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Performance of the Traditional Age, Sex, and Angina Typicality–Based Approach for Estimating Pretest Probability of Angiographically Significant Coronary Artery Disease in Patients Undergoing Coronary Computed Tomographic Angiography: Results From the Multinational Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM)

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Performance of the Traditional Age, Sex, and Angina Typicality–Based Approach for Estimating Pretest Probability of Angiographically Significant Coronary Artery Disease in Patients Undergoing Coronary Computed Tomographic Angiography

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

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Background—Guidelines for the management of patients with suspected coronary artery disease (CAD) rely on the age, sex, and angina typicality–based pretest probabilities of angiographically significant CAD derived from invasive coronary angiography (guideline probabilities). Reliability of guideline probabilities has not been investigated in patients referred to noninvasive CAD testing.

Methods and Results—We identified 14048 consecutive patients with suspected CAD who underwent coronary computed tomographic angiography. Angina typicality was recorded with the use of accepted criteria. Pretest likelihoods of CAD with $\geq$50% diameter stenosis (CAD50) and $\geq$70% diameter stenosis (CAD70) were calculated from guideline probabilities. Computed tomographic angiography images were evaluated by $\geq$1 expert reader to determine the presence of CAD50 and CAD70. Typical angina was associated with the highest prevalence of CAD50 (40% in men, 19% in women) and CAD70 (27% men, 11% women) compared with other symptom categories ($P<0.001$ for all). Observed CAD50 and CAD70 prevalences were substantially lower than those predicted by guideline probabilities in the overall population (18% versus 51% for CAD50, 10% versus 42% for CAD70; $P<0.001$), driven by pronounced differences in patients with atypical angina (15% versus 47% for CAD50, 7% versus 37% for CAD70) and typical angina (29% versus 86% for CAD50, 19% versus 71% for CAD70). Marked overestimation of disease prevalence by guideline probabilities was found at all participating centers and across all sex and age subgroups.

Conclusion—In this multinational study of patients referred for coronary computed tomographic angiography, determination of pretest likelihood of angiographically significant CAD by the invasive angiography-based guideline probabilities greatly overestimates the actual prevalence of disease. **(*Circulation*. 2011;124:2423-2432.)**

Key Words: angina ■ coronary artery disease ■ probability ■ stenosis ■ tomography, x-ray computed

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Estimating the pretest likelihood of angiographically significant coronary artery disease (CAD) is a fundamental component in the initial evaluation of symptomatic patients presenting with suspected CAD. This determination directly influences subsequent decisions for noninvasive diagnostic testing and treatment.[1] To assist the clinician in this task, vital reports from the Coronary Artery Surgery Study (CASS) Registry,[2] Diamond and Forrester,[3] and Pryor and colleagues[4,5] have convincingly shown that the prevalence of angiographically significant CAD depends on age, sex, and angina typicality. The American College of Cardiology (ACC) and American Heart Association (AHA) have since recognized these 3 characteristics as chief pretest predictors of ≥50% diameter stenotic CAD, and the resultant reference probabilities (Table 1) have been adopted for use in the Clinical Practice Guidelines for Management of Chronic Stable Angina and, more recently, in appropriate use criteria for echocardiography, radionuclide imaging, magnetic resonance imaging, and coronary computed tomographic angiography (CTA).[1,6–9]

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Importantly, the prevalence of angiographically significant CAD in the Diamond-Forrester classification, CASS Registry, and similar studies was derived from patients referred for invasive coronary angiography for clinical indications.[2–5,10] These rates have not been tested in other populations. Recently, coronary CTA using scanners with 64-detector rows has emerged as an accurate first-line method for noninvasively diagnosing angiographically significant CAD.[11–14] Accordingly, we conducted a multicenter, multinational study to examine whether the reference values for pretest probability as put forth by the ACC/AHA clinical practice guidelines and appropriate use criteria accurately predict the presence of angiographically significant CAD in patients referred for noninvasive imaging by coronary CTA.

Methods

Study Participants

The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry (CONFIRM) is a dynamic multinational registry of consecutive patients enrolled at the time of clinically indicated coronary CTA. The design of CONFIRM has been described elsewhere.[15] All patients gave informed consent for study participation, and each participating center obtained approval from an institutional review board or similar governing body (for centers outside the United States) for study execution. Of the initial 12 participating centers in CONFIRM, 3 were excluded from this study owing to the absence of information necessary for categorizing angina typicality. The present study thus included patients from 9 centers in 6 countries: 1 each in Canada, Italy, South Korea, Switzerland, and Germany and 4 in the United States. Of 19 703 consecutive adult patients at these centers, we excluded, in sequential order, those with known CAD or suspected acute coronary syndrome at the time of CTA (1994 patients), those missing age information (7 patients), patients <30 years of age (286 patients), and those with incomplete symptom information (3368 patients). The remaining 14 048 patients (71% of available population) were analyzed. All patients had a standard CAD risk factor profile (presence of hypertension, diabetes mellitus, dyslipidemia, active cigarette smoking, and family history of CAD) and chest pain symptoms recorded at the time of CTA.[16]

Table 1. Pretest Probabilities of ≥50% Diameter Stenotic Coronary Artery Disease in Patients With Chest Pain as Shown in the American College of Cardiology/American Heart Association Guidelines for Management of Chronic Stable Angina

	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

Chest Pain Categorization

Chest pain was categorized according to the classic criteria for angina pectoris.[3,17,18] Patients with typical angina (TypAng) experienced substernal, jaw, and/or arm pressure-like pain that consistently occurred with exertion and consistently resolved within 15 minutes of rest and/or use of nitroglycerin. Patients with atypical angina (AtypAng) experienced 2 of these characteristics. Patients with nonanginal chest pain (NonAng) experienced 1 or none of these characteristics. Dyspneic patients whose primary symptom was chest pain were categorized as TypAng, AtypAng, or NonAng; otherwise, they were separately categorized as having dyspnea without chest pain.[19] Asymptomatic patients had neither chest pain nor dyspnea. At each site, symptom category was prospectively ascertained through written questionnaire or interview by a physician or allied health professional.

Determining Expected Probability of Angiographically Significant CAD

Age, sex, and angina typicality for each patient were used to determine the expected probability of CAD with ≥50% luminal diameter stenosis (CAD50) from the table of probabilities within the ACC/AHA Clinical Practice Guidelines for Management of Patients with Stable Angina ("guideline probabilities"; see Table 1).[1] Patients >69 years old whose pretest CAD50 probability could not be established from guideline probabilities were assigned the pretest probability for the corresponding 60- to 69-year-old group. We further accounted for presence of diabetes mellitus, smoking, and dyslipidemia by determining the expected probability of CAD with ≥70% luminal diameter stenosis (CAD70) using the algorithm developed by Pryor et al,[4,5] assuming that all patients had normal resting ECGs (data not available in CONFIRM). Patients >70 years of age were assigned the expected pretest CAD70 probability of a 70-year-old (maximum age in the algorithm by Pryor et al) with identical symptom category and CAD risk factor profile.

Coronary CTA Acquisition and Interpretation

CTAs were performed on a single-source 64-slice scanner (Lightspeed VCT, GE Healthcare, Milwaukee, WI; SOMATOM Sensation 64, Siemens Medical Systems, Erlangen, Germany) or a dual-source scanner (Definition or Flash, Siemens Medical Systems). Before imaging, in patients without contraindications, oral and/or intravenous metoprolol was administered in an attempt to achieve a target heart rate ≤65 bpm for single-source scanners or ≤75 bpm for dual-source scanners. Whenever possible, 0.4 mg sublingual nitroglycerin was administered 3 to 5 minutes before image acquisition. Timing bolus or automated bolus tracking at the proximal ascending aorta was used to determine the time from contrast injection to optimal coronary artery enhancement. Contrast (80 to 140 mL, depending on site) followed by 50 mL of saline flush was power injected at 5 to 6 mL/s (rates >6 mL/s were reserved for very obese patients or patients with very thick chests), and whole-volume image acquisition was completed in a single breath-hold. In 11 727 patients (83% of total population), a noncontrast CT was also performed to quantify coronary calcium score, according to the method described by Agatston et al.[20]

Acquired image data were initially reconstructed in mid diastole (always) and end systole (if data were available). When image quality was suboptimal on initial reconstruction, multisector reconstruction algorithm with or without manual ECG editing was used to improve image quality. Reconstructed data were then sent to a workstation, where at least 1 highly experienced reader (who had interpreted ≥1000 prior coronary CTAs) used all necessary postprocessing techniques to determine the presence of CAD50 and CAD70 in any visible segment ≥1.5 mm in diameter. CTA interpretation was performed in an intent-to-diagnose manner; any uninterpretable segment was scored the same stenosis severity as the most adjacent proximal evaluable segment, in accordance with standard protocols from prior multicenter studies.[12,13] A 16-segment AHA coronary artery tree model was used.[21] The severity of total detected CAD on each study was further categorized by use of a modified version of the Duke CAD Prognostic Index Score, as previously described.[22,23] This CAD severity score ranged from 0 to 7: 0=no visible coronary atherosclerosis; 1=at least 1 segment with <50% stenosis; 2=at least 2 segments (including a proximal segment) with <50% stenosis; 3=at least 1 segment with 50% to 69% stenosis; 4=at least 2 segments with 50% to 69% stenosis or at least 1 segment (not proximal left anterior descending artery) with ≥70% stenosis; 5=at least 3 segments with 50% to 69% stenosis or at least 2 segments (not proximal left anterior descending artery) with ≥70% stenosis or proximal left anterior descending artery with ≥70% stenosis; 6=at least 3 segments with ≥70% stenosis or at least 2 segments (including proximal left anterior descending artery) with ≥70% stenosis; and 7=left main coronary artery with ≥50% stenosis. Scores ≥5 represented high-risk disease.

Statistical Analysis

Continuous variables were described as mean±SD or median with interquartile range. Frequencies of binary, categorical, and ordinal variables were described as percentages. Continuous variables with normal and nonnormal distributions were compared with the use of standard ANOVA and the Kruskal-Wallis nonparametric test, respectively. To evaluate differences in the prevalence of CAD50, prevalence of CAD70, rate of high-risk CAD (CAD severity score ≥5), and CAD severity scores between specific subpopulations, patients were stratified by sex, age, and symptom category in an manner identical to guideline probabilities. Asymptomatic patients and NonAng patients served as references for other symptom categories. Comparisons of prevalence were performed by use of the χ^2 test. Comparisons of CAD severity scores were performed with the Kruskal-Wallis nonparametric test. Stepwise multivariable logistic regression analysis including age, sex, and presence of TypAng was performed to determine the association between each of these 3 variables and CAD50, CAD70, and high-risk CAD; these relationships were expressed as odds ratio (OR) and 95% confidence intervals (95% CIs). A value of $P<0.05$ was considered significant.

Although prior studies have shown a general tendency for overestimating CAD stenosis severity by coronary CTA, it remained theoretically possible that, for this study, CTA underestimated the prevalence of angiographically significant CAD as a result of nondiagnostic segments, severe coronary calcification, and general limitations in predictive value. To estimate the potential impact of these factors, we performed additional sensitivity analyses. To estimate the maximum potential difference in the prevalence of angiographically significant CAD caused by nondiagnostic segments, we used results from 2 recent meta-analyses that showed a pooled false-negative CAD50 rate of 4%.[11,14] To estimate the maximum potential impact from coronary calcification, we evaluated data from the subset of 11 727 patients for whom coronary calcium scores were available to calculate the maximum number of patients with missing CAD50, assuming that all patients with calcium scores >1000 had CAD50. We further repeated these analyses by assuming that all patients with a calcium scores >600 had CAD50. To estimate the impact of variations in coronary CTA predictive value, we calculated the true CAD50 prevalence in scenarios in which the positive predicted value ranged from 55% to 85% and negative predicted value ranged from 85% to 95%. These calculations are summarized in Results, and details are shown in the online-only Data Supplement.

Results

There were 7719 men (mean age, 57±11 years) and 6329 women (mean age, 60±11 years) in the study population; of these, 4605 of the men (60%) and 4752 of the women (75%) were symptomatic. Characteristics of the study population are detailed in Table 2. The most common symptom type was AtypAng, reported by 57% of symptomatic men and 55% of symptomatic women. Multiple risk factors were present in just over half of the total population. For both sexes, patients with TypAng and dyspnea without chest pain were older and had higher rates of diabetes mellitus, hypertension, dyslipidemia, and multiple risk factors.

Prevalence of Angiographically Significant CAD

The overall prevalence of CAD50 in our study population was 18% (23% in men, 13% in women), and 10% of patients had CAD70 (12% of men, 6% of women). Of the 3368 patients ≥30 years of age without prior CAD excluded from analysis because of incomplete symptom data, stenosis information was available in 2576 patients; prevalences of CAD50 and CAD70 in this group were 20% (24% in men, 14% in women) and 9% (12% in men, 5% in women), respectively.

For all symptom categories, prevalences of CAD50 and CAD70 were significantly higher in men than in women ($P<0.001$ for all comparisons; Table 3). In both men and women, the highest prevalences were found in patients with TypAng ($P<0.001$ versus all other symptom categories).

Table 4 shows the prevalences of CAD50 and CAD70 in subgroups determined by age, sex, and symptom category, with the same stratification scheme used as in guideline probabilities. Prevalence for every symptom category increased with age. In ≥40-year-old patients (both men and women), only patients with TypAng exhibited higher prevalences of CAD50 and CAD70 than asymptomatic patients and patients with NonAng for each increasing age decade. The highest observed CAD50 prevalence was 53%, seen in men ≥70 years of age with TypAng. In patients <40 years of age, symptom category showed no relationship to the prevalence of CAD50 or CAD70. Stepwise multivariable logistic regression confirmed that age, male sex, and prevalence of TypAng were all independently associated with CAD50 and CAD70 (per increase in decade age: OR=1.82 and 95% CI=1.74–1.91 for CAD50, OR=1.81 and 95% CI=1.71–1.92 for CAD70; male sex: OR=2.62 and 95% CI=2.38–2.89 for CAD50, OR=2.63 and 95% CI=2.36–3.05 for CAD70; presence of TypAng: OR=1.95 and 95% CI=1.73–2.21 for CAD50, OR=2.55 and 95% CI=2.21–2.95 for CAD70).

CAD Severity

As shown in Table 3, CAD severity scores were higher in men than women for every symptom category. The highest scores for both sexes were found in patients with TypAng.

Table 2. Demographic Characteristics of Men and Women in the Study Population Categorized by Angina Typicality

Characteristic	Total Population	Asymptomatic	Nonanginal Chest Pain	Atypical Angina	Typical Angina	Dyspnea Only	*P*
Men							
n	7719	3114	582	2612	805	606	
Age, y	57±11	57±11	56±12	55±11	59±12	60±11	<0.001
Median age (interquartile range), y	57 (49–65)	58 (50–65)	56 (47–65)	55 (47–63)	59 (51–67)	60 (53–68)	<0.001
30–39, n (%)	513 (7)	160 (5)	44 (8)	248 (9)	40 (5)	21 (3)	
40–49, n (%)	1583 (21)	584 (19)	147 (25)	627 (24)	137 (17)	88 (15)	
50–59, n (%)	2410 (31)	1040 (33)	157 (27)	818 (31)	226 (28)	169 (28)	
60–69, n (%)	2189 (28)	916 (29)	149 (26)	662 (25)	253 (31)	209 (34)	
≥70, n (%)	1024 (13)	414 (13)	85 (15)	257 (10)	149 (19)	119 (20)	
Body mass index, kg/m^2	27.4±4.5	27.0±4.1	28.0±4.7	27.1±4.4	27.6±4.6	29.2±5.7	<0.001
Diabetes mellitus, %	13	12	13	13	15	18	0.002
Hypertension, %	47	42	48	47	57	57	<0.001
Dyslipidemia, %	58	58	52	57	63	58	0.003
Active smoking, %	18	14	25	19	21	17	<0.001
Family CAD history, %	29	29	35	26	32	30	<0.001
≥2 Risk factors, %	53	49	57	52	62	58	<0.001
Women							
n	6329	1577	671	2611	825	645	
Age, y	60±11	60±11	60±12	59±11	61±11	62±12	<0.001
Median age (interquartile range), y	60 (52–67)	60 (53–67)	60 (51–69)	59 (51–66)	61 (54–70)	63 (54–70)	<0.001
30–39, n (%)	247 (4)	47 (3)	35 (5)	125 (5)	21 (3)	19 (3)	
40–49, n (%)	915 (14)	211 (13)	111 (17)	424 (16)	99 (12)	70 (11)	
50–59, n (%)	1885 (30)	497 (32)	168 (25)	813 (31)	239 (29)	168 (26)	
60–69, n (%)	2035 (32)	527 (33)	201 (30)	836 (32)	254 (31)	217 (34)	
≥70, n (%)	1247 (20)	295 (19)	156 (23)	413 (16)	212 (26)	171 (27)	
Body mass index, kg/m^2	27.2±6.1	26.2±5.4	28.2±7.0	27.2±5.8	27.3±5.8	28.9±7.3	<0.001
Diabetes mellitus, %	14	13	13	14	15	16	0.162
Hypertension, %	53	49	53	53	58	60	<0.001
Dyslipidemia, %	58	56	54	58	64	59	<0.001
Active smoking, %	12	11	16	12	12	11	0.004
Family CAD history, %	32	27	45	29	40	33	<0.001
≥2 Risk factors, %	54	49	60	53	62	57	<0.001

CAD indicates coronary artery disease. Values are mean±SD when appropriate.

Mean CAD severity scores and rates of high-risk CAD (score ≥5) increased with age decade (all *P* for trend <0.001; see Table 5). Patients ≥70 years of age with TypAng had the highest subgroup CAD severity score and prevalence of high-risk CAD (3.2±2.1 and 30%, respectively, for men; 2.0±1.8 and 13%, respectively for women). Stepwise multivariable logistic regression confirmed that age (per increase in decade: OR=1.82, 95% CI=1.70–1.94), male sex (OR=2.98, 95% CI=2.57–3.45), and presence of TypAng (OR=2.45, 95% CI=2.08–2.88) were independently associated with high-risk CAD.

Comparisons of Observed Angiographically Significant CAD Prevalence With Expected Prevalence by Guideline Probabilities

Comparisons of observed and expected CAD50 and CAD70 prevalence were made for the 8106 patients who reported NonAng, AtypAng, and TypAng. For CAD50, overall observed prevalence was substantially lower than expected (18% versus 51%; *P*<0.001). This difference was present for both men (24% versus 61%; *P*<0.001) and women (13% versus 41%; *P*<0.001). For both sexes, the differences in observed and expected CAD50 prevalence were most marked in patients with AtypAng and TypAng across all age groups (Figure 1). Within the AtypAng and TypAng populations, observed-to-expected ratios increased with age in men (*P*<0.001 for both) but not in women. As shown in Figure 2, observed CAD50 prevalence was lower than the expected prevalence at every participating site (range of observed-to-expected ratio, 0.18–0.66).

Observed CAD70 prevalence was also substantially lower than expected (overall, 10% versus 42%; men, 14% versus 58%; women, 6% versus 26%; all *P*<0.001). As shown in Figure 3, this difference was present regardless of the number of risk factors and, similar to CAD50, was most pronounced in patients with AtypAng and TypAng.

Impact of Nondiagnostic Segments, Coronary Calcification, and Variations in CTA Predictive Value on Observed Prevalence of Angiographically Significant CAD

Additional models were constructed to determine the potential impact of known factors that may affect coronary CTA

Table 3. Observed Prevalence and Severity of Angiographically Significant Coronary Artery Disease According to Symptom Category

	Overall	Asymptomatic	Nonanginal Chest Pain	Atypical Angina	Typical Angina	Dyspnea	*P**
Men							
n	7719	3114	582	2612	805	604	
CAD50, %†	23	21	25	19	40	29	<0.001
CAD70, %†	12	10	17	9	27	16	<0.001
Mean CAD severity score†	1.7±1.8	1.6±1.6	1.8±1.9	1.4±1.7	2.4±2.1	2.1±1.8	<0.001
CAD severity score ≥5†	10	7	13	8	21	12	<0.001
Women							
n	6329	1577	671	2611	825	645	
CAD50, %	13	13	12	11	19	13	<0.001
CAD70, %	6	6	7	5	11	6	<0.001
Mean CAD Severity Score†	1.0±1.5	1.1±1.5	1.1±1.5	0.9±1.4	1.3±1.7	1.2±1.4	<0.001
CAD Severity Score ≥5, %†	4	5	4	3	8	4	<0.001

CAD50 indicates ≥50% diameter stenotic coronary artery disease; CAD70, ≥70% diameter stenotic coronary artery disease.

*Compares trend in observed stenotic CAD prevalence and measures of CAD severity across all symptom categories.

†CAD50 prevalence, CAD70 prevalence, mean CAD severity score, and frequency of CAD severity score ≥5 in men were higher than in women for every symptom category (all *P*<0.001).

diagnostic accuracy, including nondiagnostic coronary segments, severe coronary calcification, and potential differences in real-world predictive values compared with those previously reported in prospective multicenter trials. Simulation of the worst-case scenarios based on these factors estimated the minimum and maximum potential CAD50 prevalences at 14% and 28%. Details of these models and corresponding calculations are shown in the online-only Data Supplement.

Discussion

In this large prospective multinational study of asymptomatic and symptomatic patients with suspected CAD undergoing noninvasive evaluation by coronary CTA, the expected prevalence of angiographically significant CAD based on guideline probabilities significantly exceeded actual observed prevalence. Predicted rates of were ≈3-fold higher than the actual observed prevalence for CAD50 (51% versus 18%) and 4-fold higher for CAD70 (42% versus 10%), with consistent overestimation of CAD prevalence regardless of whether the method of Diamond-Forrester and CASS (restricting pretest probability determination to age, sex, and angina typicality) or the method of Pryor et al (additionally accounting for CAD risk factors) was used.[2–5] The differences were most pronounced for men and women across all age groups presenting with AtypAng and TypAng, with TypAng as the only chest pain categorization that reliably predicted greater prevalence of angiographically significant CAD.

The present results are in accordance with 3 contemporary studies that identified a systematic overestimation of angiographically significant CAD among patients referred for invasive angiography. Hoilund-Carlsen et al[24] found an absence of CAD50 in 97 of 187 men and women (52%) with

Table 4. Observed Prevalence of ≥50% and ≥70% Diameter Stenotic Coronary Artery Disease in the Study Population Stratified by Sex, Age, and Symptom Category

		CAD50, %						CAD70, %					
	Age, y	Asymptomatic	Nonanginal	Atypical Angina	Typical Angina	Dyspnea	*P**	Asymptomatic	Nonanginal	Atypical Angina	Typical Angina	Dyspnea	*P**
Men	30–39	1	5	4	3	0	0.312	0	5	1	3	0	0.134
	40–49	8	7	10	23	14	<0.001	3	3	5	16	8	<0.001
	50–59	20	22	18	38	22	<0.001	8	13	7	28	11	<0.001
	60–69	27	43	28	48	34	<0.001	13	30	13	31	15	<0.001
	≥70	36	44	39	53	45	0.005	19	29	21	35	31	0.001
P†		<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	
Women	30–39	4	3	3	5	5	0.983	0	0	2	0	5	0.404
	40–49	2	5	6	10	4	0.077	1	2	2	7	4	0.008
	50–59	9	9	7	15	10	0.004	3	7	3	10	3	<0.001
	60–69	13	13	12	19	16	0.095	6	7	5	9	6	0.240
	≥70	28	21	23	29	19	0.086	14	12	13	19	11	0.148
P†		<0.001	<0.001	<0.001	<0.001	0.012		<0.001	0.013	<0.001	0.001	0.029	

CAD50 indicates ≥50% diameter stenotic coronary artery disease; CAD70, ≥70% diameter stenotic coronary artery disease.

*Compares trend in observed prevalence of CAD50 and CAD70 across all symptom categories.

†Compares trend in observed prevalence across all decades of age.

Table 5. Observed Mean Coronary Artery Disease Severity Score and Prevalence of Severe Coronary Artery Disease, Defined as a Severity Score ≥5, Stratified by Sex, Age, and Symptom Category

		Asymptomatic		Nonanginal Chest Pain		Atypical Angina		Typical Angina		Dyspnea		*P**	
	Age, y	Mean Score	Score ≥ 5, %	Mean Score	Score ≥ 5, %	Mean Score	Score ≥ 5, %	Mean Score	Score ≥ 5, %	Mean Score	Score ≥ 5, %	Mean Score	Score ≥ 5
Men	30–39	0.2±0.6	0	0.5±1.3	5	0.3±0.8	1	0.4±0.9	3	0.3±0.6	0	0.795	0.071
	40–49	0.8±1.2	2	0.8±1.2	2	0.8±1.4	4	1.4±2.1	13	1.1±1.5	5	0.102	<0.001
	50–59	1.5±1.5	6	1.8±1.7	8	1.4±1.6	6	2.3±2.2	22	1.9±1.8	11	<0.001	<0.001
	60–69	2.0±1.6	9	2.7±1.9	21	2.0±1.8	13	2.7±2.0	22	2.4±1.6	12	<0.001	<0.001
	≥70	2.4±1.7	15	2.8±2.1	28	2.6±1.9	20	3.2±2.1	30	2.8±1.7	20	0.003	0.001
P†		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.004		
Women	30–39	0.2±0.7	0	0.2±0.6	0	0.2±0.9	2	0.2±0.9	0	0.3±1.2	5	0.952	0.404
	40–49	0.3±0.8	0	0.4±0.9	0	0.4±1.0	1	0.7±1.5	6	0.5±1.2	3	0.442	<0.001
	50–59	0.7±1.2	2	0.9±1.4	5	0.6±1.1	1	1.1±1.7	6	0.8±1.3	3	0.012	<0.001
	60–69	1.2±1.6	6	1.2±1.4	3	1.1±1.5	4	1.3±1.6	7	1.3±1.5	3	0.008	0.115
	≥70	2.0±1.7	11	1.8±1.7	10	1.8±1.6	7	2.0±1.8	13	1.7±1.5	5	0.212	0.018
P†		<0.001	<0.001	<0.001	0.001	<0.001	<0.001	<0.001	0.033	<0.001	0.891		

*Compares trend in observed values across all symptom categories.

†Compares trend in observed values across all age categories.

TypAng and a mean age of 58 years. Guideline probabilities predicted >80% prevalence in this population, leading the authors to conclude that clinical prediction was unreliable. Patel et al,[25] in >130 000 patients with TypAng from the American College of Cardiology National Cardiovascular Data Registry, observed an overall CAD50 prevalence of 50%. In the same study, in >145 000 patients with NonAng and AtypAng, CAD50 prevalence was only 25%. A recent

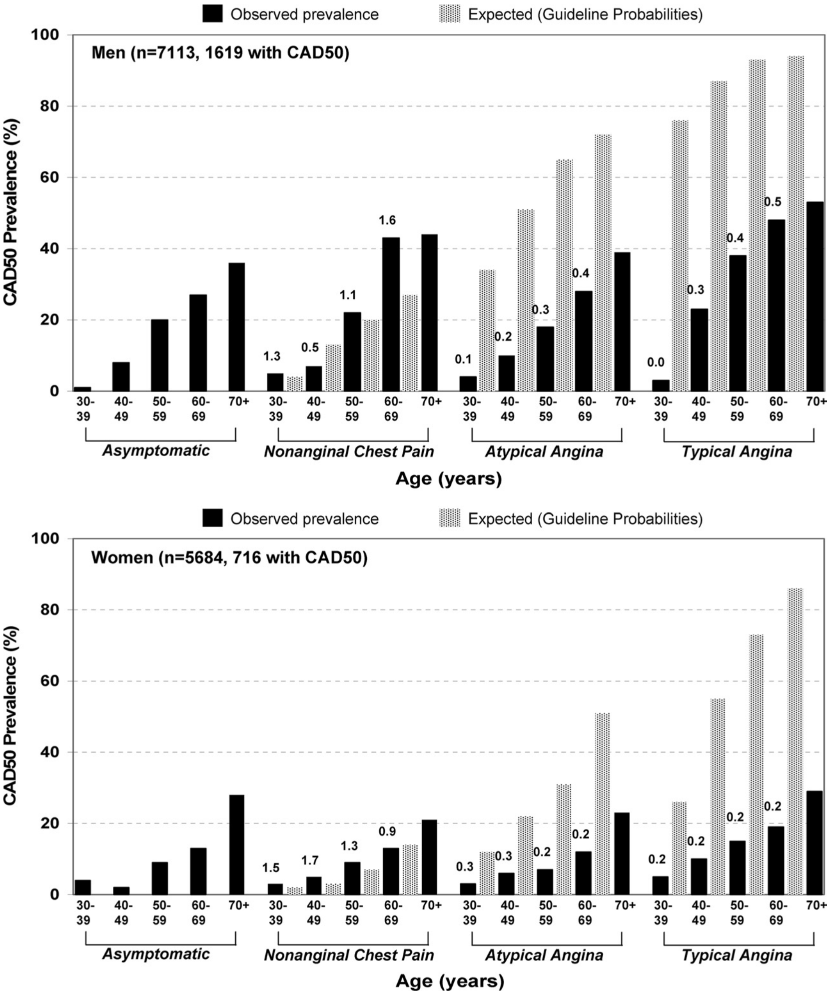
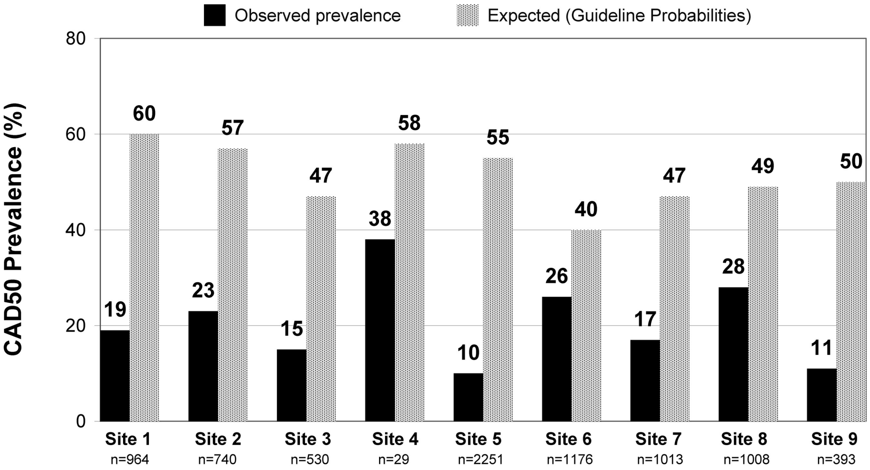


Figure 1. Observed prevalence (black bars) and expected prevalence (spotted bars) of angiographically confirmed ≥50% stenotic coronary artery disease (CAD50) in study men (top) and women (bottom) with no symptoms, nonanginal chest pain, atypical angina, and typical angina. Note that the total sample sizes shown are smaller than those in Table 1 because patients reporting only dyspnea are not included. The 4 collections of bars in each graph are grouped by symptom category and stratified by age decade. Within each symptom group, each black bar should be compared with the spotted bar to its immediate right (asymptomatic patients have no direct comparison). The value above each black bar is the ratio of observed to expected CAD50 prevalence. Expected prevalence in patients with atypical angina and typical angina were dramatically higher than observed prevalence, regardless of age. With increasing age, observed-to-expected ratios increased in men with atypical angina ($P<0.001$) and typical angina ($P<0.001$) but stayed unchanged in women.



	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6	Site 7	Site 8	Site 9
Country	US	Germany	US	Switzerland	Korea	Canada	US	Italy	US
Men	49%	61%	43%	52%	49%	43%	46%	53%	60%
Mean age	61	60	56	59	57	58	53	61	51
High RF	34%	16%	38%	28%	20%	31%	21%	39%	23%
AtypAng	49%	82%	76%	79%	81%	26%	84%	41%	85%
TypAng	39%	11%	11%	21%	17%	25%	12%	24%	13%

Figure 2. Overall observed prevalence (black bars) of angiographically confirmed ≥50% stenotic coronary artery disease (CAD50) was substantially lower than the expected prevalence (spotted bars) at every participating center. The observed-to-expected ratios ranged from 0.18 (site 5) to 0.66 (site 4), and absolute differences between observed and expected prevalence ranged from 14% to 45%. The 2 sites with the lowest observed-to-expected ratios were sites 5 and 9. Site 5 was in South Korea, the only center outside North America and Europe. Patients at site 9 were substantially younger than patients at other sites. The 2 sites with the highest observed-to-expected ratios were sites 6 and 8 (Site 4 discounted owing to a very small sample size). Populations at both sites had relatively low rates of atypical angina and relatively high rates of typical angina. Site 8 patients also had the highest rate of patients with high risk factor (RF) burden (diabetes mellitus or ≥3 risk factors other than diabetes mellitus).

multicenter effort by Genders et al[26] found an overestimation of CAD50 by the Diamond-Forrester classification in patients with TypAng, especially women. Our work extends the results of these studies by directly demonstrating that the application of data from invasive angiography dramatically overestimates the pretest likelihood of angiographically significant CAD in symptomatic patients referred for noninvasive CAD evaluation.

Of the multiple potential explanations for the extent to which guideline probabilities overestimated the actual prevalence of angiographically significant CAD in study patients with chest pain, 3 emerge as particularly strong candidates. First, guideline probabilities were developed from historical studies that evaluated patients undergoing clinically indicated invasive angiography, frequently after abnormal results from stress testing.[2,27–34] Bayesian principles dictate that the population being referred for invasive angiography will have higher disease prevalence compared with populations referred for de novo noninvasive testing. Indeed, in the present study, coronary CTA was generally used for patients at low to intermediate pretest likelihood of angiographically significant CAD, in accordance with recommendations in societal practice guidelines and appropriate use criteria.[8] For patients with a very high pretest likelihood, clinicians may have opted for referral to invasive angiography in lieu of noninvasive testing. Second, the technique of determining chest pain quality and angina typicality differed between the present study and the source data for guideline probabilities. In the present study, angina typicality was assessed in rank-order fashion with the use of responses to several fixed questions designed to replicate the criteria used by guideline probabilities. However, multiple-source studies for guideline probabilities used physician-conducted interviews or detailed chart reviews.[2,27–34] Ascertainment of angina typicality by the latter approach may have been influenced by presence of other potentially relevant features, such as chest pain frequency, severity, associated degree of functional impairment, and competing diagnoses. Finally, an increasing emphasis in developed countries by media, physicians, and insurers on preventive care for CAD over the past 2 decades has increased awareness of the potential hazards of CAD; these efforts may be prompting lower-risk symptomatic patients to seek earlier diagnostic evaluation for CAD.

Several additional findings in the present study are worthy of discussion. Ratios of observed to expected CAD50 prevalence increased with age in men but not in women, highlighting the overall reduced performance of guideline probabilities in women and the need for sex-specific prediction models. The lowest observed-to-expected ratio was found at the South Korean site, suggesting that the relationship between angina typicality and angiographically significant CAD may be influenced by ethnicity or local interpretation of chest pain characteristics. Differences in prevalence among asymptomatic patients and patients with NonAng and AtypAng were generally small, echoing a phenomenon recently reported by Patel and colleagues,[25] who found that patients with atypical chest pain actually exhibited lower rates of angiographically significant CAD than patients with no chest pain. In the present study, this finding may have been due to referral pattern, because fewer asymptomatic patients were <50 years old (Table 2). Compared with asymptomatic patients and patients with AtypAng, patients with NonAng had the highest absolute prevalence of CAD50, CAD70, and high-risk CAD. This may have been related to differences in underlying risk factor burden, as patients with NonAng in our population also reported higher rates of active smoking, family CAD history, and multiple concurrent risk factors.

The results from the present study carry significant clinical implications. An estimated 10 million noninvasive cardiac imaging tests are performed annually in the United States.[35] This volume accounts for a large portion of national healthcare expenditure and has raised concerns regarding the overuse and economic efficiency of noninvasive imaging. As a result of the absence of updated prediction models for first-line evaluation of symptomatic patients with suspected

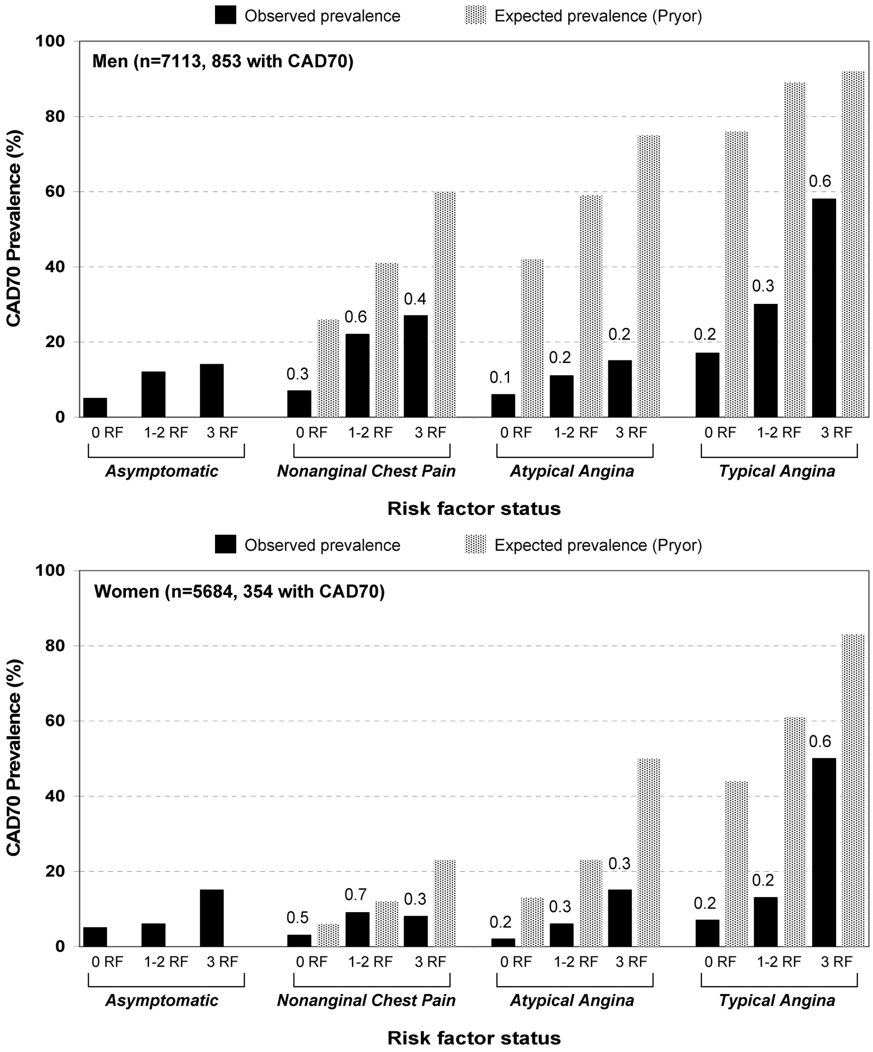


Figure 3. Observed prevalence (black bars) and expected prevalence (spotted bars) of angiographically confirmed ≥70% stenotic coronary artery disease (CAD70) in study men (top) and women (bottom). Expected prevalence was calculated with the algorithm described by Pryor and colleagues,[4] which incorporates sex, age, angina typicality, history of prior myocardial infarction, presence of Q waves on resting ECG, and presence of 3 risk factors (RFs): diabetes mellitus, dyslipidemia, and active smoking. Study patients were assumed to have no Q waves on resting ECG. Within each symptom category, patients were subgrouped by number of risk factors. The value above each black bar is the ratio of observed to expected prevalence. In all groups, expected prevalence was higher than observed prevalence. The differences were particularly dramatic in patients with atypical angina or typical angina and <3 risk factors, for whom observed-to-expected ratios were <0.4.

CAD, professional societal recommendations that guide referral to noninvasive testing have depended on guideline probabilities. Our analyses uniformly illustrate that the utility of guideline probabilities is limited by overestimation of pretest probability. This limitation is likely magnified in populations for whom noninvasive testing is the next preferred diagnostic step. Findings from our study suggest that successfully updating pretest probability estimates of CAD in populations similar to CONFIRM may identify a large percentage of low- or intermediate-likelihood patients in whom additional testing may not be warranted.

Study Limitations

The results of this study are predicated on an accurate exclusion of CAD50 by coronary CTA. Compared with invasive angiography, 64-detector row coronary CTA has consistently exhibited very high negative predictive value for the exclusion of angiographically significant CAD. Two recent meta-analyses and 2 other recent rigorously conducted multicenter studies all found ≥95% negative predicted value on a per-patient basis.[11–14] The major diagnostic limitation of CTA in individuals without known CAD has been positive predictive value, reported at 60% to 70% in recent multicenter studies.[12,13] In models adjusted for the spectrum of plausible negative predicted values (85% to 95%) and positive predicted values (55% to 85%), the maximum potential CAD50 prevalence of our study population was 28% (range, 14%–28%; see the online-only Data Supplement). Even with these conservative assumptions, overestimation of CAD50 prevalence in the CONFIRM population by guideline probabilities remains quite striking.

We examined asymptomatic and symptomatic patients with suspected CAD to provide estimates of angiographically significant CAD prevalence. Although our reported prevalence values may be useful starting points for considering the utility of noninvasive CAD testing, angina typicality was determined through questionnaire rather than physician interview in a large number cases, and other commonly obtained clinical data such as duration and severity of chest pain and resting ECG were not available. In addition, reasons for coronary CTA in asymptomatic patients were not available, and referral patterns within the present study were likely biased against patients with symptoms severe enough to warrant direct referral to invasive coronary angiography. Thus, application of our findings to patients undergoing invasive evaluation must be performed with caution.

Interpretation of coronary CTA was not blinded to available clinical data. However, these studies were meticulously evaluated by Level III–equivalent readers with $>$1000 prior CTA interpretations and in direct accordance to Society of Cardiovascular Computed Tomography guidelines.[36] Although unlikely, the open-label nature of the present study may have theoretically biased readers toward overestimating CAD50 and CAD70 in patients with TypAng. Nevertheless, if true, this bias would naturally magnify the discrepancy we found between guideline probabilities and observed angiographically significant CAD prevalence in patients with TypAng.

The intent-to-diagnose approach to CTA interpretation in CONFIRM did not account for potential inaccuracies from uninterpretable segments and coronary calcification. In all the sensitivity analyses we performed to account for these factors, marked overestimation of angiographically significant CAD by guideline probabilities persisted (online-only Data Supplement).

Conclusion

In this contemporary multinational study of patients with suspected CAD referred for noninvasive evaluation by coronary CTA, determination of the pretest likelihood of angiographically significant CAD by the invasive angiography-based guideline probabilities greatly overestimates the actual observed prevalence of disease.

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CLINICAL PERSPECTIVE

During the initial evaluation of a patient with chest pain, many clinicians use the age, sex, and angina typicality–based pretest probabilities currently cited in professional society practice guidelines (guideline probabilities) to direct decisions for subsequent diagnostic testing and treatment. However, guideline probabilities were derived from patients clinically referred to invasive angiography and have not been validated in patients undergoing noninvasive testing. In this multinational study, the investigators analyzed the performance of guideline probabilities in 14 048 consecutive patients, including 8106 patients with chest pain, referred for coronary computed tomographic angiography. Computed tomographic angiography was used to determine the presence of angiographically significant coronary artery disease. In patients with chest pain, guideline probabilities significantly overestimated the overall prevalence of $\geq$50% diameter stenotic coronary artery disease (51% versus 18% observed by computed tomographic angiography) and $\geq$70% diameter stenotic coronary artery disease (42% versus 10%). Overestimation was particularly pronounced in patients with atypical angina and typical angina across all sex, age, and risk factor subgroups. The large differences between observed and predicted disease prevalence persisted in sensitivity analyses adjusted for potential inaccuracies of coronary computed tomographic angiography. Results from this study illustrate a major limitation in the practice of applying disease prevalence derived from invasive coronary angiography to populations undergoing initial noninvasive evaluation for coronary artery disease and highlight the need for updating probabilities of angiographically significant coronary artery disease in such populations.