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ORIGINAL PAPER

Association of coronary atherosclerotic burden with clinical presentation and prognosis in patients with stable and unstable coronary artery disease

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Abstract
Background The impact of coronary atherosclerotic burden on prognosis and presentation of patients with coronary artery disease (CAD) is unknown. We investigated the association of coronary atherosclerotic burden with clinical outcome and presentation as unstable angina in patients with CAD.
Methods This study included 10,647 patients with stable ($n = 8{,}149$) and unstable ($n = 2{,}498$) CAD who underwent percutaneous coronary intervention (PCI). Coronary atherosclerotic burden was assessed by Gensini score. The primary outcome analysis was 1-year mortality.
Results Patients were divided into groups according to quartiles of Gensini score: <13 (first quartile; $n = 2{,}650$ patients), 13 to <25 (second quartile; $n = 2{,}611$ patients), 25 to <53 (third quartile; $n = 2{,}721$ patients) and ≥53 (fourth quartile; $n = 2{,}665$ patients). There were 295 deaths during follow-up: 41 deaths in the first quartile, 42 deaths in the second quartile, 83 deaths in the third quartile and 129 deaths in the fourth quartile of Gensini score (Kaplan–Meier estimates of 1-year mortality 1.6, 1.7, 3.1 and 5.0 %, respectively; adjusted hazards ratio [HR] = 1.08, 95 % confidence interval [CI] 1.02–1.14, $P = 0.007$ for each 20-point increase in Gensini score). Gensini score was an independent correlate of presentation as unstable angina (adjusted odds ratio [OR] = 1.07, 95 % CI 1.05–1.10, $P < 0.001$, for each 20-point increase in the score). Coronary stenoses with ≥75 % of lumen obstruction mediated almost all the increased risk related to the atherosclerotic burden for presentation as unstable CAD (adjusted OR = 1.08, 95 % CI 1.05–1.12, $P < 0.001$).
Conclusion In patients with CAD, coronary atherosclerotic burden is independently associated with increased risk of 1-year mortality and presentation as unstable angina.

Keywords Atherosclerosis · Coronary artery disease · Mortality · Percutaneous coronary intervention · Unstable angina

Introduction

Coronary artery disease (CAD) arising predominantly from atherosclerosis is a leading cause of death and disability worldwide. Transition from silent to clinically overt CAD is mostly related to the degree and speed of coronary obstruction leading to various degrees of myocardial ischemia. Rupture (or fissuring) of thin-cap atheromas with superimposition of thrombotic material is considered to be the underlying mechanism of acute coronary syndromes (ACS) in most, but not in all patients with CAD [1, 2]. Earlier studies suggested that acute coronary occlusions occur at the sites of tighter coronary stenoses [3–5]. However, serial angiographic studies showed that coronary occlusions resulting in ACS occur at the site of non-severe coronary artery stenoses in majority of patients [6–9]. Angiographic studies following thrombolysis have also shown that noncritical stenoses before occlusion were not uncommon in patients undergoing thrombolysis [10–12]. These studies supported the notion that mild to moderate

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coronary stenoses portend a higher risk for ACS than more severe stenoses which tend to remain unchanged [6–12]. Recent studies in more contemporaneous series of patients disputed these views and showed that majority of acute myocardial infarctions occur at the site of significant stenoses [13, 14] and that intermediate coronary stenoses assessed by free-fractional reserve[15] or intracoronary ultrasound [16] show a very low event rate at long-term follow-up.

The objective of this study was twofold: first, we investigated the association of coronary atherosclerotic burden with mortality and other adverse events in a large series of consecutive patients with stable and unstable angina after percutaneous coronary intervention (PCI) and second, we compared angiographic coronary atherosclerotic burden in patients with stable and unstable angina and assessed the impact of coronary atherosclerotic burden on clinical presentation as unstable CAD.

Methods

Patients

This study included a consecutive series of 10,647 patients with stable ($n = 8{,}149$) and unstable ($n = 2{,}498$) CAD who underwent coronary angiography and PCI in the Deutsches Herzzentrum in Munich, Germany, between March 2000 and December 2009. Patients eligible for this study were those with a clinical diagnosis of stable or unstable CAD who had angiographic confirmation of significant disease (at least one coronary stenosis with ≥50 % lumen obstruction). The diagnosis of stable angina was based on the presence of chest pain that did not change its pattern in the preceding 2 months. Unstable CAD was diagnosed using Braunwald's criteria [17] and with documentation of significant CAD in the coronary angiography. Patients with non-ST-segment elevation myocardial infarction (chest pain plus elevated fourth-generation assay cardiac troponin T level >0.03 μg/l), ST-segment elevation myocardial infarction, renal disease (serum creatinine level ≥2 mg/dl), acute infections, or known malignancies were excluded. All patients gave informed consent before recruitment in the study. The study has been carried out in accordance with the Declaration of Helsinki and approved by the institutional ethics committee.

Definitions of risk factors

Hypercholesterolemia was defined as a documented total cholesterol value ≥220 mg/dl or prior or ongoing treatment with lipid-lowering agents. Arterial hypertension was diagnosed if a patient was receiving active treatment with antihypertensive drugs or if on two separate occasions the systolic blood pressure was 140 mmHg or greater or the diastolic blood pressure 90 mmHg or greater. Smokers were defined as those currently smoking any tobacco. The criteria for diabetes included history of diabetes with active treatment with insulin or oral hypoglycemic agents on admission; an abnormal fasting blood glucose (≥125 mg/dl or ≥7.0 mmol/l) or glucose tolerance test (≥200 mg/dl or ≥11.1 mmol/l) according to World Health Organization criteria for diabetes; or a blood glucose >200 mg/dl at any time. Patients' weight and height were measured and body mass index was calculated. Congestive heart failure was graded according to New York Heart Association (NYHA) Classification. The glomerular filtration rate was estimated using the Cockcroft–Gault formula [18].

Angiographic evaluation and stent implantation

Coronary angiography was performed according to standard criteria. Angiographic data were analyzed using the same Quantitative Angiographic Core Laboratory. CAD was confirmed by the presence of coronary stenoses ≥50 % lumen obstruction in at least one of the three main coronary arteries. Offline analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS; Medis Medical Imaging Systems, Neuen, the Netherlands). Global left ventricular ejection fraction was determined by left ventricular angiography using the area-length method.

Coronary atherosclerotic burden was estimated by using Gensini score [19]. In brief, concentric lesions and eccentric plaques with 25, 50, 75, 90, 99 and 100 % lumen obstruction were angiographically quantified and scored by 1 (for 25 % obstruction), 2 (for 50 % obstruction), 4 (75 % obstruction), 8 (for 90 % obstruction), 16 (for 99 % obstruction) and 32 (for 100 % obstruction) points, respectively. Thereafter a multiplying factor was used depending on the significance of the area supplied by a given coronary segment in which the lesion resides (from 1 to 5). The final coronary artery atherosclerotic score equals the sum of all segment scores (derived from the severity of lumen obstruction multiplied by the factor of segment significance).

Stent implantation and periprocedural care were performed according to standard criteria. Postinterventional antiplatelet therapy consisted of clopidogrel (300 mg or 600 mg as a loading dose followed by 75 mg/day for at least 4 weeks to 6 months) and aspirin (200 mg/day administered orally and continued indefinitely).

Outcome measurements and follow-up

The primary outcome analysis was all-cause mortality at 1 year after PCI procedure. Other adverse events assessed

were mortality of cardiovascular origin, nonfatal myocardial infarction, stroke, target lesion revascularization, major adverse cardiac events (a composite of death, nonfatal myocardial infarction and target lesion revascularization) and presentation as unstable CAD. The follow-up protocol consisted of a phone interview at 1 month, a visit at 6 months and a phone interview at 12 months after PCI procedure. Information on deaths was obtained from hospital records, death certificates or phone contact with relatives of the patient or referring physician. Patients who had cardiac complaints any time during the follow-up underwent a complete clinical, electrocardiographic and laboratory evaluation. Death of cardiovascular origin was defined as death due to any of the following: acute coronary syndrome; arrhythmia or conduction abnormality; congestive heart failure; or any death in which a cardiac cause cannot be excluded. The diagnosis of stroke required confirmation by computed tomography or magnetic resonance imaging of the head. Follow-up information and adjudication of adverse events were performed by medical staff unaware of clinical diagnosis or coronary angiography data.

Statistical analysis

Data are presented as median (25th to 75th percentiles) or counts and proportions (%). The Kolmogorov–Smirnov test was used to assess the normality of data distribution. Categorical data were compared with Chi-square test. Continuous data were compared with the Kruskal–Wallis rank-sum test. Survival analysis was performed by applying the Kaplan–Meier method and comparison between the groups was performed with log-rank test. The multivariable Cox proportional hazards model was used to assess the association between Gensini score (entered into the model as a continuous variable) and 1-year all-cause mortality (primary outcome) while adjusting for potential confounders. All variables of Table 1 were entered into the Cox model. Multiple logistic regression model was used to test the association of coronary atherosclerotic burden with the clinical presentation (unstable vs. stable CAD). All variables of Table 2 were entered into the multiple logistic regression model. Gensini score was entered as continuous variable. All analyses were performed using S-plus statistical package (S-PLUS, Insightful Corp, Seattle, Washington). A two-tailed $P < 0.05$ was considered to indicate statistical significance.

Results

Baseline data

The study included 10,647 patients with stable ($n = 8,149$ patients) and unstable ($n = 2,498$ patients) CAD. Gensini score was obtained by analysis of 131,360 coronary segments. Patients were divided into groups according to quartiles of Gensini score which were <13 (first quartile; $n = 2,650$ patients), 13 to <25 (second quartile; $n = 2,611$ patients), 25 to <53 (third quartile; $n = 2,721$ patients) and ≥53 (fourth quartile; $n = 2,665$ patients). Main baseline demographic, clinical and angiographic characteristics of the patients are shown in Table 1. With the exception of proportions of patients with arterial hypertension and body mass index, all other variables appeared to have significant differences between groups according to quartiles of Gensini score.

Correlates of unstable CAD

Baseline demographic, clinical and angiographic data in patients with stable and unstable CAD are shown in Table 2. Gensini score (median [25th–75th percentile]) was 25.0 [12.0–56.5] in patients with stable CAD and 30.5 [14.5–63.1] in patients with unstable CAD ($P < 0.001$). Multiple logistic regression model was used to identify independent correlates of presentation with unstable CAD (see "Methods" section for variables entered into the model). The strongest factor for presentation as unstable CAD was C-reactive protein followed by Gensini score, female sex and current smoking. Prior myocardial infarction and prior coronary artery bypass surgery showed an independent inverse association with presentation as unstable CAD. High cholesterol level was close to reaching the statistical significance ($\chi^2 = 3.77$; $P = 0.052$). The adjusted odds ratios (OR) for the association with presentation pattern are shown in Table 3. As shown in Table 3, for every 20-point increase in the Gensini score and for every 5 mg/dl increase in the C-reactive protein level, the likelihood of presentation as unstable CAD increased by 7 and 6 %, respectively. The logistic regression was repeated after inclusion of critical stenoses (stenoses ≥75 %) into the model. When stenoses ≥75 % were entered into the model, this variable (OR [95 % CI] = 1.08 [1.05–1.12], $P < 0.001$; Chi-square = 20.30), but not Gensini score (OR = 1.02 [0.99–1.06], $P = 0.210$), showed a significant association with presentation as unstable CAD.

Clinical outcome

There were 295 deaths during the 1-year follow-up. Deaths according to quartiles of Gensini score were as follows: 41 deaths in the first quartile, 42 deaths in the second quartile, 83 deaths in the third quartile and 129 deaths in the fourth quartile (Kaplan–Meier estimates of 1-year mortality 1.6, 1.7, 3.1 and 5.0 %, respectively (log-rank test P value <0.001; Fig. 1). Deaths of cardiovascular origin occurred in 189 patients (64 % of all deaths). One-year

Table 1 Baseline demographic, clinical and angiographic data

Characteristic	Quartiles of Gensini score				*P* value
	First ($n = 2,650$)	Second ($n = 2,611$)	Third ($n = 2,721$)	Fourth ($n = 2,665$)	
Age (years)	66.0 [58.3; 73.0]	61.1 [59.5; 74.1]	67.1 [60.1; 74.2]	69.0 [61.5; 75.4]	<0.001
Women	739 (27.9)	647 (24.8)	575 (21.1)	416 (15.6)	<0.001
Arterial hypertension	1,899 (71.7)	1,930 (73.9)	198 (73.1)	1,984 (74.4)	0.112
Hypercholesterolemia	1,864 (70.3)	1,865 (71.4)	2,020 (74.2)	2,128 (79.8)	<0.001
Diabetes	592 (22.3)	707 (27.1)	766 (28.2)	897 (33.7)	<0.001
On insulin therapy	153 (5.8)	217 (8.3)	231 (8.5)	324 (12.2)	<0.001
Body mass index (kg/m^2)	26.9 [24.6; 29.3]	26.8 [24.6; 29.5]	26.9 [24.6; 29.7]	27.1 [24.9; 29.7]	0.066
Current smoker	420 (15.8)	347 (13.3)	319 (11.7)	293 (11.0)	<0.001
Prior myocardial infarction	733 (27.7)	738 (28.3)	921 (33.8)	1,274 (47.8)	<0.001
Prior coronary artery bypass surgery	60 (2.3)	92 (3.5)	258 (9.5)	1,317 (49.4)	<0.001
Presentation with unstable angina	518 (19.5)	582 (22.3)	699 (25.7)	699 (26.2)	<0.001
NYHA class					<0.001
1	1,669 (62.9)	1,562 (59.8)	1,472 (54.1)	1,222 (45.8)	
2	826 (31.2)	874 (33.5)	1,028 (37.8)	1,154 (43.3)	
3	142 (5.4)	162 (6.2)	205 (7.5)	263 (9.9)	
4	13 (0.5)	13 (0.5)	16 (0.6)	26 (1.0)	
Systolic blood pressure (mmHg)	150.0 [130.0; 166.0]	150.0 [130.0; 170.0]	150.0 [130.0; 170.0]	150.0 [130.0; 166.5]	0.012
Glomerular filtration rate (ml/min)	82.9 [64.1; 105.2]	81.1 [63.0; 101.2]	81.5 [61.8; 101.9]	77.3 [58.5; 100.1]	<0.001
C-reactive protein (mg/l)	2.00 [0.89; 5.28]	1.90 [0.84; 4.86]	2.00 [0.88; 5.18]	2.35 [0.98; 6.2]	<0.001
Number of affected coronary arteries					<0.001
1	961 (36.3)	431 (16.5)	259 (9.5)	71 (2.7)	
2	925 (34.9)	875 (33.5)	716 (26.3)	321 (12.0)	
3	764 (28.8)	1,305 (50.0)	1,746 (64.2)	2,273 (85.3)	
Multivessel disease	1,689 (63.7)	2,180 (83.5)	2,462 (90.5)	2,594 (97.3)	<0.001
Left main disease	46 (1.7)	146 (5.6)	496 (18.2)	772 (29.0)	<0.001
Complex lesions	1,551 (58.5)	1,812 (69.4)	2,179 (80.1)	2,228 (83.6)	<0.001
Gensini score	8.0 [5.0; 10.5]	18.0 [15.0; 21.5]	39.5 [32.0; 53.0]	94.0 [73.5; 131.5]	<0.001
Left ventricular ejection fraction (%)	60.0 [53.0; 65.0]	60.0 [53.0; 65.0]	58.0 [50.0; 63.0]	53.0 [44.0; 60.0]	<0.001

Data are median [25th; 75th percentiles] or number of patients (%)

NYHA indicates New York Heart Association

clinical outcome is shown in Table 4. As seen from the Table 4, apart from all-cause mortality, there were also significant differences between patients of various Gensini scores regarding cardiovascular mortality, nonfatal myocardial infarction, need for target lesion revascularization and major adverse cardiac events.

The association between Gensini score and 1-year mortality was also assessed according to presentation as stable or unstable CAD. There were 196 deaths in patients with stable CAD: 36 deaths among patients in the first quartile ($n = 2,132$), 31 deaths among patients in the second quartile ($n = 2,029$), 60 deaths among patients in the third quartile ($n = 2,022$) and 69 deaths among patients in the fourth quartile ($n = 1,966$) of the Gensini score (Kaplan–Meier estimates of 1-year mortality 1.7, 1.6, 3.1 and 3.6 %, respectively; log-rank test $P < 0.001$). There were 99 deaths in patients with unstable CAD: 5 deaths among patients in the first quartile ($n = 518$), 11 deaths among patients in the second quartile ($n = 582$), 23 deaths among patients in the third quartile ($n = 699$) and 60 deaths among patients in the fourth quartile ($n = 699$) of the Gensini score (Kaplan–Meier estimates of 1-year mortality 1.0, 2.0, 3.3 and 8.8 %, respectively; log-rank test $P < 0.001$). One-year mortality estimates according to clinical presentation are shown in Fig. 2.

The Cox proportional hazards model was used to test the association between the coronary atherosclerotic burden and mortality while adjusting for other demographic, clinical and angiographic factors (see "Methods" section for variables entered into the model). The model identified

Table 2 Baseline data in stable and unstable CAD

Characteristic	Stable CAD ($n = 8,149$)	Unstable CAD ($n = 2,498$)	P value
Age (years)	67.1 [59.6; 74.0]	68.0 [60.4; 75.2]	<0.001
Women	1,741 (21.0)	636 (25.0)	<0.001
Arterial hypertension	5,958 (73.1)	1,844 (73.8)	0.485
Hypercholesterolemia	6,090 (74.7)	1,787 (71.5)	0.001
Diabetes	2,274 (27.9)	688 (27.5)	0.732
On insulin therapy	710 (8.7)	215 (8.6)	0.869
Body mass index (kg/m^2)	27.0 [24.7; 29.7]	26.7 [24.6; 29.5]	0.040
Current smoker	1,009 (12.4)	370 (14.8)	0.002
Prior myocardial infarction	2,919 (36.0)	747 (30.0)	<0.001
Prior coronary artery bypass surgery	1,323 (16.2)	404 (16.2)	0.941
NYHA class			<0.001
1	4,569 (56.1)	1,356 (54.3)	
2	2,993 (36.7)	889 (35.6)	
3	561 (6.9)	211 (8.4)	
4	26 (0.3)	42 (1.7)	
Systolic blood pressure (mmHg)	150.0 [130.0; 170.0]	150.0 [130.0; 170.0]	0.202
Glomerular filtration rate (ml/min)	81.3 [62.5; 103.0]	79.0 [59.7; 100.2]	<0.001
C-reactive protein (mg/l)	1.90 [0.85; 4.82]	2.60 [1.07; 7.70]	<0.001
Number of affected coronary arteries			0.025
1	1,278 (15.7)	444 (17.8)	
2	2,164 (26.6)	673 (26.9)	
3	4,707 (57.7)	1,381 (55.3)	
Multivessel disease	6,871 (84.4)	2,054 (82.2)	0.013
Left main disease	1,074 (13.2)	386 (15.5)	0.004
Complex lesions	5,769 (70.8)	2,001 (80.1)	<0.001
Gensini score	25.0 [12.0; 56.5]	30.5 [14.5; 63.1]	<0.001
Diameter stenosis before intervention (%)	60.1 [51.7; 70.4]	63.2 [53.7; 74.1]	<0.001
Stenoses ≥75 % lumen obstruction	2.0 [1.0; 4.0]	3.0 [1.0; 4.0]	<0.001
Vessel size (mm)	2.78 [2.41; 3.23]	2.82 [1.46; 3.26]	0.001
Left ventricular ejection fraction (%)	58.0 [50.0; 63.0]	58.0 [49.0; 64.0]	0.436

Data are median [25th; 75th percentiles] or number of patients (%)

NYHA indicates New York Heart Association

Table 3 Independent correlates of presentation as unstable CAD

Variable	χ^2	Adjusted odds ratio [95 % CI]	P value
C-reactive protein (for 5 mg/dl increase)	61.87	1.06 [1.05–1.08]	<0.001
Prior myocardial infarction	27.56	0.74 [0.66–0.83]	<0.001
Gensini score (for 20 points increase in severity)	26.85	1.07 [1.05–1.10]	<0.001
Female sex	13.33	1.25 [1.11–1.41]	<0.001
Current smoking	11.69	1.29 [1.11–1.49]	<0.001
Prior coronary artery bypass surgery	7.70	0.78 [0.66–0.93]	<0.001

age, Gensini score, diabetes, congestive heart failure (NYHA class), previous coronary artery bypass surgery, impaired renal function (reduced glomerular filtration rate), C-reactive protein and left ventricular ejection fraction as independent correlates of 1-year mortality (Table 5). Of note, for every 20-point increase in the Gensini score, the adjusted risk of 1-year mortality increased by 8 %.

Discussion

The main findings of this study may be summarized as follows: (1) Coronary atherosclerotic burden predicts the occurrence of 1-year mortality, nonfatal myocardial infarction and the need for target lesion revascularization in patients with stable and unstable CAD after PCI. (2)

Coronary atherosclerotic burden is an independent factor for clinical presentation as unstable angina. (3) Severe stenoses (those with lumen narrowing ≥75 %) mediate almost all the risk related to atherosclerotic burden for presentation as unstable CAD.

The relationship between stenosis severity and acute ischemic events has been and still remains a controversial issue. Earlier, serial angiographic studies have suggested that acute ischemic events and, in particular, acute myocardial infarction are commonly produced by atherosclerotic plaques causing insignificant or mild stenosis [6–9]. It has to be emphasized that these studies included remarkably small numbers of patients, had a retrospective design and the time interval between angiographic examinations varied considerably (up to 11 years). The variable and long time interval between angiographic examinations may have hampered the exact assessment of stenosis severity at the time of acute coronary event, due to CAD progression, known to be more prominent in patients with unstable CAD [20]. Importantly, these studies were performed before massive use of antithrombotic drugs and statins—known to exert antithrombotic, anti-inflammatory and plaque-stabilizing effects [21–23]—as maintenance therapy in patients with CAD. Recent studies performed in more contemporaneous series of patients have come to different conclusions [13–16]. In a series of patients with acute myocardial infarction undergoing acute PCI, Frøbert et al. [13] showed that in 96 % of patients with reliable quantitative coronary angiography, severity of underlying stenosis was >50 % and in 66 % of patients severity of underlying stenosis was >70 %. The authors concluded that majority of plaque occlusions resulting in acute myocardial infarction occur at the site of significant stenoses. Another recent study by Manoharan et al. [14] reported that culprit stenoses responsible for acute ST-segment elevation myocardial infarction were found to have a diameter stenosis <50 % only in 11 % of the cases. The tightest stenoses were observed in patients with unstable angina and non-ST-segment elevation myocardial infarction (71 ± 12 % lumen obstruction) which were more severe than stenoses in patients with ST-segment elevation myocardial infarction or stable angina [14].

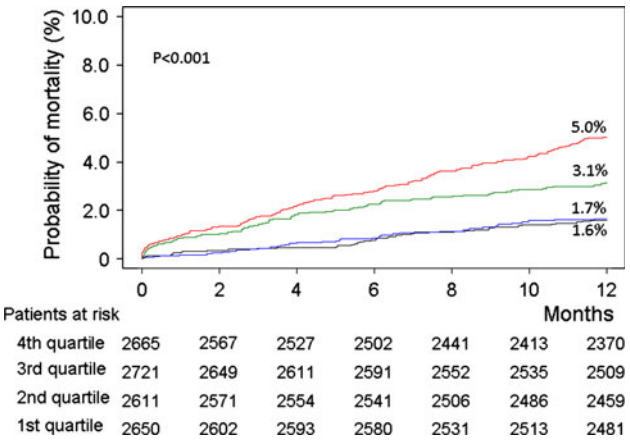

Fig. 1 Kaplan–Meier curves of all-cause mortality according to Gensini score quartiles

Recent studies have also reported an excellent long-term prognosis of non-treated insignificant plaques [15, 16]. In a 5-year follow-up of DEFER study, intermediate coronary stenoses (based on fractional flow reserve ≥0.75) had a risk of death or myocardial infarction of <1 % per year which was not decreased by stenting [15]. Along similar lines, Abizaid et al. [16] reported a low event rate over long-term follow-up (>1 year) in patients with native de novo intermediate coronary lesions in whom PCI was deferred based on intravascular ultrasound lesion examination.

In the present study, we found that patients presenting with unstable CAD had a higher coronary atherosclerosis burden and a greater number of critical stenoses than patients with stable CAD. Of note, multivariable analysis demonstrated that atherosclerotic burden was independently associated with presentation as unstable CAD and that nearly all increased risk for presentation as unstable CAD was related to critical coronary stenoses. In this

Table 4 Clinical outcome

Characteristic	Quartiles of Gensini score				*P* value*
	First (n = 2,650)	Second (n = 2,611)	Third (n = 2,721)	Fourth (n = 2,665)	
All-cause mortality	41 (1.6)	42 (1.7)	83 (3.1)	129 (5.0)	<0.001
Cardiac mortality	24 (1.0)	24 (1.0)	60 (2.3)	81 (3.2)	<0.001
Nonfatal myocardial infarction	37 (1.4)	67 (2.6)	95 (3.5)	120 (4.6)	<0.001
Stroke	6 (0.2)	13 (0.5)	16 (0.6)	16 (0.6)	0.155
Target lesion revascularization	304 (11.8)	416 (16.4)	615 (23.7)	611 (24.3)	<0.001
Major adverse cardiac events	366 (14.1)	492 (19.2)	732 (27.6)	775 (30.0)	<0.001

Data are Kaplan–Meier estimates

* Calculated with log-rank test

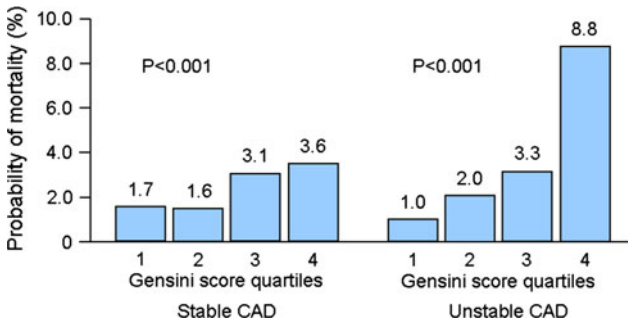

Fig. 2 Kaplan–Meier estimates of 1-year mortality in patients with stable and unstable coronary artery disease (CAD)

regard, the present study is in line with recent studies demonstrating that severe stenoses serve as culprit lesion in majority of patients with ACS. These findings however, are at odds with older studies [6–9] that showed that mild or insignificant stenoses were more prone to thrombotic occlusion and acute myocardial infarction. Although the exact reasons for this discrepancy remain unknown, we hypothesize that the massive use of statins and antithrombotic regimens, especially in patients with known CAD, may have changed the natural course of atherosclerotic plaques. The plaque-stabilizing, anti-inflammatory and antithrombotic effects of current therapies in patients with CAD may reduce the plaque vulnerability to rupture and thus plaques may reach advanced stages of lumen obstruction without complications and clinical events. Reduced incidence of acute ST-segment elevation myocardial infarction [24] could be another expression of increased stability of atherosclerotic plaques by current therapies which may reduce the vulnerability of mild plaques to rupture and acute coronary occlusion. Further studies, however, are needed to corroborate this hypothesis.

The finding that C-reactive protein was the strongest correlate of presentation as unstable CAD is agreement with current concepts on the role of inflammation in causing plaque instability and CAD progression. Moreover, recent studies have confirmed that C-reactive protein and angiographic CAD extent are independent and additive risk factors in patients with angina [25, 26]. By finding that angiographic extent of CAD and C-reactive protein were the strongest independent correlates of presentation as unstable CAD and of 1-year mortality the present study corroborates and further extends the findings of these studies.

Prior smaller-scale studies of patients with angina have shown that CAD score is an independent correlate of death or myocardial infarction up to 5 years [25]. Another study of patients with unstable angina showed that extent of coronary atherosclerosis was independently associated with worse outcome at 6 months [26]. Atherosclerotic burden of left main coronary artery was recently found to be a significant predictor of adverse cardiovascular events, especially of the need for revascularization after PCI [27]. In a large series of patients with CAD, we demonstrated that atherosclerotic burden was independently associated with increased risk of 1-year mortality. The atherosclerotic burden was assessed by Gensini score which was reported to provide more reliable prognostic information than other CAD scores [28]. Three factors may explain the association between increased atherosclerotic burden and mortality. First, a higher coronary atherosclerotic burden was associated with a worse cardiovascular risk profile (clustered cardiovascular risk in upper Gensini score quartiles) which also signifies an increased risk of mortality. Second, there was an increase in the incidence of myocardial infarction with the increase in the atherosclerotic burden. A higher incidence of myocardial infarctions in nonsurvivors at 1 year after PCI was recently reported [29]. Third, there was an association between a higher Gensini score and a greater need for revascularization within the first year after PCI. This may be seen as a sign of CAD progression, known to underlie a poorer prognosis [20].

We recognize that severity of stenoses in patients with unstable CAD may be overestimated due to overlying thrombotic material which was demonstrated in roughly 1/3 of patients with unstable angina [30]. However, since on median basis, patients with unstable CAD had one severe stenosis per patient more (3 vs. 2) than patients with stable CAD, the increased frequency of severe stenoses in patients with unstable CAD cannot entirely be explained by

Table 5 Independent correlates of 1-year mortality

Variable	Adjusted hazard ratio [95 % CI]	*P* value
Age (for 10-year increase in age)	1.25 [1.04–1.51	0.018
Gensini score (for 20 points increase in severity)	1.08 [1.02–1.14]	0.007
Diabetes	1.56 [1.19–2.05]	0.002
NYHA class (for 1 class increase in severity)	1.45 [1.21–1.73]	<0.001
Prior coronary artery bypass surgery	0.63 [0.41–0.97]	0.034
Glomerular filtration rate (for 10 ml/min decrease)	1.20 [1.11–1.30]	<0.001
C-reactive protein (for 5 mg/dl increase in concentration)	1.04 [1.03–1.06]	<0.001
Left ventricular ejection fraction (for 10 % decrease)	1.44 [1.29–1.59]	<0.001

NYHA indicates New York Heart Association

overestimation of stenosis degree by thrombotic material. Although a common link in the pathogenesis of unstable angina and myocardial infarction has been established by Ambrose et al. [31], the present findings belong to stable and unstable angina and may not be extrapolated to patients with acute myocardial infarction. Finally, it has recently been suggested that a combined use of angiographic and clinical data is essential for risk stratification of patients with CAD [32].

In conclusion, the present study showed that a higher coronary atherosclerotic burden is independently associated with increased risk of 1-year mortality in patients with stable and unstable CAD after PCI. The increased atherosclerotic burden is an independent correlate of presentation as unstable angina and the majority of risk for presentation as unstable angina is mediated by coronary stenoses with lumen narrowing of $\geq$75 %.

Conflict of interest None.

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