Coronary CT angiography: how should physicians use it wisely and when do physicians request it appropriately?

Zhonghua Sun[1], Yang Faridah Abdul Aziz[2], Kwan-Hoong Ng[2]

1. Discipline of Medical Imaging, Department of Imaging and Applied Physics, Curtin University of Technology, Perth, 6845, Australia
2. Department of Biomedical Imaging, University of Malaya, Kuala Lumpur, 50603, Malaysia

Corresponding author:

Dr Zhonghua Sun, Discipline of Medical Imaging, Department of Imaging and Applied Physics, Curtin University of Technology, GPO Box, U1987, Perth, Western Australia 6845, Australia

Tel: +61-8-9266 7509

Fax: +61-8-9266 2377

Email: z.sun@curtin.edu.au

Abstract

Coronary CT angiography has been increasingly used in the diagnosis of coronary artery disease due to rapid technological developments, which are reflected in the improved spatial and temporal resolution of the images. High diagnostic accuracy has been achieved with 64- and more slice CT scanners and in selected patients, coronary CT angiography is regarded as a reliable alternative to invasive coronary angiography. Although the tremendous contributions of coronary CT angiography to cardiac imaging are acknowledged, appropriate use of cardiac CT as the first line technique by physicians has not been well established. Optimal selection of cardiac CT is essential to ensure acquisition of valuable diagnostic information and avoid unnecessary invasive procedures. This is of paramount importance since cardiac CT not only involves patient risk assessment, prediction of major cardiac events, but also impacts physician decision-making on patient management. Applications of CT in cardiac imaging include coronary artery calcium scoring for predicting the patient risk of developing major cardiac events, followed by coronary CT angiography which is commonly used to determine the diagnostic and prognostic accuracy in the coronary artery disease. This review presents an overview of the applications of CT in cardiac imaging in terms of coronary calcium scoring and coronary CT angiography. Judicious use of both cardiac CT tools will be discussed with regard to their value in different patient risk groups with the aim of identifying the appropriate criteria for choosing a cardiac CT modality. An effective diagnostic pathway is finally recommended to physicians for appropriate selection of cardiac CT in clinical practice.

Keywords: coronary artery disease, coronary artery calcium, multislice CT, risk, radiation dose.

Introduction

Coronary artery disease (CAD) is the leading cause of mortality and morbidity in developed countries. The diagnosis and management of CAD is increasingly dependent on non-invasive imaging modalities. Recent technological advances have led to a considerable increase in image quality for coronary imaging using multislice CT. [1-3] Numerous studies have shown that coronary CT angiography (CCTA), as a less-invasive alternative to coronary angiography, has a high diagnostic accuracy for the detection of significant CAD (≥50% lumen stenosis) when compared to invasive coronary angiography. [3-9] High quality multislice CT (64-slice and higher) is not only able to provide reliable information on coronary luminal changes, but also has the potential to visualise coronary artery wall morphology, characterise atherosclerotic plaques and identify non-stenotic plaques that may be undetected by conventional coronary angiography. Studies have shown that CCTA demonstrates high prognostic value in CAD, as it is able to differentiate low-risk from high-risk patients [10-12], with very low rate of adverse cardiac events occurring in patients with normal CCTA, and significantly high rate of these events in patients with obstructive CAD.

It has been a regular procedure to perform both coronary artery calcium (CAC) scoring and CCTA for diagnosis in patients with suspected CAD. Results dealing with the incremental prognostic value of CAC scoring used in combination with CCTA have recently been published. [13] Although satisfactory results have been achieved in these studies, with strengths and weaknesses being addressed, very few studies have specifically examined the clinical applications of CCTA in the particular target population, or risk stratification and assessment with regard to the judicious use of

CCTA.[14-16] Identification of the exact role of CCTA in patients from different risk groups is clinically significant as this could lead to unnecessary examinations due to the fact that multislice CT is an imaging modality with high radiation dose. In addition, appropriate selection of CCTA is of paramount importance for physicians to choose CCTA as a gatekeeper for further diagnostic testing. This article explores how physicians should use multislice CT wisely in terms of the clinical value of coronary calcium scoring to predict the extent of coronary artery disease or cardiac events, and CCTA in patients from different risk groups with a focus on low to intermediate risk patients. The potential value and benefits of CCTA in asymptomatic patients are also explored. Finally, this articles looks at when physicians should request CCTA appropriately from a clinical point of view by following the appropriate imaging pathways.

Current status of coronary CT angiography in coronary artery disease

With recent progress in the technical developments of multislice CT scanners, images can be acquired in a very short time with very high spatial resolution. In particular, the development of 64- or more slice CT scanners allows acquisition of cardiac images with a temporal resolution that is a fraction of the length of the cardiac cycle with an isotropic volume resolution of less than 0.5 mm. [9, 17] Non-diagnostic CCTA studies have decreased from 15-25% with the early generation of 4- and 16-slice CT scanners to less than 10% with 64-slice CT scanners. [17, 18] The cost of performing a CCTA examination is much lower than that of an invasive coronary angiography, and is equivalent to an imaging stress test. Unlike invasive coronary angiography, which is associated with procedure-related complications, CCTA is a less invasive modality with very rare occurrence of complications resulting from CT examinations. Consequently, there has been extensive interest in the clinical application of CCTA in the evaluation of patients with suspected CAD.

Most studies have reported the diagnostic accuracy of CCTA by coronary artery segment, coronary artery and per patient assessment. Several meta-analyses of studies on the use of 64-slice CT reported mean sensitivities and specificities ranging from 85% to 99%, and 86% to 96%, respectively. [3, 8, 19, 20] Given the dependence of positive predictive value and negative predictive value on the prevalence of disease, the relatively high prevalence of significant CAD as determined by invasive coronary angiography in many of these selected study populations compared to the general population raises a concern in appraising the value of CCTA in clinical practice. It has been shown that significant statistical heterogeneity exists among published studies, with smaller studies reporting higher diagnostic accuracy of CCTA in CAD. [21] Two recent multicentre studies discussed several methodological limitations of CCTA, as patients with high calcium scores were excluded from the analysis of one study, while in another study, no segments were excluded from the analysis despite high calcium scores, [4, 6] Therefore, reports of the diagnostic value of CCTA in CAD in the literature need to be interpreted with caution.

Coronary artery calcium scoring –predictive value in CAD

Quantifying the amount of coronary artery calcium with unenhanced CT calcium scoring has been widely accepted as a reliable non-invasive technique for screening risk of future cardiac events [22, 23], and is usually quantified by using the Agatston score or scores such as the volume score or calcium mass. [24-26] Clinical application of CAC has been supported by evidence showing that absence of calcium reliably excludes obstructive coronary artery stenoses [27], and that the amount of CAC is a strong predictor for risk assessment of myocardial infarction and sudden cardiac death, independent of conventional coronary risk factors. [28-30] However, the prognostic value of CAC depends on the risk groups as to whether patient risk is reclassified and patient management can be changed based on CAC scores when compared to traditional risk assessments. [31] The Framingham risk score is one of the most commonly used risk-estimation systems, which enables clinicians to estimate cardiovascular risk in asymptomatic patients. It is calculated using traditional risk predictors, including age, gender, total cholesterol, high-density lipoprotein cholesterol, smoking status, and systolic blood pressure, and is represented as a 10-year risk score for the prediction of coronary heart disease events. [32] However, there is growing evidence to show that these traditional risk assessment methods, based on risk factor analysis, have significant limitations when used to guide individual patient therapy. [32-34] CAC score by multislice CT has been increasingly used as an additional assessment tool to evaluate the risk of developing major cardiac events in asymptomatic and symptomatic patients.

Coronary artery calcium scoring–predictive value in asymptomatic patients

In asymptomatic individuals, zero CAC is associated with a very low (<1% per year) risk of major cardiac events over the next 3-5 years, whereas in asymptomatic patients with extensive coronary calcification, the major cardiac events have been reported to be increased by up to 11-fold. [35-37] Several large population-based studies have reported that in asymptomatic patients without known CAD, CAC is predictive of future cardiac events above and beyond traditional risk factors [38-40]. The recent population-based multi-ethnic study of atherosclerosis, conducted in 6,722 asymptomatic patients belonging to four racial ethnic groups and followed for 3.8 years, showed a significant difference in the prevalence of CAC among different ethnic groups. Nonetheless, CAC has demonstrated incremental prognostic value over traditional risk factors, with a seven-fold increase in the incidence of cardiac events for Agatston scores >100 when compared with patients with zero CAC. [38]

Other studies evaluating the prognostic value of the measurement of CAC have shown that coronary calcification is predictive of cardiac events in asymptomatic patients with different age groups. [39-41] LaMonte *et al.* in their study consisting of nearly 11,000 patients ranging from 22 to 96 years of age who underwent a screening medical examination, reported increased cardiac events in patients with coronary calcium scores of 400 or more during a mean follow-up of 3.5 years. [40] In the Prospective Army Coronary Calcium Project among men and women 40 to 45 years of age, Talyor *et al.* concluded that the presence of coronary calcium was associated with an increase in the risk of coronary events by a factor of 12 during 3 years of follow-up. [39] Similarly, higher calcium scores were found to be associated with the relative risks of coronary events in the population-based Rotterdam Study of elderly asymptomatic patients. [41]

Coronary calcium score– prognostic value in symptomatic patients

Coronary calcification is considered only marginally related to the degree of coronary stenosis and it is well known that both obstructive and non-obstructive CAD can occur in the absence of calcification. [42-44] Significantly, coronary stenoses are frequently found to be non-calcified, and highly calcified plaques are frequently non-obstructive. Thus, the value of a zero or low calcium score (a low coronary calcium score is defined as an Agatston score of 1 to 100 because a coronary calcium score of 100 is often used as a cutoff point for risk assessment) in symptomatic patients remains unclear. Several studies have reported the presence of obstructive non-calcified plaque in up to 8.7% of symptomatic patients with zero or low calcium score.[45-47] The question has been raised as to whether only using CAC score is a reliable tool of determining the extent of CAD, since non-calcified coronary artery plaque may not be detected. Cheng *et al.* reported that low but detectable CAC scores are less reliable in predicting plaque burden due to their association with high overall non-calcified coronary artery plaque.[45] They concluded that low CAC scores are significantly less predictive of prevalence or severity of underlying non-calcified coronary plaque.

It has been recently suggested in some studies that coronary CT calcium score assessed with unenhanced CT may be supported by CCTA, or CCTA may be performed alone with the aim of acquiring more diagnostic information.[48-50] CCTA allows not only visualisation of the vessel lumen, but also of the vessel wall, including composition of atherosclerotic plaque (calcified versus non-calcified or mixed type of plaques). However, the contrast enhancement in the coronary artery vessels may obscure detection of plaque, especially the presence of extensively calcified plaques, and thus may obviate reliable measurements of plaque density. CCTA was found to underestimate higher Agatston scores.[48] It has been reported in that study that CCTA allows for the detection of CAC with high accuracy, as well as good correlation with unenhanced CT calcium score. In contrast, in patients with zero or low calcium score, CCTA was found to provide additional valuable information on patient management as CCTA detected obstructive coronary lesions in 7% of patients with a zero score and in 17% with a low CAC score. Their study indicated that in symptomatic patients with a zero or low CAC score on CT CAC scoring can be used to exclude an acute or long-term coronary syndrome, whereas CCTA is recommended as the non-invasive test of choice in these patients. [48] Similarly, van Werkhoven *et al.* in their recent report showed that CCTA provided additional prognostic information regarding stenosis severity and plaque composition when compared to CAC score for risk stratification in patients with suspected CAD. Their study involved analysis of plaque composition with CCTA, and results showed that the number of segments with non-calcified plaques and the number of segments with mixed plaques was found to be independently associated with increased risk for adverse cardiac events. [50]

Coronary CT angiography in high-risk patients

The pre-test probability of CAD may have a significant impact on the diagnostic performance of the CT scan. Pre-test probability or likelihood is defined according to Diamond and Ferrester criteria, which are based on age, gender and symptomatic status. [51] Intermediate likelihood is defined as a pre-test probability between 13.4% and 87.2%, while low and high pre-test probability are defined as less than 13.4% and more than 87.2%, respectively. It is noticed that the diagnostic performance of CCTA is different in patients from different risk groups. The diagnostic accuracy of CCTA has been extensively studied in populations with a high pre-test likelihood for CAD. [17-20] However, this population is unlikely to benefit from CCTA because most patients require invasive coronary angiography for the purpose of revascularisation. Meijboom *et al.* in their prospective study observed that, in patients with a high pre-test likelihood for CAD, interpretations using CCTA failed to significantly change the post-test probability of significant CAD. Thus, normal findings of CCTA did not result in a sufficient reduction of the post-test probability to reliably rule out the presence of significant CAD. These data indicate that the majority of these symptomatic patients are likely to proceed to invasive coronary angiography despite the negative CCTA findings.[15] CCTA is considered to be of limited clinical value in the evaluation of the high pre-test probability group. In patients with a high pre-test likelihood for significant stenosis, functional evaluation, such as myocardial perfusion imaging, may be more relevant than CCTA to determine the need for revascularisation.

Coronary CT angiography in low- and intermediate- risk patients

In contrast to the high pre-test probability group, patients with an intermediate or low pre-test likelihood for CAD might receive more benefit from CCTA. A very high negative predictive value (>99%) of CCTA reliably rules out the presence of significant CAD and can be used as a highly effective gatekeeper for invasive coronary angiography.[14, 52, 53] Thus, when CCTA is used in a patient population with a low or intermediate pre-test likelihood, the need for additional imaging will be restricted to those patients with an abnormal finding from CCTA. Consequently, the use of CCTA could avoid invasive coronary angiography in most patients. This concept is also supported by relevant data about cost-effectiveness. Min *et al.* investigated the value of CCTA as a first line test compared to myocardial perfusion imaging using single photon emission computed tomography (SPECT) in patients with a low to intermediate pre-test likelihood. They concluded that lower referral rates to invasive coronary angiography and lower healthcare costs were observed in their low-risk group.[54]

Diagnostic value of coronary CT angiography in the detection of atherosclerosis in low- to intermediate-risk groups has been confirmed in a latest study performed by 64-slice

CT compared to myocardial perfusion imaging. Iwasaki *et al.* in their study used 64-slice CT to detect subclinical atherosclerosis in 415 asymptomatic patients with more than 95% belonging to low- and intermediate-risk groups. [55] Their results showed very high prevalence (71%) of subclinical atherosclerosis in patients with low to intermediate risk patients, with one-fifth of them having significant coronary stenosis. This is supported by other studies showing the high prevalence of atherosclerosis. Hausleiter *et al.* [46] reported the prevalence of coronary plaques was 67.1%, in their study comprising of 161 patients with an intermediate risk for coronary artery disease. Choi *et al.* studied 1000 middle-aged asymptomatic patients with 64-slice CT and noticed the prevalence of 22% atherosclerotic plaques in these patients. [56] These studies further testified that coronary CT angiography is a valuable imaging modality for detection of atherosclerotic changes in the low- to intermediate-risk patients.

Coronary CT angiography in asymptomatic patients

Despite the high diagnostic accuracy of coronary artery stenosis and prognostic power of CCTA in symptomatic patients, to date there have been very limited publications evaluating the prognostic potential of CCTA in asymptomatic patients. Although only limited data are available in asymptomatic patient populations, it is possible that CCTA is valuable for risk stratification in these patients, since CCTA can be used to detect atherosclerosis for long-term risk assessment. [57-59] The prevalence of atherosclerosis was reported to be 22% in a recent study consisting of 1,000 asymptomatic individuals undergoing CCTA, with 5% and 2% being observed in ≥50% CAD and ≥75% CAD, respectively. [57] Cardiac events occurred in 1.5% of individuals during a follow-up of 17 months, all of whom had atherosclerosis on CCTA. These data indicate that CCTA is currently not acceptable as a general screening tool and CAC score testing may be a preferable option. However, non-invasive CCTA may potentially be used as a test in the workup of asymptomatic individuals with cardiac risk characteristics. [57-60]

It has been recently reported that performing CCTA before invasive coronary angiography is a cost-effective strategy in the management of patients without symptoms who have positive stress rest results. [59] It is generally believed that a patient at low risk who has a positive stress test result (such as treadmill ECG studies, stress echocardiography, and radionuclide stress studies) is often referred for cardiac catheterisation, especially when the positive stress test result is obtained in a preoperative workup. Halpern *et al.* in their study using decision tree analysis reported that when a patient with an expected CAD prevalence of less than 85% is found to have a positive test result, CCTA is a less expensive alternative to invasive coronary angiography.[59] Although most patients undergo screening for CAD with stress tests to obtain functional and perfusion information which is not available with CCTA, a meta-analysis on more than 35,000 patients with coronary angiography as the reference standard showed that only average sensitivity and specificity was achieved with stress echocardiography and SPECT.[61] Thus, the use of CCTA in asymptomatic patients can avoid unnecessary invasive cardiac angiography procedures.

Coronary CT angiography–radiation dose issue

Radiation exposure associated with coronary CT angiography has increased substantially over the past two decades and it is a major concern that needs to draw attention of both clinicians and manufacturers. The general view about radiation dose is that coronary CT angiography is associated with a risk of cancer development. The recent Biological

Effects of Ionising Radiation (BEIR) VII provides a framework for estimating cancer risk associated with radiation exposure from ionising radiation.[62] According to the report, it is estimated that 1 in 1000 people will develop cancer due to an exposure of 10 mSv. Brenner and Hall [63] estimated that approximately 1.5% to 2% of all cancers in the United States may be caused by radiation exposure from CT examinations. Davies *et al* estimated that in the UK radiation from CT scans causes 800 cancers a year in women and 1300 in men. [64] Radiation exposure is especially important for young and female patients who present with atypical symptoms, but do not have high pre-test likelihood for having haemodynamically significant coronary stenosis. A recent study reported that one in 270 women aged 40 years who undergo coronary CT angiography will develop cancer. [65]

The number of CT scans is being increased significantly in Australia. According to 2008-09 Annual Report of the CEO of ARPANSA that the number of CT examinations in Australia increased greatly from 1994 (612,438 cases) to 2008 (1,935,802 cases) which is more than a 3-fold increase. [66] Coronary CT angiography should be performed with dose-saving strategies whenever possible to reduce the radiation dose to patients. The reader is referred to several excellent review articles on dose reduction strategies currently recommended in coronary CT angiography. [9, 67-69] Judicious use of multislice CT in cardiac imaging by clinicians is essential to maximise its clinical applications while minimising the potential risk of radiation exposure.

The basic principle of radiation protection is to keep radiation exposure “as low as reasonably achievable” (the ALARA principle). Thus, if CAC scoring has no added benefit over CCTA in the routinely combined CAC scoring and CCTA scans, CAC scoring may not be necessarily incorporated into the CCTA protocol. Kwon *et al.* in their recent prospective study concluded that CCTA has positive correlation with CAC scores for prediction of major adverse cardiac events, and CCTA has better predictive value than CAC scoring in low-risk patients suspected of CAD.[70] Their results showed no added benefit to the addition of CAC scoring to CCTA, although their study population was restricted to a relatively low-risk group. Further studies based on multicentres with inclusion of large sample size are required to confirm their initial results.

Summary and Conclusion

The introduction of CCTA has significantly changed the clinical diagnostic approach to CAD. There is no doubt that, in patients with clinical suspected CAD, CCTA plays a significant role in establishing or excluding the diagnosis. With a very high negative predictive value, CCTA is widely regarded as a reliable technique in clinical practice to exclude significant CAD.

Use of CCTA for diagnosis and risk assessment in patients with low or intermediate risk or pretest probability for coronary artery disease is favourably preferred, whereas in high-risk patients, CCTA is less favourably recommended. Use of non-contrast CT for coronary artery calcium scoring is considered an appropriate approach in low- and intermediate-risk patients for prediction of cardiac events, while in symptomatic or high-risk patients, its predictive value is less reliable due to high prevalence of non-calcified plaques. Appropriate selections of cardiac CT will have a significant impact on physician decision-making and performance that will guide appropriate patient management strategies. The flow chart (Figure 1) recommends the CT imaging pathways for physicians to choose multislice CT appropriately in patients with suspected coronary artery disease and within different pre-test probabilities or risk groups. It is expected that it will assist physicians, particularly cardiologists, to make judicious use of cardiac CT in their clinical practice.

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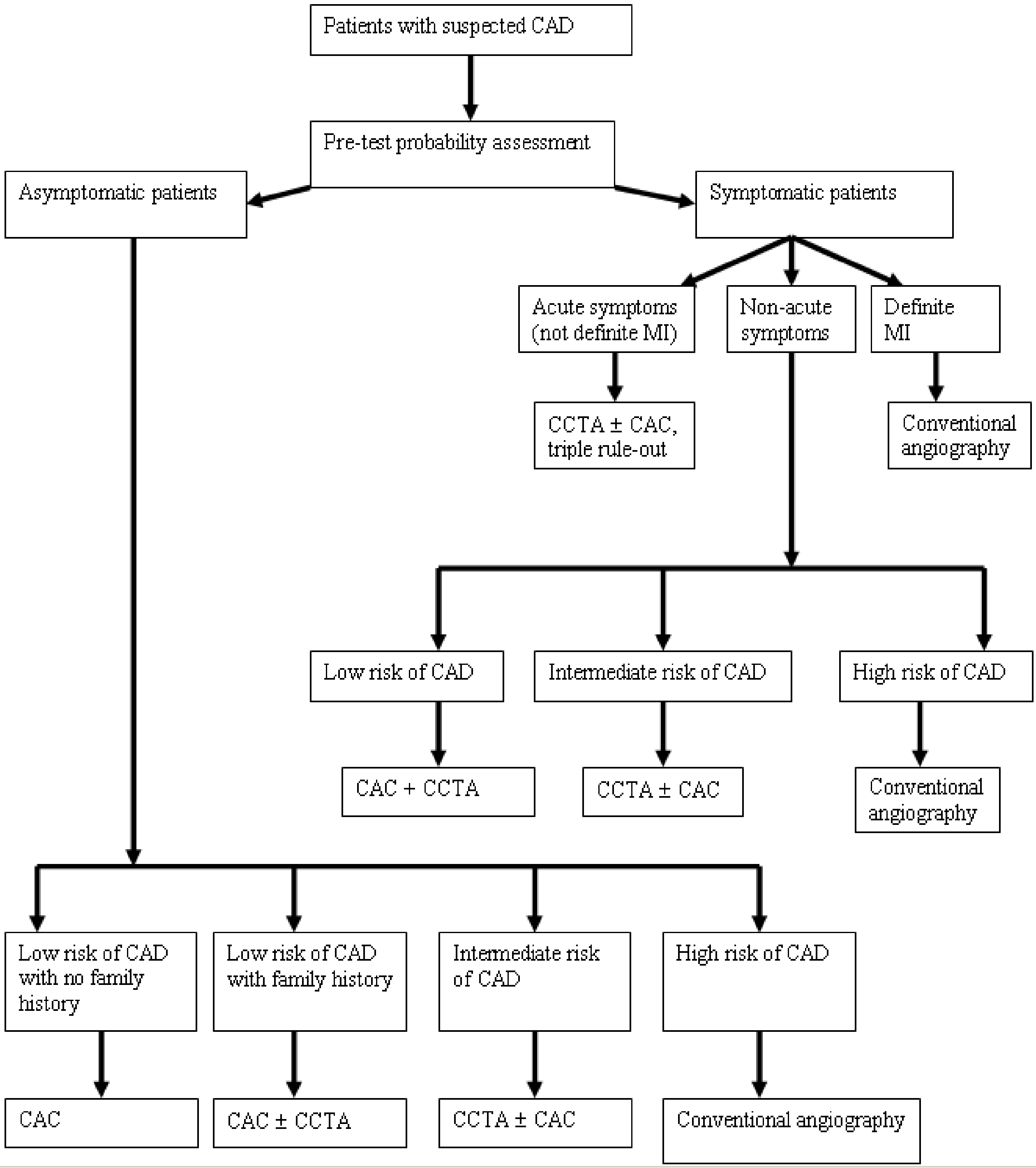
Figure legend

Figure 1. Flow chart shows the imaging pathways for appropriate selection of multislice CT in patients with suspected CAD. CAD-coronary artery disease, CCTA-coronary CT angiography, CAC-coronary artery calcium, MI-myocardial infarction.


Patients with suspected CAD
Pre-test probability assessment
Asymptomatic patients
Symptomatic patients
Acute symptoms (not definite MI)
Non-acute symptoms
Definite MI
CCTA ± CAC, triple rule-out
Conventional angiography
Low risk of CAD
Intermediate risk of CAD
High risk of CAD
CAC + CCTA
CCTA ± CAC
Conventional angiography
Low risk of CAD with no family history
Low risk of CAD with family history
Intermediate risk of CAD
High risk of CAD
CAC
CAC ± CCTA
CCTA ± CAC
Conventional angiography