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Authors

Lee, Ji Hyun
Han, Donghee
Hartaigh, Bríain Ó
et al.

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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)

Running head: Symptom typicality in patients without obstructive CAD

Ji Hyun Lee, MD[a,b], Donghee Han, MD[a,b], Bríain ó Hartaigh, PhD[a], Heidi Gransar, MSc[c], Yao Lu, MSc[a], Asim Rizvi, MD[a], Mahn Won Park, MD, PhD[a], Hadi Mirhedayati Roudsari, MD[a], Wijnand J. Stuijfzand, MD[a], Daniel S. Berman, MD[c], Tracy Q. Callister, MD[d], Augustin DeLago, MD[e], Martin Hadamitzky, MD[f], Joerg Hausleiter, MD[g], Mouaz H. Al-Mallah, MD, MSc[h], Matthew J. Budoff, MD[i], Philipp A. Kaufmann, MD[j], Gilbert Raff, MD[k], Kavitha Chinnaiyan, MD[k], Filippo Cademartiri, MD, PhD[l], Erica Maffei, MD[m], Todd C. Villines, MD[n], Yong-Jin Kim, MD[o], Jonathon Leipsic, MD[p], Gudrun Feuchtner, MD[q], Gianluca Pontone, MD[r], Daniele Andreini, MD[r], Hugo Marques, MD[s], Ronen Rubinshtein, MD[t], Stephan Achenbach, MD[u], Leslee J. Shaw, PhD[v], Hyuk-Jae Chang, MD, PhD[b], Jeroen Bax, MD, PhD[w], Benjamin Chow, MD[x], Ricardo C. Cury, MD[y], Millie Gomez, MD[a], Erica C. Jones, MD[a], Fay Y. Lin, MD[a], James K. Min, MD[a], and Jessica M. Peña, MD[a]

[a]Dalio Institute of Cardiovascular Imaging, Department of Radiology, NewYork-Presbyterian Hospital and Weill Cornell Medicine, New York, NY, USA; [b]Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea; [c]Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA, USA; [d]Tennessee Heart and Vascular Institute, Hendersonville, TN, USA; [e]Capitol Cardiology Associates, Albany, NY,

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USA; [f]Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany; [g]Medizinische Klinik I der Ludwig-Maximilians-Universität München, Munich, Germany; [h]King Saud bin Abdulaziz University of Health Sciences, King Abdullah International Medical Research Center, King AbdulAziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia; [i]Department of Medicine, Harbor UCLA Medical Center, Los Angeles, CA, USA; [j]University Hospital, Zurich, Switzerland; [k]William Beaumont Hospital, Royal Oaks, MI, USA; [l]Cardiovascular Imaging Center, Department of Radiology, SDN IRCCS Naples, Italy; [m]Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy; [n]Department of Medicine, Walter Reed Medical Center, Washington, DC, USA; [o]Seoul National University Hospital, Seoul, South Korea; [p]Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada; [q]Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria; [r]Department of Clinical Sciences and Community Health, University of Milan, Centro Cardiologico Monzino, IRCCS Milan, Italy; [s]UNICA, Cardiac CT and MRI Unit, Hospital da Luz, Lisbon, Portugal; [t]Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel; [u]Department of Medicine, University of Erlangen, Erlangen, Germany; [v]Division of Cardiology, Emory University School of Medicine, Atlanta, GA, USA; [w]Department of Cardiology, Leiden University Medical Center, HARTS, Leiden, The Netherlands; [x]Department of Medicine and Radiology, University of Ottawa, ON, Canada; [y]Baptist Cardiac and Vascular Institute, Miami, FL, USA.

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Dr. Min serves on the scientific advisory board of Arineta, has ownership in MDDX, and has a research agreement with GE healthcare. All other authors have no conflicts of interest to disclose.

Address for correspondence:

Jessica M. Peña, MD, MPH

Weill Cornell Medicine and NewYork-Presbyterian Hospital

Dalio Institute of Cardiovascular Imaging

413 E. 69th Street, Suite 108

New York, New York 10021

Phone: 646-962-6266

Fax: 646-962-0129

Email: jmp2003@med.cornell.edu

Abstract

Objective: To assess the prognostic value of symptom typicality in patients without obstructive coronary artery disease (CAD), determined by coronary computed tomographic angiography (CCTA).

Methods: 4,215 patients without prior history of CAD and without obstructive CAD (<50% CCTA stenosis) were identified. CAD severity was categorized as non-obstructive (1%-49%) and none (0%). Based upon the Diamond-Forrester criteria for angina pectoris, symptom typicality was classified as: asymptomatic, non-anginal, 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.

Results: Mean age was 57.0±12.0 years (54.9% male). During a median follow-up of 5.3 years (IQR, 4.6-5.9 years), MACE was reported in 312 (7.4%) patients. Among patients with non-obstructive CAD, there was an association between symptom typicality and MACE (p for interaction =.05), driven by increased risk of MACE among those with typical angina and non-

obstructive CAD (HR 1.62, 95% CI: 1.06-2.48, P =.03). No consistent relationship was found between symptom typicality and MACE among patients without any CAD (HR 0.73, 95% CI: 0.34-1.57, P =.08).

Conclusions: In the CONFIRM registry, patients who presented with concomitant typical angina and non-obstructive CAD had a higher rate of MACE than asymptomatic patients with non-obstructive 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; symptom typicality; major adverse cardiac events.

Abbreviations and Acronyms

ACM = All-Cause Mortality

CAD = Coronary Artery Disease

CCTA = Coronary Computed Tomographic Angiography

CI = Confidence Interval

CONFIRM = COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter

HR = Hazard Ratio

MACE = Major Adverse Cardiac Events

MI = Myocardial Infarction

INTRODUCTION

Coronary computed tomographic angiography (CCTA) is a non-invasive 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 non-obstructive CAD, a condition associated with an increased risk of adverse cardiovascular outcomes.[4] The presence of non-obstructive CAD is particularly important given the observation that the majority of plaque ruptures implicated in acute coronary syndrome arise from non-obstructive 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] While the prognosis of non-obstructive 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 non-obstructive 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 to those without typical angina.[12] However, the prognostic impact of symptom typicality in patients with non-obstructive 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.

METHODS

Study Population

The rationale and design of the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: An InteRnational Multicenter) registry has been previously described.[13]

For the purposes of this study, we used data from the CONFIRM long-term follow up registry which included participants with ≥3 years of follow-up. 17,181 patients who underwent CCTA at 17 centers in 9 countries within North America, Europe, and Asia were enrolled between December 2002 and May 2011. Patients were deemed suitable for study inclusion if they were aged 18 years or older, had undergone evaluation by CCTA scanner with 64-detector rows or greater, and presented with an interpretable CCTA. Patients with non-evaluable 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 MI or coronary revascularization such as coronary artery bypass graft surgery and percutaneous coronary intervention (n=2,248), adverse events on the day of CCTA (n=50), obstructive CAD (n=4,644), missing information for baseline factors including age or sex (n=30) as well as symptom typicality (n=1,755), severity of CAD (n=434), missing information for major adverse cardiac events (MACE) (n=3,729) 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.

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, diabetes, dyslipidemia, family history of premature CAD, and smoking status were obtained. Hypertension was defined as a systolic blood pressure of over 140 mmHg or diastolic blood pressure of over 90 mmHg and/or use of antihypertensive medication. Diabetes was defined by a fasting glucose level of over 126 mg/dl and/or use of diabetic medications. Dyslipidemia was defined as a total cholesterol level of above 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 (i.e., mother

<65 years of age or father <55 years of age). Category of chest pain was based upon the Diamond-Forrester criteria for angina pectoris[14] and categorized as either asymptomatic, non-anginal, 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.

CCTA performance and interpretation

CCTA data at each site were obtained by utilization of a 64—detector row or greater CT scanner. Each institution analyzed all CCTA images. Data acquisition, image post-processing, and data interpretation of CCTA adhered to the guidelines of the Society of Cardiovascular Computed Tomography.[15, 16] The definition of coronary atherosclerosis was any lesion ≥1mm^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. Non-obstructive 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 multi-planar-reconstruction techniques along several longitudinal axes and in the transverse plane.

Study Outcome

The primary outcome was a composite of MACE including all-cause mortality (ACM), non-fatal myocardial infarction (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]

Statistical Methods

Continuous variables are reported as means ± standard deviation, and categorical variables are presented as counts with percentages. We compared differences between continuous variables using a Student's t test. Differences between categorical variables were compared with a Chi-square or Fisher's exact test, as appropriate. Incidence of MACE per 1,000 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 (95% CI) and identify associations between symptom typicality and MACE in patients without obstructive CAD, as well as for comparisons between non-obstructive 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 <.05) between both the predictor of interest (symptom typicality) and outcome (MACE) were included in a backwards stepwise selection process with a covariant retention threshold set at P <.05. Model 1 included age, hypertension and diabetes. 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, hypertension, 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 version 14 (StataCorp LP, College Station, TX, USA), and a two-tailed p value less than 0.05 was considered statistically significant.

RESULTS

Of 4,215 patients included in the study, 1,848 (43.8%), 498 (11.8%), 1,497 (35.5%), and 372 (8.8%) were asymptomatic or had non-anginal, 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 diabetes mellitus, whereas those with non-anginal symptoms were older, more likely to smoke and had a higher prevalence of hypertension and family history of CAD (P <.001 for all). The asymptomatic group was predominantly male (P <.001).

During a median follow-up duration of 5.3 years (Interquartile range: 4.6-5.9 years), there were a total 312 (7.4%) MACE events, which included 161 (51.6%) ACM, 85 (27.2%) non-fatal MI or unstable angina, and 66 (21.2%) late revascularization events. The incidence of MACE was 7.7% (143/1,848), 8.6% (43/498), 6.0% (89/1,497), and 10.0% (37/372) in asymptomatic, non-anginal, atypical, and typical angina patients, respectively. Among patients with typical angina, 12 (32.4%) ACM, 12 (32.4%) non-fatal MI or unstable angina, and 13 (35.2%) late revascularization events occurred. Figure 1 displays the incidence of MACE per 1,000 person-years according to symptom typicality groups and CAD severity. All

symptom groups who had non-obstructive CAD demonstrated a higher incidence of MACE as compared with no CAD group. Notably, the highest incidence of MACE was observed amongst those with typical angina (43.0 per 1,000 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 non-obstructive CAD (P =.01 by log-rank test), while no association between symptom typicality and risk of MACE was found in those who had no CAD (P =.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 =.09) (Table 2), as well as among those without any CAD (HR 0.73, 95% CI: 0.34-1.57, P =.08). There was a modest trend towards increased risk of MACE among those with typical symptoms and non-obstructive CAD (P for interaction =.05). This appeared to be driven primarily by increased risk of MACE among those with typical angina and non-obstructive CAD (HR 1.62, 95% CI: 1.06-2.48, P =.03) compared to asymptomatic patients with non-obstructive CAD. In contrast, non-anginal pain or atypical angina was not related to MACE in patients with non-obstructive CAD. There was no evidence of effect modification by sex in the relationship between symptom typicality and MACE among patients with non-obstructive CAD (P for interaction=.24).

Patients without any CAD had a favorable prognosis. A higher risk of MACE was observed for patients with non-obstructive CAD, with a graded relationship observed according to the number of vessels with affected plaque (P <.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 non-typical symptoms (including asymptomatic, non-anginal, and atypical angina). Typical angina in patients with non-obstructive CAD was associated with a higher risk of MACE as compared to those with non-typical symptoms and non-obstructive CAD (Model 1: HR 1.72, 95% CI: 1.16-2.55, P =.01 and Model 2: HR 1.78, 95% CI: 1.20-2.66, P =.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 =.52 and Model 2: HR 0.81, 95% CI: 0.39-1.69, P =.57). Furthermore, typical angina was associated with a higher risk of MACE over time in those with non-obstructive CAD (P =.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 =.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 among patients with non-obstructive 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 ATPIII 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 non-obstructive CAD was no longer statistically significant (p=0.06).

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 non-obstructive CAD determined by CCTA. In particular, typical angina among those with

non-obstructive CAD was associated with a 1.6-fold increase in the risk of MACE, and may therefore portend worse prognosis as compared to asymptomatic patients with non-obstructive 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 non-obstructive 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 have 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. 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 non-obstructive 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 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, diabetes, smoking, and use of lipid-lowering agent or anti-hypertensive medication, patients with diffuse non-obstructive CAD had a higher risk of MACE (HR 1.85, 95% CI: 1.51-2.28, P <.001). As a "lumenogram" ICA is relatively insensitive for the detection of atherosclerosis. Using CCTA, a non-invasive 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. While the mechanisms explaining the relationship between typical angina and MACE in patients with non-obstructive 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, non-obstructive 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 NeXt sTeps (NXT) trial, Gaur et al.[22] reported that several characteristics such as non-calcified plaque ≥185 mm^3, low-density non-calcified 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 non-obstructive 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 vasopasm.[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 non-obstructive disease and typical angina had higher risk of MACE than 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.

Non-obstructive CAD by CCTA is a common clinical finding whose presence identifies patients at greater risk of cardiovascular events. In a prospective study of 2,583 consecutive patients without prior known CAD and without obstructive CAD, Lin et al.[26] revealed that the presence and extent of non-obstructive 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 non-obstructive 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.

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, inter-observer and multi-site 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, and 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 thus reflect the practice that patients with typical angina were more likely to undergo late revascularization than those 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 1,755 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. Last, our findings were largely driven by late revascularization and may thus reflect the practice that patients with typical angina were more likely to undergo late revascularization than those without symptoms.

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 non-obstructive CAD as compared to asymptomatic patients with non-obstructive CAD. In contrast, symptoms were not associated with a worse prognosis in patients without CCTA-visualized CAD.

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FIGURE LEGENDS

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

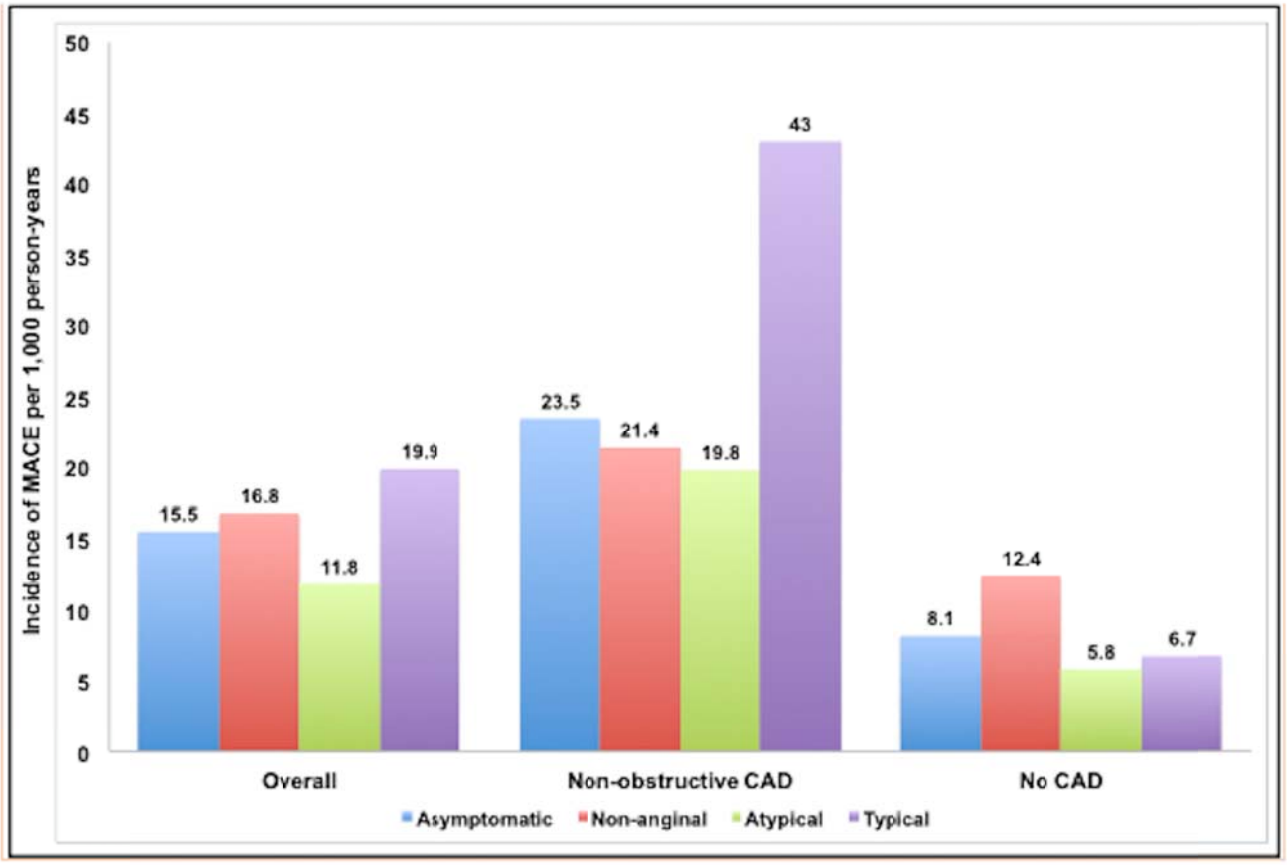

FIGURE 2. Kaplan-Meier survival curves for time-to-MACE according to symptom typicality and severity of CAD. Abbreviations: MACE = major adverse cardiac events; CAD = coronary artery disease; ASX = asymptomatic, NA = Non-anginal, ATYP = Atypical angina, TYP = Typical angina.

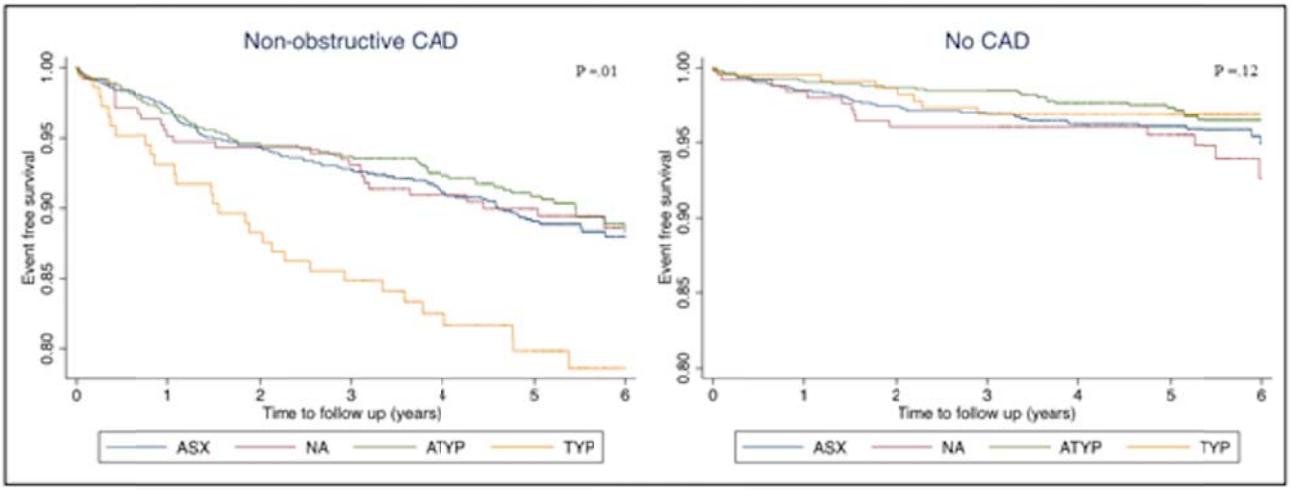

TABLE 1. Baseline characteristics

Variables	Total	Symptom typicality				
	(n=4,215)	Asymptomatic (n=1,848)	Non-anginal (n=498)	Atypical (n=1,497)	Typical (n=372)	P-value
Demographics						
Age, years	57.0±12.0	57.6±11.6	58.9±11.6	55.7±12.2	57.0±13.2	<.001
Male	2,315 (54.9)	1,140 (61.7)	234 (47.0)	769 (51.4)	172 (46.2)	<.001
Cardiac risk factors						
Hypertension	2,066 (49.3)	818 (44.5)	284 (57.3)	762 (51.4)	202 (54.5)	<.001
Diabetes	532 (12.7)	196 (10.7)	79 (15.9)	184 (12.4)	73 (20.0)	<.001
Dyslipidemia	2,131 (50.9)	905 (49.3)	277 (55.9)	766 (51.7)	183 (49.5)	.06
Family history of CAD	1,305 (31.4)	485 (26.5)	180 (37.0)	510 (34.6)	130 (35.1)	<.001
Current smoking	705 (16.9)	296 (16.2)	118 (24.0)	235 (15.9)	56 (15.1)	<.001
Extent of CAD by CCTA						
No CAD	2,274 (54.0)	946 (51.2)	253 (50.8)	848 (56.7)	227 (61.0)	<.001
Non-obstructive CAD	1,941 (46.0)	902 (48.8)	245 (49.2)	649 (43.4)	145 (39.0)	

CAD = coronary artery disease; CCTA = coronary computed tomographic angiography.

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

Symptom typicality	Unadjusted				Model 1[c]				Model 2[d]			
	HR	95% CI	[a]P-value	[b]P-value	HR	95% CI	[a]P-value	[b]P-value	HR	95% CI	[a]P-value	[b]P-value
Overall												
Asymptomatic	1 (ref)				1 (ref)				1 (ref)			
Non-anginal	1.08	0.76-1.51	.68	.03	0.97	0.69-1.36	.85	.09	0.95	0.67-1.35	.79	.09
Atypical	0.76	0.58-0.99	.04		0.76	0.58-0.99	.04		0.76	0.58-1.00	.05	
Typical	1.27	0.89-1.82	.19		1.17	0.81-1.68	.41		1.20	0.83-1.73	.33	
Non-obstructive CAD												
Asymptomatic	1 (ref)				1 (ref)				1 (ref)			
Non-anginal	0.91	0.59-1.39	.65	.01	0.85	0.55-1.30	.45	.06	0.79	0.51-1.22	.29	.03
Atypical	0.85	0.62-1.16	.29		0.86	0.62-1.17	.33		0.85	0.62-1.17	.32	
Typical	1.81	1.20-2.73	.005		1.59	1.04-2.41	.03		1.62	1.06-2.48	.02	
No CAD												
Asymptomatic	1 (ref)				1 (ref)				1 (ref)			
Non-anginal	1.49	0.83-2.66	.18	.14	1.32	0.74-2.38	.35	.13	1.39	0.77-2.52	.28	.08
Atypical	0.71	0.43-1.17	.18		0.65	0.39-1.09	.10		0.62	0.36-1.05	.08	
Typical	0.81	0.38-1.73	.58		0.71	0.33-1.53	.39		0.73	0.34-1.57	.41	

MACE = major adverse cardiac events; CAD = coronary artery disease; HR = hazard ratio; CI = confidence interval.

[a]P-value: P-value at the individual level in symptom typicality. [b]P-value: P-value at the level of the variable of symptom typicality.

[c]Model 1: Adjusted for age, hypertension, and diabetes.

[d]Model 2: Adjusted for age, sex, hypertension, diabetes, dyslipidemia, family history of CAD, and current smoking.