for modifiable risk factors in other populations*.

Guideline	Timing of initiation	Frequency
Dutch guideline[1]	• People < 40 years rarely reach the risk cut off; therefore no risk tables available for this age category	• Not reported
European guideline[2]	• Systematic CV risk assessment may be considered in men > 40 years and in women > 50 years or post-menopausal with no known CV risk factors • Systematic CV risk assessment in men < 40 years and women < 50 years of age with no known CV risk factors is not recommended	• It is recommended to repeat CV risk assessment every 5 years, and more often for individuals with risks close to thresholds mandating treatment

CV: cardiovascular

**These guidelines looked at cardiovascular disease in general, not CAD specifically.*

1. Multidisciplinaire richtlijn Cardiovasculair risicomanagement, herziening 2011
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Eur Heart J 2016;37(29):2315-2381.