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ORIGINAL RESEARCH

On the Natural History of Coronary Artery Disease: A Longitudinal Nationwide Serial Angiography Study

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BACKGROUND: The long-term course of coronary atherosclerosis has not been studied in large nationwide cohorts. Understanding the natural history of coronary atherosclerosis could help identify patients at risk for future coronary events.

METHODS AND RESULTS: All coronary artery segments with <50% luminal stenosis in patients with a first-time coronary angiogram between 1989 and 2017 were identified (n=2 661 245 coronary artery segments in 248 736 patients) and followed until a clinically indicated angiography within 15 years was performed or until death or end of follow-up (April 2018) using SCAAR (Swedish Coronary Angiography and Angioplasty Registry). The stenosis progression and incidence rates were 2.6% and 1.45 (95% CI, 1.43–1.46) per 1000 segment-years, respectively. The greatest progression rate occurred in the proximal and middle segments of the left anterior descending artery. Male sex and diabetes were associated with a 2-fold increase in risk, and nearly 70% of new stenoses occurred in patients with baseline single-vessel disease (hazard ratio, 3.86 [95% CI, 3.69–4.04]). Coronary artery segments in patients with no baseline risk factors had a progression rate of 0.6% and incidence rate of 0.36 (95% CI, 0.34–0.39), increasing to 8.1% and 4.01 (95% CI, 3.89–4.14) per 1000 segment-years, respectively, in patients with ≥4 risk factors. The prognostic impact of risk factors on stenosis progression was greatest in younger patients and women.

CONCLUSIONS: Coronary atherosclerosis progressed slowly but more frequently in the left coronary artery in men and in the presence of traditional risk factors. Coronary artery segments in patients without risk factors had little or no risk of stenosis progression, and the relative impact of risk factors appears to be of greater importance in younger patients and women. These findings help in the understanding the long-term course of coronary atherosclerosis.

Key Words: coronary artery disease ■ ischemic heart disease ■ natural history

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The long-term course of coronary atherosclerosis has not been studied in large cohorts. Information derived from autopsies of US soldiers killed in the Korean war showed that 40% had some degree of luminal narrowing.[1] Postmortem and intravascular ultrasound studies have shown that most acute coronary events coincide with thrombosis of a coronary atherosclerotic plaque caused by either rupture or erosion.[2–5] The prospective PROSPECT II (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) reported that major adverse cardiovascular events emanates from untreated angiographically mild coronary lesions with a large plaque burden with a lipid-rich core.[4] Small serial examination studies using coronary angiography and coronary computed tomography angiography (CCTA) have been conducted but follow-up time has primarily been in the range of 1 to 2 years.[6–15]

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CLINICAL PERSPECTIVE

What Is New?

- In this nationwide study of 248 736 patients with 2 661 245 coronary artery segments with <50% luminal stenosis, progression to ≥50% luminal stenosis within 15 years occurred in 2.6% of segments, with an incidence rate of 1.45 (95% CI, 1.43–1.46) per 1000 segment-years.
- Coronary atherosclerosis progressed more frequently in men, in the proximal segments of the left coronary artery, and in the presence of risk factors, the relative importance of which was greater in younger patients and women.
- Coronary atherosclerosis in patients without risk factors rarely progressed.

What Are the Clinical Implications?

- The current study estimates the rate by which coronary atherosclerosis progresses.
- These findings help in the understanding of the long-term course of coronary atherosclerosis and may inform screening evaluations and therapy approaches for primary and secondary prevention for coronary artery disease.

Nonstandard Abbreviations and Acronyms

CCTA	coronary computed tomography angiography
IR	incidence rate
PROSPECT	Prospective Natural-History Study of Coronary Atherosclerosis
PROSPECT II	Providing Regional Observations to Study Predictors of Events in the Coronary Tree
PROSPECT-ABSORB	Providing Regional Observations to Study Predictors of Events in the Coronary Tree II Combined With a Randomized, Controlled, Intervention Trial
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
SCAPIS	Swedish Cardiopulmonary BioImage Study
SWEDEHEART	Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies

SCAAR (Swedish Coronary Angiography and Angioplasty Registry) is a nationwide registry compiling results of all angiographies conducted in Sweden.[16] This database provides an opportunity to review records of coronary arteries initially considered stenosis-free until a clinically indicated repeat angiography is performed to examine the frequency and correlates of plaque development and progression.

The objectives of the present study were to describe the natural history of coronary artery atherosclerosis as assessed by coronary angiography and to characterize the progression of nonobstructive coronary artery disease (CAD) with respect to anatomic location, select risk factors (diabetes, hypertension, hyperlipidaemia, current smoking, and established CAD) and their burden, and their interaction with sex and age.

METHODS

Data Sources, Patient Cohort, and Study Design

SCAAR is part of the nationwide SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based care in Heart Disease Evaluated According to Recommended Therapies) registry in which data on all coronary angiographies and coronary interventions in Sweden since 1989 have been recorded. Complete reporting of angiographies and percutaneous coronary interventions (PCIs) by the treating cardiologist using a web-based interface is mandatory in all 29 Swedish catheterization laboratories. The registry reports angiographic data of all examined coronary artery segments and their degree of stenosis. Each Swedish resident has a unique personal identification number, and each coronary angiography and coronary intervention are assigned unique identification numbers allowing longitudinal follow-up.

Exclusion criteria and flowchart are presented in Figure S1. We included all patients enrolled for a first angiography in SCAAR between 1989 and 2017, regardless of indication (n=520 824 unique patients). As the intent was to study stenosis progression in coronary artery segments with <50% stenosis (termed "nonobstructive" CAD, 267 060 patients were excluded who had obstructive multivessel CAD (≥2 vessels containing lesions with ≥50% diameter stenosis) or those referred for coronary artery bypass grafting (CABG) or who had undergone CABG or heart transplant in the past (Figure S1)). Patients who died within 90 days of angiography (n=4931) and patients with missing vital status (n=97) were also excluded. In patients with single-vessel CAD, segments and branches in the diseased vessel were excluded (n=320 268 segments). Finally, all segments with stenosis progression within the first 90 days (n=3310) were excluded to avoid

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possible staged procedures or lesions missed on index angiography. Because of individual coronary anatomic variation that is not reflected in the registry, analyses were restricted to the following coronary artery segments: proximal left anterior descending (LAD), middle LAD, distal LAD, proximal right coronary artery (RCA), middle RCA, distal RCA, left main coronary artery, proximal left circumflex artery, distal left circumflex artery, first diagonal artery, first marginal artery, and right posterior descending artery/posterior descending artery/left posterior descending artery.

Among the final study cohort, we assessed coronary artery segments that on the baseline angiogram were nonobstructive (<50% diameter stenosis) which progressed and became obstructive (≥50% diameter stenosis) on a follow-up angiogram. Analyses were assessed at the vessel and segment level of the coronary artery tree. Follow-up continued for 15 years from index angiography or until death or conclusion of the study. Each segment/artery contributed to the analysis until it progressed to ≥50% luminal obstruction, death, or end of follow-up, after which segments/arteries become censored. Record review included all clinically indicated subsequent angiographies for each patient. Risk factor data for diabetes, hypertension, hyperlipidemia, and smoking were obtained from SCAAR and the coronary care unit registry from SWEDEHEART. To gain additional information concerning the extent of risk factors, we linked data to that of the National Patient Registry, which includes all hospital and specialized outpatient diagnoses. Hypertension was defined by use of antihypertensive medications or by elevated blood pressure requiring prescription of antihypertensive drugs at discharge or previous diagnosis of hypertension using the *International Classification of Diseases, Ninth Revision* (*ICD-9*), and the *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*) (I10, I10.9, 401). Diabetes was defined as diabetes known by the patient or by use of antidiabetic agents or insulin at index angiogram or prescription at discharge or by previous diagnosis of diabetes using *ICD* codes (E10, E11, E12, E13, E14, 250). Hyperlipidemia was defined by use of lipid-lowering drugs at index angiogram or prescription at discharge. Smoking was defined as reported smoking habits by patients. Patients were considered actively smoking even if they quit for <4 weeks. Established CAD was defined as single-vessel disease on index coronary angiography. The importance of individual risk factors as well as their cumulative influence were assessed by examining the incidence rate (IR) of nonobstructive CAD progression according to the total number of risk factors, stratified by sex and age (<50 years, 51–60 years, 61–70 years, 71–80 years, and >80 years). The current study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Table S1) and was approved by the regional ethical review board in Lund, Sweden (approval ID: 2015/297). SCAAR is part of nationwide quality of care registry and patients are informed about their participation and have the right to decline. However, no informed consent is legally required for patient inclusion. The data used in this study are legally restricted because of Swedish patient privacy and secrecy laws and the Uppsala University and Uppsala Clinical Research Center's legal department. Data are available on reasonable request to the Data Protection Officer at Uppsala County council at landstinget@lul.se.

Outcomes

The primary outcome was progression of coronary artery stenosis from nonobstructive to obstructive as assessed by clinically indicated repeat coronary angiography within the study period. Stenosis progression was defined as increasing segmental stenosis severity from <50% obstructive to ≥50% or any stenosis treated with PCI or CABG. The secondary outcome measure was progression to ≥50% stenosis treated with PCI or CABG.

Statistical Analysis

We first estimated the rates of stenosis progression from <50% to ≥50% stenosis with the Kaplan–Meier estimator. Second, we calculated the IR with 95% CIs per 1000 segment-years. Third, hazard ratios with 95% CIs were calculated using a sex- and age-adjusted Cox regression model to assess the relative risk of each independent risk factor as well as total number of risk factors (0, 1, 2, 3, or ≥4). Finally, we studied the impact of number of risk factors by age and sex with unadjusted Cox regression models. Because segments originating from the same patient cannot be regarded as entirely independent observations, we used a multilevel hierarchical Cox regression model with segments nested on the patient level to address this. To avoid selection bias and maximize power, multiple imputation was used to impute values for the 4 risk factors with missing values (hypertension [13%], diabetes [11%], hyperlipidemia [15%], and smoking [15%]) using a chained equation algorithm with 5 sets of complete data. Variables included in the imputation model were the investigated risk factors, inclusion year, age, sex, coronary artery segment, progression to clinically significant stenosis, and time to clinically significant stenosis. The estimates from each imputed data set were combined using Rubin's rules.[17] IRs were calculated on complete case data. Statistical analyses were performed using Stata version 16.0 for Macintosh (StataCorp LLC). A 2-sided $P<0.05$ was considered significant.

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RESULTS

Baseline Characteristics

A total of 248 736 patients with 2 661 245 nonobstructive coronary arterial segments within 496 636 vessels constituted the final study cohort (Figure S1). The median age was 64 years and 58.3% of patients were men (Table 1). Diabetes was present in 12.3% of patients, hypertension in 41.5%, and hyperlipidemia in 55.2%, and 16.0% were active smokers. Single-vessel disease (with ≥1 lesion with ≥50% diameter stenosis in 1 vessel) was present in 42.6% of patients, with the remainder having no detectable CAD or <50% stenosis (Table 1). The indication for the index coronary angiography was an acute coronary syndrome (ACS) in 45.8% of patients.

A total of 46 734 patients had at least 1 clinically indicated angiography performed at a later stage and a total of 69 289 repeat angiographies were performed. The median follow-up for each coronary segment was 6.6 years (quartile 1=3.3, quartile 3=10.8) and a total of 26 644 (2.6%) nonobstructive (<50% diameter stenosis) segments progressed to obstructive (≥50% diameter stenosis). The anatomical distribution of segment progression is shown in Figure 1 and the clinical characteristics of lesions are summarized in Table 2. The most common indication for angiography and progression to obstructive lesions was ACS (59.2%), followed by chronic coronary syndrome (30.7%). A total of 10 424 of 26644 (39.1%) lesions occurred within a single vessel, with the remaining lesions progressing in a multivessel setting (Table 2). The secondary outcome, progression to obstructive stenosis resulting in revascularization was observed in 16 298 of 26 644 (61.2%) lesions, translating into a Kaplan-Meier event rate of 1.6% and an IR of 0.88 (95% CI, 0.87–0.90) (Table 3). On a patient level, at least 1 segment progressed in 13 853 (12.9%) of patients, at least 1 segment was revascularized in 10 354 (9.8%) of patients, and 6710 (6.5%) of patients had an ACS with a revascularized lesion.

Table 1. Baseline Demographics and Risk Factors

	Patients	Coronary artery segments
	(n = 248 736)	(n=2 661 245)
Age, median (IQR), y	64.0 (55.0–72.0)	64.0 (55.0–72.0)
Men	144 896 (58.3)	1 514 312 (56.9)
Women	103 840 (41.7)	1 146 933 (43.1)
Diabetes	30 533 (12.3)	320 815 (12.1)
Hypertension	103 281 (41.5)	1 094 320 (41.1)
Hyperlipidemia	137 347 (55.2)	1 383 922 (52.0)
Active smoker	39 816 (16.0)	404 321 (15.2)
Single-vessel obstructive disease*	105 977 (42.6)	950 678 (35.7)
Presentation with ACS	113 893 (45.8)	1 123 818 (42.2)
Risk factors		
0	30 863 (12.4)	370 136 (13.9)
1	44 680 (18.0)	515 487 (19.4)
2	65 230 (26.2)	671 454 (25.2)
3	51 054 (20.5)	487 390 (18.3)
≥4	16 888 (6.8)	154 593 (5.8)
Missing risk factor information	40 021 (16.1)	462 185 (17.4)
Coronary artery segments		
Proximal RCA		222 698 (8.4)
Mid-RCA		222 627 (8.4)
Distal RCA		222 746 (8.4)
LMCA		248 257 (9.3)
Proximal LAD		197 845 (7.4)
Mid-LAD		197 769 (7.4)
Distal LAD		198 297 (7.5)
Proximal Cx		238 714 (9.0)
Distal Cx		238 820 (9.0)
First diagonal		193 589 (7.3)
First obtuse marginal		233 935 (8.8)
PDA/RPD/LPD		245 948 (9.2)

Values are expressed as number (percentage) unless otherwise indicated.

ACS indicates acute coronary syndrome; Cx, left circumflex artery; IQR, interquartile range; LAD, left anterior descending artery; LMCA, left main coronary artery; PDA/RPD/LPD, posterior descending artery/right posterior descending artery/left posterior descending artery; and RCA, right coronary artery.

*Compared with nonobstructive disease (all diameter stenoses <50%).

Location of New Obstructive Coronary Artery Lesions

Among 496 636 nonobstructive epicardial coronary arteries (left coronary artery [n=248 731] and RCA [n=247 905]), a total of 16 921 (8.3%) progressed to ≥50% stenosis within the study period resulting in an IR of 5.02 (95% CI, 4.94–5.09) per 1000 artery-years (Figure 2). The left coronary artery had a higher IR of plaque progression than the RCA (6.51 [95% CI, 6.39–6.63] vs 3.54 [95% CI, 3.46–3.64] per 1000 artery-years). The LAD (proximal, middle, and distal segments) had the highest stenosis progression rates among the 3 main trunks of coronary arteries (Figure 2). The plaque progression rate and IRs at segment level were 2.6% and 1.45 (95% CI, 1.43–1.46) per 1000 segment-years, lowest for the left main coronary artery, and highest in the middle segment of LAD followed by the proximal segment of LAD (Figure 2). Similar results were observed for progression to obstructive stenosis treated with PCI/CABG (Table 3).

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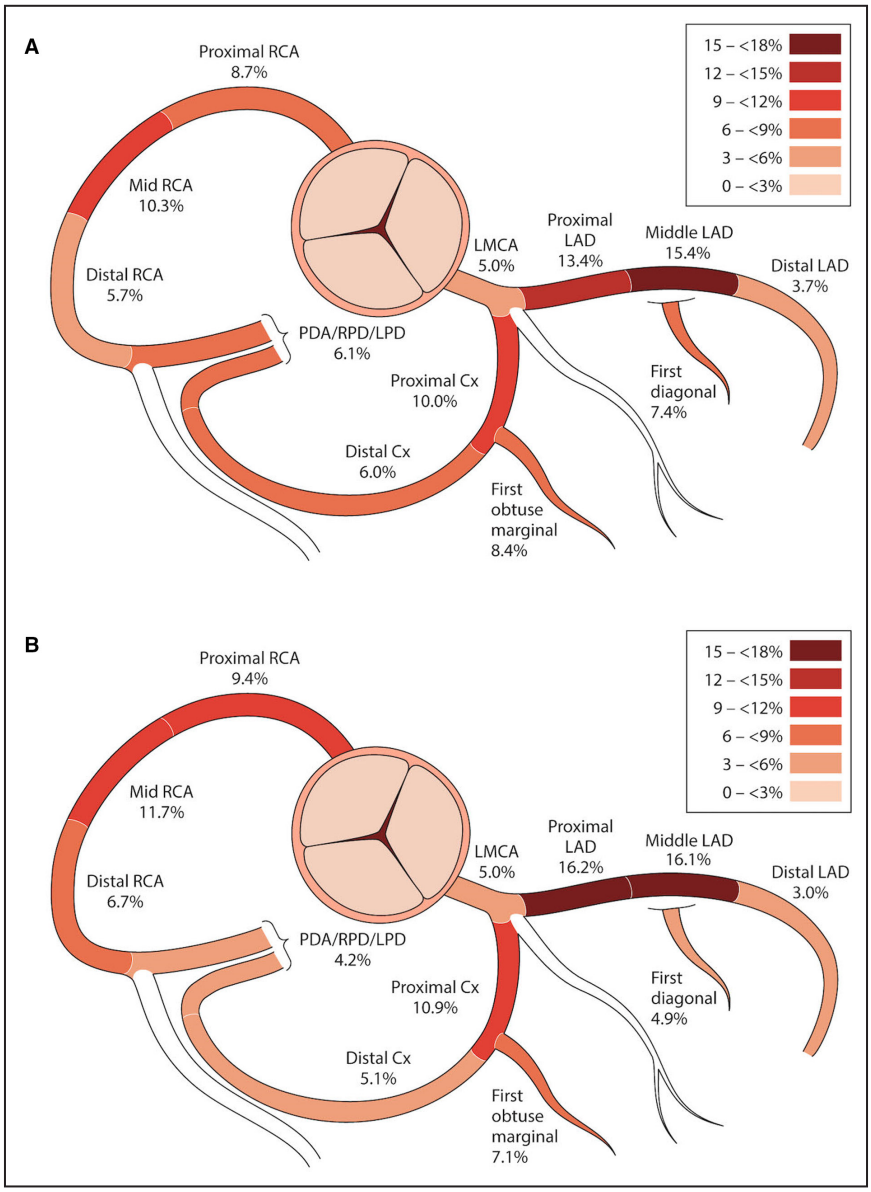

Figure 1. Distribution of progressive lesions.
(**A**) Shows the anatomical distribution of the 26644 coronary artery segments that progressed to atherosclerotic obstructive coronary artery disease. (**B**) Shows the anatomical distribution of the 16298 coronary artery segments that progressed to obstructive coronary artery disease and were revascularized with either percutaneous coronary intervention or coronary artery bypass grafting. The middle portion of the left anterior descending artery (LAD) was the most common site of progression to obstructive disease, whereas proximal LAD was the most common site when lesions were revascularized, reflecting a treatment bias. Cx indicates left circumflex artery; LMCA, left main coronary artery; PDA/RPD/LPD, posterior descending artery/right posterior descending artery/left posterior descending artery; and RCA, right coronary artery.

Natural History of Coronary Atherosclerosis Relative to Risk Factors, Risk Factor Burden, and Interaction With Sex and Age

Coronary artery segments of male patients exhibited higher rates of plaque progression and IR compared with women (3.5% and 1.89 [95% CI, 1.86–1.92] per 1000 segment-years compared with 1.5% and 0.88 [95% CI, 0.86–0.90] per 1000 segment-years; hazard ratio, 2.22 [95% CI, 2.13–2.32]). IR of stenosis progression ranged from 0.91 to 1.58 per 1000 segment-years across the 5 age groups (<50 years, 51–60 years, 61–70 years, 71–80 years, and >80 years). The specific risk

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Table 2. Characteristics of Progressive Lesions

	Lesions
All	26644 (100)
Men	19536 (73.3)
Women	7108 (26.7)
Age at follow-up procedure, y	68.3 (60.8–74.9)
Indication	
CCS	8168 (30.7)
CSS angina grade I	713 (8.2)
CSS angina grade II to IV	7239 (83.0)
Unknown	771 (8.8)
ACS	15771 (59.2)
Ambiguous chestpain	528 (2.0)
Silent ischemia	120 (0.5)
Arrhytmia/valvular/HF	1594 (6.0)
Other	463 (1.7)
Angiography results	
Single-vessel disease	10424 (39.1)
Multivessel disease or disease involving LMCA	15930 (59.8)
Lesion resulting in PCI/CABG	16298 (61.2)
Lesion resulting in PCI	15030 (56.4)
Lesion resulting in CABG*	1311 (4.9)
Lesion resulting in PCI and presenting with ACS	9671 (36.3)

Values are expressed as number (percentage) unless otherwise indicated.
ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CSS, Canadian Cardiovascular Society; and HF, heart failure; LMCA, left main coronary artery; and PCI, percutaneous coronary intervention.

factors with the highest impact on plaque progression were: (1) obstructive (single-vessel) CAD on index angiography; (2) diabetes; (3) active smoking; (4) hyperlipidemia; and (5) hypertension (Figure 3). A linear increase in plaque progression rates from 0.6% to 8.1% was observed with increased risk-factor burden from 0 to ≥4 risk factors (Figure 3). An association between the number of risk factors and plaque progression was observed in all age groups (Figure 4). The importance of risk factors was more pronounced in younger patients and women, with younger women showing the highest relative risk of stenosis progression (Figure 4). Similar associations were observed for the secondary outcome, progression to obstructive stenosis treated with PCI/CABG (Figure 5).

DISCUSSION

We assessed the progression of nonobstructive to obstructive CAD using serial coronary angiograms and a luminal stenosis of ≥50% as an arbitrary cut-off for significant disease. Using a nationwide cohort with data on 2661245 coronary artery segments with absent or mild (nonobstructive) coronary atherosclerosis in 248736 patients with a median follow-up time of 6.6 years, progression to obstructive coronary atherosclerotic disease occurred in 26644 (2.6%) coronary artery segments in 13853 (12.9%) of patients with an estimated rate of progression of 1.45 per 1000 segment-years. Atherosclerosis progressed more rapidly in the left coronary artery compared with the RCA, in proximal segments compared with distal segments, and in the middle and proximal portions of the LAD compared with other coronary artery tree segments. Atherosclerosis progression increase was most prominent in patients with diabetes and those with obstructive (single-vessel) CAD already present and, increased in a linear fashion with increased risk factor burden. The relative importance of multiple risk factors was greater in younger patients; in particular, younger women exhibited a significantly higher risk. These associations remained for lesions revascularized with PCI or CABG.

Previous reports on the natural history of coronary atherosclerosis stem from autopsies, coronary angiography including intracoronary diagnostic studies, and CCTA. Among the most recent autopsy studies, one showed that atherosclerosis was prevalent in some form in 8.5% of soldiers in the Iraq war with a mean age of 26 years.[18] Serial sampling with repeat angiography has previously been used to assess temporal aspects of coronary atherosclerosis progression but prior studies have been limited in sample size.[6–10] CCTA has provided an opportunity for noninvasive assessment of lumen narrowing as well as identification of characteristics such as plaque burden and calcification in population-based settings, reducing selection bias.[11–15] SCAPIS (Swedish Cardiopulmonary BioImage Study) is the largest CCTA study intended to assess the prevalence of coronary atherosclerosis, performed in 25182 randomly selected patients aged 50 to 64 years, free from previous myocardial infarction or coronary intervention.[19] Atherosclerosis was found in 42.1% of patients, with 5.2% having a luminal stenosis ≥50% without clinical symptoms. The prevalence of atherosclerosis increased with increasing risk factor burden.[19] Intracoronary imaging studies of patients with symptomatic CAD have further expanded our knowledge of plaque progression. The prospective PROSPECT (Prospective Natural-History Study of Coronary Atherosclerosis) natural history studies have shown that among patients with ACS in which all culprit and severe lesions were stented, unanticipated future coronary events arose most often from untreated plaques that had large plaque burden and were lipid-rich despite angiographically appearing mild.[3,4]

The current study differs from previous studies of coronary atherosclerosis progression in several aspects. To our knowledge the present report is the largest such study and the only to include all patients

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Table 3. Results of Secondary Outcome: ≥50% Luminal Obstruction Revascularized With PCI or CABG

	Segment/arteries at risk	Segment/artery-y	KM event rates	IR (95% CI)/1000 person-y	HR (95% CI)
Coronary arteries					
All	496 636 (100)	3 372 603	11 659 (5.7)	3.46 (3.39–3.52)	
RCA	247 905 (49.9)	1 695 069	3952 (4.0)	2.33 (2.26–2.41)	
LCA	248 731 (50.1)	1 677 808	7707 (7.4)	4.59 (4.49–4.70)	
Main arteries and branches					
RCA	222 879 (19.3)	1 529 315	3472 (3.9)	2.27 (2.20–2.35)	
LMCA	248 257 (21.5)	1 717 534	806 (0.8)	0.47 (0.44–0.50)	
LAD	198 404 (17.2)	1 363 836	4672 (5.7)	3.43 (3.33–3.53)	
Cx	238 944 (20.7)	1 643 836	2385 (2.5)	1.45 (1.39–1.51)	
Branches	248 699 (21.5)	1 703 562	2457 (2.5)	1.44 (1.39–1.50)	
By segment					
All	2 661 245 (100.0)	18 431 576	16 298 (1.6)	0.88 (0.87–0.90)	
Proximal RCA	222 698 (8.4)	1 539 676	1531 (1.8)	0.99 (0.95–1.05)	
Mid-RCA	222 627 (8.4)	1 537 161	1903 (2.2)	1.24 (1.18–1.29)	
Distal RCA	222 746 (8.4)	1 542 908	1093 (1.3)	0.71 (0.67–0.75)	
LMCA	248 257 (9.3)	1 717 570	806 (0.8)	0.47 (0.44–0.50)	
Proximal LAD	197 845 (7.4)	1 373 631	2639 (3.4)	1.92 (1.85–2.00)	
Mid-LAD	197 769 (7.4)	1 370 213	2616 (3.3)	1.91 (1.84–1.98)	
Distal LAD	198 297 (7.5)	1 385 931	489 (0.6)	0.35 (0.32–0.39)	
Proximal Cx	238 714 (9.0)	1 647 297	1777 (1.9)	1.08 (1.03–1.13)	
Distal Cx	238 820 (9.0)	1 652 001	826 (0.9)	0.50 (0.47–0.54)	
First diagonal	193 589 (7.3)	1 348 634	791 (1.0)	0.59 (0.55–0.63)	
First obtuse marginal	233 935 (8.8)	1 615 577	1151 (1.3)	0.71 (0.67–0.75)	
PDA/RPD/LPD	245 948 (9.2)	1 700 976	676 (0.7)	0.40 (0.37–0.43)	
Subgroup					
Women	1 146 933 (43.1)	8 086 480	4211 (0.9)	0.52 (0.51–0.54)	
Men	1 514 312 (56.9)	10 345 096	12 087 (2.1)	1.17 (1.15–1.19)	2.29 (2.18–2.41)
No diabetes	2 037 197 (76.6)	12 822 582	11 416 (1.8)	0.89 (0.87–0.91)	
Diabetes	320 815 (12.1)	1 932 673	3044 (3.1)	1.58 (1.52–1.63)	1.82 (1.72–1.92)
No hypertension	1 221 360 (45.9)	8 109 410	7295 (1.8)	0.90 (0.88–0.92)	
hypertension	1 094 320 (41.1)	6 294 251	6831 (2.3)	1.09 (1.06–1.11)	1.36 (1.31–1.43)
No Hyperlipidemia	883 835 (33.2)	5 037 208	2977 (1.6)	0.59 (0.57–0.61)	
Hyperlipidemia	1 383 922 (52.0)	8 792 140	10 823 (2.4)	1.23 (1.21–1.25)	1.95 (1.85–2.05)
No CAD	1 710 567 (64.3)	11 949 394	4991 (0.8)	0.42 (0.41–0.43)	
CAD	950 678 (35.7)	6 482 182	11 307 (3.1)	1.74 (1.71–1.78)	3.91 (3.72–4.12)
Nonsmoker	1 868 197 (70.2)	11 469 308	10 365 (1.9)	0.90 (0.89–0.92)	
Smoker	404 321 (15.2)	2 683 713	3556 (2.6)	1.33 (1.28–1.37)	1.48 (1.41–1.56)
No. of risk factors					
0	370 136 (13.9)	2 122 700	496 (0.4)	0.23 (0.21–0.26)	
1	515 487 (19.4)	3 064 681	1646 (1.3)	0.54 (0.51–0.56)	1.86 (1.67–2.06)
2	671 454 (25.2)	4 232 329	4395 (2.2)	1.04 (1.01–1.07)	3.44 (3.13–3.79)
3	487 390 (18.3)	3 060 401	4748 (3.0)	1.55 (1.51–1.60)	5.32 (4.83–3.86)
≥4	154 593 (5.8)	928 787	2089 (4.4)	2.25 (2.15–2.35)	8.39 (7.56–9.30)

Values are expressed as number (percentage). CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; Cx, left circumflex artery; HR, hazard ratio; IR, incidence rate; KM, Kaplan-Meier; LAD, left anterior descending artery; LCA, left coronary artery; LMCA, left main coronary artery; PCI, percutaneous coronary intervention; PDA/RPD/LPD, posterior descending artery/right posterior descending artery/left posterior descending artery; and RCA, right coronary artery.

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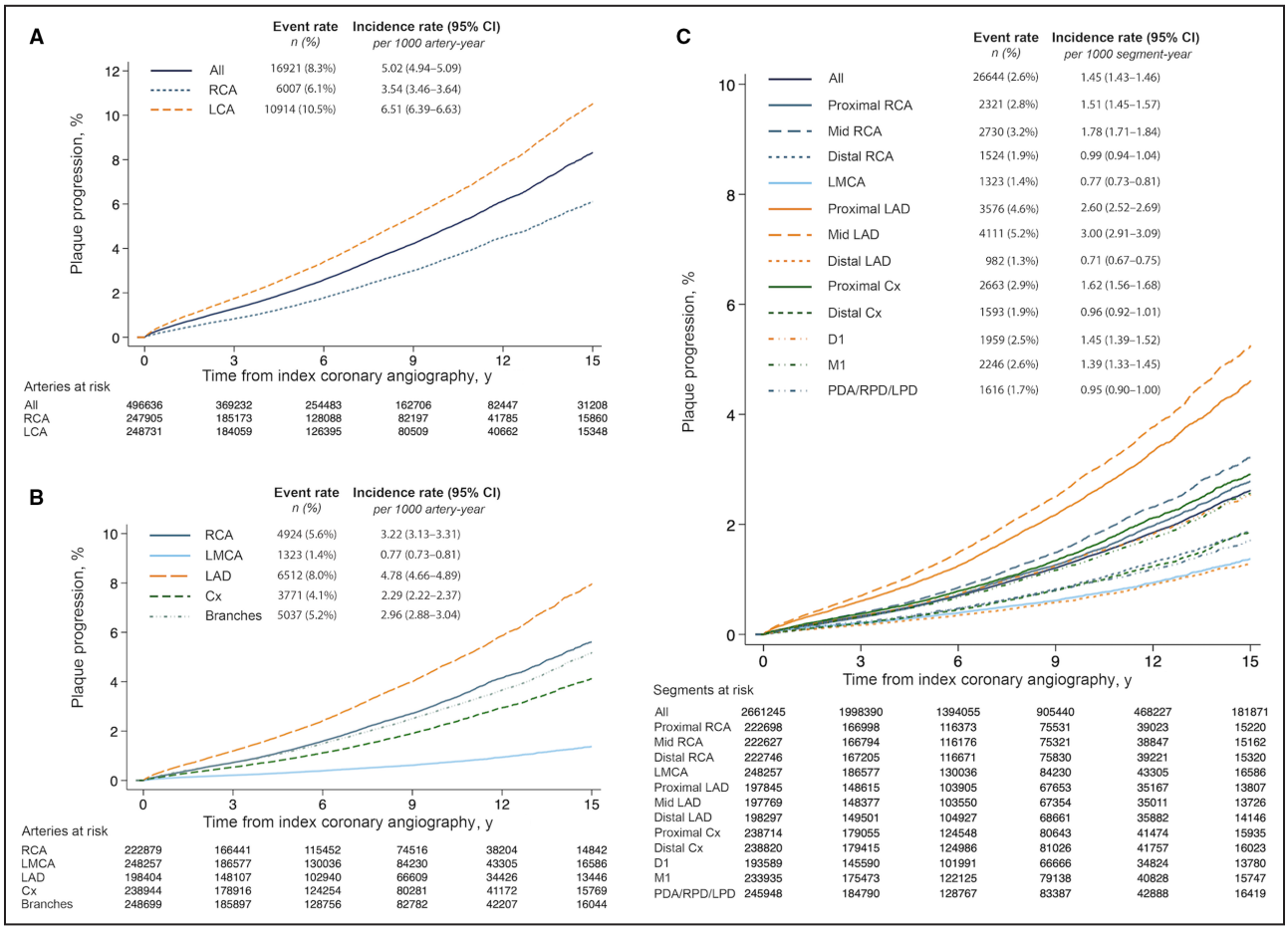

Figure 2. The natural history of coronary atherosclerosis progression with respect to anatomical location.
Cumulative probability of stenosis progression from nonobstructive (<50% diameter stenosis) to obstructive (≥50% diameter stenosis) disease over the course of 15 years in all patients and in the left vs the right coronary artery (**A**), in the main coronary arteries and their branches (**B**), and in the coronary artery segments (**C**). Branches in (**B**) include first diagonal artery (D1), first obtuse marginal artery (M1), and posterior descending artery/right posterior descending artery/left posterior descending artery (RPD/PDA/LPD). Cx indicates left circumflex artery; LAD, left anterior descending artery; LCA, left coronary artery; LMCA, left main coronary artery; and RCA, right coronary artery.

undergoing clinically indicated coronary angiography in a nationwide real-world setting. Our analyses were based on a median follow-up of 6.6 years, the longest follow-up time to date. However, our results concur with previous reports in several ways. Postmortem studies have shown that atherosclerosis is most prevalent in the proximal and mid-segments of the LAD,[1] a finding supported by CCTA studies.[19,20] Proximally located nonobstructive lesions are associated with more symptoms and higher mortality rates than are distal lesions.[21] The higher prevalence of atherosclerosis in the proximal and mid-LAD in previous cross-sectional studies indicates that similar findings in this study are not caused by bias of performing angiography for symptoms arising from proximal coronary artery lesions. In concert with prior results, the present study confirms that atherosclerosis not only develops more frequently in the proximal and mid-LAD but also that these segments are more prone to progression to obstructive atherosclerosis. Biomechanical forces caused by blood pressure, lack of shear stress, and turbulent flow have been suggested to explain the predilection for atherosclerosis development and progression in the proximal and mid–coronary tree.[22]

In the recent PROSPECT II, untreated nonculprit lesions were responsible for most future symptomatic major adverse cardiovascular events, 8.0% of the total of 13.2% at a median of 3.7-year follow-up, the majority of which were caused by progressive angina.[4] In the present study, we found a 12.9% angiographic stenosis progression rate at the patient level and a 6.5% event rate in ACS resulting in revascularization over a median follow-up time of 6.6 years. PROSPECT II reported an untreated nonculprit lesion–level major adverse cardiovascular event rate of 7% in high-risk plaques (those with both large plaque burden and high

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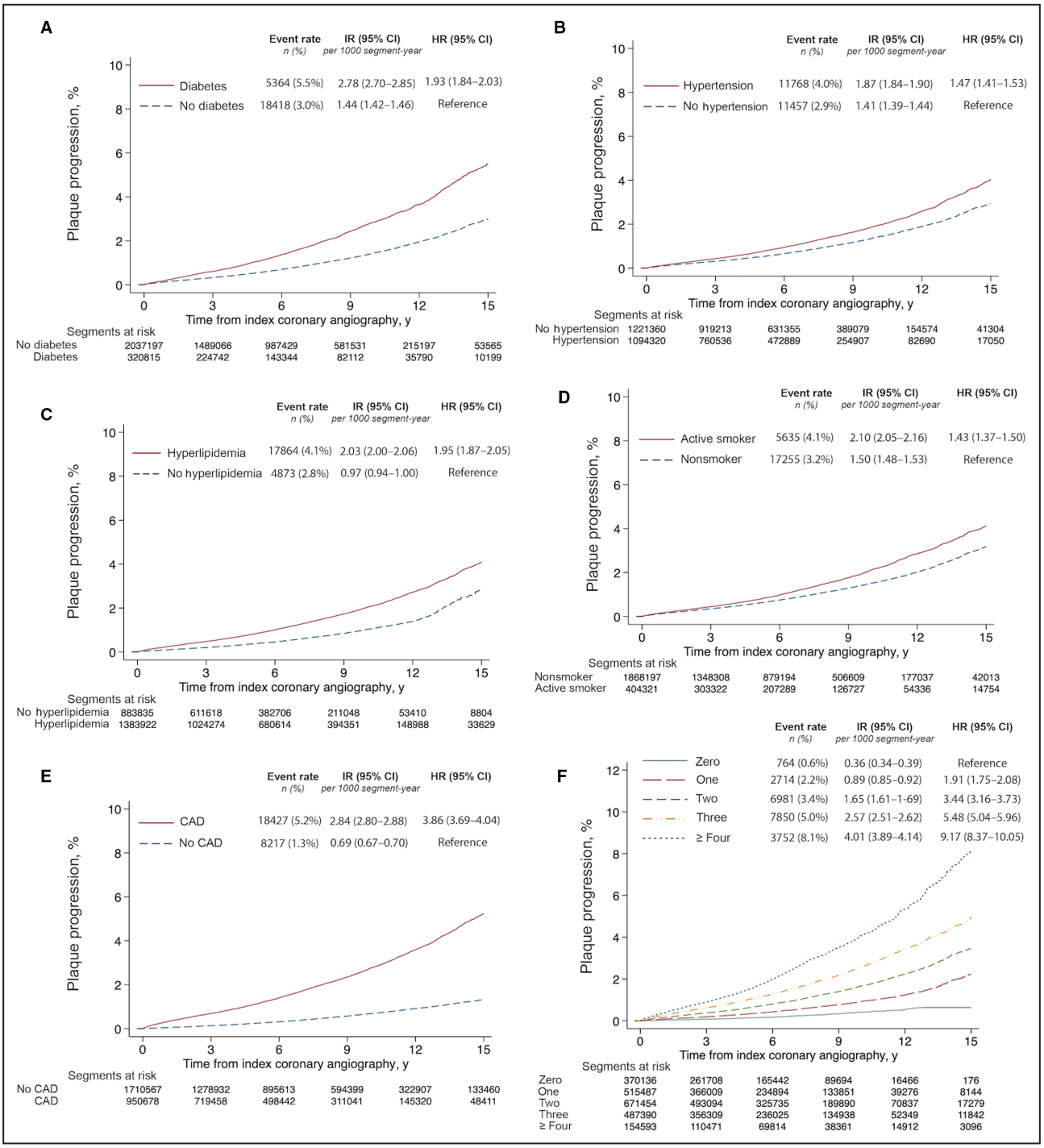

Figure 3. Impact of risk factors on coronary atherosclerosis progression.
Cumulative probability of stenosis progression from nonobstructive (<50% diameter stenosis) to obstructive (≥50% diameter stenosis) disease over the course of 15 years in patients with vs without diabetes (**A**), hypertension (**B**), hyperlipidemia (**C**), smoking (**D**), established single-vessel coronary artery disease (CAD) on index angiography (**E**), and according to the number of risk factors (**F**). HR indicates hazard ratio; and IR, incidence rate.

lipid content).[4] In our study, the segment-level stenosis progression rate increased to 5% to 8% in the presence of high-risk lesion factors such as proximal and middle LAD lesions as well as diabetes and established CAD and increasing in the presence of multiple risk factors. Longitudinal CCTA studies of nonobstructive lesions have revealed a progression rate of 2.3% after 3.8 years,[12] consistent with our angiographic findings of segment-level stenosis progression. Finally, equally important as the increased positive predictive value

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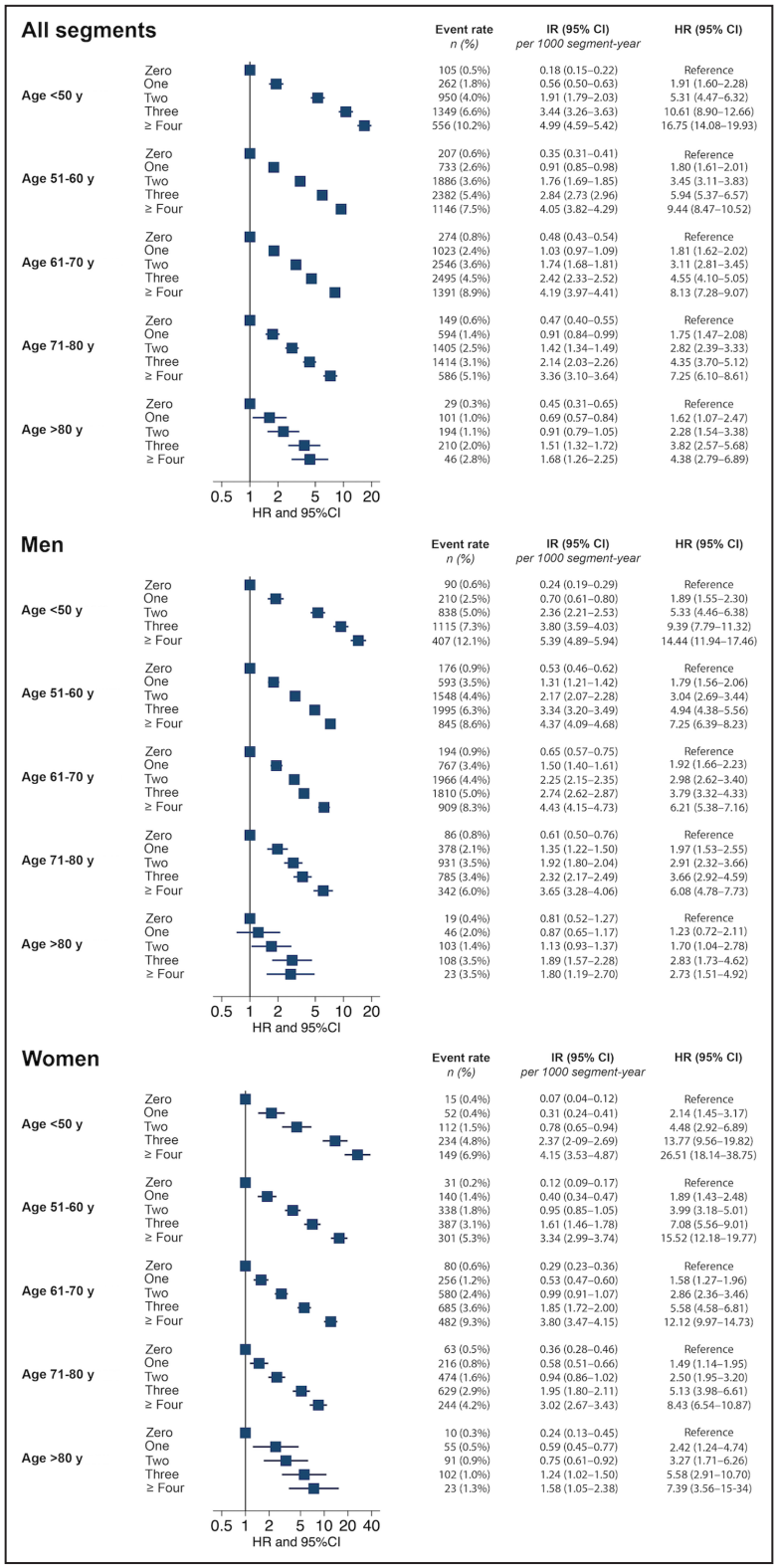

Figure 4. Impact of age, sex and the number of risk factors on coronary atherosclerosis progression.
Forest plot depicting the excess risk (hazard ratio [HR]) of stenosis progression from nonobstructive (<50% diameter stenosis) to obstructive (≥50% diameter stenosis) disease over the course of 15 years according to age category, sex, and the number of risk factors. In each analysis, zero risk factors constituted the reference group. IR indicates incidence rate.

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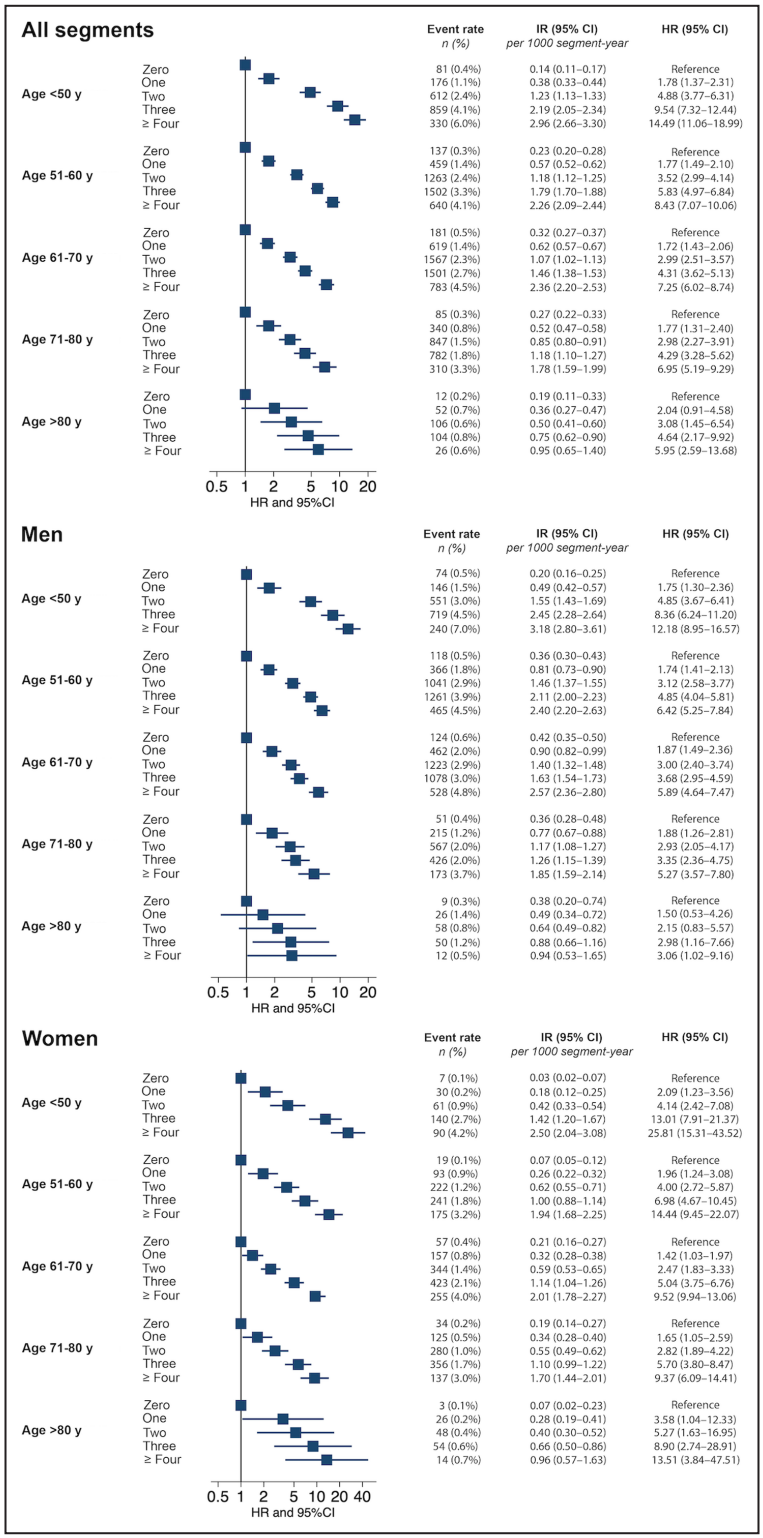

Figure 5. Impact of age, sex, and the number of risk factors on progression to revascularized lesions.
Forest plot depicting the excess risk (hazard ratio [HR]) of stenosis progression from nonobstructive (<50% diameter stenosis) to obstructive (≥50% diameter stenosis) disease requiring revascularization with percutaneous coronary intervention or coronary artery bypass grafting over the course of 15 years according to age category, sex, and the number of risk factors. In each analysis, 0 risk factors constituted the reference group. IR indicates incidence rate.

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of multiple risk factors is the high negative predictive value when risk factors are absent. In PROSPECT II, nonculprit lesions with low lipid content and plaque burden were associated with a median 3.7-year follow-up event rate of only 0.2%.[4] In the present study, plaque progression at a median follow-up duration of 6.6 years was observed in only 0.5% to 0.8% of patients with no recognized risk factors, regardless of age or sex. These findings link vulnerable plaques and vulnerable patients and indicate that patient-level and lesion-level risk factors can be combined to further characterize the natural course of coronary atherosclerosis and predict event rates. Younger patients and men in whom coronary angiography were indicated, as well as those with a high risk factor burden and proximally located nonobstructive lesions may benefit from intensified pharmacological treatment or even physiological assessment or intracoronary imaging to identify high-risk plaques. PROSPECT-ABSORB (Providing Regional Observations to Study Predictors of Events in the Coronary Tree II Combined With a Randomized, Controlled, Intervention Trial) showed that PCI of angiographically mild stenosis was safe and resulted in enlarged arterial lumen at 25 months, but, whether identification and prophylactic interventional treatment of vulnerable plaques reduces progression and risk of atherothrombotic events, has yet to be established.[23]

LIMITATIONS

The current study relied on data from patients undergoing clinically indicated coronary angiography. The most important limitation is that stenosis progression data were only available for individuals who underwent at least 1 additional clinically indicated follow-up angiography. Stenosis progression in asymptomatic patients, patients with silent ischemia, or patients with sudden death were not captured in the present study, resulting in patients being right censored. In a minority of patients, ie, asymptomatic patients or patients with mild symptoms who had a repeat angiography, the time to plaque progression was more diffuse. In such individuals, an interval censored analysis might be a better statistical method when assessing relative risks. Some individuals who had >1 repeat angiogram could have been free from plaque progression on all but the last angiogram. Estimating the IR of plaque progression from last coronary angiogram instead from the index angiogram did not alter the results (IR, 1.44 per 1000 segment-years). Stenosis severity was assessed locally in each catheterization laboratory and not at a core laboratory and in most cases additional intracoronary diagnostic procedures (such as physiologic assessment or intravascular imaging) were not performed. Coronary angiography and interventions conducted outside Sweden were not included. The stenosis progression rate may vary in other geographies according to differences in genetics, risk factors, diet, and other variables not investigated here. We did not factor in risk factors appearing (or resolving) after index angiography or duration or severity of risk factors, which may have influenced the results. Finally, because of the observational nature of the current study, residual confounding cannot be ruled out and may have affected our estimates of disease progression.

CONCLUSIONS

In this large-scale nationwide study, coronary atherosclerosis progressed slowly but more frequently in men, in the left coronary artery compared with the right, in the proximal compared with the distal segments (especially in the LAD compared with other vessels), and in patients in whom obstructive disease was already established. Atherosclerosis progression increased stepwise with increased risk factor burden. The impact of risk factors on plaque progression was of greatest relative importance in younger patients and in women. Conversely, coronary artery segments with no or mild atherosclerosis were unlikely to progress to luminal obstruction in the absence of risk factors. Knowledge of these findings may provide important guidance for prognostication and, potentially, patient-tailored screening and therapeutic guidance.

ARTICLE INFORMATION

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in the study design; collection, analysis, or interpretation of data; writing of the article; approving the article; or the decision to submit the article for publication.

Disclosures

All authors completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. All authors declare no support for the submitted work from any organization, no financial relationship in the past 3 years with any organization that might have an interest in the submitted work, and no other relationships or activities that could appear to have influenced the submitted work.

Supplemental Material

Table S1
Figure S1

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SUPPLEMENTAL MATERIAL

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Table S1. STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	8&9
		(*e*) Describe any sensitivity analyses	

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Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	8
		(c) Consider use of a flow diagram	Figure S1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	10-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

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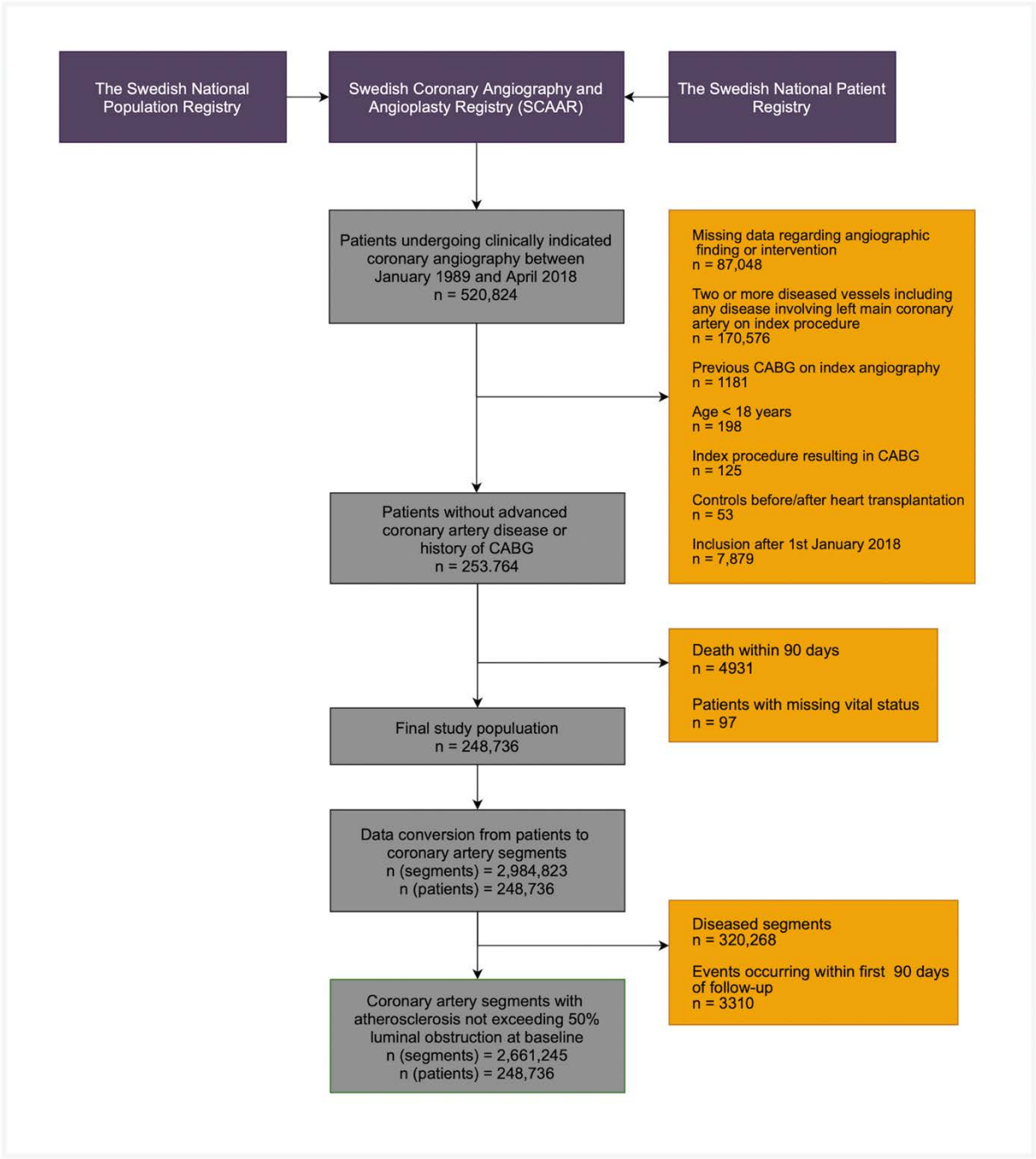
Figure S1. Flowchart



Number of patients and segments remaining in the analyses after applying inclusion and exclusion criteria.

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