Risk and timing of recurrent ischemic events among patients with stable ischemic heart disease, non–ST-segment elevation acute coronary syndrome, and ST-segment elevation myocardial infarction

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Background We aimed to compare differences in risk and timing of recurrent ischemic events among patients with stable ischemic heart disease (SIHD), non–ST-segment elevation acute coronary syndrome (NSTE-ACS), and ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).

Methods We performed an individual data pooled analysis of 5 randomized controlled all-comer trials including a total of 8,859 patients and investigated the risk and timing of recurrent ischemic events among patients with SIHD (n = 3,543), NSTE-ACS (n = 3,364), and STEMI (n = 1,952) throughout 2 years of follow-up.

Results At 2 years, all-cause mortality was higher among patients with STEMI (6.4%) and NSTE-ACS (6.1%) compared with those with SIHD (4.2%) (STEMI vs SIHD: hazard ratio [HR] 1.40, 95% CI 1.09-1.78, $P = .007$; NSTE-ACS vs SIHD: 1.40, 95% CI 1.13-1.73, $P = .002$). In a landmark analysis, the risk of mortality among patients with STEMI compared with those with SIHD was confined to the first 30 days after PCI (HR 6.19, 95% CI 3.15-12.16, $P < .001$) but was similar between 30 days and 2 years (HR 1.00, 95% CI 0.76-1.33, $P = .974$) ($P_{interaction} < .001$). Conversely, patients with NSTE-ACS had a higher risk of mortality compared with those with SIHD both within the first 30 days (HR 2.19, 95% CI 1.08-4.47, $P = .031$) and beyond (HR 1.34, 95% CI 1.07-1.67, $P = .012$) ($P_{interaction} < .001$). A similar pattern in the differential timing of events was observed for cardiac death. Beyond 30 days, the risk of myocardial infarction was comparable in patients with STEMI and SIHD, whereas the risk in patients with NSTE-ACS was increased (HR 1.65, 95% CI 1.23-2.21, $P = .001$).

Conclusion Whereas patients with NSTE-ACS are at increased risk for death at any time after PCI, the mortality of STEMI patients is higher during the first 30 days after PCI but not thereafter compared with patients with SIHD. (Am Heart J 2016;175:56-65.)

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Coronary artery disease comprises a spectrum of clinical manifestations ranging from asymptomatic individuals over those with stable symptoms to patients presenting with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) and finally those with ST-segment elevation myocardial infarction (STEMI).[1] The different clinical manifestations reflect a gradient of risk that translates into different short-term clinical outcomes and have important implications on the treatment strategy as well as different long-term clinical outcome. Although the underlying pathophysiological substrate is similar, the progression of disease and the presentation may vary across different manifestations of coronary artery disease (CAD).[2] Determinants of disease

Table I. Baseline clinical characteristics

	STEMI	NSTE-ACS	SIHD			
	n = 1952	n = 3364	n = 3543	Overall *P* value	*P* value STEMI vs SIHD	*P* value NSTE-ACS vs SIHD
Age, y	62.7 ± 12.3	65.9 ± 11.5	66.2 ± 10.1	.007	.006	.747
Female gender	426 (22%)	841 (25%)	828 (23%)	<.001	<.001	.291
Body mass index (kg/m^2)	26.9 ± 4.3	27.7 ± 4.4	27.7 ± 4.1	<.001	<.001	.881
Cardiac risk factors						
Diabetes	281 (14%)	809 (24%)	949 (27%)	<.001	<.001	.061
Insulin-requiring	117 (9%)	293 (13%)	301 (13%)	.046	.018	.683
Hypertension	1042 (53%)	2456 (73%)	2666 (75%)	<.001	<.001	.209
Hypercholesterolemia	861 (44%)	2099 (62%)	2600 (73%)	<.001	<.001	<.001
GFR (mL/min)	86.6 ± 30.1	82.0 ± 33.7	82.5 ± 29.7	.002	.001	.839
GFR <60 mL/min	299 (17%)	677 (21%)	587 (17%)	<.001	<.001	.325
Clinical history						
Previous MI	830 (43%)	884 (26%)	711 (20%)	<.001	<.001	<.001
Previous PCI	238 (12%)	1007 (30%)	1126 (32%)	<.001	<.001	.313
Previous CABG	161 (8%)	889 (26%)	1359 (38%)	<.001	<.001	<.001
LVEF (%)	47.4 ± 10.5	54.7 ± 11.2	58.2 ± 11.4	<.001	<.001	.006

Values are means (SD) or number (percentage). *GFR*, glomerular filtration rate; *CABG*, coronary artery bypass graft; *LVEF*, left ventricular ejection fraction.

Table II. Procedural characteristics

	STEMI	NSTE-ACS	SIHD			
	n = 1952	n = 3364	n = 3543	Overall *P* value	*P* value STEMI vs SIHD	*P* value NSTE-ACS vs SIHD
No. of lesions per patient	1.4 ± 0.727	1.5 ± 0.790	1.5 ± 0.767	<.001	<.001	.444
No. of vessels treated per patient	1.2 ± 0.459	1.3 ± 0.509	1.3 ± 0.492	<.001	<.001	.378
Multivessel intervention	334 (21.0%)	857 (30.9%)	865 (30.9%)	<.001	<.001	.979
Target vessel						
Right coronary artery	827 (42.4%)	1157 (34.4%)	1304 (36.8%)	<.001	<.001	.149
Left main	38 (1.9%)	118 (3.5%)	117 (3.3%)	.001	.028	.837
Left anterior descending	1005 (51.5%)	1728 (51.4%)	1775 (50.1%)	.424	.963	.190
Left circumflex	438 (22.4%)	1167 (34.7%)	1125 (31.8%)	<.001	<.001	.001
Bypass graft	5 (0.8%)	103 (3.1%)	117 (3.3%)	<.001	<.001	.779
Type of stent						
Bare metal stent	180 (9.2%)	211 (6.3%)	111 (3.1%)	<.001	.002	<.001
Paclitaxel-eluting stent	256 (13.1%)	365 (10.9%)	388 (11.0%)	.354	.174	.968
Early-gen. sirolimus-eluting stent	257 (13.2%)	473 (14.1%)	623 (17.6%)	.401	.769	.233
New-gen. sirolimus-eluting stent	211 (10.8%)	366 (10.9%)	486 (13.7%)	.159	.964	.096
Biolimus-eluting stent	135 (6.9%)	335 (10.0%)	387 (10.9%)	.015	.005	.545
Everolimus-eluting stent	561 (28.7%)	983 (29.2%)	1035 (29.2%)	.978	.832	.997
Zotarolimus-eluting stent	352 (18.0%)	631 (18.8%)	513 (14.5%)	.068	.855	.021

Depicted are means ± SD with *P* values from Poisson regression or counts (percentage) with *P* values from χ^2 tests. All tests take into account the clustering of patients in trials.

progression remain poorly understood. However, there is preclinical evidence suggesting that acute MI may accelerate the process of chronic atherosclerosis due to inflammation.[3] Moreover, patients with advanced CAD in the setting of acute coronary syndromes have worse outcome than those with disease limited to the infarct-related artery.[4] Finally, there remains controversy as to the long-term prognostic implications of different entities of CAD.[5-7]

A time-variable pattern of recurrent events following percutaneous coronary intervention (PCI) may have important implications for medical management and secondary prevention. Although the impact of early events on clinical outcomes is easily captured and may be given more weight in clinical research, late events may be underestimated but are equally important for the purpose of long-term prevention.

The objective of the present analysis was therefore to compare differential risk and timing of recurrent ischemic events among patients with SIHD, NSTE-ACS, and STEMI undergoing PCI.

Methods

Study population

We pooled individual patient data from 5 randomized controlled trials conducted between 2003 and 2014 including a total of 8,859 patients: the sirolimus-eluting and

Table IIIA. Clinical outcomes at 30 days, 1 year, and 2 years (crude analysis)

	STEMI	NSTE-ACS	SIHD	STEMI vs SIHD		NSTE-ACS vs SIHD	
	n =1952	n =3364	n =3543	Crude HR (95% CI)	*P* value	Crude HR (95% CI)	*P* value
At 30 d							
Death	42 (2.2)	25 (0.7)	11 (0.3)	6.19 (3.15-12.16)	<.001	2.19 (1.08-4.47)	.031
Cardiac death	38 (2.0)	21 (0.6)	9 (0.3)	6.50 (3.11-13.62)	<.001	2.19 (1.00-4.80)	.050
MI	50 (2.6)	180 (5.4)	176 (5.0)	0.38 (0.28-0.53)	<.001	0.89 (0.72-1.10)	.300
Definite stent thrombosis	29 (1.5)	21 (0.6)	23 (0.7)	2.54 (1.45-4.43)	.001	1.01 (0.56-1.84)	.961
Definite or probable stent thrombosis	47 (2.4)	45 (1.3)	50 (1.4)	1.87 (1.25-2.81)	.002	1.02 (0.68-1.53)	.921
At 1 y							
Death	93 (4.8)	121 (3.6)	83 (2.4)	1.82 (1.35-2.46)	<.001	1.44 (1.09-1.91)	.011
Cardiac death	73 (3.8)	88 (2.6)	50 (1.4)	2.39 (1.66-3.46)	<.001	1.75 (1.23-2.48)	.002
MI	79 (4.1)	252 (7.5)	214 (6.1)	0.51 (0.39-0.67)	<.001	1.07 (0.89-1.28)	.493
Definite stent thrombosis	39 (2.0)	33 (1.0)	33 (0.9)	2.29 (1.43-3.67)	.001	1.08 (0.67-1.76)	.746
Definite or probable stent thrombosis	63 (3.3)	68 (2.0)	68 (1.9)	1.78 (1.25-2.52)	.001	1.10 (0.79-1.55)	.565
At 2 y							
Death	124 (6.4)	203 (6.1)	148 (4.2)	1.40 (1.09-1.78)	.007	1.40 (1.13-1.73)	.002
Cardiac death	87 (4.5)	137 (4.2)	88 (2.5)	1.67 (1.24-2.26)	.001	1.58 (1.21-2.08)	.001
MI	97 (5.1)	299 (9.0)	252 (7.2)	0.56 (0.44-0.71)	<.001	1.11 (0.94-1.32)	.213
Definite stent thrombosis	44 (2.3)	45 (1.4)	45 (1.3)	1.90 (1.24-2.90)	.003	1.10 (0.72-1.67)	.656
Definite or probable stent thrombosis	70 (3.7)	90 (2.7)	91 (2.6)	1.48 (1.08-2.03)	.015	1.11 (0.82-1.48)	.504

Depicted are counts (Kaplan-Meier incidence rates %).
Hazard ratios (95% CI) and *P* values are from Cox regressions taking into account the trial effect.

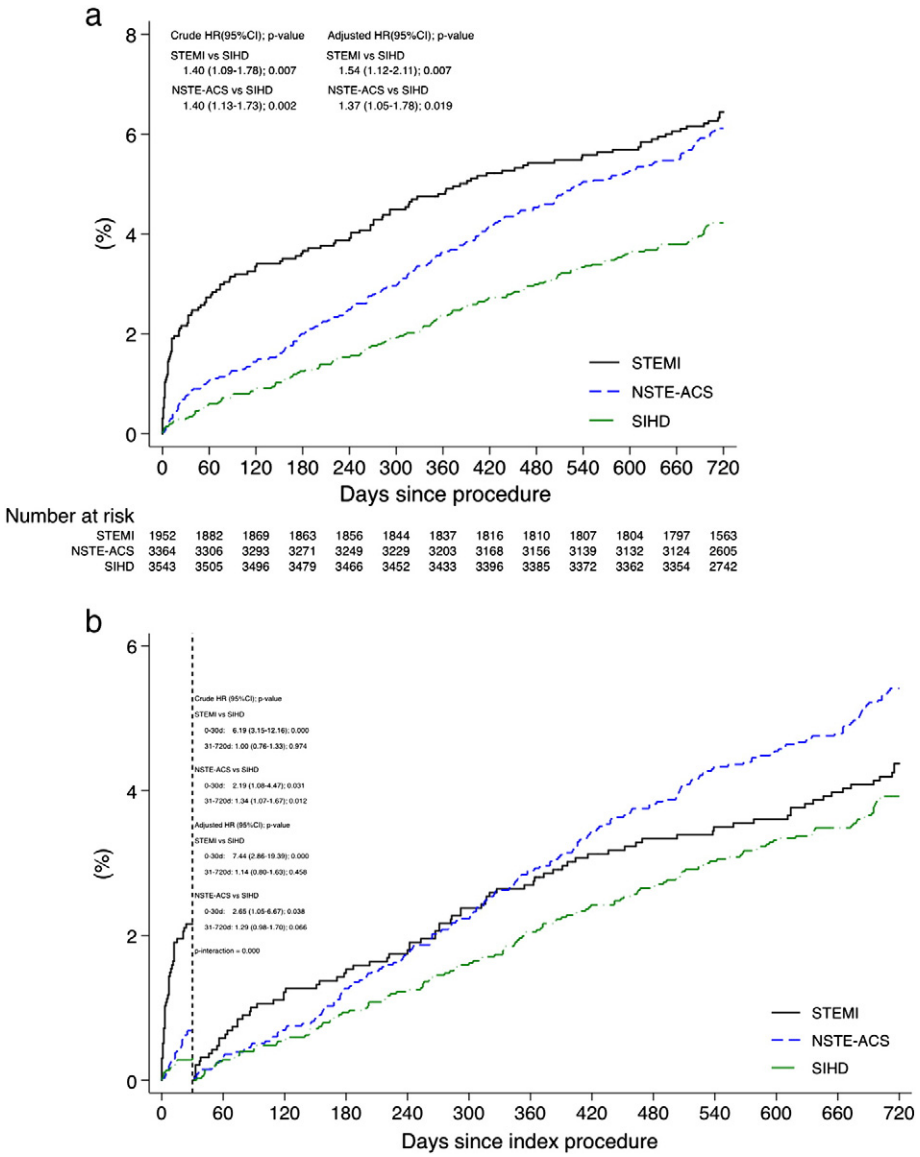
Table IIIB. Clinical outcomes at 30 days, 1 year, and 2 years (adjusted analysis)

	STEMI vs SIHD		NSTE-ACS vs SIHD	
	Adj HR (95% CI)	*P* value	Adj HR (95% CI)	*P* value
At 30 d				
Death	7.44 (2.86-19.39)	<.001	2.65 (1.05-6.67)	.038
Cardiac death	9.38 (3.04-28.98)	<.001	3.44 (1.15-10.29)	.027
MI	0.39 (0.26-0.58)	<.001	0.93 (0.72-1.21)	.598
Definite stent thrombosis	1.55 (0.75-3.18)	.237	0.77 (0.39-1.54)	.463
Definite or probable stent thrombosis	1.48 (0.87-2.53)	.150	0.92 (0.58-1.48)	.746
At 1 y				
Death	2.31 (1.54-3.47)	<.001	1.48 (1.03-2.11)	.032
Cardiac death	3.20 (1.92-5.34)	<.001	1.94 (1.22-3.08)	.005
MI	0.51 (0.36-0.71)	<.001	1.05 (0.84-1.32)	.672
Definite stent thrombosis	1.77 (0.94-3.32)	.077	0.90 (0.50-1.62)	.733
Definite or probable stent thrombosis	1.48 (0.93-2.37)	.100	0.99 (0.66-1.49)	.963
At 2 y				
Death	1.54 (1.12-2.11)	.007	1.37 (1.05-1.78)	.019
Cardiac death	2.00 (1.34-2.99)	.001	1.66 (1.19-2.33)	.003
MI	0.58 (0.43-0.78)	<.001	1.13 (0.92-1.39)	.244
Definite stent thrombosis	1.80 (1.01-3.21)	.047	1.01 (0.60-1.69)	.967
Definite or probable stent thrombosis	1.44 (0.94-2.22)	.096	1.09 (0.76-1.57)	.629

Depicted are counts (Kaplan-Meier incidence rates %).
Hazard ratios (95% CI) and *P* values are from Cox regressions taking into account the trial effect. Adjustment baseline variables are age, gender, body mass index, diabetes, hypertension, hypercholesterolemia, previous MI, GFR, LVEF, and type of stent.

paclitaxel-eluting stent for coronary revascularization (SIRTAX) trial (n = 1,012),[8] the biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS) trial (n = 1,707),[9] the comparison of zotarolimus-eluting and everolimus-eluting coronary stents (RESOLUTE All Comers) trial (n = 2,018),[10] the prolonging dual antiplatelet treatment after grading stent-induced intimal hyperplasia study (PRODIGY) (n = 2,003),[11] and the comparison of ultrathin strut biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents (BIOSCIENCE) trial (n = 2,119).[12] Broad inclusion criteria were applied in all included trials consistent with an all-comers study design. Details of the individual trials have been published elsewhere.[8-12] The trials complied with the Declaration of Helsinki and were approved by the ethics committee of each

Figure 1



A, All-cause mortality. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.**B**, Landmark analysis of all-cause mortality with the landmark set at 30 days. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.

study site. All patients provided written informed consent for participation in the study. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Procedures

Balloon angioplasty and stent implantation were performed according to standard techniques and guidelines current at the time of the study. Periprocedural anticoagulation was accomplished with unfractionated heparin or bivalirudin; the use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Dual antiplatelet treatment consisted of acetylsalicylic acid of at least 75 mg daily and a P2Y12-inhibitor in all trials, and was prescribed for at least 12 months in the SIRTAX, the LEADERS, and the BIOSCIENCE trials[8,9,12] and for at least 6 months in the RESOLUTE All Comers trial.[10] In the PRODIGY trial, patients were randomized at 30 days in a balanced fashion to either 6 or 24 months of dual antiplatelet treatment.[11] Among patients

Table IV. Landmark analysis for clinical Outcomes

	Days 0-30						
	STEMI	NSTE-ACS	SIHD	HR (95% CI) STEMI vs SIHD	*P* value STEMI vs SIHD	HR NSTE-ACS vs SIHD	*P* value NSTE-ACS vs SIHD
Crude analysis							
All-cause death	42 (2.2)	25 (0.7)	11 (0.3)	6.19 (3.15-12.16)	<.001	2.19 (1.08-4.47)	.031
Cardiac death	38 (2.0)	21 (0.6)	9 (0.3)	6.50 (3.11-13.62)	<.001	2.19 (1.00-4.80)	.050
MI	50 (2.6)	180 (5.4)	176 (5.0)	0.38 (0.28-0.53)	<.001	0.89 (0.72-1.10)	.300
Definite stent thrombosis	29 (1.5)	21 (0.6)	23 (0.7)	2.54 (1.45-4.43)	.001	1.01 (0.56-1.84)	.961
Definite or probable stent thrombosis	47 (2.4)	45 (1.3)	50 (1.4)	1.87 (1.25-2.81)	.002	1.02 (0.68-1.53)	.921
Adjusted analysis							
All-cause death	42 (2.2)	25 (0.7)	11 (0.3)	7.44 (2.86-19.39)	<.001	2.65 (1.05-6.67)	.038
Cardiac death	38 (2.0)	21 (0.6)	9 (0.3)	9.38 (3.04-28.98)	<.001	3.44 (1.15-10.29)	.027
MI	50 (2.6)	180 (5.4)	176 (5.0)	0.39 (0.26-0.58)	<.001	0.93 (0.72-1.21)	.598
Definite stent thrombosis	29 (1.5)	21 (0.6)	23 (0.7)	1.55 (0.75-3.18)	.237	0.77 (0.39-1.54)	.463
Definite or probable stent thrombosis	47 (2.4)	45 (1.3)	50 (1.4)	1.48 (0.87-2.53)	.150	0.92 (0.58-1.48)	.746

treated with bare metal stents for SIHD, clopidogrel discontinuation was allowed at any time beyond 30 days.

Definitions

The primary end point of the present analysis was all-cause mortality. Secondary end points were cardiac death, MI, definite stent thrombosis, and definite and probable stent thrombosis according to the Academic Research Consortium criteria.[13] End point definitions were comparable across the 4 trials included in the present analysis and consistent with the definitions proposed by the Academic Research Consortium[13] in the majority of trials.

Cardiac death was defined as death from cardiac causes or any death from unknown causes in SIRTAX, LEADERS, and BIOSCIENCE,[8,9,12] and as any death unless an undisputed noncardiac cause was present in the RESOLUTE All Comers trial.[10] *Myocardial infarction* was defined in SIRTAX and LEADERS as the presence of new Q waves in at least 2 contiguous leads and an elevated creatine kinase–MB fraction or—in the absence of significant Q waves—as an increase in the creatine kinase level to more than twice the upper limit of the reference range with an elevated level of creatine kinase–MB or troponin.[8,9] In the RESOLUTE All Comers and the BIOSCIENCE trials, *myocardial infarction* was defined according to an "extended historical" definition consistent with the one used in SIRTAX and LEADERS.[10] In PRODIGY, the definition of *myocardial infarction* was based on the detection of increase and/or decrease in creatine kinase–MB or troponin with at least 1 value above the upper limit of normal together with evidence of myocardial ischemia with at least 1 of the following: symptoms of ischemia, electrocardiographic changes indicative of new ischemia (new ST-T changes or new left bundle-branch block), and development of pathological Q waves.[11]

Statistical analysis

The baseline and procedural characteristics are presented as means ± SD in case of continuous variables and as frequencies and percentages in case of categorical variables. The *P* values for differences across groups are from χ^2 tests, linear regression (baseline characteristics), or Poisson regression (procedural characteristics). The clinical outcomes at 30 days, 1 year, and 2 years are presented as counts using Kaplan-Meier incidence rate and illustrated as cumulative incidence both with and without landmark analysis at 30 days. We present both crude and adjusted hazard ratios (HRs) for the clinical outcomes at 30 days, 1 year, and 2 years. We adjusted for age, gender, body mass index, diabetes, hypertension, hypercholesterolemia, previous MI, glomerular filtration rate, left ventricular ejection fraction, and type of stent. The difference across groups was estimated from Cox regressions. We refrained from stratifying the analyses according to stent type. All hypotheses were 2-sided, and a P value < .05 was deemed statistically significant. All tests of differences across groups take into account the cluster effect of the trials. The statistical analyses were performed with Stata (version 13.1).

Results

Among 8,859 patients enrolled in 5 trials, 3,543 patients (40%) presented with SIHD, 3,364 with NSTE-ACS (38%), and 1,952 with STEMI (22%). Two-year clinical follow-up was complete in 8,673 patients (98%). Baseline clinical characteristics are summarized in Table I. Patients presenting with SIHD and NSTE-ACS had a similar cardiovascular risk profile. In contrast, STEMI patients less frequently had diabetes (14% vs 27%, $P < .001$), hypertension (53% vs 73%, $P < .001$), or hypercholesterolemia (44% vs 73%, $P < .001$) as compared with patients with SIHD. Along the same line, patients with NSTE-ACS and SIHD more commonly had a history of previous MI and previous

Days 31-720							
STEMI	NSTE-ACS	SIHD	HR (95% CI) STEMI vs SIHD	*P* value STEMI vs SIHD	HR NSTE-ACS vs SIHD	*P* value NSTE-ACS vs SIHD	*P* value interaction period × stent
82 (4.4)	178 (5.4)	137 (3.9)	1.00 (0.76-1.33)	.974	1.34 (1.07-1.67)	.012	<.001
49 (2.6)	116 (3.6)	79 (2.3)	1.08 (0.75-1.55)	.676	1.53 (1.15-2.04)	.004	<.001
47 (2.6)	119 (3.9)	76 (2.3)	1.00 (0.69-1.44)	.980	1.65 (1.23-2.21)	.001	<.001
15 (0.8)	24 (0.8)	22 (0.7)	1.27 (0.65-2.48)	.482	1.18 (0.66-2.12)	.577	.118
23 (1.3)	45 (1.4)	41 (1.2)	1.03 (0.61-1.73)	.906	1.20 (0.78-1.84)	.399	.057
82 (4.4)	178 (5.4)	137 (3.9)	1.14 (0.80-1.63)	.458	1.29 (0.98-1.70)	.066	<.001
49 (2.6)	116 (3.6)	79 (2.3)	1.33 (0.84-2.12)	.225	1.55 (1.08-2.23)	.017	<.001
47 (2.6)	119 (3.9)	76 (2.3)	1.17 (0.72-1.88)	.526	1.66 (1.17-2.37)	.005	<.001
15 (0.8)	24 (0.8)	22 (0.7)	2.12 (0.81-5.60)	.127	1.39 (0.63-3.09)	.413	.118
23 (1.3)	45 (1.4)	41 (1.2)	1.31 (0.63-2.74)	.472	1.34 (0.76-2.35)	.310	.057

revascularization procedures. Both patients with STEMI (47% ± 11%) and NSTE-ACS (55% ± 11%) had a lower systolic left ventricular ejection fraction compared with patients with SIHD (58% ± 11%) ($P < .001$ and $P = .006$, respectively). Procedural characteristics are shown in Table II. Patients with STEMI had fewer lesions as compared with patients with SIHD (1.4 ± 0.7 vs 1.5 ± 0.8, $P < .001$); moreover, we observed a trend toward a lower number of vessels treated per patient among patients with STEMI as compared with patients with SIHD (1.2 ± 0.5 vs 1.3 ± 0.5, $P < .001$).

Tables IIIA and IIIB summarize crude and adjusted clinical outcomes at 30 days, 1 year, and 2 years, respectively. All-cause mortality at 30 days amounted to 2.2% among patients with STEMI, 0.7% among patients with NSTE-ACS, and 0.3% among patients with SIHD (STEMI vs SIHD adj HR 7.36, 95% CI 2.83-19.13, $P < .001$; NSTE-ACS vs SIHD adj HR 2.65, 95% CI 1.050-6.67, $P = .038$). At 2 years, all-cause mortality among patients with STEMI, NSTE-ACS, and SIHD was 6.4%, 6.1%, and 4.2%, respectively (STEMI vs SIHD adj HR 1.54, 95% CI 1.12-2.11, $P = .007$; NSTE-ACS vs SIHD adj HR 1.37, 95% CI 1.06-1.78, $P = .018$) (Figure 1, *A*). In a landmark analysis shown in Figure 1, *B* and Table IV, the risk of all-cause mortality was increased among patients with STEMI as compared with those with SIHD within the first 30 days after PCI (HR 6.19, 95% CI 3.15-12.16, $P < .001$) but was similar between 31 days and 2 years (HR 1.0, 95% CI 0.76-1.33, $P = .974$) (P for interaction < .001). In contrast, patients with NSTE-ACS had a higher risk of all-cause mortality compared with those with SIHD both within the first 30 days (HR 2.19, 95% CI 1.08-4.47, $P = .031$) and beyond (HR 1.34, 95% CI 1.07-1.67, $P = .012$). A similar pattern in the differential timing of events among patients with STEMI, NSTE-ACS, and SIHD was observed for cardiac death (Figure 2, *A* and *B*; Table IV).

Myocardial infarctions occurred less frequently among patients with STEMI as compared with SIHD throughout 2 years of follow-up (5.1% vs 7.2%, adj HR 0.58, 95% CI 0.43-0.78, $P < .001$). The difference was driven by a lower incidence of MI among patients with STEMI within the first 30 days (HR 0.38, 95% CI 0.28-0.53, $P < .001$), whereas no difference was documented for the time between 30 days and 2 years (HR 1.00, 95% CI 0.69-1.44, $P = .980$) (Figure 3, Table IV). There was no significant difference in the rate of MIs among patients with NSTE-ACS as compared with SIHD overall (9.0% vs 7.2%, adj HR 1.12, 95% CI 0.94-1.32, $P = .197$). However, there was a higher risk of MI in the period from 31 days to 2 years among patients with NSTE-ACS as compared with SIHD (HR 1.65, 95% CI 1.23-2.21, $P = .001$) (Table IV).

Rates of definite stent thrombosis amounted to 2.3%, 1.4%, and 1.3% among patients with STEMI, NSTE-ACS, and SIHD, respectively (STEMI vs SIHD adj HR 1.92, 95% CI 1.25-2.92, $P = .003$; NSTE-ACS vs SIHD adj HR 1.10, 95% CI 0.73-1.67, $P = .652$). In a landmark analysis with the landmark at 30 days, the increased risk of stent thrombosis among STEMI patients as compared with patients with SIHD was confined to the first 30 days (HR 2.54, 95% CI 1.45-4.43, $P = .001$), whereas the subsequent risk was comparable (HR 1.27, 95% CI 0.65-2.48, $P = .482$) (Figure 4, Table IV). There was no difference in the risk of stent thrombosis between patients with NSTE-ACS or SIHD within 30 days (HR 1.01, 95% CI 0.56-1.84, $P = .961$) and beyond (HR 1.18, 95% CI 0.66-2.12, $P = .577$). The findings were consistent in crude and adjusted analysis, respectively (Table IV).

Discussion

In the present individual data pooled analysis of 5 randomized controlled all-comer trials, we observed a differential in timing of ischemic events according to presentation with STEMI, NSTE-ACS, or SIHD. The principal findings of our analysis can be summarized as follows: (1) Patients with NSTE-ACS and SIHD had a comparable risk profile at baseline, whereas patients with STEMI had a lower

prevalence of cardiovascular risk factors and less frequently had a history of prior cardiovascular disease. (2) Patients with STEMI had a lower risk of recurrent MI compared with patients with SIHD throughout 2 years of follow-up. Although the risk of MI among patients with NSTE-ACS and SIHD was comparable throughout 2 years, we observed an increased risk of MI beyond the periprocedural period among patients with NSTE-ACS as compared with those with SIHD. (3) The increased risk of 30-day mortality among patients with STEMI as compared with those with SIHD was no longer apparent beyond 30 days of follow-up. In contrast, patients with NSTE-ACS had an increased risk of death as compared with those with SIHD which was sustained during the entire time of follow-up.

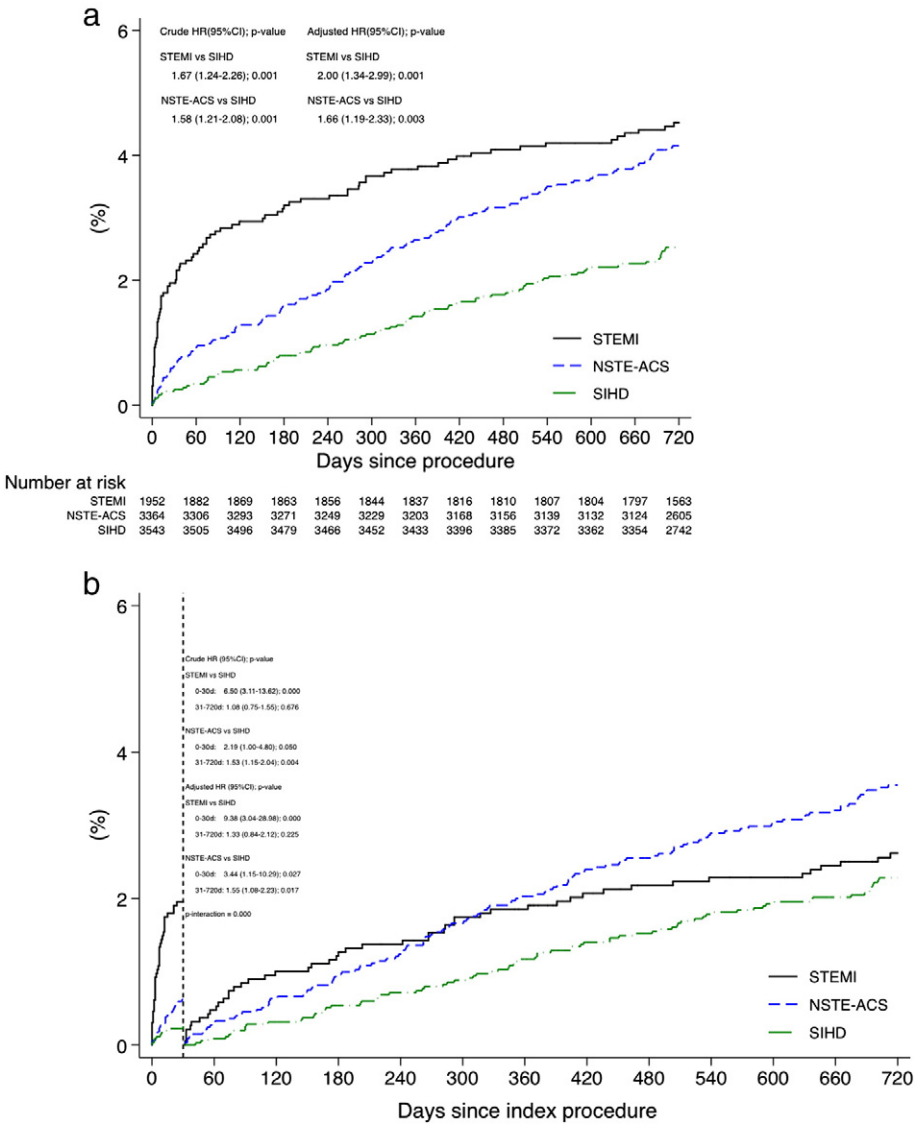
Patients undergoing PCI for NSTE-ACS or SIHD were found to have a similar prevalence of cardiovascular risk factors and comparable rates of previous revascularization procedures. In contrast, patients with STEMI were characterized by a lower rate of cardiovascular risk factors and fewer previous cardiac revascularization procedures. Moreover, patients with STEMI tended to be younger compared with patients with SIHD or NSTE-ACS and had fewer coronary lesions. STEMI may often represent the first manifestation of cardiovascular disease and results from rupture of vulnerable plaques without underlying significant coronary stenosis. Conversely, NSTE-ACS and SIHD referred for PCI may indicate advanced stages of disease with a higher number of lesions with hemodynamically significant stenosis and more gradual clinical manifestation. Absence of previous medical contacts in patients presenting with STEMI as a first manifestation of coronary artery disease may be associated with a higher rate of underdiagnosed risk factors and may have increased the risk of acquisition bias.

Patients undergoing PCI for NSTE-ACS were at highest risk to experience a recurrent MI within the subsequent 2 years, followed by patients with SIHD and STEMI, respectively. Several reasons may account for this finding. A low rate of recurrent MI may be related to ascertainment bias due to differences in definition related to periprocedural MI in the setting of STEMI as compared with SIHD; whereas the risk of recurrent MI among patients with STEMI was low within the first 30 days after PCI, a landmark analysis showed no significant difference in rates of MI beyond the periprocedural period. In addition, the increased risk of recurrent MI may be related to a higher atherosclerotic burden and therefore more advanced CAD among patient with NSTE-ACS and SIHD as compared with patients with STEMI. However, an increased risk of MI beyond the periprocedural period among patients with NSTE-ACS as compared with those with SIHD calls for an additional explanation. Progression of disease may be related to culprit or nonculprit lesions[14]. The inflammatory milieu in patients with acute coronary syndromes has been associated with generalized plaque vulnerability not limited to the culprit lesion. Healing of ruptured plaques stimulates progression of luminal narrowing and propels coronary artery disease.[15] Indeed, a recent experimental study in mice suggests that acute MI accelerates atherosclerosis by activating the chronic inflammatory disease process.[3] This mechanism may be responsible for recurrent MIs in nonculprit lesions. Furthermore, intravascular imaging studies of culprit lesions have suggested a delayed healing response among patients with acute coronary syndromes as compared with those with SIHD that was attributable to baseline lesion characteristics.[16] The latter in turn may increase the risk for repeat MIs related to the culprit vessel.

The risk of definite stent thrombosis was highest among patients presenting with STEMI, largely driven by more than 2-fold increased risk of stent thrombosis within the first 30 days after PCI in patients with STEMI as compared with SIHD. This finding is likely explained by the prothrombotic milieu of acute MI and is consistent with existing literature.

After 2 years of follow-up, patients with STEMI and NSTE-ACS had numerically comparable mortality rates that were 1.5 times higher than in patients with SIHD. A similar pattern was observed across the 3 groups for cardiac mortality. However, we observed an important differential in timing of all-cause and cardiac mortality. An increased risk of death within the first 30 days after STEMI was offset between 30 days and 2 years compared with patients with SIHD. In contrast, patients with NSTE-ACS experienced an increased risk of death compared with patients with SIHD irrespective of time after the intervention. Our findings are consistent with previous reports. In an analysis of 4,387 patients in the United States, patients with STEMI had a higher adjusted mortality risk during the first 2 months as compared with patients with NSTE-ACS (adj HR 1.85, 95% CI 1.45-2.38) and a lower risk of mortality beyond 2 months (adj HR 0.68, 95% CI 0.59-0.83). However, rates of index revascularization were rather low and amounted to 75% among patients with STEMI and 56% among patients with NSTE-ACS, respectively.[5] Adverse long-term outcome among patients with NSTE-ACS as compared with patients with STEMI has been associated with a higher prevalence of comorbidities, a greater extent of coronary artery disease, and lower rates of revascularization.[5] More recent data from South Korea corroborated these findings in >28,000 patients with STEMI or NSTE-ACS. Whereas the rates of major adverse cardiovascular events and cardiac mortality were higher in patients with STEMI as compared with patients with NSTE-ACS within the first 30 days (6.9% vs 4.5%, $P < .001$), reverse event rates were observed during the time period between 30 days and 2 years (STEMI 8.0% vs NSTE-ACS 9.1%, $P = .007$). Risk factors for both early and late cardiac death in patients with STEMI or NSTE-ACS were reduced left ventricular ejection fraction and clinical sings of congestive heart failure according to Killip class.[6] In another analysis of 13,441 patients in Poland, an adverse long-term prognosis observed in patients with NSTE-ACS as compared with

Figure 2

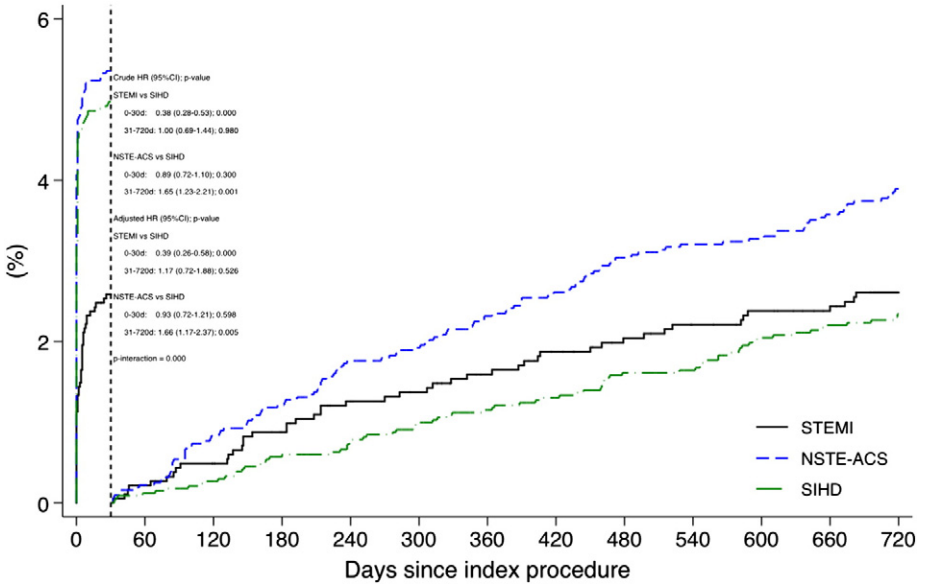


A, Cardiac mortality. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.**B**, Landmark analysis of cardiac mortality with the landmark set at 30 days. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.

patients with STEMI was offset after adjustment for baseline characteristics and treatment strategy.[7] In contrast to the above-mentioned reports, all patients included into the present analysis underwent PCI, hence eliminating the potential confounder of revascularization.

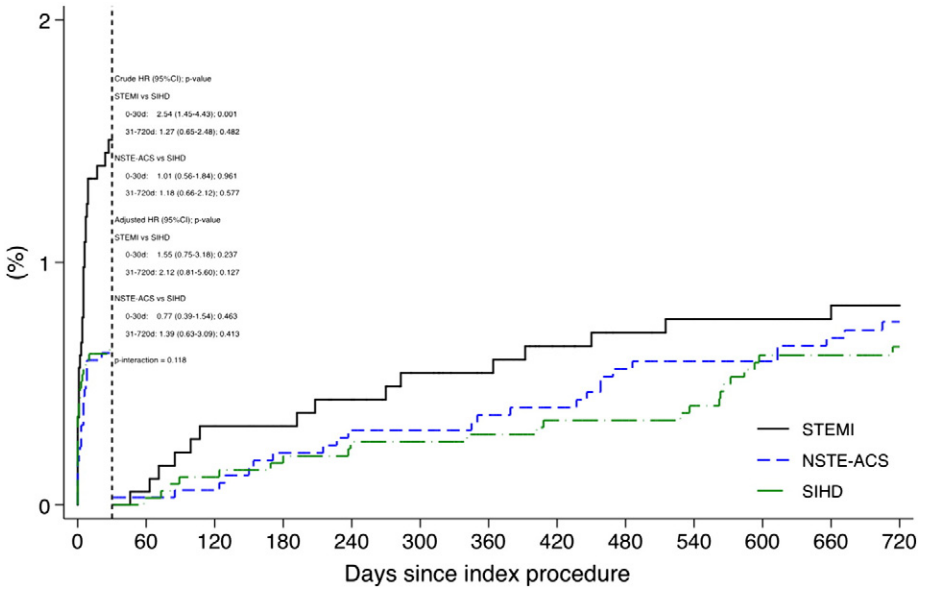
The present analysis has several limitations. First, only patients undergoing PCI were included in the present analysis, which introduces a selection bias, particularly among patients with SIHD. Patients with SIHD undergoing conservative management are not represented in the present analysis. In turn, revascularization has been identified as a confounder in previous analyses comparing patients with STEMI and NSTE-ACS only. Second, there were some minor differences in definitions of adverse events across trials. In particular, the assessment of periprocedural MIs may have been more difficult among patients with ongoing MI. In contrast, all patients were included into randomized controlled trials with a high data quality, meticulous follow-up, and independent event adjudication. Third, the combination of 5 all-comer trials performed during a time span of 10 years may be confounded by differences in temporal trends in

Figure 3



Landmark analysis of MI with the landmark set at 30 days. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.

Figure 4



Landmark analysis of definite stent thrombosis with the landmark set at 30 days. The solid black line indicates patients with STEMI, the dotted blue line patients with NSTE-ACS, and the dotted green line patients with SIHD.

revascularization therapy and optimal medical treatment. No comprehensive information on medical management and adherence to secondary prevention after PCI was available. Prolonged duration of dual antiplatelet treatment beyond 1 year or combination with novel P2Y12 ADP-receptor antagonists might have decreased the number of ischemic events. Fourth, in view of a noticeable gradient of risk across all ischemic outcomes, the absence of a

significant difference between patients with STEMI or SIHD in our analysis may reflect a lack of power. And finally, clinical follow-up was limited to 2 years. We do not know to what extent the results can be extrapolated to long-term clinical follow-up.

Conclusion

The risk and timing of recurrent ischemic events differ importantly between patients with STEMI, NSTE-ACS, and SIHD after PCI. Whereas patients with NSTE-ACS are at increased risk for death at any time after PCI, the mortality of STEMI patients is increased during the first 30 days after PCI but not thereafter compared with patients with SIHD.

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Disclosures

The authors report no conflict of interest related to the content of this article.

Impact on daily practice

The findings of the present study show a time variable pattern of recurrent events following PCI according to presentation with SIHD, NSTE-ACS, or STEMI, respectively, which may have important implications for long-term medical management and secondary prevention.

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