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Long-Term Prognosis of Patients With Intramural Course of Coronary Arteries Assessed With CT Angiography

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ABSTRACT

OBJECTIVES The aim of the present study was to evaluate, in low-to-intermediate pre-test probability patients who were referred for coronary computed tomography angiography (CTA) and did not show obstructive coronary artery disease (CAD), whether an intramural course of a coronary artery is associated with worse outcome compared with patients without an intramural course of the coronary arteries.

BACKGROUND The prognostic value of an intramural course of the coronary arteries on coronary CTA in patients without obstructive CAD is not well-known.

METHODS The study population consisted of 947 patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and who did not have obstructive CAD. During follow-up, the occurrence of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality was evaluated.

RESULTS On coronary CTA, 210 patients (22%) had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (interquartile range: 1.4 to 2.6 mm). In 84 patients (40%), the depth of the intramural course was considered deep (>2 mm surrounded by myocardium). During a median follow-up of 4.9 years (interquartile range: 3.2 to 6.9 years), a total of 43 events occurred: hospitalization due to unstable angina pectoris in 13 patients (1.4%); 7 patients (0.7%) had a nonfatal myocardial infarction; and 23 patients died (2.4%). The 6-year cumulative event rate of unstable angina pectoris requiring hospitalization (0.0% vs. 1.1%), nonfatal myocardial infarction (0.5% vs. 0.4%), all-cause mortality (1.9% vs. 2.2%) as well as the combined endpoint of all 3 events (2.4% vs. 3.7%) was similar in patients with and without an intramural course of a coronary artery.

CONCLUSIONS In patients without obstructive CAD on coronary CTA, the presence of an intramural course of a coronary artery was not associated with worse outcome. (J Am Coll Cardiol Img 2017;10:1451–8)

Coronary computed tomography angiography (CTA) is increasingly used to assess or exclude coronary artery disease (CAD) in patients with low-to-intermediate pre-test probability (1,2). When analyzing the coronary arteries for stenosis, variations in coronary anatomy are frequently observed. One of the most common findings on coronary CTA is an intramural course of the epicardial coronary arteries. The intramural course of a coronary artery is defined as any epicardial

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ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium

CAD = coronary artery disease

CT = computed tomography

CTA = computed tomography angiography

IQR = interquartile range

segment that runs intramurally through the myocardium that completely surrounds the vessel (3). The reported prevalence of the intramural course of coronary arteries on coronary CTA ranges from 6% to 58% (4). This large variation may be explained by the use of different imaging techniques and recent improvements in computed tomography (CT) technology that provide high spatial resolution and permit more precise analyses. In addition, the definition of the intramural course of the coronary artery (depth and length) differs among studies (4).

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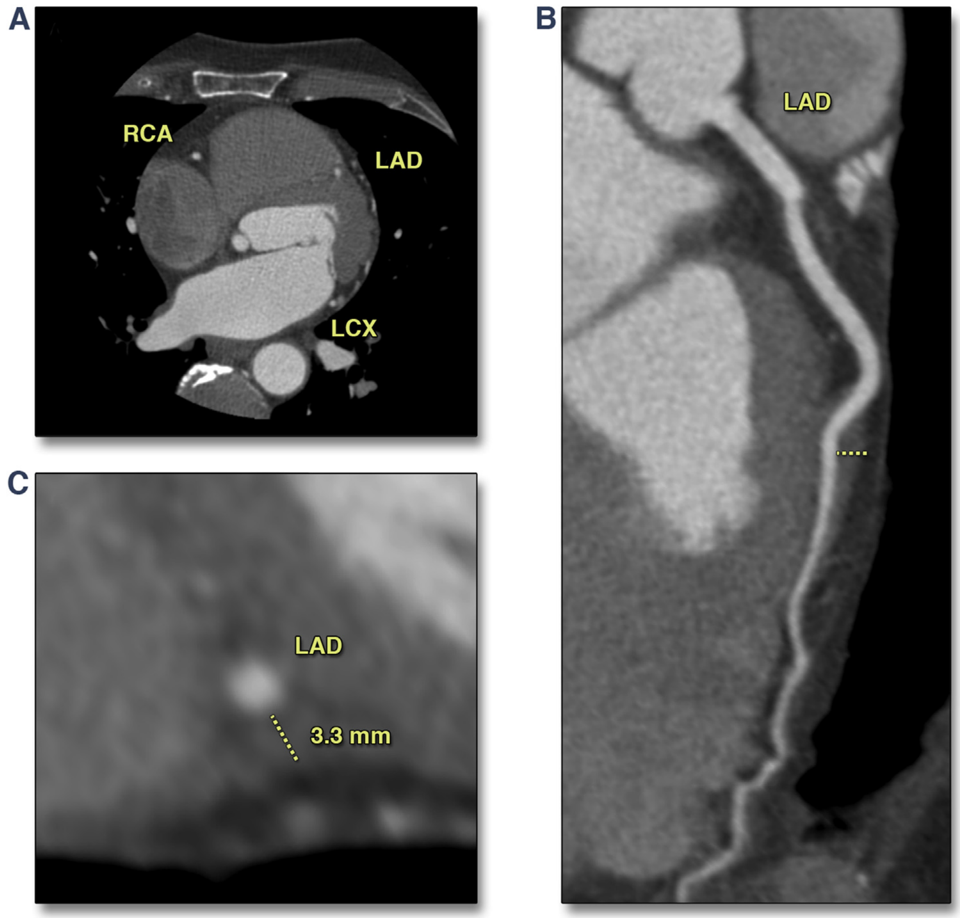
Although an intramural course of a coronary artery is considered a benign anomaly, small case series have linked the presence of an intramural course of the coronary artery to myocardial infarction (5,6), arrhythmias (7), and sudden cardiac death (8). However, prognostic data in a large population with an intramural course on coronary CTA are nonexistent. Accordingly, the present study evaluated, in patients with a low-to-intermediate pre-test probability who were referred for coronary CTA and without obstructive CAD, whether an intramural course of a coronary artery was associated with worse outcome compared with patients without an intramural course of the coronary arteries.

METHODS

PATIENTS. A total of 1,000 patients (from the Leiden University Medical Centre, Leiden, the Netherlands, and the Turku University Hospital, Turku, Finland)

FIGURE 1 Assessment of Intramural Course of Coronary Artery With Coronary Computed Tomography Angiography



Coronary computed tomography angiography images of a patient with an intramural course of the mid-left anterior descending (LAD) coronary artery demonstrated on the **(A)** axial image, **(B)** multiplanar reconstructed image, and **(C)** cross-section image at the side of the intramural course demonstrating the measurement of the depth (3.3 mm). LCX = left circumflex coronary artery; RCA = right coronary artery.

with cardiac complaints and/or an increased cardiovascular risk profile and low-to-intermediate pre-test probability (2) who were clinically referred for coronary CTA were included in the present analysis. Patients with a history of CAD (previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery), heart failure, valvular heart disease, arrhythmia, or congenital heart disease were excluded. In addition, patients with obstructive CAD on coronary CTA (defined as any coronary artery stenosis ≥50%), a nondiagnostic coronary CTA study, and patients lost to follow-up were not included in this analysis.

Clinical and coronary CTA data were prospectively entered into the database and analyzed retrospectively. For retrospective analysis of clinically acquired data, the Institutional Review Board of the Leiden University Medical Centre waived the need for written informed consent. Similarly, the Ethics Committee of the Hospital District of Southwest Finland approved the study protocol and waived the need for written informed consent. All clinically acquired data were handled anonymously.

CORONARY COMPUTED TOMOGRAPHY. All coronary CT scans were performed using a 64- or 320-detector row CT scanner (64-slice: Aquilion 64, Toshiba Medical Systems, Otawara, Japan; 320-slice: Aquilion ONE, Toshiba Medical Systems) in the Netherlands and a 64-detector row scanner (GE Discovery VCT, General Electric Medical Systems, Waukesha, Wisconsin) in Finland. A nonenhanced CT scan (for the assessment of the coronary artery calcium [CAC] score) and a contrast-enhanced CT scan (for noninvasive coronary angiography) were performed. Coronary CTA was performed as previously described (9,10). For the 64-slice scanner, a collimation of 64 × 0.5 mm, rotation time of 400 ms, and tube voltages and currents (adjusted to the body mass index) of 120 to 135 kV and 250 to 500 mA, respectively, were used. For the 320-slice scanner, a collimation of 320 × 0.5 mm, rotation time of 350 ms, and tube voltages and currents of 100 to 135 kV and 200 to 580 mA, respectively, were used. Advanced iterative reconstruction algorithms were applied. The average contrast dose was 76 ± 14 ml. For the coronary CTA data acquired in Finland, a collimation of 64 × 0.625 mm, a gantry rotation time of 350 ms, tube current between 600 and 750 mA, and voltage between 100 to 120 kV, depending on patient size, were used. The average contrast volume used was 60 to 80 ml (11). If not contraindicated, beta-blockers were administered orally (25 to 125 mg metoprolol) 1 h or intravenously (5 to 30 mg metoprolol) a few minutes before the coronary CTA in patients with a heart rate of >60 beats/min. The mean heart rate at the time of image acquisition was 57 ± 8 beats/min. Sublingual nitroglycerine (0.4 to 0.8 mg) was administered before the coronary CTA acquisition in the absence of contraindications.

Post-processing of the scans was performed with dedicated software (Vitrea FX 1.0, Vital Images, Minnetonka, Minnesota [in the Netherlands] and General Electric, GE ADW 4.5, Piscataway, New Jersey [in Finland]).

TABLE 1 Baseline Characteristics of the Patients Stratified According to the Presence or Absence of an Intramural Course on Coronary CTA

	All Patients (N = 947)	Patients With Intramural Course (n = 210)	Patients Without Intramural Course (n = 737)	p Value
Clinical characteristics				
Age, yrs	53.0 ± 12.0	54.0 ± 11.0	53.0 ± 12.0	0.19
Men	44	40	45	0.21
Risk factors				
BMI >30 kg/m^2	19	11	21	0.004
Hypercholesterolemia*	35	36	35	0.74
Hypertension†	40	40	39	0.82
Current smoking	15	16	15	0.62
Family history of CAD	48	52	47	0.21
Diabetes mellitus	27	29	26	0.35
Chest pain	57	53	58	0.37
Typical stable angina pectoris	11	9	11	0.36
Nonanginal chest pain or atypical chest pain	46	44	47	0.41
Early invasive diagnostic tests and treatment (<6 months)				
Coronary angiography (<6 months)	6.5	5.2	6.9	0.39
Revascularization (<6 months)	0.8	0.5	0.9	0.51
PCI	0.7	0.5	0.8	0.61
CABG	0.1	0.0	0.1	0.59
Coronary CTA				
Vessel dominance				0.45
Right	84	87	83	
Left	12	9	12	
Balanced	4	4	5	
Coronary artery calcium score (n = 811)	0 (0–12)	0 (0–27)	0 (0–8)	0.04
Nonobstructive CAD	58	62	57	0.24
Coronary plaques (composition)				
No. of calcified lesions	0.3 ± 1.0	0.3 ± 0.8	0.3 ± 1.0	0.27
No. of mixed lesions	0.4 ± 1.1	0.5 ± 1.1	0.4 ± 1.1	0.64
No. of noncalcified lesions	0.5 ± 1.4	0.5 ± 1.3	0.5 ± 1.4	0.76

Values are mean ± SD, %, or median (IQR). A p value <0.05 was considered statistically significant. *Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid-lowering drugs. †Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg and/or the use of antihypertensive medication.

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CTA = computed tomography angiography; IQR = interquartile range; PCI = percutaneous coronary intervention.

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TABLE 2 Distribution of Segments on CTA Among 210 Patients With an Intramural Course

LAD coronary artery	99 (47.0)
Proximal	4 (2.0)
Mid	56 (27.0)
Distal	22 (10.0)
Diagonal branch	17 (8.0)
LCX coronary artery	109 (52.0)
Intermediate/anterolateral	98 (47.0)
Proximal or distal	9 (4.0)
OM	2 (1.0)
Right coronary artery	2 (1.0)
Distal	1 (0.5)
RDP	1 (0.5)

Values are n (%).

LAD = left anterior descending; LCX = left circumflex; OM = obtuse marginal branches; RDP = right descending posterior; other abbreviation as in Table 1.

As previously described (9), the CAC score was calculated according to the algorithm of Agatston (12). All coronary CTAs were analyzed according to the modified 17-segment American Heart Association classification (13). Coronary artery segments with a diameter of ≥1.5 mm were included for analysis. The severity of coronary stenosis in each segment was stratified into 3 categories: 1) normal if no plaques were present; 2) nonobstructive CAD if the plaque covered 1% to 49% of the lumen; and 3) obstructive CAD if the plaque covered ≥50%. Coronary plaques were stratified into 3 groups: calcified (plaque containing ≥50% calcification); mixed (plaque containing <50% calcification); and noncalcified (plaque containing no calcification). To evaluate the presence of an intramural course of the coronary artery, multiplanar reconstruction images and cross-sectional views of the coronary arteries were created and interpreted (**Figure 1**). Intramural course was defined as any epicardial artery segment that ran intramurally, surrounded by at least 1 mm of myocardium (3). The intramural course was classified as superficial when the course was covered with 1 to 2 mm myocardium or as deep when covered with >2 mm myocardium (14,15).

FOLLOW-UP DATA. Follow-up data for the Dutch group of patients were obtained from hospital's files review, municipal civil registry, and contacting the patients. For the Finnish group of patients, follow-up data were obtained from the national health statistics and patients' electronic medical records. The combined endpoint consisted of time to unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, or all-cause mortality. Both unstable angina pectoris that required hospitalization (16) and nonfatal myocardial infarction (17) were defined according to standard definitions. Coronary CTA data analysis was performed blinded to the clinical follow-up data.

STATISTICAL ANALYSIS. Normally distributed continuous variables were expressed as mean ± SD and as median with 25th to 75th interquartile range (IQR) if not normally distributed. Categorical variables were presented as frequencies and percentages. Continuous variables were compared between groups with the independent samples *t* test (if normally distributed) or with the Mann-Whitney U test (for non-Gaussian variables). Categorical variables were compared between groups using the chi-square test. Cumulative event rates for the endpoints of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality, as well as the combined endpoint that included the first time of all 3 events were estimated with the Kaplan-Meier method and compared among groups using the log-rank test. Cox proportional hazard models were used to assess the association between clinical characteristics and coronary CTA results with the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality. Hazard ratios and their respective 95% confidence intervals were reported. Statistical analysis was performed using SPSS software version 22.0 (IBM Corp., Armonk, New York). A 2-sided p value <0.05 was considered statistically significant.

TABLE 3 Events Stratified to the Presence of an Intramural Course on Coronary CTA

Events	Total (N = 947)	Intramural Course (n = 210)	No Intramural Course (n = 737)	p Value
Follow-up period, yrs	4.9 (3.2–6.9)	4.6 (3.2–6.6)	5.0 (3.3–7.0)	0.15
Unstable angina pectoris requiring hospitalization	13 (1.4)	2 (1.0)	11 (1.5)	0.64
Nonfatal myocardial infarction	7 (0.7)	2 (1.0)	5 (0.7)	0.57
All-cause mortality	23 (2.4)	4 (1.9)	19 (2.6)	0.69
Combined endpoint*	43 (4.5)	8 (3.8)	35 (4.7)	0.73

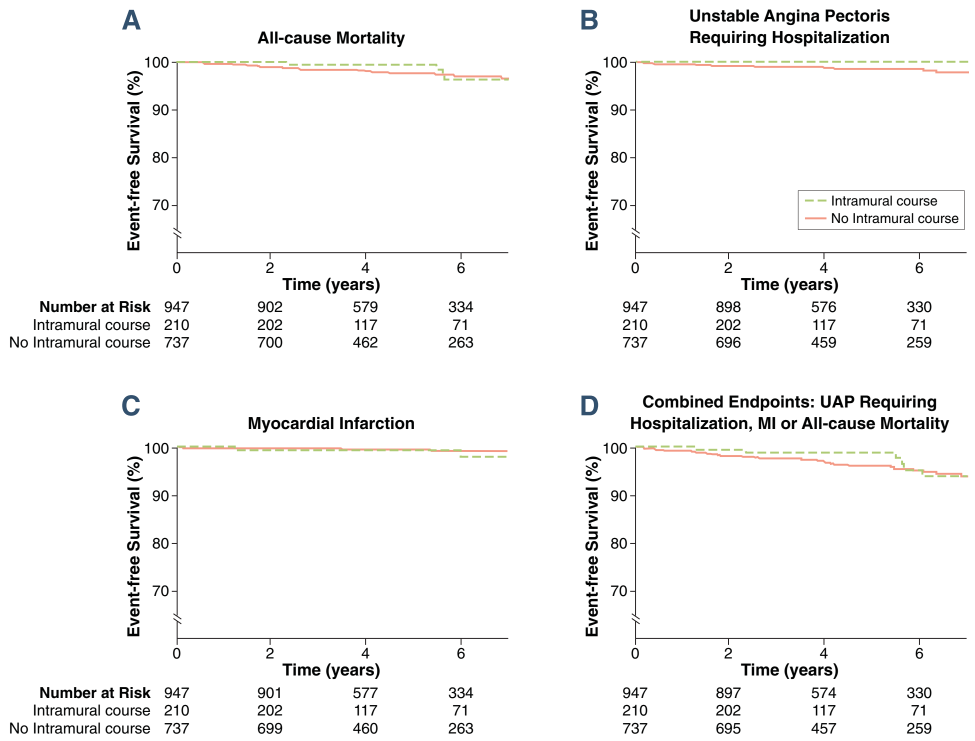
Values are median (IQR) or n (%). *Including unstable angina pectoris that required hospitalization, nonfatal myocardial infarction or all-cause mortality.

Abbreviations as in Table 1.

RESULTS

PATIENTS. Of the 1,000 patients initially included, 53 patients (5%) were lost to follow-up and excluded from the analysis. All baseline characteristics of the patients excluded from the analysis were similar to those of the patients included in the present analysis,

FIGURE 2 Kaplan-Meier Event-Free Survival Curves for Patients With and Without Intramural Course of the Coronary Artery



Kaplan-Meier curves for the endpoint, **(A)** all-cause mortality, **(B)** unstable angina pectoris (UAP) that required hospitalization, **(C)** nonfatal myocardial infarction (MI), and **(D)** the combined endpoint.

except for age, which was lower in the excluded group (47 ± 13 years vs. 53 ± 12 years; $p = 0.001$) (Online Table 1). The clinical characteristics of the remaining 947 patients without obstructive CAD on coronary CTA (56% women; mean age 53 ± 12 years) are presented in **Table 1**.

CORONARY COMPUTED TOMOGRAPHY. CAC score analysis was feasible in 811 (86%) patients. The median CAC score was 0 (IQR: 0 to 12). Most of the patients (63%) had a CAC score of 0, and 74 patients (9%) had a CAC score >100. The results of the coronary CTA are presented in **Table 1**. Nonobstructive CAD was observed in 553 (58%) patients, whereas the remaining patients (42%) had no coronary artery stenosis. The mean number of calcified segments and segments with mixed plaque were 0.3 ± 1.0 and 0.4 ± 1.1, respectively, and, on average, 0.5 ± 1.4 segments had noncalcified plaque.

PRESENCE OF AN INTRAMURAL COURSE. On coronary CTA, 210 (22%) patients had an intramural course of a coronary artery. The median depth of the intramural course was 1.9 mm (IQR: 1.4 to 2.6 mm). In 84 (40%) patients, the depth of the intramural course was considered deep (>2 mm surrounding myocardium).

Table 2 describes the segmental location of the intramural course. The most frequent segments that showed an intramural course were the mid/distal left anterior descending coronary artery (37%) and the intermediate/anterolateral coronary artery (47%).

Table 1 shows the differences in clinical characteristics between patients with an intramural course versus patients without an intramural course of the coronary artery. Patients without an intramural course of the coronary artery were more frequently obese in comparison with patients with an intramural course of the coronary artery (21% vs. 11%, respectively; $p = 0.004$). On coronary CT scan, the median CAC score was significantly higher in patients with an intramural course compared with patients without an intramural course (0; IQR: 0 to 27 vs. 0; IQR: 0 to 8, respectively; $p = 0.04$). There were no differences in the presence of nonobstructive CAD or the number of calcified/mixed and noncalcified plaques between both groups.

TABLE 4 Association of Clinical and Coronary CTA Characteristics With the Combined Endpoint: Unstable Angina Pectoris Requiring Hospitalization, Nonfatal Myocardial Infarction or All-Cause Mortality

	Event* (n = 43)	No Event* (n = 904)	Univariate Analysis		
			HR	95% CI	p Value
Clinical characteristics					
Age, yrs	60.00 ± 12.00	53.00 ± 12.00	1.06	1.03–1.09	<0.001
Women	54	56	1.04	0.57–1.90	0.90
Risk factors					
BMI >30 kg/m^2	24	18	1.54	0.75–3.13	0.24
Hypercholesterolemia†	24	36	0.61	0.3–1.24	0.17
Hypertension‡	44	39	1.07	0.58–1.98	0.83
Current smoking	14	15	0.88	0.37–2.07	0.76
Family history of CAD	37	49	0.61	0.33–1.13	0.11
Diabetes mellitus	24	27	0.88	0.43–1.79	0.72
Coronary CTA					
Calcium score (n = 811)	8 (0–247)	0 (0–11)	1.002	1.001–1.002	<0.001
Nonobstructive CAD	70	58	1.57	0.82–3.00	0.18
Intramural course of the coronary arteries	19	22	0.87	0.40–1.88	0.73
Coronary plaques (composition)					
No. of calcified lesions	0.98 ± 1.68	0.26 ± 0.90	1.34	1.16–1.56	<0.001
No. of mixed lesions	1.07 ± 1.97	0.39 ± 1.05	1.26	1.09–1.45	0.002
No. of noncalcified lesions	0.42 ± 0.76	0.49 ± 1.40	0.95	0.72–1.24	0.69

Values are mean ± SD, %, or median (IQR). A p value <0.05 was considered statistically significant. *Including unstable angina pectoris requiring hospitalization, nonfatal myocardial infarction, or all-cause mortality. †Serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl or treatment with lipid-lowering drugs. ‡Defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg, and/or the use of antihypertensive medication.

Abbreviations as in Table 1.

PATIENT OUTCOMES. As shown in Table 3, the median follow-up was 4.9 years (IQR: 3.2 to 6.9 years) and was similar in patients with and without an intramural course on coronary CTA (4.6; IQR: 3.2 to 6.6 years vs. 5.0; IQR: 3.3 to 7.0 years, respectively; p = 0.15). During follow-up, 43 events occurred; hospitalization due to unstable angina pectoris in 13 (1.4%) patients, 7 (0.7%) patients had a nonfatal myocardial infarction, and 23 (2.4%) patients died. No patient experienced >1 event. As shown in Figures 2A to 2C, unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality occurred similarly in patients with and patients without an intramural course of a coronary artery. At 6-year follow-up, the cumulative event rates for unstable angina pectoris that required hospitalization were 0.0% versus 1.1%. For nonfatal myocardial infarction, the event rates were 0.5% versus 0.4%, and for all-cause mortality, the event rates were 1.9% versus 2.2%.

The Kaplan-Meier event-free survival for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality, stratified according to the presence of an intramural course of a coronary artery, is shown in Figure 2D. Patients with an intramural course of the coronary artery had similar 6-year cumulative event rates of the combined endpoint compared with patients without an intramural course (the cumulative event rates were 2.4% vs. 3.7%, respectively; log-rank p = 0.73).

Associates for the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality are presented in Table 4. The intramural course of coronary arteries was not significantly associated with the combined endpoint (hazard ratio: 0.87; 95% confidence interval: 0.40 to 1.88; p = 0.73). In contrast, age, CAC score, and the number of calcified and mixed plaques were associated with the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, and all-cause mortality during long-term follow-up.

DISCUSSION

The present study evaluated, in a large cohort of patients without obstructive CAD, the prognostic implications of an intramural course of a coronary artery assessed on coronary CTA. An intramural course of a coronary artery was observed in 22% of patients. Patients with and without an intramural course of the coronary artery had similar low cumulative event rates for the combined endpoint of nonfatal myocardial infarction, unstable angina pectoris that required hospitalization, or all-cause mortality during long-term follow-up.

PRESENCE OF AN INTRAMURAL COURSE OF A CORONARY ARTERY. Intramural course of the coronary artery was for the first time described on invasive coronary angiography by Porstmann et al. in 1960 (18). Coronary CTA is a more sensitive imaging tool than invasive coronary angiography that characterizes the course of the coronary arteries, and, accordingly, studies have reported a prevalence of the intramural course of coronary arteries on coronary CTA that is more than twice as high as that observed on invasive angiography (0.5% to 11.8%) (19,20). Among 100 patients who underwent coronary CTA and invasive angiography, Leschka et al. (21) observed an intramural course of the coronary artery in 26 patients using coronary CTA compared with only 12 patients using invasive angiography. The lower prevalence of an intramural course on invasive angiography compared with coronary CTA can be partially explained by the fact that these 2 techniques detect different phenomena. Coronary CTA visualizes the anatomical relationship of the coronary artery with the surrounding myocardium. Conversely, invasive angiography can only detect systolic compression of the artery, which can be due to an intramural course (also referred to as myocardial bridging [22]), but occurs only in a minority of patients with an intramural course of the coronary artery. Uusitalo et al. (11) demonstrated that only approximately one-third of the patients with an intramural course on coronary CTA showed systolic compression during invasive coronary angiography.

The prevalence of an intramural course of a coronary artery on coronary CTA in the present study was 22%. This was in accordance with studies that used 64- and 128-slice CT scanners, which reported prevalences of 26% and 21%, respectively (23,24). Similar to the present study, the left anterior descending coronary artery was the coronary artery that more frequently showed an intramural course, regardless of the methodology used (15,21). In addition, the present study also demonstrated that the intermediate/anterolateral coronary artery was frequently involved.

INTRAMURAL COURSE OF THE CORONARY ARTERY AND LONG-TERM OUTCOME. Some case reports suggested that the presence of an intramural course of a coronary artery was associated with sudden cardiac death (8,25). The present study revealed similar survival rates for both groups during long-term follow-up. In addition, the occurrence of the combined endpoint of unstable angina pectoris that required hospitalization, nonfatal myocardial infarction, or all-cause mortality during long-term follow-up was similar in patients with and without an intramural course of a coronary artery. Rubinshtein et al. (26) demonstrated in 334 patients that the presence of an intramural course of a coronary artery assessed with coronary CTA did not have a prognostic impact for the composite endpoint of cardiovascular death or nonfatal myocardial infarction. In their study, during a mean follow-up of 6 years, there was no significant difference in cumulative event rates between both groups (5.1% in patients with an intramural course of a coronary artery vs. 3.2% in patients without an intramural course of a coronary artery; $p = 0.40$). The reason that the frequently present intramural course of the coronary artery on coronary CTA was not associated with adverse events was probably because an intramural course only occurred in the minority of the cases associated with systolic compression (“bridging”) (11).

STUDY LIMITATIONS. The present study visualized the anatomical relationship of the coronary artery to the surrounding myocardium, and therefore, cyclic changes in coronary artery flow nor dynamic compression could be evaluated. Because the study was retrospective, no assessment of the required sample size was performed.

CONCLUSIONS

In patients without obstructive CAD on coronary CTA, an intramural course of a coronary artery is not associated with worse outcome.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Coronary CTA is a widely available diagnostic tool to detect CAD in patients with a low-to-intermediate pre-test probability. In the group of patients without obstructive CAD found with coronary CTA, the presence of an intramural course of a coronary artery on coronary CTA was not associated with worse outcome. This finding suggested that this anatomical variation requires no extra adjustment in current (preventive) medical treatment.

TRANSLATIONAL OUTLOOK: Future research is needed to identify whether (preventive) medical treatment in patients with and without an intramural course of a coronary artery on coronary CTA (without obstructive CAD) should be equal. Furthermore, additional research is necessary to evaluate whether the outcome could be worse in the small subgroup of patients with an intramural course and systolic arterial compression (“bridging”).

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APPENDIX For a supplemental table, please see the online version of this paper.