The Emerging Roles of Coronary Computed Tomographic Angiography: Acute Chest Pain Evaluation and Screening for Asymptomatic Individuals

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Coronary computed tomographic angiography (CCTA) has been widely available since 2004. After that, the diagnostic accuracy of CCTA has been extensively validated with invasive coronary angiography for detection of coronary arterial stenosis. In this paper, we reviewed the updated evidence of the role of CCTA in both scenarios including acute chest pain and screening in asymptomatic adults.

Several large-scale studies have been conducted to evaluate the diagnostic value of CCTA in the context of acute chest pain patients. CCTA could play a role in delivering more efficient care. For risk stratification of asymptomatic patients using CCTA, latest studies have revealed incremental benefits. Future studies evaluating the totality of plaque characteristics may be useful for determining the role of noncalcified plaque for risk stratification in asymptomatic individuals.

BACKGROUND

Coronary computed tomographic angiography (CCTA) has been widely available since around 2004. From thereon, the diagnostic accuracy of CCTA has been extensively compared with invasive coronary angiography for detection of coronary arterial stenosis. Most of these studies enrolled patients with stable angina. However, more recent studies have evaluated the use of CCTA in other clinical contexts.

In this review, we intended to address current updated evidence of the role of CCTA in two scenarios, including acute chest pain and screening in asymptomatic adults (Table 1).

ACUTE CHEST PAIN

CCTA is a viable alternative to functional imaging in the assessment of patients presenting with acute chest pain (ACP) to the emergency department (ED).[1] The latest American Heart Association (AHA) scientific statement on testing of low-risk patients presenting to the ED with chest pain recommends additional testing in all pa-

Table 1. List of the recent large-scaled studies of CCTA and CACS in the context of chest pain and asymptomatic patients

Study	Study design	Conclusion
CCTA in patients with chest pain		
64-STAT trial (Goldstein et al. 2007)	Single center RCT. Enrolled 197 patients. CCTA vs. rest-stress MPI.	Coronary CTA resulted in reduced diagnostic time (3.4 hours vs. 15.0 hours; p < .001) and lowered ED costs ($1586 vs. $1872; p < .001). (7)
ACCURACY trial (Budoff et al. 2008)	Prospective multicenter RCT. Enrolled 230 subjects. CCTA vs. ICA.	CCTA compared to ICA predict > 50% stenosis, CCTA achieved 93% sensitivity, 79% specificity. And overall 99% NPV, which poses as an effective noninvasive alternative to ICA to rule out obstructive coronary artery stenosis. (8)
ROMICAT I trial (Hoffmann et al. 2009)	Observational cohort study in low to intermediate risk ACP patients. Enrolled 368 patients.	Long-term safety and established a 2-year warranty period for normal coronary CTA after discharge from the ED. (13)
The CT-STAT trial (Goldstein et al., 2011)	Multicenter RCT. Enrolled 699 patients. CCTA vs. MPI.	CCTA resulted in a 54% reduction in time to diagnosis compared with MPI. And Costs of care were 38% lower compared with standard of care in low-risk chest pain patients. (15)
The ROMICAT-II trial (Hoffmann et al. 2012)	The first multicenter RCT of CCTA vs. SOC. Enrolled 1000 subjects. CCTA vs. SOC.	CCTA as compared with SOC resulted in a reduced median length of stay time to diagnosis and increase in direct discharges. (14)
ACRIN-PA trial (Litt et al. 2012)	RCT of CCTA vs. SOC. Enrolled total 1370 patients. CCTA vs. SOC.	Patients in the CCTA group had a higher rate of direct ED discharge (50% vs. 23%) and shorter length of stay (18 hours vs. 25 hours). The results con?rmed the improved efficiency of CCTA without any compromise in patient outcomes. (16)
CCTA in asymptomatic screening		
Choi et al. (2008)	Prospectively screening study. Enrolled 1,000 middle-aged asymptomatic adults. CCTA, CCS vs. NCEP criteria.	CCTA has better sensitivity detecting potential occult CAD patients which may display low CCS and low rik in NCEP criteria. (18)
V. Russo et al. (2010)	Retrospective review. Reviewed 451 patients. CCTA vs. CCS alone.	The presence of noncalcified or mixed plaques, was found to be the strongest predictor of events (p < 0.0001) as a potential marker of plaque vulnerability. CCTA provided additional incremental prognostic value compared with CCS alone. (25)
MESA study (Detrano et al. 2008)	Prospective cohort study. 6722 asymptomatic subjects (multiethnic U.S. population). CACS vs. Risk factors evaluation.	Using ROC curves for prediction of major coronary events. When the calcium score was added to the standard risk factors, results showing incremental value to the prediction of coronary heart disease over that of the standard coronary risk factors in each of four ethnic groups. (26)
CONFIRM registry (Cho et al. 2012)	Observational registry. 27,125 studies in consecutive asymptomatic patients (7,590 patients). CCTA vs. risk factors and CACS.	Coronary CT angiography provides incremental prognostic utility for prediction of mortality and non-fatal myocardial infarction for asymptomatic individuals with moderately high CACS, but not for lower or higher CACS. (27)

ACP, acute chest pain; CACS, coronary calcium scores; CAD, coronary arterial diasease; CCS, coronary calcium score; CCTA, coronary computed tomographic angiography; CPS, chest pain syndrome; ED, emergency department; ICA, invasive coronary angiography; NCEP, National Cholesterol Education Program criteria; SOC, standard of care.

tients regardless of risk scores after initial evaluation.[2] Based on the high negative predictive value of CCTA for the detection of coronary artery disease (CAD), and the wide spread availability and rapidity of this test, it was hypothesized that if used early after ED presentation, this modality could play a role in delivering more efficient care.[3,4] Likewise, The ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography designates CCTA as appropriate for use in ACP patients with low or interme-

diate likelihood of acute coronary syndrome (ACS).[5]

Over the past 10 years, a large body of evidence has been published supporting early CCTA as a rapid, accurate, safe, and efficient diagnostic strategy for low-to-intermediate risk patients presenting with acute chest pain in the ED.[6-9] First, a number of trials compared the results of this modality in non-ACP patients with findings on invasive coronary angiography (ICA), including, most notably, the multicenter studies: Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (AC-CURACY) Trial,[7] the Coronary Artery Evaluation Using 64-Row Multi-detector Computed Tomography Angiography (CORE-64) study, and the study by Meijboom et al.[9] In these studies, on a per-patient basis, by using the CCTA to predict an equal to or greater than 50% diameter stenosis achieved 93% sensitivity, 79% specificity, 80% positive predictive value and 93% negative predictive value. The 99% negative predictive value at the patient and vessel level establishes CCTA as an effective noninvasive alternative to ICA to rule out obstructive coronary artery stenosis.[8] These values compared favorably with rest-stress myocardial perfusion imaging (MPI), often considered the standard for noninvasive evaluation of acute chest pain patients.

Second, based on these encouraging results, a number of single-center studies of ACP patients assessed the ability of coronary CTA to predict either significant coronary ischemia through contemporaneous stress testing and/or the presence of ACS as assessed by a clinical outcomes panel.[10] The ROMICAT I (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial, an observational study in low-to-intermediate risk ACP patients, further provided information on long-term safety and established a 2-year warranty period for normal coronary CTA after discharge from the ED.[10-12]

Third, in addition to these observational trials, there are several randomized clinical trials comparing CCTA with the standard of care (SOC) in ACP patients without known CAD who presented with non-ischemic electrocardiogram and normal cardiac biomarkers. The ROMICAT-II trial randomized 1000 patients to either early CCTA or to SOC.[13] Notable differences to the prior randomized studies were that TIMI scores did not limit entry criteria and that the SOC included any available management strategy deemed appropriate by the treating physicians.

These strategies included treadmill testing, stress echo and stress single-photon emission computed tomography, as well as no further diagnostic testing. CCTA as compared with SOC resulted in a reduced median length of stay (8.6 hours vs. 26.7 hours; p < .001), time to diagnosis (5.8 hours vs. 21.0 hours; p < .001), and increase in direct discharges (47% vs. 12%; p < .001).[13]

Further data from the CT-STAT (Coronary Computed Tomographic Angiography for Systemic Triage of Acute Chest Pain Patients to Treatment), which was adapted from the 64-STAT trial,[6,14] randomized a total of 697 low-to-intermediate-risk patients with acute chest pain with negative electrocardiography and TIMI score ≤ 4 to evaluation by CCTA or rest-stress MPI. Evaluation by CCTA resulted in a 54% reduction in time to diagnosis compared with MPI (median 2.9 h vs. 6.3 h, p ≤ 0.0001). The costs of care were 38% lower compared with standard treatments. Both diagnostic strategies showed no difference in major adverse cardiac events after normal index testing (0.8% in the CCTA arm vs. 0.4% in the MPI arm, p = 0.29). In emergency department acute, low-risk chest pain patients, the use of CCTA results in safer, more rapid and cost-efficient diagnosis than rest-stress MPI. Additional studies comparing CCTA to other diagnostic strategies are needed to optimize evaluation of specific patient subsets.[14]

The most important study is the ACRIN/PA (American College of Radiology Imaging Network/Pennsylvania Department of Health) trial, which randomized 1370 patients with negative EKG and cardiac biomarkers and TIMI score ≤ 2 on a 2:1 basis between CCTA (908 patients) and SOC (462 patients).[15] Similar to ROMICAT II, SOC was defined by the attending physicians and included any accepted diagnostic tests and disposition without testing. The primary outcome of the ACRIN/PA trial was safety, and the trial proved that the upper bound of the 95% confidence interval for missed ACS in patients with normal CCTA is less than 1%. Overall, ACS rates in these trials varied from 1-8%, capturing low to intermediate risk chest pain populations. Most importantly, no patient with ACS was wrongly discharged in the CT arm or in the SOC arm. Patients in the CCTA group had a higher rate of direct ED discharge (50% vs. 23%) and shorter length of stay (18 hours vs. 25 hours). The results confirmed the improved efficiency of CCTA without any compromise in patient outcomes.[15]

ASYMPTOMATIC PATIENTS

Studies evaluating the use of CCTA for silent CAD have reported a relatively high prevalence of occult atherosclerosis.[15-23]

A study of 1000 asymptomatic patients evaluated the prevalence of occult CAD on CCTA and the ability to predict future adverse coronary events.[19] Atherosclerotic plaques were found in 22% of all patients, stenosis > 50% in 5% of the patients, and stenosis > 75% in 2% of the patients. In patients with significant stenosis, 25% were initially classified as low risk according to NCEP criteria, and 58% had a low coronary artery calcium scoring (CACS, < 100). At mid-term follow-up (17 ± 2 months), all coronary events identified occurred in individuals for whom CCTA had depicted CAD.[19]

The coronary event risk prediction of CCTA was evaluated in a retrospective study of 451 asymptomatic patients with a median follow-up of 27.5 months. The results showed that CCTA led to reclassification from intermediate or high to low risk of 48% of patients.[23]

In another study of 441 patients with suspected CAD, CCTA provided an additional incremental prognostic value compared with the combined clinical risk model and CACS. The presence of non-calcified or mixed plaques, independent of the lesion severity, was the strongest predictor of events (p < 0.0001), suggesting this may be a potential marker of plaque vulnerability.[24]

The Multi-Ethnic Study of Atherosclerosis (MESA), conducted in 6722 asymptomatic subjects as a representative multiethnic US population, demonstrated an incremental prognostic value of CACS over traditional risk factors by comparison of the areas under the receiver operating characteristic curves.[25]

The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry is the latest and largest one considering asymptomatic subjects, of which 27,125 consecutive patients and 7590 individuals were enrolled. All-cause mortality and nonfatal myocardial infarction were documented. During a median follow-up of 24 months, all-cause mortality occurred in 136 individuals. After risk adjustment, compared with individuals without evidence of coronary artery disease by CCTA, individuals with obstructive 2- and 3-vessel disease or left main coronary artery disease experienced higher rates of death and composite outcome (p < 0.05 for both).[26]

Both CACS and CCTA significantly improved the performance of standard risk factor prediction models for all-cause mortality and the composite outcome (likelihood ratio p < 0.05 for all), but the incremental discriminatory value associated with their inclusion was more pronounced for the composite outcome and for CACS (C statistic for model with risk factors only was 0.71; for risk factors plus CACS, 0.75; for risk factors plus CACS plus number of involved vessels detected in CCTA, 0.77). The incremental reclassification improvement from adding CCTA to a model based on standard risk factors and CACS was actually negligible.[26]

The potential limitations of CCTA as a screening tool include the risk of overdiagnosis, resulting in unnecessary medical management for CAD, the consequences of detecting incidental non-coronary findings and lead time bias.[27] Because of the long preclinical period of CAD, the screening test may result in detection at the early stage, creating a false impression that the test — and its clinical information — prolongs survival, when in fact it only resulted in a premature diagnosis compared with traditional methods. This will be potentially addressed through large randomized controlled trials measuring overall mortality. Other challenging issues include cost, the relative complexity of the post-processing analysis, and use of nephrotoxic contrast.[27]

Concerns about radiation remain, however, but they are being addressed with technological advances such as newer dose-reducing techniques including prospective triggering,[24] adaptive statistical iterative reconstruction, and high-pitch spiral acquisition.[28] Some of these new lower radiation dose techniques could be applied in properly selected patients who have a low heart rate (< 65 beats per minute) and are in sinus rhythm.[27-30] Nationwide, CCTA typically involves effective radiation doses between 5 and 20 mSv, depending on the patient's body habitus and the type of the scanner.[29] In general, doses less than 5 mSv are acceptable for a CCTA screening test.[27-32]

In summary, there are still several arguments in favor of imaging-guided risk evaluation for CAD with CCTA. These include detecting diseases in the target organ which is likely better than simply identifying risk factors with a modest specificity and a highly variable relationship to the development of disease, the possibil-

ity of reclassification of intermediate- and low-risk patient groups assessed with traditional scoring systems, leading to altering therapy, and imaging-based identification of at-risk subjects may improve compliance and adherence to risk-modifying interventions. The latest guidelines issued jointly by the AHA and the American College of Cardiology have elevated the recommendation levels for noninvasive imaging of subclinical atherosclerosis.[10] The ACR Cardiac Imaging Appropriateness Criteria for asymptomatic patients at risk of coronary artery disease, specifically for CCTA and CACS, are as follows:

In low-risk patients, all modalities are considered "usually not appropriate," but the panel did comment that CACS may be useful in low-risk patients who have a strong family history of coronary risk. In intermediate-risk patients, CACS was determined to be "usually appropriate," as it can be used to stratify and reclassify patient risk more accurately than traditional methods. In high-risk patientsit was determined that CCTA "may be appropriate".

For further studies, more recently emerging data focused on imaging of plaque characteristics and progression, while angiography delineates the vessel lumen, and CAC detects a later stage plaque with calcification as well as CCTA can detect earlier lesions such as fibrous cap atheroma without calcifications. The composition of atherosclerotic plaque is not shown in these study entities. The additional value of IVUS (intravascular ultrasound) constitutes the current gold standard for plaque quantification.[31] A meta-analysis of IVUS trials including 7864 patients showed an association between plaque regression and decreased cardiovascular events.[32]

Noncalcified plaque was seen more frequently in acute chest pain when compared with stable angina patients.[33] The amount of noncalcified plaque was an independent predictor of adverse events in a population with stable angina.[34] In addition, from the ROMICAT II trial, the napkin sign (a ring of high attenuation around a coronary plaque), positive remodeling, and a low Houns field unit plaque and spotty calcium were associated with ACS independently of stenosis. This evidence has further warranted the importance of plaque characteristics in clinical implication and diagnosis.

Using CCTA, calcified versus non-calcified plaque canbe quantified based on CT density cutoff values, but further improvements on resolution are necessary for subclassification of non-calcified plaques into fibrous or fatty components.[35]

CONCLUSIONS

Several large-scaled randomized controlled trials were conducted to assess the role of cardiovascular CT in patients presenting to the emergency department with acute chest pain. The results are reflected in the ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria, and prompted inclusion of CCTA as a diagnostic option in the American Heart Association (AHA) scientific statement, especially in low-to-intermediate risk patient groups.[11]

Although not recommended by current guidelines,[11] a number of reports have evaluated the use of CCTA forrisk stratification in asymptomatic high-risk individuals. From the latest studies, CACS has been observed to provide powerful prognostic information and incremental prognostic value over traditional risk factors. Current data have shown the advantage by CCTA is not clinically meaningful compared with a risk model based on CACS. However, CCTA does provide added benefit over CACS. Future studies evaluating the totality of plaque characteristics may be useful for determining the role of non-calcified plaque for risk stratification in individuals without chestpain syndrome.

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