Value of Coronary Computed Tomography as a Prognostic Tool

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PREVENTION

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ABSTRACT

Coronary computed tomography angiography (CCTA) has become an important part of our armamentarium for noninvasive diagnosis of coronary artery disease (CAD). Emerging technologies have produced lower radiation dose, improved spatial and temporal resolution, as well as information about coronary physiology. Although the prognostic role of coronary artery calcium scoring is known, similar evidence for CCTA has only recently emerged. Initial, small studies in various patient populations have indicated that CCTA-identified CAD may have a prognostic value. These findings were confirmed in a recent analysis of the international, prospective Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter (CONFIRM) registry. An incremental increase in mortality was found with a worse severity of CAD on a per-patient, per-vessel, and per-segment basis. In addition, age-, sex-, and ethnicity-based differences in mortality were also found. Whether changing our management algorithms based on these findings will affect outcomes is unclear. Large prospective studies utilizing targeted management strategies for obstructive and nonobstructive CAD are required to incorporate these recent findings into our daily practice.

Introduction

Coronary artery disease (CAD) is a significant cause of morbidity and mortality in the developed world,[1] and tremendous progress has been made in its diagnosis and treatment. Coronary computed tomography angiography (CCTA) is a rapidly evolving and commonly used noninvasive modality to detect CAD with a diagnostic accuracy comparable with that of other noninvasive diagnostic tests. Recent improvements in this technology have produced an improved accuracy with the benefit of decreased radiation exposure. Criticism of CCTA has been a notable absence of prognostic information compared with coronary artery calcium (CAC) scoring and stress tests. Newer publications have now documented the prognostic value of CCTA-detected CAD in several studies, ranging from small, single-center evaluations to a recent international, multicenter registry analysis. The purpose of this article is to discuss current literature on the role of CCTA as a prognostic tool, and to propose potential areas for additional research that need further clarification.

Coronary Artery Calcium Scoring: A Prognostic Tool

Traditionally, the Framingham risk score has been used to assess 10-year risk of suffering CAD-related events. However, only 65% to 80% of future events can be predicted with this, and many people will manifest an event despite being "low risk."[2] Consequently, clinicians and researchers have continued to look for better ways to risk-stratify patients, such as utilizing biomarkers (high-sensitivity C-reactive protein [hsCRP]) and imaging studies (CAC scoring and carotid intima-media thickness). Of these, CAC has been generally accepted by clinicians for risk stratification, with studies demonstrating its efficacy as a prognostic tool[3] as well as downstream cost-effectiveness.[4] Coronary artery calcium scoring has also been compared with the other prognostic methods mentioned above. A subanalysis of the Multi-Ethnic Study of Atherosclerosis (MESA) population meeting criteria for entry into the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial found that the presence of CAC was associated with an increased risk of CAD (hazard ratio [HR]: 4.29); a similar risk was not associated with hsCRP.[5] These findings were similar to other population-based studies, indicating that CAC may be a better predictor of risk than hsCRP. Similarly, another analysis of MESA indicated that CAC score may be a better predictor of CAD than carotid intima-media thickness (area under receiver operating characteristic [ROC] curve 0.81 vs 0.78, respectively).[6] Currently, American College of Cardiology Foundation/American Heart Association guidelines give CAC scoring a class IIa recommendation in asymptomatic adults at intermediate risk (10-year risk of 10%–20%) and a class IIb recommendation for adults at low to intermediate risk (10-year risk of 6%–10%), for further risk stratification.[7]

In symptomatic subjects without known CAD, a high CAC score may indicate a higher likelihood of underlying CAD

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as a cause of the symptoms. However, CCTA is more useful in this regard, as a low CAC score does not necessarily rule out CAD. In a recent analysis of the CONFIRM registry (n = 10 037), 13% and 3.5% patients with a CAC score of zero had nonobstructive and obstructive CAD, respectively.[8] This is explained by the fact that not all CAD is calcified, and calcification can occur rather late in the atherosclerotic paradigm in certain individuals, even with vulnerable plaques.[9] In contrast, coronary anatomy can be directly visualized with a high diagnostic accuracy utilizing CCTA. Thus, although CAC scoring may have a role in risk-stratifying asymptomatic patients, it is not nearly as helpful as CCTA in those with symptoms.

The Diagnostic Role of Coronary Computed Tomography Angiography

Coronary computed tomography angiography has rapidly evolved as an important diagnostic tool for patients with CAD in the outpatient as well as in-hospital setting (Figure 1). Over the previous decade, multiple studies have compared the diagnostic ability of CCTA with qualitative coronary angiography for the detection of CAD. A meta-analysis of small, retrospective studies using older-generation, ≥16-slice CCTA revealed a sensitivity of 96% and a specificity of 74% at the per-patient level.[10] However, many vessel segments were difficult to assess (~10%) with the older technology in these studies. Subsequent, multicenter studies utilizing ≥64-detector-row CCTA have confirmed its high sensitivity as well as negative predictive value to rule out obstructive CAD, with a specificity at par with other noninvasive tools.[11–13] When compared with native coronary vessels, the diagnostic accuracy of CCTA with arterial as well as venous bypass grafts is much higher, estimated to be 100% when compared with coronary angiography (Figure 2).[14] Its role in the emergency department (ED) is well known and was separately analyzed in the Rule Out Myocardial Infarction Using Computer-Assisted Tomography (ROMICAT) trial.[15] In 368 patients with acute chest pain, those without any CAD on CCTA had no acute coronary syndrome events during hospitalization or major adverse cardiac events (MACE) at 6 months. Ongoing advances in CT technology have led to newer technologies, such as high-definition[16] and 320-detector-row CT.[17] Additional technologies such as adenosine CT myocardial perfusion imaging (MPI)[18] and calculation of CT-derived fractional flow reserve[19] may make CCTA a front-line tool for detecting CAD by providing both anatomical as well as functional imaging utilizing a single test.

Prognosis by Coronary Computed Tomography Angiography

Initial Studies

In addition to helping the clinician with a diagnosis, CCTA also provides important prognostic information for mortality as well as cardiac events. Prior to the recent CONFIRM[20] analysis, studies assessing the prognostic value of CCTA-identified CAD were smaller, single-center studies (Table 1). Also, most of these studies (unlike the CONFIRM registry study) included revascularization as an outcome, which indicates the diagnostic capability of CCTA rather than a marker of poor prognosis. Several initial studies found an increased risk of cardiac events and death with CCTA-identified CAD.[21–23] Many of these were included in a recent meta-analysis that pooled results from 18 prospective and retrospective cohort studies utilizing different generations of CT scanners in subjects with suspected or known CAD (n = 9592).[24] Over a median follow-up period of 20 months, there were 449 MACE with 180 deaths, 56 myocardial infarctions (MI), and 213 revascularizations. The pooled annualized event rate in patients with a normal CCTA was very low for MACE (0.17%) as well as death/MI (0.15%). The rates increased incrementally when stratified by none, nonobstructive (<50%), and obstructive (>50%) CAD. Coronary computed tomography angiography-detected CAD has also been stratified utilizing the modified Duke CAD index, which integrates proximal CAD, plaque extent, and left-main disease. An analysis in >1000 patients found this useful to predict an incremental increase in mortality with higher indices.[25]

Assessment of Key Subgroups

The prognostic value of CCTA has been tested in several subgroups, such as asymptomatic patients, patients with diabetes, the coronary artery bypass graft population, and those with nonobstructive CAD. In asymptomatic patients (n = 451), CCTA could reclassify approximately 70% into an appropriate risk group.[26] Similarly, in diabetics without known CAD, CCTA-identified CAD burden score improved the prognostic value of conventional risk factors.[27] A recent study evaluated the prognostic value of CCTA in 250 patients who underwent coronary artery bypass graft surgery and were followed for 20 months.[28] There was an incremental increase in risk for death and nonfatal MI in patients with 0, 1, 2, or 3 unprotected coronary territories. The number of unprotected territories was an independent predictor of death/nonfatal MI in a multivariable model and improved the area under the ROC curve to 0.76 when compared with clinical characteristics alone (0.61; $P = 0.001$). Interestingly, in a 2-center, prospective evaluation of >2500 subjects, those with nonobstructive CAD (1%–49% stenosis) had a worse prognosis when compared with subjects with no CAD (HR: 1.98, $P = 0.03$).[29]

Patients With Acute Chest Pain

Patients who present acutely to the ED with chest pain can also be classified into prognostic groups based on CCTA findings. In a prospective analysis of 500 patients with a low Thrombolysis in Myocardial Infarction risk score presenting to the ED with chest pain, a negative CCTA was associated with a <1% risk of death or MI over a follow-up period of 1 year.[30] This study did not stratify patient risk based on increasing degrees of CAD or the presence of wall-motion abnormalities. A subsequent analysis of the ROMICAT trial followed low- to moderate-risk patients with acute chest pain and negative troponin/electrocardiogram who underwent CCTA.[31] Patients with no evidence of CAD on CCTA had a 0% 2-year rate of MACE (vs 20% in the nonobstructive CAD patients). On the other hand, if a functional defect

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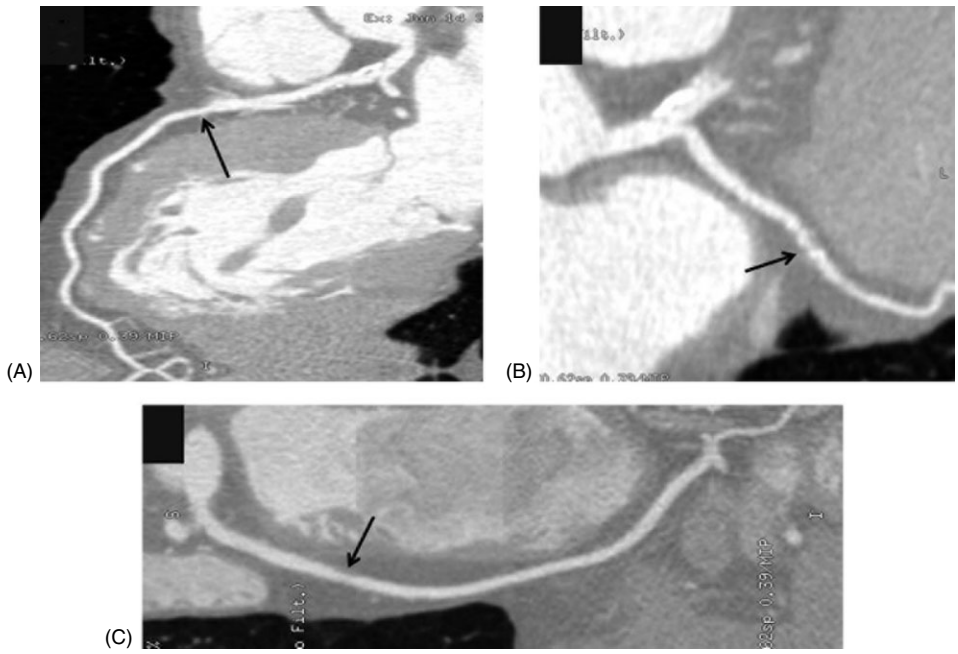

Figure 1. An example of CCTA: nonobstructive CAD (arrows) in the (A) LAD, (B) LCA, and (C) RCA. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; LAD, left anterior descending artery; LCA, left circumflex artery; RCA, right coronary artery.

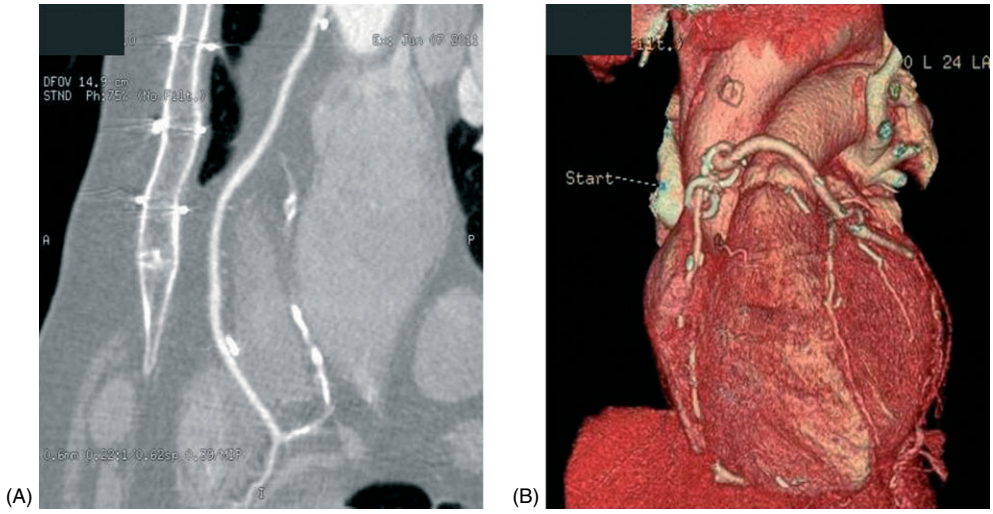

Figure 2. An example of CCTA evaluation in a CABG patient. (A) Patent LIMA to LAD. (B) Volume-rendered image demonstrating SVG grafts. Abbreviations: CCTA, coronary computed tomography angiography; CABG, coronary artery bypass graft; LAD, left anterior descending artery; LIMA, left internal mammary artery; SVG, saphenous vein grafts.

(regional wall-motion abnormality) was present along with obstructive CAD, there was a >92-fold increase in adjusted risk for MACE. Prediction of MACE improved from a C statistic of 0.61 with Thrombolysis in Myocardial Infarction risk score alone to 0.84 with addition of obstructive CAD and 0.91 with addition of both obstructive CAD and regional wall-motion abnormality.

Comparison With Other Modalities

Coronary computed tomography angiography has been compared as a prognostic tool with other noninvasive testing, such as nuclear myocardial perfusion imaging (MPI). Annual mortality rates were similar with CCTA-detected Duke CAD index and nuclear MPI-identified ischemia percentage ($P = 0.53$).[32] In fact, an incremental prognostic value was seen when CCTA-detected CAD was combined with MPI-identified ischemia[33] (Figure 3) or presence of left ventricular systolic dysfunction.[34,35] Whereas a similar incremental prognostic information was found by combining CCTA-detected CAD with CAC score in an earlier study,[36] a recent analysis of the CONFIRM registry revealed that the area under the ROC curve did not change significantly when combining CAC score to

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Table 1. Salient Studies Evaluating the Prognostic Value of Coronary Computed Tomography Angiography

No.	Study	Year	Type of Study	No. of Patients	Follow-up (mean)	Patient Population	CT Scanner	Outcomes Measured	Results
1	Pundziute et al[21]	2007	Prospective	100	16 mo	Suspected CAD	16- or 64-slice	Death, nonfatal MI, revascularization, UA readmission	Increased risk with obstructive and nonobstructive CAD
2	Hadamitzky et al[22]	2009	Prospective	1256	18 mo (median)	Suspected CAD	64-slice	Death, nonfatal MI, UA readmission	Higher risk with obstructive CAD; improved prediction than Framingham score
3	Min et al[23]	2010	Prospective	172	22 mo	Suspected or known CAD	64-slice	Death, nonfatal MI, revascularization, UA	Negative CCTA had 100% negative predictive value for events
4	Hulten et al[24]	2011	Meta-analysis	9592 (18 studies)	20 mo (median)	Suspected CAD	EBCT, 16- or 64-slice	Death, nonfatal MI, revascularization, UA readmission	Incrementally higher risk with higher-grade CAD
5	Min et al[25]	2007	Prospective	1127	15.3 mo	Suspected CAD	16-slice	Death	Increased mortality with obstructive CAD, higher-risk Duke scores and clinical plaque scores
6	Hadamitzky et al[26]	2010	Retrospective	451	27.5 mo	Asymptomatic patients	16- or 64-slice (SS or DS)	Death, nonfatal MI, unstable angina, late revascularization (>90 d)	Increased risk in obstructive CAD
7	Hadamitzky et al[27]	2010	Prospective	140	33 mo	Diabetic patients without known CAD	16- or 64-slice	Death, nonfatal MI, unstable angina	Increased risk with atherosclerotic burden; improved value of prognosis by conventional factors
8	Chow et al[28]	2011	Prospective	250	21 mo	CABG patients	64-slice	Death, nonfatal MI	Incremental risk with higher number of UCTs
9	Hollander et al[30]	2009	Prospective	481	1 y	Possible ACS in ED setting	64-slice	Death, nonfatal MI, revascularization	Very low risk of MACE in those with negative CCTA
10	Lin et al[29]	2011	Prospective	2583	3 y	Chest pain, nonobstructive CAD	64-slice	Death	Increased risk in nonobstructive CAD compared with no CAD
11	Schlett et al[31]	2011	Prospective	333	2 y	Possible ACS in ED setting	64-slice	Death, nonfatal MI, revascularization based on CT-detected CAD and RWMA	Incremental risk with CAD and RWMA
12	Min et al (CONFIRM investigators)[20]	2011	Prospective	23845	2.1 y (median)	Suspected CAD	≥64−slice	Death	Increased mortality with obstructive and nonobstructive CAD; differential risk based on age and sex

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry; CT, computed tomography; DS, dual source; EBCT, electron beam computed tomography; ED, emergency department; MACE, major adverse cardiac events; MI, myocardial infarction; RWMA, regional wall-motion abnormalities; SS, single source; UA, unstable angina; UCTs, unprotected coronary territories.

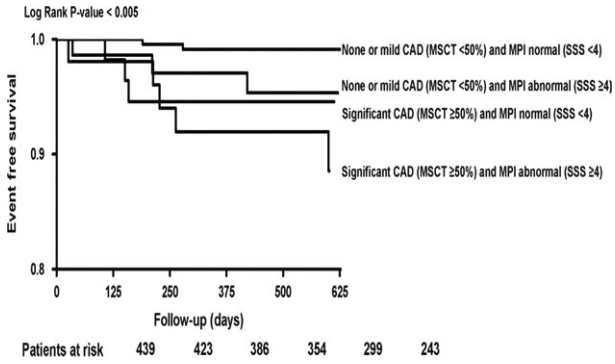

Figure 3. Kaplan-Meier curves for all-cause mortality and nonfatal infarction in patients with a normal or abnormal MPI and with or without CAD based on CCTA. Note the incremental prognostic value of abnormal CCTA when added to abnormal MPI findings. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; MPI, myocardial perfusion imaging; MSCT, multislice computed tomography coronary angiography; SSS, summed stress score. Reprinted from Journal of the American College of Cardiology, Volume 53, Issue 7, van Werkhoven et al, Prognostic value of multislice computed tomography in patients with sustected coronary artery disease, pages 623–632, Copyright (2009), with permission from Elsevier.

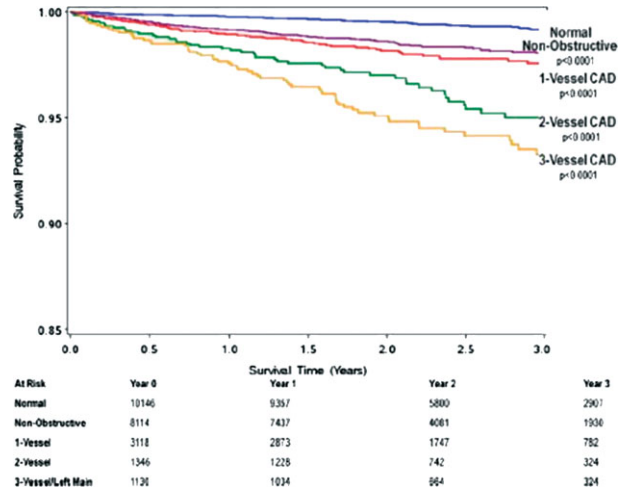

Figure 4. Unadjusted all-cause 3-year Kaplan-Meier survival by the presence, extent, and severity of CAD by CCTA in the CONFIRM registry. There was an incrementally worse prognosis with the number of vessels involved. Note the increased mortality with nonobstructive CAD when compared with those with no CAD. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CONFIRM, Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry. Reprinted from Journal of the American College of Cardiology, Volume 58, Issue 8, Min et al, Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings: results from the international multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23 854 patients without known coronary artery disease, pages 849–860, Copyright (2011), with permission from Elsevier.

CCTA-detected CAD (0.825 for CCTA alone and 0.826 for CCTA and CAC; $P = 0.84$).[8]

The CONFIRM Registry

The CONFIRM registry enrolled patients age ≥18 years with suspected CAD who underwent a ≥64-detector-row CCTA. This registry included ≥20000 patients from 12 centers across North America, Europe, and Asia, and was the first international, multicenter, prospective database evaluating the prognostic role of CCTA. In an initial analysis of subjects without known CAD from this registry (n = 2 3854), patients with both obstructive CAD (HR: 1.60, confidence interval [CI]: 1.18–2.16, $P < 0.001$) as well as nonobstructive CAD (HR: 2.60, CI: 1.94–3.49, $P = 0.0023$) were found to have an increased risk of mortality over a median follow-up of 2.3 years.[20] Unlike many prior studies evaluating the prognostic role of CCTA, revascularization was not included as an outcome, confirming that this tool can predict mortality alone. On a per-vessel analysis (Figure 4), mortality associated with nonobstructive CAD (HR: 1.62, CI: 1.20-2.19, $P = 0.0018$) was similar to that with 1-vessel obstructive CAD (HR: 2.00, CI: 1.43-2.82, $P < 0.001$), which confirmed prior findings from a smaller study.[29] This is clinically important, because CCTA now identifies a unique subset of patients with symptoms and risk factors who will have negative stress-MPI studies (similar to the "true normal" population without any CAD) but have a worse intermediate-term outcome. This study was well-powered to subanalyze subjects based on age and sex ($\beta > 0.90$, $\alpha < 0.001$). Interestingly, mortality in subjects with nonobstructive CAD was statistically significant only in subjects age <65 years and females. An increased all-cause mortality and better CAD risk-factor management in those age ≥65 years as well as males may be responsible for this difference. With normal subjects within each subgroup as a reference, subjects age <65 years with 2-vessel (HR: 4.00, CI: 2.16-7.40, $P < 0.001$) and 3-vessel/left-main (HR: 6.19, CI: 3.43-11.2, $P < 0.001$) obstructive CAD did worse than those age ≥65 years with similar disease (HR: 2.46 and 3.10 for 2- and 3-vessel/left-main disease, respectively). The authors hypothesize that younger subjects with 2- and 3-vessel disease have a more aggressive form of CAD. Similarly, females with 3-vessel/left-main disease (HR: 4.21) did worse than males (HR: 3.27) for unclear reasons. This study also substantiated the "warranty period" for a negative CCTA. In subjects without CCTA-detected CAD and ≥4 years of follow-up (n = 1089), the mortality rate was only 0.22%, indicating a minimum of a 4-year warranty period with a negative CCTA. This conclusion will need more study because this was based on a small percentage of the total study cohort.

Recently, additional analyses from the CONFIRM registry were presented at the American Heart Association 2011 Scientific Sessions.[37] Contrary to findings from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[38] and Bypass Angioplasty Revascularization Investigation With Diabetes (BARI 2D)[39] trials, subjects with stable, high-risk CAD (≥2 vessels with ≥70% stenosis and proximal left anterior descending artery involvement, 3-vessel CAD of ≥50% left-main stenosis) who underwent revascularization had an increased survival. In a separate analysis of ~15 000 patients from CONFIRM, older women had a high risk of MACE when compared with younger women and men (HR: 1.04, $P = 0.04$). Women had a smaller chance of high-risk, obstructive CAD, and hence were less likely to undergo early revascularization (within

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3 months of CCTA). However, among patients who did, the outcomes were worse for women than for men (HR for MACE/mortality: 1.9, $P = 0.006$). This finding was similar to the earlier CONFIRM analysis, where women with 3-vessel disease did worse. Finally, in an ethnicity-based analysis, the HR for death or MI with obstructive vs nonobstructive CAD was higher among Africans (HR: 4.06) when compared with whites (HR: 2.71). The risk was highest with East Asians (HR: 6.8), but the absolute event rates were lowest in this population.

Future Directions

Coronary computed tomography angiography is now an important, noninvasive tool in the evaluation of CAD. Coronary computed tomography angiography-detected CAD has important prognostic implications, but there are questions, outlined below, that remain unanswered. We also propose future research studies to answer these questions, which, while being difficult to perform, will help clinicians make important decisions in the diagnosis and management of CAD.

1. Will the prognostic value of CCTA-detected CAD change significantly with emerging technologies? Newer technologies such as dual-energy CT imaging and 320-detector-row CT will allow for more advanced assessment of CAD. Similarly, functional testing can also be added to anatomic evaluation of coronaries. Higher-risk subgroups may be identified within nonobstructive as well as obstructive CAD groups.
2. Coronary artery calcium vs CCTA: Which is better? The radiation exposure with newer-technology CCTA continues to decrease, allowing for an increased amount of valuable anatomical, functional, and prognostic information with radiation exposure that in many cases is lower than achieved by invasive coronary angiography. Head-to-head comparison of these 2 modalities utilizing a composite variable of cost, radiation exposure, and clinical benefit is not currently available.
3. Can CONFIRM findings be incorporated into our daily clinical practice to intensify risk-factor management or recommend revascularization?
    a. Nonobstructive CAD: These are the patients who would otherwise be classified as "normal" with nuclear MPI. Large, prospective studies are needed to evaluate if intensive risk-factor management in this cohort will change clinical outcomes.
    b. Obstructive CAD: This can be subclassified in different ways: 50%, or >70%, in 1, 2, or 3 vessels, with 0 to 16 segments and stenosis scores of 0 to 48. Each of these increasing degrees of CAD is associated with a higher risk of mortality and MI. It is suggested that stable, high-risk CAD may benefit from revascularization rather than medical therapy. Similar to an ongoing study utilizing stress testing,[40] randomized and prospective evaluation of the benefit with revascularization in such populations is required.
4. The age and sex conundrum: Should younger individuals and females with nonobstructive and high-grade CAD be treated differently than their counterparts with similar disease? This needs further exploration and clarification.
5. Finally, what about ethnicity? High-risk groups have been identified, and this may need to be incorporated into our risk-management algorithm.

Conclusion/Clinical Perspectives

- Coronary computed tomography angiography is an important, rapidly evolving diagnostic as well as prognostic tool for CAD.
- The prognostic value of CCTA was based on small, single-center studies. However, recent findings from the large, multicenter, and prospective CONFIRM registry has confirmed the prognostic significance of CCTA-detected CAD.
- A worse prognosis was seen with increasing grades of obstructive CAD.
- Surprisingly, nonobstructive CAD, younger age, female sex, and certain ethnic groups also portended a worse prognosis.
- A major limitation of all studies evaluating the prognostic role of CCTA is the lack of data on whether changing management strategies based on these findings will affect outcomes. Prospective, randomized, algorithm-based studies utilizing CCTA data are required to clarify this.

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