Cardiovascular computed tomography for diagnosis and risk stratification of coronary artery disease

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Chapter 9

Impact of clinical presentation and pre-test likelihood on the relation between coronary calcium score and computed tomography coronary angiography

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Abstract

The purpose of the current study was to assess the impact of clinical presentation and pre-test likelihood on the relationship between calcium score (CCS) and computed tomography coronary angiography (CTA), to determine the role of CCS as a gatekeeper to CTA in patients presenting with chest pain. In 576 patients with suspected coronary artery disease (CAD), CCS and CTA were performed. CCS was categorized as CCS 0, CCS 1-400 and CCS >400. On CTA the presence of significant CAD (≥50% luminal narrowing) was determined. Significant CAD was observed in 14 (5.8%) of 242 patients with CCS 0, in 94 (36.2%) of 260 patients with CCS 1-400, and in 60 (81.1%) of 74 patients with CCS >400. In patients with CCS 0, the prevalence of significant CAD increased from 3.9% to 4.1% and 14.3% in respectively non-anginal, atypical and typical chest pain, and from 3.4% to 3.9% and 27.3% with respectively a low, intermediate and high pre-test likelihood. In patients with CCS 1-400, the prevalence of significant CAD increased from 27.4% to 34.7% and 51.7% in respectively non-anginal, atypical and typical chest pain, and from 15.4% to 35.6% and 50% in respectively low, intermediate and high pre-test likelihood. In patients with CCS >400, the prevalence of significant CAD on CTA remained high (>72%) regardless of clinical presentation and pre-test likelihood. In conclusion, the relation between CCS and CTA is influenced by clinical presentation and pre-test likelihood. These factors should be taken into account when using CCS as a gatekeeper for CTA.

Introduction

Non-contrast enhanced computed tomography (CT) visualizes coronary calcium as a marker for coronary artery disease (CAD), and quantifies the presence and extent of coronary calcium by use of the coronary calcium score (CCS). More recently, contrast enhanced CT coronary angiography (CTA) has been introduced. This technique provides direct visualization of the coronary arteries and allows more detailed assessment of coronary atherosclerosis and stenosis severity. Several studies have suggested that CCS might be useful as a gatekeeper to CTA in diagnosis of significant CAD in patients presenting with chest pain. The absence of calcium could exclude the presence of significant CAD, indicating no need for further imaging, whereas patients with elevated CCS could be referred for CTA for additional information on stenosis severity. In order to evaluate the feasibility of such an approach, several comparative studies have been performed addressing the relationship between CCS and CTA in patients presenting with chest pain.[1-5] However, large discrepancies have been observed, which have been ascribed to differences in clinical characteristics of the studied populations. The purpose of the current study was therefore to systematically assess the impact of clinical presentation and pre-test likelihood on the relationship between CCS and CTA, to determine the role of CCS as a gatekeeper to CTA for diagnosis of significant CAD in patients presenting with chest pain.

Methods

The study population consisted of patients with suspected CAD who were clinically referred for further cardiac assessment because of chest pain. The included patients underwent both a CCS and CTA scan. Exclusion criteria were cardiac arrhythmias, renal insufficiency (defined as a glomerular filtration rate <30mL/min), known hypersensitivity to iodine contrast media, severe claustrophobia and pregnancy. In addition, patients with an uninterpretable CTA examination were excluded. Symptoms were classified as: typical angina, atypical angina, or non-anginal chest pain. Typical anginal chest pain was defined as combination of: 1) discomfort in the anterior chest, neck, shoulders, jaw, or arms; 2) precipitated by physical exertion or emotional stress; and 3) relieved by rest or nitroglycerin within minutes. Atypical chest pain was defined as chest pain with two 2 of these 3 factors and non-anginal chest pain was defined as chest pain with less than 2 of these 3 factors.[6] Pre-test likelihood was defined according to Diamond and Forrester criteria, which are based on previously observed prevalence's of significant CAD in age, gender and chest pain subgroups.[7] Thresholds for low, intermediate and high pre-test likelihood were respectively; ≤13.4, 13.5-87.2, and ≥87.3.

The examination was performed using either a 64-detector row helical scanner (Aquilion 64; Toshiba Multi-slice system, Toshiba Medical Systems, Otawara, Japan) or a 320-detector row volumetric scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan). Before CCS and CTA examinations, the patients' heart rate and blood pressure were monitored. In the absence of contraindications, patients with a heart rate exceeding the threshold of 65 bpm were administered beta-blocking medication (50-100 mg metoprolol oral). Prior to the helical scan, a non-enhanced low-dose electrocardiographically gated scan was performed to measure CCS. The CCS scan was prospectively triggered at 70% or 75% of the R-R interval and performed using the following scan parameters: 4 x 3.0 mm or 2.5 mm collimation for 64-row CT, and single rotation wide volume acquisition (320 x 0.5 mm, reconstructed to 3 mm slices) for 320-row CT; gantry rotation time, 350-500 ms; tube voltage, 120 kV; and tube current, 200-250 mA.

For the 64-row contrast enhanced scan, collimation was 64 x 0.5 mm, tube voltage 100 to 135 kV and tube current 250 tot 350 mA, depending on body mass index (BMI) and thoracic geometry. Non-ionic contrast material (Iomeron 400, Bracco, Milan) was administered with an amount of 80 tot 110 ml followed by a saline flush with a flow rate of 5 ml/sec. For the 320-row contrast enhanced scan the heart was imaged in a single heartbeat, using prospective triggering with exposure interval depending on the heart rate. Scan parameters were: 320 X 0.5 mm collimation; 350 ms gantry rotation time, 100 to 135 kV tube voltage and a tube current of 400 to 580 mA, depending on body mass index. In total, 60 to 90 ml contrast material was administered with a rate of 5-6 ml/sec followed by a saline flush.

Post-processing of the CCS and CTA examinations was performed on dedicated workstations (Vitrea 2.0 or Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA). The CCS was calculated using the Agatston method and patients were divided in three categories: CCS 0, CCS 1-400 and CCS >400. CTA angiograms were examined using the axial slices, curved multiplanar reconstructions, and maximum intensity projections. All CTA scans were interpreted by 2 experienced observers blinded to the results of CCS. CTA exams were classified according to the most severe lesion. In each patient, the presence of CAD was determined. Further differentiation was made between non-significant and significant CAD using a diameter stenosis ≥50% as a threshold for significant lesions.

Continuous variables were expressed as mean values (± standard deviation) and categorical baseline data were expressed in numbers and percentages. Differences in baseline clinical variables between the CCS subgroups were compared using Anova, Student t and chi-square tests.The prevalence of significant CAD on CTA in each CCS category was determined according clinical presentation and pre-test likelihood. All statistical analyses were performed using SPSS software version 16.0 (SPSS, Chicago, Illinois, USA).

Results

The study population consisted of 602 patients presenting with chest pain who had undergone both CCS and CTA. In 26 (4.3%) of these patients, the CTA examination was uninterpretable because of the presence of motion artefacts, increased noise owing to a high body mass index, and breathing. After exclusion of these patients, a total of 576 remained for further analysis. The baseline characteristics of the patient population are presented in Table 1.

Table 1. Patient characteristics.

Variable	All (n=576)	CS 0 (n=242)	CS 1-400 (n=260)	CS >400 (n=74)	P-value
Men	273 (47%)	93 (38%)	137 (53%)	43 (58%)	0.001
Age (years)	56 ± 12	50 ± 11	59 ± 11	66 ± 9	<0.001
Diabetes Mellitus	105 (18%)	33 (14%)	49 (19%)	23 (31%)	0.003
Hypertension	254 (44%)	66 (27%)	136 (52%)	52 (70%)	<0.001
Hypercholesterolemia	199 (35%)	57 (24%)	106 (41%)	36 (49%)	<0.001
Current smokers	115 (20%)	49 (20%)	40 (15%)	26 (35%)	0.001
BMI ≥ 30 kg/m2	109 (19%)	43 (18%)	48 (19%)	18 (24%)	0.48
Symptoms					0.017
Non-anginal chest pain	205 (36%)	103 (43%)	84 (32%)	18 (24%)	0.005
Atypical chest pain	249 (43%)	97 (40%)	118 (45%)	34 (46%)	0.42
Typical chest pain	122 (21%)	42 (17%)	58 (22%)	22 (30%)	0.06
Pre-test likelihood					<0.001
Low	117 (20%)	89 (37%)	26 (10%)	2 (3%)	<0.001
Intermediate	370 (64%)	131 (54%)	188 (72%)	51 (69%)	<0.001
High	89 (16%)	22 (9%)	46 (18%)	21 (28%)	<0.001

The median CCS of the study population was 7 (25th-75th percentile: 0-133). Calcium was absent in 242 patients (42%), a CCS of 1-400 was present in 260 patients (45.1%), and a CCS >400 in 74 patients (12.8%). Significant CAD was observed on CTA in 168 patients (29%). In the remaining 408 patients (71%) non-significant CAD was observed in 184 patients (32%) and 224 patients (39%) were classified as normal.

Figure 1 illustrates the CTA findings in the different CCS groups. In patients without any coronary calcium (CCS 0), significant CAD was observed in 14 patients (5.8%). In the group of patients with a CCS of 1-400, 94 patients (36.2%) had significant CAD on CTA. In patients with a high CCS >400, significant CAD was observed in 60 patients (81.1%).

Figures 2 and 3 illustrate the prevalence of significant CAD in the different CCS groups according to clinical presentation and pre-test likelihood.

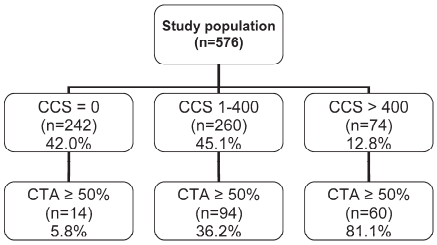

Figure 1. The prevalence of significant CAD on CTA per CCS category.

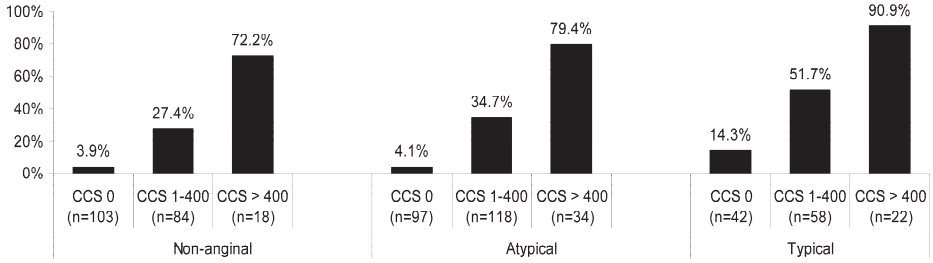

Figure 2. Prevalence of significant CAD on CTA in the various CCS categories according to patients' symptoms.

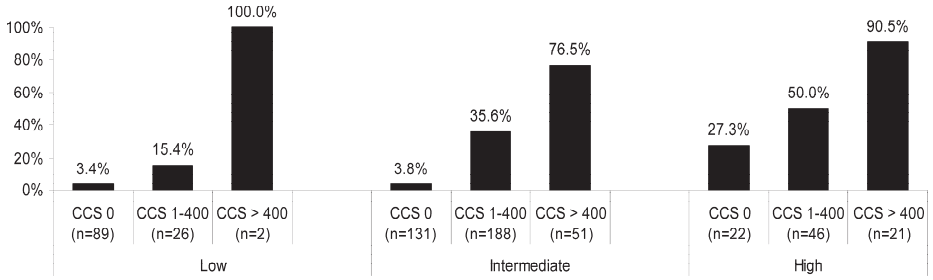

Figure 3. Prevalence of significant CAD on CTA in the various CCS categories, according to pre-test likelihood.

The impact of clinical presentation on the prevalence of significant CAD in each CCS category is illustrated in Figure 2. In patients with CCS 0, the prevalence of significant CAD was similar among patients with non-anginal and atypical complaints (respectively 3.9% and 4.1%, Figure 2). However, the prevalence increased to 14.3% in patients with typical chest pain. Accordingly, a CCS of 0 may not be useful to rule out significant CAD in patients presenting with typical chest pain complaints.

In patients with CCS 1-400, significant CAD was observed in 27.4% of patients with non-anginal chest pain. The prevalence increased to 34.7% and 51.7% in patients with atypical and typical chest pain, respectively. However, although there was an increase in

the prevalence of significant CAD according to the increase in severity of symptoms, the prevalence remained in an intermediate range.

In patients with a CCS >400, significant CAD was observed in 72.2% of patients with non-anginal complaints. The prevalence increased to 79.4% in atypical chest pain patients, and was highest (90.9%) in patients with typical chest pain. Although the prevalence of significant CAD increased with more severe chest pain symptoms, the prevalence was high in all patients with a CCS >400 regardless of clinical presentation.

The impact of pre-test likelihood on the prevalence of significant CAD in each CCS category is illustrated in Figure 3. In patients with a CCS 0, significant CAD was observed in 3.4% and 3.8% of patients with respectively a low and intermediate pre-test likelihood. The prevalence increased to 27.3% in patients with a high pre-test likelihood. Accordingly, a CCS of 0 may not be useful to rule out significant CAD in patients presenting with a high pre-test likelihood.

In patients with CCS 1-400, 15.4% of patients with a low pre-test likelihood had significant CAD. The prevalence of significant CAD increased to 35.6% in patients with intermediate pre-test likelihood and up to 50% in the high pre-test likelihood group. Although a large variance was observed in the prevalence of significant CAD on CTA according to increasingly higher pre-test likelihoods in patients with a CCS 1-400, the prevalence remained at an intermediate level.

In the group of patients with a CCS >400, a high prevalence of significant CAD was observed regardless of pre-test likelihood (Figure 3).

Discussion

The main finding of the current study is that the relation between CCS and CTA is highly influenced by clinical presentation and pre-test likelihood in patients presenting with chest pain. In each CCS category, the prevalence of significant CAD on CTA increased proportional to the severity of clinical presentation and pre-test likelihood. Clinical presentation and pre-test likelihood should therefore be taken into account when using CCS as a gatekeeper for CTA.

Several previous studies have assessed the relation between CCS and CTA in patients presenting with chest pain. A large proportion of these studies have specifically focused on the prevalence of significant CAD on CTA in patients with a CCS of 0. Within these

studies varying prevalences have been described, ranging between 1.7% in a recent study by Nieman et al. to 28% in a study by Haberl et al.[1-5] As a result of this large variation in reported prevalences, the value of a CCS of 0 to rule out significant CAD on CTA in chest pain patients has remained unclear.

Only a few comparative studies between CCS and CTA have been performed in chest pain patients with a CCS >0.2,4 In patients with a CCS 1-400, Nieman et al. observed significant CAD on CTA in 35.4% of patients.[4] The authors observed a high prevalence of 94% in patients with a CCS >400. When using CCS as a gatekeeper for CTA, Nieman et al. propose that further downstream testing with CTA is necessary in patients with a CCS 1-400 and that the value of CTA may be limited in patients with a CCS >400 as the likelihood of subsequent significant CAD is high.

In patients with a CCS of 0, the prevalence of significant CAD on CTA increased from 3.9% and 4.1% in patients with non-anginal chest pain and atypical chest pain respectively to 14.3% in patients with typical chest pain. The prevalence of significant CAD don CTA in patients with a CCS of 0 increased from 3.4% and 3.8% in patients with a low and intermediate pre-test likelihood respectively to 27.3% in patients with a high pre-test likelihood. These observations may provide a valuable link between the discrepant findings described in previous comparative studies between CCS and CTA in patients with a CCS of 0. In the study by Haberl et al. all patients had an indication for invasive coronary angiography because of chest pain and signs of ischemia on conventional stress tests.[3] As a result, the pre-test likelihood in this population was high, explaining the high prevalence (28%) of significant CAD in patients without calcium. In contrast, in a low to intermediate pre-test probability population, Nieman et al. observed a low prevalence of significant CAD similar to the prevalence observed in the subgroup of patients with a low or intermediate pre-test likelihood in the current study. Our observations suggest that when using CCS as a gatekeeper for CTA, the presence of significant CAD may be effectively ruled out in patients with non-anginal or atypical chest pain and in patients with a low or intermediate pre-test likelihood. However, a CCS of 0 may not reliably rule out the presence of significant CAD in patients with typical symptoms (17% of patients with a CCS 0 in the current) and patients with a high pre-test likelihood (9% of patients with a CCS 0 in the study population). In these patients additional evaluation with CTA may be necessary to confirm the presence or absence of significant CAD with more diagnostic certainty.

When assessing the relationship between CCS and CTA in patients with a CCS >0, we observed that the prevalence of significant CAD on CTA in patients with a CCS 1-400 increased from 27.4% to 34.7% and 51.7% in patients with non-anginal, atypical and typical chest pain respectively. When regarding pre-test likelihood, the prevalence of significant

CAD on CTA in patients with a CCS 1-400 increased from 15.4% to 35.6% and 50% in patients with respectively a low, intermediate and high pre-test likelihood. Although the prevalence of significant CAD in patients with a CCS 1-400 was therefore influenced by clinical presentation and pre-test likelihood, the likelihood of significant CAD following a CCS 1-400 remained intermediate. When using CCS as a gatekeeper for CTA, further downstream testing with CTA therefore remains necessary in all patients with a CCS 1-400 (45% of current study population) to rule out the presence of significant CAD, regardless of clinical presentation and pre-test likelihood. In patients with a CCS >400, the prevalence of significant CAD on CTA remained high regardless of clinical presentation and pre-test likelihood. When using CCS as a gatekeeper, the value of CTA following a CCS >400 may be limited, as the presence of significant CAD can be ruled out in only a small proportion of patients. In patients with a CCS >400 (13% of total study population), it may therefore be more appropriate to proceed directly to functional imaging by means of myocardial perfusion imaging or to invasive coronary angiography to further determine the extent and severity of CAD, regardless of clinical presentation or pre-test likelihood.

The radiation dose remains a cause of concern for CTA. Currently traditional 64-row CTA protocols are still associated with high radiation exposure, although the radiation dose of CTA has recently decreased substantially.[8-11] Importantly, low-dose CTA with prospective ECG-triggering has recently been shown to reduce radiation burden while maintaining image quality and a high diagnostic accuracy.[12, 13] The radiation burden with these novel acquisition techniques is approaching the level of diagnostic catheterization or even lower.[14]

Conclusion

The relation between CCS and CTA is influenced by clinical presentation and pre-test likelihood. These factors should be taken into account when using CCS as a gatekeeper for CTA.

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