



Effect of Ischemia Duration and Door-to-Balloon Time on Myocardial Perfusion in ST-Segment Elevation Myocardial Infarction

An Analysis From HORIZONS-AMI Trial (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction)

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ABSTRACT

OBJECTIVES This study sought to investigate the effect of treatment delay on microvascular reperfusion in ST-segment elevation myocardial infarction (STEMI) patients from the large, multicenter, prospective HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial.

BACKGROUND Despite restoration of epicardial blood flow during primary percutaneous coronary intervention (PCI), one-third of patients do not obtain myocardial perfusion due to impairment in the microvascular circulation.

METHODS We examined the effect of symptom onset-to-balloon time (SBT) and door-to-balloon time (DBT) on myocardial reperfusion during primary PCI in STEMI, utilizing resolution of ST-segment elevation (STR) and the myocardial blush grade (MBG). The primary analysis was the relationships between SBT ≤ 2 , >2 to 4, and >4 h and DBT ≤ 1 , >1 to 1.5, >1.5 to 2, and >2 h with MBG and STR. Clinical risk was assessed using a modified version of the Thrombolysis In Myocardial Infarction risk score for STEMI.

RESULTS In 2,056 patients, absent microvascular perfusion (MBG 0/1) and STR (STR $<30\%$) after primary PCI was significantly more common in patients with longer SBT, in patients with both low and high clinical risk profiles. By multivariable analysis, SBT ($p < 0.0001$), anterior infarction ($p < 0.0001$), reference vessel diameter ($p = 0.005$), lesion minimum lumen diameter ($p < 0.0001$), hyperlipidemia ($p = 0.03$), and current smoking ($p = 0.001$) were independent predictors of MBG 0/1, whereas SBT ($p = 0.007$), anterior infarction ($p < 0.0001$), and history of renal insufficiency ($p = 0.0002$) were independent predictors of absent STR. DBT ($p < 0.0001$) was an independent predictor of MBG 0/1. MBG 0/1 and STR $<30\%$ identified patients with increased 3-year mortality.

CONCLUSIONS The present study suggests that delay in mechanical reperfusion therapy during STEMI is associated with greater injury to the microcirculation. (J Am Coll Cardiol Intv 2015;8:1966-74) © 2015 by the American College of Cardiology Foundation.

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Timely restoration of culprit artery patency, and thereby myocardial salvage, is the primary objective of percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI). In contemporary practice, normal (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3) epicardial blood flow can be restored in the culprit vessel in approximately 90% of cases (1). However, tissue perfusion at the level of the myocardium is not restored in approximately one-third of patients (2), even after successful primary PCI, due to impairment in microvascular blood flow; in these patients, the benefits

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of reperfusion are limited (3). Small studies using cardiac magnetic resonance imaging have shown that prolonged duration of ischemia is associated with larger areas of microvascular obstruction (4,5). Larger observational studies have explored the relationship between duration of ischemia and myocardial perfusion, but these investigations have predated the routine use of stents and modern antiplatelet therapy (6), only reported a single-center experience (7), or lacked core laboratory analysis. Moreover, there is a paucity of data on the effect of door-to-balloon time (DBT) on microvascular reperfusion. We, therefore, examined the effect of symptom onset-to-balloon time (SBT) and DBT on myocardial reperfusion from a large contemporary multicenter, prospective study of primary PCI in STEMI, utilizing 2 well-validated measures of myocardial perfusion and reperfusion success, namely, resolution of ST-segment elevation (STR) (8-11) and myocardial blush grade (MBG) (12-15).

METHODS

STUDY POPULATION. The HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial has been described

in detail (1). In brief, 3,602 patients presenting with STEMI within 12 h of symptom onset were randomized before angiography to bivalirudin or heparin and a glycoprotein IIb/IIIa inhibitor (1:1 ratio). Subsequently, 3,006 patients suitable for stenting were randomized again to a drug-eluting stent or an identical bare-metal stent (3:1 ratio). Independent adjudication of clinical events and angiographic core laboratory analysis were performed at the Cardiovascular Research Foundation (New York, New York). The primary analysis was the relationships between SBT ≤ 2 , > 2 to 4, and > 4 h and DBT ≤ 1 , > 1 to 1.5, > 1.5 to 2, and > 2 h with MBG and STR. We excluded 1,546 patients from the analysis because of missing SBT, MBG, or STR data.

DEFINITIONS. SBT was defined as the time from symptom onset until balloon inflation. DBT was defined as the time from arrival at the hospital (first hospital in transferred patients) until balloon inflation. Clinical risk was assessed using a modified version of the TIMI risk score for STEMI (16). Selected variables associated with high mortality were assigned points weighted as follows: age ≥ 75 years (3 points), age ≥ 65 years (2 points), Killip class II to IV (2 points), anterior infarction (1 point), diabetes mellitus (1 point), and weight < 67 kg (1 point). For each patient, points for each of these variables were summed to give a modified TIMI clinical risk score (17).

ANGIOGRAPHIC ANALYSIS. Myocardial blush in the distribution of the infarct vessel post-PCI was analyzed using the methodology of van 't Hof et al. (13) at an independent angiographic core laboratory (Cardiovascular Research Foundation) by investigators blinded to the clinical variables. On the basis of the maximal densitometric degree of contrast opacification, microvascular perfusion was scored as MBG 0/1 (no or minimal myocardial contrast opacification), MBG 2 (moderate contrast opacification but less than

ABBREVIATIONS AND ACRONYMS

DBT = door-to-balloon time

ECG = electrocardiogram

MBG = myocardial blush grade

PCI = percutaneous coronary intervention

SBT = symptom onset-to-balloon time

STEMI = ST-segment elevation myocardial infarction

STR = ST-segment resolution

TIMI = Thrombolysis In Myocardial Infarction

STENTYS; is a consultant for Abbott Vascular, AstraZeneca, Bayer, Boston Scientific, Covidien, CSL Behring, Janssen Pharmaceuticals, Maya Medical, Merck & Co., Osprey Medical Inc., and Watermark Research Partners; is a member of the advisory board for Abbott Laboratories, Boston Scientific, Covidien, Janssen Pharmaceuticals, The Medicines Company, Merck, Sanofi, and Endothelix Inc.; and is a shareholder for Endothelix Inc. Dr. Witzembichler is a consultant for Volcano; and has received lecture fees from Elixir Medical and Atrium Medical. Dr. Guagliumi has received grant support from Abbott Vascular, Boston Scientific, and St. Jude Medical; and is a consultant for Boston Scientific and St. Jude Medical. Dr. Dudek has received consulting and lecture fees from Abbott, Adamed, Adyton Medical Polska, Abiomed Europe, AstraZeneca, Biotronik, Balton, Bayer, B. Braun, BioMatrix, Boston Scientific, Boehringer Ingelheim, Bracco, Bristol-Myers Squibb, Comesa Polska, Cordis, Cook, Covidien Polska Sp. z o.o., DRG MedTek, Eli Lilly, EuroCor, Hammermed, GE Healthcare, Glaxo, InspireMD, Iroko Cardio International, Medianet Sp. z o.o., Medtronic, The Medicines Company, Meril Life Sciences, Merck Sharp & Dohme, Orbus-Neich, Pfizer, Possis, ProCardia Medical, Promed, REVA Medical, Sanofi-Aventis, Siemens, Solvay, Stentys, St. Jude Medical, Terumo, Tyco, and Volcano. Dr. Stone has served as a consultant for Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

in either an ipsilateral or contralateral noninfarct artery), and MBG 3 (normal myocardial blush or contrast opacification, comparable with the other coronary arteries). When myocardial blush persisted (“staining”), MBG 0 was assigned.

ST-SEGMENT ANALYSIS. Electrocardiograms (ECGs) obtained pre-procedure and at 60-min post-procedure were analyzed as pairs by the ECG core laboratory by independent readers who were blinded to the clinical and angiographic data. STR was evaluated using standardized techniques (8) and categorized as complete (>70%), partial (30% to 70%), or none (<30%). All trial patients in whom both baseline and 60-min post-PCI ECG were available and interpretable were included in this analysis. Patients with left bundle branch block at baseline, paced ventricular rhythm, and patients without ST-segment deviation in 2 or more contiguous leads were excluded from ECG analysis.

STATISTICAL ANALYSIS. Continuous variables are presented as median with interquartile range and were compared using the Wilcoxon rank sum test. Categorical variables are presented as proportions and were compared using the chi-square or Fisher exact test. Multivariable models were developed using stepwise logistic regression with entry/stay criteria of 0.1/0.1 to identify independent predictors of MBG 0/1 and STR <30%. Candidate clinical variables were age, sex, diabetes mellitus, hypertension, hyperlipidemia, current smoker, prior myocardial infarction, prior PCI, prior coronary artery bypass graft surgery, peripheral vascular disease, prior angina, renal insufficiency, and Killip class. Angiographic variables were number of diseased vessels, baseline TIMI flow grade 0/1, baseline reference vessel diameter, baseline minimum lumen diameter, baseline percent diameter stenosis, and culprit artery. Direct stenting was a procedural variable included in the models. In addition to these, DBT and SBT were added in separate models. An interaction test between SBT and baseline and procedural variables on MBG 0/1 was performed. Variables included were age, sex, history of angina, diabetes mellitus, number of vessels treated, number of stents used, and number of lesions treated. Cox proportional hazard multivariable models were used to identify predictors of 3-year mortality. Variables included were MBG, STR, age, sex, diabetes mellitus, smoking, creatinine clearance, peripheral or cerebrovascular disease, prior coronary artery bypass graft surgery or PCI, PCI to left anterior descending artery, triple vessel disease, and procedural success. The significance level was set at 0.05. All analyses were performed with SAS version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CLINICAL AND PROCEDURAL CHARACTERISTICS.

There were 2,367 patients enrolled in the formal MBG and STR substudy; however, only 2,056 had complete SBT and DBT data available. Among these, 162 (7.9%), 976 (47.4%), and 918 (44.7%) patients presented within SBT of ≤ 2 , >2 to 4, and >4 h, respectively. There was no difference ($p = 0.48$) in the frequency of patients in the 3 groups who were and were not included in the MBG and STR subanalyses from the HORIZONS-AMI trial. The clinical characteristics of patients with increasing duration of SBT are summarized in **Table 1**. Patients with greater SBT were older and were more likely to be women, have diabetes mellitus, have prior angina, and have longer DBT, but were less likely to have post-procedural TIMI flow grade 3 and procedural success.

RELATIONSHIP AMONG SBT, DBT, AND MYOCARDIAL

PERFUSION. As seen in **Figure 1**, absent microvascular perfusion (MBG 0/1) after primary PCI was significantly more common in patients with longer SBT. This relationship was similar in patients with both a low (modified TIMI risk score <2 ; $p = 0.0002$) and high (modified TIMI risk score ≥ 2 ; $p = 0.0001$) clinical risk profile. Similar relationships were present between symptom-to-door time (SBT – DBT) and myocardial perfusion (**Online Figure 1**). By multivariable analysis, SBT, anterior infarction, reference vessel diameter, lesion minimum lumen diameter, hyperlipidemia, and current smoking were independent predictors of MBG 0/1 (**Table 2**). With respect to the relationship between SBT and MBG 0/1, significant interaction with baseline variables was only observed for age ($p < 0.001$) such that the effect of SBT was greater in younger patients.

Absent STR was also significantly more frequent in patients with longer SBT (**Figure 1**). This relationship was present in patients with both a low ($p < 0.0001$) and high ($p = 0.02$) clinical risk profile. By multivariable analysis, SBT, anterior infarction, and history of renal insufficiency were independent predictors of absent STR (**Table 2**).

Figure 2 summarizes the relationships between DBT and the 2 indexes of myocardial perfusion. DBT >2 h was associated with a higher frequency of absent microvascular perfusion (MBG 0/1), but there was no relationship with between DBT and absent STR. By multivariable analysis, DBT (odds ratio [OR]: 1.63; 95% confidence interval [CI]: 1.16 to 2.30; $p < 0.0001$) was an independent predictor of MBG 0/1.

When analyzed according to the SBT strata (**Figure 3**), there were no statistically significant

TABLE 1 Baseline Characteristics According to Symptom Onset-to-Balloon Time

	SBT ≤2 h (n = 162)	SBT >2 to 4 h (n = 976)	SBT >4 h (n = 918)	Combined (n = 2,056)	p Value All Groups
Age, yrs	54.1 (49.1-62.4)	58.3 (50.7-68.3)	61.4 (53.4-80.0)	59.2 (51.8-69.2)	<0.0001
Men	85.2 (138/162)	77.0 (752/976)	74.8 (687/918)	76.7 (1,577/2,056)	0.02
Body mass index, kg/m ²	27.13 (24.79-30.86)	27.13 (24.61-30.10)	27.00 (24.45-30.25)	27.06 (24.54-30.25)	0.75
Hypertension	51.2 (83/162)	49.1 (479/976)	53.5 (491/918)	51.2 (1,053/2,056)	0.16
Hyperlipidemia	46.9 (76/162)	43.3 (423/976)	41.5 (381/918)	42.8 (880/2,056)	0.39
Smoking	66.7 (108/162)	65.9 (641/973)	64.0 (584/912)	65.1 (1,333/2,047)	0.64
Diabetes mellitus	9.9 (16/162)	14.4 (141/976)	18.5 (170/918)	15.9 (327/2,056)	0.005
Prior myocardial infarction	9.3 (15/162)	10.2 (100/976)	10.5 (96/918)	10.3 (211/2,056)	0.90
Prior PCI	11.7 (19/162)	12.0 (117/976)	8.4 (77/917)	10.4 (213/2,055)	0.03
Prior coronary artery bypass graft surgery	0.6 (1/162)	2.4 (23/976)	2.8 (26/918)	2.4 (50/2,056)	0.24
Prior angina	11.7 (19/162)	17.8 (174/976)	27.5 (252/917)	21.7 (445/2,055)	<0.0001
History of congestive heart failure	1.9 (3/162)	2.2 (21/976)	2.8 (26/918)	2.4 (50/2,056)	0.56
Killip class 1	95.1 (154/162)	91.1 (888/975)	90.3 (828/917)	91.0 (1,870/2,054)	0.15
Peripheral vascular disease	0.6 (1/162)	3.8 (37/975)	4.7 (43/918)	3.9 (81/2,055)	0.05
History of renal insufficiency	1.2 (2/162)	3.2 (31/975)	3.2 (29/918)	3.0 (62/2,055)	0.38
PCI to left anterior descending artery	41.0 (71/173)	42.4 (446/1,052)	41.2 (412/1,000)	41.8 (929/2,225)	0.84
Pre-PCI TIMI 3 flow	13.9 (24/173)	18.6 (196/1,051)	20.2 (202/999)	19.0 (422/2,223)	0.13
Post-PCI TIMI 3 flow	97.1 (168/173)	95.1 (1,000/1,052)	88.9 (889/1,000)	92.4 (2,057/2,225)	<0.0001
Clopidogrel administration	100.0 (162/162)	99.9 (975/976)	99.6 (914/918)	99.8 (2,051/2,056)	0.27
Glycoprotein IIb/IIIa inhibitor use	59.9 (97/162)	53.6 (523/976)	55.7 (510/915)	55.0 (1,130/2,053)	0.28
Drug-eluting stent	70.4 (112/159)	73.2 (687/939)	70.5 (606/859)	71.8 (1,405/1,957)	0.43
Bare-metal stent	30.8 (49/159)	28.0 (263/939)	30.7 (264/859)	29.4 (576/1,957)	0.41
Door-to-balloon time, min	58 (47-73)	93 (71-115)	120 (87-172)	98.00 (72-133)	<0.0001
Procedural success*	90.8 (178/196)	90.3 (1,072/1,187)	82.7 (918/1,110)	87.0 (2,168/2,493)	<0.0001
Left ventricular ejection fraction, %	50.00 (45.00-55.00)	50.00 (45.00-59.00)	50.00 (40.00-58.00)	50.00 (43.00-58.00)	0.23

Values are median (interquartile range) or % (n/N). *TIMI flow grade 3 plus residual stenosis <50%.
 PCI = percutaneous coronary intervention; SBT = symptom onset-to-balloon time; TIMI = Thrombolysis In Myocardial Infarction.

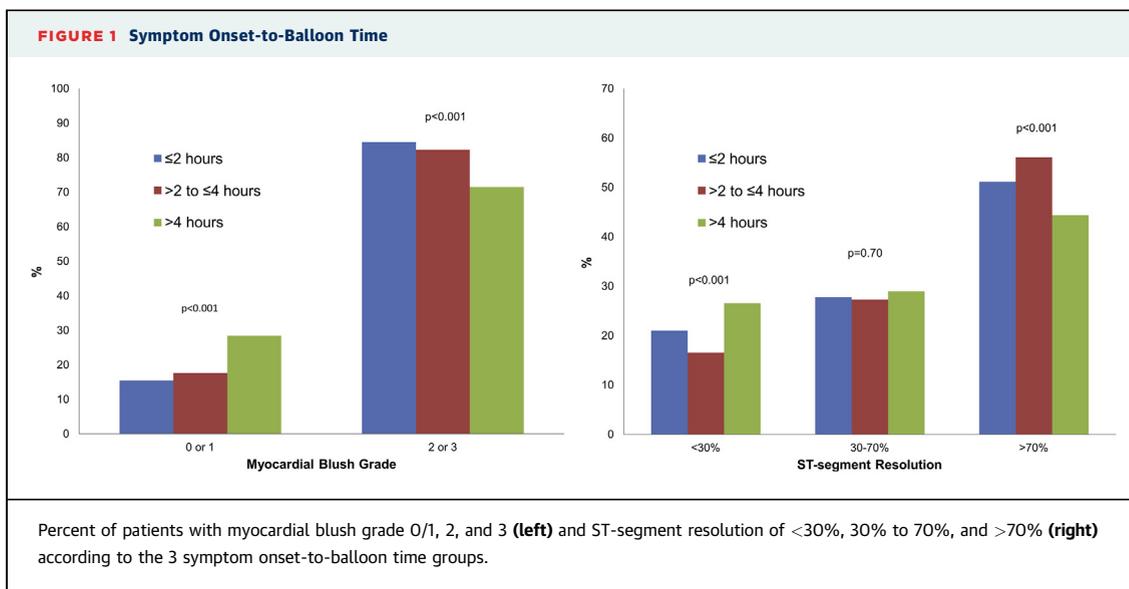
differences in the rates of normal MBG and complete STR when comparing those with DBT ≤90 min to those with DBT >90 min. However, it is worth noting that among the subgroup with SBT ≤2 h, those with DBT ≤90 min had higher rates of MBG 3 and STR >70% compared with patients with DBT >90 min. In contrast, this trend was not seen in patients presenting with SBT >2 h.

CLINICAL IMPLICATIONS OF MBG AND STR AFTER PRIMARY PCI. The 3-year unadjusted mortality rates were 2.6%, 4.4%, and 7.2% (p = 0.007, log-rank test) in the SBT ≤2, >2 to 4, and >4 h groups, respectively, and 3.6%, 4.6%, 6.3%, and 6.6% (p = 0.16) in the DBT ≤1, >1 to 1.5, >1.5 to 2, and >2 h groups, respectively. [Online Figure 2](#) shows the 3-year mortality according to the MBG and STR. MBG 0/1 and STR <30% identified patients with increased mortality. In a multivariable model that included both MBG 0/1 and STR <30%, MBG 0/1 (OR: 1.79; 95% CI: 1.17 to 2.72; p = 0.007) but not STR <30% (OR: 1.27; 95% CI:

0.82 to 1.97; p = 0.28) was an independent predictor of 3-year mortality. Other independent predictors were diabetes mellitus (OR: 2.13; 95% CI: 1.39 to 3.27; p = 0.0005), peripheral vascular disease (OR: 2.11; 95% CI: 1.16 to 3.86; p = 0.01), history of smoking (OR: 1.87; 95% CI: 1.21 to 2.89; p = 0.005), and age (OR: 1.30; 95% CI: 1.02 to 1.66; p = 0.03).

DISCUSSION

The major findings of the present study among STEMI patients undergoing contemporary primary PCI are: 1) SBT is an independent predictor of impaired myocardial perfusion, as assessed by both reduced MBG and incomplete STR; 2) DBT is an independent predictor of impaired MBG; 3) in early presenters (SBT <2 h), reductions in DBT intervals might further improve myocardial reperfusion; and 4) impaired myocardial perfusion correlates with mortality at 3 years.



We observed a “time-dependent” relationship between SBT duration and the likelihood of impaired myocardial perfusion following primary PCI. This may be a potential pathophysiological factor that might account for the higher mortality associated with longer SBT. With respect to SBT duration, patients presenting within 2 h of symptom onset were the least likely to have impaired myocardial perfusion, whereas those presenting after 4 h had the highest frequency of MBG 0/1 and STR <30% (Figure 1). This is similar to the findings by Fokkema et al. (7), who conducted a smaller single-center study and reported an adverse effect of SBT on MBG and

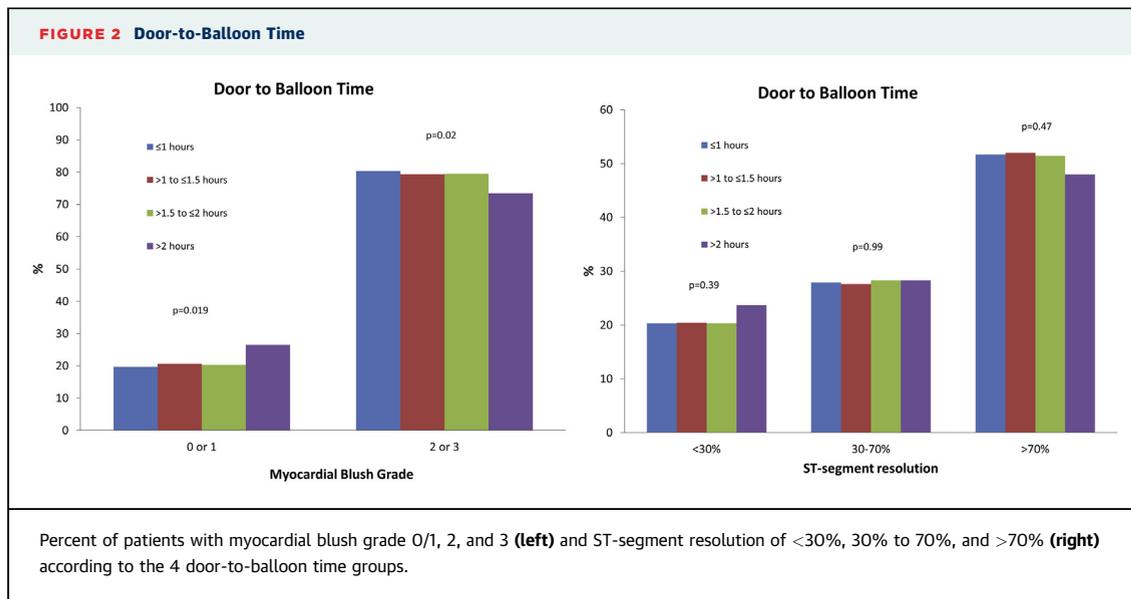
STR with an apparent threshold at approximately 4 h. The relationship between ischemia duration and myocardial perfusion in our study was independent of clinical characteristics and other angiographic variables and was observed in those with low and high clinical risk profiles. There was an interaction between age and SBT on MBG such that the adverse effect was seen in younger patients. Of note, despite the universal use of stents in the present study, the findings with regards to the relationship between SBT and MBG resemble the observations from the prior study by De Luca et al. (6), in which stents were used in <60% of cases. This indicates that optimal epicardial patency with routine use of stents does not improve or worsen (by increasing distal embolization) myocardial perfusion.

DBT is an important performance metric in the management of STEMI. The present study provides unique data regarding the relationship between DBT and myocardial perfusion. A statistically significant impairment in MBG was detected in patients who had a DBT >2 h, and this relationship was independent of clinical and angiographic variables (Figure 2). These data suggest that prolongation in DBT has an adverse effect on microvascular salvage, although the data is less compelling than that for SBT, because no relationship was detected between longer DBT and STR. The reason that DBT was associated with one measure of myocardial perfusion and not the other is unclear. Because DBT is an integral component of SBT, we examined the interaction between these 2 time metrics on myocardial perfusion (Figure 3). The present study suggests that in early presenters (SBT <2 h), DBT <90 min may result in a higher frequency of

TABLE 2 Multivariable Predictors of Absent Myocardial Perfusion in Models for SBT

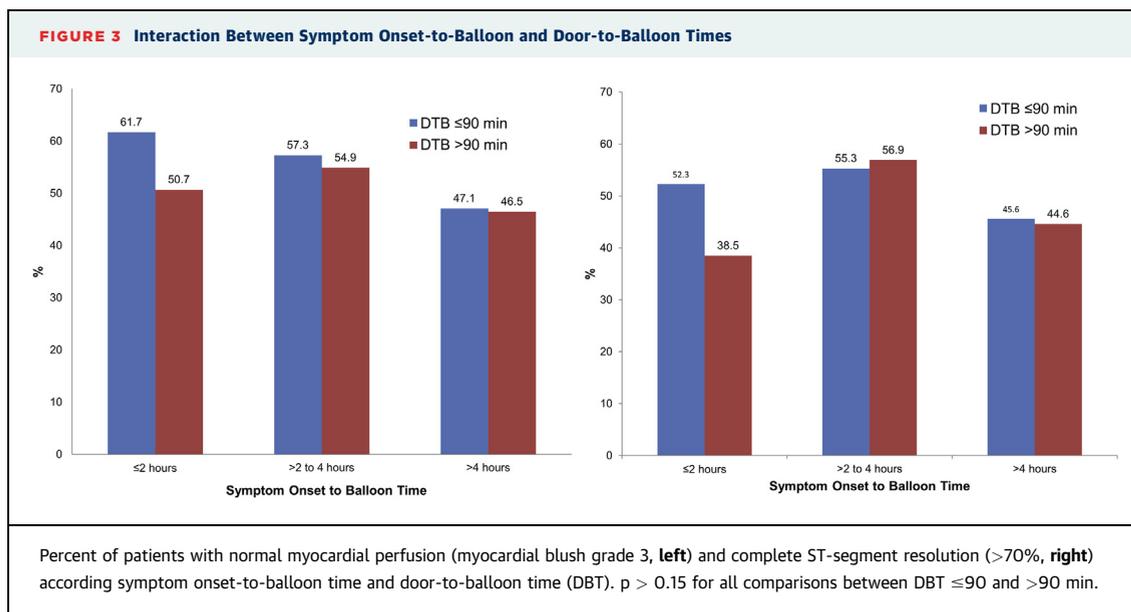
	Odds Ratio	95% Confidence Interval	p Value
Predictors of MBG 0/1			
SBT (>4 h vs. ≤2 h)	2.08	1.32-3.28	<0.0001
Anterior infarction	1.66	1.29-2.13	<0.0001
Reference vessel diameter	1.38	1.10-1.73	0.005
Lesion minimum lumen diameter	0.32	0.22-0.46	<0.0001
Hyperlipidemia	0.78	0.63-0.98	0.03
Current smoking	0.69	0.55-0.86	0.001
Predictors of STR <30%			
SBT	1.27	1.06-1.51	0.007
Anterior infarction	2.10	1.63-2.72	<0.0001
History of renal insufficiency	2.78	1.62-4.75	0.0002

MBG = myocardial blush grade; SBT = symptom onset-to-balloon time; STR = ST-segment resolution.



patients with MBG 3 and STR >70%, whereas no additional effect of short DBT intervals was found in patients with SBT >2 h. This assessment is consistent with our prior analysis among patients in the HORIZONS-AMI and CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) trials (17). Among those who presented after 90 min of symptom onset (representing the vast majority of STEMI patients), a short (≤ 90 min) DBT, compared with a longer DBT, had no significant effect on 1-year mortality. In contrast, among patients with early time to presentation (≤ 90 min), a short DBT (≤ 90 min) was associated with significantly lower 1-year mortality.

Although microvascular injury may be a surrogate for a larger infarct size, several studies have reported an independent prognostic value of indexes of myocardial perfusion (18,19). We have previously demonstrated that both MBG and STR strongly correlate with survival and that assessment of both yields incremental prognostic information beyond either measure alone (20). In the present study, 3-year mortality was significantly higher among patients with MBG 0/1 and STR <30% (Online Figure 2), with MBG as an independent predictor, which highlights the adverse clinical effect of a closed microcirculation in STEMI patients. There are likely several mechanisms by which a longer duration of



ischemia leads to impaired myocardial perfusion. These include distal macroembolization or microembolization of thrombus, which becomes increasingly organized with time and less responsive to anticoagulant and antiplatelet therapies; local formation of thrombus within the microcirculation; and increased cellular and interstitial edema and hemorrhage (21,22). It remains to be established whether these mechanisms are modifiable and whether microvascular injury can be prevented or reversed.

Currently, there are limited therapeutic options that specifically reduce microvascular injury. The recent results of the TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) and TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) trials (23,24) investigating adjunctive aspiration thrombectomy have been disappointing and have not confirmed previous reports (3). A strategy to reduce risk of embolization, such as deferring stent placement in a 2-staged procedure has shown benefit in the small proof of concept DEFER-STEMI (A Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction) trial (25) while the routine use of distal protection by a filterwire system during primary PCI (26), seemed not to improve microvascular perfusion, infarct size, or prognosis. One might speculate that microvascular injury by embolization may be a reason why some pharmacological strategies for preventing reperfusion injury have been ineffective, because a closed microcirculation would preclude delivery of any potential therapeutic agent to the target site (21). On the contrary, several randomized trials investigating pharmacological conditioning have reported promising results, such as the periprocedural regimens with exenatide (27) or cyclosporine infusion (28). Intracoronary culprit lesion site delivery of abciximab has also recently shown promise in reducing infarct size (29). A better understanding of the role of microvascular injury following STEMI is warranted to develop novel therapies, and large randomized trials such as the DANAMI-3 (Danish Study of Optimal Acute Treatment of Patients with ST-elevation Myocardial Infarction) (NCT01435408) are ongoing. Subgroup analysis in late presenters in these trials would provide valuable insight into pathophysiology and therapeutic options.

STUDY LIMITATIONS. Our retrospective analysis is subject to both recognized and unknown biases. The observational design of the study allows us to report an association between time to treatment and the extent of impairment in myocardial perfusion, but we

cannot establish a causal relationship. STR and MBG were the only markers of myocardial perfusion examined in the present study. Other imaging modalities of microcirculatory function such as contrast echocardiography, positron emission tomographic scanning, and invasive measures of coronary flow reserve (Doppler wire) may provide additional insights regarding the effect of treatment delay on microcirculatory function in patients with STEMI. We attempted to statistically adjust for the many difference in the baseline clinical characteristics in patients with longer SBT compared with those with a shorter duration of ischemia; however, we cannot exclude the possibility that measured or unmeasured confounders may have been responsible for the observed relationship between longer SBT or DBT and impaired myocardial perfusion.

CONCLUSIONS

The present study suggests that delay in mechanical reperfusion therapy during STEMI is associated with greater injury to the microcirculation. This relationship appears more robust for the ischemia duration (SBT) than for DBT. In early presenters, reducing DBT may have a beneficial effect on myocardial perfusion; however, in patients with symptom duration >120 min, the present findings of no additional benefit of DBT reduction on myocardial perfusion, as well as our prior report that DBT in patients with SBT >90 min has little effect on mortality (17), are in line with data suggesting that decrease in median DBT in recent years has not resulted in a reduction in mortality in STEMI patients (30,31). This highlights the need to reconsider the role of DBT as a performance metric and examine the utility of a broader metric of systems delay such as first medical contact to balloon time (32) as well as total ischemic time. The latter requires clinical trials focused on pre-hospital treatment strategies, and perhaps revisiting public education initiatives. Finally, recognizing that DBT appears to have an insignificant effect on outcomes in patients with SBT >90 min may improve care by allowing physicians, in appropriate circumstances, to focus on a more comprehensive clinical evaluation to ensure diagnostic accuracy and assess key issues such as comorbidities, bleeding risk, and appropriateness of prolonged dual antiplatelet therapy.

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PERSPECTIVES

WHAT IS KNOWN? The goal of reperfusion therapy in STEMI is to restore tissue perfusion, but this is not achieved in approximately one-third of cases. Microvascular injury is the major cause of this and is an important determinant of prognosis; thus, understanding the pathophysiology of microvascular dysfunction in STEMI may help in developing novel treatment approaches.

WHAT IS NEW? In contemporary practice of primary PCI, delay in reperfusion therapy, measured as the time from symptom onset to mechanical reperfusion therapy,

is associated with greater microvascular injury. DBT, a performance metric for STEMI, is also a determinant but to a lesser extent.

WHAT IS NEXT? Continued efforts are required to investigate treatment strategies aimed at preventing microvascular injury in STEMI to determine if that improves outcomes. This has proven to be an elusive goal to date; moreover, there is a need to reconsider the current focus on DBT as the primary quality metric and examine the utility of broader time metrics such as first medical contact to balloon time and total ischemic time.

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KEY WORDS ischemia duration, myocardial infarction, PCI, perfusion, STEMI

APPENDIX For supplemental figures, please see the online version of this article.