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Clinical research

Combined prognostic utility of ST-segment recovery and myocardial blush after primary percutaneous coronary intervention in acute myocardial infarction

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Aims ST-segment recovery (ΣSTR) and myocardial blush (MB) evaluate different elements of microcirculatory integrity after reperfusion therapy in acute myocardial infarction (AMI). We sought to determine whether the combination of ΣSTR and MB after primary percutaneous coronary intervention (PCI) in AMI has greater prognostic utility than either measure alone.

Methods and results The 30 days and 1 year clinical outcomes of 456 patients were assessed as a function of ΣSTR and MB after primary PCI from the CADILLAC trial. ΣSTR and MB were concordant ($\geq$70% ΣSTR and MB grade 2/3 or $<$70% ΣSTR and MB grade 0/1) in 60.1% of patients and discordant in 39.9% of patients. The greatest survival was observed among patients with complete ΣSTR ($\geq$70%) and MB grade 2/3 in whom the cumulative rates of death at 30 days and 1 year were 0.6 and 1.2%, respectively. Poorest survival was observed among patients with incomplete ΣSTR ($<$70%) and reduced MB (grade 0/1), in whom 30 days and 1 year rates of death were 8.3 and 10.1%, respectively. Intermediate outcomes were present in patients with discordant MB and ΣSTR. By multivariable analysis, however, ΣSTR was an independent correlate of survival at 30 days and 1 year ($P = 0.05$ and 0.01, respectively), whereas MB was no longer predictive ($P = 0.38$ and 0.72, respectively).

Conclusion ΣSTR and MB are not infrequently discordant after primary PCI. By univariate analysis, both measures of reperfusion success strongly correlate with survival and assessment of both yields incremental prognostic information beyond either measure alone. By multivariable analysis, however, ΣSTR is the stronger prognostic variable.

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Introduction

Despite prompt restoration of brisk epicardial blood flow with either pharmacologic or mechanical reperfusion therapy, a significant proportion of patients with acute myocardial infarction (AMI) have impairment of microvascular integrity and myocardial perfusion.[1,2] This phenomenon, also known as 'no-reflow', may have multiple aetiologies such as vasospasm, distal thromboembolism, inflammation, interstitial oedema, and myonecrosis with capillary disruption.[3,4] The degree of microvascular injury correlates with the extent of myocardial damage,[5–8] but its presence predisposes patients to unfavourable ventricular remodelling,[9–14] heart failure,[8,14,15] and a worse prognosis,[16–18] even after controlling for infarct size.[19]

Concordant with the widespread acceptance that the metric of optimal reperfusion should include measures beyond epicardial blood flow, several methods for assessing the microvasculature have been proposed.[19,20–25] Although each of these techniques independently predicts outcomes, as these measures may reflect different attributes of microvascular integrity, incremental prognostic information may theoretically be derived from their collective consideration. Recovery of electrocardiographic ST-segment elevation (ΣSTR), and restoration of normal myocardial blush (MB), the angiographic surrogate of myocardial perfusion, are two techniques that are readily available during clinical practice, but data is limited as to which is superior, or whether they provide complementary prognostic utility.[14,17,18,26,27] Utilizing data derived from a large cohort of patients in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, we sought to evaluate the relative prognostic utility of ΣSTR and MB after primary percutaneous coronary intervention (PCI) for AMI.

Methods

Study population

The details of the CADILLAC trial protocol previously have been described.[28] Briefly, non-shock patients with AMI, symptom duration of $<$12 h and ST-segment elevation in two or more contiguous electrocardiographic leads or left bundle branch block were randomized. Patients without ST-segment elevation infarction also were enrolled if angiography documented a high-grade coronary artery stenosis and an associated left ventricular wall motion abnormality. Following angiography, patients with coronary anatomy suitable for stenting were randomized in a 2$\times$2 factorial design to balloon angioplasty, with or without stenting, and, with or without, the use of abciximab. A total of 2082 patients were randomized at 76 international medical centres and followed clinically for 1 year after procedure.

As previously described, two formal substudies of the CADILLAC trial were performed to investigate the prognostic utility of ΣSTR ($n = 700$) and MB ($n = 1301$).[29,30] Both substudies utilized independent core laboratories blinded to randomization and clinical outcomes to measure indices of reperfusion success. A total of 456 common patients enrolled in both substudies who had data analyzable for both ΣSTR and MB form the study cohort of the current analysis. Patients without ST-segment elevation infarction were not included in the current investigation.

Electrocardiographic analysis

As previously described,[29] each patient in the ST-segment substudy had (i) paired electrocardiograms (ECGs) at baseline and within 4 h post-PCI (mean 1.8 $\pm$ 0.8 h); (ii) $>$1 mm of ST-segment elevation in two or more contiguous leads in the infarct territory on the baseline ECG; and (iii) absence of conditions on both ECGs that would confound interpretation, including left bundle branch block, pacing, pre-excitation, ectopy, missing leads, artifact, and multiple ECG AMI territories. Each ECG was assessed at an independent electrocardiographic core laboratory at the Beth Israel Deaconess Medical Center in Boston, MA, USA. Digital calipers were utilized to measure the absolute level of ST-segment elevation 20 ms after the end of the QRS interval to the nearest 0.01 mV, using the TP segment as the isoelectric baseline. ST-segment elevation was summated using previously validated algorithms as the sum of elevation in V_{1-6}, I, and aVL for anterior infarction and as the sum of elevation in leads II, III, aVF, V_5, and V_6 for non-anterior infarction.[5,7,14,18] ST-segment recovery (ΣSTR) was defined as the percent reduction in the summed ST-segment elevation score between ECGs obtained prior to PCI and within 4 h following the procedure (mean 1.8 $\pm$ 0.8 h). ΣSTR was classified as complete ($\geq$70%), partial (30 to $<$70%), and none ($<$30%).[5–8]

MB analysis

As previously described,[30] MB was graded from the final angiograms after PCI at an independent core angiographic laboratory at the Cardiovascular Research Foundation in New York City, NY, USA. MB grade was defined according to the method of Van't Hof *et al.*[8]: 0, no contrast density or persistent staining; 1, minimal contrast density; 2, moderate contrast density, but less than that obtained during angiography of a non-infarct-related coronary artery; and 3, normal contrast density, comparable to that obtained during angiography of a non-infarct-related coronary artery. On the basis of the MB grade, the microcirculation was classified as either closed (MB = 0 or 1) or open (MB = 2 or 3).

Definitions and data analysis

The components of the primary endpoint in the CADILLAC trial, a composite of major adverse cardiac events (MACE) consisting of death from any cause, reinfarction, disabling stroke, and repeat target vessel revascularization for ischaemia, have been previously defined.[28] To emulate prior prognostic studies of ΣSTR[5–7,9,16] and MB,[14,18] outcomes were evaluated and stratified by post-procedural MB grade (0/1 vs. 2/3), ΣSTR ($\geq$70 vs. $<$70%), and by all four combinations thereof. Categorical variables were compared with the Fisher exact test for pairwise comparisons and χ^2 test for trend for multiple comparisons. Continuous variables are expressed as medians with interquartile ranges and were compared using the Kruskal–Wallis non-parametric test. Event rates were determined and displayed with Kaplan–Meier methodology and compared with the log-rank test. Cox proportional hazard models were constructed to evaluate the independent predictors of adverse event outcomes using the following candidate predictors: age, gender, diabetes mellitus, current smoking, left ventricular ejection fraction (LVEF), creatinine clearance, triple-vessel disease, left anterior

descending artery culprit, prior myocardial infarction, pre-procedural TIMI grade flow of 0–2, symptom onset to balloon time, and post-PCI MB grade (0/1 or 2/3) and ΣSTR (≥70 or <70%).

Results

Baseline characteristics

Tables 1 and *2* lists the baseline clinical, angiographic, and procedural characteristics of the overall study population, and stratified by post-PCI MB grade and ΣSTR. Complete ΣSTR occurred in 283 patients (62.1%), whereas MB grade 2/3 was present immediately following primary PCI in 229 patients (50.2%). Both incomplete ΣSTR and reduced MB grade (0/1) correlated with anterior infarction and decreased LVEF. Renal insufficiency, smaller reference diameter, and stent implantation also were associated with incomplete ΣSTR but not with reduced MB. Reduced MB grade was associated with increased duration from symptom onset to reperfusion and decreased post-PCI TIMI-3 flow.

There was a strong correlation between the degree of ΣSTR and MB grade ($P < 0.0001$). Among the patients with ΣSTR ≥ 70%, 58.3% had MB grade 2 or 3. For patients with MB grade 2 or 3, 72.0% had ΣSTR ≥ 70%. Of note, however, among the patients with ΣSTR < 30%, 15.9% of patients had MB grade 2 and 9.1% had MB grade 3. In total, 36.2% of patients had ΣSTR ≥ 70% and MB 2/3, 25.9% had ΣSTR ≥ 70% and MB 0/1, 14.0% had ΣSTR < 70% and MB 2/3, and 23.9% had ΣSTR < 70% and MB 0/1. In summary, ΣSTR and MB were concordant in 60.1% of patients, and discordant in 39.9% of patients.

Impact of the collective consideration of ST-segment resolution and MB on adverse clinical events

As seen in *Table 3*, incomplete ΣSTR was associated with increased rates of death, recurrent ischaemia, reinfarction, stroke, and composite MACE at both 30 days and 1 year. Reduced MB grade was associated with increased rates of death and stroke at both time periods, but not with recurrent ischaemia or reinfarction.

By univariate analysis, the combination of ΣSTR and MB further stratified patients into four distinct strata of survival (*Figure 1*, top). Survival was greatest with both ΣSTR ≥ 70% and MB 2/3, intermediate when either of these measures were reduced, and worst when both were abnormal. Similar patterns were seen for the composite rate of death or reinfarction (*Figure 1*, middle) and for MACE (*Figure 1*, bottom).

Table 1 Baseline characteristics

	All patients	ΣSTR			MB grade		
	($n = 456$)	≥70% ($n = 283$)	<70% ($n = 173$)	*P*-value	2/3 ($n = 229$)	0/1 ($n = 227$)	*P*-value
Age (years)	60 (51, 69)	60 (51, 69)	62 (51, 69)	0.69	59 (51, 67)	61 (51, 70)	0.32
Male gender (%)	70.7	70.7	73.4	0.59	69.4	74.0	0.30
Anterior infarction (%)	40.8	28.3	61.3	<0.0001	25.8	55.9	<0.0001
Symptom onset to reperfusion (h)	3.7 (2.8, 5.3)	3.7 (2.8, 4.9)	3.7 (2.8, 6.8)	0.16	3.4 (2.7, 4.6)	4.0 (2.9, 6.1)	0.002
Killip class >1 (%)	8.6	8.5	10.4	0.31	8.9	8.4	0.87
Left anterior descending infarct artery (%)	41.2	28.3	62.4	<0.0001	24.5	58.1	<0.0001
Left ventricular ejection fraction (%)	50 (41, 55)	50 (41, 57)	45 (35, 55)	0.0001	50 (42, 60)	45 (35, 55)	<0.0001
Multivessel disease (%)	46.7	44.9	49.7	0.33	43.7	49.8	0.22
Prior medical history (%)							
Diabetes mellitus	18.2	17.0	20.2	0.38	17.0	19.4	0.55
Current smoker	69.7	72.8	64.7	0.07	72.9	66.5	0.15
Hyperlipidemia	37.3	37.8	36.4	0.84	39.7	34.8	0.29
Hypertension	48.2	49.1	46.8	0.70	48.5	48.0	0.93
Prior myocardial infarction	1.4	11.3	11.6	1.00	11.8	11.0	0.88
Renal insufficiency	20.6	17.5	25.7	0.04	19.0	22.2	0.48
Prior bypass graft surgery	1.8	1.8	1.7	1.00	1.7	1.8	1.00
Medical therapy (%)							
Aspirin	24.1	25.1	22.5	0.57	22.3	26.0	0.38
Beta-blockers	15.6	15.5	15.6	1.00	16.2	15.0	0.80
Statins	11.8	11.0	13.3	0.46	14.4	9.3	0.11
Calcium blockers	13.2	12.0	15.0	0.39	12.2	14.1	0.58
ACEI/ARBs	8.8	10.6	5.8	0.09	8.7	8.8	1.00
Thienopyridine	2.0	1.8	2.3	0.74	1.7	2.2	0.75

ACEI/ARB, angiotensin converting enzyme inhibitors or angiotensin receptor blockers.

Table 2 Angiographic characteristics and procedural results

	All patients	ΣSTR			MB grade		
	($n = 456$)	≥70% ($n = 283$)	<70% ($n = 173$)	*P*-value	2/3 ($n = 229$)	0/1 ($n = 227$)	*P*-value
Reference vessel diameter (mm)	2.98 (2.64, 3.41)	3.03 (2.68, 3.45)	2.92 (2.61, 3.25)	0.01	2.98 (2.64, 3.43)	2.96 (2.63, 3.36)	0.37
Baseline TIMI-3 flow (%)	17.8	18.4	16.9	0.71	20.6	15.0	0.14
Maximum device diameter (mm)	3.50 (3.00, 3.50)	3.50 (3.00, 3.50)	3.32 (3.00, 3.50)	0.19	3.50 (3.00, 3.71)	3.34 (3.00, 3.50)	0.06
Maximum balloon/artery ratio	1.10 (1.00, 1.21)	1.09 (0.99, 1.20)	1.13 (1.01, 1.21)	0.08	1.09 (1.00, 1.22)	1.11 (0.99, 1.20)	0.80
Maximum pressure (atm.)	14.0 (10.0, 16.0)	13.0 (10.0, 15.0)	14.0 (10.0, 16.0)	0.37	12.8 (10.0, 15.0)	14.0 (10.0, 16.0)	0.28
Stent implanted (%)	58.1	54.1	64.7	0.03	55.0	61.2	0.19
Abciximab administered (%)	48.9	49.8	47.4	0.63	50.2	47.6	0.58
Final minimal luminal diameter (mm)	2.47 (2.14, 2.83)	2.45 (2.15, 2.87)	2.49 (2.13, 2.80)	0.59	2.46 (2.14, 2.83)	2.47 (2.14, 2.82)	0.76
Final TIMI-3 flow (%)	95.6	96.5	94.2	0.47	99.6	92.0	<0.0001

After multivariable adjustment for differences in baseline features, ΣSTR remained predictive of death, death and reinfarction combined, and overall MACE both at 30 days and at 1 year (*Table 4*). In contrast, by multivariable analysis, MB was not significantly predictive of death, reinfarction, or MACE (*Table 4*).

Discussion

The principal findings of the current investigation are as follows (i) The correlates of achieving complete ΣSTR and an open microcirculation as measured by the angiographic MB grade after primary PCI in AMI overlap to a large extent, though some differences are present. By both measures, anterior infarction and decreased LVEF at baseline are the strongest correlates of microcirculatory dysfunction. (ii) The post-PCI ΣSTR and MB grade strongly correlate, though the results are discordant in a significant proportion (~40%) of patients. (iii) By univariate analysis, incomplete ΣSTR is strongly associated with death, recurrent ischaemia, reinfarction, stroke, and composite MACE; reduced MB grade is associated with death and stroke but not with recurrent ischaemia or reinfarction. (iv) Though assessment of both measures of reperfusion success provides additional incremental utility beyond either alone, in predicting survival at 30 days and 1 year after primary PCI, by multivariable analysis, ΣSTR is the more powerful prognostic variable.

Numerous studies in the last several years have clearly demonstrated that tissue level perfusion can be compromised despite restoration of normal epicardial blood flow.[1,2] Thus, the assessment of microvascular perfusion and integrity is integral for risk stratification in patients with AMI, especially after primary PCI, in whom TIMI-3 flow is restored in >90% of patients. In this regard, prior studies have demonstrated the prognostic utility of both ΣSTR and MB in this setting.[7,8,13,14,17,29,30] The electrocardiographic ΣSTR has been shown to be related to cell membrane integrity and myocyte function.[31] Conversely, the angiographic measure of MB reflects anatomic microvascular patency.[8] It is thus reasonable to hypothesize that the establishment of normalized ΣSTR and MB might overlap. When discordant, however, the combination of both measures might yield incremental prognostic utility beyond either alone. Moreover, ΣSTR and MB are attractive diagnostic techniques to assess myocardial perfusion as these measures are readily available and do not entail significant patient risk, costs, or personnel. Other methods of microvascular assessment such as myocardial contrast echocardiography, positron emission tomography, intracoronary Doppler, magnetic resonance imaging, and scintigraphy also are valid techniques, but their application may be difficult in the setting of acute or recent infarction.[4,15,19,20–22]

In the current investigation, anterior infarct location and reduced LVEF were both powerfully predictive of incomplete or absent ΣSTR and a closed microcirculation, consistent with prior studies.[7,8,14,16] There were differences, however, in the baseline correlates of these two

Table 3 Clinical outcomes stratified by post-procedural ΣSTR and MB grade

	All patients	ΣSTR			MB grade		
	($n = 456$)	≥70% ($n = 283$)	<70% ($n = 173$)	*P*-value	2/3 ($n = 229$)	0/1 ($n = 227$)	*P*-value
Death (%)							
30 days	3.1	1.1	6.4	0.002	1.3	4.8	0.03
1 year	5.1	2.9	8.7	0.005	2.7	7.5	0.02
Reinfarction (%)							
30 days	1.1	0.4	2.3	0.05	0.9	1.4	0.63
1 year	1.8	0.7	3.7	0.03	1.8	1.8	0.96
Recurrent ischaemia (%)							
30 days	5.9	4.3	14.5	0.04	5.7	6.2	0.79
1 year	19.0	16.6	22.9	0.08	19.2	18.8	0.95
Target vessel revascularization (%)							
30 days	2.6	1.8	4.0	0.13	3.1	2.2	0.59
1 year	11.2	9.4	14.2	0.12	12.1	10.3	0.52
Any stroke (%)							
30 days	0.9	0.0	2.3	0.01	0.0	1.8	0.04
1 year	1.6	0.7	3.0	0.06	0.5	2.7	0.05
Composite major adverse cardiac events (%)							
30 days	5.7	2.8	10.4	0.0007	4.4	7.0	0.22
1 year	16.1	12.5	22.0	0.005	15.1	17.2	0.50

measures. Similarly, both measures were concordant in 60.1% of patients, whereas in 39.9% of patients discordance was noted (complete ΣSTR with absent MB or vice versa). Although ΣSTR and MB were ascertained at slightly different times (~1.8 h apart), these observations nonetheless suggest that these two measures of myocardial reperfusion reflect different pathophysiologic processes, which might potentially provide complementary prognostic information. In this regard, Poli *et al.*[14] recently demonstrated that the combination of ΣSTR and MB synergistically predict left ventricular function after reperfusion therapy in AMI. Similarly, Angeja *et al.*[32] have shown that integration of ΣSTR and TIMI myocardial perfusion grade more accurately predict eventual infarct size than either measure alone.

By univariate analysis, the present study demonstrates that myocardial reperfusion success as assessed by both ΣSTR and MB predicts survival after primary PCI in the early post-infarction period (30 days) and after longer follow-up (1 year). Consideration of both reperfusion measures, however, yielded more prognostic information than either alone. Patients with both electrocardiographic complete ΣSTR and an angiographically open microcirculation (MB 2/3) have the greatest survival, with nearly 99% of patients still alive after 1 year. Conversely, the poorest survival was observed in patients with both incomplete ΣSTR and reduced MB (10.1% 1 year mortality, an 8.4-fold increase). Survival was intermediate for patients who had absent or partial ΣSTR despite normal or near-normal MB and for those who had reduced or absent MB despite complete ΣSTR. Furthermore, ΣSTR and MB in combination also offered incremental prognostic utility for predicting composite event rates including death and reinfarction, and MACE.

By multivariable analysis, however, after correction for the confounding impact of baseline variables, ΣSTR but not MB was independently predictive of survival at 30 days and at 1 year. Moreover, ΣSTR, but not MB, was predictive of recurrent ischaemia and reinfarction. Finally, achievement of TIMI-3 flow was significantly less common among patients with reduced MB, whereas there were no differences in TIMI-3 flow as a function of ΣSTR. This observation further supports the independent predictive value of ST-segment monitoring.

To date, only two prior studies have directly compared ΣSTR and MB for survival.[18] In a report of 253 patients by Haager *et al.*, both ΣSTR and MB were independent predictors of death after AMI. The reasons for the discrepancy between the findings of the current and prior study are unknown, but may relate to differences in patient selection, ΣSTR and MB methodology (including core laboratory reading), as well as other unidentified factors. Moreover, the current study cohort is an intermediate risk patient population; it is possible MB may have additional prognostic utility in a higher risk cohort. Conversely, in a recent analysis that utilized data from three clinical trials of full-dose fibrinolysis vs. reduced-dose fibrinolysis and glycoprotein IIb/IIIa blockade in AMI, lowest mortality was observed among those who had achieved complete ΣSTR, TIMI grade 3, and normal MB, yet ΣSTR was the strongest predictor of mortality at 30 days.[33] ΣSTR, as the electrocardiographic index of myocardial injury, may reflect the sum of pathophysiologic processes that indicate ongoing myocardial damage. Anatomic patency of the microvasculature, as evidenced by the MB grade, may provide more limited information.

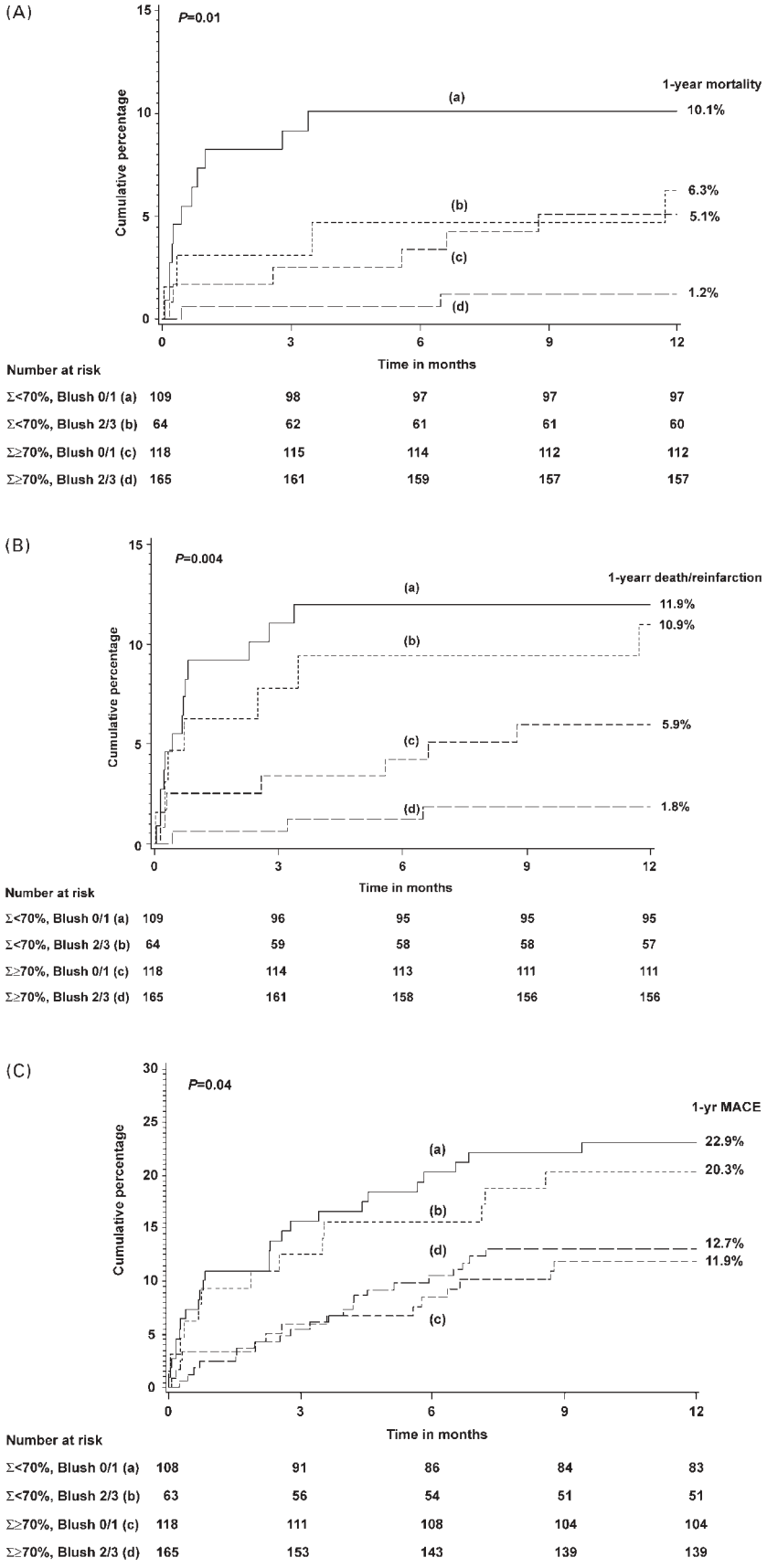

Figure 1 Cumulative adverse event rates during 1 year follow-up for patients according ΣSTR (<70 vs. ≥70%) and MB grade (0/1 vs. 2/3). (*A*) death; (*B*) death or reinfarction; (*C*) MACE.

Table 4 Multivariable predictors of adverse events

	30 days			1 year		
	Hazard ratio	95% CI	*P*-value	Hazard ratio	95% CI	*P*-value
Death						
ΣSTR < 70%	8.33	0.96–100	0.05	7.14	1.52–33.33	0.01
MB grade 0/1	2.86	0.28–25.0	0.38	1.30	0.30–5.26	0.72
Lower creatinine clearance	1.06	1.02–1.10	0.002	1.04	1.02–1.08	0.0005
Decreased LVEF	1.09	1.01–1.18	0.04	1.08	1.03–1.14	0.002
Death or reinfarction						
ΣSTR < 70%	4.17	1.33–12.5	0.01	2.63	1.15–5.88	0.02
MB grade 0/1	2.50	0.80–7.69	0.11	1.75	0.74–4.17	0.20
Lower creatinine clearance	1.05	1.01–1.03	<0.0001	1.04	1.02–1.05	<0.0001
Triple-vessel disease	—	—	—	2.64	1.16–6.00	0.02
Major adverse cardiac events						
ΣSTR < 70%	3.57	1.52–8.33	0.004	1.96	1.19–3.23	0.008
MB grade 0/1	1.39	0.60–5.88	0.44	1.16	0.70–1.92	0.51
Female gender	3.79	1.63–8.81	0.002	2.28	1.39–3.74	0.001
Lower creatinine clearance	1.01	1.00–1.03	0.06	1.84	1.04–3.24	0.036

Study limitations

The current investigation was a *post hoc* analysis and thus must be considered hypothesis generating rather than definitive. Selection bias cannot be excluded. A larger study population is required to confirm the relative prognostic importance of ΣSTR and MB. Both quantitative ST-segment evaluation and MB determination were performed as substudies of the original CADILLAC protocol, and the current cohort comprised an overlapping group with common patients from each. Nonetheless, ΣSTR and MB grade were both evaluated in core research laboratories blinded to clinical outcomes and each other. Moreover, the prognostic implications of ΣSTR and MB in the current study cohort are similar to that reported from each individual substudy,[29,30] suggesting they are representative. Finally, as mentioned previously, the results do not necessarily apply to a higher-risk patient population than that enrolled in CADILLAC, such as cardiogenic shock and saphenous vein graft intervention; conversely, as <10% of patients with AMI typically present with these conditions, the study results may apply to ~90% of all patients undergoing primary PCI.

Conclusions and clinical implications

The routine evaluation of both ΣSTR and MB grade for assessing microvascular injury identifies patients at increased risk of death and other adverse events after primary PCI for AMI. When the prognostic information from other clinical variables is considered as well, including LVEF and decreased creatinine clearance, complete ΣSTR persists as an independent determinate of survival. Additional studies are required to further explore whether MB grade contains independent prognostic information and whether interventions to improve these measures of reperfusion success translate into improved survival and freedom from MACE after primary PCI in AMI.

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