Cardiovascular Risk among Stable Individuals Suspected of Having Coronary Artery Disease with No Modifiable Risk Factors: Results from an International Multicenter Study of 5262 Patients[1]

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Purpose: To assess the prevalence, extent, severity, and risk of coronary artery disease (CAD) in patients suspected of having CAD but with no medically modifiable risk factors.

Materials and Methods: Institutional review board approval or waiver of consent was obtained at each center. This study was HIPAA compliant. From an international multicenter cohort study of 27 125 subjects undergoing coronary computed tomographic (CT) angiography from 12 centers, 5262 patients without known CAD and without modifiable risk factors were identified. CAD severity was defined as none (0%), mild (1%–49%), or obstructive (≥50%) on a per-patient, per-vessel, and per-segment basis. CAD presence, extent, and severity were related to incidence of major adverse cardiovascular event (MACE) by using Cox proportional hazards models.

Results: At a mean follow-up of 2.3 years ± 1.2 (standard deviation), MACE occurred in 106 patients. CAD was common for nonobstructive (n = 1452, 27%) and obstructive (n = 629, 12%) CAD. In risk-adjusted analysis, per-patient obstructive CAD (hazard ratio [HR], 6.64; 95% confidence interval [CI]: 3.68, 12.00; $P \leq .001$) was related to MACE. MACE was associated with a dose-response relationship to the number of vessels exhibiting obstructive CAD, increasing risk for obstructive one-vessel (HR, 6.11; 95% CI: 3.22, 11.6; $P \leq .001$), two-vessel (HR, 5.86; 95% CI: 2.75, 12.5; $P \leq .0001$), or three-vessel or left main (HR, 11.69; 95% CI: 5.38, 25.4; $P \leq .001$) CAD. The increased hazard for MACE of obstructive disease holds true for symptomatic (HR, 11.9; 95% CI: 4.81, 29.6; $P \leq .001$) and asymptomatic (HR, 6.3; 95% CI: 2.4, 16.7; $P \leq .001$) patients. No CAD at coronary CT angiography was associated with a low annualized MACE rate: 0.31% versus 2.06% with obstructive disease.

Conclusion: Among individuals suspected of having CAD but without modifiable risk factors, CAD is common, with significantly increased hazards for MACE and mortality.

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Coronary computed tomographic (CT) angiography has emerged as a highly accurate (1–3) and prognostically (4) useful noninvasive anatomic test for the diagnosis or exclusion of coronary artery disease (CAD). The prognostic value of both nonobstructive and obstructive CAD at coronary CT angiography has been documented in numerous patient cohorts, including for men, women, and those with diabetes mellitus and after revascularization and across multiple ethnicities (5,6).

At present, appropriate referral to noninvasive testing for individuals suspected of having CAD relies, in part, on clinical CAD risk factor scoring, with individuals free of any identifiable CAD risk factor generally considered to be at low risk for major adverse cardiovascular events (MACEs). To date, the prevalence of CAD and the additive prognostic value of CAD detected by using coronary CT angiography in individuals with no medically modifiable CAD risk factors are currently not known.

We sought, in this subanalysis of a prospective multicenter international observational cohort study, to assess the prevalence, extent, severity, and risk of CAD in patients suspected of having CAD but with no medically modifiable risk factors.

Advances in Knowledge

- Among stable individuals suspected of having coronary artery disease (CAD) without medically modifiable CAD risk factors, the presence of both nonobstructive and obstructive CAD is common.
- In patients without medically modifiable risk factors, the presence of increasing burden of CAD was predictive of major adverse cardiovascular events (MACEs) at the per-patient, per-vessel, and per-segment level across varying symptom and family history status.
- A relationship of increased CAD burden to all individual "hard" end-point components of MACE, including death, myocardial infarction, and late target vessel revascularization, is present.

Materials and Methods

Patients

The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry is an ongoing, prospective, international, multicenter observational cohort study designed to evaluate the relationship of coronary atherosclerosis and clinical risk factors to adverse outcomes among patients who have undergone at least 64-section coronary CT angiography for clinically referred indications. The registry has received institutional ethics board approval at all participating sites and is Health Insurance Portability and Accountability Act compliant. The rationale and design of the COMFIRM registry have been previously reported (7). Relevant to the present study, this study examined individuals from phase 1 of the CONFIRM study, which enrolled 27 125 individuals at 12 cluster sites in six countries in North America, Europe, and Asia. CONFIRM investigators or research nurses performed prospective ascertainment of baseline demographics and CAD risk factors, with relation of such clinical findings to incident risk of adverse CAD events stratified according to coronary CT angiographic findings of CAD. For the purpose of our analysis, all patients with known medically modifiable CAD risk factors—inclusive of diabetes mellitus, hypertension, dyslipidemia, and smoking—were excluded from analysis. Patients assessed were referred for the exclusion of CAD on the basis of the presence of symptoms or clinical concern often due to the presence of a family history of CAD.

Implication for Patient Care

- Coronary CT angiography allows for the identification of those at risk among patients without medically modifiable risk factors in a fashion not previously possible with traditional risk stratification tools alone.

Diabetes mellitus was defined as a fasting glucose level of 126 mg/dL (6.99 mmol/L) or higher and/or use of antidiabetic treatment. Hypertension was defined by a systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher and/or use of antihypertensive medication. Dyslipidemia was defined as a total cholesterol level of 200 mg/dL (5.18 mmol/L) or higher or use of antilipidemic medication. Patients were considered smokers for current smokers or individuals who quit smoking within 3 months of the coronary CT angiographic examination. Family history was not included as a risk factor because it is not modifiable. Prior known CAD was defined by previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass surgery; these individuals were excluded from analysis.

Chest Pain Categorization

Chest pain was categorized according to the classic criteria for angina pectoris (8,9). At each site, symptom category was prospectively ascertained through written questionnaire or interview by a physician or allied health professional. Patients with typical angina experienced substernal, jaw, and/or arm pressure-like pain that consistently occurred

Published online before print
10.1148/radiol.13121669 **Content code:** CA

Radiology 2013; 267:718–726

Abbreviations:
CAD = coronary artery disease
HR = hazard ratio
MACE = major adverse cardiovascular event

Author contributions:
Guarantor of integrity of entire study, J.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, J.L., C.M.T., B.G.H., F.C., R.C., G.F., P.A.K., E.M.; clinical studies, J.L., B.G.H., M.A.M., D.S.B., M.J.B., F.C., T.Q.C., H.J.C., J.H., R.C., G.F., Y.J.K., P.A.K., E.M., G.R., T.C.V., J.K.M.; statistical analysis, J.L., G.G., T.Q.C., L.J.S., J.K.M.; and manuscript editing, J.L., C.M.T., G.G., B.G.H., G.B.J.M., S.A., M.A.M., D.S.B., M.J.B., F.C., H.J.C., V.Y.C., K.C., B.J.W.C., J.H., R.C., G.F., P.A.K., E.M., L.J.S., T.C.V.

Conflicts of interest are listed at the end of this article.

with exertion and consistently resolved within 15 minutes of rest and/or use of nitroglycerin. Patients with atypical angina experienced two of these characteristics. Patients with nonanginal chest pain experienced one or none of these characteristics. Asymptomatic patients had no chest pain or angina equivalents.

Determining Expected Probability of Angiographically Significant CAD

Age, sex, and angina typicality for each patient was used to determine the expected probability of CAD with 50% or greater luminal diameter stenosis by the Diamond-Forrester tabular method (8), as recommended by the American College of Cardiology/American Heart Association clinical practice guidelines for treatment of patients with stable angina (9) (Table 1). Patients aged 69 years or older whose pretest probability could not be established from guideline probabilities were assigned the pretest probability for the corresponding 60- to 69-year-old group.

Coronary CT Angiography

Coronary CT angiography was performed by using a single- or dual-source 64-section (or higher) CT scanner according to Society of Cardiovascular Computed Tomography guidelines by level 3–equivalent imagers who had performed and interpreted results of several thousand coronary CT angiographic examinations, as previously described (10,11). Interpretation of coronary CT angiographic results was uniform across all study sites, with coronary segments visually scored for the presence of coronary plaque by using a 16-segment coronary artery model in an intent-to-diagnose fashion with all readers meeting level 3 certification or country equivalent (12) (J.L., 8 years of experience; M.A.M., 8 years of experience; D.S.B., 12 years of experience; M.J.B., 15 years of experience; F.C., 9 years of experience; T.Q.C., 12 years of experience; V.Y.C., 9 years of experience; A.D., 11 years of experience; B.J.W.C., 9 years of experience; M.H., 8 years of experience; J.H., 9 years of experience; G.F., 9 years of experience; R.C., 10 years of experience; T.C.V., 9 years of experience; K.C., 7 years of experience; G.R., 9 years of experience). In each coronary artery segment, coronary atherosclerosis was defined as tissue structures 1 mm^2 or greater that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue or epicardial fat; or, the percentage of obstruction of the coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. In instances in which plaque was highly calcified, two-dimensional oblique images were also visualized without maximal intensity projection (ie, 0.625- to 0.75-mm isotropic voxel resolution) or multiplanar reformations with cross-sectional views to minimize partial volume averaging artifact of calcium.

Plaque severity was graded on a per-patient, per-vessel, and per-segment level. Coronary atherosclerotic lesions were graded as normal (no atherosclerosis), mild (1%–49% stenosis), or obstructive (≥50% stenosis) in epicardial coronary arteries of at least 2 mm in diameter. Per-patient maximal plaque severity was defined by the maximal luminal stenosis in any of the coronary segments at the 50% or greater stenosis threshold on the basis of the most severe apparent stenosis. For purposes of classification of CAD for per-vessel analyses, we considered four arterial territories: left main artery, left anterior descending artery, left circumflex artery, and right coronary artery. Obstructive CAD in the diagonal branches, obtuse marginal branches, and posterolateral branches was considered part of the left anterior descending artery, left circumflex artery, and right coronary artery system, respectively. The posterior descending artery was considered part of the right coronary artery or left circumflex artery system, depending on the coronary artery dominance. A 50% or greater stenosis of any major epicardial coronary vessel was considered obstructive in all models. If a segment was considered nonevaluable, it was excluded from analysis, but if a single segment of a coronary artery displayed obstructive disease, then the artery was deemed to have obstructive disease on a per-vessel basis. Per-vessel CAD severity was scored as involving no, one, two, or three coronary artery territories. Per-segment analysis was judged for individual coronary artery segments by using a 16-segment model (12).

Outcomes

The primary end point was time to MACE, which was defined as death, nonfatal myocardial infarction, unstable angina, and late target vessel revascularization (>90 days). Death status was ascertained either by query of the Social Security Death Index or by scripted interview by experienced physician and/or nurse study investigators. Occurrence of myocardial infarction, unstable angina, and late target vessel revascularization for all centers was gathered according to clinical visits, telephone contacts, or questionnaires sent by mail, with verification of all reported events by hospital records or direct contact with a patient's attending physician.

Statistical Analysis

Software (SPSS, version 12.0, SPSS, Chicago, Ill; SAS, version 9.2, SAS Institute, Cary, NC) was used for all statistical analyses. Categorical variables were presented as frequencies, and continuous variables were presented as means ± standard deviations. Variables were compared with the χ^2 statistic for categorical variables and with the unpaired Student t test for continuous variables. Time to MACE and death were calculated by using univariable Cox proportional hazards models. In each case, the proportional hazards assumption was met. Adjusted models were also devised, including multivariable stepwise models adjusting for baseline demographics, CAD risk factors, and pretest likelihood of obstructive CAD. Adjusted models included testing for first-order interactions related to age and sex. A hazard ratio (HR) and 95% confidence interval were calculated from Cox models, with a two-tailed P value of .05 or less considered to indicate statistically significant difference. The MACE-free survival among stenosis groups was visualized by using

Table 1

Pretest Probabilities of 50% or Greater Diameter Stenotic CAD in Patients with Chest Pain

	Nonanginal Chest Pain (%)		Atypical Angina (%)		Typical Angina (%)	
Age (y)	Men	Women	Men	Women	Men	Women
30–39	4	2	34	12	76	26
40–49	13	3	51	22	87	55
50–59	20	7	65	31	93	73
60–69	27	14	72	51	94	86

Note.—Data are as shown in the American College of Cardiology/American Heart Association guidelines for management of chronic stable angina.

Table 2

Baseline Clinical and CAD Characteristics of the Study Population

Characteristic	Datum
Age (y)*	53.5 ± 11.6
Probability density function*	0.29 ± 0.28
Male patients	2912 (55.2)
Chest pain typicality	
Typical	449 (10.99)
Atypical	1663 (40.69)
Noncardiac	492 (12.04)
Asymptomatic	1483 (36.29)
Pretest CAD likelihood	
Low	1498 (36.65)
Intermediate	2396 (58.62)
High	193 (4.72)

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

* Data are means ± standard deviations.

Table 3

Clinical Characteristics Associated with CAD and MACE

Characteristic	No MACE ($n = 5178$)	MACE ($n = 106$)	*P* Value for Trend
Age (y)*	52.9 ± 13.1	66.4 ± 13.6	<.0001
Probability density function*	0.28 ± 0.27	0.37 ± 0.33	.03
Male patients	2853 (55.1)	59 (55.66)	.92
Pretest CAD likelihood			<.0001
Low	1479 (36.89)	19 (24.36)	
Intermediate	2351 (58.64)	45 (57.69)	
High	179 (4.46)	14 (17.95)	

Note.—Unless otherwise indicated, data are numbers of patients, with percentages in parentheses.

* Data are means ± standard deviations.

Kaplan-Meier survival curves and compared by using the log-rank test.

The power analysis for Cox regression (106 events, n = 5284) with two-sided t test and α .05 significance level and R^2 correlation of covariates of 0.2 and standard deviation 0.5 achieves 80% and 90% power to detect a minimum HR of 1.8 and 2.0, respectively. Thus, under the same assumptions, it was 100% powered to detect observed HRs of 6.64 and 12.42.

Results

Study Population

Among 27125 consecutive individuals undergoing coronary CT angiography at 12 centers for whom per-segment CAD data were available, 2350 individuals with a history of myocardial infarction, target vessel revascularization, and cardiac transplant were excluded. An additional 19491 individuals had a medically modifiable CAD risk factor and were excluded from the current analysis (hypertension, 11860; dyslipidemia, 4822; diabetes mellitus, 3514; smoking, 4526). The final study cohort consisted of 5284 individuals. Complete follow-up was available in 5262 (99.6%), with 22 individuals lost to follow-up. The study cohort was middle-aged (mean age, 53.5 years ± 11.6; 55.2% male patients), with a 12% prevalence of obstructive CAD (Table 2). The majority of study individuals presented with low or intermediate pretest likelihood of obstructive CAD (6).

Clinical Characteristics Associated with CAD and MACE

Clinical outcomes of MACE and mortality were examined after a mean follow-up of 2.3 years ± 1.2 (median, 2.1 years; interquartile range, 1.4–3.2 years), at which point 106 MACEs and 62 deaths were recorded. Presence of MACE was associated with increased patient age, greater angina typicality, and pretest likelihood of CAD (Table 3). No CAD at coronary CT angiography was associated with a low annualized MACE rate: 0.31% versus 2.06% with obstructive disease.

Effect of per-Patient, per-Vessel, and per-Segment CAD at Coronary CT Angiography on MACE

For both univariable and multivariable Cox regression analysis considering age and sex, time to MACE was predicted by maximal per-patient obstructive CAD (Fig 1, Table 4). Similarly, per-vessel assessment of the extent of obstructive CAD demonstrated a dose-response relationship for increased hazards for MACE for one-vessel, two-vessel, and three-vessel or left main CAD ($P < .001$ for all) (Fig 2, Table 4). Individuals who developed MACE had a greater number of coronary segments with obstructive CAD than individuals who did not experience MACE (Table 5). Individuals who died within the cohort were more likely to have proximal coronary artery stenosis, as well as mid left anterior descending and mid right coronary artery stenosis. Obstructive disease in all coronary

Figure 1

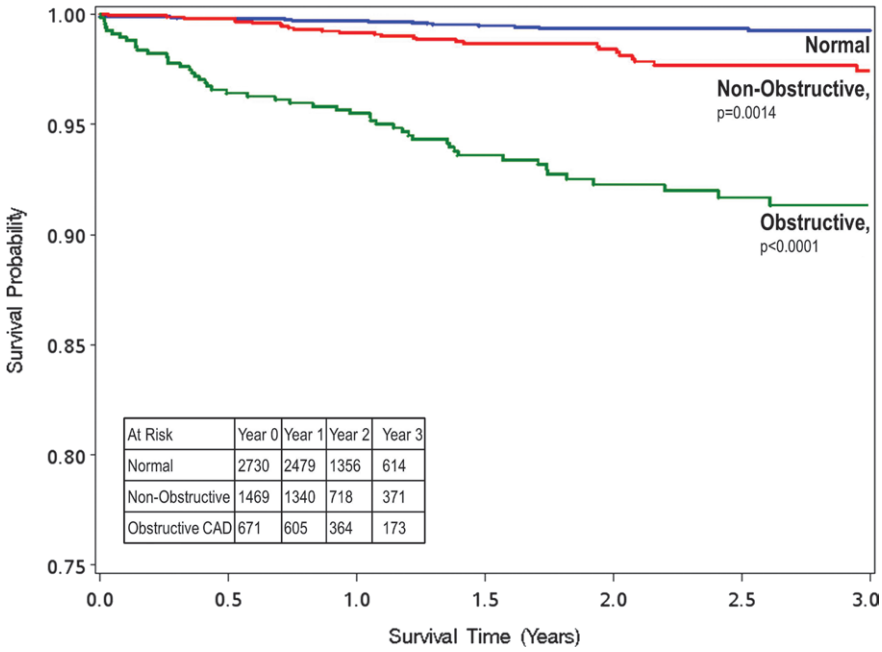

Figure 1: Unadjusted Kaplan-Meier curve for MACE-free survival on the basis of the presence of no, nonobstructive, and obstructive CAD for individuals without modifiable CAD risk factors (*P* values based on log-rank tests).

Table 4

Relative Risk of MACE Stratified by Presence and Extent of CAD on a per-Patient and per-Vessel Basis

Coronary CT Angiography Result	Univariable HR*	*P* Value	Risk-Adjusted HR*	*P* Value
Per-patient CAD (maximal stenosis severity)				
Normal	1	Reference	1	Reference
Nonobstructive	2.67 (1.47, 4.88)	.0014	1.74 (0.93, 3.26)	.0821
Obstructive CAD	12.42 (7.29, 21.2)	<.0001	6.64 (3.68, 12.0)	<.0001
Per-vessel CAD				
Normal	1	Reference	1	Reference
One-vessel obstructive	9.99 (5.48, 18.2)	<.0001	6.11 (3.22, 11.6)	<.0001
Two-vessel obstructive	11.54 (5.74, 23.2)	<.0001	5.86 (2.75, 12.5)	<.0001
Three-vessel or left main	25.55 (12.7, 51.4)	<.0001	11.69 (5.38, 25.4)	<.0001

Note.—Obstructive CAD is defined at the 50% level.

* Data in parentheses are 95% confidence intervals.

segments was predictive of MACE ($P <$ .001 for all).

Coronary CT angiography–identified CAD was related to individual components of MACE, including myocardial infarction and target vessel revascularization, with a dose-response relationship of CAD severity observed in relation to incidence of adverse event for nonobstructive and obstructive CAD (Table 5).

Relationship of CAD to Incidence of MACE Stratified by Symptom Status

Rates of incidence of MACE in accordance to symptoms are delineated in Table 6. While obstructive CAD was associated with incidence of MACE in both symptomatic and asymptomatic individuals, nonobstructive CAD was associated with incidence of MACE in only symptomatic individuals and not asymptomatic individuals.

Prevalence and Relationship of CAD to Incidence of MACE Stratified by Family History

The prevalence of nonobstructive disease was not significantly different in those patients with and those without a family history of CAD; however, obstructive disease was documented more frequently in those with a family history of premature CAD ($P <$ .001) (Table 7).

Rates of incidence of MACE in accordance to the presence or absence of a family history of CAD are presented in Table 8. Obstructive CAD was associated with increased hazard for MACE in both groups; however, nonobstructive disease was only predictive in those with a family history of premature CAD.

Discussion

In this prospective multicenter international study of 5262 individuals suspected of having CAD but with no medically modifiable CAD risk factors, we identified a high prevalence of nonobstructive and obstructive CAD. The presence of increasing burden of CAD was predictive of MACE at the per-patient, per-vessel, and per-segment level across varying symptom and family history status, with differential risk observed in accordance to pretest likelihood of CAD as well as older age. Notably, we observed a relationship of increased CAD burden to all individual "hard" endpoint components of MACE, including death, myocardial infarction, and late target vessel revascularization. In contrast, the absence of CAD at coronary CT angiography was associated with a very low risk of MACE, irrespective of pretest likelihood of CAD and age.

At present, societal guidance documents generally do not support imaging testing for individuals who are at low risk for obstructive CAD and incidence

of MACE, as determined by the Diamond-Forrester method and clinical scoring by presence of CAD risk factors, respectively. Among asymptomatic individuals, Yusuf et al (13) identified eight risk factors whose presence was associated with 90% of the population-attributable risk of incidence of myocardial infarction. Our study extended these important findings by examining a patient cohort of stable individuals suspected of having CAD, which revealed that CAD prevalence is fairly high despite the absence of traditional modifiable cardiovascular risk factors. In addition, the extent and severity of CAD at coronary CT angiography may nevertheless be associated with greater MACE risk. Given the large prospective nature derived from a contemporary cohort of individuals identified in multiple countries, the findings of this study should be considered widely generalizable. It is important, however, to recognize that our data emanate from a real-world cardiac registry that reflects current clinical practice with a proportion of patients undergoing cardiac CT for whom there would be no guideline support. Our data are not intended to suggest modification of current appropriate use criteria but to simply provide an understanding of the prevalence of disease and its prognostic value in this unique patient population. At present, no clinical risk score exists to help guide clinicians as to the risk of incidence of MACE in stable patients suspected of having CAD. Consequently, clinicians have relied on pretest likelihood algorithms for prediction of obstructive CAD as a surrogate for identifying individuals at heightened MACE risk. In this study, we identified a greater risk of MACE in individuals with higher pretest likelihood of CAD, suggesting that these Bayesian methods are useful for identifying individuals who may benefit most from further imaging testing. Nevertheless, we observed a nonnegligible prevalence of nonobstructive and obstructive CAD even in stable patients with low pretest likelihoods of CAD, a finding that was associated with increased risk of MACE. The findings advocate for more refined tools to identify individuals who require further assessment and who may benefit from anatomic determination of CAD.

Table 5

Incidence of Event according to No Atherosclerosis, Nonobstructive CAD, and Obstructive CAD

Event	Normal (n = 2740)	Nonobstructive (n = 1486)	Obstructive CAD (n = 675)	P Value for Trend
Death	12 (0.44)	2 (0.13)	30 (4.45)	<.001
Myocardial infarction	1 (0.04)	2 (0.13)	5 (0.74)	<.001
Late revascularization	1 (0.04)	4 (0.27)	19 (2.81)	<.001

Note.—Data are numbers of patients, with percentages in parentheses.

Figure 2

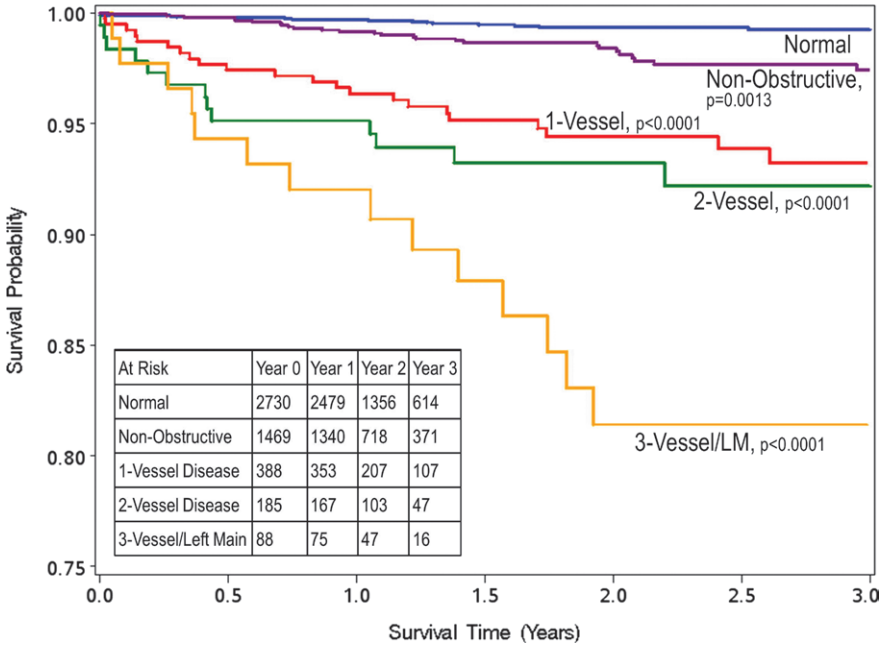

Figure 2: Unadjusted Kaplan-Meier curve for MACE-free survival on the basis of the presence of no plaque, nonobstructive atherosclerosis, and obstructive one-, two-, and three-vessel CAD for individuals without modifiable CAD risk factors (P values based on log-rank tests).

Integrated clinical risk scores derived from population-based studies whose individual components are composed of traditional CAD factors are commonly used in clinical practice to assess risk. These scores categorize individuals as low, intermediate, and high risk and include the Framingham risk score, the Reynolds risk score, the European System for Cardiac Operative Risk Evaluation, and the National Cholesterol Education Program Adult Treatment Panel III methods. While intended to be applied to an asymptomatic patient population to predict long-term risk of CAD events, clinicians have adopted the use of these scores and/or their CAD risk components as an adjunct to pretest CAD likelihood determination in an attempt to enhance the identification of individuals with higher risk of obstructive CAD and MACE. Nevertheless, the utility of each of these scores is rooted in the identification of traditional CAD risk factors to define individuals who have a greater prevalence of CAD and

Table 6

Relative Risk of MACE Stratified by Symptom Status and Presence and Extent of CAD on a per-Patient and per-Vessel Basis

	Asymptomatic Patients				Symptomatic Patients			
CAD	Univariable HR*	*P* Value	Risk-Adjusted HR*	*P* Value	Univariable HR*	*P* Value	Risk-Adjusted HR*	*P* Value
Per-patient analysis								
Normal	1	Reference	1	Reference	1	Reference	1	Reference
Nonobstructive	1.9 (0.7, 5.3)	.2088	1.34 (0.5, 3.8)	.59	5.1 (2.0, 12.9)	.0007	3.2 (1.2, 8.4)	.0201
Obstructive CAD	10.37 (4.2, 25.4)	<.0001	6.3 (2.4, 16.7)	.0002	22.6 (9.9, 51.8)	<.0001	11.9 (4.8, 29.6)	<.0001
Per-vessel analysis								
Normal	1	Reference	1	Reference	1	Reference	1	Reference
Nonobstructive	1.9 (0.70, 5.3)	.2088	1.4 (0.5, 3.9)	.5626	5.1 (2.0, 12.9)	.0007	3.3 (1.3, 8.8)	.0164
One-vessel obstructive	7.3 (2.6, 20.8)	.0002	5.0 (1.7, 15.0)	.0043	19.1 (7.8, 46.8)	<.0001	11.2 (4.3, 29.1)	<.0001
Two-vessel obstructive	12.0 (3.5, 41.1)	<.0001	7.2 (1.9, 26.8)	.0032	21.5 (7.5, 61.6)	<.0001	12.0 (3.9, 37.0)	<.0001
Three-vessel or left main	22.4 (5.8, 86.6)	<.0001	11.2 (2.6, 47.7)	.0011	58.5 (19.6, 174.7)	<.0001	24.6 (7.3, 83.4)	<.0001

* Data in parentheses are 95% confidence intervals.

Table 8

Relative Risk of MACE Stratified by Family History of Premature CAD and Extent of CAD on a per-Patient and per-Vessel Basis

	No Family History				Family History of CAD			
CAD	Univariable HR*	*P* Value	Risk-Adjusted HR*	*P* Value	Univariable HR*	*P* Value	Risk-Adjusted HR*	*P* Value
Per-patient analysis								
Normal	1	Reference	1	Reference	1	Reference	1	Reference
Nonobstructive	1.8 (0.9, 3.7)	.1031	1.2 (0.6, 2.5)	.6191	6.4 (1.8, 23.2)	.0048	4.6 (1.2, 17.8)	.0281
Obstructive CAD	12.9 (7.1, 23.2)	<.0001	7.2 (3.7, 13.8)	<.0001	13.7 (3.9, 48.2)	<.0001	8.0 (2.0, 31.9)	.003
Per-vessel analysis								
Normal	1	Reference	1	Reference	1	Reference	1	Reference
Nonobstructive	1.8 (0.9, 3.7)	.1031	1.2 (0.6, 2.6)	.5976	6.4 (1.8, 23.2)	.0048	4.9 (1.3, 19.2)	.0219
One-vessel obstructive	11.0 (5.7, 21.2)	<.0001	6.8 (3.4, 13.9)	<.0001	7.5 (1.7, 33.7)	.0082	5.2 (1.1, 24.9)	.0409
Two-vessel obstructive	10.0 (4.3, 23.7)	<.0001	5.1 (2.0, 12.8)	.0006	20.7 (5.2, 82.7)	<.0001	13.0 (2.8, 60.1)	.001
Three-vessel or left main	26.4 (12.1, 57.7)	<.0001	12.7 (5.4, 30.1)	<.0001	26.5 (5.4, 131.4)	<.0001	14.3 (2.4, 86.2)	.0036

* Data in parentheses are 95% confidence intervals.

Table 7

Prevalence of Coronary CT Angiography–identified CAD Stratified by Family History

Obstructive CAD	Total (*n* = 5255)	No Family History (*n* = 3646)	Family History of CAD (*n* = 1609)	*P* Value for Trend
				.0015
Normal	2717 (52)	1870 (51)	847 (53)	
Nonobstructive	1482 (28)	1021 (28)	461 (29)	
Obstructive	674 (13)	417 (11)	257 (16)	

Note.—Data are numbers of patients, with percentages in parentheses.

risk of MACE, and as such, cannot be successfully applied to individuals without modifiable CAD risk factors. In this regard, the present analysis represents the first of its kind to examine the prevalence, extent, and severity of CAD in relation to MACE risk in a large cohort of stable individuals suspected of having CAD but without risk factors.

Given the imperfect nature of traditional CAD risk factor scoring, numerous additional adjunctive tests have been investigated to determine the additive predictive value of identifying individuals at risk for MACE—including biomarkers and imaging tests—in both asymptomatic and symptomatic individuals. While useful for discriminating individuals with CAD at heightened risk of MACE, the most promising biomarkers—including high-sensitivity C-reactive protein and troponin—have been investigated for their use primarily in asymptomatic and acute chest pain

populations, respectively. As such, clinicians have relied heavily on the use of imaging to guide therapeutic decision-making for stable individuals suspected of having CAD. The results of the present study support the use of anatomic imaging with coronary CT angiography as a potentially effective method to discriminate individuals who do versus do not have CAD and who may benefit from more intensive medical and/or interventional therapy. Future prospective therapeutic studies will be useful in this regard and, on the basis of the current findings, now appears warranted.

This study was not without limitations. First, the data presented represent a subanalysis of a registry that is observational by nature and thus is not disencumbered from the usual biases that stem from the nonrandomized nature of the study cohort. Hence, the presence of referral and/or ascertainment bias cannot be definitively excluded, and our study findings, while provocative, cannot allow for cause-effect conclusions. Second, while we excluded individuals with all medically modifiable CAD risk factors, this information was gleaned from direct patient report, and it remains possible that adjudication of CAD risk factors from vital signs and laboratory testing may have affected our study results. Nevertheless, given the method of CAD risk factor ascertainment, the current study findings may be considered directly applicable to medical history recorded by physicians for stable individuals suspected of having CAD. Third, the present study findings were derived from a cohort of individuals who underwent imaging testing rather than from an all-inclusive cohort of stable individuals suspected of having CAD who may or may not be referred for subsequent imaging. Extrapolation of our study findings to a similar population of individuals who are not referred for imaging should be done with caution. As well, the cohort examined represents a real-world registry of patients undergoing coronary CT angiography with a number of patients not meeting current appropriateness guidelines for coronary CT angiography and with 36% of patients included being asymptomatic. Fourth, while symptoms and CAD risk factors were carefully determined, the downstream treatment of these individuals remains unknown. Treatment biases may have reduced or increased the rates of MACE on the basis of baseline CAD presence; extent and severity is not known in this study cohort. Future studies examining different treatment strategies now appear warranted. In addition, while all studies were interpreted by highly experienced readers, we lacked invasive angiographic correlation to determine the accuracy of these interpretations. Finally, we did not directly compare the CAD presence, extent, and severity to individuals with modifiable risk factors, because we have previously reported on such populations.

Among stable individuals suspected of having CAD and without medically modifiable CAD risk factors, the presence of both nonobstructive and obstructive CAD is common and is associated with significantly higher risk of MACE. Importantly, the absence of CAD at coronary CT angiography in these individuals is associated with a very low risk of MACE, irrespective of age, sex, or pretest likelihood of CAD. These findings suggest a potential need for refinement of the evaluation of individuals whose disease may be missed by traditional methods of CAD evaluation.

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Disclosures of Conflicts of Interest: J.L. Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author is board member for GE Healthcare and Vital Images; author is consultant for develops educational presentations for Edwards Lifesciences; author received modest speakers' bureau and medical advisory support from GE Healthcare. Other relationships: none to disclose. **C.M.T.** No relevant conflicts of interest to disclose. **G.G.** No relevant conflicts of interest to disclose. **B.G.H.** No relevant conflicts of interest to disclose. **G.B.J.M.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: none to disclose. Other relationships: Grants, honoraria from Merck, Pfizer, AstraZeneca, Amgen, Bristol Myers Squibb, and Sanofi for activities related to management of dyslipidemia; honorarium and stock options from Miraculins for activity as medical advisory board chair (noninvasive skin cholesterol testing). **S.A.** Financial activities related to the present article: institution receives grant from Siemens; author receives travel support from Siemens; author receives fees for review activities from Guerbet, Siemens, and Servier. Financial activities not related to the present article: author receives payment for lectures from Siemens; grant from Bayer Schering. Other relationships: none to disclose. **M.A.M.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution receives grants from American Heart Association and Blue Cross Blue Shield Foundation of Michigan, and Astellas. Other relationships: none to disclose. **D.S.B.** No relevant conflicts of interest to disclose. **M.J.B.** Financial activities related to the present article: institution receives modest grant from GE Healthcare. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **F.C.** Financial activities related to the present article: author receives grant support from GE Healthcare. Financial activities not related to the present article: author is consultant for Guerbet; author receives payment for lectures from Bracco and Siemens. Other relationships: none to disclose. **T.Q.C.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article:

author receives payment for lectures from GE Healthcare. Other relationships: none to disclose. **H.J.C.** No relevant conflicts of interest to disclose. **V.Y.C.** No relevant conflicts of interest to disclose. **K.C.** Financial activities related to the present article: author receives grant support from Bayer and Blue Cross Blue Shield Michigan. Financial activities not related to the present article: institution receives grant from American Heart Association; author received grant support from Bayer Pharma and Blue Cross Blue Shield Blue Care Michigan. Other relationships: none to disclose. **B.J.W.C.** Financial activities related to the present article: institution receives grant from GE Healthcare; institution receives provision of writing assistance, medicines, equipment or administrative support from TeraRecon. Financial activities not related to the present article: author receives research support from Pfizer and AstraZeneca. Other relationships: none to disclose. **A.D.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author receives payment for lectures from Edwards Lifesciences. Other relationships: none to disclose. **M.H.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution receives unrestricted research grant from Siemens Medical Systems. Other relationships: none to disclose. **J.H.** Financial activities related to the present article: author receives research grant from Siemens Medical Systems. Financial activities not related to the present article: author receives research grant from Siemens Medical Systems. Other relationships: none to disclose. **R.C.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author is consultant for Astellas Pharma; institution receives grants from GE Healthcare and Astellas Pharma. Other relationships: none to disclose. **G.F.** No relevant conflicts of interest to disclose. **Y.J.K.** No relevant conflicts of interest to disclose. **P.A.K.** No relevant conflicts of interest to disclose. **F.Y.L.** Financial activities related to the present article: institution receives grant from GE Healthcare. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **E.M.** Financial activities related to the present article: author received grant support from GE Healthcare. Financial activities not related to the present article: none to disclose. Other relationships: none to disclose. **G.R.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: institution receives grants from Siemens and Blue Cross Blue Shield Michigan for investigator-sponsored studies dealing with CT (but not this study); author receives grant from Bayer Pharma. Other relationships: none to disclose. **L.J.S.** No relevant conflicts of interest to disclose. **T.C.V.** Financial activities related to the present article: none to disclose. Financial activities not related to the present article: author receives payment for lecture from Boehringer Ingelheim. Other relationships: none to disclose. **J.K.M.** Financial activities related to the present article: institution receives grant from GE Healthcare. Financial activities not related to the present article: institution is board member of GE Healthcare, AstraZeneca, and Bristol Myers Squibb; institution is consultant for AstraZeneca and Bristol Myers Squibb; institution receives payment for lectures from GE Healthcare; institution has stock in TC3. Other relationships: none to disclose.

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