Summary of findings tables, grading of the evidence and detailed conclusions of evidence coronary artery disease surveillance

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.

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

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.

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.