

## Supplemental Online Content

Gal R, van Velzen SGM, Hoening MJ, et al. Identification of risk of cardiovascular disease by automatic quantification of coronary artery calcifications on radiotherapy planning CT scans in patients with breast cancer. Published online May 6, 2021. *JAMA Oncol*. doi:10.1001/jamaoncol.2021.1144

**eMethods.** Coronary artery calcium scoring

**eTable 1.** ICD-10 codes used to identify patients that experienced a cardiovascular event

**eTable 2.** Number of hospitalizations of cardiovascular disease and deaths by CAC score category during a median follow-up of 4.3 years

**eTable 3.** Number of hospitalizations for other heart diseases (I30-49, I51) during a median follow-up of 4.3 years

**eTable 4.** Risk of cardiovascular disease by  $\log(\text{CAC}+1)$

**eTable 5.** Risk of coronary artery disease by CAC score category, stratified by treatment

**eTable 6.** Risk of all-cause mortality by CAC score category, stratified by treatment (follow-up until 2018)

**eTable 7.** Number of hospitalizations of cardiovascular disease and deaths by CAC score category in patients without and with CVD hospitalization before the radiotherapy planning CT scan

**eTable 8.** Risk of cardiovascular disease by CAC score category in patients without known cardiovascular disease before the radiotherapy planning CT scan

**eTable 9.** Competing risks survival analysis of cardiovascular disease by CAC category

**eFigure 1.** Cumulative incidence curves for CVD by CAC category in the presence of competing risks (Aalen-Johansen estimates and 95% intervals)

This supplemental material has been provided by the authors to give readers additional information about their work.

Figure 1. Workflow of automatic CAC scoring and score computation. First, CAC is automatically identified and segmented using the deep learning calcium scoring algorithm. Second, CAC scores are computed using the Agatston scoring method.

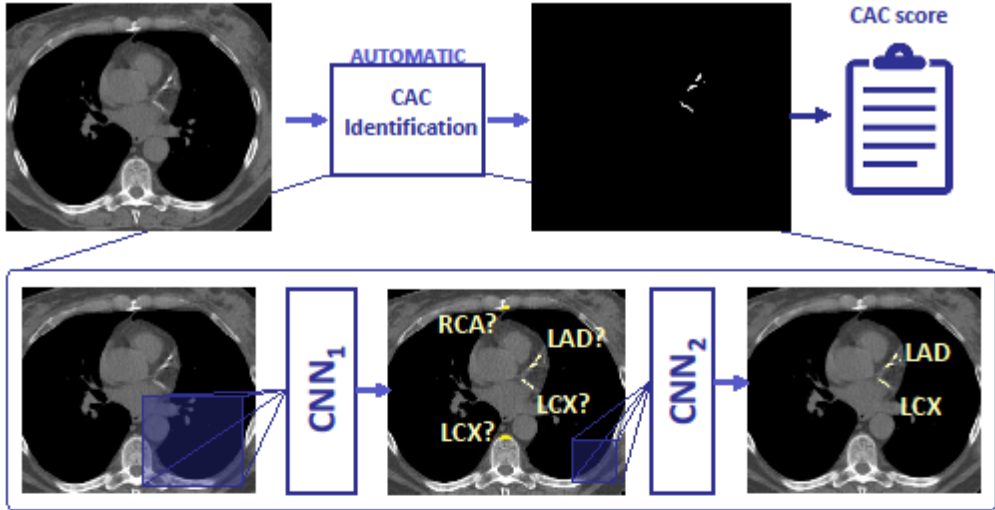
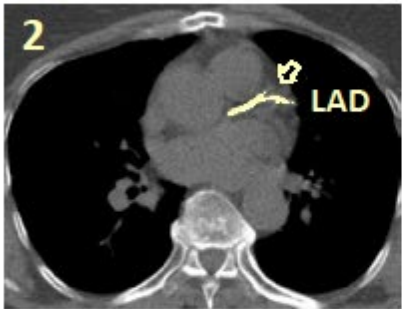
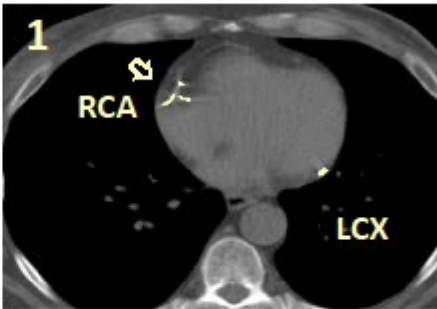


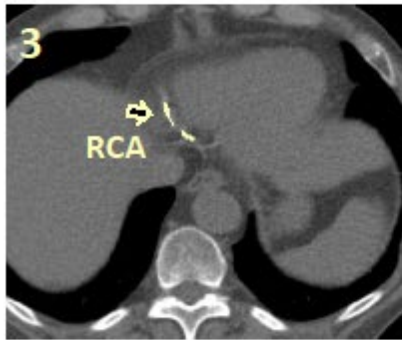
Figure 2. Examples of CAC lesions in different coronary arteries identified by the deep learning algorithm. The position of the slices within the heart is indicated in the coronal view.



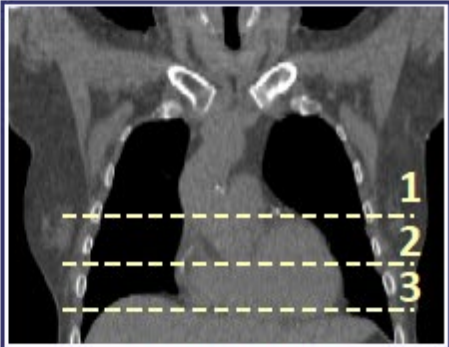
Axial view



Axial view



Axial view



Coronal view

**eTable 1 ICD-10 codes used to identify patients that experienced a cardiovascular event**

<b>Diagnosis</b>	<b>ICD-10 codes</b>
<b>Any CVD event</b>	I00-199 except I88-I89 (lymphedema) and I83-86 (varicose veins)
<b>Coronary artery disease</b>	I20-25 (e.g. myocardial infarction and angina pectoris)
<b>Heart failure</b>	I50
<b>Other heart disease</b>	I30-49, I51 (e.g. pericarditis, endocarditis, myocarditis, cardiomyopathy, atrial fibrillation and arrhythmia)
<b>Cerebrovascular diseases</b>	I60-69 (e.g. hemorrhage and cerebral infarction)
<b>Disease of the arteries, arterioles and capillaries</b>	I80-82, I87, I95-97 (e.g. thrombosis and hypotension)

**eTable 2 Number of hospitalizations of cardiovascular disease and deaths by CAC score category during a median follow-up of 4.3 years**

	Total (n = 15,915)	CAC score (Agatston units)				
		0 (n = 11,179)	1-10 (n = 1,584)	11-100 (n = 1,825)	101-400 (n = 830)	>400 (n = 497)
<b>Hospital admission, n (%)</b>						
Any cardiovascular disease	1,341 (8.4)	643 (5.8)	146 (9.2)	260 (14.3)	154 (18.6)	138 (27.8)
Coronary artery disease	336 (2.1)	127 (1.1)	37 (2.3)	70 (3.8)	51 (6.1)	51 (10.3)
Heart failure	185 (1.2)	84 (0.8)	15 (0.9)	34 (1.9)	27 (3.3)	25 (5.0)
Other heart diseases	497 (3.1)	256 (2.3)	54 (3.4)	95 (5.2)	51 (6.1)	41 (8.2)
Cerebrovascular diseases	199 (1.3)	82 (0.7)	27 (1.7)	50 (2.7)	24 (2.9)	16 (3.2)
Disease of the arteries, arterioles and capillaries	122 (0.8)	43 (0.4)	6 (0.4)	26 (1.4)	25 (3.0)	22 (4.4)
<b>Death, n (%)</b>						
All-causes	1,172 (7.4)	617 (5.5)	152 (9.6)	174 (9.5)	118 (14.2)	111 (22.3)
Any cardiovascular disease	113 (0.7)	28 (0.3)	16 (1.0)	23 (1.3)	18 (2.2)	28 (5.6)
Any cancer (including breast cancer)	804 (5.1)	481 (4.3)	108 (6.8)	107 (5.9)	56 (6.7)	52 (10.5)
Breast cancer	587 (3.7)	374 (3.3)	76 (4.8)	68 (3.7)	37 (4.5)	32 (6.4)

Cardiovascular disease was defined by ICD-10 codes I00-199, lymphedema and varicose veins excluded (I88-89 and I83-86 respectively)

Coronary artery disease was defined by ICD-10 codes I20-25, including angina pectoris and myocardial infarction

Heart failure was defined by ICD-10 code I50

Other heart diseases was defined by ICD-10 codes I30-49 and I51, including pericarditis, endocarditis, myocarditis, cardiomyopathy and arrhythmia

Cancer was defined by ICD-10 codes C00-99, non-melanoma skin cancer excluded (C44)

Breast cancer was defined by ICD-10 code 50

**eTable 3 Number of hospitalizations for other heart diseases (I30-49, I51) during a median follow-up of 4.3 years**

<b>ICD-10 code</b>	<b>Diagnosis</b>	<b>N (%)</b>
I30	Acute pericarditis	- (<1)
I31	Other diseases of pericardium	11 (2)
I33	Acute and subacute endocarditis	11 (2)
I34	Nonrheumatic mitral valve disorders	20 (3)
I35	Nonrheumatic aortic valve disorders	54 (9)
I38	Endocarditis, valve unspecified	11 (2)
I42	Cardiomyopathy	30 (5)
I44	Atrioventricular and left bundle-branch block	29 (5)
I45	Other conduction disorders	12 (2)
I46	Cardiac arrest	16 (3)
I47	Paroxysmal tachycardia	42 (7)
I48	Atrial fibrillation and flutter	276 (46)
I49	Other cardiac arrhythmias	67 (11)
I51	Complications and ill-defined descriptions of heart disease	15 (3)

Patients could have more than one hospitalization for other heart disease.

**eTable 4 Risk of cardiovascular disease by log(CAC+1)**

<b>CAC score</b> (Agatston units)	Unadjusted	Model 1	Model 2	Model 3
	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>
Log(CAC+1)	3.9 (3.4-4.4)	2.2 (1.9-2.6)	2.2 (2.0-2.6)	2.2 (1.9-2.5)

Model 1: adjusted for age at time of CT scan and stratified by calendar year of CT scan

Model 2: adjusted for age at time of CT scan, laterality, treated with anthracyclines and treated with trastuzumab, and stratified by calendar year of CT scan

Model 3: adjusted for age at time of CT scan, laterality, treated with anthracyclines and treated with trastuzumab, and stratified by calendar year of CT scan; model included interaction between log(CAC+1) and anthracyclines

**eTable 5 Number of hospitalizations for cardiovascular disease and deaths by CAC score category in patients without and with CVD hospitalization before the radiotherapy planning CT scan**

	Patients without pre-existing cardiovascular disease						Patients with pre-existing cardiovascular disease						
		CAC score (Agatston units)						CAC score (Agatston units)					
	Total (n = 14,501)	0 (n = 10,559)	1-10 (n = 1,447)	11-100 (n = 1,577)	101-400 (n = 651)	>400 (n = 267)	Total (n = 1,414)	0 (n = 620)	1-10 (n = 137)	11-100 (n = 248)	101-400 (n = 179)	>400 (n = 230)	
<b>Hospital admission, n (%)</b>													
Any cardiovascular disease	1,003 (6.9)	522 (4.9)	121 (8.4)	199 (12.6)	98 (15.1)	63 (23.6)	338 (23.9)	121 (19.5)	25 (18.2)	61 (24.5)	56 (31.3)	75 (32.6)	
Coronary artery disease	238 (1.6)	100 (0.9)	33 (2.3)	55 (3.5)	28 (4.3)	22 (8.2)	98 (6.9)	27 (4.4)	<5 (-)	15 (6.0)	23 (12.8)	29 (12.6)	
Heart failure	120 (0.8)	61 (0.6)	12 (0.8)	22 (1.4)	14 (2.2)	11 (4.1)	65 (4.6)	23 (3.7)	<5 (-)	12 (4.8)	13 (7.3)	14 (6.1)	
Other heart diseases	354 (2.4)	192 (1.8)	44 (3.0)	63 (4.0)	37 (5.7)	18 (6.7)	143 (10.1)	64 (10.3)	10 (7.3)	32 (12.9)	14 (7.8)	23 (10.0)	
<b>Death, n (%)</b>													
All-causes	962 (6.6)	555 (5.3)	128 (8.8)	133 (8.4)	87 (13.4)	59 (22.1)	210 (14.9)	62 (10.0)	24 (17.5)	41 (16.5)	31 (17.3)	52 (22.6)	
Any cardiovascular disease	70 (0.5)	20 (0.2)	12 (0.8)	16 (1.0)	13 (2.0)	9 (3.4)	43 (3.0)	8 (1.3)	<5 (-)	7 (2.8)	5 (2.8)	19 (8.3)	
Any cancer (including breast cancer)	695 (4.8)	443 (4.2)	95 (6.6)	85 (5.4)	41 (6.3)	31 (11.6)	109 (7.7)	38 (6.1)	13 (9.5)	22 (8.9)	15 (8.4)	21 (9.1)	
Breast cancer	505 (3.5)	345 (3.3)	65 (4.5)	52 (3.3)	25 (3.8)	18 (6.7)	82 (5.8)	29 (4.7)	11 (8.0)	16 (6.5)	12 (6.7)	14 (6.1)	

Cardiovascular disease was defined by ICD-10 codes I00-199, lymphedema and varicose veins excluded (I88-89 and I83-86 respectively)

Coronary artery disease was defined by ICD-10 codes I20-25, including angina pectoris and myocardial infarction

Heart failure was defined by ICD-10 code I50

Other heart diseases was defined by ICD-10 codes I30-49 and I51, including pericarditis, endocarditis, myocarditis, cardiomyopathy and arrhythmia

Cancer was defined by ICD-10 codes C00-99, non-melanoma skin cancer excluded (C44)

Breast cancer was defined by ICD-10 code C50



**eTable 6 Risk of cardiovascular disease by CAC score category in patients without and with CVD hospitalization before the radiotherapy planning CT scan**

<b>Patients without pre-existing cardiovascular disease</b>				
<b>CAC score (Agatston units)</b>	<b>n (%)</b>	<b>Events, n (%)</b>	<b>Incidence rate, per 1000 person-years</b>	<b>HR (95% CI)</b>
0	10,559 (72.8)	467 (4.4)	9.1	1.0 (ref)
1-10	1,447 (10.0)	111 (7.7)	15.0	1.2 (0.9-1.5)
11-100	1,577 (10.9)	193 (12.2)	25.1	1.8 (1.5-2.2)
101-400	651 (4.5)	93 (14.3)	33.7	1.9 (1.5-2.5)
>400	267 (1.8)	61 (22.8)	58.8	3.2 (2.4-4.3)
<b>Patients with pre-existing cardiovascular disease</b>				
<b>CAC score (Agatston units)</b>	<b>n (%)</b>	<b>Events, n (%)</b>	<b>Incidence rate, per 1000 person-years</b>	<b>HR (95% CI)</b>
0	620 (43.8)	112 (18.1)	45.6	1.0 (ref)
1-10	137 (9.7)	27 (19.7)	51.0	0.8 (0.5-1.3)
11-100	248 (17.5)	60 (24.2)	67.8	1.2 (0.9-1.7)
101-400	179 (12.7)	55 (30.7)	89.2	1.4 (1.0-2.0) <sup>a</sup>
>400	230 (16.3)	79 (34.3)	103.7	1.5 (1.1-2.0)

CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio

<sup>a</sup> 95% CI lower limit <1.0

Coronary artery disease included all coronary artery disease hospitalizations and death (ICD-10 codes I20-25), including angina pectoris and myocardial infarction

Models were adjusted for age at time of CT scan and stratified by calendar year of CT scan

**eTable 7 Risk of coronary artery disease by CAC score category, stratified by treatment**

CAC score (Agatston units)	Left-sided radiotherapy (n = 8,223)		Right-sided radiotherapy (n = 7,688)		Radiation boost (n = 5,182)		No radiation boost (n = 5,324)		Anthracyclines (n = 4,333)		No anthracyclines (n = 11,582)	
	Incidence rate, per 1000 person-years	HR (95% CI)	Incidence rate, per 1000 person-years	HR (95% CI)	Incidence rate, per 1000 person-years	HR (95% CI)	Incidence rate, per 1000 person-years	HR (95% CI)	Incidence rate, per 1000 person-years	HR (95% CI)	Incidence rate, per 1000 person-years	HR (95% CI)
0	2.3	1.0 (ref)	2.0	1.0 (ref)	1.8	1.0 (ref)	2.3	1.0 (ref)	1.3	1.0 (ref)	2.5	1.0 (ref)
1-10	5.2	1.9 (1.2-3.1)	3.7	1.4 (0.8-2.6)	4.3	1.9 (0.8-4.8)	4.7	1.6 (0.6-3.9)	3.7	2.4 (0.9-6.6)	4.7	1.6 (1.1-2.4)
11-100	9.7	3.4 (2.3-5.0)	6.7	2.3 (1.4-3.6)	6.8	2.7 (1.2-6.1)	7.8	2.8 (1.4-5.6)	6.4	3.6 (1.5-8.6)	8.5	2.8 (2.0-3.8)
101-400	15.9	5.1 (3.2-8.2)	11.6	3.4 (2.0-5.9)	8.1	2.7 (1.0-7.6) <sup>a</sup>	11.7	4.4 (2.1-9.1)	2.4	1.1 (0.2-8.9)	15.3	4.6 (3.2-6.6)
>400	27.3	8.4 (5.1-13.9)	26.0	7.4 (4.4-12.4)	46.8	14.8 (7.0-31.3)	31.0	10.5 (5.5-20.3)	20.4	9.1 (2.0-41.8)	27.0	7.8 (5.4-11.3)

CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio

<sup>a</sup> 95% CI lower limit <1.0

Coronary artery disease included all coronary artery disease hospitalizations and death (ICD-10 codes I20-25), including angina pectoris and myocardial infarction

Models in patients who received left-sided or right-sided radiotherapy, and who were treated with and without anthracyclines were adjusted for age at time of CT scan and stratified by calendar year of CT scan

Models in patients who received radiotherapy with and without boost were adjusted for age at time of CT scan, laterality, treated with anthracyclines and treated with trastuzumab, and stratified by calendar year of CT scan; model included interaction between CAC and anthracyclines

**eTable 8 Risk of all-cause mortality by CAC score category, stratified by treatment (follow-up until 2018)**

CAC score (Agatston units)	Left-sided radiotherapy (n = 8,223)		Right-sided radiotherapy (n = 7,688)		Radiation boost (n = 5,182)		No radiation boost (n = 5,324)		Anthracyclines (n = 4,333)		No anthracyclines (n = 11,582)	
	Inciden ce rate, per 1000 person- years	HR (95% CI)	Inciden ce rate, per 1000 person- years	HR (95% CI)	Inciden ce rate, per 1000 person- years	HR (95% CI)	Inciden ce rate, per 1000 person- years	HR (95% CI)	Inciden ce rate, per 1000 person- years	HR (95% CI)	Inciden ce rate, per 1000 person- years	HR (95% CI)
0	11.7	1.0 (ref)	10.0	1.0 (ref)	8.8	1.0 (ref)	13.2	1.0 (ref)	14.2	1.0 (ref)	9.7	1.0 (ref)
1-10	17.1	1.2 (1.0- 1.5) <sup>a</sup>	18.3	1.5 (1.2-1.9)	11.9	1.3 (0.8- 2.3)	20.0	1.8 (1.2- 2.7)	18.0	1.2 (0.8- 1.8)	17.6	1.4 (1.1- 1.7)
11-100	19.8	1.2 (1.0- 1.5) <sup>a</sup>	18.6	1.3 (1.0- 1.6) <sup>b</sup>	15.0	1.5 (0.9- 2.5)	17.3	1.6 (1.1- 2.3)	16.8	1.1 (0.7- 1.6)	19.7	1.3 (1.1- 1.5)
101-400	31.2	1.6 (1.2- 2.0)	30.4	1.9 (1.4-2.5)	21.3	2.3 (1.3- 3.9)	33.1	2.7 (1.9- 4.0)	23.8	1.4 (0.8- 2.5)	31.7	1.8 (1.5- 2.2)
>400	59.5	2.9 (2.2- 3.7)	46.1	2.6 (2.0-3.5)	44.2	3.9 (2.3- 6.8)	52.6	4.1 (2.9- 6.0)	76.7	4.6 (2.4- 8.6)	51.4	2.8 (2.2- 3.4)

CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio

<sup>a</sup> 95% CI lower limit <1.0

<sup>b</sup> 95% CI lower limit >1.0

Models were adjusted for age at time of CT scan (natural spline with df=3) and stratified by calendar year of CT scan

Models in patients who received left-sided or right-sided radiotherapy, and who were treated with and without anthracyclines were adjusted for age at time of CT scan and stratified by calendar year of CT scan

Models in patients who received radiotherapy with and without boost were adjusted for age at time of CT scan, laterality, treated with anthracyclines and treated with trastuzumab, and stratified by calendar year of CT scan; model included interaction between CAC and anthracyclines

**eTable 9 Competing risks survival analysis of cardiovascular disease by CAC category**

CAC score (Agatston units)	Subdistribution HR (95% CI) <sup>a</sup>		
	Model 1	Model 2	Model 3
0	1.0 (ref)	1.0 (ref)	1.0 (ref)
1-10	1.2 (1.0-1.5) <sup>b</sup>	1.2 (1.0-1.5) <sup>b</sup>	1.2 (1.0-1.5) <sup>b</sup>
11-100	1.8 (1.5-2.1)	1.8 (1.5-2.1)	1.8 (1.5-2.1)
101-400	2.2 (1.8-2.7)	2.2 (1.8-2.7)	2.2 (1.8-2.6)
>400	3.5 (2.9-4.3)	3.5 (2.8-4.3)	3.4 (2.8-4.2)

CAC = coronary artery calcium; CI = confidence interval; HR = hazard ratio; ref = reference

<sup>a</sup> Competing risk survival analysis as described by Fine and Gray (Fine 1999 J Am Stat Assoc) provides subdistribution hazard ratios.

<sup>b</sup> 95% CI lower limit >1.0

Cardiovascular disease included all cardiovascular disease hospitalizations and death (ICD-10 codes I00-199, Lymphedema and varicose veins excluded (I88-89 and I83-86 respectively))

All models were adjusted for age at time of CT scan and stratified by calendar year of CT scan

Model 1: competing risk was all-cause mortality

Model 2: competing risk was cancer hospitalization

Model 3: competing risks were all-cause mortality and cancer hospitalization

**eFigure 1 Cumulative incidence curves for CVD by CAC category in the presence of competing risks (Aalen-Johansen estimates and 95% intervals)**

Cardiovascular disease included all cardiovascular disease hospitalizations and death (ICD-10 codes 100-199, Lymphedema and varicose veins excluded (I88-89 and I83-86 respectively)). CAC = coronary artery calcium

