Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

REVIEW

# Clinical Perspective of Coronary Computed Tomographic Angiography in Diagnosis of Coronary Artery Disease

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Since a 4-detector row coronary computed tomographic angiography (CCTA) was launched in 1998, CCTA has experienced rapid improvement of imaging qualities with the ongoing evolution of computed tomography (CT) technology. The diagnostic accuracy of CCTA to detect coronary artery stenosis is well established, whereas improvements are still needed to reduce the overestimation of coronary artery disease (CAD) and assess plaque composition. CCTA has been used to evaluate CAD in various clinical settings. For example, CCTA could be an efficient initial triage tool at emergency departments for patients with acute chest pain with low-to-intermediate risk because of its high negative predictive value. In patients with suspected CAD, CCTA could be a cost-effective alternative to myocardial perfusion imaging and exercise electrocardiogram for the initial coronary evaluation of patients with intermediate pre-test likelihood suspected CAD. However, in asymptomatic populations, there is a lack of studies that show an improved prognostic power of CCTA over other modalities. Therefore, the clinical use of CCTA to detect CAD for purposes of risk stratification in asymptomatic individuals should be discouraged. As CT technology evolves, CCTA will provide better quality coronary imaging and non-coronary information with lower radiation exposure. Future studies should cover these ongoing technical improvements and evaluate the prognostic power of CCTA in various clinical settings of CAD in large, well-designed, randomized trials. (*Circ J* 2011; **75:** 246–252)

**Key Words:** Coronary artery disease; Coronary CT angiography; Prognosis

Fryback and Thornbury suggested a hierarchical model of efficacy to assess the contribution of diagnostic imaging to the patient management process: (Level 1) technical quality of the images; (Level 2) diagnostic accuracy, sensitivity, and specificity associated with interpretation of the images; (Level 3) whether the information produces change in the referring physician's diagnostic thinking; (Level 4) efficacy, which concerns effect on the patient management plan; (Level 5) effect of the information on patient outcomes; and (Level 6) societal costs and benefits of a diagnostic imaging technology.[1]

Since a 4-detector row coronary computed tomographic angiography (CCTA) was launched in 1998, CCTA has been going through each level of these tests and continuously expanding its applications at the same time. As a number of studies that used CCTA cutting edge technology have been published, clinicians are facing the gap between the current guidelines that are barely updated and state-of-the-art modalities.

This review assesses Levels 2 to 5 of the hierarchical model suggested by Fryback and Thornbury by examining the diagnostic accuracy of CCTA and the current position of CCTA in clinical practices including acute chest pain at emergency departments (EDs), suspected coronary artery disease (CAD) at outpatient clinics, and screening of asymptomatic populations.

## Diagnostic Performance of CCTA for Detection of CAD and Assessment of Coronary Atherosclerotic Plaque

Since the feasibility of the 4-detector row CCTA was demonstrated, the diagnostic accuracy of CCTA has improved as the technology has progressed.[2,3] The diagnostic accuracy of the 64-detector row CCTA to detect coronary artery stenosis compared with invasive coronary angiography (ICA) as the reference has been studied at more than 50 single centers.[4–6] Sensitivities and specificities were in the range of 85–95%. Meta-analyses of 64-detector row CCTA demonstrated sensitivities of 93% and specificities of 96%.[7,8] However, these were retrospective single center studies and had potential biases because of the exclusion of patients for baseline heart rate or coronary artery calcium scoring (CACS) and nonevaluable segments from analysis.[9] Recently, 3 prospective multicenter studies have been completed in diverse populations with the prevalence of CAD at 25–68%.[10–12] CCTA was reported to have a sensitivity of 85–99%, specificity of 64–90%, positive predictive value (PPV) of 64–91%, and negative predictive value (NPV) of 83–99%. In addition, CCTA was similar to ICA for the prediction of subsequent coronary artery revascularization. However, these studies still have limitations: the study population was already selected for ICA

Received December 2, 2010; accepted December 3, 2010; released online January 19, 2011
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ISSN-1346-9843 doi:10.1253/circj.CJ-10-1206

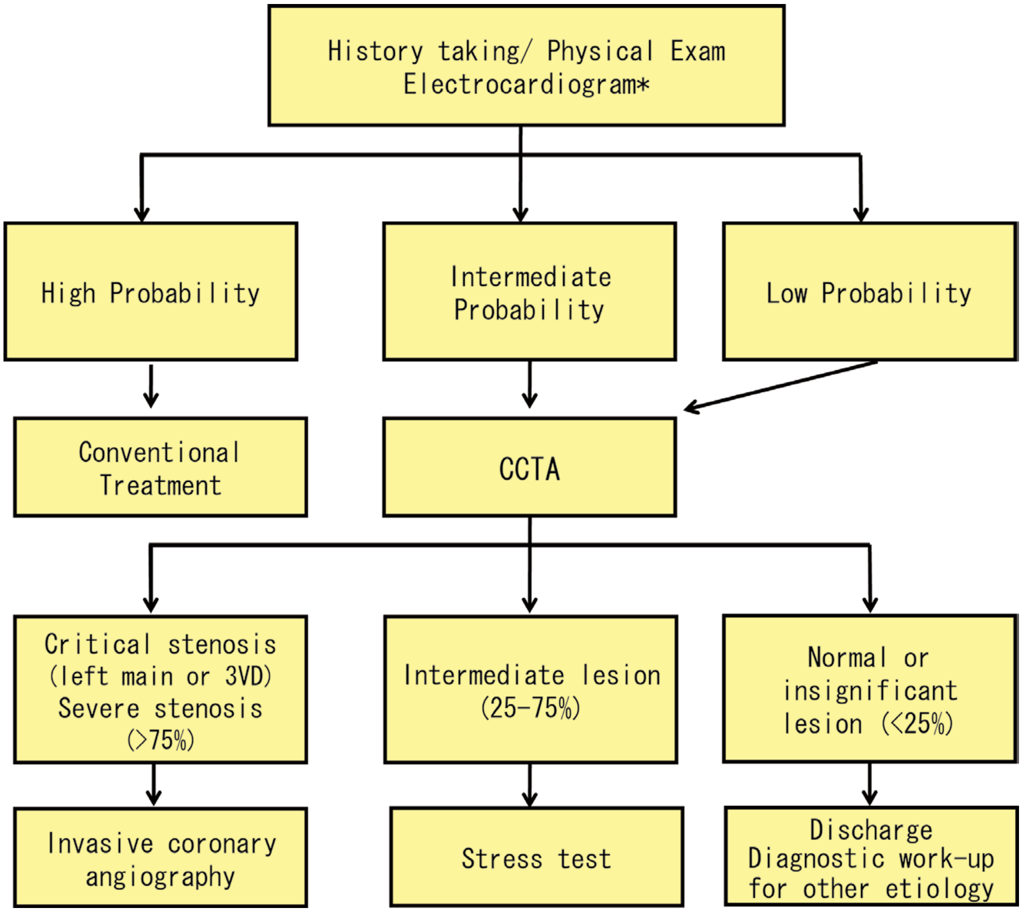


**Figure.** Proposed algorithm for the clinical use of CCTA in patients with acute chest pain in emergency department. The definition of pretest probability of having an ACS: very high, typical chest pain with ECG changes consistent with AMI; high, typical chest pain with ECG change of ST depression or T-wave inversion or with known CAD; intermediate, typical chest pain without diagnostic ECG changes and no known CAD; low, short duration of typical symptoms or prolonged atypical symptoms in patients without history of CAD and no diagnostic ECG changes; very low, atypical chest pain with an identifiable non-cardiac origin.[73] *Patients with very high or very low pretest probability of ACS were excluded. CCTA, coronary computed tomographic angiography; 3VD, triple vessel disease.

and the studies were limited to experienced centers. Nevertheless, a high NPV was found in most previous studies, especially in patients with a low pre-test likelihood of CAD.

In contrast to the detection of coronary artery stenosis, the diagnostic performance of CCTA for the assessment of plaque composition is not well established. The CCTA has been compared with intravascular ultrasound (IVUS) for the classification of plaque composition. A close correlation between CCTA and IVUS for plaque cross-sectional area and plaque volume has been demonstrated in several studies.[13–16] However, it also has been reported that CCTA substantially underestimated non-calcified plaque (NCP) volumes in comparison with IVUS.[17,18] In addition, inter-observer variability for plaque volume measurements by CCTA was reported as high as 37%, even though most of the studies were carried out in selected centers and patients.[13] Therefore, assessment of plaque composition with CCTA is currently not reliable. More accurate quantification of NCP by CCTA is expected in the near future by automated plaque quantifications with newly developed software and advances in the image quality of CCTA.

## Application of CCTA in Acute Chest Pain

Patients with acute chest pain who have normal initial cardiac enzymes or non-diagnostic electrocardiogram (ECG) are major diagnostic challenges in EDs. Although standard of care diagnostic algorithms (serial cardiac enzyme and ECG follow-up, and stress imaging studies) were employed, the rates of missed diagnoses and inappropriate discharge still ranged up to 8%,[19–22] and conventional approach is time-consuming and expensive.[23]

Because of its high NPV for exclusion of significant coronary artery stenosis, CCTA has been suggested as a feasible diagnostic modality in EDs. Several earlier studies have examined the performance to diagnosis or exclude acute coronary syndrome (ACS) in EDs.[24–26] These studies have shown that CCTA has high sensitivity (77–100%) and NPV (98–100%), but low specificity (74–92%) and PPV (25–87%) for identifying patients with ACS using the triage criteria of ≥50% stenosis by 64-detector row CCTA. In addition, CCTA facilitated early triage in patients with acute chest pain and significantly lower ED costs of care in patients with a low-risk

**Table.** Comparisons of Suggested Algorithms for Clinical Use of CCTA in Patients With Suspected CAD

| | Low pre-test probability | Intermediate pre-test probability | High pre-test probability |
|---|---|---|---|
| Current Guidelines[2,6,71,72] | Exercise ECG<br>CCTA: non-conclusive exercise ECG or stress imaging test (Class IIb, level of evidence C)*<br>CCTA: ECG uninterpretable or unable to exercise (Appropriate) | Exercise ECG<br>CCTA: ECG interpretable or able to exercise (Appropriate)<br>CCTA: ECG uninterpretable or unable to exercise (Appropriate) | Invasive angiography (Class I)* |
| Berman et al[43] | | CCTA<br>• Normal: primary prevention<br>• Critical proximal stenosis: invasive angiography<br>• Equivocal: stress test | Stress MPI<br>• Mild-moderate ischemia: medical management initially<br>• Extensive ischemia: invasive angiography |
| Schujif et al[44] | Risk factor modification | CCTA<br>• Normal: primary prevention<br>• Non-obstructive CAD: risk factor modification and close monitoring<br>• Intermediate CAD: ischemia testing<br>• Severe CAD (LM, 3VD): invasive angiography | Invasive angiography |
| Min et al[45] | ECG stress test | CCTA<br>• Mild CAD: medical treatment<br>• Intermediate (40–70%): ischemia testing<br>• Severe CAD (LM, 3VD): invasive angiography | Invasive angiography |

*Class of recommendation I: study should be performed; Class of recommendation IIb: study may be considered; level of evidence C: very limited populations evaluated, only consensus opinion of experts, case studies, or standard of care. ECG, electrocardiography; MPI, myocardial perfusion imaging; CAD, coronary artery disease; CCTA, coronary computed tomographic angiography; LM, left main disease; 3VD, triple vessel disease.

profile.[27–30] However, the appropriate timing of using CCTA in the ED and the role of CCTA in patients with an intermediate- to high-risk profile was unclear. Recently, Chang et al showed that CCTA, as part of the initial diagnostic approach for patients presenting with acute chest pain, was safe and efficiently reduced unnecessary admissions in patients with an intermediate pretest probability for ACS as well as low-risk patients in a prospective, randomized study.[31]

Taken together, in low- to intermediate-risk patients with acute chest pain in EDs, CCTA could be an efficient initial triage tool that allows safe and early discharge because of its high sensitivity and NPV. Given these findings, we propose that CCTA may be successfully used in patients with acute chest pain in EDs as a first-line test (**Figure**). In contrast to normal or severe CAD, intermediate lesions (25–75%) on CCTA could be challenges for further management after CCTA study in EDs.[32] Therefore, subsequent stress tests should be considered in this population. Future studies with larger prospective cohorts and long-term follow-up should verify the safety and effectiveness of CCTA as a first-line test.

## CCTA in Suspected CAD

Similar to the detection of myocardial ischemia by myocardial perfusion imaging (MPI) and quantification of plaque burden by CACS for predicting cardiovascular outcome, CCTA is expected to provide prognostic information in patients with suspected CAD by detecting both calcified plaque and NCP. It has been well demonstrated by 2 large trials that the severity of coronary artery stenosis detected by CCTA is related to overall mortality.[33,34] These trials recognized 2 important points: (1) a higher mortality risk was identified not only for patients with ≥50% stenosis, but also those with <50% stenosis; and (2) individuals with no CAD identified by CCTA was associated with an extremely low rate of mortality. Min et al demonstrated that CCTA measures of CAD extent, location, and distribution predicted the risk of all-cause mortality independently in 1,127 patients undergoing CCTA by 16-detector row CCTA.[33] In particular, the segment involvement score, which measures the total number of coronary segments with stenosis regardless of severity, was shown to be a significant predictor of all-cause mortality. This underscored the importance of <50% stenosis for mortality and supported previous studies that demonstrated the vast majority of acute myocardial infarction (AMI) occurred at the site of <50% stenosis.[35,36] In contrast, the annual mortality rate was very low (0.3%) in subjects without CAD evidenced by CCTA at follow-up of 15 months. Ostrom et al also demonstrated the burden of angiographic disease detected by CCTA positively correlated with the incidence of all-cause mortality in an analysis of 2,538 patients with suspected CAD during a 6.5-year follow-up.[34] Also, the presence of <50% stenosis in all 3 coronary vessels was associated with increased mortality. Furthermore, CCTA had incremental value to traditional risk factors plus CACS in the prediction of all-cause mortality.

Despite high diagnostic accuracy and power to predict the clinical outcome of CCTA, the diagnostic strategies incorporating CCTA and conventional methods including MPI, exercise ECG, and stress echocardiography in patients with suspected CAD has not been established.

To compare the prognostic potential of CCTA with MPI, van Werkhoven et al conducted a prospective, multicenter study of 541 intermediate probability patients who underwent both CCTA and MPS within 3 months.[37] The annualized hard event (all-cause mortality and nonfatal myocardial infarction (MI)) rate was 1.8% in patients with none or <50% stenosis vs. 4.8% in those with ≥50% stenosis by CCTA, and 1.1% in those with a normal MPI (summed stress score (SSS) <4) vs. 3.8% in those with an abnormal MPI (SSS ≥4). The combined use of CCTA and MPI significantly improved the prediction of a hard event. Integrated with previous studies, CCTA is capable of predicting future CAD outcomes, which is equivalent to and synergistic with that of MPI.[38,39]

Recently, it has also been recognized that CCTA could be a cost-effective alternative to MPI and exercise ECG for the initial coronary evaluation of patients with suspected CAD.[40–42] Potential algorithms for the clinical use of CCTA as an initial test for patients with suspected CAD were compared with current guidelines in **Table**.[43–45] In those suggested algorithms, the pretest likelihood of angiographic significant CAD suggested by Diamond et al was a starting point.[46] Patients with intermediate pre-test likelihood were referred to CCTA study in both suggested algorithms and current guidelines. According to the CCTA results, patients with intermediate or equivocal CAD were referred to an ischemia test with MPI. However, we still need randomized, prospective data to prove the clinical usefulness, safety, and cost-effectiveness of these potential algorithms.

## CCTA in Asymptomatic Populations

Recently, given the high diagnostic accuracy of coronary stenosis and prognostic power of CCTA in the symptomatic population, the clinical use of CCTA for the purpose of risk stratification in asymptomatic high-risk individuals has been repeatedly reported, even though current guidelines uniformly discourage it.[47–50] However, to date, there have been very limited publications evaluating the prognostic potential of CCTA in asymptomatic populations.[51,52]

Choi et al studied the midterm prognosis of 1,000 asymptomatic Korean patients who underwent 64-slice CCTA as part of a self-referral general health check-up.[51] This study revealed that the prevalence of CAD in an asymptomatic population was not negligible. The prevalence of ≥50% CAD and ≥75% CAD were 5% and 2%, respectively. There was no cardiac event in subjects without CAD, but 15 cardiac events occurred in those with CAD on CCTA: 1 unstable angina (UA) and 14 revascularization procedures during a follow-up of 17±2 months. However, there was no non-procedural event including death or nonfatal MI, and most cardiac events (87%) were revascularization procedures prompted by the CCTA results within 90 days. Therefore, the clinical implication of CAD in asymptomatic populations was not clearly demonstrated, and the CCTA results could not be compared with the National Cholesterol Education Program (NCEP) risk assessment data for risk prediction purposes.

Recently, Hadamitzky et al retrospectively analyzed 451 consecutive asymptomatic subjects who underwent CCTA due to high-risk cardiovascular profile.[52] The prevalence of <50% CAD, ≥50% CAD, and ≥75% CAD was 54%, 24%, and 3%, respectively. During a mean follow-up of 27.5 months, there were 2 cases of UA and 8 late revascularizations (>90 days after CCTA study) for stable angina, but death or nonfatal MI was not observed. Patients with ≥50% CAD had a significantly higher event rate than those without obstructive CAD (HR 13.9, 95%CI 4.0–48.0). They also demonstrated that a combined model of CCTA and Framingham Risk Score (FRS) could predict cardiac events significantly better than FRS alone. However, the predictive value of CCTA for death or nonfatal MI could not be evaluated because of an absence of those events, and a direct comparison of CCTA with CACS in the prediction of cardiac events was not presented. Therefore, the prognosis of occult CAD evidenced by CCTA in asymptomatic populations has not been defined from the evidence to date.

So far, a number of modalities are used for cardiovascular risk assessment in asymptomatic populations, and general guidance with regard to the use of these modalities was offered by American College of Cardiology Foundation/American Heart Association (ACCF/AHA) practical guidelines.[3] Among these modalities, CACS and carotid intima–media thickness (IMT) measured by B-mode ultrasound imaging are the most widely used imaging modalities for the detection of subclinical atherosclerosis.[53] Numerous studies have demonstrated that CACS provide prognostic information over traditional risk factor assessment including FRS in asymptomatic populations of multiple ethnic groups and both genders.[54–57] Carotid IMT was also a well-defined modality that provided prognostic information in an asymptomatic population.[58,59] The prognostic value of both studies has been compared in previous studies. Folsom et al showed that CACS was a stronger predictor of cardiovascular events than carotid IMT in a multicenter prospective asymptomatic cohort of the Multi-Ethnic Study of Atherosclerosis (MESA).[60] Conversely, Newman et al demonstrated that CACS and carotid IMT had similar hazard ratios for total cardiovascular disease and coronary heart disease in asymptomatic subjects that were >70 years of age in the Cardiovascular Health Study.[61] Therefore, it is impossible to conclude whether these tests are clinically equivalent from the evidence to date.

CCTA was expected to provide better prognostic information than these modalities in asymptomatic populations because of the following unique characteristics: (1) identification of NCP component; and (2) direct visualization of coronary arteries that allows the identification of critical stenosis including left main stenosis and 3-vessel disease as well as plaque burden. However, to date, there are no studies that show improved prognostic power of CCTA over other modalities. Firstly, this is due to the recent introduction of CCTA, so the accumulation of cardiac events after study has been limited. Secondly, given the very low cardiovascular event rate in asymptomatic populations, it is substantially more difficult to demonstrate prognostic values of CCTA than in symptomatic populations. Finally, given the lower prevalence of CAD in asymptomatic populations compared with symptomatic populations, imperfect specificity of CCTA can lead to low positive predicted values and mislabel more people who do not have CAD.

Therefore, given the fact that CCTA requires injection of a contrast agent and radiation exposure, which is much lower or unnecessary in CACS or carotid IMT, the clinical use of CCTA to detect plaque for the purposes of risk stratification in asymptomatic individuals has to be discouraged as current guidelines uniformly state this until additional data justify its applications. At present, an open-label, international, multicenter observational registry (CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter Registry) designed to evaluate associations between CCTA findings and clinical presentation, and their ability to predict cardiovascular outcome is quarrying and its outcome data in an asymptomatic cohort will be published in the near future.[62]

## Future Perspective of CT in Cardiovascular Disease

With advances in CT technology, there has been a growing interest in applying this tool to non-coronary cardiac applications. First of all, cardiac CT is capable of assessing stroke volume, ejection fraction, and regional wall motion abnormalities by taking motion picture images of the heart throughout the cardiac cycle.[63,64] It is also known that cardiac CT could be used to assess myocardial viability. Delayed enhancement of cardiac CT images correlate well with delayed enhancement of MRI images, which reliably detect myocardial scarring and is routinely used to predict the success of revascularization therapy.[65–67] Furthermore, cardiac CT under adenosine-induced stress could detect reversible myocardial ischemia by analyzing the iodine volume within the myocardium.[68–70] These non-coronary applications of cardiac CT technique will allow simultaneous evaluation of coronary artery stenosis, physiologic evaluation on myocardial perfusion, and myocardial viability with a "one-stop" single study. At present, however, the non-coronary applications of cardiac CT have some limitations: increased radiation exposure, limited publications evaluating effectiveness, safety, and cost of cardiac CT compared with standard modalities.

## Conclusion

In conclusion, the diagnostic accuracy of CCTA detecting obstructive CAD is well established in prospective multicenter trials, whereas improvements are still needed for reducing the overestimation of CAD severity and assessment of plaque composition. CCTA could be an efficient initial triage tool in patients with acute chest pain with low-to-intermediate risk in EDs because of its high sensitivity and NPV. In patients with suspected CAD, CCTA could be a cost-effective alternative to MPI and exercise ECG for the initial coronary evaluation in patients with intermediate pre-test likelihood of suspected CAD. However, in asymptomatic populations, there is lack of study that shows an improved prognostic power of CCTA over other modalities including CACS and carotid IMT. Therefore, the clinical use of CCTA to detect plaque for purposes of risk stratification in asymptomatic individuals has to be discouraged.

CCTA has experienced rapid improvement of imaging qualities with the ongoing evolution of CT technology. As CT technology evolves, CCTA will undoubtedly provide better quality coronary imaging and non-coronary findings including structural and functional imaging of myocardium with lower radiation exposure. Future studies should cover these ongoing technical improvements, and evaluate the prognostic power of CCTA in various clinical settings of CAD with large, well-designed, randomized, controlled trials.

## Disclosure

The authors declare no conflict of interest.

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