Received: 3 November 2017 | Revised: 27 February 2018 | Accepted: 4 March 2018

DOI: 10.1002/clc.22940

WILEY CLINICAL CARDIOLOGY

CLINICAL TRIAL UPDATES

Influence of symptom typicality for predicting MACE in patients without obstructive coronary artery disease: From the CONFIRM Registry (Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry)

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Funding information
Foundation for the National Institutes of Health, Grant/Award Number: R01 HL115150; Dalio Institute of Cardiovascular Imaging; Michael Wolk Foundation; The research reported in this study was funded by the National Institute of Health (Bethesda, Maryland) under grant number R01 HL115150. The research was also funded, in part, by a generous gift from the Dalio Institute of Cardiovascular Imaging (New York, New York) and the Michael Wolk Foundation (New York, New York)

Our objective was to assess the prognostic value of symptom typicality in patients without obstructive coronary artery disease (CAD), determined by coronary computed tomographic angiography (CCTA). We identified 4215 patients without prior history of CAD and without obstructive CAD (<50% CCTA stenosis). CAD severity was categorized as nonobstructive (1%–49%) and none (0%). Based upon the Diamond-Forrester criteria for angina pectoris, symptom typicality was classified as asymptomatic, nonanginal, atypical, and typical. Multivariable Cox proportional hazards models were used to assess the risk of major adverse cardiac events (MACE), comprising all-cause mortality, myocardial infarction, unstable angina, and late revascularization, according to symptom typicality. Mean patient age was 57.0 ±12.0 years (54.9% male). During a median follow-up of 5.3 years (interquartile range, 4.6–5.9 years), MACE were reported in 312 (7.4%) patients. Among patients with nonobstructive CAD, there was an association between symptom typicality and MACE (*P* for interaction = 0.05), driven by increased risk of MACE among those with typical angina and nonobstructive CAD (hazard ratio: 1.62, 95% confidence interval: 1.06–2.48, *P* = 0.03). No consistent relationship was found between symptom typicality and MACE among patients without any CAD (hazard ratio: 0.73, 95% confidence interval: 0.34–1.57, *P* = 0.08). In the CONFIRM registry, patients who presented with concomitant typical angina and nonobstructive CAD had a higher rate of MACE than did asymptomatic patients with nonobstructive CAD. However, the presence of typical angina did not appear to portend worse prognosis in patients with no CAD.

KEYWORDS

Coronary Artery Disease, Coronary Computed Tomographic Angiography, Major Adverse Cardiac Events, Symptom Typicality

1 | INTRODUCTION

Coronary computed tomographic angiography (CCTA) is a noninvasive imaging modality commonly used in the evaluation of patients with suspected coronary artery disease (CAD). Favorable test characteristics include high diagnostic performance for ruling out obstructive CAD.[1–3] CCTA is also useful for the detection of nonobstructive CAD, a condition associated with an increased risk of adverse cardiovascular outcomes.[4] The presence of nonobstructive CAD is particularly important given the observation that the majority of plaque ruptures implicated in acute coronary syndrome arise from nonobstructive plaques.[5–7]

Among patients undergoing evaluation for suspected CAD, chest pain is a frequent symptom that may present a clinical and therapeutic challenge.[8] Although the prognosis of nonobstructive CAD among patients with chest pain had once been considered to be benign, several recent studies using invasive angiography have elucidated the adverse prognosis associated with nonobstructive CAD.[9,10] Previous investigations have shown that among patients with stable chest pain, typical angina pectoris provides valuable diagnostic information for identification of obstructive CAD by invasive coronary angiography.[11] In addition, typical angina is associated with higher prevalence of obstructive CAD on CCTA compared with those without typical angina.[12] However, the prognostic impact of symptom typicality in patients with nonobstructive CAD by CCTA remains unclear. In the present study, we sought to determine the extent to which symptom typicality adds prognostic information in patients without obstructive CAD by CCTA.

2 | METHODS

2.1 | Study population

The rationale and design of the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry has been previously described.[13] For the purposes of this study, we used data from the CONFIRM long-term follow-up registry that

included participants with ≥3 years of follow-up. Enrolled were 17 181 patients who underwent CCTA at 17 centers in 9 countries within North America, Europe, and Asia between December 2002 and May 2011. Patients were deemed suitable for study inclusion if they were age ≥ 18 years, had undergone evaluation by CCTA scanner with ≥64 detector rows, and presented with an interpretable CCTA. Patients with nonevaluable segments were not included in this analysis. Patients were excluded according to the following criteria: known prior CAD at the time of CCTA, as defined by prior myocardial infarction (MI) or coronary revascularization, such as coronary artery bypass graft surgery and percutaneous coronary intervention (n = 2248); adverse events on the day of CCTA (n = 50); obstructive CAD (n = 4644); missing information for baseline factors, including age or sex (n = 30) as well as symptom typicality (n = 1755); severity of CAD (n = 434); missing information for major adverse cardiac events (MACE; n = 3729); and early revascularization <90 days from index CCTA (n = 322).

Each of the study centers' institutional review boards approved the study protocol, and all study participants provided written informed consent.

2.2 | Clinical characteristics and chest pain categorization

All patients were assessed at the time of CCTA examination. Baseline demographics and cardiovascular risk factors such as age, sex, hypertension (HTN), diabetes mellitus (DM), dyslipidemia, family history of premature CAD, and smoking status were obtained. HTN was defined as a systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg and/or use of antihypertensive medication. DM was defined by a fasting glucose level > 126 mg/dL and/or use of antidiabetic medications. Dyslipidemia was defined as a total cholesterol level > 200 mg/dL and/or the use of lipid-lowering agent. Family history of premature CAD was defined as a primary relative with a diagnosis early in life (ie, mother age < 65 years or father age < 55 years). Category of chest pain was based upon the Diamond-Forrester criteria for angina pectoris[14] and categorized as either asymptomatic, nonanginal, atypical, or typical angina. Symptom typicality was determined through either written survey or interview by a doctor or allied health professional at each site and documented at the site level.

2.3 | CCTA performance and interpretation

CCTA data at each site were obtained by utilization of a ≥ 64-detector-row CT scanner. Each institution analyzed all CCTA images. Data acquisition, image postprocessing, and data interpretation of CCTA adhered to the guidelines of the Society of Cardiovascular Computed Tomography (SCCT).[15,16] The definition of coronary atherosclerosis was any lesion ≥1 mm^2 that existed either within the lumen of the coronary artery or adjacent to the coronary artery lumen that could be distinguished from surrounding pericardial tissue, epicardial fat, or the artery lumen itself. CAD was defined as the presence of any plaque in the coronary artery. Nonobstructive CAD was defined as coronary artery segment plaque with a luminal diameter stenosis >0% and < 50%. Patients with 0% stenosis or a normal CCTA were considered to have no CAD. For further reliability and accuracy, all identified lesions were interrogated via numerous methods such as maximum-intensity-projection and multiplanar-reconstruction techniques along several longitudinal axes and in the transverse plane.

2.4 | Study outcome

The primary outcome was a composite of MACE including all-cause mortality (ACM), nonfatal MI, unstable angina, and late target-vessel revascularization (>90 days). Specific causes of death were not recorded in the CONFIRM registry. Trained personnel from each site adjudicated ACM by direct interview with physicians or by querying national medical databases. Other events such as MI and late target revascularization were collected via a combination of direct questioning of patients using a scripted interview and examination of the patients' medical records as previously described.[13]

2.5 | Statistical methods

Continuous variables are reported as mean ±SD, and categorical variables are presented as counts with percentages. We compared differences between continuous variables using a Student *t* test. Differences between categorical variables were compared with a χ^2 or Fisher exact test, as appropriate. Incidence of MACE per 1000 person-years was estimated by dividing the number of MACE by the absolute number of person-years at risk. We evaluated the relationship between symptom typicality and MACE according to the severity of CAD using the Kaplan–Meier method with log-rank tests for equality. Unadjusted and multivariable Cox regression models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) and identify associations between symptom typicality and MACE in patients without obstructive CAD, as well as for comparisons between nonobstructive CAD and no CAD. Candidate variables were selected for consideration in multivariable models based on a priori clinical knowledge. In the first model (Model 1), variables with significant univariate associations ($P < 0.05$) between both the predictor of interest (symptom typicality) and outcome (MACE) were included in a backward stepwise selection process with a covariant retention threshold set at $P < 0.05$. Model 1 included age, HTN, and DM. In an additional analysis (Model 2), we further adjusted for clinically important risk factors not selected in the stepwise selection process. Model 2 included age, sex, HTN, DM, dyslipidemia, family history of CAD, and current smoking. We performed additional sensitivity analyses adjusting for estimated Framingham risk and excluding late revascularization from the composite outcome.

The prognostic utility of symptom typicality was further assessed by use of the likelihood ratio test, wherein symptom typicality and CAD extent by likelihood ratio tests were compared by use of Cox proportional regression models with and without tests for interaction. All statistical analyses were performed using Stata software, version 14 (StataCorp LP, College Station, TX), and a 2-tailed *P* value <0.05 was considered statistically significant.

3 | RESULTS

Of 4215 patients included in the study, 1848 (43.8%), 498 (11.8%), 1497 (35.5%), and 372 (8.8%) were asymptomatic or had nonanginal, atypical, and typical angina, respectively. Overall, the mean age of the cohort was 57.0 ±12.0 years and 54.9% were male (Table 1). Participants with typical angina had a higher prevalence of DM, whereas those with nonanginal symptoms were older, more likely to smoke, and had a higher prevalence of HTN and family history of CAD ($P < 0.001$ for all). The asymptomatic group was predominantly male ($P < 0.001$).

During a median follow-up duration of 5.3 years (interquartile range, 4.6–5.9 years), there were a total of 312 (7.4%) MACE events, which included 161 (51.6%) ACM, 85 (27.2%) nonfatal MI or unstable angina, and 66 (21.2%) late revascularization events. The incidence of MACE was 7.7% (143/1848), 8.6% (43/498), 6.0% (89/1497), and 10.0% (37/372) in asymptomatic, nonanginal, atypical, and typical angina patients, respectively. Among patients with typical angina, 12 (32.4%) ACM, 12 (32.4%) nonfatal MI or unstable angina, and 13 (35.2%) late revascularization events occurred. Figure 1 displays the incidence of MACE per 1000 person-years according to symptom typicality groups and CAD severity. All symptom groups who had nonobstructive CAD demonstrated a higher incidence of MACE as compared with the no-CAD group. Notably, the highest incidence of MACE was observed amongs those with typical angina (43.0 per 1000 person-years), whereas no significant relationships were noted between symptom typicality and MACE in patients without any CAD.

Typical angina was associated with a higher risk of MACE in patients with nonobstructive CAD ($P = 0.01$ by log-rank test), whereas no association between symptom typicality and risk of MACE was found in those who had no CAD ($P = 0.12$ by log-rank test; Figure 2). Multivariable Cox regression revealed no consistent relationship between symptom typicality and MACE in the overall cohort (HR: 1.20, 95% CI: 0.83–1.73, $P = 0.09$; Table 2), as well as among those without any CAD (HR: 0.73, 95% CI: 0.34–1.57, $P = 0.08$). There was a modest trend toward increased risk of MACE among those with typical symptoms and nonobstructive CAD (P for interaction = 0.05). This appeared to be driven primarily by increased risk of MACE among those with typical angina and nonobstructive CAD (HR: 1.62, 95% CI: 1.06–2.48, $P = 0.03$) compared with asymptomatic patients with nonobstructive CAD. In contrast, nonanginal pain or atypical angina was not related to MACE in patients with nonobstructive CAD. There was no evidence of effect modification by sex in the relationship between symptom typicality and MACE among patients with nonobstructive CAD (P for interaction = 0.24).

Patients without any CAD had a favorable prognosis. A higher risk of MACE was observed for patients with nonobstructive CAD, with a graded relationship observed according to the number of vessels with affected plaque ($P < 0.001$ by log-rank test). In multivariable Cox regression analysis, the presence of 1-, 2-, and 3-vessel disease increased the risk of MACE by 2.10 (95% CI: 1.55–2.86), 2.79 (95% CI: 1.98–3.92), and 3.59 (95% CI: 2.50–5.16), respectively, when compared with no plaque.

In an additional analysis, we compared typical angina with all nontypical symptoms (including asymptomatic, nonanginal, and atypical angina). Typical angina in patients with nonobstructive CAD was associated with a higher risk of MACE as compared with those with nontypical symptoms and nonobstructive CAD (Model 1, HR: 1.72, 95% CI: 1.16–2.55, $P = 0.01$; and Model 2, HR: 1.78, 95% CI: 1.20–2.66, $P = 0.01$). For those without any CAD, typical angina was not a significant predictor of MACE in both multivariable models (Model 1, HR: 0.79, 95% CI: 0.38–1.65, $P = 0.52$; and Model 2, HR: 0.81, 95% CI: 0.39–1.69, $P = 0.57$). Furthermore, typical angina was associated with a higher risk of MACE over time in those with nonobstructive CAD ($P = 0.001$ by log-rank test), whereas no relationship was present between typical angina and MACE in patients diagnosed as having no CAD by CCTA ($P = 0.68$ by log-rank test).

We performed a series of sensitivity analyses to evaluate the consistency of our main findings. First, we performed an analysis adjusted for estimated Framingham risk score. Our results remained consistent after adjustment for Framingham risk score, with typical symptoms being associated with a HR of 1.74 (95% CI: 1.15–2.63) for MACE

TABLE 1 Baseline characteristics of patients

		Symptom Typicality				
Variables	**Total, N = 4215**	**Asymptomatic, n = 1848**	**Nonanginal, n = 498**	**Atypical, n = 1497**	**Typical, n = 372**	***P* Value**
Demographics						
Age, y	57.0 ± 12.0	57.6 ±11.6	58.9 ±11.6	55.7 ±12.2	57.0 ±13.2	<0.001
Male sex	2315 (54.9)	1140 (61.7)	234 (47.0)	769 (51.4)	172 (46.2)	<0.001
Cardiac risk factors						
HTN	2066 (49.3)	818 (44.5)	284 (57.3)	762 (51.4)	202 (54.5)	<0.001
DM	532 (12.7)	196 (10.7)	79 (15.9)	184 (12.4)	73 (20.0)	<0.001
Dyslipidemia	2131 (50.9)	905 (49.3)	277 (55.9)	766 (51.7)	183 (49.5)	0.06
Family history of CAD	1305 (31.4)	485 (26.5)	180 (37.0)	510 (34.6)	130 (35.1)	<0.001
Current smoking	705 (16.9)	296 (16.2)	118 (24.0)	235 (15.9)	56 (15.1)	<0.001
Extent of CAD by CCTA						
No CAD	2274 (54.0)	946 (51.2)	253 (50.8)	848 (56.7)	227 (61.0)	<0.001
Nonobstructive CAD	1941 (46.0)	902 (48.8)	245 (49.2)	649 (43.4)	145 (39.0)	

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; DM, diabetes mellitus; HTN, hypertension; SD, standard deviation. Data are presented as n (%) or mean ± SD.

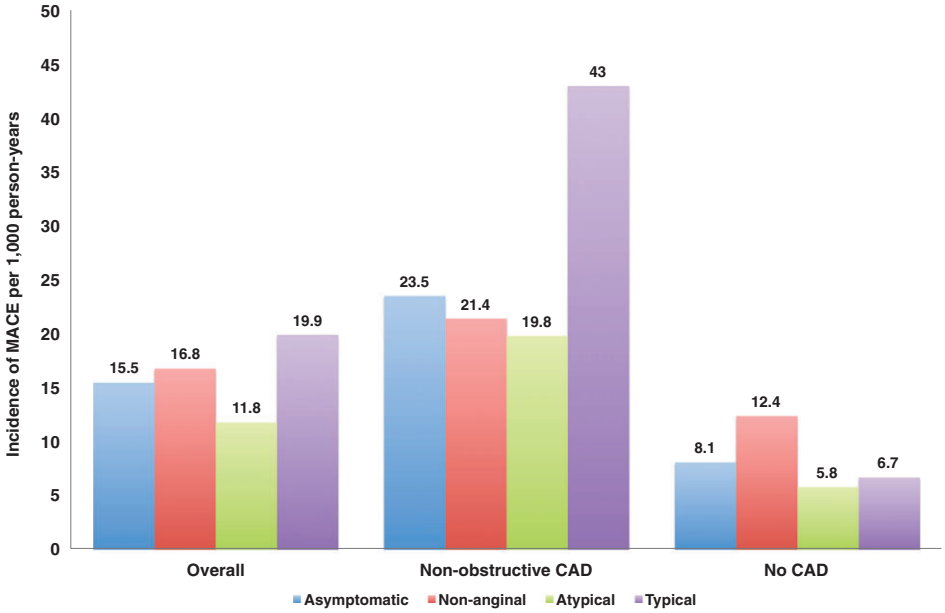

FIGURE 1 Incidence of MACE according to symptom typicality and severity of CAD. Abbreviations: CAD, coronary artery disease; MACE, major adverse cardiac events

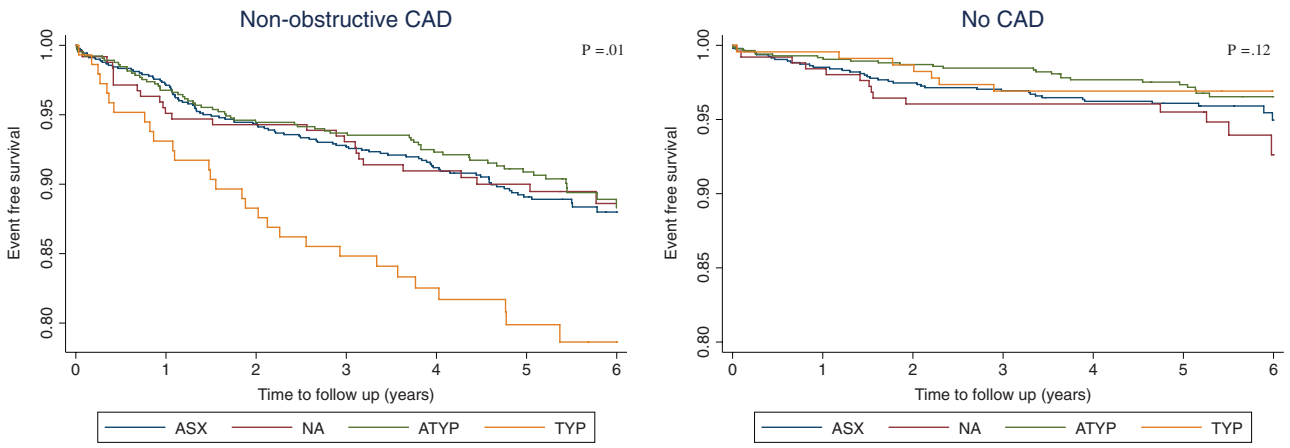

FIGURE 2 Kaplan–Meier survival curves for time to MACE according to symptom typicality and severity of CAD. Abbreviations: ASX, asymptomatic; ATYP, atypical angina; CAD, coronary artery disease; MACE, major adverse cardiac events; NA, nonanginal; TYP, typical angina

among patients with nonobstructive CAD. No relationship was observed between typical symptoms and MACE in patients without CAD (HR: 0.74, 95% CI: 0.34–1.59). An additional sensitivity analysis adjusting for estimated Adult Treatment Panel III risk also yielded consistent findings (not shown). In an analysis excluding late revascularization from the composite outcome of MACE, our finding of a relationship between typical symptoms and MACE in patients with nonobstructive CAD was no longer statistically significant (P = 0.06).

4 | DISCUSSION

In a large prospective, international, multicenter registry, we observed an independent association between typical angina pectoris and increased risk of MACE among patients with nonobstructive CAD determined by CCTA. In particular, typical angina among those with nonobstructive CAD was associated with a 1.6-fold increase in the risk of MACE, and may therefore portend worse prognosis as compared with asymptomatic patients with nonobstructive CAD. These findings, however, were largely driven by late revascularization. Conversely, we found no relationship between symptom typicality and MACE in patients with a normal CCTA. These findings underscore the prognostic significance of typical angina in patients diagnosed as having CCTA-visualized nonobstructive CAD in a routine clinical setting.

The current study observations are fitting with some,[9,10] but not all,[17–19] prior observations. Previously, several studies documented that chest pain without obstructive CAD is associated with low rates of adverse cardiovascular outcomes. However, these studies were limited by factors such as small sample sizes, limited endpoint ascertainment, and cohorts that may not reflect contemporary clinical practice.[17–19] More recently, the Women's Ischemia Syndrome Evaluation (WISE) study reported that women with symptoms and signs suggestive of ischemia but without obstructive CAD are at increased risk of cardiovascular events compared with asymptomatic women, emphasizing that these women should not be considered low-risk.[9] Although the WISE study was limited to women, our study findings in a population of both men and women enrolled in a contemporary registry extend the findings of WISE to a broader population.

TABLE 2 Cox proportional regression analysis for MACE according to the severity of CAD among patients without obstructive CAD

	Unadjusted				Model 1[a]				Model 2[b]			
Symptom typicality	HR	95% CI	[c]*P* Value	[d]*P* Value	HR	95% CI	[c]*P* Value	[d]*P* Value	HR	95% CI	[c]*P* Value	[d]*P* Value
Overall												
Asymptomatic	1 (Ref)			0.03	1 (Ref)			0.09	1 (Ref)			0.09
Nonanginal	1.08	0.76–1.51	0.68		0.97	0.69–1.36	0.85		0.95	0.67–1.35	0.79	
Atypical	0.76	0.58–0.99	0.04		0.76	0.58–0.99	0.04		0.76	0.58–1.00	0.05	
Typical	1.27	0.89–1.82	0.19		1.17	0.81–1.68	0.41		1.20	0.83–1.73	0.33	
Nonobstructive CAD												
Asymptomatic	1 (Ref)			0.01	1 (Ref)			0.06	1 (Ref)			0.03
Nonanginal	0.91	0.59–1.39	0.65		0.85	0.55–1.30	0.45		0.79	0.51–1.22	0.29	
Atypical	0.85	0.62–1.16	0.29		0.86	0.62–1.17	0.33		0.85	0.62–1.17	0.32	
Typical	1.81	1.20–2.73	0.005		1.59	1.04–2.41	0.03		1.62	1.06–2.48	0.02	
No CAD												
Asymptomatic	1 (Ref)			0.14	1 (Ref)			0.13	1 (Ref)			0.08
Nonanginal	1.49	0.83–2.66	0.18		1.32	0.74–2.38	0.35		1.39	0.77–2.52	0.28	
Atypical	0.71	0.43–1.17	0.18		0.65	0.39–1.09	0.10		0.62	0.36–1.05	0.08	
Typical	0.81	0.38–1.73	0.58		0.71	0.33–1.53	0.39		0.73	0.34–1.57	0.41	

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; MACE, major adverse cardiac events; Ref, reference; Ref, reference.

[a] Model 1: Adjusted for age, HTN, and DM.

[b] Model 2: Adjusted for age, sex, HTN, DM, dyslipidemia, family history of CAD, and current smoking.

[c] *P* Value: *P* value at the individual level in symptom typicality.

[d] *P* Value: *P* value at the level of the variable of symptom typicality.

Importantly, our main findings were consistent irrespective of sex, without evidence of effect modification by sex. These findings are in keeping with a previous analysis from the CONFIRM registry demonstrating similar prognosis among men and women with nonobstructive CAD matched for age, symptoms, and risk factors.[20]

The present study findings are also in keeping with those with of Jespersen et al., who examined the prognostic implications of stable angina pectoris in patients without obstructive CAD by invasive coronary angiography (ICA) in a retrospective analysis of 11 223 patients with suspected stable angina followed for 7.5 years.[10] In a multivariable model adjusted for several factors such as age, body mass index, DM, smoking, and use of lipid-lowering agent or antihypertensive medication, patients with diffuse nonobstructive CAD had a higher risk of MACE (HR: 1.85, 95% CI: 1.51–2.28, $P < 0.001$). As a "lumenogram," ICA is relatively insensitive for the detection of atherosclerosis. Using CCTA, a noninvasive imaging modality, our study further extends prior investigations using ICA-based strategies for evaluating patients with chest pain.[9,10]

The presence of typical angina is one of the hallmarks of ischemic heart disease. Although discussing the mechanisms explaining the relationship between typical angina and MACE in patients with nonobstructive CAD was beyond the scope of this study, several different mechanisms are possible. The first plausible scenario is the underestimation of coronary artery stenosis determined by CCTA. Although CCTA has high negative predictive value, it is possible that underestimation of coronary artery stenosis occurs in the subset of patients close to the threshold of 50% stenosis. Second, nonobstructive CAD is a simplistic categorization that describes anatomy without elucidation of factors germane to coronary physiology, such as plaque characteristics. Plaque characteristics by CCTA, such as low-attenuation plaque, spotty calcification, and positive remodeling, have been shown to improve the prediction of lesions that cause ischemia.[21] In a substudy of the Analysis of Coronary Blood Flow Using CT Angiography: Next Steps (NXT) trial, Gaur et al..[22] reported that several characteristics such as noncalcified plaque ≥185 mm^3, low-density noncalcified plaque ≥30 mm^3, total plaque volume ≥ 195 mm^3, and plaque length ≥ 30 mm predicted lesion-specific ischemia (fractional flow reserve ≤0.80) in nonobstructive CAD (≤50% stenosis) as well as obstructive CAD. Finally, symptoms as a result of myocardial ischemia may result from endothelial dysfunction, microvascular dysfunction, or coronary vasospasm.[8,23,24] As demonstrated by Graf et al, reduced coronary flow reserve was found in approximately 65% of patients with typical angina undergoing positron emission tomography.[25] Such impairment in coronary flow reserve may explain the mechanism by which patients with typical angina and without obstructive CAD experience adverse outcomes. Our finding that patients with nonobstructive disease and typical angina had higher risk of MACE than did those without typical symptoms likely reflects the identification of patients with ischemia. Interestingly, we observed no relationship between symptom typicality and MACE in patients without any CAD, highlighting the importance of atherosclerosis in the relationship between symptoms and adverse cardiac events. Assessment of microvascular ischemia by myocardial perfusion imaging was outside the scope of this study and we are unable to determine the extent to which patients with no CAD and typical symptoms had evidence of microvascular ischemia.

Nonobstructive CAD by CCTA is a common clinical finding whose presence identifies patients at greater risk of cardiovascular events. In a prospective study of 2583 consecutive patients without prior known CAD and without obstructive CAD, Lin et al[26] revealed that the presence and extent of nonobstructive plaques enhanced mortality risk prediction. Our study corroborates and expands the results of the latter study. We have shown that beyond plaque burden, the presence of symptoms influences prognosis in patients with nonobstructive CAD. Our data support the notion that stratification by symptoms is important in both the decision to refer to CCTA and the clinical interpretation of CCTA.

4.1 | Study limitations

Our study design is strengthened by the use of a large, contemporary international registry that reflects real-world patients. However, the limitations of our study design are noteworthy. Given the observational nature of this registry, our study may have been prone to potential biases such as heterogeneity in the population, interobserver and multisite variability in CCTA interpretation, and residual confounding. However, in an effort to minimize such biases, standardized data definitions were prospectively utilized, and only experienced CCTA centers with trained experts participated.[13] Given our study design, we were unable to consider the effect of cardiac medications that may have influenced symptom typicality. The CONFIRM study design did not allow for determination of cardiac mortality or further understanding of causes of death in patients with no CAD. However, prior studies have shown that use of cause-specific death can be inaccurate due to misclassification or misreporting of death, which can lead to an overestimation of cardiac deaths.[27] There were few "hard" events in this study, and thus our findings were largely driven by late revascularization and may reflect the practice that patients with typical angina were more likely to undergo late revascularization than were patients without symptoms.

Although the presence of symptoms was prospectively determined at the time of CCTA, information regarding the typicality of symptoms was assessed at select enrollment sites and missing in 1755 patients. Further, our null findings with respect to symptom typicality in patients without any CAD raise a question of whether there was sufficient power in this group. However, a post hoc power analysis demonstrated 80% power to detect the observed effect estimates in both unadjusted and adjusted models, with the exception of typical angina, which was slightly underpowered at 58% in the unadjusted model.

5 | CONCLUSION

In this prospective, international registry of patients undergoing CCTA, we observed an increased risk of MACE including late revascularization among patients who have concomitant typical angina and nonobstructive CAD, as compared with asymptomatic patients with

nonobstructive CAD. In contrast, symptoms were not associated with a worse prognosis in patients without CCTA-visualized CAD.

Conflicts of interest

Dr. Min serves on the scientific advisory board of Arineta, has ownership in MDDX, and has a research agreement with GE Healthcare. The authors declare no other potential conflicts of interest.

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REFERENCES

1. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324–2336.
2. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732.
3. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol*. 2008;52:2135–2144.
4. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. *Circ Cardiovasc Imaging*. 2014;7:282–291.
5. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation*. 2005;111:3481–3488.
6. Falk E, Shah PK, Fuster V. Coronary plaque disruption. *Circulation*. 1995;92:657–671.
7. Fuster V. Lewis A. Conner Memorial Lecture. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation*. 1994;90:2126–2146.
8. Yilmaz A, Sechtem U. Angina pectoris in patients with normal coronary angiograms: current pathophysiological concepts and therapeutic options. *Heart*. 2012;98:1020–1029.
9. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: a report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med*. 2009;169:843–850.
10. Jespersen L, Hvelplund A, Abildstrøm SZ, et al. Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J*. 2012;33:734–744.
11. Genders TS, Steyerberg EW, Alkadhi H, et al; CAD Consortium. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J*. 2011;32:1316–1330.
12. Nakanishi R, Rana JS, Rozanski A, et al. Relationship of dyspnea vs. typical angina to coronary artery disease severity, burden, composition and location on coronary CT angiography. *Atherosclerosis*. 2013;230:61–66.
13. Min JK, Dunning A, Lin FY, et al. Rationale and design of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) Registry. *J Cardiovasc Comput Tomogr*. 2011;5:84–92.
14. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary-artery disease. *N Engl J Med*. 1979;300:1350–1358.
15. Hendel RC, Patel MR, Kramer CM, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol*. 2006;48:1475–1497.
16. Mark DB, Berman DS, Budoff MJ, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;121:2509–2543.
17. Proudfit WL, Bruschke VG, Sones FM Jr. Clinical course of patients with normal or slightly or moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. *Circulation*. 1980;62:712–717.
18. Lichtlen PR, Bargheer K, Wenzlaff P. Long-term prognosis of patients with anginalike chest pain and normal coronary angiographic findings. *J Am Coll Cardiol*. 1995;25:1013–1018.
19. Kemp HG, Kronmal RA, Vlietstra RE, et al. Seven-year survival of patients with normal or near normal coronary arteriograms: a CASS registry study. *J Am Coll Cardiol*. 1986;7:479–483.
20. Leipsic J, Taylor CM, Gransar H, et al. Sex-based prognostic implications of nonobstructive coronary artery disease: results from the international multicenter CONFIRM study. *Radiology*. 2014;273:393–400.
21. Nakazato R, Park HB, Gransar H, et al. Additive diagnostic value of atherosclerotic plaque characteristics to non-invasive FFR for identification of lesions causing ischaemia: results from a prospective international multicentre trial. *EuroIntervention*. 2016;12:473–481.
22. Gaur S, Øvrehus KA, Dey D, et al. Coronary plaque quantification and fractional flow reserve by coronary computed tomography angiography identify ischaemia-causing lesions. *Eur Heart J*. 2016;37:1220–1227.
23. Agarwal M, Mehta PK, Bairey Merz CN. Nonacute coronary syndrome anginal chest pain. *Med Clin North Am*. 2010;94:201–216.
24. Pepine CJ, Ferdinand KC, Shaw LJ, et al; ACC CVD in Women Committee. Emergence of nonobstructive coronary artery disease: a woman's problem and need for change in definition on angiography. *J Am Coll Cardiol*. 2015;66:1918–1933.
25. Graf S, Khorsand A, Gwechenberger M, et al. Typical chest pain and normal coronary angiogram: cardiac risk factor analysis versus PET for detection of microvascular disease. *J Nucl Med*. 2007;48:175–181.
26. Lin FY, Shaw LJ, Dunning AM, et al. Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2583 patients undergoing 64-detector row coronary computed tomographic angiography. *J Am Coll Cardiol*. 2011;58:510–519.
27. Lloyd-Jones DM, Martin DO, Larson MG, et al. Accuracy of death certificates for coding coronary heart disease as the cause of death. *Ann Intern Med*. 1998;129:1020–1026.

How to cite this article: Lee JH, Han D, Hartaigh Bríain ó, et al. Influence of symptom typicality for predicting MACE in patients without obstructive coronary artery disease: From the CONFIRM Registry (Coronary Computed Tomography Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry). *Clin Cardiol*. 2018;41:586–593. https://doi.org/10.1002/clc.22940