

# Clinical Evidence for CCT

## What is CCTA?

Coronary Computed Tomography Angiography (CCTA) is a diagnostic non-invasive medical imaging tool used to detect and exclude coronary artery disease (CAD), the most common type of heart disease, in patients experiencing symptoms.

## CCTA is a Proven Technology

CCTA is a proven technology to rule out heart disease with 99% accuracy. This technology is used in over 2,000 centers nationwide and has been approved by local Medicare carriers in all 50 states. CCTA has been readily adopted by the scientific community, in large part due to positive data from numerous peer-reviewed scientific studies that indicate its efficacy as a non-invasive method to exclude coronary heart disease and avoid unnecessary downstream testing and/or invasive procedures.

**CCTA coverage is appropriate and necessary because of the large and continually growing evidence base that demonstrates the favorable impact of CCTA in clinical practice.**

## 1. Diagnostic accuracy of CCTA

Three landmark trials have assessed the diagnostic performance of CCTA in prospective multi-center trials. The ACCURACY trial, published in the *Journal of the American College of Cardiology*, evaluated 230 chest pain patients by CCTA, who were being referred for elective coronary angiography at 16 centers. In this study, the prevalence of obstructive coronary artery stenosis was 14%. Two important observations should be noted: 1) in this population of patients being referred for invasive coronary angiography—in large part, due to abnormal stress tests—the prevalence of obstructive coronary artery disease was low, reflecting the inadequacy of current diagnostic testing for identifying which individuals would benefit most from further invasive testing; 2) the diagnostic performance of CCTA within the ACCURACY trial was performed on a cohort of individuals with an intermediate prevalence of coronary artery disease. In this population with a low - to intermediate prevalence of coronary artery stenosis, CCTA demonstrated a sensitivity, specificity, PPV and NPV of 94%, 83%, 48%, 99%, respectively, to identify a >70% stenosis compared to QCA at the per-patient level.

Similarly, the CORE 64 trial, published in the *New England Journal of Medicine*, enrolled 291 primarily high risk patients >40 years of age from nine centers who were electively referred for invasive coronary angiography. In this study of individuals with coronary artery calcium scores <600, diagnostic performance of CCTA was assessed for all coronary vessels >1.5mm. In this group with an overall prevalence of obstructive CAD of 51%, CCTA demonstrated a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect a >50% luminal stenosis by quantitative coronary angiography (QCA) of 85%, 90%, 91% and 83%.

Finally, a multicenter, multivendor study (Meijboom et al) in the *Journal of the American College of Cardiology* evaluated 360 symptomatic patients between 50 and 70 years of age referred for invasive coronary angiography. In this study, the prevalence of stenosis  $\geq$ 50% was 68%. In comparison to QCA, CCTA demonstrated sensitivity, specificity, PPV, and NPV of 99%, 64%, 86% and 97%, respectively.

These prospective multicenter trials confirm the high diagnostic performance of CCTA that has been identified in >50 single center studies. Furthermore, the exceptionally high NPV of CCTA in populations with low - to intermediate prevalence of obstructive coronary artery stenosis establishes it as a highly effective non-invasive alternative to exclude the presence of obstructive coronary artery stenosis in symptomatic patients with chest pain.

**Key Finding: CCTA is the most accurate non-invasive diagnostic modality for the detection and, of equal import, exclusion of CAD in chest pain patients.**

## 2. Clinical significance of a negative CCTA

Given the high negative predictive value of coronary CCTA to exclude coronary artery stenosis, several studies have evaluated the ability of CCTA to identify symptomatic patients with suspected CAD who may require NO further testing.

*Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. JACC 2007; 50: 1161-117.*

In this study of 1,127 low - to intermediate risk patients followed for 15 months, only one death occurred in 333 patients without evident coronary artery plaque (0.24% per year; or 2.4% 10-year risk of death) Furthermore, CCTA plaque measures of obstructive coronary artery stenosis, plaque location, and plaque distribution were all predictive of future all-cause mortality.

**Key Finding: In low - to intermediate risk patients, a negative CCTA portends an exceptionally low risk of future death for potentially greater than 12 months. Furthermore, CCTA plaque measures, including stenosis severity, location, and distribution are strongly predictive of future risk of death.**

*Pundziute G, Schuijf JD, Wouter J, Boersma E, de Roos A, van der Wall EE, Bax JJ. Prognostic value of multislice computed tomography coronary angiography in patients with known or suspected coronary artery disease. JACC 2007; 49: 62-70.*

In a study of 100 individuals, the first year rate of major adverse cardiac events (MACE) in patients with normal CCTA (no coronary atherosclerosis) was 0%. Conversely, the rate of revascularization was 30% and the rate of hard cardiovascular events was 5% within one year in individuals with CCTA-identified coronary atherosclerotic plaque.

**Key Finding: In patients with suspected CAD, a negative CCTA portends an exceptionally low risk of future MACE in the first 12 months. Furthermore, CCTA plaque measures including stenosis severity and location are predictive of future risk of MACE.**

*Lesser JR, Flygenring B, Knickelbine T, Hara H, Henry J, Kalil A, Pelak K, Lindberg J, Pelzel J, Schwartz RS. Clinical utility of coronary CT angiography: coronary stenosis detection and prognosis in ambulatory patients. Catheter Cardiovasc Interv. 2007;69:64-72.*



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In this retrospective study of 994 patients with chest pain syndrome or equivocal stress tests who underwent CCTA, only 160 patients required further evaluation with invasive coronary angiography at a 6 month follow-up. Notably, amongst the remaining patients judged not to require invasive coronary angiography by CCTA, only two patients with obstructive coronary artery stenosis required invasive coronary angiography in follow-up.

**Key Finding: In patients with chest pain syndrome or equivocal stress tests and no coronary artery stenosis >50% by CCTA, 6 month outcomes are very favorable with exceptionally low rates of further downstream invasive coronary angiography rates.**

*Hadamitzky M, Freissmuth B, Meyer T, Hein F, Kastrati A, Martinoff S, Schomig A, Hausleiter J. Prognostic value of coronary computed tomographic angiography for prediction of cardiac events in patients with suspected coronary artery disease. JACC Cardiovasc Imaging 2009;2:404-11.*

This prospective study evaluated 1,256 patients with CCTA and assessed outcomes at a median follow-up of 18 months. In the 802 patients without obstructive CAD, there was only one severe cardiac event, versus five severe events amongst 348 patients with obstructive CAD, representing a significant difference. Additionally, the rate of all cardiac events in patients without obstructive CAD was significantly lower than predicted by the Framingham risk score.

**Key finding: The absence of obstructive CAD by CCTA is associated with a low cardiac risk, which is lower than that predicted by the Framingham risk score.**

### 3. Cost Containment and Reductions in Resource Utilization by CCTA

Numerous contemporary studies have addressed the ability of CCTA to safely reduce resource utilization and overall healthcare costs.

*Min JK, Shaw LJ, Berman DS, Gilmore A, Kang N. Costs and clinical outcomes in individuals without known coronary artery disease undergoing coronary computed tomographic angiography from an analysis of Medicare category III transaction codes. Am J Cardiol. 2008;102:672-8.*

A recent study evaluated Medicare category III T-code use of CCTA dedicated to coronary artery evaluation for costs and clinical outcomes. In a multi-center observational cohort study embodying >10 million insured lives, 142,535 adults were identified who underwent either CCTA (n=3676) or single-photon emission computed tomography myocardial perfusion imaging (SPECT MPI) (n=138,859). Accounting for potential confounders, CCTA patients (n=2313) were matched 1:4 to SPECT patients (n=9252) for age, demographics, cardiovascular risk factors, baseline co-morbidities, health plan type and Medicare Advantage status. In a nine month follow-up of intermediate risk adults undergoing CCTA, cost savings were identified for adults without known CAD by an average of \$445 compared to matched adults undergoing SPECT. Despite these cost differences, no differ-

ences were noted with regard to rates of CAD-related hospitalization, incident myocardial infarction, or angina.

**Key Finding: After the introduction of Medicare category III T-codes, the use of CCTA in intermediate risk individuals without known CAD, as compared to SPECT, is cost-efficient.**

*Min JK, Kang N, Shaw LJ, Devereux RB, Robinson M, Lin F, Legorreta AP, Gilmore A. Costs and clinical outcomes after coronary multidetector CT angiography in patients without known coronary artery disease: comparison to myocardial perfusion SPECT. Radiology. 2008;249:62-70.*

A similar analysis was performed examining adults without known CAD undergoing CCTA under coronary heart disease-specific chest CT angiography with and without contrast (CPT 71275) between 2002-5. (14) CCTA patients (1,833) patients undergoing SPECT MPI (n=7,332) for age, demographics, cardiovascular risk factors, and cardiac-related medications. In this low risk group of patients, CAD-related costs for adults undergoing CCTA were \$1,716 (95% CI, \$361-\$4,649) lower than in matched adults undergoing SPECT MPI. Despite overall total healthcare and CAD-related costs, CCTA adults incurred slightly lower rates of CAD-related hospitalization (0.01 vs. 0.02, p=0.003) and myocardial infarction or angina (0.05 vs. 0.08, p<0.0001).

**Key Finding: The use of CCTA in low risk individuals without known CAD, as compared to SPECT, is cost-efficient.**

*Danciu SC, Herrera CJ, Stecy PJ, Carell E, Saltiel F, Hines JL. Usefulness of multislice computed tomographic coronary angiography to identify patients with abnormal myocardial perfusion stress in whom diagnostic catheterization may be safely avoided. Am J Cardiol. 2007;100:1605-8.*

A recent study of 421 patients with suspected CAD was performed to establish whether CCTA could act as an effective 'gatekeeper' to the use of invasive coronary angiography (ICA) in symptomatic patients with intermediate risk after SPECT. Subjects with intermediate risk after SPECT MPI underwent CCTA, and if severe stenosis or moderate stenosis matching a perfusion defect was found, ICA was performed. Main outcome measures were number of patients sent for ICA, immediate revascularization after ICA, and adverse outcomes (death, myocardial infarction, and late revascularization). After SPECT-CCTA 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, one non-ST-segment elevation myocardial infarction, one death, and five patients requiring repeat ICA, three of whom underwent late revascularization. In the medically managed group, six patients required late ICA, one of whom underwent revascularization.

**Key Finding: In symptomatic patients with suspected CAD and intermediate-risk SPECT MPI results, CCTA can identify up to 80% of patients at low risk of events in whom ICA may be safely avoided.**



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Cole J, Chunn VM, Morrow A, Buckley RS, Phillips GM. Cost implications of initial computed tomography angiography as opposed to catheterization in patients with mildly abnormal or equivocal myocardial perfusion scans. *JCCT* 2007; 1:21-26.

In a similar study of 206 patients with mildly abnormal or equivocal nuclear SPECT exams, patients underwent CCTA imaging first, undergoing invasive angiography selectively only if obstructive coronary artery stenosis was identified by CCTA. Amongst the patient cohort, only 32% of patients possessed obstructive coronary artery plaque by CCTA and only these adults underwent selective catheterization, resulting in a cost savings of \$1,454 per patient.

**Key Finding: CCTA performed in individuals with mildly abnormal or equivocal SPECT MPI exams reduces the need for invasive coronary angiography and results in cost savings.**

Chow BJ, Abraham A, Wells GA, Chen L, Ruddy TD, Yam Y, Govas N, Galbraith PD, Dennie C, Beanlands RS. Diagnostic accuracy and impact of computed tomographic coronary angiography on utilization of invasive coronary angiography. *Circ Cardiovasc Imaging* 2009;2:16-23.

This study of 7017 consecutive patients before and after implementation of a CCTA program examined the effect on ICA referrals in comparison to 11,508 control patients at three sites without CCTA programs. 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.

**Key Finding: Implementation of a CCTA program significantly decreased the frequency of normal ICA studies, suggesting a decrease in unnecessary ICA procedures.**

## 4. Utility of CCTA in Acute Chest Pain Patients Presenting to the Emergency Department

Goldstein JA, Gallagher MJ, O'Neill WW, Ross MA, O'Neil BJ, Raff GL. A randomized controlled trial of multi-slice coronary computed tomography for evaluation of acute chest pain. *JACC*. 2007;49:863-71.

In a recent randomized trial of 197 low risk patients, 99 patients were randomized to CCTA and compared to 98 patients who underwent standard of care that included SPECT imaging. While both methods were shown to be 100% safe, CCTA immediately excluded or identified coronary artery stenosis as the source of chest pain in 75% of patients. The CCTA approach resulted in reduced diagnostic time in the emergency department, significantly lower costs, and fewer repeat evaluations for recurrent chest pain during 6 month follow-up.

**Key Finding: CCTA use in low risk patients presenting with acute chest pain in the emergency department results in reduced diagnostic time, cost savings, fewer repeat evaluations for chest pain, and is very safe.**

Hoffmann U, Nagurney JT, Moselewski F, Pena A, Ferencik M, Chae CU, Cury RC, Butler J, Abbara S, Brown DF, Manini A, Nichols JH, Achenbach S, Brady TJ. Coronary multidetector computed tomography in the assessment of patients with acute chest pain. *Circulation*. 2006; 114:2251-60. Erratum in: *Circulation*. 2006 Dec 19;114:e651.

In a blinded, prospective study of 103 consecutive low - to intermediate risk patients who presented to the ED with acute chest pain without ECG changes and negative initial biomarkers, CCTA exclusion of obstructive coronary artery stenosis identified the absence of acute coronary syndrome with 100% accuracy. Furthermore, addition of coronary artery plaque identification by CCTA incrementally improved identification of patients experiencing acute coronary syndrome in a manner incremental to traditional risk factors or clinical estimates. In individuals CCTA-identified non-obstructive or absent coronary artery plaque, no adverse outcomes during a 5.2 month follow-up.

**Key Finding: CCTA exclusion of obstructive coronary artery plaque excludes the presence of acute coronary syndrome with very high accuracy. Furthermore, CCTA-identified obstructive plaque predicts the occurrence of acute coronary syndrome in a manner incremental to traditional risk factors and clinical estimates.**

Rubinshtein R, Halon DA, Gaspar T, Jaffe R, Goldstein J, Karkabi B, Flugelman MY, Kogan A, Shapira R, Peled N, Lewis BS. Impact of 64-slice cardiac computed tomographic angiography on clinical decision-making in emergency department patients with chest pain of possible myocardial ischemic origin. *Am J Cardiol*. 2007;100:1522-6.

In a prospective study of 58 intermediate risk patients presenting with chest pain and no new ECG changes and negative enzymes, no or minimal coronary artery plaque as identified by CCTA, rates of major adverse cardiovascular events was low, and prognosis was favorable in a 12-month follow-up.

**Key Finding: In symptomatic intermediate risk patients presenting to the emergency department, CCTA exclusion of obstructive coronary artery plaque predicts favorable outcomes at 12 months.**

Hollander JE, Chang AM, Shofer FS, Collin MJ, Walsh KM, McCusker CM, Baxt WG, Litt HI. One-year outcomes following coronary computerized tomographic angiography for evaluation of emergency department patients with potential acute coronary syndrome. *Acad Emerg Med* 2009;16:693-8.

This prospective study examined low - to intermediate risk patients with CCTA performed in the emergency room for evaluation of possible ACS. Follow-up was performed in 481 patients with no evidence of significant CAD or ejection fraction <30%, cocaine use, or comorbidity such as cancer associated with a potential reduction in life expectancy. At follow-up at one year, only 11% of patients were re-hospitalized and only 11% had additional diagnostic testing; there was one death of unclear etiology, and there were no myocardial infarctions reported.



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**Key Finding: Low - to intermediate risk patients presenting with possible ACS to the emergency room with a negative CCTA have low rates of additional testing or re-hospitalization, and have very low rates of cardiovascular events over the following year.**

Hoffmann U, Bamberg F, Chae CU, Nichols JH, Rogers IS, Seneviratne SK, Truong QA, Cury RC, Abbara S, Shapiro MD, Moloo J, Butler J, Ferencik M, Lee H, Jang IK, Parry BA, Brown DF, Udelson JE, Achenbach S, Brady TJ, Nagurney JT. Coronary computed tomography angiography for early triage of patients with acute chest pain: the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial. *J Am Coll Cardiol* 2009;53:1642-50.

The ROMICAT I study was an observational cohort study of patients presenting to the emergency room with chest pain, and normal electrocardiogram and cardiac markers. A CCTA was performed and the results were not disclosed. In the 368 patients enrolled, 50% had no CAD, 31% had nonobstructive CAD, and 19% had significant CAD (>50% stenosis) or an inconclusive test. The presence or absence of any CAD on CCTA was associated with a 100% sensitivity, 54% specificity, and 100% NPV for an ACS, while stenosis >50% was associated with a sensitivity of 77%, specificity of 87%, and NPV of 98%.

**Key Finding: Low - to intermediate risk patients presenting with chest pain to the emergency room had no CAD by CCTA in 50% of cases, and CCTA could accurately detect and exclude patients with ACS.**

The 2-year outcomes of the above ROMICAT I study were recently presented at the American Heart Association 2009 Scientific Sessions: "Computed Tomography Angiography Results Predict Long-term Major Adverse Cardiac Events in Patients with Chest Pain from the Emergency Department: Two-year Outcome of the ROMICAT (Rule Out Myocardial Infarction using Computer Assisted Tomography) trial."

Two-year follow-up was completed in 303/337 patients who presented to the emergency room with acute chest pain and were ruled-out for an ACS. Patients were queried for adverse events including cardiac death, myocardial infarction, or revascularization. Patients with stenosis >50% by CCTA had a significantly higher rate of adverse events (15% vs. 0.4%), and a significant increase in hazard (hazard ratio 50).

**Key Finding: In patients presenting with chest pain to the emergency room who are deemed to not have an ACS, the absence of significant stenosis by CCTA is associated with a very low event rate at 2 years. In contrast, patients with significant stenosis have a higher rate of subsequent adverse events.**

Data from the Computed Tomographic Angiography for the Systematic Triage of Acute Chest Pain Patients to Treatment (CT-STAT) trial, were recently presented at American Heart Association 2009 Scientific Sessions.

This randomized prospective multicenter study evaluated 750 patients with chest pain presenting to the emergency room with normal electrocardiograms and cardiac markers. Patients were randomized to a standard diagnostic strategy using MPI versus a CCTA strategy. CCTA patients with severe stenosis underwent ICA, while patients with noninterpretable studies or intermediate stenosis underwent MPI; patients with abnormal MPI were referred for ICA, while those with normal studies were discharged. The primary study endpoints were time to diagnosis and hospital cost. The CCTA strategy, in comparison to the standard diagnostic strategy using MPI, was associated with significantly shorter time to diagnosis (3 versus 7 hours) and significantly reduced costs (\$2,000 versus \$3,500).

**Key Finding: In low risk patients presenting to the emergency room with chest pain, a CCTA strategy is associated with significantly shorter time to diagnosis and reduced hospital costs in comparison to a standard strategy using MPI.**

**CCTA coverage is appropriate and necessary because it is in accordance with ACCF Appropriate Use Guidelines.**

## Appropriate Use Criteria Addresses Layering of Tests:

"Appropriate use" criteria for CCTA use have already been developed by the specialty societies to address this issue. The American College of Cardiology (ACC), along with SCCT and multiple other professional society partners, has published criteria for SPECT MPI, CCT, CMR, and echocardiography. Each of these documents contains one or more tables outlining the appropriateness of ordering a test within a specific time frame when prior test results are available. The indications were developed with the direct input of health plan medical directors who served on the technical panels for each of these documents. It was based on their input that the criteria have evolved. Examples of inappropriate indications for multiple testing are listed below:

1. Evaluation of Chest Pain (Use of CCTA) with prior evidence of severe ischemia on stress test (exercise, perfusion, or stress echo)
2. Asymptomatic or Stable Symptoms with prior known CAD on catheterization or abnormal prior stress imaging study within one year (Use of SPECT MPI or Stress Echo)
3. Asymptomatic or Stable Symptoms with prior normal stress imaging study and high CHD risk within one year of prior test (SPECT MPI or Stress Echo)
4. Asymptomatic (Use of CCTA) with high CHD risk within two years of prior invasive angiogram without significant obstructive disease

The current appropriate use criteria underscore the strong commitment of physicians and their societies to providing direct recommendations aimed at reducing the use of subsequent downstream testing when it is not warranted.

**CCTA coverage is appropriate and necessary because the large and rapidly accruing evidence base that support its use as safe, clinically effective, and economically efficient.**



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