The Use of Coronary CT Angiography for the Evaluation of Chest Pain

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Abstract: Coronary computed tomography angiography (CCTA) may improve the diagnosis and management of acute and stable chest pain syndromes. The key for caregivers of patients presenting with acute chest pain is the early identification and management of life-threatening conditions, such as acute coronary syndromes, pulmonary embolism, and acute aortic dissection. The main goal in stable chest pain syndromes is to determine the extent and severity of coronary artery disease. This review article will critically evaluate the current literature supporting the evidence for the clinical use of CCTA in acute and stable chest pain syndromes, considering the latest innovations in CCTA technology and their potential impact on patient care.

Key Words: acute chest pain syndrome, stable chest pain syndrome, computed tomographic angiography

(*Cardiology in Review* 2014;22: 117–127)

ACUTE CHEST PAIN SYNDROME

Epidemiology

In the United States, more than 7 million patients are admitted to the emergency department (ED) each year with acute chest pain as their main complaint, making it one of the most frequent causes of ED visits.[1] However, only 2–8% of those patients are diagnosed with an acute coronary syndrome (ACS).[2] The remainder of patients are diagnosed with noncardiac etiologies, including pulmonary, vascular, gastrointestinal, and musculoskeletal causes.

ACS includes acute myocardial infarction (AMI), encompassing both ST-elevation myocardial infarction (STEMI) and non-ST segment myocardial infarction (NSTEMI), and unstable angina pectoris (UA).[3,4] The presence of an STEMI is usually identified on initial electrocardiogram (ECG), whereas UA and NSTEMI require further clinical evaluations. UA is defined as chest pain due to ischemia without the presence of myocardial necrosis, whereas NSTEMI requires the presence of myocardial necrosis, manifested by troponin elevation. It should be noted that UA and NSTEMI are therefore indistinguishable until serial troponin or other biomarkers of myocardial injury are assessed.[4,5]

The pathophysiology leading to ACS is classically due to rupture of an atherosclerotic plaque (approximately 60%) or plaque erosion (approximately 40%),[6,7] followed by subsequent thrombus formation and obstruction of coronary blood flow to downstream coronary segments. These "high-risk" culprit plaques are morphologically characterized by a large lipid/necrotic core, thin fibrous cap, high density of macrophages, and potentially small calcified embedded nodules.[6] They may not necessarily be associated with severe luminal stenosis, which may explain why no significant lesions are identified by standard invasive angiogram for 5–20% of events.[6,8] Alternatively, ACS can be developed in the setting of significant luminal narrowing due to stenosis progression, with either reduced downstream blood flow and oxygen supply or increased myocardial demand. Rarer causes of ACS with distinctly different pathophysiological mechanisms include coronary vasospasm and microvascular dysfunction of the myocardium.[9]

The Immediate Value of Coronary Computed Tomography Angiography in Acute Chest Pain Syndrome

A traditional diagnostic work-up of acute chest pain (Fig. 1) includes an initial clinical assessment and determining whether the patient is suffering from ACS; determination is done by patient's history, physical examination, 12-lead ECG, and laboratory findings, such as cardiac biomarkers.[4] Patients with high-risk findings can be readily diagnosed and referred for invasive diagnosis and treatment. Low-risk patients can be readily discharged for outpatient follow-up. However, a large proportion of patients remain in the ED or in a dedicated chest pain unit until ACS can be reliably ruled out. These patients undergo serial cardiac biomarkers and ECG testing during the next 24 hours, frequently followed by a stress test for risk stratification, if subsequent ECG and biomarkers tests are inconclusive. Although the number of missed ACS events can be reduced with this common strategy, it leads to increased test burden, length of hospitalization, and prolonged stay in the chest pain unit. Despite the conservative triage practice, 2–3% of all patients suffering from ACS within 72 hours of ED presentation are erroneously discharged, contributing to the fact that missed ACS is the number one cause for ED malpractice costs in the United States.[10,11]

To overcome these problems, early coronary computed tomography angiography (CCTA) has been suggested to be a safe, fast, and cost-effective modality. In addition, CCTA facilitates early triage of acute chest pain patients in the ED and has been recognized as a viable alternative to the traditional standard of care. This is the result of several studies including more than 3000 patients which have been conducted to evaluate CCTA for the triage of patients presenting to the ED (Table 1), which are discussed in detail below.

Diagnostic Accuracy of Coronary Computed Tomography Angiography for Acute Coronary Syndrome

Over the last few years, CCTA has evolved into a dependable tool for the assessment of coronary artery disease (CAD). In particular, with the introduction of 64-slice scanners in 2003, the temporal and spatial resolution reached a sufficient level to reliably determine the presence of obstructive atherosclerotic disease. A meta-analysis including 18 studies, which compared 64-slice CCTA with invasive angiography, demonstrated good diagnostic accuracy of CCTA for obstructive CAD although specificity was limited due to artifacts and

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1061-5377/14/2203-0117
DOI: 10.1097/CRD.0000000000000015

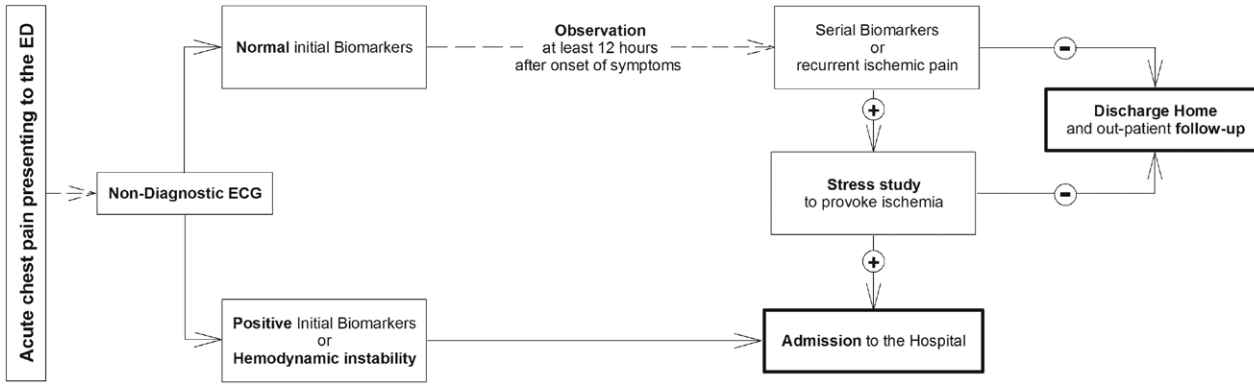

FIGURE 1. Traditional triage of patients with acute chest pain syndrome. ECG indicates electrocardiography; ED, emergency department.

TABLE 1. Randomized, Controlled Trials With CCTA as a Diagnostic Intervention in Patients with Acute Chest Pain

Authors (trial name)	Year	No. Patients/ No. Controls	Subjects	Intervention	Control	Outcome of Interest	Observed Difference (CCTA vs. Control)
Goldstein et al[33]	2007	179/1	Negative troponin Nondiagnostic ECG Age: 49 ± 12 yr Female: 50%	CCTA	MPI	Prevalence of AMI MACE during follow-up Direct ED discharges* Time to diagnosis* Invasive catheterization* ED cost* Radiation dose	0% vs. 0% 1% vs. 0% 88% vs. 97% 3.4 hr vs. 15.0 hr 11% vs. 3% $1586 vs. $1872 *Not available*
Goldstein et al[30] (CT-STAT)	2011	749/16	Negative troponin Nondiagnostic ECG Age: 50 ± 10 yr Female: 54%	CCTA	MPI	Prevalence of AMI MACE during follow-up Direct ED discharges* Time to diagnosis* Invasive catheterization ED cost* Radiation dose*	0.3% vs. 1.5% 0.8% vs. 0.4% 73% vs. 81%† 2.9 hr vs. 6.2 hr 7% vs. 6% $2137 vs. $3458 12 mSv vs. 13 mSv
Litt et al[32]	2012	1370/5	Negative troponin Nondiagnostic ECG Age: 49 ± 10 yr Female: 53%	CCTA	SOC	Prevalence of AMI MACE during follow-up Direct ED discharges* Time to diagnosis* Invasive catheterization ED cost Radiation dose	1% vs. 1% 3% vs. 1% 50% vs. 23% 18.0 hr vs. 24.8 hr 4% vs. 4% *Not available* *Not available*
Hoffmann et al[31] (ROMICAT II)	2012	1000/7	Negative troponin Nondiagnostic ECG Age: 54 ± 8 yr Female: 47%	CCTA	SOC	Prevalence of AMI MACE during follow-up Direct ED discharges* Time to diagnosis* Invasive catheterization ED cost Radiation dose*	2% vs. 3% 0.4% vs. 1.2% 47% vs. 12% 5.8 hr vs. 21.0 hr 11% vs. 7% $2101 vs. $2566 14 mSv vs. 5 mSv

The work-up in the ED using CCTA was compared either to a work-up strategy requiring nuclear MPI or to a traditional SOC work-up strategy.
*Significant difference ($P < 0.05$).
†Estimated from presented data.
AMI indicates acute myocardial infarction; CCTA, coronary computed tomography angiography; ECG, electrocardiogram; ED, emergency department; MACE, major adverse coronary events; MPI, myocardial perfusion imaging; mSv, millisievert; ROMICAT, Rule Out Myocardial Infarction using Computer-Assisted Tomography; SOC, standard-of-care; STAT, Systematic Triage of Acute Chest Pain Patients to Treatment.

anatomical severity of stenosis was variably associated with hemodynamic significance.[12] Similarly, the probability in detecting any CAD by CCTA reached more than 90% if the plaque's maximal intimal thickness was more than 1 mm, as measured by intravascular ultrasound.[13] CCTA also allows the assessment of left ventricular (LV) morphology and function, myocardial perfusion, and quantitative plaque and stenosis measurements.[14]

In 2007, Rubinshtein et al[15] found in 58 patients with acute chest pain and the absence of new ECG changes or elevated biomarkers that CCTA-based assessment of obstructive CAD has a high sensitivity (100%) and specificity (92%), with good positive predictive values (PPVs) and excellent negative predictive values (NPV) (87% and 100%, respectively) for ACS. Furthermore, they suggested that CCTA may allow for a safe and early discharge, because no death or AMI occurred among those who were directly discharged from the ED based on CCTA results. These initial findings were substantiated and extended by a larger prospective observational cohort study, the Rule Out Myocardial Infarction using Computer-Assisted

Tomography (ROMICAT I) trial published in 2009,[16] which evaluated the potential of CCTA for the triage of patients with acute chest pain in the ED. This trial is the only study in which the CCTA results remained blinded to the caregivers and patients. Therefore, the diagnostic performance of CCTA for ACS and its association with other test findings could be studied in a truly unbiased manner. The trial included 368 patients from the ED with acute chest pain with an initial inconclusive assessment. CCTA detected no evidence of CAD in roughly half of the cohort, whereas approximately 20% were found to have obstructive CAD. The absence of CAD by CCTA accurately predicted the absence of ACS (100% NPV), and obstructive CAD (>50% luminal narrowing) was associated with 77% sensitivity and 87% specificity for ACS.[16] Not surprisingly, the presence and extent of coronary plaque and stenosis were superior in their discriminative capacity for ACS, as compared with clinical risk scores such as Thrombolysis In Myocardial Infarction (TIMI) or Goldman.[17]

Studies also demonstrated that the mere detection of obstructive CAD by CCTA does not equate to a diagnosis of ACS. For example in the ROMICAT I trial, 20 of 34 patients with obstructive CAD had ACS;[16] in a trial by Hollander et al,[18] only 7 of 54 patients with obstructive CAD in CCTA had a stenosis on invasive coronary angiography (ICA) or developed a major adverse coronary event (MACE) within 30 days. Combined with the low prevalence of ACS in population with acute chest pain (2–8% have ACS), CCTA shows a low PPV for ACS (approximately 35–50%). Further reduction of specificity may occur based on the reliance of CCTA on morphology and on the definition of significant stenosis, as not all luminal narrowing of more than 70% are hemodynamically significant when compared with fractional flow reserve (FFR).[12]

To improve the PPV of CCTA for ACS, different strategies have been evaluated:

1. Assessing global and regional LV function. The results demonstrated that the presence of regional LV dysfunction incrementally and independently improves the diagnostic accuracy for ACS beyond morphological evaluation of coronary arteries in patients with CAD (sensitivity of coronary stenosis versus coronary stenosis *and* LV dysfunction for ACS: 77% versus 87%, respectively).[19] However, the assessment of LV function comes with the expense of radiation and excludes the application of novel computed tomography (CT) acquisition protocols, see below.
2. Detailed plaque assessment. For example, if more than 1 stenosis was to be found, it would subsequently increase the PPV.[16] Furthermore, a score based on plaque morphology, including low CT attenuation, length of stenosis, and positive remodeling, resulted in a PPV of 100% for ACS in patients with obstructive lesions.[20] In other studies, plaque morphology, in particular the triad of low attenuation plaque (signifying a lipid-rich necrotic core), positive remodeling, and spotty calcification, has been shown to be associated with culprit lesions. More recently, the "napkin-ring sign" has been described as the most specific CT plaque morphology sign for the identification of fibroatheroma, with a large necrotic core or potentially high-risk plaques.[21] However, the assessment of plaque morphology is not routinely performed in clinical practice and further data are needed to support these findings.
3. Evaluation of myocardial perfusion. In an observational study by Feuchtner et al,[22] 76 patients with acute chest pain in an ED setting underwent CCTA, including assessment of myocardial perfusion abnormities. Although the PPV for the presence of stenosis in this selected cohort was 67%, it increased to 90% when CT-based myocardial perfusion information was added. This is supported by other small ED studies.[23] Results from experimental studies showed a good correlation of CT-based rest and stress myocardial perfusion imaging (MPI) with in-vivo reference standards.[24] However, this new CT application, especially the value of resting myocardial perfusion in the acute setting, warrants further investigation before its clinical value can be fully determined.

In summary, the absence of CAD determined by CCTA is observed in 50% of population with acute chest pain presented in the ED, providing an NPV (for ACS) of approximately 100%. In contrast, obstructive coronary disease, as determined by CCTA, is associated with ACS during index hospitalization. The PPV for ACS can be improved by additional assessments, such as regional LV dysfunction, plaque morphology, or myocardial perfusion. As a result, CCTA has a class IIa, level of evidence B recommendation for the evaluation of patients with acute chest pain with a low–intermediate pretest probability of ACS and inconclusive initial ECG and biomarkers.[25,26]

Coronary Computed Tomography Angiography for the Simultaneous Rule-Out of Acute Coronary Syndrome, Pulmonary Embolism, and Acute Aortic Syndrome

Acute chest pain syndromes also include 2 other common and life-threatening diagnoses: pulmonary embolism and acute aortic syndrome. Triple rule-out CT angiography protocols have been developed to simultaneously provide sufficient contrast enhancement of the thoracic aorta, coronary arteries, and pulmonary arterial circulation.[27] Compared with CCTA, more iodinated contrast agent is needed to account for the transit time between pulmonary and aorta/coronary opacification (approximately 10 s), and the scan coverage is lengthened as the entire thorax needs to be assessed. Similar to dedicated CCTA, the use of advanced CT technology with dose-saving acquisition algorithms has significantly lowered the exposure resulting from triple rule-out protocols.[27]

Several studies have demonstrated the clinical feasibility and high accuracy of a triple rule-out CT protocol.[28,29] Based on this limited evidence, a triple rule-out protocol may be most appropriate for patients presenting with undifferentiated acute chest pain and at low–intermediate risk for ACS. In these patients, traditional work-up includes stress testing to rule out ACS, which is often followed by an initial CTA for pulmonary embolism. However, the precise clinical indications and the appropriate patient population in which the triple rule-out CTA may be preferable to traditional work-up remain unclear.

Change in Patient Management

CCTA use in the setting of patients with chest pain and at low–intermediate risk presenting to the ED may have a large impact on patient management. One of the major drawbacks of the standard triage, including stress testing, is the extended hospitalization for serial biomarkers, ECG, and risk-stratification testing (Fig. 1). Based on the fact that 50% of this population has no CAD, it seems that CCTA could significantly and safely reduce the duration of the hospital stay (Fig. 2). Four large, multicenter, randomized trials have tested these hypotheses (Table 1).

In the Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment trial by Goldstein et al,[30] 749 patients with acute chest pain but negative ECG and initial biomarkers were randomized to early CCTA or to rest-stress single-photon emission computed tomographic myocardial perfusion imaging (SPECT-MPI). The CT-based strategy reduced the time to diagnosis when compared with the SPECT-MPI, by more than 50% (2.9 versus 6.2 hours). CCTA was also associated with a reduced radiation exposure when compared with SPECT-MPI, with similar MACE rates at a 6-month follow-up for patients directly discharged from the ED (0.8% for CCTA versus 0.4% for SPECT-MPI).

The recently published ROMICAT II trial by Hoffmann et al[31] compared 2 management strategies in low–intermediate risk patients with acute chest pain—one including early CCTA as a first diagnostic test. This was performed versus standard-of-care (SOC) ED

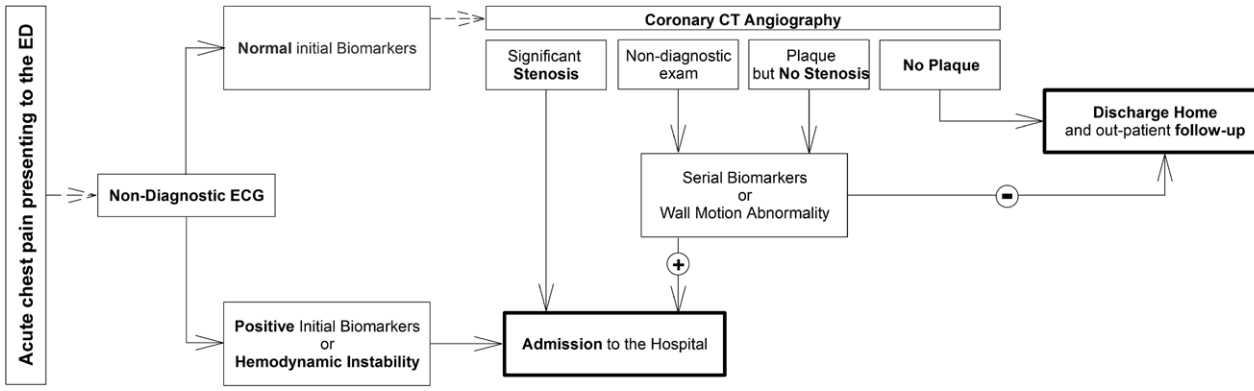

FIGURE 2. Incorporation of CCTA into the triage of patients with acute chest pain syndrome. CCTA indicates coronary computed tomography angiography; CT, computed tomography; ECG, electrocardiography; ED, emergency department.

evaluation, which included all options of stress testing or no testing. They found a shorter length of stay (18 versus 25 hr) in the CCTA strategy, driven by a higher rate of direct discharge from the ED (50% versus 22%). The third trial published by Litt et al[32] enrolled 1370 subjects, of which 908 were in the CCTA group and 462 in the SOC group. The main objective of this trial was to establish safety of CCTA discharge, as defined by an upper 95% confidence interval (CI) less than 1% for missed ACS or death during the 30-day follow-up.

There is a concern that CCTA may lead to a higher number of secondary diagnostic testing, such as cardiac catheterizations. In a randomized, controlled trial published in 2007 by Goldstein et al,[33] 24 of 99 patients had either "stenosis of unclear significance" or unevaluable segments, requiring a stress myocardial perfusion scan, 21 of which showed no perfusion defect. The cumulative rate of cardiac catheterization was 12% for the CCTA strategy versus 7% for SPECT-MPI. Recent studies have yielded similar results. In the ROMICAT II trial (total N = 1000),[31] the rate of cardiac catheterization was 11% in the CCTA group versus 7% in the SOC groups (P = 0.06). A total of 27% were referred for a second diagnostic test after an initial CCTA, significantly more than in the SOC group.

In summary, usage of CCTA in the early phase of managing patients with acute chest pain reduces the total length of stay but may increase downstream testing. In a recent meta-analysis by Hulten et al,[34] an absolute increase in invasive angiography after CCTA of 21 (95% CI, 2–45) per 1000 CCTA scans was determined. Similarly, the rate of revascularizations increased by 20 (95% CI, 5–41) per 1000 CCTA scans. Unfortunately, neither LV function nor myocardial perfusion nor advanced plaque assessment for further evaluation regarding hemodynamic significance were used to guide patient management in these trials. Whether increased percutaneous coronary intervention rates after CCTA may result in improved long-term health outcomes is possible but has not been established yet. In addition, FFR was not used in a standardized manner during invasive angiography in any of these trials. It remains unclear how far novel biomarkers such as high-sensitivity troponin could provide a similar outcome as compared with CCTA if used as gatekeepers in patients with acute chest pain syndrome presenting to the ED. Despite these shortcomings, CCTA has been established as a viable alternative to standard functional testing.

The Long-Term Value of Coronary Computed Tomography Angiography in Patients With Acute Chest Pain

The presence and extent of CAD are universally recognized as the strongest predictors of future coronary events.[35] Similarly, this information acquired from the CCTA scan may have prognostic value in patients with acute chest pain. The 2-year follow-up of the ROMICAT I trial published by Schlett et al[36] observed MACE in 5 of 300 patients (1 STEMI, 3 NSTEMI, and 4 percutaneous coronary intervention (PCI)) without ACS during index hospitalization. It should be noted that 4 of 5 events occurred in patients with obstructive CAD detected by CCTA. The estimated 2-year event rate for late MACE (>30 days) was 0% for no CAD, 1.2% for nonobstructive CAD, and 8.9% for obstructive CAD ($P < 0.0003$). The presence of LV dysfunction on CCTA also provided incremental value for the long-term prognosis (estimated 2-year event rate for late MACE for patients with obstructive CAD and regional LV dysfunction was 18.5%).

The evidence that patients with acute chest pain without CAD on CCTA remain event free over a long period was further supported by a study by Sozzi et al,[37] where 222 patients were followed for a mean of 5 years. In those patients without the evidence of CAD, no one developed MACE. Conversely, the annual reported event rate was 1.2% for patients with nonobstructive CAD and 4.2% with obstructive CAD. Similar findings were observed in a registry study (median follow-up, 13 months),[38] where patients with acute chest pain at low to intermediate risk for CAD underwent both calcium scoring and CCTA. Out of 458 patients, without evidence of ACS at discharge, 70 (15%) experienced MACE. Although the absence of any CAD excluded the occurrence of MACE, patients with the absence of coronary calcification demonstrated a cumulative event rate of 6% after 2 years. Accordingly, at least a 2-year event-free "warranty" period is given for patients with acute chest pain with no CAD defined by CCTA.[36] By using the prognostic power of CCTA is a key to increase the risk–benefit ratio and the efficacy of CCTA in the acute chest pains setting.

Cost and Cost-Effectiveness of Coronary Computed Tomography Angiography in Acute Chest Pain Syndrome

Optimally, CCTA would reduce costs and provide more cost-effective care in the triage of patients with acute chest pain. Overall, a significant reduction in length of stay, but no reduction in overall costs, was observed.[31] However, a reduction of ED costs by 18% as compared with SOC ($2101 versus $2566) was observed (Table 1). In contrast, the costs during hospitalization were slightly increased using CCTA ($4026 versus $3874). Costs in the CCTA group were driven by a higher number of revascularizations due to the increased sensitivity of CCTA in detecting obstructive CAD.[31] As previously discussed, it remains unclear whether this translates into an improvement in quality of life or health outcomes.

Previous work by Khare et al[39] found that a triage strategy including CCTA would dominate other strategies, such as stress echocardiography or stress ECG, regarding its cost-effectiveness

(incremental cost-effectiveness ratio was $29,738/quality adjusted life years (QALY) for CCTA, if compared with stress echocardiography, and $7332/QALY, if compared with the stress ECG). When comparing CCTA with SOC (eg, stress ECG), CCTA was more expensive for men when compared with women ($10,190 versus $6630), resulting in an incremental cost-effectiveness ratio of $6400/QALY for men and cost-savings for women.[40]

In summary, it seems that CCTA is a cost-effective alternative to stress testing. However, it may be more cost-effective in women than in men, due to the lower disease prevalence in women.

Appropriate Use of Coronary Computed Tomography Angiography

The appropriateness of a diagnostic test is strongly associated with the pretest probabilities and the change in probability by the test results. This has been demonstrated for CCTA in acute chest pain.[41] Because of its high NPV, CCTA is most efficient in patients with low (2–10%) pretest likelihood for CAD, less in patients with intermediate, and very little in patients with high pretest probability (Fig. 3).[16,30] Due to the low specificity of stress testing, CCTA is very efficient in patients with equivocal stress testing, as most of these patients do not have CAD. The current appropriateness criteria are explicitly defined in the consensus statement.[25]

STABLE CHEST PAIN SYNDROME

Epidemiology

Approximately 9 million people in the United States experience stable angina pectoris resulting from flow-limiting coronary artery stenoses.[2] Classically, stable angina is a substernal chest tightness that worsens with exertion and improves with rest. However, the diagnosis of stable angina may not be straightforward, as patients may present with atypical features. Stable angina is often seen as an early manifestation of CAD and is associated with an annual event rate of approximately 3% for developing an AMI.[42,43]

Stable angina is due to an imbalance between myocardial oxygen demand and myocardial oxygen supply.[44] With increasing oxygen demand in the setting of physical or emotional stress, the normal physiological response is coronary vasodilatation, which results in increased myocardial blood flow.[45] However, in the case of coronary atherosclerotic disease, this vasodilatory capacity is reduced.[45] Furthermore, an obstructive coronary stenosis of 75–95% of the cross-sectional vessel area (or approximately 50% of the luminal diameter) is associated with a decrease in coronary flow and accordingly affects the myocardial oxygen supply.[44] This link between coronary blood flow and narrowing of the coronary diameter provides the rationale for anatomical imaging techniques such as CCTA. Notably, the degree of stenosis is not the only indicator of resistance to blood flow, as the entrance and exit angles, lesion length, and plaque morphology also affect downstream coronary flow.[46] These considerations might explain the incremental value of functional imaging in the detection and characterization of CAD in patients with chronic stable chest pain.

The Immediate Value of Coronary Computed Tomography Angiography in Stable Chest Pain Syndromes

Diagnostic Accuracy

Compared with ICA as a reference, CCTA has consistently shown high diagnostic accuracy in detecting obstructive CAD. Many investigators believe that the clinical value of CCTA is its ability to rule out significant diseases due to the excellent sensitivity and NPV.

Few prospective multicenter studies of 64-slice or better multidetector CT technology are available with patients with stable chest pain (Table 2). Although the Coronary Artery Evaluation Using

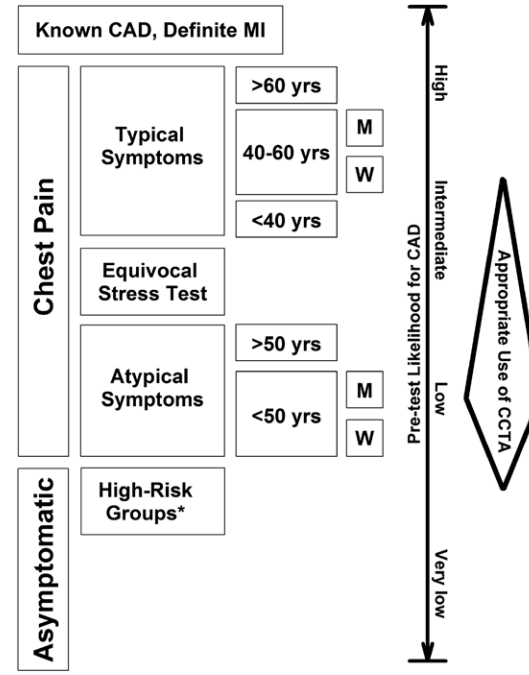

FIGURE 3. Appropriate use of CCTA for the evaluation of CAD. Simplified algorithms modified from the current consensus for the appropriate use of CCTA. CCTA is most symptomatic patients with low pretest likelihood for CAD and an equivocal stress test result given the low specificity of stress testing. Pretest probability for CAD is considered as high if >90%, intermediate if 10–90%, low if 5–10%, very low <5%, as detailed elsewhere.[25] CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; MI, myocardial infarction; M, male patients; w, female patients; yrs, years.

64-Row Multidetector CT Angiography (CORE64) trial[47] and the study published by Meijboom et al[48] included patients with known CAD and UA, respectively, the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) trial only included patients with stable chest pain without known CAD being referred to ICA.[49] The Ontario Multidetector Computed Tomographic Coronary Angiography study (OMCAS) included 2 groups of patients.[50] One group consisted of symptomatic but stable patients, with an intermediate pretest probability, which were referred for ICA. The second group included asymptomatic patients, referred for ICA for nonchest pain evaluation (eg, congenital heart disease, aortic disease, and cardiomyopathy). It should be noted that none of these studies excluded patients based on an elevated body mass index or calcium score. All vessels were included in the analysis, regardless of image quality. Accordingly, the prevalence of obstructive CAD varies significantly between studies from 25% to 68%.

The results from the ACCURACY and OMCAS trials may be most applicable due to their inclusion criteria.[49,50] Both trials showed a sensitivity and specificity of more than 80% (Table 2). However, PPV and NPV were surprisingly different, probably due to the differences in CAD prevalence. In the ACCURACY trial,[49] NPV was 99% and PPV 64%, whereas they were 78% and 97% in the OMCAS trial,[50] respectively. Similarly, the CORE64 trial found better PPV than NPV.[47] Importantly, one major inconsistency between those trials is the way investigators handled unevaluable coronary artery segments.

TABLE 2. Diagnostic Accuracy of CCTA for Significant CAD in Patients With a Stable Chest Pain Syndrome

Authors (trial name)	Year	No. Patients/ No. Controls	Subjects	Age, yr	Female, %	CAD Prevalence, %	Sensitivity (95% CI)	Specificity (95% CI)
Budoff et al[49] (ACCURACY)	2008	230/16	No known CAD, stable chest pain, or abnormal functional stress testing	57 ± 10	41	25	95% (85–99%)	83% (76–88%)
Meijboom et al[48]	2008	360/3	No known CAD, presenting with stable, or acute chest pain	60 ± 6	32	64	99% (98–100%)	64% (55–73%)
Miller et al[47] (CORE64)	2008	291/9	Symptomatic patients with suspected or known CAD	60 ± 6	26	56	85% (79–90%)	90% (83–94%)
Chow et al[50] (OMCAS)	2011	117*/4	Chest pain with intermediate probability of significant CAD	60 ± 10	40	61	81% (72–90%)	97% (86–100%)

In all studies, presence of stenosis by CCTA was compared with significant CAD as determined by invasive angiography.
*Subgroup of symptomatic patients.
ACCURACY indicates Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; CORE64, Coronary Artery Evaluation Using 64-Row Multidetector CT Angiography; OMCAS, Ontario Multidetector Computed Tomographic Coronary Angiography Study.

In most studies, these unevaluable segments are classified as "positive" for obstructive CAD, whereas in the CORE64 trial, these segments were considered as "normal" for the purpose of analysis. It is possible and concerning that these published results therefore do not accurately reflect clinical scenarios. Clinically, readers are far more concerned to miss a significant lesion ("under-call") rather than to overcall it. Therefore, translation or application of these results into clinical practice is challenging.

Hence, in clinical reality, CCTA will likely result in a low PPV, but a high NPV. A low PPV carries the risk of unnecessary invasive diagnostic procedures and interventions. Data from a broader range of real clinical readers with varying levels of experience are necessary to assess the diagnostic accuracy of CCTA in real life. As an example, significantly lower diagnostic performance was observed in less experienced centers,[50] a fact that highlights the necessity of standardization of training.

Change of Management

Data on the effect of CCTA on the clinical management of patients with stable chest pain are sparse. Therefore, large-scale, randomized, comparative effectiveness trials such as the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) and the Randomized Evaluation of Patients with Stable Angina Comparing Usage of Diagnostic Examinations (RESCUE) are underway to evaluate the diagnostic differences between CCTA and other noninvasive imaging tests, such as myocardial perfusion scintigraphy or exercise ECG testing, see below for details. Today, most data are based on the international multicenter Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry (CONFIRM), which examined the referral patterns to ICA (with or without revascularization) after CCTA.[35] In 15,207 intermediate-risk patients from 8 sites in 6 countries, the rates for ICA were low (<10%) in patients with no or nonobstructive CAD detected by CCTA. In contrast, nearly half of all patients with obstructive CAD by CCTA underwent subsequent ICA (44.3% for 1-vessel, 53.3% for 2-vessel, and 69.4% for 3-vessel obstructive CAD). The majority of ICA (79%) occurred within the first 3 months after CCTA acquisition. In patients with obstructive CAD on CCTA, a marginal risk reduction for all-cause mortality was observed if an invasive coronary angiogram (with or without revascularization) was performed. These findings support the role of CCTA as a gatekeeper for invasive diagnostics and interventions.

Furthermore, the detection of subclinical disease (ie, nonobstructive CAD) by CCTA could guide primary care physicians to modify lifestyle and tailor preventative medical therapy. There are a few studies that have highlighted this potential role of CCTA. In the Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in Coronary Artery Disease registry with 1703 intermediate–high-risk patients who were examined for 90-day post-test rates of medication changes, post-test medical therapy intensification increased in proportion to the degree of abnormal findings in imaging.[51] Specifically, aspirin and lipid-lowering agent use was greater in patients undergoing CCTA versus other noninvasive imaging modalities, such as SPECT and positron emission tomography, likely related to the detection of nonobstructive CAD.[51] More recently, Cheezum et al[52] evaluated a lower-risk symptomatic population and find that optimization of medical therapy based on CCTA-detected CAD resulted in a favorable impact on blood pressure and lipid profiles. Similarly, Ovrehus et al[53] showed in a cohort of 1055 consecutive patients with suspected stable angina pectoris, a decrease in antiplatelet therapy use in patients with no CAD, and an increase in lipid-lowering agents and antiplatelet therapy in patients with CAD, as determined by CCTA. It is conceivable that these changes of risk factors, secondary to CCTA-guided medical therapy adjustments, may ultimately improve patient outcomes. The current use of information, based on CCTA to tailor therapy, is not mandated by guideline recommendations, and prospective randomized trials are warranted to justify change in therapy.

The Long-Term Value of Coronary Computed Tomography Angiography in Stable Chest Pain Syndrome

Prognostic Information

The prognostic value of CCTA in patients with stable chest pain has been evaluated in several small studies and summarized thus far in 3 meta-analyses.[54–56] In addition, several studies were based on the international multicenter CONFIRM registry.[57–61] A normal CCTA was associated with an annualized event rate of 0.17–0.40%, based on different meta-analyses[54–56] and the CONFIRM registry.[59] This large range in annualized event rate is explained by the fact that some studies, such as the CONFIRM registry, include only all-cause mortality instead of MACE as an endpoint.[59,62,63] This underscores the prognostic value of the high NPV of CCTA, particularly when compared with the prognosis after normal ICA or stress testing.[64–66]

The length of the event-free "warranty period" is unclear after a CCTA reveals no CAD. In a subanalysis of the CONFIRM registry, the annualized death rate was only 0.22% in patients with

more than 4-year follow-up (1816 patients).[59] Based on these data, 4 years seems like a reasonable event-free warranty period to ascribe to CCTA, but further studies are needed to evaluate prognosis for endpoints beyond all-cause mortality, such as AMI and UA.

In contrast, the annualized event rate for patients with obstructive disease detected by CCTA ranged from 9% to 16%, driven predominantly by coronary revascularizations.[54–56] After excluding revascularizations, obstructive CAD, as determined by CCTA, remained a significant predictor for a worse outcome (annualized rate: 3.2% for death or MI, 6.4% for MACE excluding revascularization).[54,56] If the endpoint is restricted to all-cause mortality, as shown in the CONFIRM registry, annualized death rates ranged from 2.9% to 4.95%, depending on whether a single vascular territory stenosis or a high-risk CAD profile, consisting of left main stenosis and/or 2- to 3-vessel stenosis, was present.[60] Several authors showed that the prognostic value of obstructive CAD was dependent on the degree of stenosis (hazard rate ratio, 2.60 and 3.13 in patients with more than 50% and 70% stenoses) or the complaint of diabetes mellitus (hazard rate ratio, 13.25 versus 9.25 for 3-vessel stenosis, respectively).[59] Notably, a significant coronary stenosis (>50%) can be present in patients with a calcium score of zero (3.5% prevalence in more than 5000 patients with zero calcium scoring).[61] In those patients (obstructive CAD, but zero calcium score), 3.9% (7 of 177) died during the follow-up period of up to 1500 days.

Nonobstructive plaque (<50% stenosis) derived by CCTA is associated with an annualized MACE rate of 1.41% and mortality event rate of 0.74–1.99%.[56,60] Interestingly, the CONFIRM registry showed a similar mortality risk between patients with nonobstructive CAD and those with 1-vessel obstructive CAD (hazard ratio, 1.62 versus 1.75, respectively).[59] This points out the value of identifying the extent of CAD in addition to severity and is supported by further analyses showing dose–response relationships for increased hazards of death in patients with 1-vessel, 2-vessel, and 3-vessel disease.[59] In general, CAD can be quantified either manually, with a per-segment analysis, or using semi-automated tools. Regardless of methodology, increased risks for future events and mortality were observed with a larger extent of CAD.[54,59] In addition, the location of obstructive CAD matters, as stenoses in the left main and proximal left anterior descending coronary arteries were associated with increasing event rates.[54,59,60] Accordingly, the Duke Prognostic CAD index was modified to account for stenosis severity, extent, and location, providing improved predictive value for mortality.[62] Similarly, a new grading system is being developed, based on the CONFIRM registry, incorporating traditional risk factors with plaque severity, extent, location, and morphology.

Plaque morphology has been widely studied for its predictive value. Although several studies showed that partially calcified plaque yielded a higher risk for developing events, existing data are inconsistent.[67–69] To date, in most studies, the plaque characterization is limited to classification, such as noncalcified, calcified, and partially calcified (mixed plaque), which may be not sufficient to describe high-risk plaque morphology and hence lead to these inconsistent findings.

All these findings must be interpreted carefully, considering several limitations. Most studies included late coronary revascularization (>90 days) as part of the definition of MACE. However, this endpoint may be directly related to the results of CCTA findings. There is a "verification bias" with respect to taking a patient with indeterminate and moderate–severe stenosis from CCTA to invasive angiography for finding confirmation. In studies with all-cause mortality set as an endpoint, causality between CCTA findings and endpoint may not be given, considering the recent data from the Framingham Heart Study showing that the proportion of true cardiovascular-associated death is decreasing and cardiac death only presents 40% of all deaths.[70] Finally, large heterogeneity exists across almost every important variables, that is, pretest probability, inclusion of known CAD, inclusion of minorities, inclusion of younger patients, CAD reporting schemes (eg, >50% or >70% luminal narrowing for obstructive CAD). These heterogeneities challenge the generalization of conclusions and highlight the difficulties in conducting high-quality, valuable prognostic studies. Accordingly, more evidence on the prognostic value of coronary CCTA has been demanded by the Centers for Medicare/Medicaid Services and the most recent CCTA expert consensus statements.[46,71]

Quality of Life

Few studies in patients with stable chest pain have focused on quality of life. A recent study by Min et al,[72] where 180 patients with stable chest pain with suspected CAD were randomized to CCTA or SPECT, found no difference in the health status as assessed by the Seattle Angina Questionnaire. Further research in this field is needed to determine whether patients benefit differently regarding their quality of life from different imaging modalities.

Cost and Cost-Effectiveness of Coronary Computed Tomography Angiography in Stable Chest Pain Syndrome

Cost-effectiveness in patients with stable angina is dependent of test characteristics and pretest probability of CAD.[73–75] Depending on the assumed willingness-to-pay, and other assumptions, CCTA cost-effectiveness was compared with invasive angiography for pretest probability between 37% and 49%,[73–75] with higher pretest probability values for men than for women.[74]

Based on the ACCURACY study, Min et al[76] showed that the combination of CCTA with adjacent SPECT acquisition resulted in the lowest cost per correct diagnosis ($1770 per patient). CCTA, followed by invasive angiography, was more effective and hence resulted in a more favorable incremental cost-effectiveness ratio and remained the most cost-effective strategy, especially in a long-term perspective. It should be noted that those calculated data are based on a pretest probability of 30% for obstructive CAD. A comparable study by Ladapo et al,[77] with a typical case of a 55-year-old female or male patient with atypical chest pain and a pretest probability of 30% and 70%, respectively, showed that the use of CCTA followed by stress ECG in male patients was the most cost-effective approach, with an incremental cost-effective ratio of $26,200/QALY versus $35,000/QALY for female patients. However, women received the most favorable health outcome per unit cost when receiving the combined CCTA and stress ECG strategy. Analyzing real-world data, Medicare data showed a decrease of CAD-related costs after 9 months, if patients with low risk for adverse cardiac events underwent CCTA rather than SPECT.[78]

Results regarding costs and outcomes from the major, currently recruiting, randomized, controlled trial in patients with stable chest pain (eg, PROMISE, RESCUE, and International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) must be awaited before valid conclusions can be made regarding the cost-effectiveness of CCTA in this population.

RADIATION DOSE OF CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY IN CHEST PAIN EVALUATION

One of the major concerns using CCTA has been patient radiation exposure.[79,80] Over the last several years, aggressive efforts have been made by the cardiovascular imaging community to lower the effective radiation dose by optimizing acquisition protocols. These efforts, plus improvements in technology, have resulted in a

significant reduction of radiation dose, without the need to sacrifice image quality.[81–84] Key developments in the reduction of radiation, such as iterative image reconstruction algorithms (see below), and prospective gating protocols, play an important role.

Prospective ECG-Triggered Axial Acquisition

This technique is also referred to as "step-and-shoot" imaging, in which the scanner table moves in a step-wise manner for every other heart beat until the full scan length is acquired. At each step, radiation exposure is limited to only one phase of the cardiac cycle although "padding" can be used around this phase, resulting in substantially lower effective radiation dose (approximately 3–4 mSv), but requires stable and slow heart rhythms.[85–87]

Prospective ECG-Triggered, High-Pitch Acquisition

This relatively new acquisition technique relies on a fast table speed (high pitch), allowing the acquisition of the entire heart in 0.6 seconds. Given the speed of acquisition, a breath hold is not even required and radiation exposure can be reduced to approximately 1 mSv for a coronary acquisition.[88,89]

CURRENT DEVELOPMENTS IN CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY TECHNIQUES

Several novel developments have emerged over the last few years, promising an improvement of CCTA. Those with particularly strong potential include iterative image reconstruction algorithms and computational algorithms predicting FFR.

In comparison with the common filtered-back projection method for image reconstruction, iterative reconstruction algorithms synthesize raw data, which are iteratively corrected and compared with acquired raw data.[90] The largest benefit has been observed regarding the reduction in image noise and improvement in image quality.[91] Accordingly, tube voltage (and therefore effective radiation dose) can be further reduced without altering the diagnostic quality of the scan.[92,93] Additional benefits, such as decreased blooming artifact from coronary calcification, have been observed, but the implications for clinical practice need to be evaluated.

Based on a novel computation algorithm, FFR can be predicted based on any regularly acquired CCTA scan. Recently, FFR has increased in popularity in invasive cardiology after large randomized control trials have shown improved clinical outcomes for FFR-guided therapy.[94,95] Based on CCTA datasets, a calculated FFR (CT-FFR) was evaluated in the Determination of Fractional Flow Reserve by Anatomic Computed Tomographic Angiography (DeFACTO) study, a multicenter observational cohort trial.[96] This study compared a CT-FFR of 252 patients with the invasively measured FFR, finding that CT-FFR is a significantly better predictor for FFR when compared with the presence and severity of stenosis detected by CCTA. Although the correlation of CT-FFR with invasively measured FFR was good on a per-patient level, it was lower on a per-vessel level, which is where CT-FFR could potentially provide its greatest value.[2] However, the per-vessel perspective may be more relevant for a subsequently testing strategy.

Although this is quite promising and would enable CCTA to provide more than morphological information, the use of this novel technology needs to be analyzed in real-world practice. CT-FFR is not yet approved by the Food and Drug Administration. Furthermore, it should be determined whether CT-FFR has any ability to improve resource usage and clinical outcomes for patients with chest pain. Because the calculation of CT-FFR is currently a time-consuming endeavor, this novel algorithm may be more suitable for patients with stable chest pain.

SUMMARY AND FUTURE DIRECTIONS

For patients with acute or stable chest pain syndromes, CCTA is a safe and effective diagnostic modality. The strength of CCTA is its high NPV to rule out CAD, which carries independent prognostic value for short- and long-term coronary events, better than any individual or combination of risk factors or any other diagnostic test.

Early CCTA is a viable alternative to stress testing in the triage of patients with an acute chest pain syndrome. By using CCTA, the length of hospital stay is reduced dramatically, allowing for a faster yet safe discharge from the ED or chest pain unit. To improve cost-effectiveness, biomarkers may be an efficient gatekeeper for further testing. There is further need to establish the potential long-term health and economic benefits of CCTA in acute chest pain, including those of percutaneous coronary intervention resulting from CCTA. Similarly, initial evidence of CCTA-derived benefits in patients with stable chest pain must be extended.

For patients with stable chest pain, the clinical benefit of CCTA is less established. Two large multicenter, randomized, controlled trials are currently being conducted: the PROMISE trial and the RESCUE trial. The PROMISE trial is targeting an enrollment of 10,000 patients with stable chest pain from approximately 200 U.S. sites and will compare CCTA-based anatomical testing with functional testing, including exercise tolerance testing and stress nuclear imaging. The primary endpoint of the study is frequency of death, MI, and/or major periprocedural complications, applying each diagnostic strategy. Furthermore, PROMISE trial will address questions regarding the effect of CCTA on medical costs, resource usage, cost-effectiveness, and quality of life. The RESCUE trial is targeting recruitment of 4300 patients with stable chest pain from 80 institutions internationally. Patients are randomized to CCTA or nuclear stress testing and followed for a composite endpoint of MACE, including revascularization and cross-over to revascularization, over a period of up to 2 years. Both trials will be pivotal in guiding our use of CCTA in the setting of patients with stable, chronic chest pain.

With the usage of improved technology and optimized scan protocols, the average reported radiation dose for CCTA is comparable with or even below other diagnostic testing procedures, such as nuclear stress testing or invasive angiography. A further reduction of the radiation dose is feasible and may encourage the clinical use of CCTA over other imaging modalities for the evaluation of patients with both acute and stable chest pain.

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