



# STREAM-2: Half-Dose Tenecteplase or Primary Percutaneous Coronary Intervention in Older Patients With ST-Segment–Elevation Myocardial Infarction: A Randomized, Open-Label Trial

Frans Van de Werf<sup>1</sup>, MD, PhD; Arsen D. Ristić, MD, PhD; Oleg V. Averkov<sup>2</sup>, MD, PhD; Alexandra Arias-Mendoza<sup>3</sup>, MD; Yves Lambert, MD; José F. Kerr Saraiva<sup>4</sup>, MD, PhD; Pablo Sepulveda<sup>5</sup>, MD; Fernando Rosell-Ortiz<sup>6</sup>, MD, PhD; John K. French<sup>7</sup>, MBChB, PhD; Ljilja B. Musić, MD; Katleen Vandenberghe, PhD; Kris Bogaerts<sup>8</sup>, PhD; Cynthia M. Westerhout<sup>9</sup>, PhD; Alain Pagès, MD; Thierry Danays<sup>10</sup>, MD; Kevin R. Bainey<sup>11</sup>, MD; Peter Sinnaeve, MD, PhD; Patrick Goldstein, MD; Robert C. Welsh<sup>12</sup>, MD; Paul W. Armstrong<sup>13</sup>, MD; on behalf of the STREAM-2 Investigators

**BACKGROUND:** ST-segment–elevation myocardial infarction (STEMI) guidelines recommend pharmaco-invasive treatment if timely primary percutaneous coronary intervention (PCI) is unavailable. Full-dose tenecteplase is associated with an increased risk of intracranial hemorrhage in older patients. Whether pharmaco-invasive treatment with half-dose tenecteplase is effective and safe in older patients with STEMI is unknown.

**METHODS:** STREAM-2 (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction) was an investigator-initiated, open-label, randomized, multicenter study. Patients  $\geq 60$  years of age with  $\geq 2$  mm ST-segment elevation in 2 contiguous leads, unable to undergo primary PCI within 1 hour, were randomly assigned (2:1) to half-dose tenecteplase followed by coronary angiography and PCI (if indicated) 6 to 24 hours after randomization, or to primary PCI. Efficacy end points of primary interest were ST resolution and the 30-day composite of death, shock, heart failure, or reinfarction. Safety assessments included stroke and nonintracranial bleeding.

**RESULTS:** Patients were assigned to pharmaco-invasive treatment (n=401) or primary PCI (n=203). Median times from randomization to tenecteplase or sheath insertion were 10 and 81 minutes, respectively. After last angiography, 85.2% of patients undergoing pharmaco-invasive treatment and 78.4% of patients undergoing primary PCI had  $\geq 50\%$  resolution of ST-segment elevation; their residual median sums of ST deviations were 4.5 versus 5.5 mm, respectively. Thrombolysis In Myocardial Infarction flow grade 3 at last angiography was  $\approx 87\%$  in both groups. The composite clinical end point occurred in 12.8% (51/400) of patients undergoing pharmaco-invasive treatment and 13.3% (27/203) of patients undergoing primary PCI (relative risk, 0.96 [95% CI, 0.62–1.48]). Six intracranial hemorrhages occurred in the pharmaco-invasive arm (1.5%): 3 were protocol violations (excess anticoagulation in 2 and uncontrolled hypertension in 1). No intracranial bleeding occurred in the primary PCI arm. The incidence of major nonintracranial bleeding was low in both groups ( $<1.5\%$ ).

**CONCLUSIONS:** Halving the dose of tenecteplase in a pharmaco-invasive strategy in this early-presenting, older STEMI population was associated with electrocardiographic changes that were at least comparable to those after primary PCI. Similar clinical efficacy and angiographic end points occurred in both treatment groups. The risk of intracranial hemorrhage was higher with half-dose tenecteplase than with primary PCI. If timely PCI is unavailable, this pharmaco-invasive strategy is a reasonable alternative, provided that contraindications to fibrinolysis are observed and excess anticoagulation is avoided.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02777580.

**Key Words:** percutaneous coronary intervention ■ pharmaco-invasive therapy ■ reperfusion ■ ST-segment-elevation myocardial infarction ■ tenecteplase

Correspondence to: Frans Van de Werf, MD, PhD, Department of Cardiovascular Sciences at KU Leuven, Herestraat 49, B-3000 Leuven, Belgium. Email [frans.vandewerf@kuleuven.be](mailto:frans.vandewerf@kuleuven.be)  
This manuscript was sent to Cindy Grines, Guest Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material, the podcast, and transcript are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/CIRCULATIONAHA.123.064521>.

For Sources of Funding and Disclosures, see page 763.

© 2023 American Heart Association, Inc.

Circulation is available at [www.ahajournals.org/journal/circ](http://www.ahajournals.org/journal/circ)

## Clinical Perspective

### What Is New?

- This study demonstrates that in patients  $\geq 60$  years of age with ST-segment–elevation myocardial infarction, half-dose tenecteplase in a pharmaco-invasive strategy provides effective reperfusion based on of the resolution of ST deviations, angiographic results, and 30-day clinical outcomes.
- The rate of intracranial hemorrhage was higher than anticipated.

### What Are the Clinical Implications?

- If timely percutaneous coronary intervention is unavailable, the pharmaco-invasive strategy as used in this study is a reasonable alternative in older patients with ST-segment–elevation myocardial infarction.
- Contraindications to fibrinolysis such as uncontrolled hypertension must be observed and excess anticoagulation avoided to reduce the risk of intracranial hemorrhage.

Delays in achieving timely reperfusion with either fibrinolysis or primary percutaneous coronary intervention (PCI) are well recognized to be associated with excess death.<sup>1</sup> Contemporary ST-segment–elevation myocardial infarction (STEMI) guidelines indicate that primary PCI is recommended for reperfusion of STEMI when performed within 2 hours after first medical contact.<sup>2,3</sup> Because this goal is unattainable in the majority of patients who present to non-PCI-capable hospitals and the attendant delay results in increased mortality,<sup>4–7</sup> a pharmaco-invasive strategy is a recommended alternative. In the STREAM-1 study (Strategic Reperfusion Early After Myocardial Infarction), we found that in patients with STEMI presenting within 3 hours of symptom onset, unable to attain PCI within 1 hour of first medical contact, a pharmaco-invasive strategy resulted in similar rates of death, shock, heart failure, or reinfarction, compared with primary PCI.<sup>8</sup> An excess of intracranial hemorrhage (ICH) in patients  $\geq 75$  years of age in that study prompted an amendment that halved the dose of weight-adjusted bolus tenecteplase; no subsequent intracranial bleeding occurred in 97 patients so treated. A review of bleeding complications with full-dose tenecteplase and alteplase in the ASSENT (Assessment of the Safety of a New Thrombolytic) and STREAM-1 trials in nearly 24 000 patients revealed increasing rates of intracranial and major nonintracranial bleeding starting at  $\approx 60$  years of age.<sup>9–13</sup> Hence, in the current study, we explored whether half-dose tenecteplase is an effective

## Nonstandard Abbreviations and Acronyms

<b>ASSENT</b>	Assessment of the Safety of a New Thrombolytic
<b>ICH</b>	intracranial hemorrhage
<b>PCI</b>	percutaneous coronary intervention
<b>STEMI</b>	ST-segment–elevation myocardial infarction
<b>STREAM</b>	Strategic Reperfusion Early After Myocardial Infarction
<b>TIMI</b>	Thrombolysis In Myocardial Infarction

and safe pharmaco-invasive treatment in older patients with STEMI, presenting within 3 hours of symptom onset, and unable to undergo primary PCI within 1 hour. Standard primary PCI was the reference reperfusion treatment.

## METHODS

### Data Availability Statement

After 2 years have elapsed from the time of the publication, requests for STREAM-2 trial (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction) data will be considered by the executive committee provided that the data are requested in writing by qualified researchers with an outline of proposed objectives that address any potential conflicts of interest. Data sharing will be accompanied by an expectation that any outcomes will be shared with the STREAM-2 executive committee, which reserves the right to review any proposed publication of the work.

### Patients

The current study was an investigator-initiated, open-label, prospective, randomized, multicenter trial conducted in 49 centers in 10 countries. The final version of the full protocol (version 5) is available at <https://www.clinicaltrials.gov>. The list of committees and local investigators is provided as [Supplemental Material](#). The study was sponsored by the University of Leuven (KU Leuven), Belgium, and funded in part by Boehringer-Ingelheim, which had no role in the study design or data collection, analysis, and interpretation, but was given the opportunity to review the manuscript for medical and scientific accuracy. The trial was performed in accordance with the Declaration of Helsinki principles. The protocol was approved by national regulatory authorities and local ethics committees at each of the participating centers and has been published previously.<sup>9</sup>

Whereas the original protocol included patients  $\geq 70$  years of age, slow recruitment prompted an amendment to include patients  $\geq 60$  years of age, further informed by our previous analysis of excess bleeding starting around this age.<sup>9</sup> Hence, in the current study, patients  $\geq 60$  years of age, weighing  $\geq 55$  kg, and presenting within 3 hours after symptom onset with electrocardiographic evidence of STEMI (ST-segment elevation of at least 2 mm in 2 contiguous leads) were eligible for randomization if they were unable to undergo primary PCI within 1 hour

but before 3 hours after first medical contact. A list of inclusion and exclusion criteria is provided as [Supplemental Material](#). All patients provided informed consent.

### Randomization, Study Design, and Organization

Patients were randomly assigned (ratio 2:1) to either a pharmaco-invasive strategy or primary PCI by using an interactive voice response or web-based system. Patients assigned to prehospital pharmaco-invasive treatment in ambulances or at community hospitals received half-dose, weight-adjusted bolus tenecteplase (details provided as [Supplemental Material](#)), 150 to 325 mg of aspirin, 300 mg of clopidogrel, and 0.75 mg/kg of subcutaneous enoxaparin, and an additional intravenous dose of 30 mg in patients  $\leq 75$  years (after amendment). Depending on successful reperfusion 60 to 90 minutes after bolus tenecteplase, defined as  $\geq 50\%$  ST resolution in the ECG lead with maximum ST-segment elevation and clinical stability, coronary angiography was undertaken 6 to 24 hours after randomization. Rescue PCI was performed if failed reperfusion occurred on the basis of insufficient ST resolution or clinical instability. Patients randomly assigned to primary PCI were to receive aspirin, a P2Y<sub>12</sub> antagonist, and anticoagulants, according to local care guidelines.

Study data were collected with an electronic record form and sent to the Biostatistical Center of KU Leuven for independent statistical analysis. All ECGs were interpreted by experienced personnel blinded to clinical outcomes at the Canadian VIGOUR Center core ECG laboratory, University of Alberta, according to methods described previously.<sup>14</sup> A minimum of one on-site monitoring per site was performed during the trial. All stroke cases were monitored and centrally adjudicated.

### Outcomes

The efficacy end points of primary interest were reperfusion efficacy based on the proportion of patients with  $\geq 50\%$  ST-segment-elevation resolution in the lead with worst ST-segment elevation, resolution of ST deviations (in percentages and in millimeters) after last angiography, and the composite of all-cause mortality, shock, heart failure, and reinfarction at 30 days.

Other efficacy end points of interest were investigator-reported Thrombolysis In Myocardial Infarction (TIMI) flow grade at first and last coronary angiography and incidence of aborted myocardial infarction (definition provided as [Supplemental Material](#)). The need for rescue PCI is centrally adjudicated by the ECG core laboratory. Safety evaluation was based on the occurrence of stroke and nonintracranial bleeding.

### Statistical Analysis

Approximately 600 patients were initially planned to be randomly assigned, with 400 patients receiving a pharmaco-invasive treatment and 200 receiving primary PCI. After 50% of the planned recruitment, a formal interim analysis by the data monitoring committee was prespecified to advise the executive committee on extending the study into a confirmatory trial with a primary hypothesis on the combined clinical end point at 30 days (the same primary clinical end point as in STREAM-1). On December 10, 2020, the data monitoring committee did not formally recommend a trial expansion after reviewing data from 326 patients. Issues associated with slower-than-anticipated

recruitment, the emergence of the COVID-19 pandemic, and limitations of funding further precluded this extension.

In the statistical analysis plan (available on <https://www.clinicaltrials.gov>), we identified ST resolution after last angiography and the composite of death, heart failure, shock, and reinfarction within 30 days as the efficacy end points of primary interest. Although the study is not powered to show a difference in clinical events, we presumed the older nature of the population would provide ample efficacy and safety events to assess. On the basis of the 30-day outcomes in patients  $\geq 60$  years of age in STREAM-1, we estimated an 18% to 20% composite event rate of death, shock, heart failure, and reinfarction.<sup>8</sup> We chose a 2:1 randomization strategy to enhance comparison with the half-dose treatment used after amendment in STREAM-1.

Baseline characteristics according to assigned treatment are reported as means $\pm$ SD, medians and interquartile ranges, or numbers and percentages, as appropriate. Time differences in the study treatment arms (eg, time from randomization to bolus tenecteplase or sheath insertion) are compared by means of a Wilcoxon rank sum test. Successful ST-segment-elevation resolution ( $\geq 50\%$ ) after last angiography is reported as observed event rates per assigned treatment arm and compared by calculating relative risk with 2-sided 95% CIs obtained by means of a Poisson regression model with robust error variance. ST-deviation resolution in millimeters and percentages after last angiography is reported as the median (Q1–Q3) and compared by the Wilcoxon rank sum test. TIMI flow grade before and after PCI is reported per assigned treatment and compared by the Cochran-Armitage test for trend.

The clinical efficacy end points (ie, composite and its components) and safety end points at 30 days are reported as obtained by means of a Poisson regression model with robust error variance. Subgroup analyses of the treatment effect within selected patient characteristics at randomization were prespecified for the clinical composite efficacy end point (ie, interactions tested and *P* values reported). The treatment according to the composite clinical end point is also expressed as Kaplan-Meier curves, and the log-rank test is reported. An observed case analysis was performed except for analyses in which there was a proportion of missing data of  $>1\%$ , for which a multiple imputation analysis using 100 imputations was performed. The imputation model used baseline characteristics together with all single efficacy (with the exception of sum of ST deviations) and safety end points. The statistical analysis plan was finalized on November 17, 2022, before the lock of the trial database on December 28, 2022.

All analyses were performed on an intention-to-treat basis with SAS software, version 9.4.

A prespecified per-protocol analysis was also performed. In this analysis, 33 patients (24 in the pharmaco-invasive and 9 in the primary PCI group) were excluded. Because the results were similar, only the intention-to-treat analysis is reported here.

## RESULTS

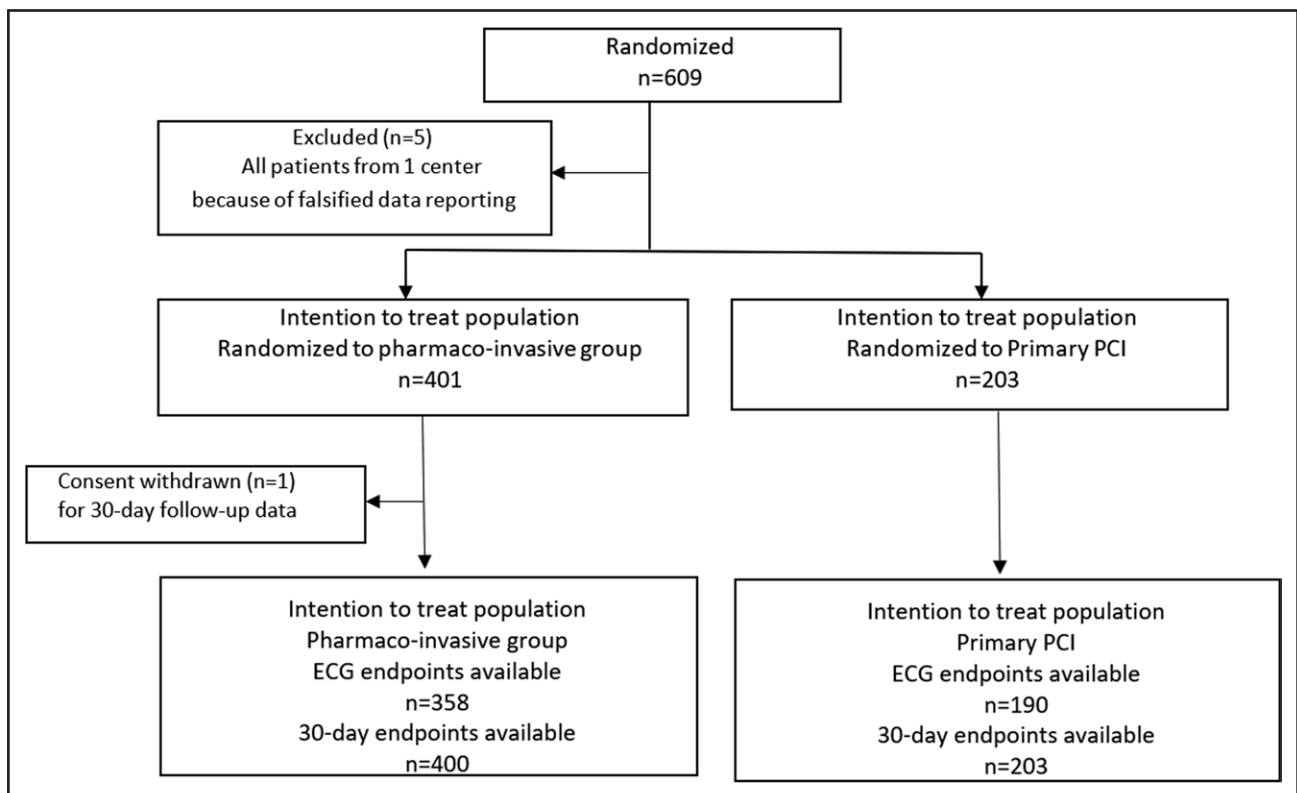
### Characteristics of the Patients and Times to Treatment

Between August 1, 2017, and September 12, 2022, a total of 609 patients were randomly assigned at 49 sites.

All 5 patients from one center were excluded because of falsified reporting (Figure 1). Of the remaining patients, 401 were allocated to a pharmaco-invasive strategy, and 203 were allocated to primary PCI. Baseline characteristics were well balanced (Table 1). The mean age was 70.5 years; 166 patients (27.5%) were  $\geq 75$  years of age. Nearly one-third were women, and comorbidities commensurate with this older STEMI population were evident in the median TIMI risk score of 4 in both groups. The number of patients randomly assigned pre-hospital in ambulances (286/603; 47.4%) was similar to the proportion from community hospitals (317/603; 52.6%). Overall median times from symptom onset to randomization were 97 minutes for pharmaco-invasive and 92 minutes for primary PCI patients (Table 1). The corresponding median times from symptom onset to randomization in the cohorts of patients randomly assigned in ambulances and community hospitals are also listed in Table 1. Bolus tenecteplase was given 10 minutes (median) after randomization, and arterial sheath insertion occurred after 81 minutes in the primary PCI arm. Whereas patients randomly assigned to pharmaco-invasive treatment received tenecteplase within 10 minutes, irrespective of their randomization location, the time to sheath insertion was shorter for patients undergoing PCI randomly assigned in an ambulance versus community hospital (medians of 65 versus 110 minutes, respectively).

### Efficacy and Safety End Points

In Table 2, ECG results are shown. At baseline, the absolute amount of ST-segment elevation in the lead showing the greatest ST-segment elevation, and the extent of ST deviations in all leads, as well, was similar in the 2 treatment groups. Repeat ECG assessment 90 minutes (median, Q1–Q3: 80–93) after tenecteplase indicates that 70.3% of the patients receiving pharmaco-invasive treatment achieved  $\geq 50\%$  resolution in the lead with the greatest ST-segment elevation, of which its median declined from 3.0 to 1.0 mm, and the median amount of ST deviations declined from 15.0 to 6.5 mm. Comparison of the 2 treatment groups at the prespecified times early after PCI or last angiography (if no PCI was performed) showed that 85.2% versus 78.4% of the patients in the pharmaco-invasive versus primary PCI arms achieved  $\geq 50\%$  ST-segment-elevation resolution. Values for the worst single-lead absolute residual ST-segment elevation, residual ST deviations, and proportion of ST-deviation resolution relative to their baseline ECG were at least comparable at these times. Angiographic data are also shown in Table 2. Investigator-reported TIMI flow grade 3 after tenecteplase in the pharmaco-invasive group was 53.8% versus 18.9% before primary PCI. After PCI or at the last angiography, similar TIMI-3 flow grades of  $\approx 87\%$  were observed in both groups (Table 2). In 168 (42.2%) patients randomly assigned to a pharmaco-invasive strategy, investigators performed urgent



**Figure 1. Trial profile.** PCI indicates percutaneous coronary intervention.

**Table 1. Characteristics of the Patients at Baseline and Key Time Intervals**

Characteristics	Pharmaco-invasive strategy (n=401)	Primary PCI (n=203)	P value
Age			
Mean, y	70±8	71±8	
≥75 years, n (%)	112 (27.9)	54 (26.6)	
Female sex, n (%)	131 (32.7)	66 (32.5)	
Weight, kg	79±14	80±17	
Killip class, n/total n (%)			
I	368/397 (92.7)	185/202 (91.6)	
II/III	28/397 (7.1)	16/202 (7.9)	
IV	1/397 (0.3)	1/202 (0.5)	
Heart rate, beats/min	76±18	75±17	
Systolic blood pressure, mm Hg	135±23	134±24	
Infarct location, n/total n (%)			
Anterior	168 (41.9)	92 (45.3)	
Inferior	231 (57.6)	111 (55.0)	
Other	30 (7.5)	12 (5.9)	
Cardiovascular history, n/total n (%)			
Previous heart failure	5/394 (1.3)	2/199 (1.0)	
Previous PCI	35/395 (8.9)	18/200 (9.0)	
Previous myocardial infarction	49/396 (12.4)	25/199 (12.6)	
Hypertension	262/400 (65.5)	136/200 (68.0)	
Diabetes	101/394 (25.6)	42/198 (21.2)	
TIMI risk score	4 (2–5)	4 (3–5)	
Median time delays (Q1–Q2), min			
Symptom onset to randomization	97 (71–131)	92 (62–130)	0.47
Ambulance	91 (64–128)	81 (55–125)	0.27
Community hospital	102 (75–134)	102 (71–134)	0.94
Symptom onset to PCI hospital admission	181 (138–228)	165 (117–211)	0.006
Symptom onset to start of reperfusion treatment (tenecteplase or sheath insertion)	110 (80–142)	190 (142–238)	<0.001
Qualifying ECG to start of reperfusion treatment (tenecteplase or sheath insertion)	25 (16–35)	99 (75–140)	<0.001
Randomization to PCI hospital admission	77 (38–112)	70 (29–105)	0.02
Randomization to start reperfusion treatment (tenecteplase or sheath insertion)	10 (6–16)	81 (59–120)	<0.001
Ambulance	10 (5–16)	65 (52–81)	<0.001
Community hospitals	10 (6–16)	110 (78–136)	<0.001

PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis In Myocardial Infarction  
\*Values are means ± SD, medians (Q1–Q3), or numbers (%).

angiography for possible rescue PCI at a median time of 142 minutes from randomization. The combined clinical efficacy end point at 30 days occurred in a similar proportion of patients in the pharmaco-invasive (12.8%) and primary PCI group (13.3%; relative risk, 0.96 [95% CI, 0.62–1.48]; Table 3). The time to the first event of the composite clinical end point revealed similar findings for both groups (Figure 2). In only one patient, vital status at 30 days was unavailable (consent withdrawal). All-cause and cardiac deaths were 9.3% and 7.3% in the pharmaco-invasive and 8.9% and 8.4% in the PCI arm, respectively. Three of the noncardiac deaths in the

pharmaco-invasive arm were related to ICH; 4 were related to respiratory infection, and the cause of death in one patient was unknown; the noncardiac death in the PCI arm was also related to respiratory infection. Although cardiogenic shock and heart failure were nominally less in the pharmaco-invasive group, no significant differences were evident in any of the single clinical end points. Aborted myocardial infarction was uncommon and occurred in 4% of the patients in both groups. In Figure 3, the prespecified subgroups demonstrate outcomes similar to the overall results, except that there was a lower incidence of the composite end point in the



**Table 2. ECG Measurements by Core Laboratory and Investigator-Reported Angiographic Outcomes**

ECG measurements	Pharmaco-invasive strategy	Primary PCI	P value
<b>Baseline ECG</b>			
No. of patients with baseline ECG	401	203	
Time symptom onset to qualifying ECG, min	77 (53, 113)	75 (47, 115)	0.51
Worst-lead ST-segment elevation, mm	3.0 (2.0, 4.0)	3.0 (2.0, 4.5)	0.79
Sum ST deviations, mm	15.0 (10.0, 20.5)	15.0 (11.0, 21.5)	0.23
<b>ECG after bolus tenecteplase</b>			
No. of patients with paired baseline ECGs	380	--	--
Time symptom onset to posttenecteplase ECG, min	195 (165, 228)	--	--
Worst-lead ST-segment elevation, mm*	1.0 (0.0, 2.0)	--	--
Worst-lead ST-segment elevation resolution ≥50%, n/total n (%)	265/377 (70.3)	--	--
Sum of residual ST deviations, mm*	6.5 (3.5, 12.0)	--	--
ST-deviation resolution, %*	53 (20, 75)	--	--
<b>ECG after last angiography (if no PCI performed) or PCI</b>			
No. of patients with paired baseline ECGs	366	193	--
Time symptom onset to postangiography or PCI ECG, min	524 (315, 1180) <sup>†</sup>	263 (210, 316)	<0.001
Worst-lead ST-segment elevation, mm <sup>‡</sup>	1.0 (0.0, 1.5)	0.5 (0.0, 2.0)	0.27
Worst-lead ST-segment-elevation resolution ≥50%, n/total n (%)	305/358 (85.2)	149/190 (78.4)	0.05
Sum of residual ST deviations, mm <sup>§</sup>	4.5 (2.5, 8.0)	5.5 (2.5, 10.5)	0.02
ST-deviation resolution, % <sup>§</sup>	71 (46, 84)	62 (36, 82)	0.03
<b>TIMI blood flow<sup>  </sup></b>			
<b>Before PCI:</b>			
0	80/374 (21.4)	111/190 (58.8)	<0.001
1	27/374 (7.0)	13/190 (6.8)	
2	65/374 (17.8)	30/190 (15.5)	
3	202/374 (53.8)	36/190 (18.8)	
<b>After PCI</b>			
0	7/376 (3.2)	4/195 (2.8)	0.74
1	5/376 (1.3)	0/195 (0.5)	
2	32/376 (8.2)	20/195 (10.3)	
3	332/376 (87.3)	171/195 (86.9)	
Rescue PCI or urgent angiography, n/total n (%)	168/398 (42.2)	NA	
Radial artery access, n/total n (%)	362/385 (94.0)	182/199 (91.5)	0.24
PCI, n/total n (%)	345/401 (86.0)	186/203 (91.6)	0.05
Stents placement, n/total n (%)	335/344 (97.4)	178/186 (95.7)	0.18
Index hospitalization coronary artery bypass grafting, n/total n (%)	9/401 (2.2)	4/203 (2.0)	1.00

NA indicates not applicable; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis In Myocardial Infarction.

\*Based on 377 patients with data.

<sup>†</sup>Include patients with rescue and scheduled angiography and PCI.

<sup>‡</sup>Based on 358 and 190 patients with data, respectively.

<sup>§</sup>Based on 357 and 190 patients with data, respectively.

<sup>||</sup>Percentages and P values are obtained from a multiple imputation analysis. In case only one coronary angiography was performed, the TIMI flow measurement was used for both the first and the last coronary angiography.

pharmaco-invasive group randomly assigned within 1 hour of symptom onset ( $P_{\text{interaction}}=0.004$ ).

The safety data within 30 days are reported in Table 3. A total of 10 strokes occurred. Six ICHs were observed in the pharmaco-invasive arm (1.5%), of which 3 were fatal (0.75%). None of the ICHs occurred in patients ≥75 years of age; their ages ranged from 60 to 74 years, and

3 were women. More detailed information on the strokes is shown in Table 4. Major protocol violations were found in 3 of these patients: in 2 patients, therapeutic doses of unfractionated heparin were given during rescue PCI despite full-dose intravenous and subcutaneous enoxaparin being given shortly before, at the time of randomization; uncontrolled hypertension was present in the third

**Table 3. Clinical Efficacy and Safety End Points at 30 Days**

End points	Pharmaco-invasive strategy (n=401), n/total n (%)	Primary PCI (n=203), n/total n (%)	Relative risk (95% CI)
Clinical efficacy end points			
Composite clinical efficacy end point: death, heart failure, shock, reinfarction at 30 days	51/400 (12.8)	27/203 (13.3)	0.96 (0.62–1.48)
Death from any cause	37/400 (9.3)	18/203 (8.9)	1.04 (0.61–1.79)
Cardiogenic shock	18/400 (4.5)	11/203 (5.4)	0.83 (0.40–1.72)
Heart failure	14/400 (3.5)	9/203 (4.4)	0.79 (0.35–1.79)
Reinfarction	10/400 (2.5)	5/203 (2.5)	1.02 (0.35–2.93)
Death from cardiac causes	29/400 (7.3)	17/203 (8.4)	0.87 (0.49–1.54)
Rehospitalization for cardiac causes	6/400 (1.5)	1/203 (0.5)	3.04 (0.37–25.12)
Safety end points			
Total stroke	9/400 (2.3)	1/203 (0.5)	4.57 (0.58–35.80)
Intracranial hemorrhage*	6/400 (1.5)	0/203 (0.0)	6.61 (0.81–53.89)
Ischemic stroke	3/400 (0.8)	1/203 (0.5)	1.52 (0.16–14.54)
Major nonintracranial bleeding	5/400 (1.3)	2/203 (1.0)	1.27 (0.25–6.48)
Blood transfusion	2/400 (0.5)	1/203 (0.5)	1.01 (0.09–11.13)

Calculations are based on available data. Data are numbers (%).

\*Three intracranial hemorrhages were fatal.

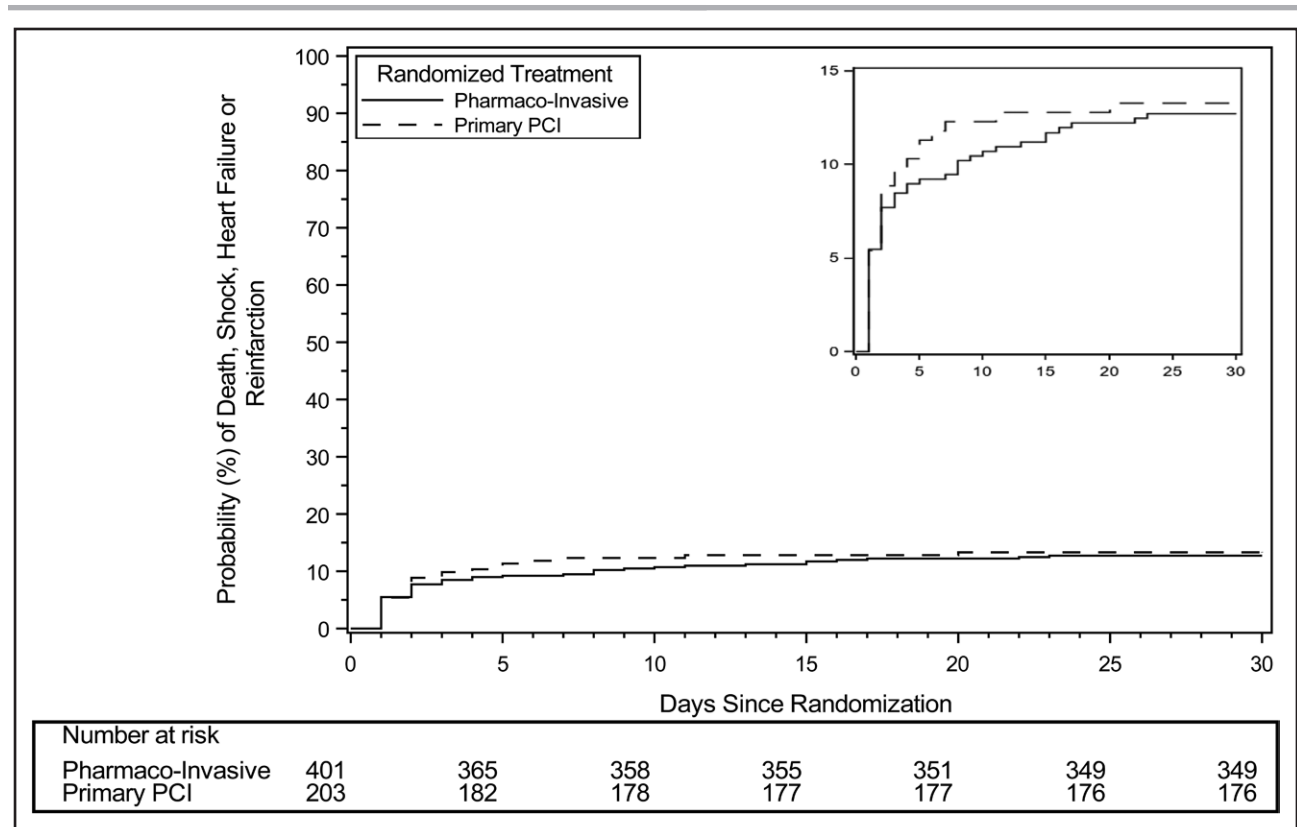
patient. There was no ICH in the primary PCI group. Three ischemic strokes occurred in the pharmaco-invasive group (0.75%) and one in the primary PCI arm (0.5%). The incidence of major nonintracranial bleedings and the need for blood transfusion was low in both groups.

## DISCUSSION

In this investigator-initiated study, patients with STEMI  $\geq 60$  years of age who presented within 3 hours after symptom onset, unable to undergo primary PCI within 1 hour, assigned to receive a pharmaco-invasive treatment of half-dose tenecteplase, showed rates of resolution of ST-segment elevation and deviation at least as extensive as those in patients in the primary PCI arm. Resolution of ST-segment elevation and deviation has been used in previous studies to evaluate the success of reperfusion treatment.<sup>15–17</sup> The current ECG results demonstrate the efficacy of the pharmaco-invasive treatment we used. Independent core ECG readings affirmed comparable evidence of ischemia at baseline in both groups. The current results are well aligned with our finding of similar clinical efficacy outcomes in the 2 study arms. It is noteworthy that despite nearly identical TIMI-3 epicardial flows at final angiography, the ECG data raise the possibility of enhanced myocardial perfusion in the pharmaco-invasive arm. A difference between angiographic findings and the amount of ST resolution has been previously observed: even in the presence of TIMI grade 3 flow, ST resolution has shown better alignment with a prognosis that was presumed to be related to effects on microvascular obstruction.<sup>18</sup> It could be argued that the different ascertainment times for evaluating changes in ST resolu-

tion between the treatment groups were advantageous for pharmaco-invasive patients by allowing more time for favorable ST-evolution. In this regard, it is noteworthy that Wong et al<sup>19</sup> found that ST resolution after either fibrinolysis or primary PCI had a similarly good prognostic relationship to 30-day mortality; that finding was not influenced by the timing of the postreperfusion ECG. In addition, in a large registry comparing a pharmaco-invasive strategy with primary PCI, greater resolution of both ST-segment elevation and deviation was also demonstrated with pharmaco-invasive therapy, assessed at similar postreperfusion times: these findings were also associated with a lower incidence of all-cause death, shock, heart failure, and recurrent myocardial infarction (multivariable adjusted) at 1 year.<sup>20</sup> It is of interest to relate our findings to those of the EARLY-MYO trial (Early Routine Catheterization after Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Elevation Myocardial Infarction), which compared half-dose alteplase as part of a pharmaco-invasive strategy to primary PCI in 334 low-risk Chinese patients with STEMI 18 to 75 years of age within 6 hours or symptom onset.<sup>21</sup> Despite somewhat longer median times from symptom onset to pharmaco-invasive therapy (210 minutes) and primary PCI (280 minutes) than we report in the current study, they also demonstrated better epicardial and myocardial tissue reperfusion with pharmaco-invasive treatment than with primary PCI using angiographic measurements.

In 42.2% of the patients in the pharmaco-invasive arm, investigators performed urgent angiography at a median time of 142 minutes after randomization. A lower rate of urgent intervention was observed in the STREAM-1 study: 36.3%.<sup>8</sup> Whether all these patients



**Figure 2. Kaplan-Meier curves for the composite clinical efficacy end point within 30 days.**

The clinical efficacy end point of primary interest was a composite of death from any cause, shock, heart failure, or reinfarction within 30 days ( $P=0.83$  by the log-rank test). The inset shows the same data on an enlarged y axis. PCI indicates percutaneous coronary intervention.

had insufficient ST resolution after tenecteplase or other indications for rescue intervention will be analyzed in a subsequent article. Access to urgent-rescue PCI remains a key part of a pharmaco-invasive strategy.

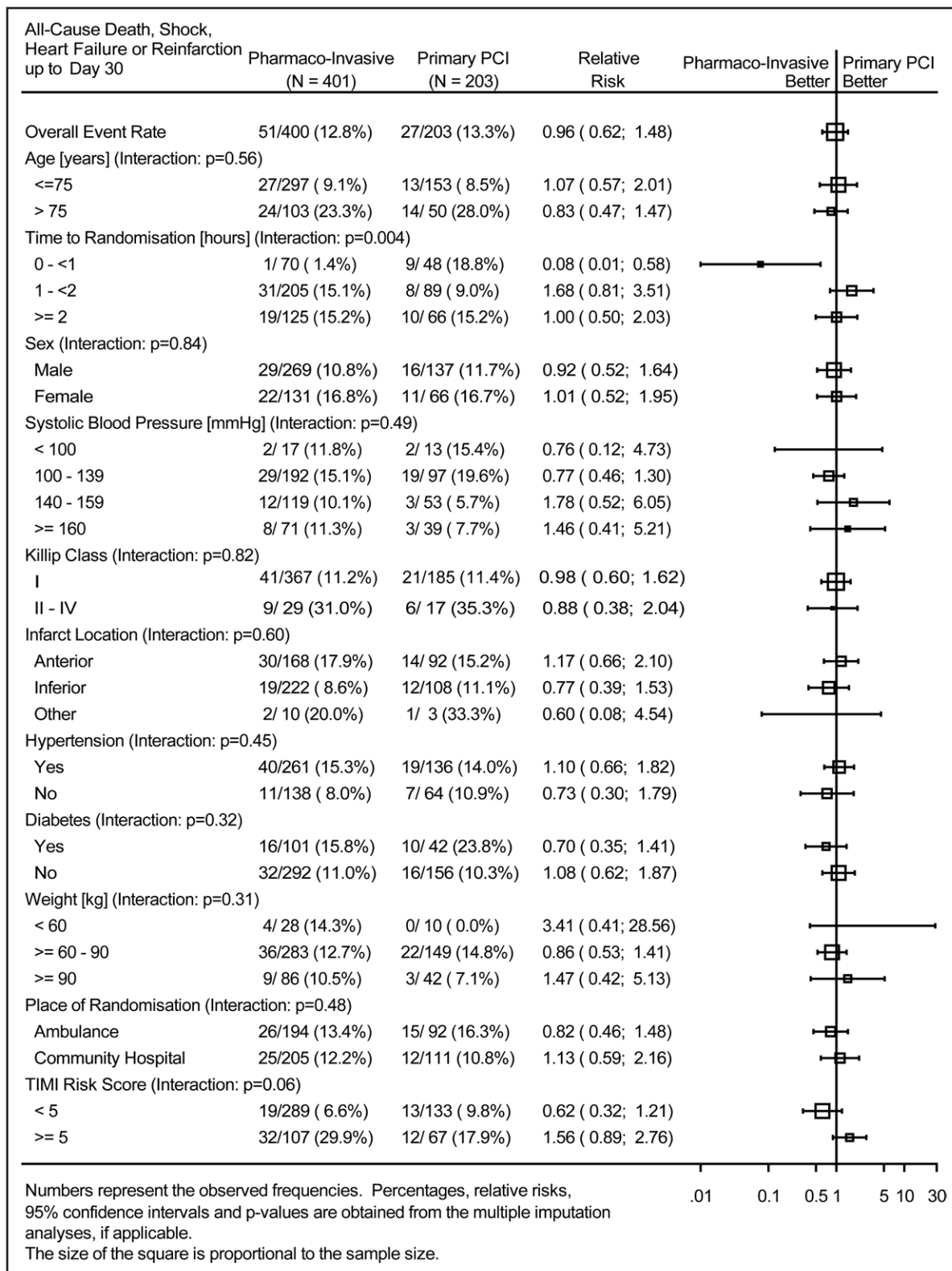
It is important to underscore that reperfusion therapy was started expeditiously in both arms of the current trial that included an evenly balanced distribution of ambulance and community hospitals. Median time from randomization to bolus tenecteplase was 10 minutes. Despite excluding patients who were able to undergo PCI within 1 hour, the median time from qualifying ECG to commencing PCI was 99 minutes (median). Moreover, as recommended by guidelines and evident from the upper quartile of time from qualifying ECG to sheath insertion (Table 1), PCI was commenced within 120 minutes of the diagnostic ECG in the majority of patients undergoing PCI. Although previous work showed a longer PCI-related delay in patients presenting to community hospitals,<sup>22</sup> we found that this additional delay to PCI increased by an average of 45 minutes beyond that in patients randomly assigned in ambulances (median times 110 versus 65 minutes), emphasizing the continuing challenge in accessing timely PCI even in developed STEMI networks. It is noteworthy that the population randomized in our study was >10 years older (with 27.5% of patients  $\geq 75$  years of age) and at a higher risk than in STREAM-1.

In STREAM-1, the median TIMI scores were 2.0 in both treatment groups, whereas the TIMI scores were double those in the present study. Although the combined clinical outcome of death, shock, heart failure, or reinfarction at 30 days was very similar in both studies, mortality was twice as high, whereas heart failure occurred about half as commonly as in STREAM-1, thereby counterbalancing the overall event rates. The rates of aborted infarction were equal in both treatment groups and far lower than observed in STREAM-1: this likely relates to our previous use of creatine kinase and creatine kinase-MB as the default biomarker strategy, whereas cardiac troponin was used in the current study. Four of the noncardiac deaths in the pharmaco-invasive group and one in the primary PCI group were related to respiratory failure at the height of the COVID-19 pandemic.

The use of half-dose tenecteplase with improved anti-thrombotic treatment in the pharmaco-invasive strategy, more frequent use of radial access (>90% in both groups), and advances in interventional technologies may have contributed to the lower-than-anticipated and comparable clinical efficacy outcomes and low incidence of major non-intracranial bleeding in our higher-risk population.

Our finding of improved clinical outcome with a pharmaco-invasive treatment in the prespecified early patient cohort presenting within 1 hour after symptom onset is





**Figure 3. Subgroup analyses for the composite clinical end point.** PCI indicates percutaneous coronary intervention; and TIMI, Thrombolysis In Myocardial Infarction.

well aligned with the classic finding of a “golden hour” in a meta-analysis of placebo-controlled trials of fibrinolytic therapy in >50 000 patients with STEMI, underscoring

the value of very early treatment<sup>23</sup> and consistent with observations of better dissolubility of recently formed thrombi.<sup>24</sup>

**Table 4. Detailed Information on Patients Experiencing Stroke**

Sex	Age, y	Weight, kg	Blood pressure, mm Hg	Tenecteplase dose, mg	Enoxaparin 30 mg IV	Enoxaparin first SC dose, mg	Clopidogrel initial dose, mg	Unfractionated heparin, IU	Day of stroke	Days to death	Fatal or modified ranking scale
Intracranial hemorrhages											
Male	66	82	110/54	22.5	No	60	300	No	2		Grade 5
Male	61	71	125/84	20.0	Yes	60	300	5000 during rescue PCI	1	8	Fatal
Female	72	68	160/90	17.5	Yes	60	<300	7000 during rescue PCI	2	2	Fatal
Female	60	80	170/100	22.5	Yes	80	300	No	1		Grade 4
Male	73	59	145/75	17.5	No	50	300	No	1	2	Fatal
Female	74	63	174/117	17.5	yes	63	300	no	2		Grade 2
Ischemic strokes											
Male	61	80	115/103	20		60	300	Pre-PCI hospital	15		Grade 3
Male	63	82	125/85	20	Yes	82	300	No	8		Grade 1
Male	71	83	100/60	22.5	yes	80	300	No	2		Grade 0
Female*	66	78	160/100	NA	NA	NA	NA	No	1		Grade 4

NA indicates not applicable; and PCI, percutaneous coronary intervention.

\*Patient was randomly assigned to primary PCI.

Although the rate of ICH with half-dose tenecteplase was higher than we anticipated, its exclusive occurrence in patients <75 years of age is noteworthy. More detailed analysis of the cases underscores the hazard of excess anticoagulant treatment with heparin and enoxaparin and the need to avoid fibrinolysis when uncontrolled hypertension coexists. It also reinforces the need for clear and timely communication regarding given treatments between various members of the health care team when rapid transitions in STEMI care unfold. Unlike in STREAM-1, we used an early loading dose of 300 mg of clopidogrel in the current study in addition to half-dose tenecteplase and anticoagulant therapy in patients ≥75 years of age, as previously described by Larson et al.<sup>25</sup>

Our study has some limitations. Despite nominally similar clinical composite end points in the 2 treatment groups, the broad 95% CIs do not allow statistical confirmation of similarity of the 2 treatment groups. We cannot discriminate why the ICH rate we observed was higher than anticipated despite the use of half-dose tenecteplase, but major protocol violations in half of the cases were probably contributing factors. This study was necessarily unblinded, and we cannot exclude bias in investigator reporting. However, the core ECG laboratory measures were conducted without knowledge of clinical outcomes. Because of the differences in elapsed time of acquiring the postangiogram ECG data, we cannot rule out some natural evolution in some of the ST-segment changes in the pharmaco-invasive group. The significant improvement in both the conventional and the more robust ECG estimates of myocardial reperfusion by the

ECG core laboratory is reassuring support for the clinical efficacy end points of the pharmaco-invasive strategy studied in this trial. Our results are applicable to early presenting patients with STEMI unable to undergo PCI within 1 hour of first medical contact.

In summary, provided that contraindications to fibrinolysis are observed and excess anticoagulation is avoided, a pharmaco-invasive treatment as used in this trial is an effective reperfusion strategy in older, early presenting patients with STEMI. Finally, our study confirms that primary PCI can be effectively and safely performed in this population. Both reperfusion therapies appear to be legitimate options in appropriately selected patients within a global context in which it is not possible to achieve timely PCI.

## ARTICLE INFORMATION

Received February 22, 2023; accepted June 16, 2023.

### Affiliations

Department of Cardiovascular Sciences, KU Leuven, Belgium (F.V.d.W., K.V., P.S.). Department of Cardiology, University Clinical Center of Serbia, University of Belgrade, Serbia (A.D.R.). Pirogov Russian National Research Medical University and City Clinical Hospital #15, Moscow, Russian Federation (O.V.A.). Coronary Care Unit, National Institute of Cardiology, Mexico City, Mexico (A.A.-M.). Centre Hospitalier de Versailles, SAMU 78 and Mobile Intensive Care Unit, France (Y.L.). Cardiology Discipline, Pontifical Catholic University of Campinas School of Medicine, Brazil (J.F.K.S.). Pontificia Universidad Católica de Chile, Santiago (P.S.). Servicio de Urgencias y Emergencias 061 de La Rioja, Spain (F.R.-O.). School of Medicine, University of New South Wales, Sydney, Department of Cardiology, Liverpool Hospital, Sydney, School of Medicine, Western Sydney University, New South Wales, Australia (J.K.F.). Cardiology Clinic, University Clinical Center of Montenegro, University of Podgorica, Medical Faculty (L.B.M.). Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat), KU Leuven, Leuven and University Hasselt, Belgium (K.B.). The Canadian Virtual Coordinating Centre for

Global Collaborative Cardiovascular Research (Canadian VIGOUR Centre), University of Alberta, Edmonton (C.M.W., K.R.B., R.C.W., P.W.A.), Boehringer Ingelheim GmbH, Ingelheim am Rhein, Germany (A.P.), TDC, Aix en Provence, France (T.D.), Emergency Department and SAMU, Lille University Hospital, France (P.G.).

### Sources of Funding

This investigator-initiated trial received funding from the Department of Research and Development of KU Leuven, Life Science Research Partners, and Boehringer Ingelheim.

### Disclosures

Dr Van de Werf reports institutional grants from Boehringer Ingelheim. Dr Ristić reports grants from Boehringer-Ingelheim and Novartis and travel fees from Astra Zeneca and Pfizer. Dr Arias-Mendoza reports grants from Merck and Novo Nordisk and personal fees from Novartis, Roche, Bayer, Boehringer Ingelheim, and Asofarma. Dr Saraiva received personal fees from Boehringer Ingelheim, Astra Zeneca, Novo Nordisk, Lilly, Janssen, Daichii Sankyo, Bayer, Novartis, Nova Quimica Brazil, and Albert Einstein ARO Brazil. Dr Musić reports a grant from Boehringer Ingelheim and travel fees from Astra Zeneca and Pfizer. Dr Westerhout reports consulting fees from Bayer Canada. Dr Pagès is a senior medical advisor of Boehringer Ingelheim. Dr Danays reports consulting fees from Boehringer Ingelheim. Dr Baine reports personal fees from Bayer, Astra Zeneca, Boehringer Ingelheim, and HLS Therapeutics. Dr Sinnaeve reports consulting fees to his institution (KU Leuven). Dr Welsh reports personal fees and travel fees from Boehringer Ingelheim. Dr Armstrong reports institutional and personal grants from Merck, Bayer, CLS Limited, Eli Lilly, and Boehringer Ingelheim and personal fees from Merck, Boehringer Ingelheim, Bayer, and Novo Nordisk. All other authors report no competing interests.

### Supplemental Material

STREAM-2 committees and investigators

Inclusion and exclusion criteria

Definitions of clinical events

Supplemental Table: Reduced weight-adjusted dose of tenecteplase in different weight categories

### REFERENCES

- Nallamothu B, Fox KA, Kennelly BM, Van de Werf F, Gore JM, Steg PG, Granger CB, Dabbous OH, Kline-Rogers E, Eagle KA; GRACE Investigators. Relationship of treatment delays and mortality in patients undergoing fibrinolysis and primary percutaneous coronary intervention. The Global Registry of Acute Coronary Events. *Heart*. 2007;93:1552–1555. doi: 10.1136/hrt.2006.112847
- O'Gara P, Kushner F, Ascheim D, Casey D, Chung M, de Lemos J, Ettinger S, Fang J, Fesmire F, Franklin B, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:E78–E140. doi: 10.1016/j.jacc.2012.11.019
- Ibanez B, James S, Agewall S, Antunes M, Bucciarelli-Ducci C, Bueno H, Caforio A, Crea F, Goudevenos J, Halvorsen S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39:119–177. doi: 10.1093/eurheartj/ehx393
- Jollis J, Granger C, Zegre-Hemsey J, Henry T, Goyal A, Tamis-Holland J, Roettig M, Ali M, French W, Poudel R, et al. Treatment time and in-hospital mortality among patients with ST-segment elevation myocardial infarction, 2018–2021. *JAMA*. 2022;2033:2040. doi: 10.1001/jama.2022.20149
- Danchin N, Popovic B, Puymirat E, Goldstein P, Belle L, Cayla G, Roubille F, Lemesle G, Ferrieres J, Schiele F, et al; FAST-MI Investigators. Five-year outcomes following timely primary percutaneous intervention, late primary percutaneous intervention, or a pharmaco-invasive strategy in ST-segment elevation myocardial infarction: the FAST-MI programme. *Eur Heart J*. 2020;41:858–866. doi: 10.1093/eurheartj/ehz665
- Lambert L, Brown K, Segal E, Brophy J, Rodes-Cabau J, Bogaty P. Association between timeliness of reperfusion therapy and clinical outcomes in ST-elevation myocardial infarction. *JAMA*. 2010;303:2148–2155. doi: 10.1001/jama.2010.712
- Jamal J, Idris H, Faour A, Yang W, McLean A, Burgess S, Shugman I, Wales K, O'Loughlin A, Leung D, et al. Late outcomes of ST-elevation myocardial infarction treated by pharmaco-invasive or primary percutaneous coronary intervention. *Eur Heart J*. 2022;44:516–528. doi: 10.1093/eurheartj/ehac661
- Armstrong P, Gershlick A, Goldstein P, Wilcox R, Danays T, Lambert Y, Sulimov V, Ortiz F, Ostojic M, Welsh R, et al. Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;368:1379–1387. doi: 10.1056/NEJMoa1301092
- Armstrong P, Bogaerts K, Welsh R, Sinnaeve P, Goldstein P, Pages A, Danays T, Van de Werf F. The second strategic reperfusion early after myocardial infarction (STREAM-2) study optimizing pharmaco-invasive reperfusion strategy in older ST-elevation myocardial infarction patients. *Am Heart J*. 2020;226:140–146. doi: 10.1016/j.ahj.2020.04.029
- Van de Werf F, Adgey J, Ardissino D, Armstrong P, Aylward P, Barbash G, Betriu A, Binbrek A, Califf R, Diaz R, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet*. 1999;354:716–722. doi: 10.1016/S0140-6736(99)07403-6
- Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 Investigators. Efficacy and safety of tenecteplase in combination with enoxaparin, abciximab, or unfractionated heparin: the ASSENT-3 randomised trial in acute myocardial infarction. *Lancet*. 2001;358:605–613. doi: 10.1016/S0140-6736(01)05775-0
- Wallentin L, Goldstein P, Armstrong P, Granger C, Adgey A, Arntz H, Bogaerts K, Danays T, Lindahl B, Makijarvi M, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin, or unfractionated heparin in the prehospital setting: the assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT)-3 PLUS randomised trial in acute myocardial infarction. *Circulation*. 2003;108:135–142. doi: 10.1161/01.CIR.0000081659.72985.A8
- Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-4 PCI) Investigators. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST-segment elevation acute myocardial infarction (ASSENT-4 PCI): randomised trial. *Lancet*. 2006;367:569–578. doi: 10.1016/S0140-6736(06)68147-6
- Buller C, Fu Y, Mahaffey K, Todaro T, Adams P, Westerhout C, White H, Hof A, Van de Werf F, Wagner G, et al. ST-segment recovery and outcome after primary percutaneous coronary intervention for ST-elevation myocardial infarction: insights from the Assessment of PEXelizumab in Acute Myocardial Infarction (APEX-AMI) trial. *Circulation*. 2008;118:1335–1346. doi: 10.1161/CIRCULATIONAHA.108.767772
- de Lemos J, Antman E, Giugliano R, McCabe C, Murphy S, Van de Werf F, Gibson C, Braunwald E, Infarction TM. ST-segment resolution and infarct-related artery patency and flow after thrombolytic therapy. *Am J Cardiol*. 2000;85:299–304. doi: 10.1016/S0002-9149(99)00736-5
- Tjandrawidjaja M, Fu Y, Westerhout C, White H, Todaro T, Van de Werf F, Mahaffey K, Wagner G, Granger C, Armstrong P, et al. Resolution of ST-segment depression: a new prognostic marker in ST-segment elevation myocardial infarction. *Eur Heart J*. 2010;31:573–581. doi: 10.1093/eurheartj/ehp494
- Welsh R, Van de Werf F, Westerhout C, Goldstein P, Gershlick A, Wilcox R, Danays T, Bluhmki E, Lopes R, Steg P, et al. Outcomes of a pharmaco-invasive strategy for successful versus failed fibrinolysis and primary percutaneous intervention in acute myocardial infarction (from the Strategic Reperfusion Early After Myocardial Infarction [STREAM] Study). *Am J Cardiol*. 2014;114:811–819. doi: 10.1016/j.amjcard.2014.06.011
- Brener SJ, Westerhout CM, Fu Y, Todaro TG, Moliterno DJ, Wagner GS, Granger CB, Armstrong PW, APEX-AMI Investigators. Contribution of angiographic and electrocardiographic parameters of reperfusion to prediction of mortality and morbidity after acute ST-elevation myocardial infarction: insights from the Assessment of Pexelizumab in Acute Myocardial Infarction trial. *Am Heart J*. 2009;158:755–760. doi: 10.1016/j.ahj.2009.09.009
- Wong C, de la Barra S, Herbison P. Does ST resolution achieved via different reperfusion strategies (fibrinolysis vs percutaneous coronary intervention) have different prognostic meaning in ST-elevation myocardial infarction? A systematic review. *Am Heart J*. 2010;160:842–U889. doi: 10.1016/j.ahj.2010.06.050
- Baine K, Armstrong P, Zheng Y, Brass N, Tyrrell B, Leung R, Westerhout C, Welsh R. Pharmaco-invasive strategy versus primary percutaneous coronary intervention in ST-elevation myocardial infarction in clinical practice insights from the Vital Heart Response Registry. *Circ Cardiovasc Interv*. 2019;12:e008059. doi: 10.1161/CIRCINTERVENTIONS.119.008059

21. Pu J, Ding S, Ge H, Han Y, Guo J, Lin R, Su X, Zhang H, Chen L, He B; EARLY-MYO Investigators. Efficacy and safety of a pharmaco-invasive strategy with half-dose alteplase versus primary angioplasty in ST-segment-elevation myocardial infarction EARLY-MYO trial (Early Routine Catheterization After Alteplase Fibrinolysis Versus Primary PCI in Acute ST-Segment-Elevation Myocardial Infarction). *Circulation*. 2017;136:1462–1473. doi: 10.1161/CIRCULATIONAHA.117030582
22. Welsh R, Goldstein P, Sinnaeve P, Ostojic M, Zheng Y, Danays T, Westerhout C, Van de Werf F, Armstrong P. Relationship between community hospital versus pre-hospital location of randomisation and clinical outcomes in ST-elevation myocardial infarction patients: insights from the Stream study. *Eur Heart J Acute Cardiovasc Care*. 2018;7:504–513. doi: 10.1177/2048872617700872
23. Boersma E, Maas A, Deckers J, Simoons M. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;348:771–775. doi: 10.1016/S0140-6736(96)02514-7
24. Silvain J, Collet J, Nagaswami C, Beygui F, Edmondson K, Bellemain-Appaix A, Cayla G, Pena A, Brugier D, Barthelemy O, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol*. 2011;57:1359–1367. doi: 10.1016/j.jacc.2010.09.077
25. Larson D, Duval S, Sharkey S, Garberich R, Madison J, Stokman P, Dirks T, Westin R, Harris J, Henry T. Safety and efficacy of a pharmaco-invasive reperfusion strategy in rural ST-elevation myocardial infarction patients with expected delays due to long-distance transfers. *Eur Heart J*. 2012;33:1232–1240. doi: 10.1093/eurheartj/ehr403