ST–Segment-Elevation Myocardial Infarction Patients Randomized to a Pharmaco-Invasive Strategy or Primary Percutaneous Coronary Intervention: Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-Year Mortality Follow-Up

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ST–Segment-Elevation Myocardial Infarction Patients Randomized to a Pharmaco-Invasive Strategy or Primary Percutaneous Coronary Intervention Strategic Reperfusion Early After Myocardial Infarction (STREAM) 1-Year Mortality Follow-Up

Peter R. Sinnaeve, MD, PhD; Paul W. Armstrong, MD; Anthony H. Gershlick, MD; Patrick Goldstein, MD; Robert Wilcox, MD; Yves Lambert, MD; Thierry Danays, MD; Louis Soulat, MD; Sigrun Halvorsen, MD, PhD; Fernando Rosell Ortiz, MD, PhD; Katleen Vandenberghe, PhD; Anne Regelin, PhD; Erich Bluhmki, PhD; Kris Bogaerts, PhD; Frans Van de Werf, MD, PhD; for the STREAM investigators*

Background—In the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial, a pharmaco-invasive (PI) strategy was compared with primary percutaneous coronary intervention (pPCI) in ST—segment-elevation myocardial infarction patients presenting within 3 hours after symptom onset but unable to undergo pPCI within 1 hour. At 30 days, the PI approach was associated with a nominally but nonstatistically significant lower incidence of the composite primary end point of death, shock, congestive heart failure, and reinfarction when compared with pPCI. The aim of the present study was to determine the effect of these strategies on 1-year mortality.

Methods and Results—Vital status at 1 year was available in 936 of 944 (99.2%) and 941 of 948 (99.3%) patients in the PI and pPCI arm, respectively. At 1 year, all-cause mortality rates (6.7% versus 5.9%) were similar for PI and pPCI–treated patients (P=0.49; risk ratio, 1.13; 95% confidence interval, 0.79–1.62). Cardiac mortality rates were similar as well (4.0% versus 4.1%, P=0.93; risk ratio, 0.98; 95% confidence interval, 0.62–1.54). Overall, only 34 patients died between day 30 and 1 year, 20 in the PI arm and 14 in the pPCI arm, of whom 20 died of noncardiac reasons (13 in the PI and 7 in the pPCI arm). There was no significant difference in 1-year all-cause mortality between the 2 groups among the prespecified key subgroups.

Conclusions—At 1 year, mortality rates in the PI and pPCI arms were similar in ST—segment-elevation myocardial infarction patients presenting within 3 hours after symptom onset and unable to undergo pPCI within 1 hour.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00623623.

(Circulation. 2014;130:1139-1145.)

Key Words: anticoagulants ■ catheterization ■ myocardial infarction ■ thrombolysis, therapeutic

Guidelines recommend a primary percutaneous coronary intervention (pPCI) as the preferred reperfusion modality in patients presenting with ST—segment-elevation myocardial infarction (STEMI). Because most STEMI patients initially present to hospitals without PCI facilities, performing a pPCI in a timely fashion constitutes a significant logistic challenge in many healthcare systems across the world. Despite

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concerted efforts to decrease transfer times, PCI-related system delays remain substantial in many countries. Because these delays clearly have an unfavorable effect on morbidity and mortality, early fibrinolysis followed by timely angiography often constitutes a faster reperfusion option in many patients than transfer for standard primary PCI.

In the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study, we explored the strategy of prehospital fibrinolysis with bolus tenecteplase given before transport to a PCI-capable hospital, followed by timely coronary angiography, in STEMI patients presenting within 3 hours but unable to undergo primary PCI within 1 hour. The primary end point was the composite of death, shock, congestive heart failure, and reinfarction. At 30 days, we found that the pharmaco-invasive (PI) approach was associated with a nominally (not statistically significant) lower primary end point compared with primary PCI. Because of an excess of bleeding complications in the elderly, including intracranial hemorrhage (ICH), the dose of tenecteplase was reduced by 50% in patients aged ≥75 years, after enrolling ≥20% of the ultimate study population. After implementing the age-adjusted dose, no more ICH were seen in patients aged ≥75 years assigned to the PI arm, but a small nonsignificantly increased risk of ICH remained in the total population studied.

We also observed a nonsignificant 1.5% absolute lower incidence of both cardiogenic shock and congestive heart failure in the PI arm. In the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) study, prehospital fibrinolysis in the subset of STEMI patients presenting within 2 hours of symptom onset was associated with lower 30-day rates of both cardiogenic shock and death, as compared with transfer for primary PCI. A combined analysis of the CAPTIM and Which Early ST-Elevation Myocardial Infarction Therapy (WEST) studies also suggests a beneficial effect at 1 year from a PI therapy in patients presenting early after symptom onset. Furthermore, the 5-year data from the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI) suggested that fibrinolysis administered early in the prehospital settings resulted in lower mortality than pPCI during long-term follow-up. The aim of the present study was to evaluate 1-year mortality between the 2 treatment strategies in STREAM.

Methods
The design and primary results of The Strategic Reperfusion Early After Myocardial Infarction (STREAM, NCT00623623) study, an open-label, prospective, randomized, parallel, comparative, and international multicenter trial, have been reported previously. The study protocol was approved by national regulatory authorities as well as the local ethics committee at each study center. Patient’s informed consent was obtained. In summary, patients were eligible for enrollment in STREAM if they presented within 3 hours of symptom onset, demonstrated acute STEMI on their qualifying ECG (at least 2 mm in 2 contiguous peripheral or precordial leads), and could not undergo pPCI within 1 hour after first medical contact. The emphasis of the trial was on prehospital randomization, but in an amendment, recruitment was extended to patients presenting to community hospitals without PCI facilities but with access to PCI facilities in an established hub-and-spoke relationship. Ultimately, 4 out of 5 patients were randomized in the prehospital setting.

The patients initially treated pharmacologically received tenecteplase coupled with antplatelet and anticoagulant therapy followed by coronary angiography within 6 to 24 hours. In the event that there was <50% ST-resolution in the single lead with maximum elevation, or clinical evidence of failed reperfusion 90 minutes after fibrinolysis, rescue coronary intervention was performed. Tenecteplase was administered in a weight-based dose and combined with enoxaparin, aspirin, and clopidogrel according to current guidelines. Urgent coronary angiography in the PI arm was permitted at any time should hemodynamic or electric instability, worsening ischemia, or progressive or sustained ST-elevation develop, which in the judgment of the investigator required immediate coronary intervention. This PI strategy was compared with pPCI performed according to guideline based, best accepted local practice with early use of concomitant antplatelet and anticoagulant medications as well as additional discretionary glycoprotein IIb/IIIa antagonists. All patients were transferred to a PCI-capable hospital; for those non-PCI community hospitals participating, a well-developed hub-and-spoke relationship with a PCI-capable site was required. The primary end point of the trial was the 30-day composite comprising all-cause death, shock, heart failure, and reinfarction. Single efficacy end points as well as safety end points consisting of ischemic stroke, ICH, nonintracranial bleeding, and other serious clinical events were recorded and are defined in the Appendix of the 30-day results article. Cardiac mortality includes the following causes of death: reinfarction, cardiogenic shock, arrhythmia/sudden death, asystole/cardiac arrest, cardiac rupture, or ‘other cardiac’ event, but excluded stroke or ICH, major (non-ICH) bleeding, or ‘other noncardiac’ event.

After 21% of the ultimate population had been enrolled the Executive Committee, with the advice of the Data and Safety Monitoring Board, amended the protocol on August 24, 2009 to reduce the dose of tenecteplase by 50% in patients aged ≥75 years because of an excess of ICH in this age category. The dose adjustment was based on previous work by Larson et al. Additionally, to better align the ECG entry criteria with contemporary STEMI trials the inclusion criteria for inferior myocardial infarction were changed at that time from ≥3 mm ST-elevation in 2 contiguous inferior leads to ≥2 mm ST-elevation in 2 contiguous inferior leads.

The STREAM trial was designed as a proof-of-concept study. All statistical tests were of an exploratory nature. Baseline characteristics are reported as mean (SD) or number (%) where appropriate. One-year mortality event rates were estimated by using the Kaplan–Meier method, and a risk ratio (RR) with a 95% confidence interval (CI) was calculated. In addition, the event times were compared between treatment groups using a log-rank test. For cardiac mortality, we present the complement of the cumulative incidence function with noncardiac death as competing risk. A risk ratio at 1 year with a 95% CI was calculated. Gray’s test was used to compare the cumulative incidence functions, that is the subdistribution hazards, between the 2 treatment groups over the whole follow-up time. In addition, the cause-specific hazards for cardiac death were calculated by censoring the noncardiac deaths. Note that the cumulative incidence functions are influenced by the number of patients who experienced the competing risk, whereas the cause-specific hazards are not. We also undertook the following prespecified subgroup analyses: age, sex, Killip class, time to randomization, place of randomization, infarct location, systolic blood pressure, weight, history of diabetes mellitus or hypertension, thrombolysis in myocardial infarction, risk score, and before or after the protocol amendment. We evaluated the interactions between treatment and subgroups. All analyses were by intention to treat and done with SAS (version 9.2). P values are provided for descriptive purposes only.

Results
Vital status at 1 year was available for 936 of 944 (99.2%) and 941 of 948 (99.3%) patients in the PI and pPCI arm, respectively. Key baseline characteristics, shown in Table 1, were similar in both treatment arms. At 1 year, 63 patients (6.7%) had died in the PI arm, versus 56 (5.9%) in the pPCI arm (P=0.49; RR, 1.13; 95% CI, 0.79–1.62). Cardiac mortality at 1 year was also similar for both treatment strategies: 4.0% and 4.1% for PI treatment and pPCI, respectively (P=0.93; RR, 0.98; 95% CI, 0.62–1.54). There was a numeric excess of 8 noncardiac deaths in the PI.
and 14 in the pPCI arm (1.6%). There were 7 cardiac deaths in each treatment arm, but there was an excess of 6 noncardiac deaths in the PI arm. In this group, 2 patients died from a stroke and 11 from other noncardiac causes after day 30; in the pPCI arm, 1 patient died from a major bleeding, whereas 6 died from other noncardiac causes. Among the 7 patients in the PI arm who experienced a stroke or intracranial hemorrhage but survived through the first month, only 1 died between day 30 and 1 year. Table 2 gives an overview of the causes of death up to 1 year.

Up to 30 days, significantly more patients underwent coronary bypass surgery in the PI arm (44 versus 20 after pPCI). Of these, only 1 patient in each group died before 30 days. No coronary bypass surgery–managed patients died beyond 30 days in the pPCI group, versus 4 in the PI arm, of whom 2 initially underwent rescue PCI and died from a cardiac cause.

There was no significant difference in 1-year all-cause mortality rates between patients randomized to PI therapy or pPCI among the prespecified key subgroups except for randomization before the amendment (Figure 3). We observed a significant treatment interaction between patients randomized before versus after the amendment (P=0.035), however. The survival curves for all-cause mortality before versus after the amendment are shown in Figure 4. Before the amendment (at which time 21% of the total patient population had been enrolled) there was a significant excess of death in the PI group versus pPCI (9.9% versus 4.3% for pPCI, P=0.031; RR, 2.32; 95%CI, 1.09–7.51). In contrast, the curves for both treatment arms converged after implementing the amendment (5.9% versus 6.3%, respectively, P=0.71; RR, 0.93; 95% CI, 0.61–1.39). Cardiac mortality rates were not significantly different between the PI and pPCI arms before (4.7% versus 3.2%, respectively; P=0.455) or after the amendment (3.9% versus 4.4%, respectively; P=0.634, Pinteraction=0.380).

Before implementing the amendment, there were 9 cardiac deaths in the PI arm and 6 in the pPCI arm at 1 year. Of the 10 noncardiac deaths in the PI arm, 5 died from an ICH or stroke. Before the amendment, only 2 patients in the pPCI arm died from a noncardiac cause (including 1 from a major bleeding).

**Discussion**

Although pPCI is the reperfusion strategy of choice in STEMI patients when performed by an experienced team in a timely

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**Table 1. Key Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Pharmaco-Invasive (n=944)</th>
<th>Primary PCI (n=948)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (mean±SD)</td>
<td>59.7±12.4</td>
<td>59.6±12.5</td>
</tr>
<tr>
<td>Age ≥75 y, n (%)</td>
<td>134/944 (14.2%)</td>
<td>121/948 (12.8%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>194/944 (20.6%)</td>
<td>208/948 (21.9%)</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>81/940 (8.6%)</td>
<td>98/947 (10.3%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>113/934 (12.1%)</td>
<td>123/939 (13.1%)</td>
</tr>
<tr>
<td>Weight &lt;60 kg, n (%)</td>
<td>47/944 (5.0%)</td>
<td>54/948 (5.7%)</td>
</tr>
<tr>
<td>Killip class II–IV, n (%)</td>
<td>53/895 (5.9%)</td>
<td>50/894 (5.6%)</td>
</tr>
<tr>
<td>TIMI risk score ≥5, n (%)</td>
<td>116/888 (13.4%)</td>
<td>119/867 (13.7%)</td>
</tr>
<tr>
<td>Time to randomization from symptom onset</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to &lt;1 h, n (%)</td>
<td>170/944 (18.0%)</td>
<td>187/948 (19.7%)</td>
</tr>
<tr>
<td>≥1 to &lt;2 h, n (%)</td>
<td>475/944 (50.3%)</td>
<td>456/948 (48.1%)</td>
</tr>
<tr>
<td>≥2 h, n (%)</td>
<td>299/944 (31.7%)</td>
<td>305/948 (32.2%)</td>
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<tr>
<td>Infarct location</td>
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<tr>
<td>Anterior, n (%)</td>
<td>453/942 (48.1%)</td>
<td>431/946 (45.6%)</td>
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<tr>
<td>Inferior, n (%)</td>
<td>468/942 (49.7%)</td>
<td>497/946 (52.5%)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>21/942 (2.2%)</td>
<td>18/946 (1.9%)</td>
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<tr>
<td>Place of randomization</td>
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<tr>
<td>Ambulance, n (%)</td>
<td>768/944 (81.4%)</td>
<td>761/948 (80.3%)</td>
</tr>
<tr>
<td>Community hospital, n (%)</td>
<td>176/944 (18.6%)</td>
<td>187/948 (19.7%)</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; and TIMI, thrombolysis in myocardial infarction.

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**Figure 1. All-cause mortality Kaplan–Meier curves.** PCI indicates percutaneous coronary intervention; and TNK, Tenecteplase.
manner, fibrinolysis remains a more feasible and often the only available reperfusion modality in many regions across the world. STREAM assessed the merits of predominantly prehospital fibrinolysis with contemporary antithrombotic cotherapies followed by a planned angiography or rescue PCI if appropriate in STEMI patients presenting early but unable to undergo primary PCI within 60 minutes, as compared with transport for primary PCI. The 1-year results from STREAM confirm that mortality rates were low, and that a PI strategy resulted in a similar mortality as pPCI. Among the 1792 patients surviving beyond 30 days, there were only 34 more deaths within the first year of follow-up, representing less than one third of total 1-year mortality. Although we did observe an excess of 6 non-cardiac deaths after 30 days in the PI arm, the cardiac as well as all-cause mortality were similar between the 2 arms. These findings were consistent across key prespecified subgroups.

The mortality benefit of transfer for pPCI over on-site fibrinolysis significantly declines when transfer times, including door-in-door-out delays, increase.4 Despite the per-protocol mandate of an expected delay of at least 60 minutes for pPCI, treatment delays were remarkably short in STREAM, in part because of the prehospital triage. In fact, the median delay between first medical contact and primary PCI was 107 minutes, well within the 120-minute guideline-recommended target and shorter than often reported in other trials and real-world registries.1,2 The relatively short treatment delays in both treatment arms might in part explain the lack of a difference in 1-year mortality between the 2 reperfusion strategies in STREAM. Outside the setting of a clinical trial, or in the absence of prehospital triage, however, transfer delays to achieve pPCI are expected to be considerably longer.4,11 Although unproven, one could speculate that, in real-world circumstances, a PI strategy could lead to a greater clinical benefit compared with transfer for primary PCI, given the typically longer PCI-related delays.8

In STREAM, significantly more lytic-treated patients underwent coronary bypass surgery within the first 30 days.7 This is likely attributable in part to the planned angiography between 6 and 24 h after successful fibrinolysis, allowing for a more considered appraisal of the best and more complete revascularization in patients with multi-vessel disease as compared with pPCI patients. Because the number of deaths was also low among patients managed with bypass surgery, it remains unclear from our data whether the longer interval before angiography followed by the appropriate mode of revascularization including coronary bypass surgery would result in improved outcome. It is likely that any potential benefit of such an approach would only become apparent after a longer follow-up.

Pooled data from the CAPTIM and WEST trials suggest that the risk of death at 1 year is lower with early fibrinolysis compared with pPCI in patients presenting within 2 hours of symptom onset.9 In the CAPTIM trial, prehospital fibrinolysis was associated with a lower risk of both cardiogenic shock and death in patients presenting early after symptom onset, compared with transport for primary PCI.4 In STREAM, the composite end point of death, shock, congestive heart failure, and reinfarction was numerically lower in the PI arm at 30 days. This difference was mainly driven by a nonsignificant higher absolute 1.5% incidence of cardiogenic shock and congestive heart failure after pPCI. At 1 year, this beneficial trend did

<table>
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<tr>
<th>Table 2. Causes of Death at 1 Year</th>
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<tr>
<td>Cause</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
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<tr>
<td>Reinfarction</td>
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<tr>
<td>Cardiogenic shock</td>
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<tr>
<td>Cardiac arrest/sudden death*</td>
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<tr>
<td>Other cardiac</td>
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<tr>
<td>Noncardiac†</td>
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<tr>
<td>Stroke or ICH</td>
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<tr>
<td>Major (non-ICH) bleeding</td>
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<tr>
<td>Other noncardiac event</td>
</tr>
</tbody>
</table>

Causes of death were reported by the investigators. ICH indicates intracranial hemorrhage; and PCI, percutaneous coronary intervention.

*Cardiac arrest/sudden death includes death reported to be caused by arrhythmia, asystole, or cardiac rupture; there were 6 cardiac ruptures in the pharmaco-invasive arm, vs 1 after primary PCI.
†Noncardiac causes of death prospectively collected as 3 categories: stroke or ICH, major (non-ICH) bleeding, or other noncardiac event.
not translate into lower mortality rates, however, perhaps in part related to the offsetting small excess of noncardiac death. In addition, the effect of a reduction in cardiogenic shock or heart failure might need longer follow-up to detect an effect on mortality as suggested by observations of other STEMI treatment strategies. Indeed, lower rates of cardiogenic shock in the early-presenting patients with fibrinolysis in CAPTIM were associated with significantly lower 5-year mortality rates.12 In addition, observational 5-year data from the French FAST-MI study suggest a significant long-term survival benefit for prehospital lysis versus primary PCI as well.13

After approximately one fifth of the planned population had been enrolled, the tenecteplase dose was halved in patients aged ≥75 years because of an excess of intracranial hemorrhage in this age group. This change was recommended by the Data and Safety Monitoring Board, and inspired by a successful strategy of half-dose tenecteplase followed by immediate transfer applied in STEMI patients presenting to rural hospitals.14 In the same amendment, the inclusion threshold of 3 mm elevation in at least 2 contiguous leads was decreased to 2 mm for inferior wall myocardial infarction as well. We observed a significant treatment interaction...
for 1-year all-cause mortality in patients randomized before versus after the amendment. In essence, the mortality curves for both arms converged after the amendment. Because no intracranial hemorrhages were observed in the elderly after reducing the tenecteplase bolus, the reduction of tenecteplase bolus might indeed have played a role in mitigating the excess mortality after the amendment. Our observations also suggest that a half-dose bolus might be a safer dosage for elderly patients. Because mortality rates were low, however, we cannot exclude the play of chance. In addition, other factors not related to the amendment might have contributed to the convergence of mortality rates. After the initial start-up of the trial, more international and perhaps less experienced sites started to randomize patients, possibly contributing to the increase in deaths in the primary PCI arm. On the other hand, more experience with the rigorous in- and exclusion criteria with time might have contributed to the decrease in mortality in the PI arm as well.

STREAM was an exploratory randomized, clinical trial without a primary hypothesis. The current findings do not apply to patients who would be able to undergo pPCI within 1 hour after first medical contact, or patients who present beyond 3 hours after symptom onset, or treated with other fibrinolytic agents. Taken together, our 1-year findings support the current 120-minute guideline-recommended maximum tolerable delay overall for transfer to primary PCI as well as the shorter time window of 60 minutes for high-mortality in STEMI patients worldwide.

**Acknowledgments**

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**Disclosures**

Drs Sinnaeve, Gershlick, and Goldstein have received consultancy and travel fees from Boehringer Ingelheim. Dr Armstrong received funding grants from Boehringer Ingelheim, Hoffmann LaRoche, sanofi-aventis Canada Inc, Merck & Company, travel fees from Boehringer Ingelheim, consultancy fees from Eli Lilly, Merck & Company Inc, Hoffmann LaRoche Ltd, and lecture fees from Astra Zeneca and Eli Lilly. Dr Wilcox has received consultancy and travel fees from Boehringer Ingelheim and Daiichi Sankyo. Dr Lambert has received consultancy fees and lecture fees from Boehringer Ingelheim. Drs Danays and Bluthmi are Boehringer Ingelheim employees. Drs Soulat and Ortiz have received consultancy fees from Boehringer Ingelheim. Dr Halvorsen has received speakers honoraria from Boehringer Ingelheim. Dr Vandenberghe has received travel fees through her institution from Boehringer Ingelheim. Dr Regelin is a former Boehringer Ingelheim employee. Drs Danays and Bluthmi have received consultancy fees and travel fees through their institution from Boehringer Ingelheim. Dr Werf has received grants, consultancy fees, and travel and lecture fees from Boehringer Ingelheim.

**References**


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**CLINICAL PERSPECTIVE**

In spite of significant reductions in door-to-balloon time, early mortality rates after primary percutaneous coronary intervention (PCI) remained unchanged, indicating that other components of the total ischemic time such as transport times need to be targeted. Fast transport of a ST—segment-elevation myocardial infarction patient to a PCI hospital is not always possible. In these patients early fibrinolysis, followed by timely angiography, constitutes an alternative reperfusion strategy. In the Strategic Reperfusion Early After Myocardial Infarction (STREAM) study, we compared a pharmaco-invasive treatment with transfer for primary PCI in patients presenting within 3 hours after symptom onset but unable to undergo primary PCI within 1 hour. The pharmaco-invasive strategy consisted of prehospital tenecteplase given before transport, followed by coronary angiography between 6 and 24 hours, or by rescue coronary intervention if there was evidence of failed reperfusion. At 1 year, STREAM showed that the pharmaco-invasive strategy resulted in similar mortality rates as transfer for routine primary PCI. These findings supported the current 60-minute guideline-recommended maximal tolerable delay for transfer for primary PCI in high-risk patients presenting early. In addition, the increased risk of intracranial hemorrhage with fibrinolysis observed early in the trial was significantly attenuated after halving the bolus tenecteplase in patients aged ≥75 years. Taken together, because timely primary PCI remains unattainable in many healthcare systems, an age-adjusted pharmaco-invasive approach as studied in STREAM seems to offer a safe and effective alternative reperfusion therapy to a substantial proportion of ST-segment elevation myocardial infarction patients worldwide. More studies with half-dose tenecteplase in elderly are needed to confirm these findings.
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