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New Insights from Major Prospective Cohort Studies with Cardiac CT

Sumbal A. Janjua and Udo Hoffmann

Division of Cardiac CT/PET/MR, Department of Radiology, Massachusetts General Hospital, 165 Cambridge Street, Suite 400, Boston, MA 02114, USA

Sumbal A. Janjua: sjanjua@partners.org; Udo Hoffmann: uhoffmann@mgh.harvard.edu

Abstract

Each year, 11 million patients present in the USA with new symptoms suggestive of obstructive coronary artery disease (CAD). Most undergo stress testing but <10 % demonstrate myocardial ischemia. Moreover, up to 60% will have CAD which adversely affects outcomes. Cardiac computed tomography (CCT) is being used increasingly as an alternative to stress testing to rule out obstructive CAD in symptomatic patients, and large cohort studies in asymptomatic patients have identified burden of coronary atherosclerosis as a predictor of major adverse cardiovascular events (MACE). This review article will critically evaluate major clinical studies on the use of CCT in both symptomatic and asymptomatic patients and discuss the lessons for the clinical use of CCT.

Keywords

Cardiac computed tomography; Coronary artery disease; Coronary artery calcification score; Chest pain; Symptomatic; Asymptomatic

Introduction

Cardiac computed tomography (CCT), due to the revolutionary development in hardware and software and resulting improved image quality with reduced radiation doses, has become a viable alternative to assess for coronary artery disease (CAD) [1]. Since its introduction in 2001, CCT has been an area of very active research with large cohort studies in asymptomatic patients, registries for stable chest pain and randomized trials for acute chest pain syndromes. This review provides a critical appraisal of the major studies of the use of CCT and their potential clinical impact on patient management.

Correspondence to: Udo Hoffmann, uhoffmann@mgh.harvard.edu.

Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent All studies performed by the authors included in this review have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Conflict of Interest Sumbal A. Janjua declares no conflict of interest.

Traditional Imaging to Improve Management of Coronary Artery Disease

In the USA, about 11 million patients [2], among them 4 million de novo [3], present annually with symptoms suggestive of obstructive CAD, such as chest pain or dyspnea on exertion, making this one of the most common patient presentations. The ability of traditional cardiovascular risk factors and clinical presentation to discriminate those with and without ischemic heart disease is limited [4]. For example, the Diamond and Forrester classification [5] significantly overestimates the likelihood of obstructive CAD (predicted vs. observed prevalence of obstructive CAD, 42 vs. 10 %; $p<0.001$) in both patients with atypical and typical angina (37 and 71 % vs. 7 and 19 %, respectively, both $p<0.001$) [6]. As a result, most symptomatic patients undergo noninvasive functional testing for further evaluation, including standard exercise treadmill testing (ETT), nuclear myocardial perfusion imaging with single-photon emission computed tomography (SPECT), and stress echocardiography. These functional tests are designed to provoke myocardial ischemia by using exercise or pharmacological stress agents either to increase myocardial work and oxygen demand or to induce vasodilation-elicited heterogeneity in induced coronary flow. An abnormal ETT is typically defined as ST changes consistent with ischemia, a positive SPECT is defined as inducible ischemia in at least one coronary territory, and a positive stress echo as ischemia with wall motion abnormality during stress in at least one coronary territory. Most data on the diagnostic accuracy of these tests stem from clinical referral populations. In meta-analyses, high sensitivities have been reported for image-based stress testing (SPECT 87 % and echocardiography 86 %) with lower sensitivity for ETT (68 %). In contrast, specificity is moderate across modalities (SPECT, 73 %; echocardiography, 81 %; ETT, 77 %) [7–9]. After adjustment for referral, however, specificities further decrease below 40 % [10–12]. Consequently more than half of subsequently performed invasive coronary angiograms do not demonstrate flow-limiting stenosis [13]. Overall, the work-up of nearly 90 % of symptomatic patients undergoing noninvasive diagnostic testing for obstructive CAD does not demonstrate myocardial ischemia or a flow-limiting stenosis in invasive angiography [8, 9, 11, 14]. Stress testing also does not detect coronary atherosclerosis that is non-flow limiting, which is present in approximately 60 % of these patients [15•].

Cardiac CT

Over the past two decades, computed tomography (CT) has rapidly evolved. Contemporary scanners acquire 64–320 cross-sections per rotation, depicting vascular details with a spatial resolution <0.5 mm. Faster rotation, efficient reconstruction algorithms, or multiple X-ray sources allow very fast imaging, and combined with heart rate-reducing medication, it is now possible to image the coronary arteries without motion artifacts in most patients. ECG-synchronized, contrast-enhanced images of the heart and coronary artery vessels can be acquired in one to five heartbeats. CCT has evolved into a robust and reliable technique for detection and assessment of coronary stenosis and atherosclerotic plaque. The radiation exposure has dramatically decreased over the past years, and doses <5 mSv are now common practice at leading centers and doses of 10 mSv or less are seen in large registries. While the use of CCT is growing, it is still underutilized in comparison to functional tests. In the USA, stress myocardial perfusion imaging by SPECT is performed 50 times more

frequently than CCT. Given the direct coronary visualization, CCT appears as an attractive diagnostic alternative to functional testing.

Multicenter Trials to Determine Accuracy to Detect Nonobstructive and Obstructive CAD

In meta-analyses of a large number of single-center trials, CCT has been established as a noninvasive diagnostic test with excellent sensitivity (97.2; 95 % confidence interval [CI], 96.2 to 98.0 %) and very good specificity (87.4 %; 95 % CI, 84.5 to 89.8 %) for the detection of >50 % coronary artery stenosis as compared to the gold standard invasive coronary angiography [16]. Several prospective multicenter studies [1, 3, 17] have confirmed these results (Table 1). For example, the Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography (ACCURACY) trial reported a sensitivity of 95 % and a specificity of 83 % for the detection of obstructive CAD. ACCURACY is most relevant to clinicians because the prevalence of CAD (25 %) and the CT technology used (64 slice) represent a common clinical scenario. The CORE 64 trial was an exception; the reported sensitivity was lower than the specificity. This was explained by a higher threshold to diagnose obstructive CAD [3]. Studies using newer CT technology suggest that the technological improvements are used to lower radiation dose to sub-millisievert levels while maintaining excellent sensitivity and good specificity [18•]. Most commonly, a non-contrast coronary artery calcium scan is obtained prior to the CCT and studies have reported lower specificity of 50 % in patients with an Agatston score (AS) >400. In clinical practice, patients do not often go onto a CCT if the AS is >800 and the scan is performed with 64 slice technology.

Very intriguing are the results of two studies using fractional flow reserve (FFR) as determined in invasive coronary angiography as a gold standard, which report a significant decrease in specificity to 40 % or lower [19, 20]. However, there is good cause for optimism as these studies also suggest that FFR can be computed noninvasively based on anatomic knowledge of the CT scan (FFR-CT) resulting in much higher specificity while maintaining excellent sensitivity both across all patients and among those with intermediate lesions (30–70 % luminal narrowing). Hence, adding information on physiological significance of stenosis has the potential to elevate CCT from a triage tool for the cath lab to a tool informing the decision to treat with optimal medical therapy (OMT) or to perform percutaneous coronary intervention (PCI).

Role of CCT in Acute Chest Pain

This is the most researched area, and several cohort and multicenter randomized studies have evaluated the role of CCT in acute chest pain. The Rule Out Myocardial Infarction using Computer-Assisted Tomography (ROMICAT I) trial is a large prospective observational cohort study, which rendered unbiased insights into the association of CCT findings with other diagnostic tests and clinical outcomes as the caregivers remained blinded to the results of CCT. Among the more eminent findings were that roughly half of the cohort had no CAD, 30 % had nonobstructive CAD, and 20 % had obstructive CAD. The absence of CAD had 100 % NPV for acute coronary syndrome (ACS), while only 50 % of

obstructive lesions (>50 % luminal narrowing) were associated with ACS [21••]. Following ROMICAT I, several noncontrolled randomized comparative effectiveness trials investigated the safety and economic performance of CCT in acute chest pain [22•, 23, 24]. The CT-STAT trial directly compared SPECT vs. CCT while the American College of Radiology Imaging Network (ACRIN-PA) and ROMICAT II trials compared CCT to standard of care (SOC). Patients were at very low to intermediate risk. Together, these trials comprised more than 3000 patients and demonstrated that not a single patient was discharged with a missed diagnosis of ACS based on the CCT results. The ACRIN-PA trial formally confirmed this (0 % MACE; 95 % CI, 0 to 0.57). Across the trials, a significant reduction in length of stay, hospital admissions, and ED cost with a higher rate of invasive coronary angiography and PCI were observed. A major shortcoming is that we do not know whether the improved sensitivity for the detection of obstructive CAD by CCT and the subsequently increased number of PCI will also result in improved long-term health outcomes. Nevertheless, the reporting of these trials, especially ACRIN-PA and ROMICAT II, has established CCT as a viable alternative to functional testing.

Prognostic Value of CCT in Stable and Acute Chest Pain Syndromes

Data predominantly from retrospective studies and registries including well over 30,000 patients (Table 1) demonstrate that presence and extent of obstructive CAD is an independent predictor of mortality and cardiovascular events [25–32]. The evidence is less clear for the burden of atherosclerosis with some studies suggesting that presence of nonobstructive CAD alone is not an independent predictor [15••]. Also CCT scores such as the Duke CAD prognostic index have been suggested to predict MACE. Overall, the data, albeit limited to qualitative assessments and referral populations that include asymptomatic patients, supports the notion that noninvasive assessment of the burden of atherosclerosis may improve risk stratification beyond risk factors and CACS [15••, 33•, 34]. Similar to acute chest pain populations, the distribution of CAD was 50 % normal, 35 % nonobstructive CAD, and 15 % obstructive CAD [33•]. Similar results have been observed in the follow-up of patients presenting with acute chest pain. After a median follow-up of 23 months, 6.8 % of patients suffered a MACE with probability of MACE increasing from 0 % without CAD to 4.6 % in nonobstructive CAD and 30.3 % in obstructive CAD [35•].

Prognostic Value of CT in Asymptomatic Adults

The utility of AS measurements in risk stratification of asymptomatic individuals has been investigated in several large prospective trials, and AS has added incremental value in predicting cardiovascular events over the traditionally established Framingham Risk Score (FRS). Table 2 lists the major prospective cohort studies evaluating the ability of the AS to predict cardiovascular events [36–38]. Overall, these studies enrolled 11,000 patients between the ages of 59–71 who had 369 MACE (variably defined but including coronary death and myocardial infarction) during an average follow-up of 4 years. The Multiethnic Study of Atherosclerosis (MESA) followed a population-based sample of 6722 men and women for a median of 3.8 years. One hundred sixty-two coronary events were noted, of which 89 were major events, including myocardial infarction or death from coronary heart disease. The risk of having a coronary event increased with AS scores of 1–100, 101–300,

and >300 (HR 3.61 (1.96–6.65), 7.73 (4.13–14.47), and 9.67 (5.20–17.98), respectively) [38]. Another subset of MESA population study included 1330 participants at intermediate FRS and confirmed these results [39]. Polonsky et al. also in the MESA cohort suggested that 25 % of patients can be correctly reclassified to higher or lower risk by AS to a prediction model based on traditional risk factors (NRI 0.25 (95 % CI 0.16–0.34), $p < 0.001$) [40]. Overall, all major studies established AS as an independent predictor of MACE in particular for coronary heart disease (CHD). Across the studies, this association was seen consistently for AS >100. However, the 10 % of the population with AS >300 is at a tenfold higher risk for MACE as compared to those without CACS adjusted for CVD risk factors and hence represents a group of asymptomatic individuals who would benefit from risk factor modification similar to secondary prevention. These results have led to incorporation of coronary artery calcification score (CACS) in the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines [41] and the appropriate use criteria [42] which both recommend that CACS may be appropriate to evaluate asymptomatic individuals at intermediate risk (10–20 % 10-year risk; class IIa indication) as well as in individuals with diabetes (class IIa indication). Hence, while there is evidence that non-contrast CT with very low radiation exposure (usually <1 mSv) may have a place in imaging of selected patients, the question remains whether this could be done in a cost-effective manner. Of course, a randomized trial perhaps designed similarly to the Jupiter Trial [43] would be the ultimate study to assess the role of non-contrast CT imaging.

Figure 1 describes the potential role of CCT in risk stratification and management of asymptomatic and symptomatic populations based on the currently available data. This figure will be informed by data from Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, a prospective, randomized comparative effectiveness trial comparing CT angiography with functional testing for the occurrence of MACE over a median of 2 years.

Conclusions

Fifteen years after the introduction of multislice CT technology, high-quality research including large cohort studies in asymptomatic patients, registries for stable chest pain, and randomized trials for acute chest pain syndromes have established CCT as a valuable tool to noninvasively assess for coronary artery plaque and stenosis with the goal to improve risk stratification of both symptomatic and asymptomatic populations. Probably most established is the role of CCT in the early triage of patients with acute chest pain and the exclusion of significant stenosis in patients with stable chest pain syndrome. Most promising is the addition of functional or physiological information such as FFR-CT to the anatomic information. Research is needed to determine whether this would elevate CCT from a triage tool to decision tool for treatment of patients with obstructive CAD with OMT vs. PCI noninvasively. Overall, more work is needed to determine whether CCT in asymptomatic and symptomatic individuals for risk stratification and treatment will save lives in a cost-effective manner, for example, via a decrease in invasive coronary angiography and revascularization.

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Fig. 1.
Description of the potential role of CCT in risk stratification and management of asymptomatic and symptomatic populations based on the currently available data

Table 1

Prognostic value of CCT in stable and acute chest pain syndromes

Study (year)	Number of patients	Age (years)	Subjects (stable)	CAD prevalence	Sensitivity (95 % CI)	Specificity (95 % CI)	NPV (95 % CI)	PPV (95 % CI)
Accuracy of CCT to detect obstructive CAD (ICA)								
Budolf et al. (ACCURACY) (2008)	230	57±10	No known CAD, stable chest pain, or abnormal functional stress testing	25 %	95 % (85–99 %)	83 % (76–88 %)	99 % (96–100 %)	64 % (53–75 %)
Miller et al. (CORE64) (2008)	291	60±6	Symptomatic patients with suspected or known CAD	56 %	85 % (79–90 %)	90 % (83–94 %)	83 % (75–89 %)	91 % (86–95 %)
Meijboom et al. (2008)	350	60±6	No known CAD presenting with stable or acute chest pain	64 %	99 % (98–100 %)	64 % (55–73 %)	97 % (94–100 %)	86 % (82–90 %)
Accuracy of CCT (anatomy and CT FFR) to detect hemodynamically significant CAD (ICA-FFR)								
Min et al. (JAMA 2012)	252	63±8	Suspected CAD	69 %	CT 84 % (77–90 %)	42 % (34–51 %)	72 % (61–81 %)	61 % (53–67 %)
Norgaard et al. (NXT 2014)	254	64±10	Suspected CAD	65 %	CT-FFR 90 % (84–95 %)	54 % (46–83 %)	84 % (74–90 %)	67 % (60–74 %)
Role of CCT in acute chest pain	699	50±10	Negative troponin Nondiagnostic ECG	CCT	CT	93 % (85–97 %)	91 % (81–96 %)	37 % (31–44 %)
					CT-FFR	85 % (74–91 %)	92 % (87–96 %)	63 % (53–72 %)
					Control	Outcome of interest	Observed difference (CCT vs. control)	
					MACE during follow-up	0.8 vs. 0.4 %		
					Direct ED	73 vs. 81 % ^a		
Goldstein et al. (CT-STAT) (2011)	1370	49±10	Negative troponin Nondiagnostic ECG	CCT	MPI	Discharges	Time to diagnosis	2.9 vs. 6.2 h
Litt et al. (2012)	1000	54±8	Negative troponin Nondiagnostic ECG	CCT	SOC	MACE during follow-up	Direct ED discharges	3 vs. 1 %
Hoffmann et al. (ROMICAT II) (2012)	1000	54±8	Negative troponin Nondiagnostic ECG	CCT	SOC	Time to diagnosis	Direct ED discharges	50 vs. 23 %
						MACE during follow-up	Time to diagnosis	18.0 vs. 24.8 h
						Direct ED discharges		0.4 vs. 1.2 %
								47 vs. 12 %

Study (year)	Number of patients	Age (years)	Subjects (stable)	CAD prevalence	Sensitivity (95 % CI)	Specificity (95 % CI)	NPV (95 % CI)	PPV (95 % CI)
Prognostic value Of CCT in stable and acute chest pain								
Abdulla et al. (2011)	5675	58±11	Population Stable, symptomatic, and intermediate risk	Median follow-up (months) 21	Adjusted OR/HR Normal vs. nonobstructive: OR 6.38 (3.01–14.82), CI: 95 % $p<0.0001$ Normal vs. Obstructive: OR 41.19 (22.56–75.18), CI: 95 % $p<0.0001$	Time to diagnosis 5.8 vs. 21.0 h		
Cho et al. (2012)	7590	58±12	No chest pain syndrome or history of CAD	24	Nonobstructive CAD: HR 1.19 (0.71–1.98) Obstructive 1 vessel disease: HR 1.42 (0.80–2.53) Obstructive 2 vessel disease: HR 2.20 (1.19–4.16) Obstructive 3 vessel disease: HR 2.91 (1.55–5.47)			
Al-Mallah et al. (2014)	8627	56.6±12	Suspected but without known CAD	25	Any obstructive CAD: HR 3.9 (2.7–5.5) Left main disease: HR 1.7 (1.2–2.4) Segment stenosis score: HR 1.09 (1.07–1.10), Segment involvement score: HR 1.18 (1.13–1.24)			
Schlett CL et al. ROMICAT I (2011)	333	53±12	Patients presenting to the ED with acute chest pain	23	No stenosis 1.00 Stenosis: HR 16.00 (5.92–43.22)			

^aEstimated from presented data

Table 2

Prognostic value of CT in asymptomatic adults: major cohort studies

Study (year)	Number of patients	Mean age	Median follow-up (years)	Agatston score (AS)	MACE rate (%)	Number of events (n)	Adjusted RR/HR (traditional CV risk)
St. Francis Heart Study (2005)	4613	59±5	4.3	0	0.54	119	RR: (95% CI) 1.0
				1–99	1.00		1.9 (0.8–4.2)
				100–399	5.5		10.2 (4.8–21.6)
				>400	14.0		26.2 (12.6–53.7)
The Rotterdam Heart Study (2005)	1795	71±5.7	3.3	0–100	2.3	88	RR: (95 % CI) 1.0
				101–400	5.4		1.9 (1.0–3.4)
				401–1000	7.4		2.4 (1.3–4.5)
				>1000	12.2		3.9 (2.1–7.3)
Multietnic Study of Atherosclerosis (MESA) (2008) (Detrano et al.)	6722	62±10	3.8	0	0.4	162	HR (95 % CI) 1.00
				1–100	2.25		3.61 (1.96–6.65)
				101–300	5.45		7.73 (4.13–14.47)
				>300	8.04		9.67 (5.20–17.98)