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Validation and Prognosis of Coronary Artery Calcium Scoring in Nontriggered Thoracic Computed Tomography

Systematic Review and Meta-analysis

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Background—Coronary calcium score (CS), traditionally based on electrocardiography-triggered computed tomography (CT), predicts cardiovascular risk. Currently, nontriggered thoracic CT is extensively used, such as in lung cancer screening. The purpose of the study was to determine the correlation in CS between nontriggered and electrocardiography-triggered CT, and to evaluate the prognostic performance of the CS derived from nontriggered CT.

Methods and Results—PubMed, Embase, and Web of Knowledge were searched until November 2012. Two reviewers independently screened 2120 records to identify studies reporting the CS in nontriggered CT and extracted information. Study quality was evaluated by standardized assessment tools. Cohen κ was extracted for agreement of CS categories between nontriggered and electrocardiography-triggered CT (validation). Hazard ratio (HR) was extracted for prognostic performance. Five studies about validation comprising 1316 individuals were included. Five studies about prognosis comprising 34 028 cardiac asymptomatic individuals, mainly from lung cancer screening trials, were included. All studies were of high quality. Meta-analysis could only be performed for validation studies because studies on prognostic performance were highly heterogeneous. Pooled Cohen κ for agreement between the 2 techniques was 0.89 (95% confidence interval, 0.83–0.95) for increasing CS categories. Increasing CS categories were associated with increasing risk of cardiovascular death or events. Nontriggered CT yielded false-negative CS in 8.8% of individuals and underestimated high CS in 19.1% of individuals.

Conclusions—Our analysis shows the prognostic value and potential role of nontriggered assessment of coronary calcium, but it does not suggest that electrocardiography-triggered CT should be replaced by nontriggered examinations. **(*Circ Cardiovasc Imaging*. 2013;6:514-521.)**

Key Words: calcium score ■ computed tomography ■ meta-analysis ■ nontriggered cardiac imaging technique ■ review, systematic

The amount of coronary artery calcium, based on computed tomography (CT) and traditionally expressed as calcium score (CS) according to Agatston,[1] is a strong predictor of cardiovascular events.[2–5] Calcium scoring has been found to improve cardiovascular risk stratification beyond cardiovascular risk factors.[4,6] Because of the irregular and periodic movements of coronary arteries, electrocardiography-triggered cardiac acquisition techniques are applied in CT to minimize motion artifacts and optimize calcium scoring.[3]

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Compared with electrocardiography-triggered CT, nontriggered CT is extensively used. In 2007, 13.6 million nontriggered thoracic CT examinations were performed in the United States, in contrast to 0.7 million electrocardiography-triggered CT examinations for calcium scoring.[7] Recent trial results have increased the interest in lung cancer screening by thoracic CT.[8] Thus, the number of nontriggered examinations will likely further increase. Age and smoking, the current selection criteria for lung cancer screening, are also correlated with coronary calcification and coronary heart disease.[9] In lung cancer screening, coronary calcification is a frequent finding.[10] If nontriggered CT can be used for calcium scoring, to stratify individuals in categories of cardiovascular risk and to identify

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those at high cardiovascular risk, there may be an enormous unused primary prevention potential.[11] Also, deriving the CS from the same examination as used in lung cancer screening may positively impact the cost-effectiveness of screening.

Because motion of coronary arteries influences calcium scoring,[12] the use of coronary calcium scoring in nontriggered CT is still being debated.[13] With the increasing interest in lung cancer screening, this is an optimal moment to investigate the potential use of nontriggered CT for calcium scoring. However, compared with the extensive publications in electrocardiography-triggered cardiac CT, the literature on calcium scoring in nontriggered thoracic CT is relatively limited. Therefore, we performed a systematic review and meta-analysis to investigate the validity and prognostic value of calcium scoring derived from nontriggered thoracic CT.

Methods

This study was performed according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[14]

Information Sources and Search

We searched PubMed, Embase, and Web of Knowledge until November 2012, using terms related to CT, nontriggered thoracic examination, and coronary calcium without language restrictions (Table I in the online-only Data Supplement). Unpublished studies were not included.

Study Selection

Two reviewers (XQ.X. and YR.Z.) with ≥8 years of experience in thoracic and cardiovascular radiology participated in literature selection. Each record was evaluated independently. Disagreement in literature selection was resolved by consensus. Studies were included in the systematic review when they (1) evaluated cardiac asymptomatic adult humans or phantoms; (2) analyzed one of the following topics about calcium scoring in nontriggered CT: agreement between nontriggered and electrocardiography-triggered CT, or prognostic performance to predict death or events; (3) used ≥16-row multidetector CT as electrocardiography-triggered examination when electrocardiography-triggered CT was used as reference examination. Sixteen-row multidetector CT was used as minimum CT generation because previous research showed higher accuracy and reproducibility in calcium scoring for 16-row multidetector CT compared with earlier generation CT systems.[15]

Articles were excluded when they (1) were reviews, abstracts, case reports, or letters; (2) investigated participants with confounding factors, for example, pacemaker or defibrillator implant, and cardiac surgery. When multiple similar publications based on the same trial were identified, only the study with the largest sample size was included to avoid possible duplicate reporting.

Subsequently, meta-analysis was performed in studies on agreement between nontriggered and electrocardiography-triggered CT, when the studies used the same calcium scoring method, that is, continuous CS and 4 CS categories (0, 1–99, 100–399, and ≥400). No meta-analysis could be performed on the studies on prognostic value because of large heterogeneity in calcium quantification methods, CS categorization, and outcomes.

Data Collection Process

A standardized data extraction form was used to collect study and participant characteristics, methodology, and main results. Two reviewers (XQ.X. and YR.Z.) collected data independently. Disagreement in data collection was resolved by consensus.

For results of studies on agreement of calcium scoring between nontriggered and electrocardiography-triggered CT, a correlation coefficient was extracted for continuous data, and Cohen κ and concordance percentage were extracted for categorical data. When available, the subject number with CS of >0, <400, and ≥400 was extracted for the 2 techniques. A CS of ≥400 is commonly considered as indicating high cardiovascular risk.[3,5] Thereafter, the diagnostic performance of nontriggered CT was calculated using electrocardiography-triggered CT as reference. The percentage of false-negative CS was calculated as the percentage of subjects with zero CS in nontriggered CT among subjects with CS>0 in electrocardiography-triggered CT. The percentage of underestimated high-risk CS was considered as the percentage of subjects with CS<400 in nontriggered CT among subjects with CS≥400 in electrocardiography-triggered CT. The percentage of overestimated high-risk CS was calculated as the percentage of subjects with CS≥400 in nontriggered CT among subjects with CS<400 in electrocardiography-triggered CT.

For prognostic performance of calcium scoring in nontriggered CT, HR for increasing CS categories derived from nontriggered CT to predict cardiovascular death or cardiovascular events (coronary heart disease, cerebrovascular disease, heart failure, peripheral arterial disease, aortic aneurysm, etc) was extracted. When possible, unadjusted and adjusted HR with 95% confidence interval was extracted. Furthermore, the number of subjects with zero CS was extracted, as well as the number of subsequent cardiovascular deaths or events among these subjects.

Study Quality Assessment

Two reviewers (XQ.X. and YR.Z.) evaluated study quality independently on the studies included in the systematic review. Disagreement in quality assessment was resolved by consensus. Two quality assessment tools for different type of study were used to evaluate methodological quality and potential sources of bias, as described next.

For validation studies on agreement between nontriggered and electrocardiography-triggered CT, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) with 14 standard items was used.[16] For each study, a quality score was derived by assigning 1 point to each fulfilled item, 0.5 to an unclear item, and 0 to an unmet item, with a total possible score of 14 (Table II in the online-only Data Supplement).

For prognostic studies, the quality assessment criteria to evaluate reports on prognosis of coronary artery calcium (CAC) in the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline with 8 standard criteria were used.[5] For each study, a quality score was derived by assigning 0 to 3 points to each criterion, with a total possible score of 16 (Table III in the online-only Data Supplement).

Synthesis of Results and Risk of Bias

Pooling calculations of agreement between the 2 techniques were performed using the Hedges-Vevea random effects model and Z test for overall effect. Pooling calculation was performed if there were ≥2 studies reporting the same measurement. Heterogeneity was tested using Q statistic and I^2 index. A 2-sided P value for Q statistic <0.10 or I^2>50% was considered to indicate heterogeneity. The random effects model was used regardless of the heterogeneity test, although results in Q statistics and I^2 index were still stated. Publication bias was evaluated with the Begg and Mazumdar rank correlation and Egger regression test if the number of effect size in the included studies was ≥3. For other statistical analysis, a 2-sided P value <0.05 was considered as significant. Statistical analysis was performed using R version 2.14.2 (R Foundation, Vienna, Austria) and Stata version 11.0 (Statacorp LP, College Station, TX).

Results

Study Selection

The search of the 3 databases elicited 2120 records after removal of duplicate records. Ten studies were included in systematic review, including 5 on agreement between nontriggered and electrocardiography-triggered CT,[17–21] and 5 on prognostic performance.[10,22–25] Subsequently, meta-analysis was performed in 3 studies[20,22,24] with consistent methodology

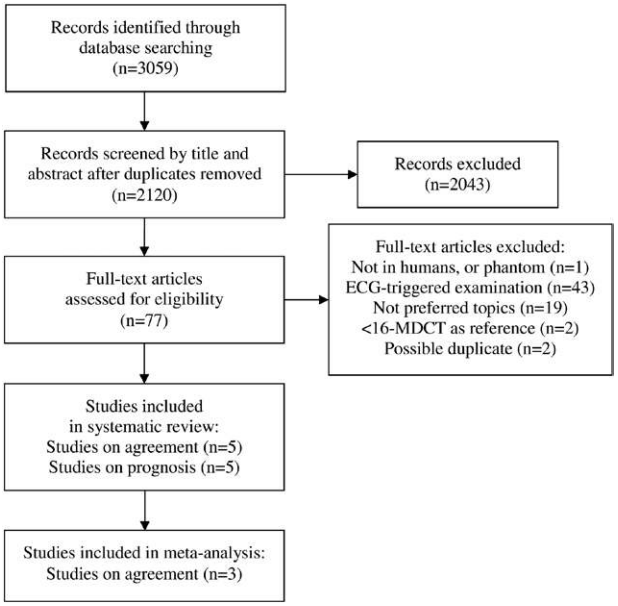

Figure 1. Flowchart of literature review and selection. MDCT indicates multidetector computed tomography.

on agreement between nontriggered and electrocardiography-triggered CT (Figure 1).

Study Characteristics

The systematic review included 35 344 participants (range of mean age, 51–65 years), comprising 21 558 (61%) men, 13 736 (39%) women, and 50 (0.1%) individuals without indicated sex (Tables 1 and 2). Six (60%) studies were prospective, and 4 (40%) studies were retrospective. Four studies (40%) were from North America, 3 (30%) from Europe, and 3 studies (30%) from Asia. All studies were published in English.

Different CT modalities were used, ranging from single-slice to 64-row multidetector CT. Also CT systems as part of single-photon emission CT/CT and positron emission tomography/CT were used.[18] Low-dose acquisition was applied in 8 studies (80%), and normal dose was applied in 1 study (10%). In 1 (10%) study, the radiation dose was not reported. Scan data derived from nontriggered CT were reconstructed with different slice thicknesses, ranging from 1.25 to 10 mm (Tables 1 and 2). The most commonly used slice thicknesses were 2.5/3 mm and 5 mm. Four studies used a (medium-) smooth kernel,[10,20,21,25] the other studies did not indicate the applied kernel. Six studies used Agatston scoring,[10,17–19,21,25] whereas 4 others used visual grading of the presence and extent of coronary calcification. No study used contrast media. No phantom study was included.

Study Quality

All 5 studies on agreement between the nontriggered and electrocardiography-triggered CT were of high quality (score≥10 according to the QUADAS tool). Suboptimal scores were present in 2 QUADAS items: no study mentioned uninterpretable results (item 13); 3 studies did not mention whether there were withdrawals (item 14; Table II in the online-only Data Supplement).

All 5 studies on prognostic performance were of high quality (a score≥12 according the quality assessment criteria to evaluate prognosis of coronary calcification). Suboptimal scores were present for criterion 4: no study reported results by ethnicity (Table III in the online-only Data Supplement).

Validation of Calcium Scoring in Nontriggered CT

Five studies were included in the systematic review, comprising 1316 cardiac asymptomatic participants (Table 1).[17–21] Diagnostic performance of nontriggered CT was calculated in 4 studies with 1153 subjects (Table 3),[17–19,21] in which, 137 (11.9%) subjects had CS of 100 to 400 in nontriggered CT. Fifty-five subjects (8.8%) showed no coronary calcification in nontriggered CT examination among 625 subjects with CS>0 in electrocardiography-triggered CT. In those 55 subjects, 52 (8.3%) had CS 1 to 100 in electrocardiography-triggered CT, and 3 (0.5%) subjects had CS 100 to 400. Among 162 subjects

Table 1. Characteristics of Studies on Agreement of Calcium Scoring Between Nontriggered and Triggered CT

								Slice Thickness, mm	
Studies, y	Patients, n	Men, %	Age, y±SD	Setting of Study	Type of Participants	CT Type	Radiation Dose Setting	Nontriggered CT	Electrocardiography-Triggered CT
Budoff 2011[17]	50	n/a	n/a	COPD cohort	Invited smokers of >10 pack-years	64-MDCT	Low	2.5	2.5
Einstein 2010[18]	492	44	n/a	Routine clinical population	Consecutively referred adults	16-SPECT/CT 16-PET/CT 64-PET/CT	Low	n/a	n/a
Kim 2008[19]	128	100	52±7	Lung cancer screening	Consecutively referred elder smokers	40-MDCT	Low	2.5	2.5
Kirsch 2011[20]	163	78	51±9	Asymptomatic	Consecutively referred elder adults	16- and 64-MDCT	Normal	5.0	3.0
Wu 2008[21]	483	66	62±13	Lung cancer screening	Self-referred elder adults	16-MDCT	Low	3.0	3.0

COPD indicates chronic obstructive pulmonary disease; CT, computed tomography; MDCT, multidetector computed tomography; n/a, not available; PET, positron emission tomography; and SPECT, single-photon emission computed tomography.

Table 2. Characteristics of Studies on Prognostic Performance of Calcium Scoring for Cardiovascular Death or Events

Studies, y	Patients, n	Men, %	Age, y±SD	Setting of Study	Type of Participants	CT Type	Radiation Dose Setting	Slice Thickness, mm	Cohort Name
Itani 2004[22]	6120	55	61±11	Lung cancer screening	Invited elder adults	Single-slice CT	Low	10	Nagano
Jacobs 2011[23]	10 410	58	62±12	Routine clinical population	Retrospectively included elder adults	4-, 8-, 16-, 40- and 64-MDCT	n/a	3.0–10	PROVIDI
Jacobs 2012[10]	7557	83	60±6	Lung cancer screening	Invited elder heavy smokers	16-MDCT	Low	3.1	NELSON
Shemesh 2010[24]	8782	49	65±7	Lung cancer screening	Invited elder heavy smokers	Single- and multislice CT	Low	1.25–5	I-ELCAP
Sverzellati 2012[25]	1159	68	58±6	Lung cancer screening	Invited elder heavy smokers	16-MDCT	Low	5	MILD

CT indicates computed tomography; I-ELCAP, international early lung cancer action program; MDCT, multidetector computed tomography; MILD, multicentric Italian lung detection; n/a, not available; NELSON, the Dutch–Belgian randomized lung cancer screening trial; and PROVIDI, the prognostic value of unrequested information in diagnostic imaging.

with CS≥400 in electrocardiography-triggered CT, nontriggered CT underestimated the CS in 31 subjects (19.1%). In these 31 subjects, 2 (1.2%) had CS 1 to 100 in nontriggered CT, and 29 (17.9%) subjects had CS 100 to 400. However, among 991 subjects with CS<400 in electrocardiography-triggered CT, nontriggered CT showed a CS≥400 in 26 subjects (2.6%) and, thus, overestimated the CS. In those 26 subjects, 1 (0.1%) had CS 1 to 100 in electrocardiography-triggered CT, and 25 (2.5%) subjects had CS 100 to 400.

Meta-analysis was performed in 3 studies comprising 661 participants (Figure 2).[17,19,21] The study by Kirsch et al[20] could not be included because it evaluated the amount of coronary calcification using visual grading score. The pooled correlation coefficient for CS was 0.94 (95% confidence interval, 0.89–0. 97). The pooled Cohen κ was 0.89 (95% confidence interval, 0.83–0.95) for 4 categories of the CS. Heterogeneity was found in the pooling calculation of the CS (P for Q statistic <0.001 and I^2 >50%). No publication bias was found in the pooling calculation of the CS (P>0.05). Publication bias testing was not performed in the pooling calculation of 4 CS categories because of insufficient number of studies.

Prognosis of Calcium Scoring in Nontriggered CT

Five studies were included, comprising 34 028 cardiac asymptomatic participants (Table 2).[10,22–25] In the 5 studies, mean follow-up duration was 45 months (range, 10–72 months). None of the participants in the included studies had a history or symptoms of cardiovascular diseases before CT examination.

Table 3. Agreement of Coronary Calcium Scoring Between Nontriggered Thoracic and Electrocardiography-Triggered Cardiac CT, and Diagnostic Performance of Calcium Scoring in Nontriggered CT

	Agreement			Diagnostic Performance*		
Studies, y	Scoring in Nontriggered CT	Reference Scoring in Triggered CT	Agreement Between Nontriggered and Triggered CT	False-Negative Calcium Score, %	Underestimated High Calcium Score, %	Overestimated High Calcium Score, %
Budoff 2011[17]	CS	CS	r=0.96	0	0	8.6
	4 categories of CS†	4 categories of CS†	κ=0.90, concordance=94%			
Einstein 2010[18]	6 categories of CS‡	6 categories of CS‡	κ=0.89, concordance=63%	14.0	23.4	4.9
Kim 2008[19]	CS	CS	r=0.89	9.3	0	0
Kirsch 2011[20]	Visual grading score§	CS	r=0.83	n/c	n/c	n/c
Wu 2008[21]	CS	CS	r=0.95	2.3	15.2	0.9
	4 categories of CS†	4 categories of CS†	κ=0.89, concordance=93%			

CS indicates calcium score; CT, computed tomography; and n/c, not calculated because different scoring systems were used in nontriggered and electrocardiography-triggered CT.

*False-negative calcium score is indicated as percentage of CS=0 in nontriggered CT among those with CS>0 in triggered CT. Underestimated high-risk calcium score is indicated as percentage of CS<400 in nontriggered CT among those with CS≥400 in triggered CT. Overestimated high-risk calcium score is indicated as percentage of CS≥400 in nontriggered CT among those with CS<400 in triggered CT.

†Four categories of CS defined as 0, 1–99, 100–399, and ≥400.

‡Six categories of CS, defined as 0, 1–9, 10–99, 100–399, 400–999, and ≥1000.

§Score assigned to each major coronary artery. 0, no calcification; 1, single pixel calcification; 3, dense calcification with blooming artifact; 2, calcification between 1 and 3. The visual grading score (range, 0–12) was calculated by summing the score for each artery.

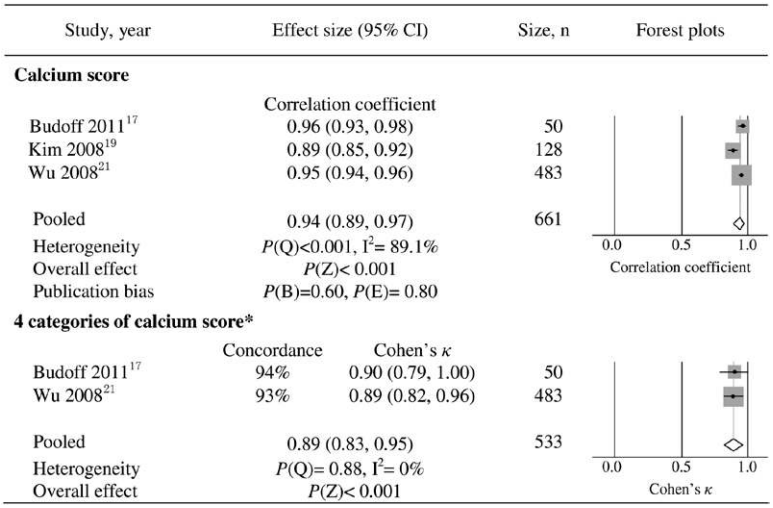

Figure 2. Forest plots for agreement of coronary calcium scoring between nontriggered and electrocardiography-triggered computed tomography examinations. *P*(Q)=*P* value for Q statistic; *P*(Z)=*P* value for *Z* test; *P*(B)=*P* value for Begg and Mazumdar rank correlation test; *P*(E)=*P* value for Egger regression test. *The 4 categories of the calcium score were defined as 0, 1 to 99, 100 to 399, and ≥400. CI indicates confidence interval.

During follow-up, 207 cardiovascular deaths and 675 cardiovascular events were observed. Overall, with increasing CS categories, increasing unadjusted and adjusted HR for cardiovascular death or events was observed. Risks in CS categories were not consistently reported; however, in 1 study, unadjusted and adjusted HR increased up to 7.5 and 5.3 for CS>1000, respectively (Table 4).[10]

A small percentage of subjects with zero CS in nontriggered CT had cardiovascular death or events. During a mean follow-up of 45 months, 47 cardiovascular deaths (0.55%) were found in 8487 subjects with zero CS,[22,24] whereas 72 cardiovascular events (1.3%) occurred in 5249 subjects with zero CS.[10,23] However, the event rate for subjects with positive CS was higher. During follow-up, 160 cardiovascular deaths (2.5%) were found in 6415 subjects with positive CS,[22,24] whereas 570 cardiovascular events (4.5%) occurred in 12 718 subjects with positive CS.[10,23]

Discussion

In this systematic review and meta-analysis, we aimed to investigate whether coronary calcium scoring can be performed in nontriggered thoracic CT, for instance, used in lung cancer screening. A strong correlation in CS categories between nontriggered and electrocardiography-triggered CT was found. In cardiac asymptomatic elderly and smokers, mainly from lung cancer screening trials, increasing coronary calcium burden translated into a higher risk of cardiovascular death or events.

CS for individual atherosclerotic lesions is greatly influenced by motion.[12] Regardless, we found that the correlation in CS between nontriggered and electrocardiography-triggered CT was excellent (r=0.94) on a group level. In broad CS categories, we found a high agreement between nontriggered and electrocardiography-triggered CT (Cohen κ=0.89). Thus, for an individual patient, although variability in CS between nontriggered and electrocardiography-triggered CT is likely considerable, broad CS categories can potentially be used for cardiovascular risk stratification.[3,4]

Absence of coronary calcification in electrocardiography-triggered CT is associated with a very low cardiovascular risk and, thus, is commonly used to rule out coronary artery disease.[3,26] We found that nontriggered CT can yield a false-negative CS in ≈9% of individuals compared with electrocardiography-triggered CT. Furthermore, we found that a zero CS in nontriggered CT indicates a low cardiovascular risk, although nontriggered CT cannot reliably exclude coronary calcification. When a high CS (≥400) is found in asymptomatic individuals, the risk of cardiovascular events is elevated. The ACCF/AHA consensus document suggests to consider these individuals as candidates for intensive preventive therapies.[5] The probability of overestimating the CS is low and, thus, it is reasonable to assume an elevated cardiovascular risk in case of a CS≥400 in nontriggered CT. However, nontriggered CT underestimated the CS in a non-negligible percentage of individuals with CS≥400 in electrocardiography-triggered CT, thus, underestimating cardiovascular risk. In the validation study, 11.9% had a CS of 100 to 400 in the nontriggered CT examination. In this relatively small proportion of the included study populations, dedicated electrocardiography-triggered CT could be considered, to assess whether the CS is actually ≥400. This proportion is much lower than the population percentage in which calcium scoring could be considered according to current consensus documents (40%).[27]

In this study, HRs of CS categories for cardiovascular events were generally lower than in a previous systematic review on calcium scoring derived from electrocardiography-triggered CT.[5] For example, adjusted HR for cardiovascular events was up to 5.3 for CS>1000 in our study, <10.8 in a previous report in electrocardiography-triggered CT in an elderly population.[28] The relative risk is usually based on the risk of subjects without coronary calcium at baseline as reference category. During a mean follow-up of 45 months, we found that 1.3% subjects without coronary calcium had a cardiovascular event. In contrast, a meta-analysis by Sarwar et al[26] on electrocardiography-triggered CT reported only 0.47% of subjects without coronary calcium had a cardiovascular event during a mean follow-up of 50 months. In that meta-analysis, studies mainly consisted of middle-aged individuals at low-to-intermediate cardiovascular risk, referred for cardiovascular risk evaluation. In contrast, the majority of the populations in the prognostic studies on calcium scoring using nontriggered CT comprised participants of lung cancer screening trials. The generally higher age and heavier smoking history in the prognostic studies included in our study likely at least partly explain the higher event rate in individuals with zero CS.

Table 4. Prognostic Performance of Coronary Calcium Scoring for Cardiovascular Death or Events in Nontriggered CT

Studies, y	Follow-Up, mo (range)	End Point Event, n	Calcium Scoring Method in Nontriggered CT	Calcium Scoring Cutoff	Event Number/Category Number, %	Unadjusted Hazard Ratio of Calcium Score (95% CI)	Adjusted Hazard Ratio of Calcium Score (95% CI)	Adjusted for Factors
Itani 2004[22]	48	Cardiac death, 14	Presence of coronary calcification	Zero calcium score	4/4914, 0.08	1.0 (reference)	n/a	n/a
				Positive calcium score	10/1206, 0.83	2.7 (0.8–9.4)		
Jacobs 2011[23]	18	Cardiovascular event, 515	4 categories of visual grading score*	Visual score: 0	62/3435, 1.8	1.0 (reference)	1.0 (reference)	Age, sex, indication for CT, image quality, and type of medical center
				Visual score: 1–2	113/2498, 4.5	2.8 (2.0–3.8)	2.2 (1.6–3.0)	
				Visual score: 3–5	149/2603, 5.7	3.8 (2.9–5.2)	2.5 (1.8–3.4)	
				Visual score: 6–12	191/1874, 10.2	6.9 (5.2–9.2)	3.7 (2.7–5.2)	
Jacobs 2012[10]	10 (1–21)	Cardiovascular event, 127	4 categories of calcium score	Calcium score: 0	10/1814, 0.6	1.0 (reference)	1.0 (reference)	Age, sex, smoking status, hypertension, hypercholesterolemia, and diabetes mellitus
				Calcium score: 1–100	27/2191, 1.2	1.9 (0.9–4.2)	1.8 (0.8–3.9)	
				Calcium score: 101–1000	32/2267, 1.4	2.2 (1.0–4.8)	1.9 (0.9–4.2)	
				Calcium score: >1000	58/1285, 4.5	7.5 (3.6–15.7)	5.3 (2.5–11.6)	
Shemesh 2010[24]	72 (1–92)	Cardiovascular death, 193	3 categories of visual grading score†	Visual score: 0	43/3573, 1.2	1.0 (reference)	1.0 (reference)	Age, sex, and smoking pack-years
				Visual score: 1–3	66/3569, 1.8	1.6 (1.1–2.4)	1.0 (0.7–1.5)	
				Visual score: 4–12	84/1640, 5.1	4.7 (3.6–6.8)	2.1 (1.4–3.1)	
Sverzellati 2012[25]	36 (1–54)	Cardiovascular event, 33	2 categories of calcium score	Calcium score: ≤400	26/1079, 2.4	n/a	1.0 (reference)	Age, sex, diabetes mellitus, hypertension, smoking status, and smoking duration
				Calcium score: >400	7/80, 8.8		2.9 (1.1–7.3)	

CI indicates confidence interval; CT, computed tomography; and n/a, not available.

*Grading score assigned to each major coronary artery. 0, no calcification; 1, 1–2 calcifications; 2, >2 calcifications, or 1 calcification extending ≥2 slices; 3, calcification covering a large coronary segment. Four visual grades were stratified by the sum of the score (0, 1–2, 3–5, and 6–12).

†Grading score assigned to each major coronary artery. 0, no calcification; 1, less than or equal to one third of artery length showing calcification; 2, one third to two thirds; 3, greater than or equal to two thirds. Three visual grades were stratified by the sum of the score (0, 1–3, and 4–12).

Besides, this higher event rate in case of zero CS for nontriggered CT may also be explained by the fact that a proportion of the individuals without coronary calcification on the nontriggered CT, actually have a positive CS in electrocardiography-triggered CT. Because this reference risk is higher, the relative risk for increasing CS categories also yields lower values. Our finding does suggest that presence of coronary calcification in nontriggered CT is an independent predictor of cardiovascular events. Also, we found that higher calcium burden translated into a higher cardiovascular risk in a large aggregated sample.

Reproducibility of calcium scoring in repeated nontriggered CT has been investigated. Jacobs et al[29] investigated 584 subjects who underwent 2 nontriggered examinations of the thorax, and calculated the CS for both examinations. The CSs were divided into the commonly used categories of 0, 1 to 100, 101 to 400, and >400. In 440 cases (75%), the CSs of the 2 CT examinations fell in the same category. In 138 subjects (24%), CSs differed by 1 category, and in 6 subjects (1%) by >1 category. The intraclass correlation coefficient was 0.94. However, reproducibility of calcium scoring in electrocardiography-triggered CT is also not perfect. Using electrocardiography-triggered CT, Rutten et al[30] reported that 76% to 85% of individuals ended up in the same CS category and, in 15% to 24%, the results differed by 1 category.

The agreement of repeated calcium scoring in nontriggered CT within and between observers is high, although slightly lower than in electrocardiography-triggered CT. Nearly all studies in this systematic review investigated either intraobserver or interobserver variability of calcium scoring in nontriggered CT. For example, in 483 subjects, Wu et al[21] reported an interobserver variability of 3.6% for electrocardiography-triggered CT, and of 9.6% for nontriggered CT. However, all studies found a very strong concordance in score categorization within and between observers (κ=0.77–0.91; intraclass correlation coefficient, 0.93–0.99).[10,18,20,21,23–25]

The majority of included studies (80%) were based on low-dose thoracic CT,[10,17–19,21,22,24,25] which has a lower radiation dose than a dedicated cardiac CT for calcium scoring. A typical effective radiation dose for low-dose CT used in lung cancer screening is 0.8 to 0.9 mSv for normal sized body.[8,21] However, the mean dose for a cardiac CT for calcium scoring is ≈1.0 to 2.9 mSv, depending on scanner type and scanning protocol.[21,31]

Clinical Implication

A large number of nontriggered CT examinations are annually performed worldwide. In the aging and smoking population, coronary calcification is a common finding. A lung cancer screening trial reported that >70% of the participants had coronary calcification.[10] The group at risk for lung cancer

overlaps with the group at highest risk of cardiovascular diseases because at least aging and smoking are 2 major risk factors for both diseases. There may be an enormous primary prevention potential if the CS can be derived from the same examination, at least in participants of lung cancer screening trials. Although results from the 1 study in a clinical population suggest that the extent of coronary calcification is also predictive outside lung cancer screening setting, more studies are needed to confirm the value of calcium scoring in routine clinical thoracic CT.

We observed that CS categorization between nontriggered and electrocardiography-triggered CT correlated very well, and increasing CS categories based on nontriggered CT are predictive of increasing cardiovascular risk. Thus, for subjects who were examined by nontriggered thoracic CT, the cardiovascular risk could potentially be stratified by performing calcium scoring. Subjects identified in nontriggered CT as having high CS could be considered as candidates of intensive risk factor modification, especially in an aging and smoking population, such as the participants in lung cancer screening. However, a zero CS in nontriggered CT does not exclude coronary calcification.

Furthermore, cardiovascular event rate of subjects without CS in nontriggered CT is higher than in electrocardiography-triggered CT. Absent coronary calcification in nontriggered CT may not reliably exclude the risk of cardiovascular events. Future studies on this topic are needed to provide stronger support for coronary calcium scoring in nontriggered CT.

Limitations

First, despite our favorable results it remains to be clarified whether differences in the accuracy between nontriggered and electrocardiography-triggered CS measures translate into differences in prognostic value. For example, a zero CS in nontriggered CT may render a positive CS in electrocardiography-triggered examinations. Second, for agreement in calcium scoring between nontriggered and electrocardiography-triggered CT, the number of studies and participants in the meta-analysis was relatively low. To compare calcium scoring between nontriggered and electrocardiography-triggered CT, the patients have to be scanned twice in a short time interval, and at doubled radiation dose. This could contribute to the relatively small number of studies in this field. Our conclusions are not only based on the pooling calculations, but also on the systematic review. Besides, for the second part of our study, about the prognostic value, the aggregated sample size was >30 000 individuals. Third, different calcium scoring methods were used in studies on prognostic performance. Therefore, meta-analysis could not be performed to assess predictive value of the CS derived from nontriggered CT. However, heavier calcium burden was in the systematic review associated with increasing cardiovascular risk. Finally, included studies were fairly heterogeneous in terms of participant population, imaging equipment, and acquisition protocol. Those factors weakened the strength of meta-analysis. We used a random effects model to compensate for at least some of the heterogeneity in the pooling calculation. However, the differences in imaging procedures also reflect the heterogeneity of procedures in clinical practice. Despite different CT equipment and calcium scoring methods, at least the presence or absence of coronary calcium is clear. Results on the presence and absence of coronary calcification should not differ significantly based on important CS categories. Thus, our conclusions based on findings related to those points are solid.

Conclusions

In this systematic review and meta-analysis, strong agreement in CS categorization was found between nontriggered CT and electrocardiography-triggered CT. Compared with electrocardiography-triggered CT, a high CS category in nontriggered CT is a fairly reliable finding. However, nontriggered CT yielded false-negative CS in 8.8% of individuals, and underestimated high CS in 19.1%. In cardiac asymptomatic participants mainly from lung cancer screening trials, increasing CS categories in nontriggered CT were associated with increasing risk of cardiovascular events. Our analysis presents preliminary evidence for the prognostic value and potential role of calcium scoring in nontriggered CT. However, it does not suggest that nontriggered examinations can replace dedicated, electrocardiography-triggered CT.

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Disclosures

None.

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CLINICAL PERSPECTIVE

In this study, coronary calcium score categories based on nontriggered computed tomography (CT) were fairly comparable with electrocardiography-triggered CT results. Thus, cardiac asymptomatic individuals, such as those taking part in lung cancer screening trials, can be stratified into broad categories of cardiovascular risk based on one and the same CT examination. Calcium scoring derived from nontriggered thoracic CT has great potential to identify individuals with heavy coronary calcium burden, who are at increased cardiovascular risk and who could qualify for stricter cardiovascular risk factor control. Despite our favorable results, it remains to be clarified whether differences in the accuracy between nontriggered and electrocardiography-triggered calcium score measures translate into differences in prognostic value. For example, a zero calcium score in nontriggered CT may render a positive calcium score in electrocardiography-triggered examinations.

SUPPLEMENTAL MATERIAL

Online-only Data Supplement Table A. Literature search strategy

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PubMed

("Tomography, X-Ray Computed"[MeSH] OR "computed tomography"[tiab] OR CT[tiab] OR "MDCT") AND ("untriggered" OR "ungated" OR "non-gated" OR "non-triggered" OR "non-electrocardiogram" OR "thorax"[MeSH] OR "chest" OR "thoracic" OR "lung" OR "pulmonary" OR "torso") AND ("coronary vessels"[MeSH] OR "Coronary") AND ("Calcium" OR "calcification" OR "calcific" OR "calcified") AND 1900/01:2012/11[dp]

EmBase

#1: ((Computed tomography) OR CT:ab,ti OR MDCT) AND (untriggered OR ungated OR non-gated OR non-triggered OR non-electrocardiogram OR thorax OR chest OR thoracic OR lung:ab,ti OR pulmonary:ab,ti OR torso) AND Coronary AND (Calcium OR calcification OR calcific OR calcified)

Grammar in advanced search: #1 AND [1-1-1900]/sd NOT (#1 AND [30-11-2012]/sd)

Web of Knowledge

#1 topic: ((Computed tomography) OR CT OR MDCT)

#2 topic: (untriggered OR ungated OR non-gated OR non-triggered OR non-electrocardiogram OR thorax OR chest OR thoracic OR lung OR pulmonary OR torso)

#3 topic: Coronary

#4 topic: (Calcium OR calcification OR calcific OR calcified)

Grammar: #1 topic and #2 topic and #3 topic and #4 topic

Online-only Data Supplement Table B. Quality assessment for validation studies on agreement and diagnostic performance, by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool

	Item1: Representative patient sample	Item2: Selection criteria clearly described	Item3: Acceptable reference standard	Item4: Acceptable delay between tests*	Item5: Partial verification avoided	Item6: Differential verification avoided	Item7: Incorporation avoided	Item8: Adequate index test description	Item9:Adequate reference standard description	Item10: Index test blinded to reference standard	Item11: Reference standard blinded to index test	Item12: Clinical data available as in practice	Item13: Uninterpretable test results reported	Item14: Withdrawals explained	Score†
Budoff 2011[1]	+	+	+	+	+	+	+	+	+			+			12.0
Einstein 2010[2]	+	+	+	+	+	-	+	+	+	+	+	+			12.0
Kim 2008[3]	+	+	+	+	+	+	+	+	+			+		+	12.5
Kirsch 2011[4]	+	+	+	+	+	+	+	+	+	+	+	+			13.0
Wu 2008[5]	+	+	+	+	+	+	+	+	+	+	+	+		+	13.5

"+" = yes; "-" = no; empty = unclear

*Maximum delay of 2 months between non-triggered and reference examination was considered as acceptable

†For each study, a quality score was accumulated by assigning 1 point to "yes" item, 0.5 point to "unclear" item, and 0 to "no" item. The total possible score was 14. A score of ≥10 points was considered as high quality, and a score between 6 and 9 points as moderate quality, a score of ≤5 as low quality.

Online-only Data Supplement Table C. Quality assessment for studies on prognosis, by the quality assessment criteria of prognostic studies on coronary artery calcium in American College of Cardiology Foundation / American Heart Association (ACCF/AHA) guideline

	Criterion 1: Retrospective vs. prospective study	Criterion 2: Potential for referral bias	Criterion 3: Reporting coronary calcification by CHD death or myocardial infarction	Criterion 4: Reporting of results by gender or ethnicity	Criterion 5: Sample size greater than 1000	Criterion 6: Potential for limited challenge	Criterion 7: Risk factor reporting	Criterion 8: Covariate or risk-adjusted outcomes	Score*
Itani 2004[6]	2	1	2	1	1	1	3	0	11
Jacobs 2011[7]	1	2	2	0	1	2	2	1	11
Jacobs 2012[8]	2	2	2	0	1	2	3	1	13
Shemesh 2010[9]	2	2	2	1	1	2	3	1	14
Sverzellati 2012[10]	2	2	2	1	1	2	3	1	14

CHD = coronary heart disease.

*For each study, a quality score was accumulated by assigning a score for each criterion as the following:

- Criterion 1: Retrospective vs. prospective study (1=retrospective, 2=prospective).
- Criterion 2: Potential for referral bias (0=clinically referred patients, 1=unselected cohort, 2=population sample).
- Criterion 3: Reporting coronary calcification by CHD death or myocardial infarction (1=no, 2=yes).

- Criterion 4: Reporting of results by gender or ethnicity (0=no, 1=gender only, 2=ethnicity only, 3=both).
- Criterion 5: Sample size ≥ 1000 (0=no, 1=yes).
- Criterion 6: Potential for limited challenge (1=no reporting of calcium outcomes in low- to high-risk global risk scores, 2=reporting of calcium outcomes in low- to high-risk global risk scores).
- Criterion 7: Risk factor reporting (1=historical only, 2=measured in subset, 3=measured in all subjects).
- Criterion 8: Covariate or risk-adjusted outcomes (0=no, 1=yes).

Total possible score was 16. A score of ≥11 points was considered as high quality, and a score between 7 and 10 points as moderate quality, a score of ≤6 as low quality.

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