Relationship Between ST-Segment Recovery and Clinical Outcomes After Primary Percutaneous Coronary Intervention

The HORIZONS-AMI ECG Substudy Report

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***Background*—**In patients with ST-segment elevation myocardial infarction undergoing thrombolytic therapy, the degree of ST-segment resolution (STR) correlates with long-term cardiovascular mortality. The long-term predictive value of STR after primary percutaneous coronary intervention (PCI) is less well understood. We sought to determine the long-term prognostic value of STR after primary PCI in ST-segment–elevation myocardial infarction.

***Methods and Results*—**In a formal substudy from the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, 2484 patients with ST-segment–elevation myocardial infarction undergoing primary PCI with interpretable baseline and 60-minute post-PCI electrocardiograms had at least 1 mm of baseline ST-segment elevation in ≥2 contiguous leads. Patients were categorized by the degree of STR at 60 minutes: (1) complete (>70%); (2) partial (30%–70%); and (3) absent (<30%). Absent, incomplete, and complete STR were achieved in 514 (20.7%), 712 (28.7%), and 1258 (50.5%) patients, respectively. STR <30% was associated with a greater likelihood of hypertension, diabetes mellitus, longer symptom onset to balloon time, lower left ventricular ejection fraction, and final thrombolysis in myocardial infarction flow <3. At 3 years, patients with STR<30% experienced a higher rate of major adverse cardiovascular events (death, reinfarction, ischemia-driven target vessel revascularization or stroke; 29.9% versus 20.1% versus 19.6%; $P<0.0001$), ischemia-driven target vessel revascularization (20.4% versus 14.0% versus 11.7%; $P<0.001$), and mortality (8.4% versus 5.0% versus 5.6%; $P=0.03$) than those with partial and complete STR, respectively. By multivariable analysis, STR<30% was an independent predictor of 3-year major adverse cardiovascular events (hazard ratio, 1.58; 95% confidence interval, 1.24–2.00; $P=0.0002$) and 3-year ischemia-driven target vessel revascularization (hazard ratio, 1.87; 95% confidence interval, 1.41–2.48; $P<0.0001$).

***Conclusions*—**In this large international study, absent STR 60 minutes after primary PCI was present in ≈1 in 5 patients with ST-segment–elevation myocardial infarction and was a significant independent predictor of major adverse cardiovascular events and target vessel revascularization at 3 years.

Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT00433966 (Circ Cardiovasc Interv*. 2013;6:216-223.)**

Key Words: ECG ■ myocardial infarction ■ prognosis

Considerable research has been devoted to risk stratification in patients with acute ST-segment–elevation myocardial infarction (STEMI).[1,2] The presence of ST-segment resolution (STR) within the first 60 to 120 minutes after both pharmacological and mechanical reperfusion therapy is highly predictive of infarct-related artery patency and the degree of effective microvasculature perfusion.[3] Compared with fibrinolytic therapy, primary percutaneous coronary intervention (PCI) leads to more rapid and sustained infarct-related artery patency, and has become widely accepted as the optimal reperfusion modality in STEMI. It has also been suggested that STR may be inversely related to infarct size, and can be used to compare the relative efficacy of different therapies at the time of PCI.[3] In this regard, STR has the advantage of being noninvasive, inexpensive, and is easy to apply widely.[4] Few studies, however, have examined the impact of STR after PCI on late survival.

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WHAT IS KNOWN

- The presence of ST-segment resolution within the first 60 to 120 minutes after both pharmacological and mechanical reperfusion therapy is highly predictive of infarct-related artery patency and the degree of effective microvasculature perfusion.
- Compared with fibrinolytic therapy, primary percutaneous coronary intervention leads to more rapid and sustained infarct-related artery patency, and has become widely accepted as the optimal reperfusion modality ST elevation myocardial infarction.
- ST-segment resolution may be inversely related to infarct size, and can be used to compare the relative efficacy of different therapies at the time of percutaneous coronary intervention.

WHAT THE STUDY ADDS

- Absent ST-segment resolution 60 minutes after primary percutaneous coronary intervention was present in ≈1 in 5 patients with ST elevation myocardial infarction.
- ST-segment resolution was a significant independent predictor of major adverse cardiovascular event and target vessel revascularization at 3 years.

We therefore sought to evaluate the correlation of the degree of STR with late adverse cardiovascular events in the large-scale Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, and to determine whether there were differences in the degree of STR between the different antithrombotic and stent therapies out of 3 years of follow-up.

Methods

Trial Design

Before angiography, 3602 patients with ongoing STEMI (ST-segment elevation of ≥1 mm in at least 2 contiguous leads, or new onset left bundle–branch block or true posterior infarction) and symptom onset <12 hours were prospectively assigned to bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor (GPI; 1:1 randomization). After angiography, eligible patients were randomized again to TAXUS Express paclitaxel-eluting stents (PES) versus Express bare-metal stents (BMS; 3:1 randomization). The patient eligibility criteria, design details, and primary results of both randomization arms have been previously published.[5,6] The present report represents the principal results from the prespecified formal electrocardiographic substudy of the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial.

Electrocardiographic Procedures

Per protocol, standard 12-lead ECG was performed at baseline (at the time of qualification for the trial) and 60 minutes after the completion of revascularization with PCI. ECGs were also obtained at hospital discharge and at 1 month and 1 year after discharge. All ECGs were interpreted at the ECG Core Laboratory at the Cardiovascular Research Foundation in New York, NY, by independent trained and certified faculty readers who were blinded to the randomized assignments and patient outcomes. ST-segment deviation was evaluated using standardized techniques.[7] In brief, the J point was manually identified to the nearest 0.5 mm in all leads except aVR. Using the TP segment as the isoelectric baseline, the extent of ST-segment elevation to the nearest 0.05 mV was measured 80 ms after the J point. STR was calculated by the reduction in the sum of the ST-segment elevation in all leads except aVR from the baseline ECG to the 60-minute ECG. The director of the ECG Core Laboratory (J.R.) monitored quality control by randomly evaluating 10% of study ECGs as a second reader for accuracy by repeat measurement. This process confirmed >95% accuracy.

All trial patients in whom primary PCI was performed and in whom both baseline and 60-minute post-PCI ECGs were available and interpretable were included in the present analysis. We excluded patients with left bundle–branch block at baseline, paced ventricular rhythm, and patients without ST-segment elevation in ≥2 contiguous leads. Patients were categorized into the following groups by the degree of STR on the 60-minute post-PCI ECG: (1) complete STR (>70%); (2) partial STR (30%–70%); and (3) absent STR (<30%). Under the category of absent STR, we identified a subgroup with <0% STR (ie, further ST-segment elevation).

Outcome Measures

The present study represents a prespecified substudy, but without powered end points. The clinical end points of interest for the HORIZONS-AMI STR study were the 30-day and 3-year rates of composite major adverse cardiovascular events (MACE), consisting of mortality, reinfarction, ischemia-driven target vessel revascularization (TVR) or stroke, as well as the individual components of MACE and stent thrombosis, each of which were adjudicated by an independent clinical events committee blinded to randomization arm and STR.

Statistical Analysis

Baseline patient characteristics were summarized as medians with 25th and 75th percentiles for continuous variables and percentages for dichotomous variables. For continuous variables, comparisons were made using the Wilcoxon rank-sum test, whereas for dichotomous variables, comparisons were made using the χ^2 test or Fisher exact test. Event analyses were performed using time-to-event data (for which patients were censored at the time of withdrawal from the study or at last follow-up), are displayed using Kaplan–Meier plots, and were compared with the log-rank test. Multivariable predictors of 30-day and 3-year outcomes were determined using Cox proportional hazards regression with entry and stay criteria of 0.1. To avoid overfitting, the following variables considered to be among the most important determinates for outcomes after primary PCI were considered in the multivariable models: age, sex, diabetes mellitus, baseline Killip class (I versus II–IV), baseline hemoglobin, baseline white blood cell count, baseline platelet count, baseline creatinine clearance, time from symptom onset to PCI, number of diseased epicardial coronary vessels, infarct artery (left anterior descending versus nonleft anterior descending), baseline thrombolysis in myocardial infarction flow (0/1 versus 2/3), prerandomization heparin use (yes versus no), thienopyridine loading dose (clopidogrel 600 mg versus other), randomization arm (bivalirudin versus heparin plus a GPI), final thrombolysis in myocardial infarction flow, final blush score, stent type and STR (forced into the model). The following additional variables were added to the models for 3-year ischemia-driven TVR: the number of lesions treated, lesion reference vessel diameter, and lesion length, using a Cox proportional hazards marginal model with robust sandwich covariance estimates to correct for possible clustering effects. For all analyses, $P<0.05$ was considered significant, and all P values are 2-sided. All analyses were performed with SAS version 9.2 (SAS Institute, Inc., Cary, NC). P values for pairwise comparisons were adjusted using the Sidak correction.

Results

Study Patients and Baseline Characteristics

Of the 3602 patients enrolled in the HORIZONS-AMI trial, 3345 patients underwent primary PCI. From this group, both

Table 1. Baseline Demographic Characteristics, Medications, and Laboratory Results According to ST-Segment Resolution

	a) STR>70% (N=1258)	b) STR 30% to 70% (N=712)	c) STR<30% (N=514)	*P* Value all Groups	*P* Value (a) vs (b)	*P* Value (a) vs (c)	*P* Value (b) vs (c)
Age, y	59.2 (52.1–68.6)	60.1 (51.7–69.7)	61.6 (53.9–70.0)	0.02	0.82	0.01	0.34
Female	24.4% (307/1258)	21.2% (151/712)	21.4% (110/514)	0.18	0.31	0.52	1.00
Race—white	93.8% (1180/1258)	93.4% (665/712)	94.7% (487/514)	0.61	1.00	1.00	0.97
Body mass index, kg/m^2	27.04 (24.49–29.98)	26.83 (24.52–30.40)	27.04 (24.49–30.42)	0.82	1.00	1.00	1.00
Medical history							
Hypertension	49.7% (625/1258)	51.5% (367/712)	56.9% (292/513)	0.02	1.00	0.02	0.18
Hyperlipidemia	41.8% (526/1258)	41.4% (295/712)	47.0% (241/513)	0.10	1.00	0.14	0.16
Current smoking	51.2% (642/1253)	44.8% (317/708)	41.2% (210/510)	0.0002	0.02	0.0004	0.62
Diabetes mellitus	12.1% (152/1258)	17.3% (123/712)	21.6% (111/513)	<0.0001	0.004	<0.0001	0.16
Previous myocardial infarction	10.9% (137/1258)	7.4% (53/712)	12.5% (64/513)	0.009	0.04	1.00	0.009
Previous PCI	10.7% (134/1258)	7.6% (54/712)	12.3% (63/513)	0.02	0.08	0.95	0.02
Previous CABG	2.1% (26/1258)	2.2% (16/712)	3.5% (18/513)	0.19	1.00	0.23	0.55
Previous angina	20.9% (263/1258)	21.1% (150/712)	25.5% (131/513)	0.08	1.00	0.10	0.20
Laboratory results							
Creatinine clearance, mL/min*	88.68 (69.37–110.05)	89.96 (68.37–116.72)	85.88 (64.82–111.52)	0.18	1.00	0.52	0.22
Creatinine clearance <60 mL/min	15.0% (178/1185)	15.5% (101/650)	19.5% (93/478)	0.08	1.00	0.08	0.25
Hemoglobin, g/dL	14.5 (13.6–15.5)	14.7 (13.6–15.8)	14.7 (13.6–15.5)	0.15	0.15	1.00	1.00
White blood cell count, ×10^3	11.1 (8.9–13.5)	11.5 (9.2–13.8)	11.0 (8.6–13.7)	0.07	0.03	0.81	0.06
Platelet count	247 (208–291)	249 (209–294)	245 (201–288)	0.52	1.00	1.00	0.82
Medications at home							
Aspirin	24.7% (310/1256)	19.8% (141/712)	25.1% (129/513)	0.03	0.04	1.00	0.08
Thienopyridine	2.8% (35/1258)	2.4% (17/712)	1.8% (9/514)	0.44	1.00	0.61	1.00
Pre-PCI medications							
Aspirin	99.8% (1256/1258)	100.0% (712/712)	99.6% (511/513)	0.24	0.85	1.00	0.28
Thienopyridine	99.5% (1252/1258)	99.6% (709/712)	99.6% (511/513)	0.96	1.00	1.00	1.00
Bivalirudin	49.7% (625/1258)	48.3% (344/712)	52.3% (269/514)	0.38	1.00	0.92	0.49
Heparin+IIb/IIIa inhibitor	50.3% (633/1258)	51.7% (368/712)	47.7% (245/514)	0.38	1.00	0.92	0.49
Prerandomization Heparin	67.4% (848/1258)	62.9% (448/712)	62.8% (322/513)	0.06	0.04	0.06	0.96

CABG indicates coronary artery bypass graft surgery; PCI, percutaneous coronary intervention; and STR, ST resolution.
*Estimated by the Cockcroft–Gault formula. Continuous data are presented as median (interquartile range).

baseline and post-PCI 60-minute ECGs were available in 2671 patients (79.8%). We excluded another 187 patients because of the absence of ST-segment elevation of ≥1 mm in at least 2 contiguous leads (n=185) or left bundle–branch block (n=2).Thus, the final study cohort consisted of 2484 patients, in whom STR of <30%, ≥30% but ≤70%, and >70% were achieved in 514 (20.7%), 712 (28.7%), and 1258 (50.5%) of patients, respectively.

The baseline demographic and laboratory characteristics of the study cohort according to the STR achieved at 60 minutes are presented in Table 1. When compared with the patients with complete (>70%) STR, those with absent (<30%) STR were more likely to have diabetes mellitus, hypertension, hyperlipidemia, be current smokers, and have a history of previous angina. Angiographic data and procedural results according to STR are presented in Table 2. Patients with STR<30% had longer door-to-balloon times, were more likely to have a left ventricular ejection fraction <40%, and were less likely to achieve final thrombolysis in myocardial infarction-3 flow in the infarct-related artery (82.2% versus 90.8%; *P*<0.0001). There were no baseline differences between randomization arms (bivalirudin versus heparin plus a GPI) in the patients analyzed in this prespecified substudy. The overall loss to follow-up rate was 7.7% at 3 years with no significant differences between the 3 categories of STR.

Patient Outcomes According to 60-Minute STR

Acute (within 24-hour) stent thrombosis was less common in those with STR>70% compared with those with STR<30%, 0.5% versus 1.4%, *P*=0.04. Event rates after hospital discharge according to the degree of STR on the 60-minute post-PCI ECG are shown in Table 3 and Figure 1A through D. At 30 days, the rate of MACE was the highest in patients with absent STR, intermediate in patients with incomplete STR, and the lowest in patients with complete STR. The 30-day rates of death, reinfarction, ischemia-driven TVR, and stent thrombosis were also the highest in patients with absent STR. Similar patterns according to STR were present at 3 years. By multivariable analysis, STR<30% on the 60-minute post-PCI ECG was an independent predictor of the 3-year rate of MACE and ischemia-driven TVR, but not of mortality or

Table 2. Baseline Angiography and Procedural Results According to ST-Segment Resolution

	a) STR>70% (N=1258)	b) STR 30% to 70% (N=712)	c) STR<30% (N=514)	*P* Value all Groups	*P* Value (a) vs (b)	*P* Value (a) vs (c)	*P* Value (b) vs (c)
Preprocedure							
Single vessel disease	44.5% (553/1242)	46.1% (325/705)	39.8% (203/510)	0.08	1.00	0.21	0.09
Double vessel disease	35.6% (442/1242)	32.2% (227/705)	35.7% (182/510)	0.27	0.38	1.00	0.60
Triple vessel disease	19.6% (244/1242)	21.6% (152/705)	24.3% (124/510)	0.09	0.92	0.09	0.76
LVEF <40%—site reported	10.3% (113/1093)	19.6% (116/591)	21.0% (89/423)	<0.0001	<0.0001	<0.0001	1.00
PCI target and procedure							
No. treated lesions, mean±SD	1.14±0.43	1.12±0.35	1.12±0.34	0.33	0.39	0.51	1.00
Multiple lesions treated	11.2% (138/1234)	10.5% (74/704)	10.8% (54/499)	0.90	1.00	1.00	1.00
No. vessels treated, mean±SD	1.04±0.21	1.04±0.20	1.04±0.20	0.92	0.92	1.00	0.95
Multiple vessels treated	4.1% (50/1234)	3.7% (26/704)	4.2% (21/499)	0.89	1.00	1.00	1.00
Target vessel=LAD	30.1% (450/1493)	54.6% (465/851)	52.9% (324/613)	<0.0001	<0.0001	<0.0001	1.00
Lesion length, mm	14.83 (10.52–20.00)	14.78 (10.32–20.26)	14.77 (10.00–22.10)	0.92	1.00	1.00	1.00
Reference vessel diameter, mm	2.91 (2.56–3.23)	2.84 (2.48–3.18)	2.83 (2.49–3.21)	0.02	0.04	0.10	1.00
TIMI flow							
0/1	59.9% (783/1307)	64.2% (475/740)	65.4% (351/537)	0.04	0.16	0.08	1.00
2	12.9% (169/1307)	13.5% (100/740)	13.0% (70/537)	0.93	1.00	1.00	1.00
3	27.2% (355/1307)	22.3% (165/740)	21.6% (116/537)	0.009	0.04	0.04	1.00
≥1 stents implanted	95.5% (1201/1258)	93.7% (667/712)	91.4% (470/514)	0.004	0.25	0.003	0.40
Any drug-eluting stent implanted	72.1% (867/1203)	72.0% (482/669)	72.0% (339/471)	1.00	1.00	1.00	1.00
Any aspiration catheter used	11.7% (146/1245)	13.3% (94/707)	11.4% (58/507)	0.52	0.92	1.00	0.99
Symptom to balloon time, min, median (IQR)	204.0 (153.0–290.0)	221.0 (160.0–345.0)	250.0 (169.0–325.0)	<0.0001	0.0007	<0.0001	0.01
Door-to-balloon time, min, median (IQR)	95.5 (70.0–128.0)	97.0 (73.0–131.0)	100.0 (73.0–135.0)	0.15	1.00	0.16	0.96
Postprocedure							
Final TIMI 3 flow	90.8% (1187/1307)	83.1% (613/738)	82.2% (442/538)	<0.0001	<0.0001	<0.0001	1.00
Final TIMI frame count, median (IQR)	38 (28, 48)	42 (31, 54)	40 (32, 52)	<0.0001	0.0002	0.0008	1.00

IQR indicates interquartile range; LAD, left anterior descending; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; STR, ST resolution; and TIMI, thrombolysis in myocardial infarction.

reinfarction (Table 4). There was a strong trend toward increased stent thrombosis with STR<30%, but this did not reach statistical significance. Among 950 patients with 1128 lesions undergoing routine 13-month angiographic follow-up, binary in-segment restenosis was present in 9.6%, 14.6%, and 19.1% of patients with complete, partial, and absent STR, respectively (P<0.001).

Patients With Worsening ST-Segment Elevation

A total of 198 patients (8.0%) had worsening ST-segment elevation (STR<0%) on the 60-minute ECG after PCI compared with baseline. When compared with the 313 patients with STR 0% to <30%, those with worsening ST-segment elevation post-PCI had higher 30-day rates of ischemia-driven TVR (5.1% versus 1.6%; P=0.02), with nonsignificantly different rates of death 3.0% versus 3.2%; P=0.92), reinfarction (3.6% versus 2.6%; P=0.50), and MACE (9.6% versus 6.4%; P=0.17).

Impact of Antithrombotic Therapy and Stent Type on STR

The rates of complete, partial, and absent STR at 60 minutes were not significantly different in patients randomized to bivalirudin versus heparin plus a GPI (Table 5). Similarly, there were no significant differences in the rates of STR with randomization to PES versus BMS (Table 5).

Discussion

The usability of STR in STEMI as a prognostic tool was well established in the thrombolytic era.[1] The role of STR in the contemporary primary PCI era has been less well characterized because of limitations in earlier PCI studies, including the nonroutine use of stents, the lack of data with drug-eluting stents, failure to prospectively standardize the timing of postreperfusion ECGs, and relatively short-term follow-up.[8–11] The present report, representing a formal, prespecified substudy from the contemporary, international, prospective, randomized HORIZONS-AMI trial, overcomes many of these limitations. Strengths of the present study include its large size, standardization of baseline and 60-minute post-PCI ECG collection, use of a blinded ECG core laboratory, randomization of patients to bivalirudin as well as heparin plus GPI (the former recommended with a class Ib level of evidence in both the United States and European Union guidelines),[12,13] as well as randomization to PES versus BMS, and clinical follow-up to 3 years. As such, the HORIZONS-AMI STR substudy is the largest data set to date examining the long-term prognostic usability of STR after primary PCI in STEMI. The results

Table 3. Clinical Outcomes According to ST-Segment Resolution

	a) STR>70% (N=1258)	b) STR 30% to 70% (N=712)	c) STR<30% (N=514)	*P* Value all Groups	*P* Value (a) vs (b)	*P* Value (a) vs (c)	*P* Value (b) vs (c)
30-d events							
Death	1.8% (23)	1.3% (9)	3.1% (16)	0.06	0.34	0.09	0.02
Reinfarction	1.3% (16)	2.4% (17)	3.0% (15)	0.04	0.06	0.02	0.56
Ischemia-driven TVR	1.6% (18)	2.5% (16)	3.3% (15)	0.09	0.19	0.03	0.43
Stroke	0.4% (5)	1.0% (7)	0.6% (3)	0.27	0.11	0.59	0.45
MACE	3.7% (47)	4.8% (34)	7.6% (39)	0.003	0.26	0.0006	0.04
Stent thrombosis*	1.7% (21)	2.5% (17)	3.5% (17)	0.08	0.25	0.02	0.30
3-y events							
Death	5.6% (68)	5.0% (35)	8.4% (42)	0.03	0.62	0.02	0.02
Reinfarction	6.6% (78)	8.4% (58)	8.1% (39)	0.21	0.10	0.22	0.80
Ischemia-driven TVR	11.7% (139)	14.0% (96)	20.4% (98)	<0.0001	0.10	<0.0001	0.005
Stroke	1.1% (13)	2.5% (17)	1.6% (8)	0.07	0.02	0.33	0.34
MACE	19.6% (239)	21.0% (147)	29.9% (150)	<0.0001	0.31	<0.0001	0.0004
Stent thrombosis*	4.8% (56)	5.9% (39)	8.2% (38)	0.02	0.29	0.006	0.13

MACE indicates major adverse cardiovascular events; STR, ST-segment resolution; and TVR, target vessel revascularization.
*Definite or probable according to the Academic Research Consortium criteria.

of the present study demonstrate that the degree of STR on the 60-minute ECG is a significant, independent predictor of MACE as long as 3 years after primary PCI. And notably, there were no significant differences in postprocedural STR in patients randomized to bivalirudin versus heparin plus a GPI, or PES versus BMS.

Previous studies have examined the prognostic value of STR after primary PCI in STEMI, with conflicting results. The CADILLAC investigators reported that the degree of STR after balloon angioplasty and BMS were independent predictors of both 30-day and 1-year death and reinfarction.[11] The Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) investigators found that the degree of STR after primary PCI correlated well not only with the 90-day rate of mortality, but also with the combined end point of death, heart failure, or shock.[14] A real-world registry from northern Italy has also recently reported that the degree of STR at 60 minutes post-PCI was an independent predictor of 30-day mortality in 3403 patients with STEMI.[15] In contrast, the DANAMI-2 investigators compared the long-term prognostic value of STR in 1421 patients treated with fibrinolysis compared with primary PCI, finding that STR at 90 minutes was an important predictor of short- and long-term (4.2 years) mortality after fibrinolysis but not after PCI.[4] Whether the differences between this and previous studies relate to patient selection, ECG analysis methodology, or the examination of outcomes at an early versus late time point is uncertain. Nonetheless, this report raised uncertainty as to the long-term prognostic value of STR after primary PCI in STEMI.

In the present study, the degree of STR measured 60 minutes post-PCI in 2484 patients with STEMI was an independent predictor of 3-year MACE and ischemia-driven TVR. Angiographic restenosis at 13 months was also greater in patients with lesser degrees of STR, supporting this finding. Further studies are required to determine the mechanisms underlying the greater degree of clinical and angiographic restenosis in patients with suboptimal STR after primary PCI. STR was a predictor of 3-year mortality in univariable analysis, but not after adjustment for important baseline differences between the groups, including diabetes mellitus, reduced left ventricular ejection fraction, and longer symptom onset to balloon time, all of which were more frequent in patients with absent STR after PCI. The degree of STR was also related to the occurrence of reinfarction at 30 days (similar to our previous findings from CADILLAC), but in the present study, absent STR was not a significant predictor of reinfarction at 3 years by either univariable or multivariable analysis. The higher rates of stent thrombosis observed in patients with absent STR both at 30 days and 3 years are a novel finding that requires validation in future studies.

Three issues that deserve discussion are the timing of the post-PCI ECG, the degree of STR, and the method of STR determination. In the HORIZONS-AMI trial, STR was assessed 60 minutes after the final angiogram, compared with 30 minutes earlier in APEX-AMI. In patients undergoing PCI, both time points seem to be clinically useful given the high rates of epicardial coronary artery patency achieved early after PCI (compared with the stuttering degree of reperfusion after lytic therapy, which does not plateau until ≈90 minutes). Which of these time intervals (30 versus 60 minutes post-PCI) has greater prognostic accuracy is unknown. With regard to the thresholds for the degree of STR, both the triple categorization of <30%, 30% to 70%, and >70% resolution and the binary outcome of <50% or >50%[12] seem to be useful to predict future cardiovascular events. In HORIZONS-AMI, the binary categorization of STR<30% versus ≥30% seemed optimal for predicting death and MACE in short- and long-term follow-up. Finally, several previous studies have investigated whether single or numerous leads should be used to assess STR, and whether the absolute or relative amount of STR has the greatest prognostic utility after primary PCI.[11,12] In the present analysis, the summation of ST-segment elevation in

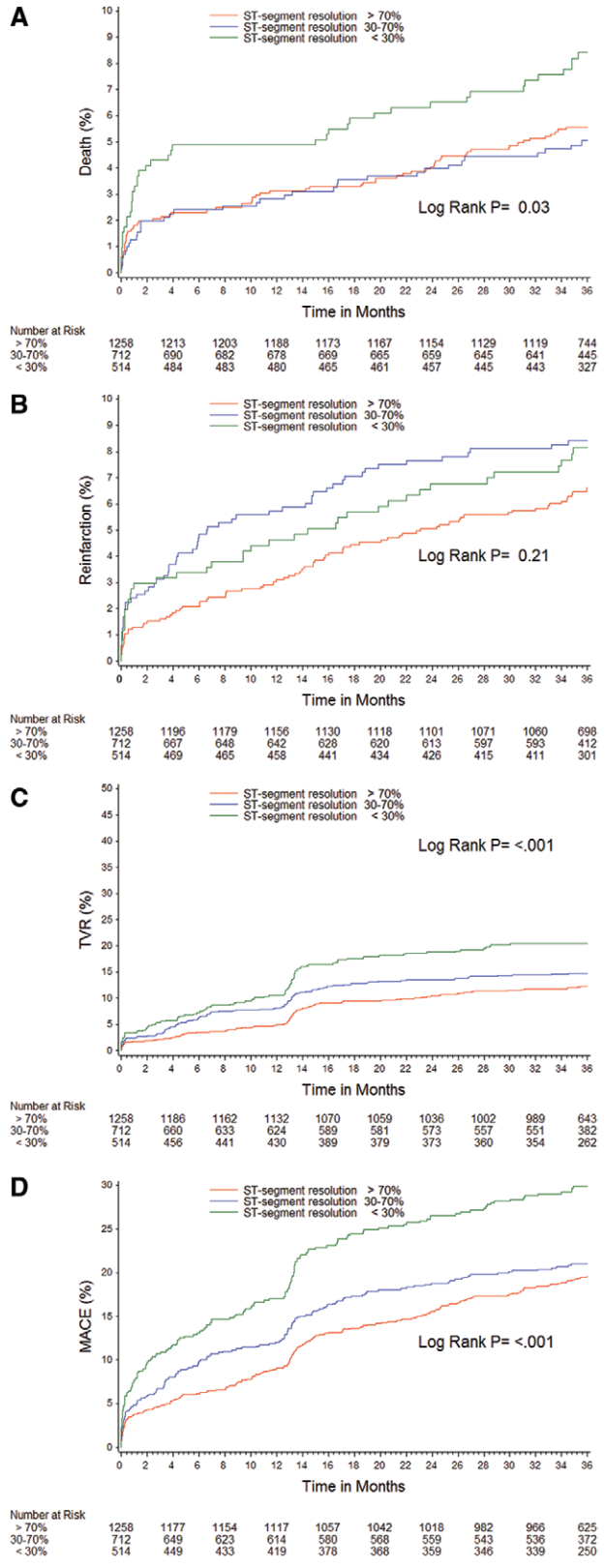

Figure 1. Time-to-event curves to 3 years according to complete, partial, or absent ST-segment resolution on the 60-minute postrevascularization ECG. (**A**) All-cause mortality; (**B**) reinfarction; (**C**) ischemia-driven target vessel revascularization (TVR); (**D**) major adverse cardiovascular events (MACE).

Table 4. Independent Predictors of 3-Year Adverse Events

End points	HR (95% CI)	*P* Value
All-cause death		
ST-segment resolution <30%	1.05 (0.68–1.61)	0.82
Serum creatinine	1.71 (1.45–2.03)	<0.0001
Killip class 2–4	2.30 (1.50–3.53)	0.0001
TIMI 3	0.60 (0.39–0.93)	0.023
Age (per 10 y increase)	1.90 (1.61–2.25)	<0.0001
White blood cell count	1.09 (1.04–1.14)	<0.0001
Reinfarction		
ST-segment resolution <30%	1.13 (0.75–1.71)	0.55
Serum creatinine	1.43 (1.20–1.71)	<0.0001
Platelet count	1.00 (1.00–1.01)	<0.0001
LAD treated	1.54 (1.06, 2.24)	0.02
Ischemia-driven TVR		
ST-segment resolution <30%	1.87 (1.41–2.48)	<0.0001
ST-segment resolution 30% to 70%	1.36 (1.02–1.80)	0.033
Male	0.68 (0.49–0.91)	0.003
Serum creatinine	1.30 (1.10–1.54)	0.002
Platelet count	1.00 (1.00–1.00)	0.007
DES vs BMS	0.73 (0.57–0.95)	0.018
Bivalirudin (vs UFH+IIb/IIIa)	1.29 (1.02–1.63)	0.037
MACE		
ST-segment resolution <30%	1.58 (1.24–2.00)	0.0002
Serum creatinine	1.45 (1.28–1.64)	<0.0001
Platelet count	1.00 (1.00–1.00)	0.02
DES vs BMS	0.80 (0.65–1.00)	0.048
LAD treated	1.41 (1.14–1.74)	0.002
Multiple vessels treated	1.62 (1.08–2.43)	0.02
Age (per 10 y increase)	1.20 (1.11–1.30)	<0.001
White blood cell count	1.03 (1.00–1.06)	0.048

ST-segment resolution was forced into each model. BMS indicates bare-metal stent; CI, confidence interval; DES, drug-eluting stent; HR, hazard ratio; LAD, left anterior descending coronary artery; MACE, major adverse cardiovascular events; TIMI, thrombolysis in myocardial infarction; TVR, target vessel revascularization; and UFH, unfractionated heparin.

all leads, excluding aVR, was prognostically useful. Further work in this area to determine the simplest technique, which has acceptable accuracy, is warranted.

A unique aspect of our trial was the determination of the degree of STR in patients randomized to bivalirudin versus heparin plus a GPI, and to PES versus BMS, and the examination of the extent to which this explains the long-term outcomes between these therapeutic interventions. At 60 minutes post-PCI, the rates of complete (>70%), partial (30%–70%), and absent (<30%) resolution were not significantly different between the 2 anticoagulation regimens and the 2 stent types. However, despite having similar rates of STR, bivalirudin significantly decreased all-cause mortality compared with heparin plus a GPI at both 30 days and 3 years, without significant differences in MACE, reinfarction, and TVR.[5,16]

Table 5. Impact of Antithrombotic Therapy and Stent Randomization on ST-Segment Resolution at 60 Minutes

	Bivalirudin	Heparin+GPI	Combined	*P* Value
ST resolution <0%	8.5% (105/1238)	7.5% (93/1246)	8.0% (198/2484)	0.35
ST-segment resolution <30%	21.7% (269/1238)	19.7% (245/1246)	20.7% (514/2484)	0.21
ST-segment resolution 30% to 70%	27.8% (344/1238)	29.5% (368/1246)	28.7% (712/2484)	0.33
ST-segment resolution >70%	50.5% (625/1238)	50.8% (633/1246)	50.6% (1258/2484)	0.87
ST resolution (continuous), median [IQR]	70.7 [39.0–95.4]	70.9 [40.5–94.1]	70.8 [40.0–94.6]	0.8766
	Paclitaxel-Eluting Stent	Bare-Metal Stent	Combined	*P* Value
ST-segment resolution <30%	20.9% (353/1687)	19.6% (109/557)	20.6% (462/2244)	0.49
ST-segment resolution 30% to 70%	28.6% (482/1687)	29.4% (164/557)	28.8% (646/2244)	0.69
ST-segment resolution >70%	50.5% (852/1687)	51.0% (284/557)	50.6% (1136/2244)	0.84

GPI indicates glycoprotein IIb/IIIa inhibitor; and IQR, interquartile range.

The mechanism for the survival benefit of bivalirudin likely relates more to its ability to reduce major bleeding[17] than to restore microvascular perfusion, which is what STR gauges. Similarly, PES compared with BMS reduced MACE and TVR at 1 and 3 years,[6,16] despite both stent types having comparable rates of STR, which itself was also an independent predictor of both MACE and TVR. These disparate findings highlight the numerous mechanisms that must be considered to understand (and therefore optimize) the long-term prognosis after primary PCI in STEMI. These directionally incongruent results also demonstrate that STR may not be a perfect surrogate for clinical outcomes in STEMI, although early and late patient prognosis is more likely to be favorable if complete STR early after reperfusion is achieved.

Limitations and Implications

A small but not negligible proportion of patients did not have both baseline and 60-minute ECGs available for interpretation. Because the analysis of STR was done by a core laboratory with ST evaluated at 80 ms in numerous leads, it may or may not reflect what would be seen in bedside assessment that is less rigorous. We did not use continuous ST-segment monitoring, which might have permitted analysis of STR at different time intervals and permitted analysis of ST-segment instability. Finally, as a nonpowered observational study, the results from the present analysis should be considered hypothesis generating. Nonetheless, rapidly restoring effective myocardial metabolism is a major goal of reperfusion therapy in STEMI, and the results of the present study confirm that evaluation of the 60-minute postintervention ECG can be used to assess the success of the primary PCI procedure and provide independent prognostic information for at least 3 years after presentation.

Disclosures

None.

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