Infarct Size, Shock, and Heart Failure: Does Reperfusion Strategy Matter in Early Presenting Patients With ST-Segment Elevation Myocardial Infarction?

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Background—A pharmacoinvasive (PI) strategy for early presenting ST-segment elevation myocardial infarction nominally reduced 30-day cardiogenic shock and congestive heart failure compared with primary percutaneous coronary intervention (PPCI). We evaluated whether infarct size (IS) was related to this finding.

Methods and Results—Using the peak cardiac biomarker in patients randomized to PI versus PPCI within the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial, IS was divided into 3 groups: small (≤2 times the upper limit normal [ULN]), medium (>2 to ≤5 times the upper limit normal) and large (>5 times the upper limit normal). The association between IS and 30-day shock and congestive heart failure was subsequently examined. Data on 1701 of 1892 (89.9%) patients randomized to PI (n=853, 50.1%) versus PPCI (n=848, 49.9%) within STREAM were evaluated. A higher proportion of PPCI patients had a large IS (PI versus PPCI: small, 49.8% versus 50.2%; medium, 56.9% versus 43.1%; large, 48.4% versus 51.6%; P=0.035), despite comparable intergroup ischemic times for each reperfusion strategy. As IS increased, a parallel increment in shock and congestive heart failure occurred in both treatment arms, except for the small IS group. The difference in shock and congestive heart failure in the small IS group (4.4% versus 11.6%, P=0.026) in favor of PI likely relates to higher rates of aborted myocardial infarction with the PI strategy (72.7% versus 54.3%, P=0.005). After adjustment, a trend favoring PI persisted in this subgroup (relative risk 0.40, 95% CI 0.15 to 1.06, P=0.064; no difference in treatment-related outcomes was evident in the other 2 groups.

Conclusion—A PI strategy appears to alter the pattern of IS after ST-segment elevation myocardial infarction, resulting in more medium and fewer large infarcts compared with PPCI. Despite a comparable number of small infarcts, PI patients in this group had more aborted myocardial infarctions and less 30-day shock and congestive heart failure.

Clinical Trial Registration—URL: http://ClinicalTrials.gov. Unique identifier: NCT00623623. (J Am Heart Assoc. 2015;4:e002049 doi: 10.1161/JAHA.115.002049)

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With the emergence of prehospital care for ST-segment elevation myocardial infarction (STEMI), contemporary STEMI practice has witnessed a significant decrement in times from symptom onset to first medical contact, leading to more timely access to reperfusion therapy. Nonetheless, a multitude of logistical factors, including initial presentation at facilities not capable of performing percutaneous coronary intervention (PCI), continue to delay the delivery of timely, guideline-recommended primary PCI (PPCI) to these patients. The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial enrolled STEMI patients who presented within 3 hours of symptom onset and unable to undergo PPCI within...
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published previously.7 In brief, acute STEMI patients who presented within 3 hours of symptom onset and who were unable to undergo PPCI within 1 hour of fi rst medical contact and randomized them to a pharmacoinvasive (PI) or PPCI strategy.

Although no signifi cant difference in the primary composite endpoint of 30-day death, cardiogenic shock (henceforth described as shock), congestive heart failure (CHF), or reinfarction was noted between the 2 reperfusion modalities, a signal indicated that less shock and CHF emerged in patients assigned to a PI strategy.2 In fact, when these 2 prespecified single endpoints were jointly analyzed retrospectively, a signifi cant reduction in the composite of shock/CHF with the PI strategy was observed.5 This fi nding was aligned with prior reports of prehospital fibrinolysis in trials comparing pharmacologic and mechanical reperfusion modalities.4,6 Because a difference in infarct size (IS) is a plausible hypothesis to explain these clinical fi ndings, we evaluated whether a relationship existed between randomized treatment and IS and, secondly between IS and the 30-day composite of shock/CHF.

Methods

The STREAM trial was an open-label, prospective, randomized, parallel-group, multicenter trial, the design of which has been published previously.7 In brief, acute STEMI patients who presented within 3 hours of symptom onset and who were unable to undergo PPCI within 1 hour of fi rst medical contact were randomized to either fibrinolysis with a protocol-defl ned PI strategy or PPCI. In the PI strategy, bolus weight-based tenecteplase, aspirin, clopidogrel, and enoxaparin were administered according to guideline recommendations and followed by either rescue PCI or scheduled angiography (within 6 to 24 hours). The need for rescue PCI was determined by site investigators according to <50% ST-segment resolution in the ECG lead, with the maximal ST-segment elevation 90 minutes after tenecteplase bolus, hemodynamic instability, or refractory ventricular arrhythmias, as mandated by the study protocol. PPCI was conducted after expeditious transfer from the point of randomization and early initiation of aspirin, clopidogrel, and antithrombotic therapy including discretionary glycoprotein IIb/IIIa antagonists based on best standard practice. The study protocol was approved by national regulatory authorities and by the local ethics committee at each study center. All patients provided written informed consent.

We analyzed data available on IS and 30-day shock/CHF (primary endpoint for the current study) in 1701 of 1892 (89.9%) patients enrolled in STREAM. Shock and CHF were defned by protocol and assessed by participating investigators.2

The following time delays were defned for analysis: (1) presentation delay (symptom onset to randomization; pre-specifi ed cut point at 2 hours) and (2) total ischemic time (symptom onset to assigned treatment delivery).

Infarct Size Estimation

Cardiac biomarkers were collected at baseline, 8 to 12 and 24±4 hours after randomization. Using peak biomarkers (selected in the following order: creatinine kinase-MB isoenzyme, creatinine kinase if CK-MB was not available), we recategorized patients into 3 groups according to IS: small infarct (<2 times the upper limit of normal), medium infarct (>2 and ≤5 times the upper limit of normal), and large infarct (>5 times the upper limit of normal). Small infarcts also conformed to the biomarker defnition of an aborted myocardial infarction (MI; a prespecifi ed endpoint in STREAM).8

Patients with minimal or no rise in cardiac biomarkers and without evolutionary changes between their qualifying and discharge ECGs were classifi ed as infarct masquerade and excluded from the analysis (n=45), as reported previously.8

The Sylvester 54-criteria/32-point QRS scoring system,9 a validated ECG estimate of IS, was also measured at the time of hospital discharge. All ECGs were evaluated at the Canadian VIGOUR Centre ECG core laboratory in Edmonton, Canada, and each discharge ECG was manually scored according to the QRS scoring system. Each point in this system represents ≈3% of the left ventricle, and patients were categorized in 3 groups as QRS score ≤3 (small infarct, <10% myocardium), 4 to 7 (medium infarct, 10% to 20% myocardium), and ≥8 (large infarct, >20% myocardium), as described previously.10 Data on QRS infarct score and outcome were available for 1273 of 1701 (74.8%) patients.

Statistical Analysis

Discrete variables were reported as percentages, and continuous variables were summarized as medians with 25th and 75th percentiles. Group differences were tested using the chi-square test or the Fisher exact test for discrete variables and Wilcoxon rank-sum or Kruskal–Wallis tests for continuous variables. The analysis was based on the intention-to-treat principle.

The association between IS and the composite of shock/CHF at 30 days was examined using a Poisson regression model with robust error variance. The interaction between IS and study treatment at the 30-day composite endpoint of shock/CHF was also examined. Relative risk with 95% CIs and P values were reported. These relationships were adjusted using the Thrombolysis in Myocardial Infarction (TIMI) risk score to account for imbalances in baseline patient characteristics.11 A subgroup analysis was performed to stratify this relationship according to time from symptom onset to randomization within 2 hours and beyond 2 hours. The above analysis was repeated in the cohort of patients with valid discharge QRS score.
All statistical tests were 2-sided, and \( P<0.05 \) was considered statistically significant. Statistical analyses were performed using SAS version 9.3 (SAS Institute).

**Results**

In Figure 1, the distribution of the current study cohort is shown. Patients were categorized according to biomarker-determined IS and then by treatment assignment. Those patients with available QRS infarct score at discharge and derived from this initial cohort are shown in the bottom panel.

**Patient Characteristics**

In Table 1, the baseline patient characteristics are similarly categorized. Age and sex were comparable across the 3 groups, as was the distribution of selected traditional cardiovascular risk factors. At baseline, the incidence of prior CHF was low, and within the small IS subgroup treated with PPCI, a slightly lower proportion of prior CHF was evident. A trend toward fewer patients with TIMI risk score \( \geq 5 \) was noted in the large infarct group compared with the other groups. The patients with large IS had greater cumulative baseline ST-segment elevation, ST-segment deviation and more frequent Q waves on their baseline ECG.

Whereas the distribution of patients from the small infarct group stratified by treatment was comparable, there were more PI patients within the medium infarct group and fewer PI patients within the large infarct group (PI versus PPCI: small, 49.8\% versus 50.2\%; medium, 56.9\% versus 43.1\%; large, 48.4\% versus 51.6\%; \( P=0.035 \) for different patient distribution across the 3 groups) compared with the PPCI strategy. It is also noteworthy that there was a higher frequency of aborted MI with the PI versus PPCI strategy (72.7\% versus 54.3\%, \( P=0.005 \)) in the small infarct group.

Figure 1. Selection of the study cohort by infarct size, based on peak biomarker and discharge QRS score. CK indicates creatinine kinase; CK-MB, creatinine kinase-MB isoenzyme; DC, discharged; PI, pharmacoinvasive; PPCI, primary percutaneous coronary intervention; pts, patients; ULN, upper limit normal.
As illustrated in Figure 2, the median times from symptom onset to randomization and from symptom onset to administration of tenecteplase were comparable across the 3 IS groups. A trend toward decrements in time to PPCI was noted with increasing IS (90, 79, and 75 minutes, respectively; \( P = 0.145 \)).

Assessment of the posttreatment ECG revealed less resolution of both ST-segment deviation and elevation in large infarcts and a higher frequency of residual (\( \geq 2 \) mm) ST-segment elevation. For those patients with QRS scores available at hospital discharge, a higher median QRS score was observed for large versus medium and small infarcts.

**Angiographic and ECG Findings**

In Table 2, angiographic characteristics across the IS groups are shown according to treatment strategies. The need for rescue angiography in patients assigned to a PI strategy was comparable for the small and medium infarct groups but \( \approx 2 \)-fold greater for the large infarct group. The great majority of these patients underwent subsequent rescue PCI. Baseline pre-PCI TIMI 3 flow in the PPCI strategy was lower in large infarcts compared with medium and small infarcts but was comparable after PCI. This finding was also evident in PI patients. The proportion of angiographically normal coronaries in the aborted MI population was very low, with 1 patient in each treatment strategy.

**Association With 30-Day Shock/CHF**

Large IS was associated with higher risk of shock and CHF at 30 days compared with small IS (11.8% versus 8.0%, relative risk 1.66, 95% CI 1.07 to 2.58, \( P = 0.024 \) after adjustment), whereas medium IS showed risk similar to that of patients with small infarct (6.7% versus 8.0%, relative risk 0.84, 95% CI 0.47 to 1.52, \( P = 0.568 \) after adjustment).

The relationship between treatment strategy and the 30-day rates of the composite of shock/CHF stratified by biomarkers IS is illustrated in Figure 3. Note in the upper panel that the incidence of shock/CHF increased with corresponding increases in IS for PI patients, but this relationship was less

### Table 1. Selected Baseline Characteristics According to Infarct Size and Treatment

|                  | ≤2 × ULN | >2 to ≤5 × ULN | >5 × ULN |
|------------------|---------|----------------|---------|
|                  | All     | PI PPCI        | All     | PI PPCI        | All     | PI PPCI        |
| n                | 277     | 138            | 139     | 297            | 169     | 128            | 1127    | 546            | 581     |
| Age, y           | 60 (52 to 70) | 60 (52 to 69) | 61 (53 to 72) | 60 (52 to 70) | 60 (52 to 70) | 59 (52 to 70) | 59 (50 to 68) | 59 (50 to 68) | 59 (51 to 67) |
| Female sex, %    | 24.2    | 24.6           | 23.7    | 24.6           | 24.3    | 25.0           | 19.3    | 18.1           | 20.5    |
| Hypertension, %  | 48.2    | 43.7           | 52.6    | 48.0           | 50.6    | 44.5           | 44.7    | 47.0           | 42.5    |
| Diabetes, %      | 14.9    | 12.3           | 17.4    | 15.0           | 12.0    | 19.0           | 11.4    | 11.9           | 11.0    |
| Previous MI, %   | 14.4    | 12.3           | 16.5    | 11.4           | 13.6    | 8.6            | 7.3     | 5.3            | 9.1     |
| Prior PCI, %     | 11.6    | 6.5            | 16.5    | 8.4            | 8.9     | 7.9            | 6.1     | 5.1            | 6.9     |
| Prior CHF, %     | 1.1     | 1.5            | 0.7     | 1.4            | 0.0     | 3.1            | 0.8     | 0.2            | 1.4     |
| Heart rate, bpm  | 75 (64 to 85) | 73 (62 to 80) | 75 (64 to 90) | 74 (60 to 83) | 73 (60 to 83) | 75 (64 to 84) | 75 (62 to 86) | 75 (61 to 88) | 75 (63 to 85) |
| Systolic blood pressure, mm Hg | 138 (120 to 160) | 138 (120 to 157) | 139 (120 to 160) | 136 (120 to 150) | 132 (120 to 150) | 140 (120 to 160) | 135 (120 to 150) | 134 (120 to 150) | 135 (120 to 150) |
| Killip class >4, % | 8.9     | 7.5            | 10.3    | 4.3            | 3.8     | 5.0            | 5.3     | 6.4            | 4.2     |
| TIMI risk score ≥5, % | 17.2    | 12.3           | 22.0    | 16.4           | 16.0    | 16.8           | 11.4    | 12.5           | 10.4    |
| Inferior MI*, %  | 45.1    | 42.8           | 47.4    | 57.3           | 59.3    | 54.7           | 49.9    | 48.9           | 50.8    |
| Baseline \( \Sigma \) ST-segment elevation, mm | 7 (4 to 12) | 8 (5 to 12) | 6 (3 to 11) | 7 (5 to 11) | 7 (4 to 10) | 7 (5 to 11) | 10 (6 to 15) | 10 (7 to 16) | 10 (6 to 15) |
| Baseline \( \Sigma \) ST-segment deviation, mm | 11 (7 to 17) | 11 (8 to 18) | 11 (7 to 17) | 12 (8 to 16) | 12 (8 to 16) | 12 (9 to 16) | 16 (11 to 22) | 16 (11 to 22) | 15 (11 to 22) |
| Q waves in the infarct territory at baseline*, % | 24.0    | 22.5           | 25.5    | 27.1           | 28.7    | 25.0           | 34.9    | 35.6           | 34.2    |

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*bpm indicates beats per minute; CHF, congestive heart failure; MI, myocardial infarction; PI, pharmacoinvasive; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ULN, upper limit normal.

*Evaluated by the core ECG laboratory. Continuous variables presented as median (25th to 75th percentiles).
evident for PPCI patients. There was an absolute reduction in shock/CHF in patients with small infarcts (4.4% versus 11.6% \( P = 0.026 \)) favoring the PI strategy. A trend favoring PI persisted after adjusting for TIMI risk score in this subgroup (relative risk 0.40, 95% CI 0.15 to 1.06, \( P = 0.064 \)); however, no difference in treatment-related outcomes was evident in the other 2 IS groups, and there was no significant interaction between treatment and outcomes by IS (\( P = 0.173 \)).

In patients randomized within 2 hours of symptom onset (Figure 3, lower panel), those patients with small infarcts randomized to PI tended to have less 30-day shock/CHF than the PPCI group (adjusted relative risk 0.23, 95% CI 0.05 to 1.02, \( P \) for interaction=0.067). If randomization was delayed beyond 2 hours of symptom onset, no association between IS and treatment was observed (\( P \) for interaction=0.923).

In Figure 4, the relationship between treatment strategy and discharge IS assessed by QRS score is shown. As IS increased, clinical outcomes worsened. Similar to IS based on biomarkers, patients with small QRS-defined infarcts and randomized to PI tended to have lower risk of 30-day shock/CHF compared with PPCI patients. Again, with increasing IS, outcomes worsened progressively for PI patients, but this was observed only with the large infarcts for PPCI patients. No significant interaction between treatment and outcomes by IS was observed (\( P \) for interaction=0.107).

**Discussion**

Our study of 2 reperfusion strategies and their relationship to IS and 30-day shock/CHF demonstrated 2 key, novel findings. First, the administration of a PI strategy led to a trend of lower adjusted 30-day shock/CHF in patients with small IS. Our adjustment procedure incorporated the factors composing the TIMI risk score, many of which would suggest a worse clinical outcome in the small infarct group. This advantage favoring the PI strategy in the small IS group was driven largely by the increased frequency of aborted MIs associated with this reperfusion strategy. No difference in shock/CHF was seen in patients with medium or large infarcts, regardless of the reperfusion strategy. Second, the PI strategy was associated with an increased frequency of medium-sized infarcts and a lower frequency of large infarcts compared with PPCI. This occurred in the context of comparable times from symptom onset to treatment across the 3 IS groups, regardless of treatment strategy. A trend toward shorter time to PPCI in the large IS group may have been modulated by clinical urgency. Not surprisingly, PI patients requiring rescue PCI had the largest infarcts. We also noted a consistent relationship between reduced pre-PCI TIMI 3 epicardial flow and larger infarcts, regardless of treatment strategy. Although the post-PCI TIMI 3 flows were comparable across groups, this was not the case for the extent of ST-segment resolution, which was consistently less in the large infarct group compared with the small and medium cohorts. Coupled with the finding of a greater proportion of patients with residual ST-segment elevation in the large infarct group, these data are supportive of more impairment of microvascular flow and are consistent with prior observations. The trend toward lower incidence of 30-day shock/CHF in STREAM in favor of fibrinolysis over PPCI is reminiscent of similar findings observed in the Comparison
Table 2. Angiographic and Posttreatment ECG According to Infarct Size and Treatment

| Infarct Size and Treatment | ≤2 × ULN | >2 to ≤5 × ULN | >5 × ULN |
|----------------------------|---------|---------------|---------|
|                            | All     | PI            | PPCI    | All     | PI            | PPCI    | All     | PI            | PPCI    |
| n                          | 277     | 138           | 139     | 297     | 169           | 128     | 1127    | 546           | 581     |
| Rescue angiogram, %        | —       | 21.9          | —       | —       | 27.2          | —       | —       | 50.2          | —       |
| No. undergoing rescue angiogram (n) | 30       | —             | —       | 46      | —             | —       | 272     | —             | —       |
| Rescue angioplasty, %      | —       | 80.0          | —       | —       | 80.4          | —       | —       | 91.2          | —       |
| Multivessel disease, %     | 48.0    | 48.4          | 47.5    | 48.4    | 54.8          | 40.0    | 45.4    | 44.3          | 46.6    |
| Baseline angiogram TIMI grade, % |         |               |         |         |               |         |         |               |         |
| 0/1                        | 30.0    | 17.1          | 43.0    | 33.3    | 18.0          | 53.3    | 56.8    | 31.5          | 80.4    |
| 2                          | 13.2    | 14.7          | 11.7    | 15.6    | 18.0          | 12.5    | 11.7    | 15.0          | 8.6     |
| 3                          | 56.8    | 68.2          | 45.3    | 51.1    | 64.1          | 34.2    | 31.5    | 53.6          | 11.1    |
| PCI, %                     | 75.6    | 70.7          | 80.5    | 81.0    | 74.2          | 89.7    | 91.2    | 87.2          | 95.0    |
| No. of patients receiving PCI, n | 201     | 94            | 107     | 234     | 121           | 113     | 1015    | 469           | 546     |
| Stent placement during PCI, % | 95.5    | 95.7          | 95.3    | 95.0    | 95.6          | 96.2    | 96.4    | 96.0          |         |
| Post-PCI TIMI Grade, %     |         |               |         |         |               |         |         |               |         |
| 0/1                        | 4.6     | 5.4           | 3.8     | 2.2     | 1.7           | 2.7     | 2.6     | 2.8           | 2.4     |
| 2                          | 2.5     | 2.2           | 2.9     | 1.3     | 1.7           | 0.9     | 4.7     | 5.3           | 4.3     |
| 3                          | 92.9    | 92.4          | 93.3    | 96.5    | 96.5          | 96.4    | 92.6    | 91.9          | 93.3    |
| CABG, %                    | 4.3     | 6.5           | 2.2     | 4.0     | 4.7           | 3.1     | 2.8     | 4.0           | 1.7     |
| Posttreatment ECG          |         |               |         |         |               |         |         |               |         |
| ST-segment deviation resolution, % | 73 (43 to 92) | 71 (45 to 92) | 74 (42 to 94) | 73 (45 to 90) | 71 (41 to 88) | 74 (54 to 90) | 63 (33 to 83) | 55 (14 to 78) | 68 (46 to 86) |
| ST-segment deviation resolution ≥50%, % | 71.4 | 73.1          | 69.6    | 72.8    | 68.5          | 78.5    | 63.9    | 55.4          | 71.7    |
| Worst-lead ST-segment elevation resolution, % | 83 (57 to 100) | 83 (57 to 100) | 82 (57 to 100) | 80 (50 to 100) | 80 (50 to 100) | 80 (53 to 100) | 67 (40 to 88) | 60 (25 to 83) | 75 (50 to 93) |
| Worst-lead ST-segment elevation resolution ≥50%, % | 85.1 | 85.3          | 84.9    | 79.8    | 77.0          | 83.5    | 72.6    | 62.6          | 81.8    |
| Worst-lead residual ST-segment elevation, % |         |               |         |         |               |         |         |               |         |
| <1 mm                      | 55.8    | 61.0          | 50.8    | 53.4    | 59.0          | 46.3    | 36.7    | 41.7          | 32.4    |
| 1 to <2 mm                 | 34.9    | 30.9          | 38.9    | 33.9    | 33.3          | 34.7    | 38.0    | 37.1          | 38.8    |
| ≥2 mm                      | 9.2     | 8.1           | 10.3    | 12.6    | 7.7           | 19.0    | 25.3    | 21.3          | 28.9    |
| QRS score at discharge     | 3 (1 to 6) | 3 (1 to 6) | 3 (1 to 6) | 3 (2 to 6) | 4 (2 to 6) | 3 (2 to 5) | 6 (3 to 8) | 6 (3 to 8) | 6 (4 to 9) |
| [valid n]                  | [207]   | [102]         | [105]   | [248]   | [139]         | [109]   | [818]   | [398]         | [420]   |

Continuous variables presented as median (25th to 75th percentiles). CABG indicates coronary artery bypass grafting; PI, pharmacoinvasive; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; ULN, upper limit normal.
of Primary Angioplasty and Prehospital Fibrinolysis in Acute Myocardial Infarction (CAPTIM) and Which Early ST-Elevation Myocardial Infarction Therapy (WEST) trials. Interestingly, this study not only reaffirms the findings of CAPTIM and WEST in a much earlier treated STEMI population but also identifies a subgroup for which the benefit of a PI strategy is likely to accrue the most benefit, namely, those with smaller infarcts. This suggests—as shown in patients with medium and large infarcts assigned to either reperfusion strategy—that once a critical myocardial IS unfolds, no difference in shock/CHF occurs, regardless of treatment strategy. Furthermore, the clinical benefit favoring the PI strategy for small IS is most pronounced if ischemic time is less than the presuperscribed period of 2 hours. This 2-hour threshold during which the administration of fibrinolysis confers a favorable outcome advantage over PPCI is consistent with that observed in the combined CAPTIM-WEST analysis and reaffirms the implications of timely reperfusion according to current STEMI guidelines. In our study, the median times from symptom onset to administration of fibrinolysis are strikingly shorter, whereas times from symptom onset to delivery of PPCI remain comparable to CAPTIM-WEST. In addition, we found fairly comparable times from symptom onset to randomization and treatment across all 3 IS groups for either treatment strategy. This reflects the significant gains made in prehospital delivery of acute coronary syndrome care and, in combination with contemporary antithrombotic agents, probably accounts for the significant difference in aborted MIs in favor of the PI strategy. The concept of an aborted MI (a prespecified endpoint in STREAM) in patients with STEMI and its translation to improved clinical outcomes in patients assigned either to fibrinolysis or PPCI were reported previously. In the STREAM trial, a significantly higher proportion of aborted MIs was noted in association with the PI

**Figure 3.** Relative risk plot of the 30-day composite endpoint of shock/CHF. Upper panel: infarct size groups and 30-day shock/CHF by treatment strategy. Lower panel: infarct size groups and 30-day shock/CHF by treatment strategy and pre-specified 2-hour time from symptom onset to treatment randomization cut-off. *Adjusted for thrombolysis in myocardial infarction risk score. CHF indicates congestive heart failure; PI, pharmacoinvasive; PPCI, primary percutaneous coronary intervention; ULN, upper limit normal.

| Infarct Size | PI (n=853) | PPCI (n=848) | Relative Risk* (95%CI) |
|--------------|------------|-------------|------------------------|
| ≤2xULN       | 6/138 (4.4)| 16/138 (11.6)| 0.40 (0.15 to 1.06)    |
| >2 to ≤5xULN | 12/169 (7.1)| 8/128 (6.3)  | 1.27 (0.53 to 3.05)    |
| >5xULN       | 62/542 (11.4)| 70/578 (12.1)| 0.88 (0.64 to 1.21)    |

| Time to randomization | PI (n=591) | PPCI (n=571) | Relative Risk* (95%CI) |
|-----------------------|------------|-------------|------------------------|
| <2 hours              |            |             |                        |
| ≤2xULN                | 2/98 (2.0)| 10/87 (11.5)| 0.23 (0.05 to 1.02)    |
| >2 to ≤5xULN          | 6/111 (5.4)| 2/84 (2.4)  | 2.25 (0.45 to 11.28)   |
| >5xULN                | 45/379 (11.9)| 51/398 (12.8)| 0.80 (0.55 to 1.16)    |

| Time to randomization | PI (n=262) | PPCI (n=277) | Relative Risk* (95%CI) |
|-----------------------|------------|-------------|------------------------|
| ≥2 hours              |            |             |                        |
| ≤2xULN                | 4/40 (10.0)| 6/51 (11.8)  | 0.75 (0.20 to 2.78)    |
| >2 to ≤5xULN          | 6/58 (10.3)| 6/44 (13.6)  | 0.82 (0.31 to 2.19)    |
| >5xULN                | 17/163 (10.4)| 19/180 (10.6)| 1.12 (0.60 to 2.08)    |

| 0.0 | 1.0 | 2.0 | 3.0 |
|-----|-----|-----|-----|
| PI better | PPCI better |
strategy and translated into favorable outcomes in comparison to nonaborted infarcts.\(^8\)

The present data also highlight the prognostic utility of previously established, relatively simple 12-lead ECG metrics in relation to patient outcomes in STEMI. In our study, myocardial IS estimated by increasing QRS score correlated with increasing incidence of shock/CHF, regardless of treatment strategy. Again, similar to the biomarker data described, the PI strategy resulted in a trend to lower shock/CHF in patients with a low QRS score (≤3); this advantage over PPCI was once again attenuated by higher QRS scores and after adjusting for the TIMI risk score. The prognostic utility of QRS score for outcomes in STEMI has been well documented. In a large PPCI cohort, Tjandrawidjaja et al\(^10\) showed adverse outcomes (all-cause death, CHF, and shock) in patients with higher QRS scores (>4). In a STEMI cohort, Kalogeropoulos et al\(^15\) also showed the prognostic utility of lower QRS scores (<3) for lower incidence of heart failure after discharge. The utilization of worse lead residual ST-segment elevation, another previously established prognostic ECG metric,\(^12,14,17\) corresponded with biomarker-based evaluation of IS in the current study.

The current study has some limitations. We used 3 time points for biomarker measurements and may have missed the peak biomarker due to the rapid washout associated with reperfusion. Nonetheless, a strong correlation between the peak creatinine kinase-MB isoenzyme or creatinine kinase and area under the biomarker curves for IS determination has been documented previously for both reperfusion strategies.\(^18,19\) Use of an imaging modality might have provided a superior estimation of IS; however, overall propensity for worsening outcomes with larger infarcts and the independent QRS assessment of IS in a smaller number of patients later in their clinical course are supportive of the biomarker data. Our sample size, when categorized into biomarker groups, was modest, likely accounting for some of the trends we observed; therefore, larger confirmatory numbers would be required to be more definitive.

In summary, in this study evaluating the association between IS and 30-day shock/CHF for 2 treatment strategies, the PI strategy was associated with a trend of lower shock/CHF in the group of patients with small IS, and no difference in 30-day shock/CHF existed for patients with medium or large infarcts assigned to either reperfusion strategy. Overall, the incidence of shock and heart failure rose as IS increased.

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Shavadia has no conflicts to declare; Zheng has no conflicts to declare; Huber discloses lecture fees from Boehringer Ingelheim; Halvorsen discloses lecture fees from Boehringer Ingelheim; Goldstein discloses speakers bureau support from AstraZeneca and Bayer; honoraria from Sanofi, Boehringer Ingelheim, Eli Lilly and Medicines Company; Gershlick discloses grant support and honoraria from Boehringer Ingelheim and advisory board honoraria from AstraZeneca and Daichii Sankyo; Wilcox has no conflicts to declare; Van de Werf discloses research grant, other support from Boehringer Ingelheim; and Armstrong discloses grant support and honoraria from Boehringer Ingelheim. Dr Armstrong’s financial activities outside the submitted work are posted and routinely updated through http://www.vigour.ualberta.ca/About/RelationshipsWithIndustry.aspx.

References
1. Armstrong PW, Boden WE. Reperfusion paradox in ST-segment elevation myocardial infarction. Am Intern Med. 2011;155:399–391.
2. Armstrong PW, Gershlick AH, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Roselli-Ortiz F, Ostojic M, Welsh RC, Carvalho AC, Nanas J, Arntz HR, Halvorsen S, Huber K, Grajek S, Fresco C, Bluhmki E, Regelin A, Vandenberghe K, Bogaerts K, Van de Werf F. STREAM Investigative Team. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. N Engl J Med. 2013;368:1379–1387.
3. Giovannattista R. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction [comment to Editor]. N Engl J Med. 2013;368:1379–1387.
4. Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, Cattan S, Boulleenger E, Machecourt J, Lacroute JM, Cassagnes J, Dissait F, Touboul P. Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction study group. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. Lancet. 2002;360:825–829.
5. Buller CE, Welsh RC, Westerhout CM, Webb JG, O’Neill B, Gallo R, Armstrong PW. The influence of time from symptom onset and reperfusion strategy on 1-year survival in ST-elevation myocardial infarction: a pooled analysis of an early fibrinolytic strategy versus primary percutaneous coronary intervention from CAPTIM and WEST. Am Heart J. 2011;161:283–290.
6. Westerhout CM, Bonnefoy E, Welsh RC, Steg PG, Bouttie F, Armstrong PW. Prognostic utility of TIMI flow grades, and ST-segment resolution on infarct size and infarct transmurality as assessed by delayed enhanced magnetic resonance imaging. Eur Heart J. 2007;28:1433–1439.