CORONARY CT ANGIOGRAPHY- HISTORICAL AND CURRENT PERSPECTIVES

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WHAT IS CORONARY CT ANGIOGRAPHY AND WHAT IS ITS HISTORY?

Coronary computed tomography angiography (coronary CTA) is a non-invasive imaging modality that uses computed tomography angiography (CTA) to obtain high-resolution, thin slice (sub-millimeter), three-dimensional (3D) pictures of the heart, its arteries, and the great vessels. Contemporary scanners have multiple rows of detectors, referred to as multidetector row CT (MDCT), and deliver X-rays timed to the patient's heart rhythm through the application of electrocardiogram (ECG) gating to rapidly produce high quality images of the coronary arteries.

The first attempts at imaging the coronary arteries with coronary CTA started in the late 1990s. Increased interest in its potential as a non-invasive modality for diagnosis of coronary artery disease has led to rapid advances in both equipment and analytic software. Contemporary CT scanners offer excellent imaging at ultra-low radiation exposure. The *Biologic Effects of Ionizing Radiation Report* (*BEIR VII report*) published in 2006 used 100 milliSieverts (mSv) exposure as the threshold for low dose. By contrast, current systems can provide clinical coronary CTA exams at 10 to 100 times lower exposure (1-10 mSv), comparable to the average annual exposure in the US from natural sources (3 mSv). This level of exposure is significantly less than that historically required to perform nuclear myocardial perfusion imaging (15-60 mSv) or invasive angiography, and coronary CTA is a non-invasive alternative to invasive coronary angiography (ICA).

This document will review that evidence, controlled/randomized clinical trials, and multicenter observational cohort registries concerning the diagnostic accuracy, prognostic ability, and cost-effectiveness of coronary CTA in the outpatient, inpatient, and emergency department settings. Our assessment is that the evidence is persuasive that coronary CTA is an equal, and often superior, technology for the diagnosis and management of coronary artery disease in appropriately selected patient populations.

DIAGNOSTIC ACCURACY OF CORONARY CTA

Modern coronary CTA is a reliable modality that can image coronary arteries with high diagnostic accuracy, often equivalent to the gold standard of ICA. Coronary CTA using MDCT requires thin detector collimation (detector width of 0.625 or less), thin slice reconstruction (image thickness ≤1.0 mm), multiple simultaneous images (e.g., 64 or more slices) and cardiac gating (often requiring beta blockers for ideal heart rate). Coronary CTA provides unparalleled spatial resolution compared to other non-invasive modalities.

The accuracy and reliability of coronary CTA was validated in 2008 with the publication of three landmark controlled clinical trials: ACCURACY, CORE 64, and Meijboom, et al. [1-3] These trials compared the sensitivity, specificity, and diagnostic accuracy of 64-slice coronary CTA with traditional ICA in over 1,000 low to intermediate risk patients referred for elective cardiac catheterization for evaluation of possible coronary artery disease (CAD). Taken together, 881 patients had interpretable scans. On a per-patient basis, coronary CTA identified a stenosis of equal or greater than 50% with high sensitivity (85% to 99%) and high negative predictive value (NPV), ranging between 83% and 99%.[1-3] The diagnostic accuracy of coronary CTA in the three studies noted above confirmed results that had been demonstrated by more than 50 previous single center trials, alsosuggestingthat other common non-invasive imaging modalities (for example myocardial perfusion imaging) may be inadequate tools for cardiovascular risk stratification in appropriate patient populations.

Since the publication of these landmark trials, we have seen continual technological advancement in the field of cardiac computed tomography (cardiac CT). Newer CT imaging platforms offer increased numbers of detectors (resulting in larger coverage per gantry rotation), improved temporal resolution (resulting in better diagnostic imaging at higher heart rates), and improvements in post-acquisition image reconstruction. Dual-source coronary CTA involves two radiation sources which increases temporal resolution, allowing for better image quality at higher heart rates and, in some cases, stable arrhythmias like atrial fibrillation. Ropers et al. observed that there was no

difference in diagnostic accuracy between patients with heart rates of ≥65 beats per minute (bpm) and <65 bpm using dual source CT. [13]

Recent work has also demonstrated that a post-acquisition processing method using iterative reconstruction (IR) complements efforts to reduce radiation exposure while maintaining image quality. Leipsic et al. and others compared coronary CTA using post-scan IR techniques compared to standard filtered back projection, and have shown preserved image quality with lower radiation exposure to the patient.[14-15] Coronary CTA also has shown high diagnostic accuracy in selected patients with intracoronary stents and post-coronary artery bypass grafting (CABG).

Coronary/cardiac CTA is poised to offer even more comprehensive evaluation of patients. The emerging techniques of myocardial CT perfusion (myocardial CTP) and CT guided fractional flow reserve (FFR-CT) have established that cardiac CT is capable of diagnosing myocardial ischemia with high diagnostic accuracy when compared with various reference standards such as nuclear myocardial perfusion imaging, magnetic resonance myocardial perfusion imaging, invasive angiography, and invasive fractional flow reserve (FFR).[16-21]

In summary, compared to traditional invasive coronary angiography, there is robust data confirming the high diagnostic accuracy of coronary CTA for the evaluation of patients with suspected and known coronary artery disease.[5-12] The exceptionally high negative predictive value of coronary CTA in populations with low to intermediate prevalence of significant CAD establishes it as a highly effective non-invasive imaging modality to exclude obstructive coronary disease in symptomatic patients. The current and next generation CT scanners are combining multiple advanced techniques, resulting in higher diagnostic accuracy across a variety of heart rates with very low radiation exposure to the patient, and are poised to offer the addition of functional information regarding the presence of ischemia.[17-21]

PROGNOSIS AFTER CORONARY CTA

Given its high diagnostic accuracy and negative predictive value, the prognostic implications of coronary CTA have received much interest in recent years. Several recent studies have shown coronary CTA is a good predictor of medium to long-term risk in both symptomatic and asymptomatic individuals. Most notably, studies have consistently confirmed the excellent prognosis conferred from a "normal" study (that is, the absence of coronary artery disease as demonstrated by coronary CTA). An overview of these data follows.

Multiple studies published prior to 2012 demonstrated that patients with no evidence of coronary artery disease as determined by coronary CTA had low risk for major adverse cardiovascular events (MACE). [22-26] In a retrospective study of 994 patients with chest pain syndrome suggestive of coronary artery disease or an equivocal stress test who underwent coronary CTA, Lesser *et al.* showed that only 160 patients required further evaluation with ICA at a 6 month follow-up. In the remaining patients not requiring ICA, only 2 patients were subsequently identified to have obstructive coronary artery disease at a later follow-up with ICA.

Pundziute *et al.*[23] evaluated a cohort of 104 coronary CTA patients after a 16 month follow up and found that the first year rate of MACE in patients with normal coronary arteries on coronary CTA was 0%. The study also showed that coronary CTA identified other independent predictors of MACE including:

- presence of obstructive coronary artery disease,
- presence of any coronary plaque (irrespective of stenosis severity),
- the number of coronary segments with plaques, and
- the number of coronary arteries with mixed plaque.

Overall, the rate of revascularization was 30% and the rate of hard cardiovascular events was 5% within one year among individuals with plaque identified on coronary CTA-. [23] This was the first report suggesting that atherosclerotic burden in the coronary arteries may influence patient prognosis beyond stenosis severity. It is notable that other non-invasive modalities for cardiovascular risk stratification (for example, myocardial

perfusion imaging) only evaluate for the presence of ischemia-producing coronary artery disease, thus providing no information about the presence or burden of non-obstructive plaque.

In a later study, Min *et al.* followed 1,127 low to intermediate risk patients for 15 months and found only one death in 333 patients without evident coronary artery disease by coronary CTA (0.24% per year or 2.4% 10-year risk).[26] Additionally, measurement of plaque location, distribution, and severity on coronary CTA were predictors of all-cause mortality. In another prospective study, Hadamitzky, *et al.* evaluated 1,256 patients with coronary CTA and assessed outcomes at a median follow-up of 18 months. In the 802 patients without obstructive coronary artery disease, there was only 1 severe cardiac event (0.1%), versus 5 severe events among 348 patients with obstructive coronary artery disease (1.4%), representing a statistically significant difference. Additionally, the rate of all cardiac events in patients without obstructive coronary artery disease was significantly lower than predicted by the Framingham risk score.[25]

More recent work has shown that the excellent prognosis conferred from a normal coronary CTA extends beyond five years, a timeframe unsurpassed by other imaging modalities. In 2012, Andreini *et al.* published a study in *JACC Cardiovascular Imaging* looking at long-term prognosis after coronary CTA.[27] Among approximately 1,234 patients followed for a mean of 52 months after coronary CTA, a total of 475 events were recorded, with 136 hard events (18 cardiac deaths and 118 nonfatal myocardial infarctions) and 123 late revascularizations. Cumulative event-free survival was 100% for both hard events and all events in patients with normal coronary arteries; 88% and 72% for hard events and all events, respectively, in patients with non-obstructive coronary artery disease; and 54% and 31% for hard events and all events, respectively, in patients with obstructive coronary artery disease. Not surprisingly, multivessel and left main coronary artery disease was associated with higher rates of hard cardiac events.[27] The same group (Andreini *et al.*) demonstrated similar findings in patients with diabetes. Among 426 diabetic patients studied, normal coronary arteries on coronary CTA portended an excellent prognosis with 100% event-free survival.[28]

In a meta-analysis of 18 studies conducted by Hulten *et al.*, annualized rates of MACE (death, MI, and revascularizations) were analyzed for 9,592 symptomatic evaluated with CTA with a median follow-up of 20 months. The pooled annualized event rate for obstructive (any vessel with >50% luminal stenosis) versus normal coronary CTA was 8.8% versus 0.17% per year for MACE ($p < 0.05$) and 3.2% versus 0.15% for death or MI ($p < 0.05$). The pooled negative likelihood ratio for MACE after normal CTA findings was 0.008 (95% confidence interval [CI]: 0.0004 to 0.17, $p < 0.001$), the positive likelihood ratio was 1.70 (95% CI: 1.42 to 2.02, $p < 0.001$), sensitivity was 0.99 (95% CI: 0.93 to 1.00, $p < 0.001$), and specificity was 0.41 (95% CI: 0.31 to 0.52, $p < 0.001$). Stratifying by no CAD, non-obstructive CAD (worst stenosis <50%), or obstructive CAD, there were incrementally increasing adverse events. The authors concluded that increasing CAD by CTA showed incrementally increased risk for future adverse cardiovascular events, and that adverse cardiovascular events are rare among patients with normal CTA findings. [70]

Finally, a very recent smaller study by Dougoud *et al.* studied event rates in 218 patients after 64-slice coronary CTA over a follow up period of 6.9 years. Images were analyzed with regard to the presence of non-obstructive (less than 50 % stenosis) or obstructive (greater or equal to 50 % stenosis) coronary artery disease. Major adverse cardiovascular events were defined as death, nonfatal myocardial infarction, or urgent coronary revascularization. Of the 218 patients, coronary CTA revealed normal coronaries in 49, non-obstructive lesions in 94, and obstructive coronary artery disease in 75 patients.[29] Over a median follow-up period of 6.9 years, MACE occurred in 45 patients (21%). Annual MACE rates were 0.3%, 2.7%, and 6.0 % ($p = 0.001$) for patients with normal coronary CTA, non-obstructive, and obstructive coronary artery disease, respectively. Additionally, the study found that the presence of obstructive disease and the number of segments with any plaque were independent predictors of MACE, consistent with results from Pundziute *et al.*[23] The authors concluded that patients with normal coronary arteries demonstrated by coronary CTA have an excellent cardiac prognosis beyond 6 years of follow up, while prognosis is progressively worse in patients with non-obstructive and obstructive coronary artery disease.[29]

Several studies analyzing data from the CONFIRM registry have shown that CTA is predictive of risk in a variety of settings:

- One study by Cheng, *et al*., which involved 14,048 consecutive patients with suspected CAD who underwent CTA, evaluated for observed prevalence of CAD versus that predicted by ACC/AHA 2002 clinical practice guidelines. Results from this study showed that observed rates of significant stenosis on CTA were less than that predicted by guideline based probability models.[71]

- A study by Villines *et al*. showed that a calcium score of zero did not rule out the presence of obstructive CAD among 10,037 patients from the CONFIRM registry. Overall, 84% of patients with a zero calcium score had no CAD, 13% had non-obstructive disease, and 3.5% had obstructive disease (>50% stenosis). The study showed no significant difference in all-cause mortality for patients with obstructive disease but there was a difference in the combined endpoint of all-cause mortality, nonfatal MI, or coronary revascularization (p<0;001).[72]

- Another study by Min et al. analyzed data from 24,775 patients from CONFIRM and showed that all-cause mortality was higher in patients with both obstructive and non-obstructive CAD; and that mortality risk was increasingly higher for patients with non-obstructive, one-vessel, two-vessel, and three-vessel obstructive disease.

- In another recent study analyzing data from over 20,000 patients in the CONFIRM registry, Hadamitzky, et al. analyzed the predictive value of CTA in patients and devised a predictive tool for patient mortality based upon their CTA findings. In this study, the best CTA parameter for prediction of mortality was the number of proximal segments with mixed or calcified plaques (C-index 0.64, p < 0.0001) and the number of proximal segments with a stenosis >50% (C-index 0.56, p = 0.002). CTA significantly improved overall risk prediction beyond that from National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). The authors concluded that both plaque burden and stenosis noted on CTA, particularly in proximal segments, has incremental prognostic value, and

that a prognostic scoring tool based upon these data could improve risk prediction beyond traditional clinical risk scores.[73]

Additional data suggests a potential survival benefit from the use of coronary CTA. In a case-control study from 2014, Budoff *et al.* evaluated 4,244 symptomatic patients without known coronary artery disease and compared them to 1706 patients who underwent standard of care in an academic cardiology clinic.[59] Patients were matched by gender, age, ethnicity, cardiovascular risk factors and follow-up duration. Over the follow up period of 80 ± 11 months, the overall death rate was 6.3% (270 deaths). The death rate was significantly lower in the coronary CTA group (n = 106, 4.2%) as compared to the control group (n = 184, 10.8%, p = 0.001) and event-free survival was 95.8% and 89.2% in the coronary CTA and standard of care groups, respectively. The risk-adjusted hazard ratio of death was 2.5 (95%CI: 1.6-6.7, p = 0.003) in the standard of care cohort as compared to the coronary CTA group. Multivariate analysis demonstrated that undergoing coronary CTA resulted in a risk reduction of 32%, p = 0.0001. The authors concluded that patients in the coronary CTA group may have benefitted from improved anti-atherosclerotic therapies based upon identification of atherosclerosis on coronary CTA compared to those in the control group, and suggested additional study was warranted.[59]

In summary, multiple studies over the last several years have demonstrated that patients with no evidence of coronary artery disease on coronary CTA have an excellent prognosis with very low incidence (less than 1%) of MACE. Not unexpectedly, the presence of obstructive coronary artery disease is associated with significantly higher rates of MACE. These results parallel those of other common modalities such as stress myocardial perfusion imaging, stress echocardiography, and invasive coronary angiography. Normal coronary arteries on coronary CTA portend an excellent cardiovascular prognosis.[23-29]

IMPACT OF CORONARY CTA ON PATIENT MANAGEMENT AND OUTCOMES

Aside from accurately diagnosing the presence or absence of obstructive coronary artery disease, coronary CTA also can identify the presence of plaque in cases where other functional imaging techniques (e.g. myocardial perfusion imaging) would otherwise be unremarkable. Detection of subclinical coronary artery disease may impact patient management and outcomes. Recent data have shown that patients with extensive non-obstructive plaque (e.g. involving more than 4 segments) have a higher rate of cardiovascular death or myocardial infarction.[63] Two retrospective studies have further demonstrated that treatment with statins of patients with non-obstructive plaque identified by coronary CTA is associated with a reduction in hard cardiovascular events [64] or all-cause death.[65] One mechanism underlying the observed reduction in events in such patients is the fact that identification of plaque on coronary CTA leads to intensification of preventive medical therapy. [64, 66, 67]

PROSPECTIVE RANDOMIZED TRIALS COMPARING CORONARY CTA TO FUNCTIONAL TESTING

PROMISE

The PROMISE study [68] randomized 10,003 symptomatic outpatients with suspected coronary artery disease to a strategy of anatomical testing with coronary CTA versus function testing (with exercise ECG treadmill testing, stress echocardiography, or nuclear stress testing). Over a median follow-up period of 25 months, the primary end-point (a composite of death, myocardial infarction, hospitalization for unstable angina, or major procedural complication) occurred in 164 of 4,996 patients in the coronary CTA group (3.3%) and in 151 of 5007 (3.0%) in the functional-testing group (p=0.75). While both testing strategies led to comparable outcomes, it is notable that the observed event rate was far lower than predicted, suggesting this study was underpowered to detect a difference in event rates. Importantly, the CT arm also demonstrated less downstream testing.

An economic analysis of the PROMISE trial revealed that x-year costs for coronary CTA did not differ from that of the functional testing. However, in comparison to functional testing, the use of coronary CTA was associated with a lower rate of invasive catheterizations showing no obstructive coronary artery disease, which was a pre-specified secondary end point. Overall, 1015 patients underwent at least one cardiac catheterization within 90 days after randomization: 609 of 4996 patients (12.2%) in the CTA group and 406 of 5007 (8.1%) in the functional-testing group. The results for 170 of the 609 patients (27.9%) in the CTA group, as compared with 213 of the 406 (52.5%) in the functional-testing group, showed no obstructive CAD.[75]

SCOT HEART

The SCOT HEART trial randomized 4,146 patients (9% with known coronary artery disease) with suspected angina to standard care versus coronary CTA standard care. As part of standard care, 85% of patients in both groups underwent exercise treadmill testing. Over a median follow-up of 1.7 years, the use of coronary CTA plus standard care was associated with a trend towards lower coronary artery disease death and myocardial infarction (p=0.053). Patients randomized to coronary CTA plus standard of care were also more likely to be prescribed new preventive therapies. While there was a trend toward more coronary revascularization in patients randomized to coronary CTA plus standard care (p=0.06), the rate of invasive angiography was similar in both groups (12% vs. 13%, p=0.056). The study also found that adding coronary CTA to standard care helped improve physician certainty with which coronary artery disease and angina were diagnosed. Of note, the radiation dose of coronary CTA was low at 4.1mSv.

COST-EFFECTIVENESS AND RESOURCE UTILIZATION OF CORONARY CTA IN THE DIAGNOSIS AND MANAGEMENT OF SUSPECTED CORONARY ARTERY DISEASE

Given the high negative predictive value and excellent prognostic ability of coronary CTA, its cost-effectiveness and ability to positively influence resource utilization and healthcare costs has been the topic of much interest. Multiple studies have studied and

demonstrated that coronary CTA can save costs and possibly reduce downstream testing in appropriately selected patients. An overview of several of these studies follows.

Two early studies by Min *et al.* compared costs between coronary CTA and single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) in the evaluation of intermediate risk patients without known coronary artery disease. The first compared 1,935 patients who underwent coronary CTA to 7,752 who underwent SPECT-MPI. The patients were matched on several demographic and clinical characteristics and followed for 9 months.[30] Adjusted total health care and coronary artery disease expenditures were 27% (p <0.001) and 33% (p <0.001) lower, respectively, for patients who underwent coronary CTA compared with those who underwent SPECT, which translated to an average reduction of $467 per patient for coronary artery disease expenditures. There was no difference in rates of coronary artery disease-related hospitalization, myocardial infarction or angina.[30]

A second study involved a similar analysis of low risk patients without known coronary artery disease undergoing coronary CTA (1,833 patients) or SPECT-MPI (7,732 patients).[31] Patients were matched for age, demographics, cardiovascular risk factors, and cardiac related medications, and were followed for one year to compare cost and clinical outcome. Adjusted coronary artery disease costs in the coronary CTA group were 25.9% lower than in the SPECT-MPI group, an average of $1075 per patient. Those in the coronary CTA group were more likely to undergo downstream testing with SPECT-MPI, while those in the SPECT-MPI group were more likely to undergo downstream testing with invasive angiography. The coronary CTA group was less likely to undergo coronary revascularization (hazard ratio, 0.76; 95% CI: 0.75, 0.77; P < .001) than the SPECT-MPI group. There was no significant difference between coronary CTA and SPECT-MPI groups for rates of myocardial infarction (0.4% for both) or coronary artery disease hospitalization (0.7% vs. 1.1%), while rates of angina were significantly lower in the coronary CTA group (4.3% vs. 6.4%, p<0.001).[31]

A 2007 study of 421 patients with suspected coronary artery disease was performed to establish whether coronary CTA could act as an effective 'gatekeeper' to the use of invasive coronary angiography in symptomatic patients with intermediate risk results

after SPECT-MPI.[32] Patients underwent coronary CTA, with subsequent ICA if severe stenosis or moderate stenosis matching a perfusion defect was found. Outcomes studied were number of patients sent for ICA, number of patients requiring immediate revascularization after ICA, and adverse outcomes (death, myocardial infarction, and late revascularization). After SPECT-coronary CTA assessment, only 78 patients (18.5%) were sent for ICA and 343 (81.5%) were medically managed. Follow-up was 15 ± 3 months. In the group referred for ICA, there were 50 cases of immediate revascularization, 1 non-ST-segment elevation myocardial infarction, 1 death, and 5 patients requiring repeat ICA, 3 of whom underwent late revascularization. In the medically managed group, 6 patients required late ICA, 1 of whom underwent revascularization. The authors concluded that in symptomatic patients with suspected coronary artery disease and intermediate-risk results on SPECT-MPI, coronary CTA can identify up to 80% of patients at low risk of events in whom ICA may be safely avoided.[32]

In a similar study by Cole *et al.*, 206 patients with mildly abnormal or equivocal results on SPECT-MPI underwent coronary CTA imaging first, followed by invasive angiography if obstructive coronary artery disease was identified by coronary CTA.[33] Only 32% of patients required ICA based upon obstructive coronary artery disease identified on coronary CTA, which resulted in cost savings of $1,454 per patient. Cole *et al.* concluded that coronary CTA was a cost-effective 'gatekeeper' prior to ICA in patients with suspected coronary artery disease and equivocal or mildly abnormal SPECT-MPI results.[33]

With respect to use of coronary CTA for evaluation of acute chest pain, Hulten *et al.* [69] performed a cost analysis which compared the actual observed costs under usual care (UC) with projected costs (based on blinded coronary CTA results) among patients with acute chest pain in the *Rule Out Myocardial Infarction Using Computer Assisted Tomography I* (ROMICAT I) study. This study demonstrated that the potential cost savings of coronary CTA are highly dependent on the prevalence of obstructive coronary artery disease. While cost-savings are anticipated in acute chest pain populations that have a prevalence of potentially obstructive coronary artery disease <30%, increased cost

related to downstream testing would be anticipated in populations with higher prevalence of disease.

Two additional decision analytic models evaluating the clinical and cost-effectiveness of coronary CTA were published in 2010. Halpern *et al.* used a decision tree to evaluate coronary CTA cost-effectiveness and radiation dose in asymptomatic low to intermediate risk patients with abnormal stress test results.[34] Specifically, the authors studied costs and radiation dose associated with performing coronary CTA prior to invasive coronary angiography, with ICA performed only if significant coronary artery disease was identified by coronary CTA. The authors demonstrated that cost-effectiveness depended on prevalence of coronary artery disease, with less cost savings for high coronary artery disease prevalence rates. Despite that, the authors estimate that there would be cost savings up to coronary artery disease prevalence rate of 85%. Assuming a prevalence of coronary artery disease of 50%, the authors estimated a cost savings of $789 per patient with a 2.5% false negative rate (similar to stress testing) and without significant increase in radiation exposure. The authors concluded that use of coronary CTA in low to intermediate risk patients with abnormal stress test results could safely reduce costs and unnecessary cardiac catheterization procedures. These results were similar to those reported by Dewey *et al.*, who demonstrated using a decision tree model that coronary CTA saved costs compared to ICA in patients up to a 70% coronary artery disease prevalence rate.[34]

Min *et al.*[35] performed a decision analysis to examine several strategies to evaluate for coronary artery disease in low-to-intermediate risk patients. The authors evaluated near- and long-term costs using a base case of a 55-year old man with a 30% risk for obstructive coronary artery disease undergoing the following diagnostic strategies:

- coronary CTA followed by ICA for positive or equivocal findings (coronary CTA only),
- coronary CTA followed by ICA for positive findings and MPI for equivocal findings (coronary CTA first),
- MPI followed by ICA for positive/equivocal findings (MPI only),

- MPI followed by ICA for positive findings and coronary CTA for equivocal findings (MPI first), and
- ICA.

The authors concluded that a coronary CTA first strategy was the least expensive, followed by coronary CTA only (incremental cost- effectiveness ratio (ICER) of $17,516). For long-term cost-effectiveness, a coronary CTA only strategy demonstrated a favorable ICER of $20,429 per quality-adjusted life-year (QALY) relative to the least expensive coronary CTA first strategy. Coronary CTA first and coronary CTA only strategies remained dominant up to a baseline coronary CTA test cost of $1100 and 80% coronary artery disease prevalence.[35]

Several studies have evaluated downstream test utilization with coronary CTA as an index test or as a second test prior to another modality. Nielsen *et al.*[36] evaluated how downstream test utilization was impacted by the use of exercise stress testing with MPI, versus coronary CTA as the initial diagnostic test for symptomatic patients at low-to-intermediate risk for coronary artery disease.   Downstream testing was less frequent in the coronary CTA group compared with stress testing (21% vs. 32%, p =0.003, respectively). Subsequent ICA and MPI utilization was more frequent in the stress test group compared with coronary CTA group (23% vs. 18%, p = 0.15, and 9% vs. 4% p = 0.03 respectively). In patients with an abnormal result on the first test, revascularization was performed in 17% of stress test group compared to 45% for the coronary CTA group (p = 0.002). The authors concluded that upfront use of stress testing in symptomatic patients resulted in more downstream diagnostic test utilization compared to coronary CTA.[36]

Chow *et al.* studied the referrals for invasive coronary angiography before and after implementation of a coronary CTA program on 7,017 consecutive patients in comparison to 11,508 control patients at three sites without coronary CTA programs.[37] After starting the program, the percentage of normal ICA decreased significantly from 32% to 27%, while there were no changes in the percentage of normal ICA at the three control sites. The authors concluded that coronary CTA had a positive impact by reducing the

frequency of normal ICA, and that the operating characteristics of CTA supported its potential role in ruling out obstructive coronary artery disease. [37]

Karlsberg et al.[38] compared utilization of noninvasive ischemia testing, ICA and percutaneous coronary intervention (PCI) 2 years before and 2 years after introduction of 64-slice MDCT in a large urban primary and consultative cardiology practice. The introduction of coronary CTA resulted in significant decrease in the utilization of ICA (45% decrease in ICA, 2083 procedures in 2004 vs. 1150 procedures in 2007, p<0.01) and a corresponding significant increase in the percentage of ICA cases requiring PCI (19% in 2004 vs. 28% in 2007, p < 0.001) supporting the concept that coronary CTA can reduce the rate of unnecessary cardiac catheterizations.[38]

Two more recent studies from 2012 compared clinical and cost outcomes in symptomatic patients evaluated by MPI vs. coronary CTA.   Cheezum et al. retrospectively studied a group of 241 patients without known coronary artery disease who underwent MPI and compared to 252 age- and sex-matched symptomatic patients without known coronary artery disease who underwent coronary CTA.[39] During mean follow-up of 30±7 months, no difference was found between coronary CTA and MPI in per-patient rates of any post-test evaluation, 24.6% versus 27.7% (P= 0.44). Coronary CTA patients had lower utilization of invasive angiography (3.3% vs. 8.1%; p=0.02) and a non-significant trend toward reduced downstream cardiac testing (11.5% vs. 17.0%; p=0.08). Including the evaluation of significant incidental findings (7.1% in the coronary CTA group), mean direct costs using coronary CTA were significantly lower than using MPI ($808 vs. $1,315). The authors concluded that low-intermediate risk patients without known coronary artery disease who underwent coronary CTA, compared with MPI, had similar rates of posttest evaluations, fewer invasive catheterizations, and lower overall evaluation costs.[39]

In a prospective pilot trial, Min et al. randomized 180 patients presenting with stable chest pain and suspected coronary artery disease at two sites to initial diagnostic evaluation by coronary CTA vs. MPI.[40] The primary outcome was near-term angina-specific health status; the secondary outcomes were incident medical and invasive

treatments for coronary artery disease, health care costs, and estimated radiation dose. No patients experienced myocardial infarction or death with 98.3% follow-up at 55±34 days. Both arms experienced comparable improvements in angina-specific health status. Patients who received coronary CTA had increased incident aspirin (22% vs. 8%; p=0.04) and statin (23.5% vs. 7%; P = 0.03) use, similar rates of coronary artery disease - related hospitalization, invasive coronary angiography, noninvasive cardiac imaging tests, and increased revascularization (8% vs. 1%; p=0.03). Coronary CTA had significantly lower total costs ($781 vs. $1,215, P<0.001) with no difference in induced costs. Coronary CTA also had a significantly lower total estimated effective radiation dose. The authors concluded that in patients with suspected stable coronary artery disease, coronary CTA evaluation was associated with more aggressive medical therapy, increased coronary revascularization, lower total costs, and lower effective radiation dose compared with MPI.[40]

In a CONFIRM registry analysis, Shaw *et al.*[41] evaluated post-coronary CTA patterns of ICA and revascularizations and found that the rate of ICA and revascularizations were low for no coronary artery disease or mild coronary artery disease, and increased proportionately with increasing prevalence of coronary artery disease (1-vessel, 2-vessel, and 3-vessel disease). [41]

Not all studies compared favorably early in the history of coronary CTA, although later studies have not demonstrated such results. Shreibati *et al.* performed a retrospective, observational analysis of administrative data on Medicare beneficiaries 66 years and older who underwent non-acute evaluation for coronary artery disease. In that study, use of coronary CTA was associated with increased likelihood to undergo subsequent invasive cardiac procedures, percutaneous revascularization, and coronary artery bypass surgery, and demonstrated higher coronary artery disease-related spending than patients who underwent stress testing. This result may not be surprising in light of an older patient population with likely higher prevalence of significant coronary artery disease. [42] In a meta-analysis published in 2014, Nielsen *et al.* reviewed studies published from 2002 to 2013 that compared the diagnostic accuracy and post-test outcomes of coronary CTA vs conventional exercise stress testing or stress MPI. Eleven studies evaluated the

diagnostic accuracy of coronary CTA to conventional stress testing/stress-MPI, and 7 compared outcomes among the same modalities. On a per- patient basis, sensitivity/specificity of coronary CTA compared to conventional exercise testing were 98% and 82%, respectively vs 67% and 46%, respectively. Compared to stress–MPI, sensitivity was 99% and 73%, respectively, and specificity was 71% and 48%, respectively. The authors concluded that the upfront diagnostic performance of coronary CTA was higher than both conventional stress testing and stress-MPI, but also found that coronary CTA was associated with increased downstream test utilization and coronary revascularization. [43]

The majority of published reports, in particular those in recent months and years, have favorably evaluated cost-effectiveness and resource utilization of coronary CTA for the evaluation of possible coronary artery disease. A very recently published review by Zeb *et al.* evaluated 42 published articles that studied the issue of coronary CTA cost-effectiveness and downstream resource utilization. The authors concluded that overall, the data supports use of coronary CTA as a first line or as a follow-up test, and may represent a cost-effective strategy in both the near and long term for evaluation of patients with low to intermediate prevalence (10-50%) of significant coronary artery disease.[44]

In summary, multiple peer-reviewed manuscripts have demonstrated cost savings and reduced downstream resource utilization using coronary CTA for the evaluation of low to intermediate risk, symptomatic patients with possible coronary artery disease. The benefit appears to be present with use of coronary CTA as an initial test or as a secondary test prior to invasive coronary angiography.

CORONARY CTA IN THE EVALUATION AND MANAGEMENT OF ACUTE CHEST PAIN/POSSIBLE ACUTE CORONARY SYNDROME

Acute chest pain is a leading reason for patients to seek evaluation in the emergency department (ED)[45] with up to 8 million visits per year, resulting in up to US $6 billion annual costs. Despite the fact that the majority of patients presenting for ED evaluation

have non-cardiac causes for their symptoms, the consequences of missing acute coronary syndrome (ACS) are great with short-term mortality rates of 10-20%. Despite large expenditure of healthcare resources, approximately 2-3% of ACS patients are inappropriately discharged from the ED.[45] The traditional approach to the management of acute chest pain/possible ACS in patients with a normal or near normal ECG and normal initial biomarkers (troponin) has been observation and trending of biomarkers followed by non-invasive risk stratification, commonly with stress-myocardial perfusion imaging.[46]

Given its excellent performance characteristics in terms of negative predictive value and prognostic value as well as its demonstrated potential for cost savings in the evaluation of stable chest pain in the outpatient setting, much interest has been devoted to the question of whether coronary CTA can be used safely and effectively to rapidly triage low to intermediate risk patients presenting to the ED with chest pain/possible ACS.[46] An issue of secondary but not trivial importance is whether use of coronary CTA in emergency department evaluation of acute chest pain can reduce total hospital and downstream costs.

A growing body of evidence supports the use of coronary CTA as a safe and effective modality in the definitive management of low to intermediate risk patients presenting to the emergency department with chest pain and the diagnosis of possible acute coronary syndrome. Initial work in this area was the 2007 publication of a single-center, randomized trial by Goldstein *et al.*, which randomized 197 patients with low to intermediate risk presentation of chest pain to coronary CTA or rest-stress MPI. [47] Compared to MPI, coronary CTA resulted in reduced time to diagnosis (3.4 hours vs 15.0 hours; *P* < .001), lowered ED costs ($1,586 vs $1,872; *P* < .001), and resulted in fewer subsequent evaluations for chest pain. Both strategies were safe, with no missed ACS. [47]

An observational study – the *Rule Out Myocardial Infarction Using Computer Assisted Tomography,* or ROMICAT trial – was published in 2009.[48] ROMICAT evaluated 368 patients presenting to the emergency department for acute chest pain with a normal initial troponin and non-ischemic electrocardiogram). Sensitivity and negative predictive value

for ACS were both 100% in the 50% of patients without evidence of coronary artery disease. At two year follow up, this cohort of patients continued to have an excellent prognosis with 0% rate of major adverse cardiac events. ROMICAT I, an observational study in low to intermediate risk acute chest pain patients, further provided information on long-term safety and established a 2-year warranty period for normal coronary CTA after discharge from the ED.[48]

The first randomized, multicenter trial studying coronary CTA in the emergency department was published in 2011. The *Coronary Computed Tomographic Angiography for Systematic Triage of Acute Chest Pain Patients to Treatment* (CT-STAT) trial studied 699 patients with low to intermediate risk presentation of acute chest pain (Thrombolysis in Myocardial Infarction (TIMI) scores ≤4) at 16 sites. Patients were randomized to either coronary CTA (n = 361) or rest-stress MPI (n = 338).[49] The primary and secondary outcomes studied were time to diagnosis and emergency department costs of care and safety (defined as freedom from MACE in patients with normal index tests) at 6 months, respectively. Outcomes were similar to those found by Goldstein *et al.* Time to diagnosis was reduced in the coronary CTA arm (2.9 hours vs 6.3 hours; p<0.001), and ED costs were lower ($2,137 vs $3,458; p<0.001). The study also showed coronary CTA to be safe without any missed ACS. [49]

In 2012, the ROMICAT-II trial randomized 1,000 patients to either early coronary CTA or to usual standard of care (SOC).[50] Unlike prior randomized studies, TIMI scores did not limit entry criteria. In addition, the SOC evaluation was at the discretion of the treating physicians and included exercise treadmill testing, stress echo and stress single-photon emission myocardial perfusion imaging. Compared to the other SOC modalities, coronary CTA resulted in a reduced median length of stay (8.6 vs. 26.7 hours; *p*<0.001), time to diagnosis (5.8 hours vs. 21.0 hours; *P* < .001), and increase in direct discharges (47% vs. 12%; p<0.001). The rate of major adverse cardiac events in the SOC vs. the coronary CTA group at 30 days was similar (6 vs. 2 events; p=0.18). ROMICAT II also reported costs of care including hospital costs, which were similar between coronary CTA and SOC ($4,026 vs. $3,874, p=). [50]

Finally, the ACRIN-PA trial randomized 1,370 patients with negative ECG and cardiac biomarkers and TIMI score ≤2 on a 2:1 basis between coronary CTA (908 patients) and standard of care (462 patients).[51] Similar to ROMICAT II, standard of care was defined by the attending physicians and included any accepted diagnostic tests and even 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 coronary CTA is less than 1%. Overall, ACS rates in these trials varied from 1% to 8%, capturing low to intermediate risk chest pain populations. Most importantly, no patient with ACS was wrongly discharged in the CT or SOC arm. Patients in the coronary CTA arm had a higher rate of direct ED discharge (50% vs 23%) and shorter length of stay (18 vs. 25 hours).

A 2013 meta-analysis by Hulten *et al.* analyzed the data from all four of the published randomized trials.[52] Of all patients presenting for evaluation of acute chest pain, 1,869 patients underwent coronary CTA and 1,397 patients had usual care. There were no deaths, and there was no statistical difference in the very low incidence of myocardial infarction between the coronary CTA and SOC management strategies. Similarly, there was no significant difference between post-discharge repeat emergency department visits and repeat hospitalization for patients undergoing coronary CTA compared with patients who underwent usual care. However, while the four individual trials showed no difference, pooled analysis showed an increased incidence of invasive coronary angiography) and coronary revascularization (PCI and CABG) among patients evaluated by coronary CTA.[52]

A very recent observational study by Jones *et al.* compared use of coronary CTA to conventional management of patients with low to intermediate risk presentation of chest pain/possible ACS in a large military medical center.[53] In this study, 183 patients with initial non-ischemic ECG and normal troponin underwent a rapid coronary CTA protocol compared with an age-matched cohort of 184 patients treated with traditional care that usually involved admission for serial biomarkers and functional assessment. In a follow up of 9-11 months, there were no major adverse cardiac events for either group, consistent with their low-intermediate risk presentation. Notable findings from this

report were:

- decreased length of hospital stay (average 5.9 hours for the coronary CTA group vs 25 hours for the standard group),

- decreased hospitalization (9.3% for the coronary CTA vs 98.9% for the standard group), and

- significantly reduced total estimated hospital cost in coronary CTA group when compared to usual care ($182,065 vs $685,191; p<0.001).[53]

Return visits to the ED due to recurrent chest discomfort are potentially problematic, particularly when patient symptoms seem anginal in nature. Several recent studies suggest that return visits to the ED are reduced following demonstration of benign coronary CTA findings. For example,

- Miller *et al.* randomized 60 acute chest pain patients to standard of care vs. SOC plus coronary CTA and found a 33% reduction in repeat ED visits in the coronary CTA group (p =0.007). [60]

- El Hayek and colleagues conducted a meta-analysis of 7 studies involving a total of 4,466 ED patients with acute chest pain (2,508 coronary CTA and 1,958 SOC) and found a 37% trend in reduction in recidivism in the coronary CTA arm (p=0.09).[61] A multivariate analysis of 894 ED patients presenting with acute chest pain demonstrated a 5-fold reduction of return visits with coronary CTA vs. SOC (p=0.02).[62]

These studies suggest that the anatomic demonstration of widely patent coronary arteries by coronary CTA is more reassuring to the patient, perhaps due to a greater diagnostic certainty on the part of the discharging physician.

In summary, multiple observational studies and four randomized trials have demonstrated that the use of coronary CTA to evaluate patients with low-to-intermediate pretest probability of ACS is safe and appears to be cost-effective. While there is need for longer term follow-up of patients undergoing coronary CTA for possible ACS in the ED, established data support the safe discharge of patients without significant coronary artery disease on coronary CTA with an excellent prognosis. Further, the use of coronary CTA

for triage of acute chest pain appears to lower hospital admissions and their associated costs.

Coronary CTA for the evaluation of acute chest pain/possible ACS in the ED is now supported by the ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. [54] Use of coronary CTA for patients presenting with low-to-intermediate likelihood for ACS is appropriate by these criteria. As noted in the Society of Cardiovascular Computed Tomography guidelines on the use of coronary CTA for patients presenting with acute chest pain to the emergency department, inclusion of this modality as a diagnostic option is supported by the American Heart Association (AHA) scientific statement on testing of low-risk patients presenting to the emergency department with chest pain, the American College of Radiology (ACR) appropriateness criteria on chest pain suggestive of acute coronary syndrome, the 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction, and the United Kingdom National Institute for Health and Clinical Excellence guidelines on chest pain of recent onset.[55-58]

In summary, there is compelling evidence that the use of coronary CTA in the ED setting for the evaluation of acute chest pain/possible ACS is safe, effective, and may be cost-effective in terms of reducing ED length of stay hospital admissions, downstream testing and associated costs for patients with low-to-intermediate risk acute chest pain. The time for widespread implementation of coronary CTA for the evaluation of acute chest pain/possible ACS has arrived.

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