


Outcomes among non-ST-segment elevation acute coronary syndromes patients with no angiographically obstructive coronary artery disease: observations from 37,101 patients

European Heart Journal: Acute Cardiovascular Care
2014, Vol. 3(1) 37–45
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DOI: 10.1177/2048872613489315
acc.sagepub.com


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Abstract

Aims: Limited data exist concerning outcomes of patients with non-ST-segment elevation acute coronary syndromes (NSTEMI) with no angiographically obstructive coronary artery disease (non-obstructive CAD). We assessed the frequency of clinical outcomes among patients with non-obstructive CAD compared with obstructive CAD.

Methods and results: We pooled data from eight NSTEMI randomized clinical trials from 1994 to 2008, including 37,101 patients who underwent coronary angiography. The primary outcome was 30-day death or myocardial infarction (MI). Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for 30-day death or MI for non-obstructive versus obstructive CAD were generated for each trial. Summary ORs (95% CIs) across trials were generated using random effects models. Overall, 3550 patients (9.6%) had non-obstructive CAD. They were younger, more were female, and fewer had diabetes mellitus, previous MI or prior percutaneous coronary intervention than patients with obstructive CAD. Thirty-day death or MI was less frequent among patients with non-obstructive CAD (2.2%) versus obstructive CAD (13.3%) (OR_{adj} 0.15; 95% CI, 0.11–0.20); 30-day death or spontaneous MI and six-month mortality were also less frequent among patients with non-obstructive CAD (OR_{adj} 0.19 (0.14–0.25) and 0.37 (0.28–0.49), respectively).

Conclusion: Among patients with NSTEMI, one in 10 had non-obstructive CAD. Death or MI occurred in 2.2% of these patients by 30 days. Compared with patients with obstructive CAD, the rate of major cardiac events was lower in patients with non-obstructive CAD but was not negligible, prompting the need to better understand management strategies for this group.

Keywords

Acute coronary syndromes, angiography, atherosclerosis, coronary disease, infarction

Received: 4 February 2013; accepted: 16 April 2013

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Introduction

A small proportion of patients with non-ST-segment elevation acute coronary syndrome (NSTEMI) have no significant obstructive coronary lesions detected at coronary angiography.^{1–4} In patients with a clear diagnosis of NSTEMI, the absence of obstructive coronary artery disease (CAD) upon angiography is always puzzling and calls into question the appropriateness of the usual therapeutic approach. Indeed, these patients have no indication for coronary revascularization,⁵ and practice guidelines recommend that patients found to have non-obstructive CAD are discharged rapidly or shifted to a different management strategy.⁶ Based on this, these patients are often reassured that they have no significant disease and have an excellent prognosis. As a consequence, they are significantly less frequently treated with secondary prevention agents, both in the hospital and at discharge.⁷

More than one-third of women with myocardial infarction (MI) and no angiographically obstructive CAD (non-obstructive CAD) may have plaque rupture or ulceration when examined with intravascular ultrasound.⁸ Also, recent data suggest that patients with typical symptoms of ACS but without critical coronary obstruction on visual angiography have a prognosis that may not be as benign as previously thought.³ The uncertainties regarding the prognosis of patients with non-obstructive CAD are reflected in the unstable angina/non-ST-segment elevation myocardial infarction 2011 guidelines focused update, which indicates (with level of evidence C) that antiplatelet and anticoagulant therapy should be administered to these patients at the discretion of the clinician.⁶

No large study has compared the outcomes of NSTEMI ACS patients both with and without angiographic evidence of obstructive CAD. Therefore, using data from eight randomized clinical trials that enrolled patients with NSTEMI ACS, we examined the frequency of non-obstructive CAD and the outcomes of these patients compared with those with obstructive CAD.

Methods

Study population

Patient-level data from eight large randomized clinical trials (GUSTO IIb, PURSUIT, PARAGON A, PARAGON B, SYNERGY, PRISM, PRISM-PLUS and EARLY ACS) were used for our analyses.^{9–16} The key features of these trials are summarized in Supplementary Table 1. From 51,132 patients randomized, we included all patients for whom angiographic data were available ($n=37,101$ (73%)).

Data collection and clinical endpoint definition

Baseline demographics, medical history, medications, procedures, complications and clinical events were collected

prospectively on the case report form for each trial. Each trial also collected information on the degree of coronary obstruction in major epicardial coronary arteries (Supplementary Table 1). Based on angiographic results as reported in the case report form, patients were classified as having non-obstructive CAD if no major epicardial vessels or their primary branches had $\geq 50\%$ luminal stenosis. Thus, the group with non-obstructive CAD includes both patients with stenoses of $< 50\%$ and those with angiographically normal arteries. Patients with previous coronary artery bypass grafting were assigned to the obstructive CAD group.

The primary endpoint for the current analysis was the composite of death or MI at 30 days. Secondary endpoints included all-cause mortality at 30 days and six months (six-month mortality was not available for PRISM or PRISM-PLUS) and the following composite endpoints at 30 days: death or spontaneous MI (i.e. procedure-related MI was excluded from the MI endpoint) and death, MI, or recurrent ischemia requiring urgent revascularization.

Statistical methods

All analyses were performed with SAS software, version 9 (SAS Institute, Cary, NC, USA). Categorical variables are reported as counts with percentages, and continuous variables are reported as medians with interquartile ranges. The Global Registry for Acute Coronary Events (GRACE) risk score was calculated for in-hospital death and in-hospital death/MI using validated algorithms.¹⁷ Factors included in the calculations were age, systolic blood pressure, heart rate, serum creatinine, Killip class, ST-segment change and enrolling MI.

For each trial, we examined the rates of the primary and secondary endpoints according to extent of CAD (non-obstructive versus obstructive). We conducted a meta-analysis employing random effects modeling to pool these rates and generated both unadjusted and adjusted summary odds ratios (ORs) (95% confidence intervals (CIs)) across all trials for each endpoint for the comparison of patients with non-obstructive CAD versus obstructive CAD. Adjusted comparisons considered the following baseline characteristics derived from prior modeling and risk scores: age, sex, weight, enrolling MI, prior percutaneous coronary intervention (PCI), prior MI, diabetes, and systolic blood pressure.^{18–20} To determine whether sex differences in non-obstructive CAD persisted after adjusting for baseline characteristics, random effects models for death/MI were created. First, sex and the sex-by-CAD interaction were tested when no other baseline covariates were included, followed by inclusion of baseline covariates.

Our study complied with the Declaration of Helsinki. All patients enrolled provided written informed consent, and the trials were approved by the institutional review boards and ethics committees of participating sites. Use of

Table 1. Demographics and baseline characteristics.

	Extent of disease	
	Non-obstructive CAD	Obstructive CAD
Total number of patients	3550	33,551
Age, median (25th, 75th percentiles)	62.0 (51.0, 69.4)	65.7 (57.5, 73.0)
Female sex	1974/3550 (55.6)	9849/33,551 (29.4)
Weight, kg		
No.	3548	33,543
Median (25th, 75th percentiles)	76.7 (66.0, 90.0)	79.3 (70.0, 90.0)
White	2938/3549 (82.8)	29,730/33,540 (88.6)
Current smoker	876/3536 (24.8)	9348/33,479 (27.9)
Diabetes	536/3550 (15.1)	8834/33,545 (26.3)
Prior CABG	0/3549 (0.0)	5335/33,542 (15.9)
Prior CHF	261/3541 (7.4)	3011/33,513 (9.0)
Prior MI	513/3549 (14.5)	10,659/33,503 (31.8)
Prior PCI	367/3550 (10.3)	6603/33,536 (19.7)
Prior PVD	118/3550 (3.3)	3416/33,544 (10.2)
Heart rate, bpm		
No.	3527	33,410
Median (25th, 75th percentiles)	74.0 (64.0, 85.0)	72.0 (63.0, 84.0)
Diastolic BP, mmHg		
No.	3544	33,476
Median (25th, 75th percentiles)	77.0 (68.0, 86.0)	78.0 (68.0, 87.0)
Systolic BP, mmHg		
No.	3547	33,502
Median (25th, 75th percentiles)	131.0 (120.0, 150.0)	135.0 (120.0, 150.0)
Hypertension	2047/3550 (57.7)	20,734/33,548 (61.8)
Killip class, n (%)		
Presentation	3190 (100)	29,658 (100)
I	2941 (92.2)	26,543 (89.5)
II	202 (6.3)	2584 (8.7)
III	37 (1.2)	417 (1.4)
IV	10 (0.3)	114 (0.4)
Creatinine at enrollment, mg/dl		
No.	3500	32,990
Median (25th, 75th percentiles)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)
Creatinine clearance		
No.	3497	32,978
Median (25th, 75th percentiles)	80.2 (62.2, 103.8)	76.2 (58.2, 97.6)
Qualifying event		
Elevated cardiac markers	1442/3533 (40.8)	21,174/33,496 (63.2)
ECG changes ^a	1541/3524 (43.7)	18,350/33,388 (55.0)
GRACE risk (in-hospital death)		
No.	3550	33,551
Median (25th, 75th percentiles)	116.1 (95.7, 136.3)	129.0 (110.6, 147.9)
GRACE risk (in-hospital death/MI)		
No.	3550	33,551
Median (25th, 75th percentiles)	139.0 (92.5, 165.9)	159.1 (132.3, 199.1)

Values are presented as *n*/total (%) unless otherwise noted.

BP: blood pressure; CAD: coronary artery disease; CABG: coronary artery bypass graft; CHF: congestive heart failure; ECG: electrocardiogram; GRACE: Global Registry for Acute Coronary Events; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.

^aECG changes = transient or persistent ST-segment depression of more than 0.5 mm; persistent, definite T-wave inversion of more than 1 mm; transient ST-segment elevation of more than 0.5 mm lasting less than 20 minutes.

Table 2. Medications and procedures according to extent of coronary artery disease.

	Extent of disease	
	Non-obstructive CAD	Obstructive CAD
Total number of patients	3550	33,551
Pre-randomization		
ACE inhibitors	784/3245 (24.2)	8713/30,130 (28.9)
Aspirin	2074/3083 (67.3)	21,496/28,956 (74.2)
Beta-blockers	1443/3245 (44.5)	16,284/30,133 (54.0)
Statins/LLAs	670/3245 (20.6)	10,125/30,130 (33.6)
Thienopyridines	637/2686 (23.7)	9052/26,344 (34.4)
Index hospitalization		
ACE inhibitors	1165/2911 (40.0)	15,453/27,026 (57.2)
Aspirin	3061/3162 (96.8)	29,007/29,586 (98.0)
Beta-blockers	2147/3084 (69.6)	24,039/29,049 (82.8)
Statins/LLAs	1122/2927 (38.3)	16,837/27,895 (60.4)
Thienopyridines	877/2233 (39.3)	16,632/23,760 (70.0)
In-hospital procedures		
PCI performed	0/3550 (0.0)	16,194/33,550 (48.3)
CABG performed	0/3550 (0.0)	6552/33,548 (19.5)

Values are presented as *n*/total (%).

ACE: angiotensin-converting enzyme; CABG: coronary artery bypass graft; CAD: coronary artery disease; LLAs: lipid-lowering agents; PCI: percutaneous coronary intervention.

Table 3. Meta-analysis of clinical outcomes among patients with no angiographically obstructive coronary artery disease compared with those with obstructive disease.

Parameter	Extent of disease, <i>n</i> /total (%)		OR (95% CI)	
	Non-obstructive CAD	Obstructive CAD	Unadjusted	Adjusted
Total number of patients	3550	33,551		
Death/MI 30 days	76/3528 (2.2)	4441/33,484 (13.3)	0.13 (0.10–0.16)	0.15 (0.11–0.20)
Death 30 days	20/3542 (0.6)	927/33,532 (2.8)	0.20 (0.14–0.29)	0.32 (0.23–0.44)
Death/spontaneous MI 30 days	76/3528 (2.2)	3587/33,484 (10.7)	0.16 (0.13–0.20)	0.19 (0.14–0.25)
Death/MI/RIUR 30 days	96/3521 (2.7)	6236/33,394 (18.7)	0.12 (0.06–0.24)	0.13 (0.06–0.26)
Death six months	41/3211 (1.3)	1478/29,989 (4.9)	0.25 (0.17–0.36)	0.37 (0.28–0.49)

CAD: coronary artery disease; CI: confidence interval; MI: myocardial infarction; OR: odds ratio; RIUR: recurrent ischemia requiring urgent revascularization.

trial data for the current analyses was approved by the institutional review board of the Duke University Medical Center.

Results

Patient population, baseline clinical characteristics and medical treatment

Among 37,101 patients included in the analyses, 3550 patients (9.6%) had non-obstructive CAD. The prevalence ranged from 6.9% in EARLY ACS to 13.0% in PARAGON B. Overall, 17% of women and 7% of men had non-obstructive CAD. Non-obstructive CAD patients were younger, more were female, and they were less likely to have diabetes mellitus, previous MI or prior PCI (Table 1). Among the

3550 patients with non-obstructive CAD, more detailed angiographic data were available for 2001 patients, among whom a normal coronary angiogram (0% stenosis) was present in 995 (50%), and 1006 (50%) patients had a coronary stenosis >0% and <50%.

Patients with non-obstructive CAD were treated slightly less often with guidelines-recommended pharmacotherapy before angiography (Table 2), and this difference increased after angiography.

Clinical outcomes

Primary and secondary endpoint rates with ORs (95% CIs) among patients with non-obstructive CAD versus obstructive CAD are displayed in Table 3. Thirty-day death or MI occurred in 12.2% of patients overall and was much less

Table 4. Demographics and baseline characteristics of non-obstructive CAD patients with and without 30-day death or MI.

	Death or MI in 30 days	
	No	Yes
Total number of patients	3452	76
Age, years, median (25th, 75th percentiles)	62.0 (51.4, 69.5)	62.1 (52.5, 70.5)
Female sex, <i>n</i> (%)	1929 (55.9)	35 (46.1)
Weight, kg		
No.	3450	76
Median (25th, 75th percentiles)	76.5 (66.0, 90.0)	77.5 (66.0, 90.8)
White	2852/3451 (82.6)	69/76 (90.8)
Current smoker	847/3438 (24.6)	20/76 (26.3)
Diabetes	519/3452 (15.0)	12/76 (15.8)
Prior CABG	0 (0)	0 (0)
Prior CHF	244/3443 (7.1)	14/76 (18.4)
Prior MI	490/3451 (14.2)	16/76 (21.1)
Prior PCI	357/3452 (10.3)	8/76 (10.5)
Prior PVD	110/3452 (3.2)	8/76 (10.5)
Heart rate, bpm		
No.	3430	76
Median (25th, 75th percentiles)	74.0 (64.0, 85.0)	77.5 (68.0, 94.0)
Diastolic BP, mmHg		
No.	3446	76
Median (25th, 75th percentiles)	77.0 (68.0, 86.0)	76.5 (70.0, 84.0)
Systolic BP, mmHg		
No.	3449	76
Median (25th, 75th percentiles)	131.0 (120.0, 150.0)	129.0 (120.0, 151.5)
Hypertension	1995/3452 (57.8)	43/76 (56.6)
Killip class, <i>n</i> (%)		
Presentation	3101 (100)	67 (100)
I	2861 (92.3)	58 (86.6)
II	193 (6.2)	9 (13.4)
III	37 (1.2)	0 (0.0)
IV	10 (0.3)	0 (0.0)
Creatinine at enrollment, mg/dl		
No.	3402	76
Median (25th, 75th percentiles)	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)
Creatinine clearance		
No.	3399	76
Median (25th, 75th percentiles)	80.2 (62.3, 103.7)	76.7 (56.4, 106.4)
Qualifying event		
Elevated cardiac markers	1397/3435 (40.7)	43/76 (56.6)
ECG changes ^a	1495/3426 (43.6)	34/76 (44.7)
GRACE risk (in-hospital death/MI)		
No.	3452	76
Median (25th, 75th percentiles)	139.0 (92.3, 165.5)	149.8 (120.2, 183.1)
Medications		
Pre-randomization		
ACE inhibitors	759/3152 (24.1)	22/71 (31.0)
Aspirin	2017/2992 (67.4)	41/70 (58.6)
Beta-blockers	1406/3152 (44.6)	29/71 (40.8)
Statins/LLAs	654/3152 (20.7)	10/71 (14.1)
Thienopyridines	625/2611 (23.9)	12/62 (19.4)

(Continued)

Table 4. (Continued)

	Death or MI in 30 days	
	No	Yes
Index hospitalization		
ACE inhibitors	1129/2823 (40.0)	33/66 (50.0)
Aspirin	2971/3069 (96.8)	68/71 (95.8)
Beta-blockers	2089/2996 (69.7)	46/66 (69.7)
Statins/LLAs	1097/2842 (38.6)	19/63 (30.2)
Thienopyridines	859/2168 (39.6)	17/52 (32.7)
Detailed coronary angiography		
0% stenosis	977/1947 (50.2)	15/50 (30.0)
>0% stenosis <50%	970/1947 (49.8)	35/50 (70.0)

Values are presented as *n*/total (%) unless otherwise noted.

ACE: angiotensin-converting enzyme; BP: blood pressure; CAD: coronary artery disease; CABG: coronary artery bypass graft; CHF: congestive heart failure; ECG: electrocardiogram; GRACE: Global Registry for Acute Coronary Events; LLAs: lipid-lowering agents; MI: myocardial infarction; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease.

^aECG changes = transient or persistent ST-segment depression of more than 0.5 mm; persistent, definite T-wave inversion of more than 1 mm; transient ST-segment elevation of more than 0.5 mm lasting less than 20 minutes.

frequent among patients with non-obstructive CAD (2.2%) versus obstructive CAD (13.3%). Adjusting for differences in baseline confounders, patients with non-obstructive CAD were significantly less likely to experience death or MI at 30 days (OR_{adj} 0.15; 95% CI, 0.11–0.20). Thirty-day death or spontaneous MI was also less frequent among patients with non-obstructive CAD versus obstructive CAD (OR_{adj} 0.19; 95% CI, 0.14–0.25). Patients with non-obstructive CAD were also less likely to die by 30 days or six months; 52% of deaths by six months in the non-obstructive CAD group occurred after 30 days; however, 63% of deaths by six months in the obstructive CAD group occurred before 30 days. The 30-day composite endpoint of death, MI, or recurrent ischemia requiring urgent revascularization was also less likely among patients with non-obstructive CAD. Random effects models disclosed no interaction between sex and CAD group with respect to 30-day death or MI.

Risk stratification within the non-obstructive CAD group

Table 4 compares the characteristics of non-obstructive CAD patients who did or did not have 30-day death or MI. The GRACE risk score among patients with 30-day death or MI was higher than among those without. Furthermore, 57% of patients in the non-obstructive CAD group who experienced death or MI within 30 days had elevated cardiac markers at presentation.

Death or MI within 30 days occurred in 38 of 2134 (1.8%) patients with a GRACE score <150 and in 38 of 1394 (2.7%) patients with a GRACE score ≥150. Among 995 patients with 0% stenosis in any vessel, 30-day death or MI occurred in 15 (1.5%) patients, compared with 35 (3.5%) of 1006 patients with stenosis >0% and <50%.

Discussion

In our analysis of 37,101 NSTEMI ACS patients undergoing coronary angiography, one in 10 had non-obstructive CAD. Although these patients had significantly lower risks of 30-day and six-month ischemic events and mortality, their risk was not negligible: more than 2% suffered death or MI by 30 days, and 1.3% died by six months. These findings underscore the need to better understand the mechanisms of NSTEMI ACS in the absence of obstructive CAD and to appropriately evaluate the best treatment strategies for this important subgroup of patients.

Prevalence of non-obstructive CAD

The prevalence of non-obstructive CAD in reports from randomized clinical trials of ACS patients has ranged from 9.1% to 14%,^{2,3} and is similar to estimates reported from population registries.⁴ Our results are consistent with and extend those from previous studies, providing important insight into both clinical factors and study design that may influence prevalence estimates. We found that several baseline characteristics were more common among patients with non-obstructive CAD, including female sex and younger age. Conversely, patients with non-obstructive CAD less frequently had diabetes mellitus, peripheral vascular disease or a history of CAD. These differences may reflect mechanistic differences in coronary disease development and NSTEMI ACS in patients with and without obstructive coronary disease. For example, women are believed to more frequently have plaque erosion and thrombus without obstruction and less luminal encroachment of plaques.²¹

Study-related factors may also influence observed prevalence of non-obstructive CAD. First, not all patients

presenting with a diagnosis of NSTEMI ACS ultimately undergo angiography, creating selection bias (including selection of those with the highest likelihood of obstructive disease, but also those who have no contraindications to undergoing angiography). These factors may have competing effects on observed frequency of non-obstructive CAD; however, if 100% of suspected ACS patients underwent angiography, the prevalence of non-obstructive CAD might be higher than we observed. Second, the prevalence of observed non-obstructive CAD will also likely vary depending on the likelihood of true NSTEMI ACS in the population studied. For example, EARLY ACS, in which 84% of patients had baseline positive markers and in which patients were selected based on their high-risk characteristics at baseline, had the lowest rate of non-obstructive CAD at 6.9% (despite that 97% of patients underwent angiography). A prevalence of 7.4% was reported from a single center in which >90% of patients underwent angiography and alternative diagnoses were actively sought.⁷

A 7.5% prevalence equates to >100,000 patients each year with NSTEMI ACS in the United States alone²² who are found to have non-obstructive CAD. Uncertainty regarding their risk and best medical treatment may explain why we, as have others,^{5,7} found that these patients were less frequently treated with secondary prevention pharmacologic agents, including beta-blockers, statins and thienopyridines, although aspirin use was high and similar across groups (perhaps reflecting protocol-required aspirin use).

Outcome

This large meta-analysis showed that although NSTEMI ACS patients with non-obstructive CAD had significantly lower major cardiac event rates than did patients with significant obstructive CAD, these rates were not negligible. Therefore, the presence of non-obstructive CAD alone should not justify discounting secondary prevention in NSTEMI ACS patients. The results of the recently reported Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) Study²³ support this. Among patients with ACS treated with culprit lesion PCI, subsequent non-culprit coronary events occurred at the site of a <50% coronary stenosis in 67% of cases. However, a previous, smaller study suggested that within this group of patients, those with angiographic evidence of some CAD had more events than patients with angiographically normal coronary arteries, and further suggested that the Thrombolysis In Myocardial Infarction risk score may be a means to identify high-risk individuals from among those with no angiographically obstructive CAD.³

In the Women's Ischemia Syndrome Evaluation (WISE) study of women with suspected ischemia but non-obstructive CAD,²⁴ five-year cardiovascular event rates were 16.0% among women with coronary artery stenosis >0%–50%; 7.9% among women with angiographically normal

coronary arteries; and 2.4% in an asymptomatic control group. The association between non-obstructive coronary artery plaques and subsequent events also has been suggested in a recent study of patients undergoing coronary computed tomographic angiography.²⁵

The present study found a 30-day rate of death or MI of 3.5% among patients with coronary stenosis compared with a 1.5% rate among patients with angiographically normal coronary arteries. We believe that the persistence of high rates of non-obstructive CAD and stable event rates over time among these ACS patients, together with prior mechanistic and imaging studies, suggests the need to better understand the mechanisms underlying NSTEMI ACS with 'non-significant' coronary artery abnormalities and associated clinical events in order to shape cause-specific treatment strategies that may include greater use of evidence-based secondary prevention.

Limitations

Only patients who were randomized into a clinical trial and then underwent coronary angiography were evaluated. In addition, angiographic information was limited to the degree of stenosis in coronary arteries, and no information on lesion characteristics, presence of thrombus, or coronary flow was available. Intravascular ultrasound was not routinely performed in these clinical trials, nor were invasive measurements of coronary reactivity or microvascular function. Coronary stenosis was measured by visual estimation by experienced angiographers rather than by quantitative evaluation, consistent with clinical practice worldwide. However, regardless of how precisely measured, the angiogram of a complex lesion poorly represents the real lumen size.²⁶ Also, some patients enrolled in the trials may have had clinical conditions that mimicked NSTEMI ACS, such as myocarditis, rather than 'true' NSTEMI ACS, despite meeting trial entry criteria. However, this study was large and included patients with NSTEMI ACS based on objective clinical trial entry criteria. Finally, although data on cardiac markers were available in 99.8% of patients, in the earlier studies CK-MB was used rather than troponin. The hypothesis that the use of troponin may have increased the specificity of NSTEMI ACS diagnosis is supported by the fact that the prevalence of non-obstructive CAD is >10% in earlier trials but <10% in the more recent trials using troponin as a biomarker.

Finally, most trials in our meta-analysis collected only all-cause mortality, and we cannot provide reliable estimates of mortality strictly related to CAD. However, the expected six-month mortality rate of patients aged 55–64 years in the United States between 1999 and 2006 was <0.5% (0.47%, Centers for Disease Control and Prevention data); thus, the observed 1.3% mortality rate does appear to describe an additional risk related to the NSTEMI ACS episode above that in the general population.

Implications

The present study suggests the need to reconsider our approach to secondary prevention among patients with a typical clinical picture of NSTEMI ACS and non-obstructive CAD. Reassurance of an excellent prognosis is inappropriate in light of a 30-day risk of death or MI >2% overall and >3% among patients with minimal coronary artery abnormalities (>0% but <50% stenosis). Our study should also prompt: 1) the development of more precise tools to better risk-stratify NSTEMI ACS patients with non-obstructive CAD and 2) the conduct of prospective trials to assess the benefit of intensive medical therapy in these patients.

Conclusions

Among patients with NSTEMI ACS, one in 10 had non-obstructive CAD, and the 30-day rate of death or MI in these patients was >2%. Compared with patients with obstructive CAD, patients with non-obstructive CAD experienced lower rates of major cardiac events but remained at substantial risk and should be treated accordingly.

Acknowledgements

We thank Morgan deBleecourt for her editorial assistance with preparation of the manuscript for submission.

Conflict of interest

GMDF: consulting fees and lecture fees from Merck & Co., Inc. KAAF: research support from Sanofi-aventis, Bristol-Myers Squibb, Eli Lilly and Co., and Bayer Corporation. JAW: no relationships to disclose; RPG: consulting fees from Sanofi-aventis; lecture fees from Bristol-Myers Squibb and Sanofi-aventis; research grant support, advisory board, and honoraria from Merck/Schering-Plough, Inc.; and research support from Daiichi-Sankyo, Inc. PTr: advisory board for and receiving research funding from Merck & Co., Inc. HRR: no relationships to disclose. JSH: advisory board for Merck/Schering-Plough and Eli Lilly and Co. CMG: research support from Merck/Schering-Plough. PTh: research support from Schering-Plough (now Merck and Co., Inc.); serving on the advisory board for Sanofi-aventis, Bristol-Myers Squibb, AstraZeneca, and Boehringer Ingelheim; and receiving speaker fees from Schering-Plough, Sanofi-aventis, and AstraZeneca. RAH: research funding from Schering-Plough (now Merck and Co., Inc.) for the EARLY ACS trial. A complete listing of RAH's relationships with industry is available at <https://dcri.org/about-us/conflict-of-interest>. FVW: research funding from Merck/Schering-Plough. HDW: research funding from Merck/Schering-Plough. RMC: research funding from Schering-Plough (now Merck and Co., Inc.) for the EARLY ACS trial. A complete listing of RMC's relationships with industry is available at <https://dcri.org/about-us/conflict-of-interest>. LKN: research funding from Schering-Plough (now Merck & Co., Inc.) through Duke University for the EARLY ACS trial and from Merck and Co., Inc. in support of the analysis for this manuscript. A complete listing of LKN's relationships with industry is available at <https://dcri.org/about-us/conflict-of-interest>.

Funding

This work was supported by Schering-Plough Corporation (now Merck & Co., Inc.) and Merck & Co., Inc., Whitehouse Station, NJ, USA; ClinicalTrials.gov ID number: NCT00089895.

Disclaimer

The sponsor had no role in the study design or conduct; collection, management, statistical analyses, or interpretation of the data; preparation and review of the draft manuscript; or approval of the final manuscript for submission.

References

1. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes IIB Investigators. *N Engl J Med* 1999; 341: 226–232.
2. Diver DJ, Bier JD, Ferreira PE, et al. Clinical and arteriographic characterization of patients with unstable angina without critical coronary arterial narrowing (from the TIMI-III Trial). *Am J Cardiol* 1994; 74: 531–537.
3. Bugiardini R, Manfredi O and De Ferrari GM. Unanswered questions for management of acute coronary syndrome. Risk stratification of patients with minimal disease or normal findings on coronary angiography. *Arch Intern Med* 2006; 166: 1391–1395.
4. Gehrie ER, Reynolds HR, Chen AY, et al. Characterization and outcomes of women and men with non-ST-segment elevation myocardial infarction and nonobstructive coronary artery disease: Results from the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) quality improvement initiative. *Am Heart J* 2009; 158: 688–694.
5. Roe MT, Harrington RA, Prosper DM, et al. Clinical and therapeutic profile of patients presenting with acute coronary syndromes who do not have significant coronary artery disease. The Platelet Glycoprotein IIB/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial Investigators. *Circulation* 2000; 102: 1101–1106.
6. Anderson JL, Adams CD, Antman EM, et al.; 2011 Writing Group Members; ACCF/AHA Task Force Members. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2011; 123: e426–e579.
7. De Ferrari GM, Leonardi S, Baduena L, et al. Patients with acute coronary syndrome and non-obstructive coronary disease in the real world are markedly undertreated. *J Cardiovasc Med (Hagerstown)* 2011; 12: 700–708.
8. Reynolds HR, Srichai MB, Iqbal SN, et al. Mechanisms of myocardial infarction in women without angiographically obstructive coronary artery disease. *Circulation* 2011; 124: 1414–1425.
9. The Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIB Investigators. A comparison of

- recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med* 1996; 335: 775–782.
10. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy. *N Engl J Med* 1998; 339: 436–443.
 11. PARAGON Investigators. International, randomised, controlled trial of lamifiban (a platelet glycoprotein IIb/IIIa inhibitor), heparin or both in unstable angina. *Circulation* 1998; 97: 2386–2395.
 12. Mukherjee D, Mahaffey KW, Moliterno DJ, et al. Promise of combined low-molecular-weight heparin and platelet glycoprotein IIb/IIIa inhibition: Results from Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network B (PARAGON B). *Am Heart J* 2002; 144: 995–1002.
 13. Ferguson JJ, Califf RM, Antman EM, et al.; SYNERGY Trial Investigators. Enoxaparin vs unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. *JAMA* 2004; 292: 45–54.
 14. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998; 338: 1498–1505.
 15. Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998; 338: 1488–1497.
 16. Giugliano RP, White JA, Bode C, et al.; EARLY ACS Investigators. Early versus delayed provisional eptifibatide in acute coronary syndromes. *N Engl J Med* 2009; 360: 2176–2190.
 17. The Global Registry for Acute Coronary Events (GRACE). <http://www.outcomes.org/grace> (accessed 31 July 2012).
 18. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infracting myocardium early II trial substudy. *Circulation* 2000; 102: 2031–2037.
 19. Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation* 2000; 101: 2557–2567.
 20. Eagle KA, Lim MJ, Dabbous OH, et al.; GRACE Investigators. A validated prediction model for all forms of acute coronary syndrome: Estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; 291: 2727–2733.
 21. Bairey Merz CN, Shaw LJ, Reis SE, et al.; WISE Investigators. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: Gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. *J Am Coll Cardiol* 2006; 47(3 Suppl.): S21–S29.
 22. American Heart Association. *Heart and Stroke 2011 Statistical Update*. http://my.americanheart.org/professional/General/Heart-and-Stroke-2011-Statistical-Update_UCM_424014_Article.jsp (2011, accessed 19 December 2012).
 23. Stone GW, Maehara A, Lansky AJ, et al.; PROSPECT Investigators. A prospective natural-history study of coronary atherosclerosis. *N Engl J Med* 2011; 364: 226–235.
 24. Gulati M, Cooper-DeHoff RM, McClure C, et al. Adverse cardiovascular outcomes in women with nonobstructive coronary artery disease: A report from the Women's Ischemia Syndrome Evaluation Study and the St James Women Take Heart Project. *Arch Intern Med* 2009; 169: 843–850.
 25. Kristensen TS, Kofoed KF, Kühl JT, et al. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: A multidetector computed tomography study. *J Am Coll Cardiol* 2011; 58: 502–509.
 26. Topol EJ and Nissen SE. Our preoccupation with coronary luminology. The dissociation between clinical and angiographic findings in ischemic heart disease. *Circulation* 1995; 92: 2333–2342.