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Coronary Computed Tomographic Angiography as a Gatekeeper to Invasive Diagnostic and Surgical Procedures

Results From the Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) Registry

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Objectives This study sought to examine patterns of follow-up invasive coronary angiography (ICA) and revascularization (REV) after coronary computed tomography angiography (CCTA).

Background CCTA is a noninvasive test that permits direct visualization of the extent and severity of coronary artery disease (CAD). Post-CCTA patterns of follow-up ICA and REV are incompletely defined.

Methods We examined 15,207 intermediate likelihood patients from 8 sites in 6 countries; these patients were without known CAD, underwent CCTA, and were followed up for 2.3 ± 1.2 years for all-cause mortality. Coronary artery stenosis was judged as obstructive when ≥50% stenosis was present. A multivariable logistic regression was used to estimate ICA use. A Cox proportional hazards model was used to estimate all-cause mortality.

Results During follow-up, ICA rates for patients with no CAD to mild CAD according to CCTA were low (2.5% and 8.3%), with similarly low rates of REV (0.3% and 2.5%). Most ICA procedures (79%) occurred ≤3 months of CCTA. Obstructive CAD was associated with higher rates of ICA and REV for 1-vessel (44.3% and 28.0%), 2-vessel (53.3% and 43.6%), and 3-vessel (69.4% and 66.8%) CAD, respectively. For patients with <50% stenosis, early ICA rates were elevated; over the entirety of follow-up, predictors of ICA were mild left main, mild proximal CAD, respectively, or higher coronary calcium scores. In patients with <50% stenosis, the relative hazard for death was 2.2 ($p = 0.011$) for ICA versus no ICA. Conversely, for patients with CAD, the relative hazard for death was 0.61 for ICA versus no ICA ($p = 0.047$).

Conclusions These findings support the concept that CCTA may be used effectively as a gatekeeper to ICA. (J Am Coll Cardiol 2012;60:2103–14) © 2012 by the American College of Cardiology Foundation

Abbreviations and Acronyms

ACS = acute coronary syndrome(s)
CABG = coronary artery bypass graft
CAC = coronary artery calcium
CAD = coronary artery disease
CCTA = coronary computed tomographic angiography
ICA = invasive coronary angiography
MI = myocardial infarction
PCI = percutaneous coronary intervention
REV = revascularization
ROC = receiver-operating characteristic

Stress testing and the provocation of inducible ischemia have been the mainstay of cardiac diagnostic testing but have limitations because of a diminished diagnostic accuracy when compared with the gold standard of invasive coronary angiography (ICA). In a recent report from the American College of Cardiology's National Cardiovascular Data Registry, the rate of nonobstructive coronary artery disease (CAD) was exceedingly high—59%—for patients with a positive functional test before undergoing ICA (1). Coronary computed tomographic angiography (CCTA) has emerged as a noninvasive, diagnostic imaging modality that directly visualizes the coronary anatomy with a reportedly high diagnostic accuracy (2–5). Given the high accuracy of CCTA compared with conventional stress testing, it remains plausible that CCTA may more effectively identify patients with CAD who are more often candidates for ICA and who might benefit from revascularization (REV). However, few reports have examined post-CCTA management.

In 2008, the Centers for Medicare and Medicaid Services (CMS) completed its review of the scientific evidence concerning CCTA and indicated that no national coverage determination was appropriate because of a paucity of evidence in certain indications (6,7). After careful review of the published evidence, the panel ranked the ability of CCTA to act as a gatekeeper to ICA or in replacement of ICA as "unsure" (7). Since then, ongoing observational evidence has been accruing, including the development of and initial publications from the CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter) registry (8–12). One of the main goals of the CONFIRM registry was to evaluate post-CCTA utilization patterns and to evaluate the role of CCTA as a gatekeeper to downstream ICA and coronary REV Moreover, given the national coverage determination by CMS (7), a secondary aim was to examine the impact of CCTA evidence on downstream resource utilization in a population generalizable to Medicare beneficiaries (i.e., elderly patients enrolled in the CONFIRM registry).

Methods

Enrollment criteria. Details of the CONFIRM registry design and data elements have been published (8–11). Inclusion criteria for this subset of patients were those referred for suspected CAD. Patients were excluded from the study if they had a prior diagnosis of myocardial infarction, catheterization-defined CAD, or prior REV. Thus the remaining CONFIRM cohort included a total of 15,207 patients. A total of 8 sites from 6 countries participated in this substudy. All participating sites enrolled a consecutive series of patients who were prospectively followed up for the occurrence of death from all causes, for ICA, or for REV. Each site had institutional review board approval for all registry procedures, including follow-up methodologies.

Clinical history data. Uniform data collection methods were applied at all participating sites. Each site systematically collected data on each consecutive patient, applying standardized definitions for suspected cardiac symptoms, risk factors, and angiographic CAD extent and severity. The CONFIRM design article contains detailed information on this case report form and data collection methodologies (8). In brief, data were collected on traditional cardiac risk factors, including hypertension, diabetes, dyslipidemia, current smoking, and a family history of premature CAD. Patients treated for or with a prior diagnosis of hypertension, diabetes, or dyslipidemia, respectively, were categorized as having that risk factor. A family history of premature CAD was defined as a primary relative with a diagnosis early in life (i.e., mother <65 years of age or father <55 years of age). The presence of excessive dyspnea was recorded. Chest pain was categorized by the interviewing physician as nonanginal, atypical angina, or typical angina. A pretest CAD likelihood was calculated using the patient's age, sex, and typicality of chest pain symptoms (13).

CCTA protocol and interpretation. Standardized protocols for image acquisition as defined by the Society of Cardiovascular Computed Tomography were used at all participating sites. Specific details of the CCTA procedures have been defined in detail elsewhere (8–11).

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Each site applied the standard anatomic segmental analysis for image interpretation. All segments were coded for the presence and severity of coronary stenosis and graded for or using a 7-point scoring system (0 = none, 1 = 1% to 24%, 2 = 25% to 49%, 3 = 1% to 49%, 4 = 50% to 69%, 5 = 70% to 99%, and 6 = 100%). Some sites used a scoring of 25% to 49%, whereas others used a score of 1% to 49%. For this analysis, "no CAD" was defined as a score of 0 in all major epicardial arteries. Mild CAD was defined as a score of 1 to 3. CAD extent was coded as the number of vessels with ≥50% stenosis and was categorized as none, 1-vessel, 2-vessel, and 3-vessel/left main CAD, respectively.

Coronary artery calcium (CAC) scoring was performed in a subset of 10,754 patients. The methods for CAC scoring have been previously published (10). CAC scores were categorized as 0, 1 to 10, 11 to 99, 100 to 399, and ≥400, respectively.

Follow-up methods. All patients were prospectively followed up for a mean of 2.3 ± 11.2 years (range 0.01 to 6.2 years). The occurrence of all-cause death was ascertained by study personnel or by querying of national medical databases. Secondary endpoints included a: hospital stay for an acute coronary syndrome (ACS) or myocardial infarction (MI). Standardized definitions for ACS/MI were used. An ACS hospital stay was defined as the occurrence of unstable angina symptoms with electrocardiographic changes. For an acute MI, biomarker confirmation also was confirmed during the hospital stay. Additional details on the methods used to ascertain clinical endpoints have been published previously (8–10,12,14). Detailed information on the occurrence and date of follow-up ICA or REV was collected. All patients were queried using a scripted interview, and all procedures were confirmed by review of each patient's medical records. A total of 99 patients (0.8%) were lost to

Table 1 Clinical Characteristics of the CONFIRM Registry Suspected CAD Cohort (n = 15,207)

	None (n = 7,028)	Mild CAD (n = 5,380)	1-Vessel CAD (n = 1,713)	2-Vessel CAD (n = 705)	3-Vessel CAD/Left Main (n = 381)	p Value
Age (yrs)						<0.0001
<40	14.1%	2.2%	1.1%	1.0%	0.3%	
40–49	26.9%	14.2%	10.6%	8.2%	5.8%	
50–59	32.1%	30.8%	28.4%	27.2%	23.4%	
60–69	21.5%	34.9%	36.3%	37.2%	39.4%	
70–79	4.9%	15.6%	20.0%	22.0%	24.1%	
≥80	0.6%	2.2%	3.6%	4.4%	7.1%	
Female	54.6%	39.6%	34.5%	26.7%	24.2%	<0.0001
Any chest pain						<0.0001
None	32.9%	43.6%	39.8%	36.7%	34.1%	
Noncardiac	8.1%	8.7%	7.6%	10.0%	11.3%	
Atypical	50.3%	39.3%	36.7%	34.4%	32.4%	
Typical	8.8%	8.4%	15.9%	18.9%	22.3%	
Dyspnea	23.2%	26.5%	27.1%	28.5%	28.1%	<0.0001
Pre-test likelihood						<0.0001
Very low	35.5%	22.2%	16.6%	14.2%	9.9%	
Low	25.0%	32.7%	30.9%	29.9%	29.9%	
Intermediate	34.5%	39.1%	41.0%	41.8%	44.0%	
High	5.0%	6.0%	11.5%	14.1%	16.2%	
Previous stress test	47.8%	48.7%	47.8%	49.9%	50.3%	0.82
Obesity (kg/m^2)	22.0%	25.6%	25.2%	26.9%	25.9%	<0.0001
Hypertension	41.0%	51.1%	58.1%	61.4%	67.6%	<0.0001
Diabetes mellitus	8.8%	14.3%	19.5%	23.6%	23.9%	<0.0001
Dyslipidemia	47.5%	58.5%	65.6%	69.1%	69.0%	<0.0001
Family history of CAD	27.5%	29.6%	33.8%	40.4%	40.9%	<0.0001
Medication use						
Aspirin	29.1%	43.9%	49.5%	55.2%	54.7%	<0.0001
Beta-blockers	24.2%	33.8%	38.9%	43.9%	42.6%	<0.0001
CCB	18.2%	26.2%	25.6%	25.5%	19.1%	<0.0001
ACE inhibitors	11.3%	19.8%	26.6%	26.7%	32.4%	<0.0001
Nitrates	10.1%	10.4%	14.2%	13.4%	11.7%	<0.0001
Statins	21.6%	39.6%	50.8%	58.3%	61.6%	<0.0001
Insulin	0.6%	2.1%	3.0%	0.7%	2.9%	<0.0001

ACE = angiotensin converting enzyme; CAD = coronary artery disease, CCB = calcium channel blocker; CONFIRM = Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter registry.

follow-up. Patients lost to follow-up were similar to those presented herein.

Statistical methods. We compared categorical variables by the presence and extent of obstructive CAD according to CCTA using a likelihood ratio or linear-by-linear association chi-square statistic. The frequency of patients and their ensuing clinical characteristics undergoing ICA use with and without REV was calculated. A multivariable logistic regression model was used to estimate clinical and angiographic variables associated with follow-up ICA use. The odds ratio and 95% confidence intervals were calculated. Model statistics including classification results were calculated. Model overfitting procedures were considered by limiting 1 variable in the multivariable model for every 10 incident dependent outcomes. Significant colinearity was avoided by limiting inclusion of variables with a correlation <0.8. A similar logistic regression model was applied to examine estimators of early ICA occurring within 90 days of CCTA. A final multivariable logistic regression model included estimators of ICA use for patients with CCTA defined as <50% stenosis. For these models, the enrolling site was not a multivariable predictor. Using the methods of McNeill, a receiver operating characteristics (ROC) curve was used to estimate ICA and REV use by including the pretest CAD likelihood variable along with the CCTA-defined CAD, whereby areas were compared using an asymptotic p value calculation (15).

We calculated the time to downstream ICA and REV using a Cox proportional hazards survival model. The median (interquartile range) time to ICA was 0.05 (0.01 to 0.20) years. For persons undergoing ICA, the median (interquartile range) time to percutaneous coronary intervention was 1.4 (0.08 to 2.4) years; it was 2.0 (1.3 to 3.2) years for time to coronary artery bypass surgery.

Adjusted survival also was calculated using a stratified Cox proportional hazards regression model using the primary endpoint of time to all-cause death. In every case, the proportional hazards assumptions were met. We considered model overfitting by limiting our multivariable model to only 1 variable for every 10 deaths. A total of 185 deaths were observed in this patient cohort. We a priori identified several clinical covariates to include in the multivariable model, including age, symptoms, and cardiac risk factors. The Cox models were stratified by CCTA-defined CAD to examine differences in survival by ICA and REV. We further compared the crude rates of early (i.e., ≤90 days) ACS and MI for patients having early ICA. This comparison was done in an attempt to cull the patients with worsening symptom status

Table 2 Clinical Characteristics of Patients Undergoing ICA With and Without Coronary REV After CCTA

				ICA (n = 1,896)		
	No ICA (n = 13,327)	ICA (n = 1,896)	p Value	No REV (n = 955)	REV (n = 941)	p Value
Age deciles (yrs)			<0.0001			0.001
<40	8.3%	1.2%		1.7%	0.7%	
40–49	20.4%	10.8%		11.7%	9.8%	
50–59	31.1%	28.6%		30.7%	26.6%	
60–69	27.8%	38.1%		38.2%	37.9%	
70–79	10.7%	18.1%		14.8%	21.6%	
≥80	1.7%	3.2%		2.9%	3.4%	
Female	46.2%	35.8%	<0.0001	41.3%	30.2%	<0.0001
Chest pain			<0.0001			<0.0001
None	38.0%	35.1%		38.1%	32.1%	
Noncardiac	8.4%	8.8%		9.0%	8.5%	
Atypical	44.5%	38.2%		38.8%	37.6%	
Typical	9.1%	17.9%		14.1%	21.8%	
Dyspnea	25.1%	25.8%	0.52	25.8%	25.8%	0.99
Pre-test likelihood			<0.0001			<0.0001
Very low	28.8%	15.3%		18.0%	12.6%	
Low	28.7%	28.8%		30.3%	27.3%	
Intermediate	36.6%	43.3%		41.4%	45.1%	
High	5.9%	12.7%		10.3%	15.0%	
Prior stress test	47.9%	50.5%	0.078	49.7%	51.2%	0.58
Obesity	23.6%	26.5%	0.006	26.5%	26.5%	0.98
Hypertension	47.1%	55.3%	<0.0001	52.3%	58.4%	0.009
Diabetes mellitus	12.0%	19.8%	<0.0001	16.7%	23.0%	0.001
Current smoker	16.3%	17.6%	0.19	15.8%	19.4%	0.042
Dyslipidemia	53.4%	66.0%	<0.0001	62.3%	69.8%	0.29
Family history of CAD	28.5%	39.9%	<0.0001	38.7%	41.1%	0.29

CAD = coronary artery disease; CCTA = coronary computed tomographic angiography; ICA = invasive coronary angiography; REV = revascularization.

from the overall early rates. Within 90 days, a total of 193 MI and 259 ACS cases were identified.

Results

Clinical characteristics of the CONFIRM diagnostic cohort. In this cohort, 46.2% had no CAD, 35.4% had mild CAD, 11.3% had 1-vessel CAD, 4.6% had 2-vessel CAD, and 2.5% had 3-vessel/left main CAD, respectively. Table 1 depicts the comparative characteristics of the patient cohort by CCTA findings. Patients with more severe and extensive CAD were more often older and less likely to be female, and cardiac risk factors were prevalent.

Clinical characteristics of downstream ICA and REV. Patients referred for ICA and REV generally were older, less likely to be female, and more likely to have presenting chest pain symptoms (Table 2).

Cox proportional hazards estimating follow-up ICA and REV. The cumulative rate of ICA at 36 months was 2.5%, 8.3%, 44.3%, 53.3%, and 69.4%, respectively, for none, mild CAD, 1-vessel CAD, 2-vessel CAD, and 3-vessel/left main CAD (Fig. 1, $p < 0.0001$). Most instances of ICA (79.2%) occurred within 90 days after the patient underwent CCTA. The rate of ICA was similar for asymptomatic patients and those presenting for evaluation of chest pain (unadjusted $p = 0.15$, adjusted $p = 0.41$). A similar relationship for downstream REV also was documented (Fig. 2). Of note, the rate of late REV (i.e., >90 days) was 0.1%, 1.0%, 7.8%, 13.3%, and 26.0%, respectively, for none, mild, 1-vessel, 2-vessel, and 3-vessel CAD ($p < 0.0001$).

Figure 3 breaks down the type of REV by the severity of CAD. For patients with no CAD, 0.2% underwent percutaneous coronary intervention (PCI) and 0.1% underwent coronary artery bypass graft (CABG). For patients with mild CAD, 2.0% underwent PCI and 0.2% underwent CABG. For patients with obstructive CAD, 28.5% underwent PCI and 7.3% underwent CABG. The rates of PCI and CABG were substantially higher for patients with 1-vessel to 3-vessel/left main CAD. The ICA/REV ratio, representing the proportion of patients who underwent ICA who were referred for REV, was 53.1%, 66.0%, and 80.1% for persons with 1-vessel, 2-vessel, and 3-vessel/left main CAD according to CCTA.

In an ROC analysis estimating ICA use, the area under the curve was 0.85 (0.84 to 0.86) for CCTA-defined CAD compared with 0.60 (0.58 to 0.61) for pre-test CAD likelihood ($p < 0.0001$). Similarly, the area under the curve for REV was incrementally higher for CCTA-defined

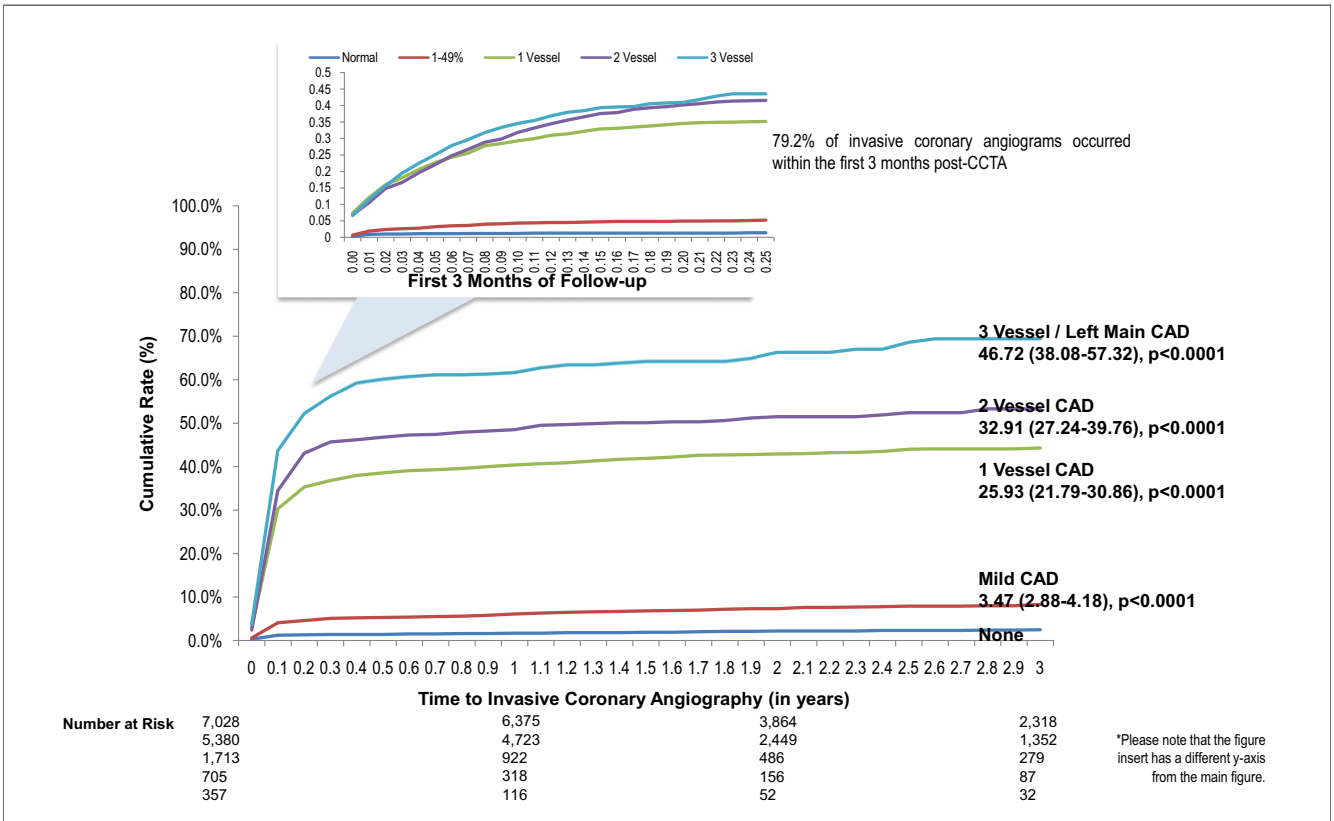


Figure 1 Post-CCTA Rates of Follow-Up ICA

Cumulative rate of follow-up invasive coronary angiography (ICA) after coronary computed tomographic angiography (CCTA). CAD = coronary artery disease.

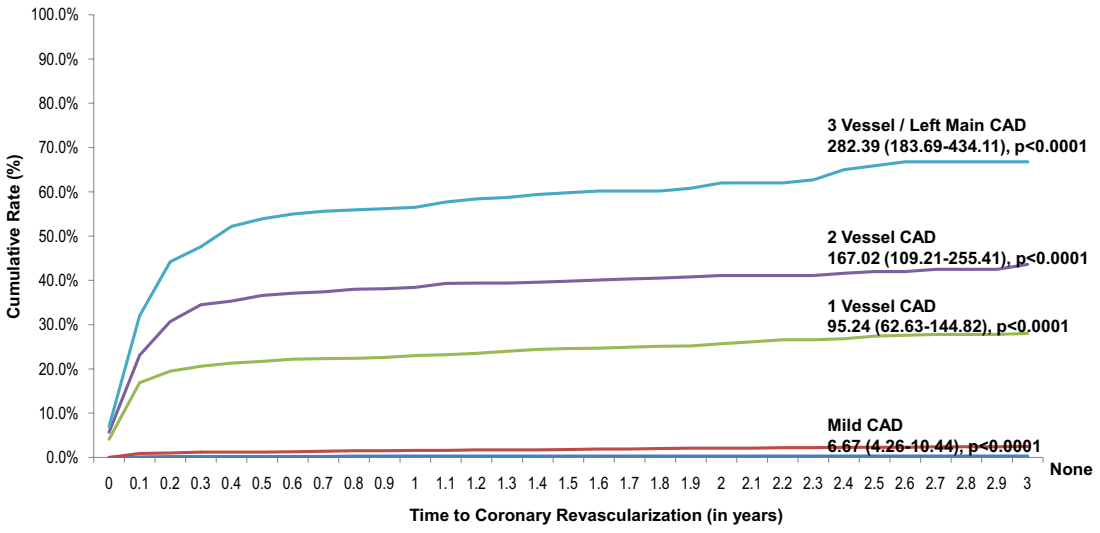


Figure 2 Post-CCTA Rates of Follow-Up REV

Cumulative rate of follow-up coronary revascularization (REV) after coronary computed tomographic angiography (CCTA). The number at risk is reported in Figure 1. CAD = coronary artery disease.

CAD (0.906, 0.91 to 0.92) compared with the pre-test CAD likelihood (0.63, 0.62 to 0.65) variable ($p < 0.0001$).

For the patients undergoing early ICA (i.e., ≤90 days), Figure 4 reports the frequency of preceding ACS or acute MI. For all CAD subsets, the frequency of preceding MI or ACS, before early ICA was low. For patients with no CAD, a preceding MI or ACS, before ICA, occurred in 4.2% and 6.3% of patients, respectively.

Multivariable models estimating downstream ICA. Significant clinical estimators of downstream ICA included family history of CAD ($p < 0.0001$), statin use ($p < 0.0001$), and typical angina ($p = 0.003$) (Table 3). The adjusted odds of ICA increased from 27.0-fold to 42.1-fold for patients with 1- to 3-vessel CAD ($p < 0.0001$). Even for patients with mild CAD, the adjusted odds ratio for ICA was elevated 3.6-fold ($p < 0.0001$). When examining estimators of early ICA within 90 days after CCTA (Table 4), the adjusted odds for ICA was elevated 3.8-fold, 4.6-fold, and 4.2-fold, respectively, for 1-vessel, 2-vessel, and 3-vessel CAD ($p < 0.0001$). Interestingly, for early ICA, the adjusted odds ratio (1.3, 0.9 to 2.0) for mild CAD was not significant ($p = 0.18$). The median time to ICA in patients with <50% stenosis was 2.0 years (25th to 75th percentile: 1.2 to 3.2 years). In patients with <50%

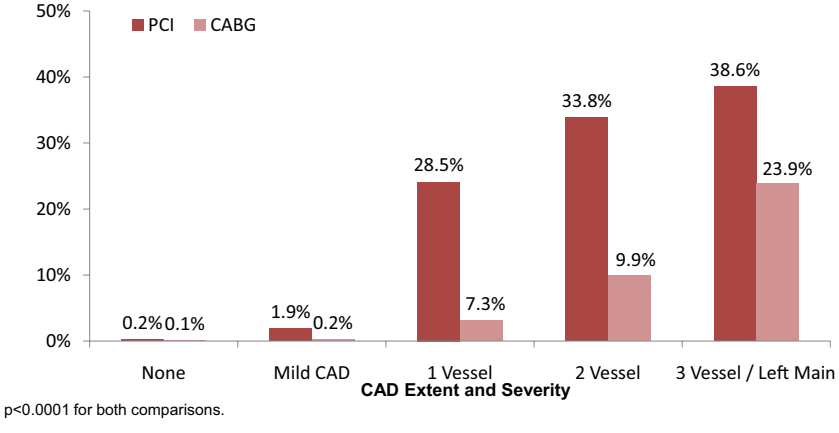
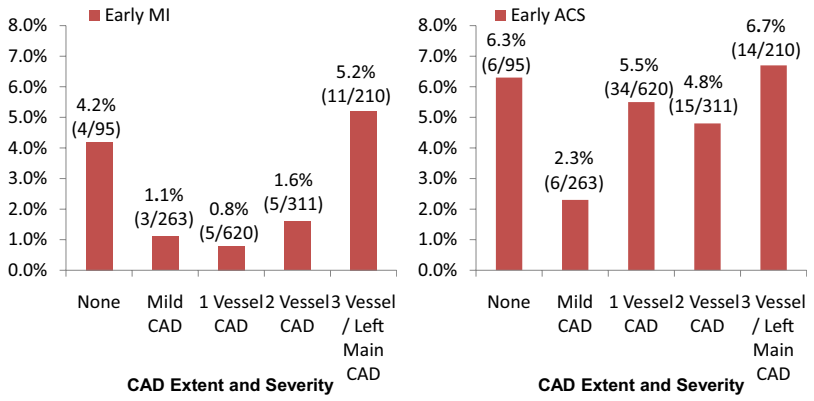


Figure 3 Follow-Up REV by CCTA-Defined CAD Extent

Follow-Up revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]) by the number of vessels with coronary artery disease (CAD) by coronary computed tomographic angiography (CCTA).



MI: p=0.002; Comparison of None vs. Mild – 3 Vessel / Left Main CAD: p=0.096
ACS: p=0.144; Comparison of None vs. Mild – 3 Vessel / Left Main CAD: p=0.56

Figure 4 **Follow-Up ICA After MI or ACS**

The occurrence of early (≤90 days) preceding myocardial infarction (MI) or acute coronary syndrome (ACS) and invasive coronary angiography (ICA) by coronary artery disease (CAD) defined by coronary computed tomographic angiography (CCTA). For example, of the 95 patients with no CAD who had an early ICA, only 4.2% and 6.3% had a preceding acute MI or ACS.

stenosis, ICA use occurred in only 8.0% of 1,288 patients within 90 days.

For patients with <50% stenosis, advancing age ($p < 0.0001$) and typical angina ($p = 0.002$) were significant estimators of ICA (Table 5) over the duration of follow-up. Additional estimators included the presence of mild CAD in the left main coronary artery ($p < 0.0001$), proximal left anterior descending coronary artery ($p = 0.006$), proximal right coronary artery ($p < 0.0001$), and proximal left circumflex coronary artery ($p = 0.005$), respectively. The rate of downstream ICA was similar in obese and nonobese patients without obstructive CAD ($p = 0.84$).

A subset of 11,873 patients without CAD also had CAC scoring results, including a 0 score in 54.7%, a 1 to 10 score in 7.8%, an 11 to 99 score in 18.1%, a 100 to 399 score in 12.7%, and ≥400 score in 6.7%, respectively. The rate of ICA increased with the CAC score (Fig. 5) and ranged from 2.5% for a 0 score to 8.1% for patients with a score ≥400 ($p < 0.0001$). Importantly, few of these patients with evidence of CAC underwent REV (Fig. 5). For example, only 2.1% of patients with a CAC score ≥400 underwent REV. When classifying ICA, the area under the ROC curve for CCTA-defined CAD (0.84 [0.83 to 0.85]) was significantly higher than for CAC (0.72 [0.70 to 0.73], $p < 0.0001$). A similar pattern of a higher ROC curve area for CCTA-defined CAD when compared with CAC also was reported for REV.

Elderly patient subset analysis. Compared to patients <65 years of age, the odds of referral to ICA was elevated 2.0-fold for patients age 65 years and older ($p < 0.0001$). Figure 6 reports the use of ICA and REV in elderly (≥65 years of age) and nonelderly (<65 years of age) patients. As

Table 3 **Multivariable Logistic Regression Predictors of ICA Utilization**

	Odds Ratio	95% CI	Wald Chi-Square	p Value
Age (by decade)	1.1	0.98–1.1	2.0	0.16
Family history of CAD	1.5	1.3–1.8	26.3	<0.0001
Statin use	1.4	1.4–1.6	16.6	<0.0001
Chest pain			11.0	0.012
Noncardiac	1.2	0.9–1.6	1.2	0.27
Atypical	0.9	0.8–1.2	0.0	0.95
Typical	1.4	1.1–1.7	8.7	0.003
CCTA CAD extent			1,140.0	<0.0001
Mild CAD	3.6	2.8–4.5	106.9	<0.0001
1-vessel	27.0	21.0–34.5	688.1	<0.0001
2-vessel	36.5	27.1–49.0	569.3	<0.0001
3-vessel/left main	42.1	29.4–60.2	419.1	<0.0001

Model chi square = 1,815.2; $p < 0.0001$; model classification = 88.1%. Coronary artery calcium (CAC) is significant in the aforementioned model when CCTA-defined CAD is not included. However, CAC scoring is no longer significant when added CCTA-defined CAD is added to the model ($p = 0.41$).

CI = confidence interval; other abbreviations as in Table 2.

Table 4 **Multivariable Logistic Regression Predictors of Early ICA Use Within 90 Days of CCTA**

	Odds Ratio	95% CI	Wald Chi-Square	p Value
Age (by decade)	0.9	0.8–0.97	6.4	0.011
Chest pain			6.2	0.10
Noncardiac	0.9	0.6–1.4	0.3	0.60
Atypical	1.4	1.0–1.8	4.6	0.032*
Typical	1.1	0.8–1.5	0.1	0.74
CCTA CAD extent			95.0	<0.0001
Mild CAD	1.3	0.9–2.0	1.8	0.18
1-vessel	3.8	2.5–5.7	39.4	<0.0001
2-vessel	4.6	2.8–7.3	39.4	<0.0001
3-vessel/left main	4.2	2.5–7.1	29.6	<0.0001

Model chi square = 103.4; $p < 0.0001$; model classification = 79.6%. *Higher rate of family history of CAD and smoking.

Table 5 Multivariable Logistic Regression Predictors of Catheterization in 12,408 Patients With CCTA Stenosis ≤50%

	Odds Ratio	95% CI	Wald Chi-Square	p Value
Age (per decade)	1.2	1.1–1.4	22.5	<0.0001
Chest pain			12.6	0.006
Noncardiac	1.1	0.8–1.7	0.8	0.38
Atypical	0.9	0.8–1.2	0.2	0.66
Typical	1.6	1.2–2.2	9.5	0.002
Mild left main stenosis	1.7	1.3–2.1	14.5	<0.0001
Mild proximal LAD stenosis	1.4	1.1–1.7	7.4	0.006
Mild proximal RCA stenosis	2.4	1.6–3.7	16.1	<0.0001
Mild proximal LCX stenosis	1.5	1.1–1.9	8.0	0.005

Model chi square = 177.8; $p < 0.0001$; model classification = 95.9%.
CCTA = coronary computed tomographic angiography; CI = confidence interval; LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery.

with younger patients, the rate of ICA and REV increased with the extent and severity of CCTA-defined CAD. In a multivariable logistic regression model, when considering other covariates from Table 3, age was not a significant estimator of ICA use ($p = 0.65$). However, in unadjusted comparisons, the overall rate of ICA was higher in elderly patients with mild and 1-vessel CAD (Fig. 6).

Exploratory survival differences in ICA and REV by CCTA-defined CAD. We performed a stratified Cox regression model to examine survival differences for patients proceeding to ICA and REV after undergoing CCTA. Figure 7A reports the results of survival differences for patients with <50% stenosis who underwent ICA and REV. The observational survival results in patients with <50% stenosis reveal an adjusted relative hazard of 2.2 for ICA ($p = 0.011$) and 1.6 ($p = 0.43$) for REV, including covariate adjusted by symptoms and cardiac risk factors (Fig. 7A). Conversely, in patients with CCTA-defined obstructive CAD, the relative hazard for ICA was 0.61 ($p = 0.047$) and for REV it was 0.63 ($p = 0.11$) (Fig. 7B).

Discussion

The concept of a noninvasive test being applied as a gatekeeper to ICA has long been touted as a means of selectively identifying patients with a higher likelihood of undergoing CAD and reducing diagnostic workup costs (16–18). An effective gatekeeping function is defined when, after the test is performed, therapeutic management is promptly targeted by the noninvasive test findings. Within the CONFIRM registry, we observed that most instances (79%) of ICA use occurred within 90 days of CCTA, supporting a CCTA-directed strategy that linked to near-term ICA and REV use. However, to be effective, this link must target appropriate patient candidates who benefit from referral for additional testing or treatment. We observed that the rates of ICA were low in patients with no to mild CAD, increased with the extent and severity of CCTA-defined CAD and were as high as 44% to 69% for 1- to 3-vessel/left main CAD ($p < 0.0001$). Similarly, the observed REV rates for patients with 1- to 3-vessel/left main CAD ranged from 28% to 69% ($p < 0.0001$).

When associations between diagnostic findings result in targeted therapeutic intervention, improvements in CAD outcomes may occur. We have seen recent examples when post-test management was ill-defined after noninvasive testing (16,19–23) and, as such, the link between testing and outcomes often remains disconnected. In an exploratory analysis within the CONFIRM study, we observed trends toward improved survival for patients with CAD as identified by CCTA who underwent ICA ($p = 0.047$); despite no mandate of specific post-CCTA therapy. This analysis suggests that CCTA-defined CAD may enhance the correlation with ICA-defined CAD and improve targeted

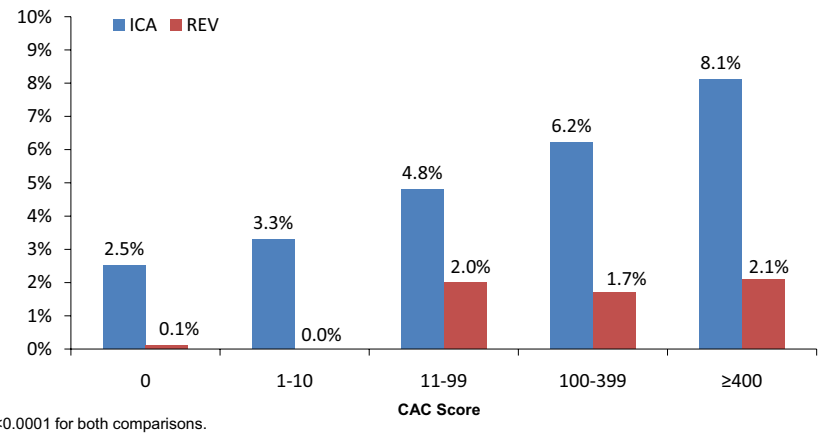


Figure 5 ICA and REV by Coronary Calcium Scores

Frequency of invasive coronary angiography (ICA) and coronary revascularization (REV) by coronary artery calcium (CAC) scores.

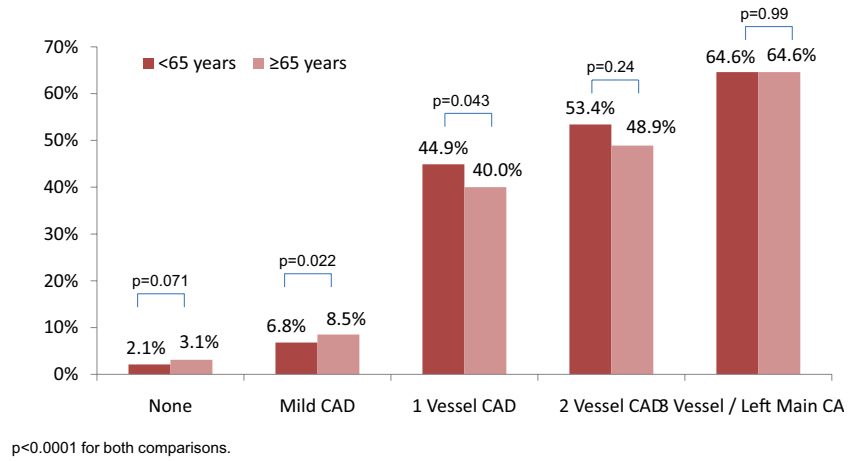


Figure 6 **Follow-Up ICA by Age**

Cumulative rate of follow-up invasive coronary angiography (ICA) in elderly (≥65 years) and nonelderly (<65 years of age) patients. CAD = coronary artery disease.

REV, resulting ultimately in improved clinical outcomes. From this observational assessment, the importance of integrating ischemia with anatomic CAD to optimally guide management and therapeutic risk reduction is unclear (24).

From one recent report, the introduction of CCTA resulted in a 45% reduction in the use of diagnostic ICA (17). We reported a relatively low overall rate of ICA (12.5%), suggesting that CCTA was operating as a filter, with most ICA referrals limited to persons with obstructive CAD. In a similar report by Tandon et al. (25), only 10.6% of patients undergoing CCTA were referred for ICA. However, a recent report using claims data revealed higher ICA rates (22.9% at 6 months) after CCTA compared with the rate of 12.5% at 3 years for the CONFIRM study (26). From the SPARC (Study of Myocardial Perfusion and Coronary Anatomy Imaging Roles in CAD) registry, in a smaller subset of 590 patients with a high frequency of prior stress testing, 13.2% of patients who underwent CCTA were referred for ICA at 90 days (27). Given that there is no CMS national coverage decision on the use of CCTA, the prior data analyses may include unique test indications, such as a prior indeterminate stress test, which may have altered the likelihood of referral for ICA. Additionally, Bayesian theory would dictate that referral probabilities would be higher after a second diagnostic procedure when compared with the ICA likelihood after an index diagnostic workup with CCTA alone.

Although we observed a relatively low rate of downstream ICA in patients with no CAD (2.5%) to mild CAD (8.3%), we hypothesized that compromised image quality or reduced interpretive confidence may have prompted referral to ICA in this cohort with no CAD to mild CAD in the early application of CCTA use; particularly in the presences of dense coronary calcium. Given the documented challenges in interpretation in the setting of CAC, we explored ICA use after CCTA by an increasing Agatston score. We reported in patients with nonobstructive CAD, we reported an increased utilization of ICA for patients with high-risk CAC scores, such that nearly 1 in 14 patients with a CAC score of 400 or higher were referred for ICA. From 1 recent survey, the results of CCTA were reported to improve risk reclassification in only 58% of patients (28), which may explain some of the imprecise management observed in the CONFIRM subset of patients with no CAD to mild CAD.

These findings of ICA use in patients with nonobstructive CAD represent opportunities for improvement and efficiency in CCTA-guided management. In 1 previous report, positive CCTA findings were associated with additional testing ($p < 0.0001$) and REV ($p < 0.0001$) within 90 days (29). Although no guided therapy or management trials after use of CCTA have been performed, the prognostic findings from prior CONFIRM (8,10,11) and other series (14,30–33) support the hypothesis that these patients with <50% stenosis are at lower risk of major adverse CAD events. Of note, in our exploratory survival analysis, we observed an elevated hazard (2.2-fold) for death for patients with mild CAD who underwent ICA ($p = 0.011$). Moreover, current guidelines for stable ischemic heart disease (34) limit ICA use to patients with high-risk findings on diagnostic testing. With increased awareness of the low event rates associated with mild CAD findings, CCTA-guided care may become more efficient and effective if medical management of patients with <50% stenosis is applied. In several cases, early ICA was preceded by an ACS, which is consistent with guideline-accepted best practices (34). However, most early ICA use was not event driven.

Several previous series have examined the frequency of downstream invasive procedural use in patients with and

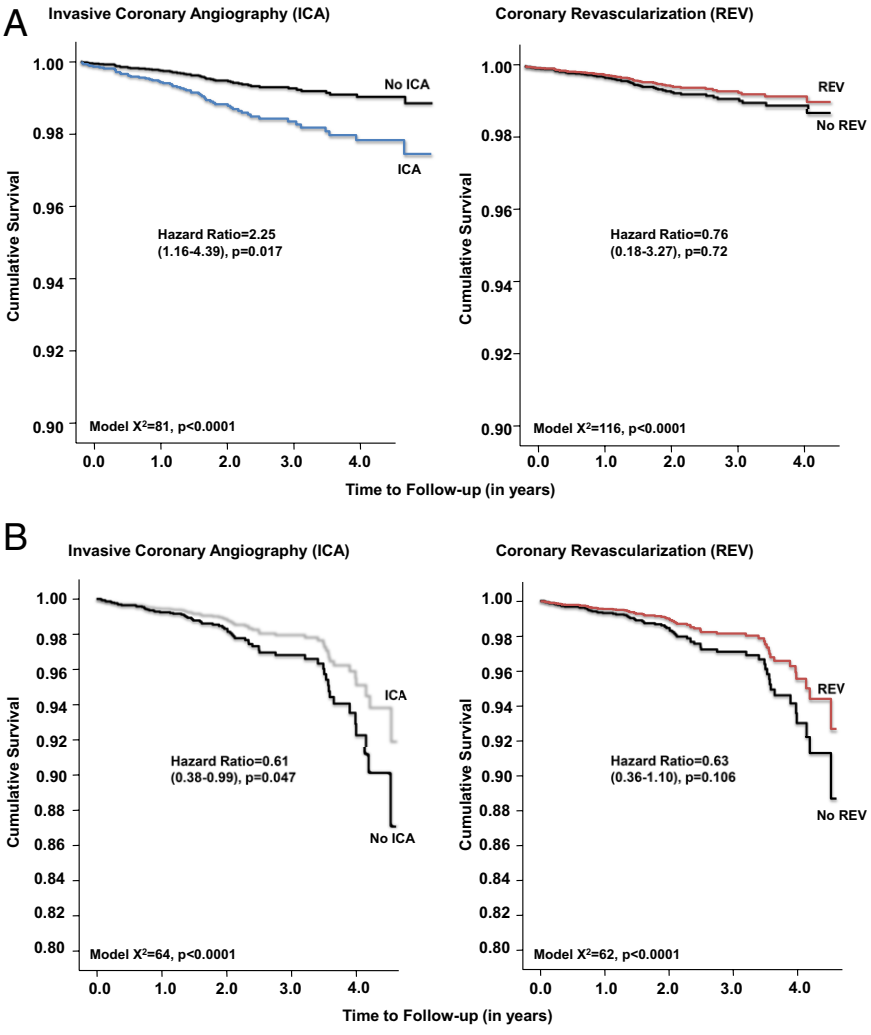


Figure 7 Cumulative Survival by ICA and REV in Patients With Mild CAD and CAD

(A) Observational comparison of survival for 5,380 patients with mild coronary artery disease (CAD) undergoing post–coronary computed tomographic angiography invasive coronary angiography (ICA) and coronary revascularization (REV). **(B)** Observational comparison of survival for 2,799 patients with obstructive CAD undergoing post-coronary computed tomographic angiography ICA and coronary REV. Model covariates: age, gender, chest pain symptoms, dyspnea, and cardiac risk factors.

without documented CAD upon CCTA (29,35). In 1 report with a mean duration of follow-up of 1.4 years, no patients with no CAD to mild CAD underwent REV (35). Our results further examine the impact of near- and long-term ICA use in this cohort with mild CAD. In this subset of patients with mild CAD, a novel finding reported herein noted that the adjusted odds of early ICA within 90 days was not statistically significant ($p = 0.18$). For longer term follow-up, however, the presence of mild CAD, in particular in the setting of a proximal lesion, increased the adjusted odds of a downstream ICA ($p < 0.0001$). It remains plausible that the CCTA findings of mild CAD might have increased the relative odds of undergoing ICA over the length of follow-up influencing the consideration on the part of physicians that disease progression may have occurred in these patients. Thus, it is likely that CCTA may increase longer term downstream costs for patients with mild CAD, and in particular for the cohorts with proximal, mild CAD. Further research is needed in this cohort to examine clinical strategies to optimize risk detection and target treatments for this cohort with nonobstructive CAD, and in particular to identify strategies curbing unnecessary downstream ICA use whenever possible.

Study limitations. We used several analyses to explore the consequences of reported overestimation of the percentage of stenosis by CCTA; but the observational nature of this registry causality cannot be determined. Detailed information on the target lesion or graft would aid in delineating the accuracy of CCTA to identify revascularizable disease. The role of nonobstructive atherosclerosis and progressive disease, as well as persistent or worsening symptoms, remains

unexplored in relation to the use of ICA and REV. Moreover, our database did not include the information on previous stress test results. The inclusion of stress testing results could have added further to our understanding of the role of anatomic and functional data in the decision to undergo ICA and REV. We included a nonrandom observational comparison of the effectiveness of ICA and REV in terms of survival reduction. This analysis should be viewed within the context of selection bias and other unadjusted factors that contribute to the reported findings. Importantly, this analysis is exploratory and should be viewed as such.

Conclusions

These data support the concept that CCTA may be used effectively as a gatekeeper to ICA. Patients with no or mild CAD were uncommonly referred to ICA, while in those with more extensive and severe obstructive CAD, a gradient increase in ICA and REV use was observed. Optimal targeting of high-risk patients with CAD based on CCTA may facilitate targeted intervention and improved outcome of patients undergoing a diagnostic workup for suspected CAD. The implications of CCTA as an effective gatekeeper is that direct referral for ICA may be circumvented in the large proportion of patients with no to mild CAD. However, it also appears from the CONFIRM data that further reductions in ICA use may be realized in patients with no to mild CAD who may be managed medically unless worsening clinical status ensues during follow-up. Strategies should be targeted to reduce ICA use in patients with nonobstructive CAD and to foster initial medical management approaches, with referral for ICA limited to patients with refractory symptoms.

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