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Brief title: Evolution of premature coronary artery disease

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ABSTRACT
Background: The long-term evolution of premature coronary artery disease (CAD) is unknown.
Objectives: To describe the evolution of coronary atherosclerosis in young patients and identify the risk factors of poor outcomes.
Methods: Participants aged 45 years or less with acute or stable obstructive coronary artery disease were prospectively enrolled and followed-up. The primary endpoint was all-cause death, myocardial infarction, refractory angina requiring coronary revascularization and ischemic stroke.
Results: 880 patients with premature CAD were included. They were aged 40.1 years (±5.7), mainly males, smokers, with a family history of CAD or hypercholesterolemia. . At baseline presentation, 91.2 % underwent coronary revascularization, predominantly for acute MI (78.8%). Over a follow-up to 20 years, one third (n=264) presented a total of 399 ischemic events, of whom 36% had at least a second recurrent event. Myocardial infarction was the most frequent first recurrent event (n=131/264) mostly related to new coronary lesions (17.3 % vs 7.8%, p=0.01, HR=1.45, 95% CI [1.09-1.93] for new versus initial culprit lesion). All-cause death (n=55, 6.3%) occurred at 8.4 years (median time). Ethnic origin (sub-Saharan African vs Caucasian, adjHR: 1.95, 95% CI [1.13-3.35], p=0.02), inflammatory disease (adjHR: 1.58 95%CI [1.05-2.36], p=0.03)) and persistent smoking (adjHR: 2.32, 95% [1.63-3.28], p<0.01) were the strongest correlates of a first recurrent event. When considering all recurrent events, the same factors and Asian ethnicity predicted poor outcome, but persistent smoking had the greatest impact on prognosis.
Conclusions: Premature CAD is an aggressive disease despite the currently recommended prevention measures with high rates of recurrent events and mortality. Ethnicity and concomitant inflammatory disease are associated with a poor prognosis along with insufficient control of risk factors.

CONDENSED ABSTRACT: This prospective cohort study reports the contemporary natural history of obstructive CAD over 20 years in 880 patients aged ≤45 years. Ischemic recurrences were frequent (4.68 per 100 patient-years) with a fast progression towards multivessel disease. Ethnicity, chronic inflammation and behavior-related risk factors were the major contributors of poor prognosis. When considering all recurrent events, multivessel disease also predicted poor outcome, but persistent smoking had the greatest impact on prognosis. Premature CAD carries a high risk burden compared with atherothrombosis in middle-aged patients. Specific prevention should be implemented in these young patients to prevent the rapid progression of the disease.

Keywords: Premature coronary artery disease; young; myocardial infarction; long-term outcomes, recurrent event

Abbreviations
AFIJI: Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention
CABG: Coronary Artery Bypass Graft
CAD: Coronary Artery Disease
HIV: Human Immunodeficiency Virus
MACE: Major Adverse Cardiovascular Events
NSTEMI: Non ST-Segment Elevation Myocardial Infarction
PCI: Percutaneous Coronary Intervention

STEMI: ST-Segment Elevation Myocardial Infarction
AdjHR: adjusted hazard ratio

Introduction

Ischemic heart disease accounts for the majority of premature deaths in the world (1). Coronary artery disease (CAD) risk factors explain more than 90% of the attributable risk of CAD, of which nearly half can be reduced by the adoption of a heart-healthy lifestyle (2, 3). However, the incidence of CAD increases in many regions of the world and starts at an earlier age, despite major advances in the prevention and treatment of atherosclerosis (4). The long-term evolution of these young CAD patients in the contemporary era of secondary prevention remains, however, poorly known.

Premature CAD, defined as the occurrence of symptomatic obstructive coronary atherothrombotic lesions before the age of 45 years, has been described in a few registries of limited size, and restricted to the description of the patients baseline characteristics in a retrospective approach (5–10). Neither the long-term outcome nor the precise contribution and evolution of the risk factors have been precisely reported. Such data are critical to know better the burden of CAD and its prognosis under optimal treatment, when the disease starts two decades in advance.

The *Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention (AFIJI)* multicenter prospective cohort was launched in 1996 to better characterize the patient profile, treatment and follow-up of premature CAD in the contemporary era of percutaneous myocardial revascularization, arterial coronary bypass graft (CABG) and potent secondary prevention pharmacotherapy. The goal was also to provide these young patients with optimal cardiovascular prevention measures and follow their evolution after a first unexpected serious cardiac event. We tested the hypothesis whether secondary events were more likely related to new coronary lesion or to the initial culprit lesion.

Methods

Study design and eligibility

Between April 1, 1996, and June 2017, 880 patients aged <45 years who survived the first manifestation of CAD were enrolled in the prospective ongoing AFIJI multicenter cohort study. This program was designed to identify risk factors of premature coronary artery disease and to provide a continuous prospective long-term follow-up (11–13). Premature CAD was defined as the occurrence of an acute myocardial infarction or a symptomatic myocardial ischemia with an obstructive coronary artery disease (stenosis ≥ 70 %) before the age of 45 years. Myocardial infarction due to non-obstructive coronary artery disease was an exclusion criterion when ischemia or necrosis was not confirmed by cardiac MRI, as well as myocarditis, Tako-Tsubo myocardiopathy and coronary spasm. This prospective study was approved by the local Ethics committee, sponsored by the Assistance Publique-Hôpitaux de Paris, supported and driven by the ACTION Study Group. All patients provided a written informed consent prior to enrolment.

Data collection and follow-up

Baseline characteristics including risk factors, medical history, ethnicity and treatments were reported prospectively as previously described(11–13). Familial history of CAD was defined as any coronary event that occurred in first-degree relatives before 60 years of age in men and 65 years in women.

Participants were followed-up by general cardiologists with also regular visits to participating tertiary centers (at least once every two years). All information was collected and updated in all patients, presenting or not an event. General follow-up surveys were carried out regularly (2003/2007/2009/2012/2017) to collect additional clinical information including risk

factors, symptoms, treatments, regular stress tests and echocardiograms as well as the socio-professional status. Incentives to participate in educational programs were also launched. In addition to classical risk factors, the presence of chronic inflammatory or immunosuppressive disease such as HIV infection, viral hepatitis or any other chronic inflammatory disease including cancer was recorded. Baseline and repeated coronary angiograms were reviewed by independent investigators at the ACTION study group angiography core laboratory. New ischemic events were classified as being related to the initial treated coronary lesion or to a new lesion on another coronary segment or artery.

Study objectives

The primary study objective was to determine the rate of a first recurrent major adverse cardiovascular event (MACE) at maximal follow-up and the related independent risk factors of MACE. The second objective was to determine whether recurrent events were related to the initial culprit lesion or to the occurrence of new lesions. The third objective was to determine the rate of repeated recurrences and identify their related independent correlates.

Endpoint Definitions

The primary endpoint was a composite of all cause death, myocardial infarction, refractory angina leading to coronary revascularization and ischemic stroke. Ischemic stroke was defined as an acute episode of focal or global neurological dysfunction as result of cerebral infarction. Myocardial infarction was defined as type 1 according to the Third Universal Definition of 2012(14). Secondary endpoints were the individual components of the primary endpoint related to a new lesion site, the occurrence of heart failure (NYHA>2) and major bleedings according to the TIMI definition. Events were adjudicated by physicians not involved in the recruitment and follow-up of patients in the AFIJI program.

Statistical Analysis

Participants were classified according to the occurrence of a first MACE during the follow-up in the study. Continuous variables are presented as mean and standard deviation (SD) or median, as appropriate and compared using Student t-test in case of Gaussian distribution or Mann-Whitney U test in case of non-Gaussian distribution. Categorical variables are presented as counts and percentages and compared using Chi square test or Fisher's exact test in case of low number of events. Cumulative incidence rates were calculated and expressed as the number of new cardiovascular events divided by the number of patient-years of follow-up (number of events per 100 patient-years).

The primary analyses were based on the occurrence of a first MACE. To describe the frequency of cardiovascular events according to time, we used Kaplan-Meier curves for cumulative event-free survival for the prespecified primary endpoint. Follow-up of patients was censored at the 30th of June 2017 irrespective of whether a first recurrent event corresponding to the primary endpoint had occurred. For the first set of analyses, the time to first cardiovascular event was also compared according to whether the event was related to the initial culprit lesion or to a new lesion using log-rank tests.

The secondary analyses involved the time evolution of diabetes and smoking status. Time to recurrences and time to risk factor evaluations were stratified and matched between patients with and without recurrences. For each variable, we evaluated the cumulative exposures from baseline to the first, second or third recurrent event for patients with MACEs, and to the last known status within the corresponding period of time for patients without recurrence. A generalized estimating equation with a trend test was used to assess the differences in the cumulative exposures of each risk factor between patients with or without recurrence.

The third set of analyses assessed the independent factors of recurrences. Because of the time-dependence between risk factors like LDL-C, smoking or diabetes and events, a stratified Cox procedure including these time-dependent covariates was performed to identify the independent variables associated with a first occurrence of MACE. This cox model was stratified according to the time delay from the disease onset to follow-up and recurrent MACE as previously described (15). Variables with a univariate p-value<0.2 as well as age, initial presentation (myocardial infarction or stable coronary artery disease), ethnicity, cardiovascular risk factors (familial history of CAD, active smoking, hypertension and dyslipidemia), LDL-C level, inflammatory disease and revascularization status were included in the model. Eventually, a pooled analysis using repeated measurements with time-dependent covariates was performed to identify the risk factors associated with multiple recurrences. The two-sided significance level was fixed at 5%. All the analyses were performed using the SAS software (9.4, SAS Institute, Cary NC, USA).

Results

Baseline characteristics

Patients were predominantly young males, active smokers, with a frequent family history of CAD and hypercholesterolemia while diabetes was less common. Mean LDL-cholesterol at baseline was 1.69±1.3 g/dL (Table 1). One out of ten patients had a chronic inflammatory or immunosuppressive disease including HIV (4.0%), viral hepatitis (1.3%), systemic auto-immune disease including polyarthritis or systemic lupus with antiphospholipid syndrome (1.3%) and cancer (3.5%) (**Table 1**). Acute myocardial infarction due to single vessel disease with subsequent percutaneous coronary revascularization was the most frequent clinical pattern. Few patients presented with coronary dissection (n=10) or coronary thrombosis after heavy physical

exertion (n=11) without underlying stenosis. Secondary prevention treatments were used as recommended per guidelines and did not differ according to the occurrence of MACE (**Table 1**). Fewer patients were exposed to ticagrelor in the MACE group versus the event-free group (5.6% versus 10.1%, p=0.006) and very few patients were on oral anticoagulation (**Table 1**).

Time to first event analyses

Detailed cardiovascular outcomes and vital status were obtained for all patients, except for five patients who were lost to follow-up (0.57%). The description of lipid-lowering therapies along follow-up and dual antiplatelet therapy durations are displayed in online table 1 and 2.

Over the 20-year follow-up, 30% of patients (n=264) presented a total of 399 MACEs corresponding to 4.68 (4.23-5.18) events per 100 patient-years (Table 2). Myocardial infarction was the most frequent first recurrent event (2.6 per 100 patient-years) while all-cause death (1.60 per 100 patient-years) and stroke (0.70 per 100 patient-years) were less frequent. The first non-fatal recurrent ischemic event was related to a new lesion site in 152 patients and to the initial culprit lesion in 69 patients (17.3% vs 7.8%, p=0.01, HR=1.45, 95% CI [1.09; 1.93] for new versus initial lesion, respectively) (**Central Illustration**). Among the 522 patients with single coronary vessel disease at baseline, 112 evolved towards symptomatic multivessel disease. Death as the first recurrent event was three times less frequent than myocardial infarction and occurred at a much later stage (8.4 vs. 3.7 years). Stroke occurred in less than 1% of patients (**Table 2**).

Patients with a first MACE were more likely to have uncontrolled risk factors with more frequent active smoking, diabetes, and with a higher LDL-cholesterol level prior to the first recurrent event; they were also more likely to be of Sub-Saharan Africa or of Asian origin (Table 1). Patients with multivessel disease were also more likely to suffer from an ischemic recurrence, as well as patients initially treated by CABG.

Twenty-one patients (2.4%) developed severe heart failure, five patients underwent heart transplantation and thirteen had a major bleeding. More than one-third of the patients of the AFIJI registry (295/880) had an event during follow-up as defined according to secondary endpoints.

Time to second or third recurrence

Of the 255 patients with a first non-fatal recurrence, 81 patients (36.0 %) had at least a second recurrent MACE (table 2).. The continuous monitoring of risk factors showed more frequent new diabetes and a greater exposure to active smoking before each recurrent MACE (Figure 1 A and B). The exposure to active smoking decreased but remained high in patients with multiple recurrences (from 50.9% to 35.0%) compared with patients free or ischemic recurrences (41.8% to 1.5%). Interestingly, one out of three patients with multiple recurrences eventually developed diabetes as compared to one out of ten among event-free patients.

Independent risk factors of poor outcome

The multivariate stratified Cox regression model based on repeated measurements with time-dependent covariates demonstrated that persistent smoking was the greatest correlate of a first recurrent event (adjHR: 2.32, 95% [1.63-3.28], p<0.01). Ethnic origin, (sub-Saharan African vs Caucasian, adjHR: 1.95, 95% CI [1.13-3.35], p=0.02), diabetes, (adjHR: 1.75, 95%CI [1.20 – 2.55], p<0.01) as well as chronic inflammatory disease (adjHR: 1.58 95%CI [1.05-2.36], p=0.03 and multivessel disease at baseline were strong independent risk factors of a first recurrent MACE. When considering all recurrent events, the same factors plus hypertension and Asian ethnicity predicted poor outcome, but persistent smoking had by far the strongest impact on prognosis (adjHR: 2.70, 95% CI [2.05-3.55], p<.001) (**Figure 2 A and B**, Online Table 3 and 4).

Discussion

The AFIJI cohort provides a prospective description of the contemporary long-term evolution of coronary atherothrombosis occurring in a cohort of young patients. Recurrent events were frequent, occurred early in the course of the disease and were mainly due to new coronary lesions. Insufficient control of modifiable risk factors, concomitant chronic inflammatory disease and Asian/sub-Saharan ethnicities were the major factors associated with a poor prognosis. Our findings shed light on where our efforts should focus to blunt this unfavorable evolution in one out of three patients who presented a first event before the age of 45 years.

All patients of the AFIJI registry were all-comers screened during hospital stay or at the outpatient clinic of the investigating centers. The large majority of patients had angiographically established CAD with and most of them presented with ST-elevation myocardial infarction. The few who did not undergo coronary revascularization presented with a myocardial infarction due to a coronary dissection (mostly in women) or to acute coronary thrombosis without significant underlying coronary stenosis. The high rate of recurrent myocardial infarction in the AFIJI registry demonstrates that premature CAD is an evolving disease. This high rate of ischemic events persisted through the different therapeutic eras, in spite of the advent of drug eluting stents, potent $P2Y_{12}$ inhibitors and second-generation statins (Online Figure 1). Half of recurrences occurred within the first 4 years and 75% within the first 10 years of follow-up. Most of the secondary prevention trials testing the long-term benefits of secondary prevention interventions reported lower event rates than AFIJI, certainly because of a less aggressive disease in older patients, a shorter follow-up of these studies and consideration of the first recurrent event only(16–19) (online table 5). Remarkably, the first recurrent MACE on optimal secondary prevention occurred before the age of 60 in 98% of our patients, an age corresponding to the median age of CAD revelation in the general population.

Multivessel disease at baseline was logically an independent predictor of first recurrence and multiple recurrences. This was also true for patients who underwent CABG surgery with recurrent events in more than half of them. The progression of atherothrombosis from single to multivessel disease paralleled the number of recurrences. The PROSPECT study reported that major recurrent events were equally distributed between culprit and non-culprit lesions and we report here that new coronary lesions were involved in 2 out of 3 patients suggesting a fast progression of the disease in these young patients (20). This aggressive progression towards new lesion sites demonstrates the need for non-invasive multi-modal strategies able to capture the evolution and instability of subclinical atherosclerosis in young patients (21). Among the promising technical advances, computed tomography angiography have enabled to describe the remodeling and necrotic aspects of plaques and relate them to the risk of coronary events (22).

Poor control of cardiovascular risk factors is obviously of paramount prognostic importance. One out of two patients was still an active smokers at the time of the first recurrence, a rate that is consistent with recent European surveys (23). A 7-fold decrease of active smoking was obtained with education programs but still 11% of the patients were active smokers at the end of our follow-up. Our data indirectly confirm that smoking cessation is the most efficient secondary prevention measure, especially before the age of 40 years (24). The other modifiable risk factors –diabetes and hypertension – were also independently associated with multiple recurrent MACEs, emphasizing the need for an aggressive secondary prevention in this population. Larger infarct size, poor recovery from myocardial injury, comorbidities and persistent inflammation are the known consequences of persistent active smoking triggering coronary recurrences, heart failure and cardiovascular death (25, 26). The average level of LDL cholesterol in these young patients was noticeably higher than the average usual MI population

(27). Although improving over time, the proportion of patients with on-treatment LDL cholesterol plateau levels above 0.7 g/L was high, suggesting unrecognized heterozygous familial hypercholesterolemia but also insufficient treatment intensity (online Table 1). (28, 29). The increasing proportion of new onset of diabetes over time in patients with recurrent adverse event is another intriguing finding which indicates partial failure of our behavioral programs with respect to physical activity and diet.

The 10% of patients with chronic inflammatory disease had accelerated atherothrombosis with more frequent recurrent events. Chronic inflammation together with the cardiometabolic effects of corticosteroids or antiretroviral drugs may have participated to CAD progression. High platelet reactivity on P2Y12 inhibitors and potential drug-drug interactions are also additional explanatory factors (30). Ethnicity is a non-modifiable risk factor involving both genetics and habits - that impacted long-term outcomes of young patients (31). Young sub-Saharan African patients carried the higher burden of cardiovascular disease. Previous similar findings have associated this higher risk with a more frequent hypertension, diet habits and unequal access to prevention and healthcare (32). Asian ethnicity is particular to the AFIJI registry recruitment with patients originating from south-east Asia where the prevalence of diabetes and multivessel disease is high. Several Indian and South-east Asian registries have described an early onset of coronary artery disease, with a median age of 55 years old compared to 65 years old in western countries (33).

Ethnicity, chronic inflammatory disease, familial history of premature CAD and early menopause have been listed as risk-enhancers in the American guidelines on blood cholesterol management (34). The present results display additional evidence and variables to support tailored secondary prevention strategies for these young patients. Non-invasive imaging methods

to better predict the potential evolution of the non-culprit coronary plaques in these specific subgroups needs further investigation. In particular, CT scan data combined with deep phenotyping including LDL-cholesterol on statin therapy may further help refinement of the intensity of lipid-lowering therapies with dedicated machine learning algorithms (34–36).

Whether we can improve the long-term prognosis of these patients is a pending issue. Better control of the risk factors and treatment adherence are known challenges for secondary prevention. It is likely that a more aggressive secondary prevention using PCSK9 inhibitors and new antidiabetic drugs, which reduce both MACE and mortality, would be of incremental value in this high-risk population with frequent dyslipidemia and new onset of diabetes (37–39). Lifestyle changes is often difficult to obtain but the potential benefit of the Mediterranean diet and physical activity are well demonstrated (2, 40). The residual risk related to chronic inflammation is another target in this young population. Interleukin-1β inhibition with canakinumab was effective in reducing cardiovascular events in a different high-risk atherosclerosis population, particularly those with elevated markers of inflammation (41). Anti-inflammatory therapy may have cardiovascular efficacy in AFIJI-type patients considering the independent risk prediction of inflammatory disease we observed. Whether tailored therapy according to inflammatory biomarkers may improve outcome of these young patients needs to be addressed.

Limitations

There are several limitations inherent to this long-term prospective registry. First, advances in secondary pharmacological prevention treatment and in myocardial revascularization technology may have created a time-confounding bias not entirely addressed by the use of time-dependent variables and the time-stratified cox model. Similarly, statistical

modelling could only partially balance the discrepancies in the measurement of time-dependent variables between patients with and without recurrent events. Second, asymptomatic patients did not undergo systematic coronary imaging investigations and we may have underestimated progression of the disease in some of these patients. Third, this AFIJI cohort outlines the role of ethnicity which may be confounded by other socio-economic factors. Finally, changes in physical activity or diet were not captured in this survey as well as psychological traits, all being additional prognostic factors of coronary disease.

Conclusions

Premature coronary artery disease is a chronic and aggressive disease, with a high rate of recurrences and a rapid evolution towards multivessel disease. Ethnicity and chronic inflammation, along with traditional modifiable risk factors including pursuit of smoking and new onset of diabetes appear to be important factors of poor outcomes. Intensification of the current secondary prevention measures is desirable to prevent the evolution of the disease towards multivessel disease, repeated coronary events and heart failure.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge: Ethnicity, chronic inflammation and behavior-related risk factors are the most important contributors to the poor prognosis of young patients with premature coronary artery disease.

Translational Outlook: More research is needed to design and validate specific programs that reduce the incidence of ischemic events in patients with premature coronary artery disease through modification of behavioral and biological risk factors.

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Figure Legends

Figure 1: Cumulative exposure to time-dependent major risk factors according to the occurrence of major cardiovascular events: new onset of diabetes (A) and smoking status (B). *Time delays to recurrences and to risk factor evaluations were stratified and matched between patients with recurrences and patients without recurrences. Cumulative rates of diabetes (A) and active smoking (B) in patients with ischemic recurrences from baseline to first, second or third recurrence is compared with the cumulative rate of each risk factor in patients without ischemic recurrence, from baseline to last known status within a corresponding period of time.

Figure 2: Hazard Ratio plot of multivariate stratified Cox Model using repeated measurements for first recurrence (A) and multiple recurrences (B). Both models were time-stratified Cox regression model including variables with a univariate p-value<0.2as well as age, initial presentation (myocardial infarction or stable coronary artery disease), ethnicity, cardiovascular risk factors, LDL-C level, inflammatory disease and revascularization status. LDL-C, diabetes, and active smoking were treated as time-dependent co-variates. *Caucasian was used as a reference. ACS stands for acute coronary syndrome, CAD for coronary artery disease, LDL-C for low-density lipoprotein cholesterol.

Central Illustration: Primary endpoint according to new lesions versus initial culprit lesion. Time-to-Event Curves for Major Adverse Cardiovascular Events after inclusion in the AFIJI cohort. MACE stands for major adverse cardiovascular events, HR stands for Hazard Ratio.

Table 1: Baseline patient's characteristics according to occurrence of a first MACE.

Baseline characteristics	Total Population n= 880	Recurrent events n = 264	No recurrent events n=616	P value
Age - year (mean)	40.1 ± 5.7	39.6±5.7	40.2±5.7	0.1
age – year (median)	41.4 (36.5-44.2)	41.5 (36.9–44.3)	41.1 (36.0-44.0)	
Age < 35 %	160 (18.2%)	58 (22.0%)	102 (16.6%)	
Female gender	117 (13.3%)	33 (12.5%)	84 (13.6%)	0.1
Body mass index (kg/m^2)	26.1 ± 4.3	26.1 ± 4.7	26.1 ± 4.2	
Ethnic group				
White European	638 (72.5%)	189 (71.6%)	449 (72.9%)	0.3
North Africa & Middle East	166 (18.9%)	45 (17.0%)	121 (19.6%)	0.5
Sub-Saharan Africa	46 (5.2%)	16 (6.1%)	30 (4.9%)	0.2
Asian continent	30 (3.4%)	14 (5.3%)	16 (2.6%)	0.02
Admission event				
Myocardial infarction	693 (78.8%)	195 (73.9%)	498 (80.8%)	0.8
Anterior	311 (35.3%)	87 (32.6%)	224 (36.3%)	
Inferior	274 (31.1%)	72 (27.7%)	202 (32.8%)	
Lateral	63 (7.2%)	19 (7.2%)	44 (7.1%)	
Non-specific electric signs	45 (5.1%)	17 (6.4%)	28 (4.5%)	
Stable angina	187 (21.3%)	69 (26.1%)	118 (19.1%)	0.5
Risk factors*				
Familial history of CAD	359 (40.8%)	121 (45.8%)	238 (38.6%)	0.09
Active cigarette smoking	680 (77.3%)	210 (79.6%)*	470 (76.3%)*	0.1
Dyslipidaemia	443 (50.3%)	155 (58.7%)	288 (46.8%)	0.01
LDL-Cholesterol (g/L)	1.69±1.30	1.99±1.46*	1.56±1.20*	0.004
Arterial hypertension	178 (20.3%)	75 (28.4%)	103 (16.7%)	0.002
Diabetes	94 (10.7%)	41 (15.5%)*	53 (8.6%)*	<0.001
Creatinine Clearance	130.3±44.9	126.7 ± 58.8	131.9±37.4	0.3

(mL/min)				
Chronic inflammatory disease*	87 (9.9%)	45 (17.0%)	42 (6.8%)	<0.001
Coronary artery lesions				
MINOCA**	10 (1.1%)	1 (0.4%)	9 (1.4%)	
One-vessel disease	522 (59.3%)	111 (42.0%)	411 (66.7%)	<0.001
Two-vessel disease	181 (20.6%)	73 (27.7%)	108 (17.5%)	
Three-vessel disease	167 (18.9%)	79 (29.9%)	88 (14.3%)	
Number of lesion / patient	1.6±0.8	1.8±0.9	1.5±0.7	
LVEF*	55.3 ± 9.4	54.2 ± 10.4	55.8 ± 8.9	
Revascularization				
Yes	803 (91.2%)	252 (95.4%)	551 (89.4%)	
CABG	58 (6.6%)	29 (11.0%)	29 (4.7%)	0.02
PCI with DES	452 (51.4%)	126 (47.7%)	326 (52.9%)	0.6
PCI with BMS	293 (33.3%)	97 (36.7%)	196 (31.8%)	0.05
Medical treatment				
Aspirin	858 (97.5%)	257 (97.3%)	601 (97.6%)	0.6
Clopidogrel	528 (60.0%)	189 (71.6%)	339 (55.0%)	0.006
Ticagrelor	80 (9.1%)	18 (6.8%)	62 (10.1%)	0.006
Prasugrel	132 (15.0%)	32 (12.1%)	100 (16.2%)	0.1
Statins	820 (93.2%)	243 (92.0%)	577 (93.7%)	0.2
Beta-blockers	786 (89.3%)	238 (90.2%)	548 (89.0%)	0.1
ARB / ACE-inhibitors	683 (77.6%)	213 (80.7%)	470 (76.3%)	0.2
Oral anticoagulants	50 (5.7%)	16 (6.1%)	34 (5.5%)	0.4

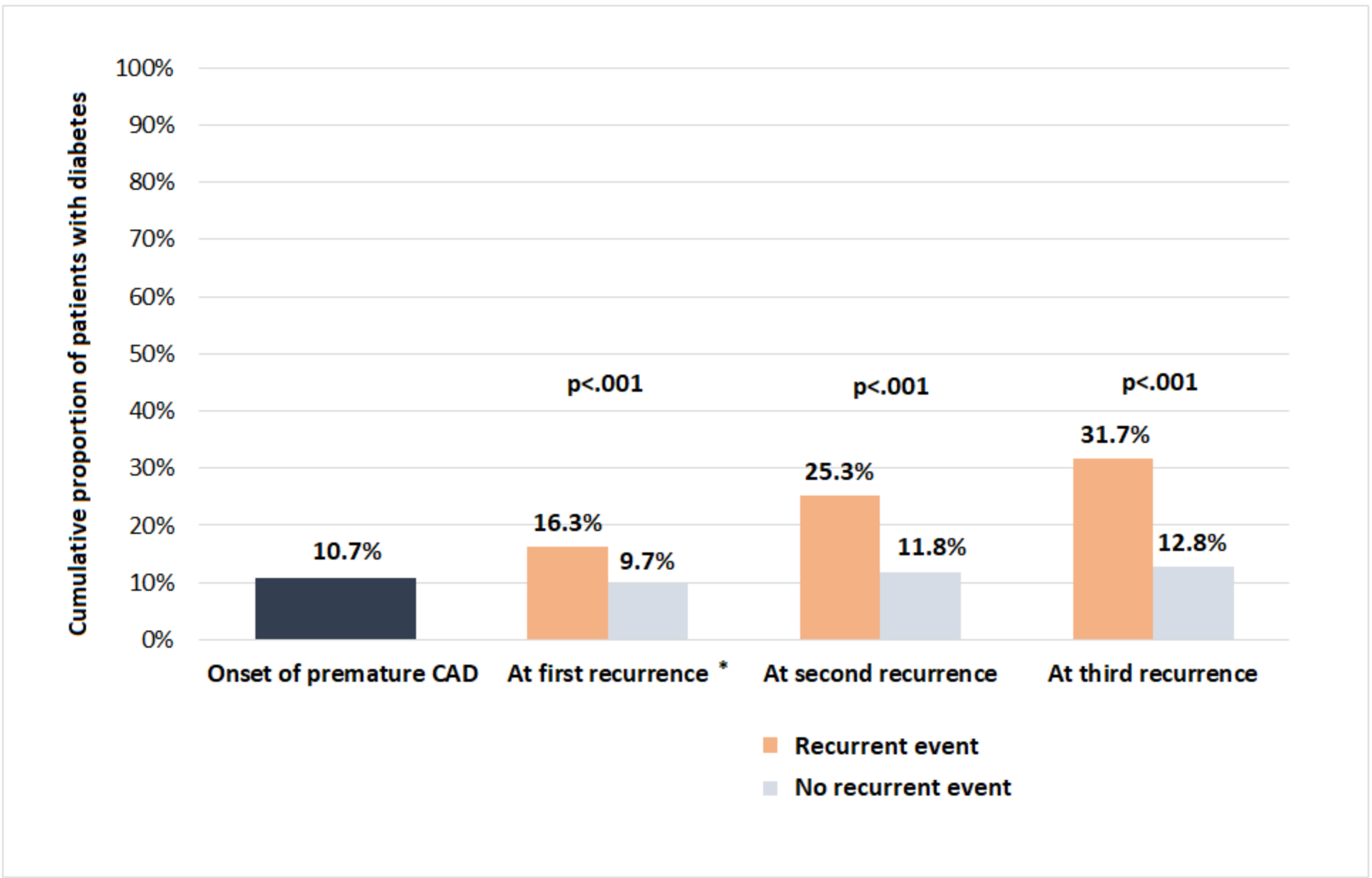
Footnote: CAD stands for coronary artery disease, LDL-Cholesterol for low-density lipoprotein cholesterol, MINOCA for myocardial infarction with non-obstructive coronary artery disease, LVEF for left ventricle ejection fraction, CABG for coronary artery bypass grafting, PCI for percutaneous coronary intervention, DES for drug-eluting stent, BMS for bare-metal stent, ARB for angiotensin II receptor blockers, ACE-inhibitors for Angiotensin converting enzyme inhibitors. *corresponds to the values observed before the first recurrence. * *Human immunodeficiency virus (n=34), viral hepatitis (n=10), HIV-Hepatitis C co-infection (n=1) cancer (n=31) or systemic auto-immune disease (n=11)* ** Only when confirmed by cardiac MRI.

Table 2: Major adverse cardiovascular events.

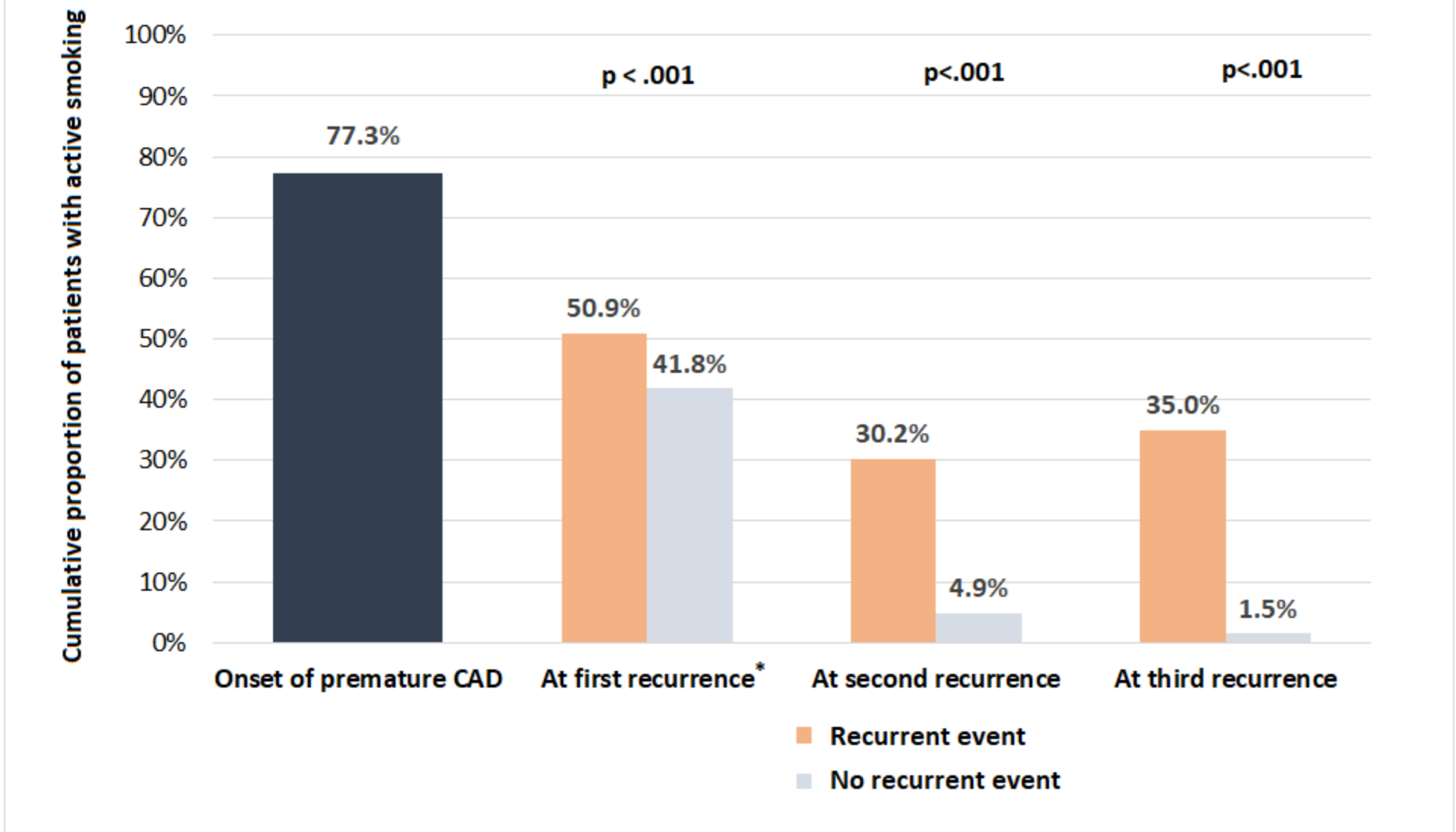
	1st recurrence n=264/880 (30.0%)	**Time in years median, (25th and 75th percentile)**	**2nd recurrence n=81/225* (36.0%)**	**Recurrences ≥ 3 n=54/70** (77.1%)**	**Total Events Counts**
All-cause Death	39 (4.4)	8.4, (3.2-15.9)	11 (4.9)	5 (7.1)	55
Myocardial Infarction	131 (14.9)	3.7, (0.8 -7.8)	40 (17.8)	38 (54.3)	209
STEMI	47 (5.3)	4.1, (0.8-7.9)	10 (4.4)	12 (17.1)	69
NSTEMI	84 (9.5)	3.5, (0.7-7.7)	30 (13.3)	26 (37.1)	140
Refractory Ischemia requiring revascularization	88 (10.0)	5.1, (1.4-11)	28 (12.4)	11 (15.7)	127
PCI	66 (7.5)	6.3, (1.7-10.7)	18 (8.0)	2 (2.9)	85
CABG	22 (2.5)	2.8, (0.9-12.3)	10 (4.4)	9 (12.9)	41
Ischemic Stroke	6 (0.7)	5.4, (1.8-8.4)	2 (0.9)	0 (0)	8
Primary endpoint	264 (30.0)	4.2, (1.3-9.8)			399 total events 4.68 (4.23-5.18) events per 100 patient-years

Footnote: * (%) is the percentage of patients with a second recurrent MACE out of patients who had a first non-fatal recurrent MACE ; ** (%) is the percentage of patients with 3 or more recurrent MACE out of patients with a second non-fatal second recurrent MACE. STEMI stands for ST-segment elevation Myocardial Infarction, NSTEMI for Non-ST-segment elevation myocardial infarction, PCI for Percutaneous Coronary Intervention, CABG: coronary artery bypass grafting.

A

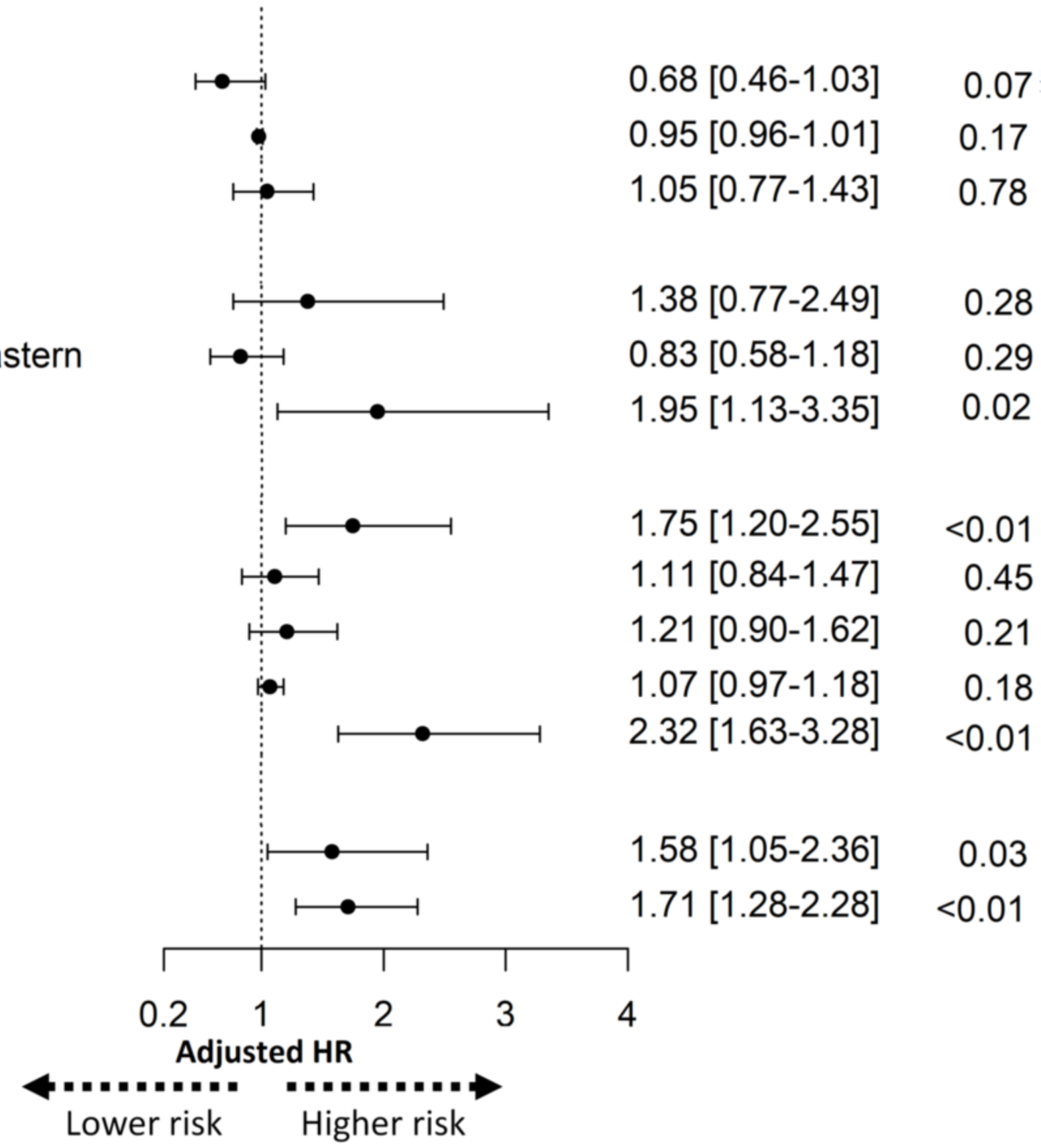

Cumulative proportion of patients with diabetes
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
p<.001
p<.001
p<.001
10.7%
16.3%
9.7%
25.3%
11.8%
31.7%
12.8%
Onset of premature CAD
At first recurrence *
At second recurrence
At third recurrence
Recurrent event
No recurrent event

B


Cumulative proportion of patients with active smoking
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
p < .001
p<.001
p<.001
77.3%
50.9%
41.8%
30.2%
4.9%
35.0%
1.5%
Onset of premature CAD
At first recurrence*
At second recurrence
At third recurrence
Recurrent event
No recurrent event

A

	Adjusted HR [95% CI]	p -value
Women	0.68 [0.46-1.03]	0.07
Age (per 1 year)	0.95 [0.96-1.01]	0.17
ACS at presentation	1.05 [0.77-1.43]	0.78
Ethnic group*		
Asian	1.38 [0.77-2.49]	0.28
North African and Middle Eastern	0.83 [0.58-1.18]	0.29
Sub-Saharan African	1.95 [1.13-3.35]	0.02
Risk Factors		
Diabetes	1.75 [1.20-2.55]	<0.01
Familial history of CAD	1.11 [0.84-1.47]	0.45
Hypertension	1.21 [0.90-1.62]	0.21
LDL-C (per 1 g/L)	1.07 [0.97-1.18]	0.18
Pursuit of active smoking	2.32 [1.63-3.28]	<0.01
Inflammatory disease	1.58 [1.05-2.36]	0.03
Multivessel disease	1.71 [1.28-2.28]	<0.01



B

	Adjusted HR [95% CI]	p -value
Women	0.84 [0.59-1.21]	0.35
Age (per 1 year)	0.99 [0.97-1.01]	0.28
ACS at presentation	0.88 [0.66-1.16]	0.35
Ethnic group*		
Asian	1.56 [0.98-2.49]	0.06
North African and Middle Eastern	0.91 [0.67-1.24]	0.55
Sub-Saharan African	1.64 [1.07-2.52]	0.02
Risk Factors		
Diabetes	1.48 [1.12-1.96]	<0.01
Familial history of CAD	1.11 [0.88-1.40]	0.39
Hypertension	1.21 [1.02-1.69]	0.03
LDL-C (per 1 g/L)	1.07 [0.96-1.14]	0.31
Pursuit of active smoking	2.70 [2.05-3.55]	<0.01
Inflammatory disease	1.74 [1.29-2.35]	<0.01
Multivessel disease	1.44 [1.12-1.85]	<0.01