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RESEARCH LETTER

Half-Dose Tenecteplase or Primary Percutaneous Coronary Intervention in Older Patients With ST-Elevation Myocardial Infarction: STREAM-2 1-Year Mortality Follow-Up

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Delays in achieving reperfusion with either fibrinolysis or primary percutaneous coronary intervention (PPCI) are associated with excess mortality. ST-elevation myocardial infarction guidelines recommend a pharmacoinvasive (PI) treatment strategy if timely PPCI is unavailable.[1,2] However, PI treatment with full-dose tenecteplase is associated with an increased risk of intracranial hemorrhage in older patients.[3] In STREAM-2 (Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction [URL: https://clinicaltrials.gov; Unique identifier: NCT02777580]), we tested a half-dose, tenecteplase-based PI strategy in patients ≥60 years with ST-elevation myocardial infarction, presenting <3 hours of symptom onset and unable to undergo PPCI <1 hour. Because of similar angiographic and clinical 30-day outcomes—except for an excess of intracranial bleedings in the PI arm, in part because of protocol violations including excessive anticoagulation[4]—we performed a prespecified exploratory analysis of mortality and cardiac rehospitalization rates at 1 year.

As previously reported, institutional review boards approved STREAM-2 (n=604) and informed consent was obtained.[3,4] After 2 years from the time of the publication, requests for STREAM-2 trial 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 were randomized (2:1) to either a PI strategy or PPCI. Patients assigned to PI treatment received half-dose, weight-adjusted bolus tenecteplase, 150 to 325 mg aspirin, 300 mg clopidogrel, and subcutaneous enoxaparin 0.75 mg/kg, with patients ≤75 years receiving an additional IV dose of 30 mg. Depending on successful reperfusion 60 to 90 minutes after bolus tenecteplase, coronary angiography was undertaken 6 to 24 hours after randomization. All-cause and cardiac mortality were estimated using Kaplan—Meier curves. Cardiac rehospitalizations ≤1 year were calculated using competing risk methodology. In a prespecified per-protocol analysis, 31 patients (24 PI; 9 PPCI) were excluded.

One-year vital statuses for 399 of 401 (99.5%) patients in the PI arm and 201 of 203 (99.0%) patients in the PPCI arms were available. The mean age was 70±8 years, and 27% were ≥75 years of age. The median time from symptom onset to start of reperfusion was relatively short in both arms, and 80 minutes shorter in the PI versus PPCI arm (Figure [A]). The median delay between

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CORRESPONDENCE

Nonstandard Abbreviations and Acronyms

PI	pharmacoinvasive
PPCI	primary percutaneous coronary intervention
STREAM-2	Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction

qualifying ECG and sheath insertion was only 70 minutes for PPCI.

One-year all-cause mortality was 12.0% in the PI arm versus 11.8% for PPCI (RR, 1.01 [95% CI, 0.65—1.71]; *P*=0.958). One-year cardiac mortality was also similar for both treatment strategies: 8.5% versus 9.9% for PI and PPCI, respectively (RR, 0.86 [95% CI, 0.51—1.57]; *P*=0.587). Kaplan—Meier survival curves for all-cause mortality are shown in the Figure [B].

All-cause death amongst 30-day survivors occurred infrequently in both treatment arms. Overall, 17 patients died between 1 month and 1 year: 11 (2.7%) in the PI group and 6 (3.0%) in the PPCI group. The rate of 1-year cardiac rehospitalization was low (n=20); nominally lower in the PI arm (2.7%) compared to the PPCI arm (4.5%; Gray's test *P*=0.282; Figure). Between day 30 and 1 year, only 5 (1.2%) and 8 (3.9%) patients were hospitalized for cardiac causes in the PI and PPCI arms, respectively.

A

Median Time delays (interquartile range) – min	Fibrinolysis (n=401)	Primary PCI (n=203)	P value
Symptom onset to randomization	97 (71-131)	92 (62-130)	0.47
Symptom onset to PCI hospital admission	181 (138-228)	165 (117-211)	0.006
Symptom onset to start of reperfusion treatment*	110 (80-142)	190 (142-238)	p<0.001
Qualifying ECG to start of reperfusion treatment*	25 (16-35)	99 (75-140)	p<0.001
Randomization to PCI hospital admission	77 (38-112)	70 (29-105)	p=0.02
Randomization to start reperfusion treatment*	10 (6-16)	81 (59-120)	p<0.001

* *tenecteplase or sheath insertion*

B

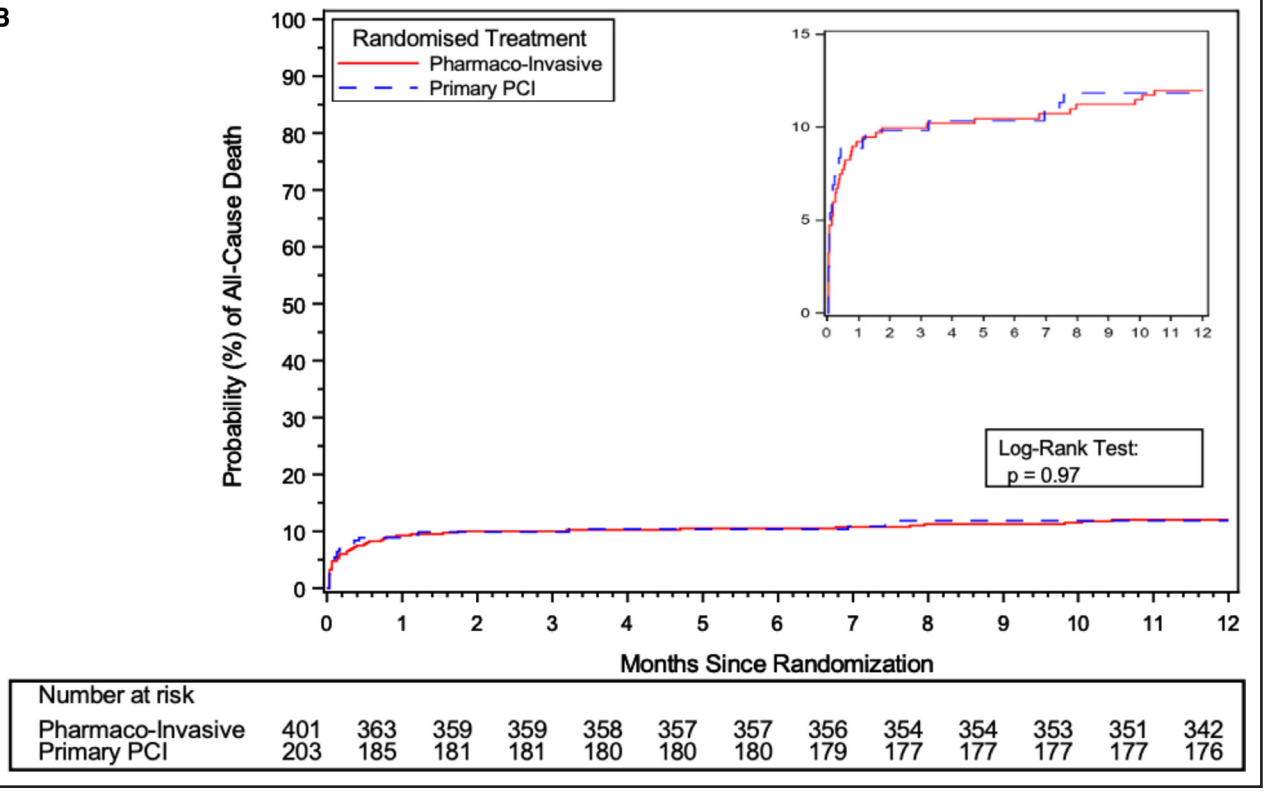

Figure. Patients randomized to a pharmacoinvasive strategy versus primary percutaneous coronary intervention.
A, Time delays. **B,** Cumulative event rates for all-cause mortality.

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Evaluation of prespecified subgroups revealed a significant treatment interaction for time from symptom onset to randomization (P=0.0005). Patients randomized within 1 hour of symptom onset derived greater benefit from a PI strategy (RR, 0.09 [95% CI, 0.0—0.26]). A significant interaction regarding infarct location (P=0.0166) and TIMI (Thrombolysis in Myocardial Infarction) risk score (P=0.0295) also existed: PI patients with an anterior infarction or TIMI risk scores ≥5 appeared to have worse outcomes (RR, 1.95 [95% CI, 1.05—5.28] and RR, 1.76 [95% CI, 1.01—3.98]), but only the early treatment interaction persisted with per-protocol analysis. No significant differences in all-cause mortality rates occurred in other prespecified subgroups.

Treatment delays were short, despite the required expected delay of ≥60 minutes for PPCI, and considerably shorter than the guideline-recommended targets. This may, in part, explain the lack of mortality difference at 1 year in STREAM-2. In STREAM (Strategic Reperfusion Early After Myocardial Infarction [URL: https://clinicaltrials.gov; Unique identifier: NCT00623623]), clinical outcomes in the PI arm were superior to PPCI when percutaneous coronary intervention—related delays exceeded guideline-mandated targets.[5] The relative benefit of a PI strategy in patients presenting <1 hour after symptom onset is in line with the time-dependent efficacy of fibrinolysis, and consistent with 30-day results.[4] Our observations would also support shorter than the ESC guideline—recommended 120-minute maximal estimated treatment delays between first medical contact and PPCI.[1,2]

Some limitations exist in the present analysis. STREAM-2 was a moderate-sized, open-label exploratory study not powered for mortality. These results are not applicable to patients able to undergo PPCI within 1 hour from symptom onset or those presenting beyond 3 hours after symptom onset. Because of the limited numbers of events and no correction for multiple testing, we cannot exclude the play of chance in our prespecified subgroups. Finally, cardiac rehospitalization occurred infrequently in both treatment arms in the year after randomization.

Our 1-year findings add support to considering a PI strategy with half-dose tenecteplase in patients ≥60 years presenting early after symptom onset, and in whom a significant delay to percutaneous coronary intervention is anticipated.

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