Contemporary Mortality Differences Between Primary Percutaneous Coronary Intervention and Thrombolysis in ST-Segment Elevation Myocardial Infarction

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Background: Current ST-segment elevation myocardial infarction guidelines regarding reperfusion strategy are based on trials conducted before the application of routine invasive evaluation after thrombolysis. Modern thrombolysis may affect the previously observed mortality difference between primary percutaneous coronary intervention (PPCI) and thrombolysis.

Methods: In-hospital mortality was prospectively assessed in 5295 patients with ST-segment elevation myocardial infarction admitted to 73 Belgian hospitals from July 1, 2007, through December 31, 2009. A total of 4574 patients (86.4%) were treated with PPCI and 721 (13.6%) received thrombolysis; of these thrombolysis patients, 603 (83.6%) underwent subsequent invasive evaluation. The Thrombolysis in Myocardial Infarction risk score was used to stratify the study population by low (n=1934), intermediate (n=2382), and high (n=979) risk.

Results: In-hospital mortality in the PPCI patients was 5.9% vs 6.6% in the thrombolysis patients. After adjustment for differences in baseline risk profile, a significant mortality benefit was only present in the high-risk groups: 23.7% in the PPCI patients vs 30.6% in the thrombolysis patients. For patients not at high risk, the mortality difference was marginal. For low-risk patients, mortality was 0.3% in the PPCI patients vs 0.4% in the thrombolysis patients. For intermediate-risk patients, mortality was 2.9% in the PPCI patients vs 3.1% in the thrombolysis patients. Subgroup analysis revealed that the mortality benefit of PPCI compared with early thrombolysis (door-to-needle time <30 minutes) was offset if the door-to-balloon time exceeded 60 minutes.

Conclusions: Modern thrombolytic strategies have substantially attenuated the absolute mortality benefit of PPCI over thrombolysis, particularly in patients not at high risk. Our study findings suggest that target door-to-balloon time should be less than 60 minutes to maintain the lowest mortality rates.

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CURRENT GUIDELINES FOR the management of ST-segment elevation myocardial infarction (STEMI) recommend that primary percutaneous coronary intervention (PPCI) is the preferred treatment strategy if it can be conducted in a timely fashion by an experienced catheterization team.[1,2] These

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guidelines are based on several trials and subsequent meta-analyses that demonstrated a mortality benefit of PPCI over thrombolysis independent of the initial baseline risk profile of the patient.[3,4] Most of these studies were conducted before the use of newer adjunctive pharmacotherapies or the application of routine invasive evaluation after thrombolysis, both of which have been associated with better outcomes.[5-9] Hence, there is a need for a more up-to-date evaluation of the benefit of PPCI vs thrombolysis. In addition, because many regions still experience restricted immediate access to a PCI center, many patients will still receive thrombolysis as their initial reperfusion treatment. Thus, selecting those patients who may benefit most from PPCI on admission is important. The Thrombolysis in Myocardial Infarction (TIMI) risk score for STEMI is a simple arithmetic score that predicts short-term mortality based on clinical data easily obtained at admission.[10] This score was developed by the Intravenous nPA [Novel Plasminogen Activator] for Treatment of Infarcting Myocardium Early (InTIME-II) trial and validated with community-based populations that included thrombolysis and PPCI patients. It remains unclear whether this risk

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score could also be helpful in identifying the high-risk patients who would benefit most from invasive treatment. Hence, the present study was designed to evaluate the present-day mortality differences of PPCI over thrombolysis in an unselected community-based population.

METHODS

STUDY POPULATION AND DATA SOURCE

The study population consisted of patients with ST elevation or presumed new left bundle branch block who received reperfusion therapy within 12 hours of symptom onset. The data were extracted from the National STEMI Database of Belgium, a prospective observational database containing demographics, practice patterns, and health outcomes of unselected patients with STEMI. The data were collected for consecutive STEMI patients from 25 hospitals with PCI facilities and 48 hospitals without PCI facilities beginning on July 1, 2007. All treatment decisions were made at the discretion of the treating physicians. The database is managed by an independent electronic data-capture provider (Lambda Plus SA, Gembloux, Belgium), which also manages internal data quality. The data validity was checked in 10.0% of the patient files by an external auditing commission. The database was registered with clinicaltrials.gov (NCT00727623). Informed consent was obtained from all patients.

At the time of analysis, the registry included a total of 6494 patients who sought medical attention from July 1, 2007, through December 31, 2009. We excluded 1199 patients who did not undergo reperfusion therapy and/or were admitted to the hospital more than 12 hours after onset of pain, resulting in a total of 5295 study patients. Of these, 1998 were admitted to a non-PCI center, where thrombolysis was chosen for 566 patients (28.3%), and 1432 patients (71.7%) were transferred immediately to a PCI center for PPCI. The other 3297 patients were directly admitted to a PCI center; most patients (3142 [95.3%]) underwent PPCI, whereas a few (155 [4.7%]) received thrombolysis. Thus, the total study population consisted of 721 thrombolysis patients and 4574 PPCI patients. As many as 83.6% of thrombolysis patients underwent subsequent invasive evaluation in the acute phase of rescue PCI (29.7%) or electively during index hospitalization (53.9%).

TIME DELAYS FOR REPERFUSION THERAPY

Periods related to the initiation of reperfusion therapy were recorded according to the following time delays: less than 30, 30 through 59, 60 through 89, 90 through 120, and more than 120 minutes. A PCI-related time delay was defined as the period between diagnosis of STEMI and first balloon inflation and was expressed as door-to-balloon time (DBT). Data regarding DBT were available for 4469 PPCI patients. The DBT was subdivided into early (DBT $<$60 minutes), intermediate (DBT $\geq$60 and $\leq$120 minutes), and late (DBT $>$120 minutes).

A thrombolysis-related time delay was defined as the period between diagnosis of STEMI and intravenous administration of the thrombolytic agent and was expressed as door-to-needle time (DNT). Data regarding DNT were available for 721 thrombolysis patients. The DNT was subdivided into early (DNT $<$30 minutes), intermediate (DNT $\geq$30 and $\leq$60 minutes), and late (DNT $>$60 minutes).

ASSESSMENT OF RISK AND OUTCOME

The TIMI risk score was used to stratify the patient population into different risk groups. The TIMI risk score was derived from 30-day postpresentation mortality rates but displayed stable prognostic performance across multiple time points, including time to discharge.[10]

For each patient, the TIMI risk score was calculated as the arithmetic sum of the following variables obtained at admission: age of 75 years or older (3 points); age of 65 to 74 years (2 points); history of coronary artery disease, diabetes mellitus, or hypertension (1 point); systolic blood pressure less than 100 mm Hg (3 points); heart rate greater than 100/min (2 points); Killip class 2 to 4 (2 points); weight less than 67 kg (1 point); anterior ST-segment elevation or left bundle branch block (1 point); and time from symptom onset to treatment greater than 4 hours (1 point). Time to treatment was defined as time from symptom onset to start of thrombolysis or time from symptom onset to first balloon inflation.

Patients were classified as low risk if their TIMI score was 0 to 2, intermediate risk if it was 3 to 6, and high risk if it was 7 to 14. In addition, data regarding cardiac arrest before initiation of reperfusion therapy and regarding the personal history of peripheral artery disease were collected. The primary end point was in-hospital death from all causes as late as 30 days after admission. Vital status was assessed in the final hospital before discharge to home.

STATISTICAL ANALYSIS

Continuous variables are presented as the mean values with corresponding SDs, and comparisons between groups were made with an unpaired *t* test. Differences between proportions were assessed by χ^2 analysis. Independent determinants of in-hospital death were determined by means of multiple logistic regression analysis and reported as odds ratios (ORs) and 95% confidence intervals (CIs). Analyses of possible interaction between attributed TIMI risk score and treatment strategy were performed by entering an interaction term into the regression model. Comparison of adjusted mortality ORs between different DNT/DBT subgroups was achieved by adding an interaction term between treatment strategy and DNT/DBT to that logistic regression model. For all analyses, $P<.05$ was considered statistically significant. All statistical analyses were performed using SAS statistical software, version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS

The total study population consisted of 5295 patients, of whom 1934 (36.5%) had a low TIMI risk profile, 2382 (45.0%) had an intermediate TIMI risk profile, and 979 (18.5%) had a high TIMI risk profile. Baseline characteristics of the patients receiving thrombolysis and of those undergoing PPCI are given in **Table 1**. The PPCI patients compared with the thrombolysis patients had more anterior infarctions and were more hemodynamically compromised. However, thrombolysis patients had a shorter ischemic time delay and tended to have less severe concomitant vascular disease. The overall TIMI risk score tended to be slightly lower for thrombolysis patients than for PPCI patients (3.8 vs 4.1).

Early DNT ($<$30 minutes) was achieved in 55.5% of thrombolysis patients, whereas early DBT ($<$60 minutes) was achieved in 57.3% of PCI patients. Fibrinolysis was given before hospitalization in 16.8% of thrombolysis patients.

Table 1. Baseline Patient Characteristics[a]

Characteristic	PPCI (n=4574)	Thrombolysis (n=721)	*P* Value
Age, mean (SD), y	62.2 (12.9)	62.0 (12.7)	.70
Male sex	77.2	75.5	.30
Weight <67 kg	17.5	19.0	.33
Previous CAD	20.0	17.2	.09
Previous PAD	9.9	7.9	.10
Arterial hypertension	43.3	45.3	.31
Diabetes mellitus	13.9	14.4	.76
Killip class >1	21.6	16.4	.001
Heart rate >100 bpm	13.5	13.2	.86
Blood pressure <100 mm Hg	20.7	14.7	<.001
Cardiopulmonary resuscitation	12.3	10.8	.27
Infarction location, anterior or LBBB	42.9	40.2	.03
Time from symptom onset to treatment, h			
<4	68.4	79.1	<.001
4-8	23.7	15.7	
>8-12	7.8	5.3	
Door-to-needle/balloon			<.001
Early	56.0	48.0	
Intermediate	33.1	18.6	
Late	8.6	19.8	
Not available	2.3	13.6	
TIMI risk score, mean (SD)	4.1 (2.8)	3.8 (2.7)	.06
TIMI risk score group			
Low (0-2)	36.2	38.3	.36
Intermediate (3-6)	45.0	45.0	
High (7-14)	18.7	16.8	

Abbreviations: CAD, coronary artery disease; LBBB, left bundle branch block; PAD, peripheral artery disease; PPCI, primary percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.
[a]Data are presented as percentage of patients unless otherwise indicated.

IN-HOSPITAL MORTALITY AND REPERFUSION STRATEGY

The in-hospital mortality rate of the total group was 6.0% and occurred a median of 2 days (25th and 75th percentiles, 0-7 days) after admission. The mortality rate in the thrombolysis patients was 6.6% vs 5.9% in the PPCI patients (unadjusted $P=.40$). To correct for differences in risk score profile between the 2 study groups, the mortality rates for the thrombolysis and PPCI groups were compared across different risk categories (**Figure 1**).

A nonlinear relationship was found between risk score and mortality for thrombolysis and PPCI patients, with a nearly 30-fold increase in risk between patients with a score of 0 and those patients with a score of 8 or higher (range, <1% to >30%). The mortality benefit of PPCI vs thrombolysis appears to be mainly driven by the benefit observed in the high-risk groups. The absolute mortality benefit in the high-risk group was 7.1% (30.6% in the thrombolysis patients vs 23.7% in the PPCI patients, adjusted $P=.03$), whereas the absolute mortality difference was marginal in the intermediate-risk (0.2%; 3.1% in the thrombolysis patients vs 2.9% in the PPCI patients; adjusted $P=.30$) and low-risk (0.1%; 0.4% in the thrombolysis patients vs 0.3% in the PPCI patients; adjusted $P=.60$) groups.

Table 2 summarizes the independent predictors of in-hospital mortality, including the individual factors of the TIMI risk score and additional factors, such as sex, cardiopulmonary resuscitation on presentation, previous peripheral arterial disease, hospital admission (PCI or non-PCI center), and treatment time delay (DNT/DBT) not captured by the TIMI risk score. The most important independent risk factors for in-hospital death were age, Killip class greater than 1, low blood pressure, cardiopulmonary resuscitation, history of peripheral arterial disease, longer treatment delay, anterior infarction location, and female sex. Treatment strategy also remained an important independent predictor in favor of PPCI for high-risk patients, for whom the OR was 0.54. For the low- and intermediate-risk groups, no significant difference was found between PPCI and thrombolysis. No significant interaction effect was found between attributed TIMI risk group and treatment strategy.

Finally, **Figure 2** shows the adjusted mortality OR of different DBT and DNT subgroups (early, intermediate, or late) compared with the early PCI subgroup. All subgroups showed a significantly higher OR than the early PCI group, suggesting that the DBT should be less than 60 minutes to maintain the lowest mortality rates. Additional analysis showed no significant difference in adjusted mortality OR between early thrombolysis and the intermediate PCI subgroup (OR, 1.5; 95% CI, 0.7-3.1).

COMMENT

Our findings indicate that the mortality benefit of PPCI compared with thrombolysis in STEMI patients has been substantially attenuated, particularly in the low- and intermediate-risk groups and most likely because of im-

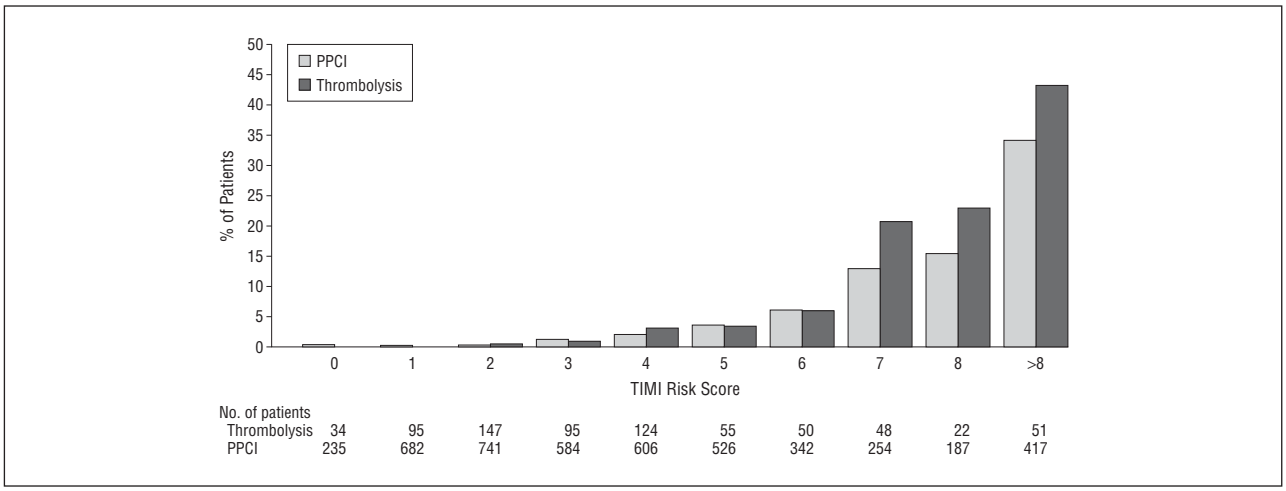

Figure 1. In-hospital mortality rates stratified according to the Thrombolysis in Myocardial Infarction (TIMI) risk score for study patients treated with primary percutaneous coronary intervention (PPCI) vs study patients treated with thrombolysis.

proved outcomes of thrombolysis. According to the most recent systematic analysis of 23 randomized trials, published by Keeley et al[3] in 2003, PPCI was associated with an overall 27% relative risk reduction compared with thrombolysis (95% CI, 14%-38%) of short-term death and an average absolute risk reduction of 2% (5% vs 7%). This benefit was found irrespective of the type of fibrinolytic regimen used, the PPCI modality (on site or after transfer), or patient risk (high vs low). These findings were subsequently reproduced in large STEMI registries, such as the National Registry of Myocardial Infarction 3. In this registry, patients treated with PPCI had a lower risk of in-hospital mortality compared with patients treated with thrombolysis, irrespective of the initial baseline risk profile.[11]

The present study demonstrates that, over time, this benefit of PPCI might have changed substantially. The actual absolute mortality difference between PPCI and thrombolysis was less than 0.5% in low- and intermediate-risk groups. Those patients had an in-hospital mortality rate of less than 5.0% irrespective of the modality of reperfusion therapy used. Only in high-risk patients did the absolute mortality benefit of PPCI continue to be substantial (>5.0%), with an adjusted relative risk reduction of 45.7%.

The most important reason for the observed lack of benefit in non–high-risk groups appears to be the improved outcome of thrombolysis patients. Comparison of the present data with the historical data from InTIME-II revealed a clear shift toward lower in-hospital mortality rates mainly in the non–high-risk groups (data not shown).[10] Higher use of invasive evaluation after thrombolytic therapy (83.6% in the current population vs 30% in InTIME-II) might explain this favorable mortality trend. Recent data have indeed shown that a pharmacoinvasive strategy combining thrombolysis with a liberal use of PCI yields early and 1-year survival rates that are comparable to those of PPCI.[7,12,13] The beneficial effect on mortality in those studies was mainly driven by lower rates of reinfarction and/or recurrent ischemia.

In addition, improvements in adjunctive pharmacotherapy, such as those obtained with clopidogrel bisulfate and enoxaparin sodium, might contribute to improved survival after thrombolytic therapy. Although concomitant medications were not recorded in this study, based on our knowledge of the standard STEMI treatment protocols used in each of the participating hospitals, we may assume that many thrombolysis patients received adjunctive therapy with clopidogrel and/or enoxaparin. These more efficient antithrombotic agents improve outcome, particularly by reducing the reinfarction rate.[5,6]

The clinical consequences of our findings may be of particular interest for hospitals with limited urgent access to PCI facilities. Although the rate of PPCI has in-

Table 2. Predictors of In-Hospital Mortality

Characteristic	OR (95% CI)
Age	1.04 (1.03-1.06)
Killip class >1	6.5 (4.3-9.9)
Cardiopulmonary resuscitation	5.1 (3.7-7.0)
Blood pressure <100 mm Hg	2.2 (1.5-3.2)
Previous PAD	2.3 (1.6-3.3)
Female sex	1.8 (1.3-2.5)
Anterior infarction location, %	1.35 (1.01-1.80)
PPCI vs thrombolytic therapy	
TIMI risk score	
Low (0-2)	0.58 (0.10-5.30)
Intermediate (3-6)	0.64 (0.30-1.40)
High (7-14)	0.54 (0.30-0.90)
DBT/DNT category	
Early vs intermediate	0.7 (0.5-1.0)
Early vs late	0.5 (0.3-0.7)
Intermediate vs late	0.7 (0.4-1.1)
Ischemic time >4 h	1.4 (1.0-1.9)
Heart rate >100 bpm, %	1.2 (0.9-1.7)
Weight <67 kg, %	0.9 (0.6-1.3)
Previous CAD, %	1.0 (0.8-1.5)
Arterial hypertension, %	1.1 (0.8-1.5)
Diabetes mellitus, %	1.0 (0.7-1.5)
Admission to PCI center	1.2 (0.9-1.6)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DBT/DNT, door-to-balloon time/door-to-needle time; OR, odds ratio; PAD, peripheral artery disease; PPCI, primary percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

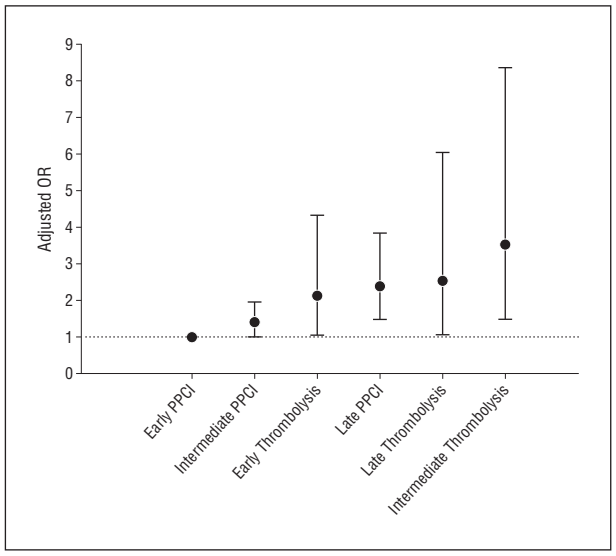

Figure 2. Adjusted mortality odd ratios (ORs) with 95% confidence intervals (error bars) of different door-to-balloon and door-to-needle time groups compared with the early percutaneous coronary intervention (PCI) subgroup.

creased over time, the penetration rate of PCI still remains less than 50% in many regions in Europe and the United States.[14,15] Many regions still rely on thrombolysis as the first-line reperfusion therapy because of the limited availability of hospitals with catheterization facilities and/or the limited or poorly organized local medical transport systems. Hence, our findings provide reassurance to physicians at these hospitals that treating patients according to the guidelines (ie, early administration of lytic therapy when PCI is unavailable and planning early angiography) is associated with excellent prognosis in a real-word setting. The present study also highlights that the TIMI risk score, which was previously established as a prognostic risk score, can also identify which patients will benefit most from PPCI. This finding is in line with that of a recent post hoc analysis of the Danish Multicenter Randomized Study on Fibrinolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction showing no benefit of PPCI over thrombolysis in low-risk groups.[16] According to our database, patients with a TIMI risk score greater than 6 will benefit most from PPCI. They represent approximately 20% of the STEMI population and consist mainly of elderly (older than 75 years) patients with hemodynamic instability. Compared with other acute coronary syndrome risk scores, such as the Global Registry of Acute Coronary Events, the TIMI risk score has the advantage of using only clinical data that are easily obtained at admission (or even before hospitalization) without any need for complex calculations.[17]

Our findings may also have clinical consequences for regions with easy direct access to a catheterization laboratory. For these regions PPCI clearly remains the preferred reperfusion therapy independent of the baseline risk profile because it is associated with the lowest mortality rates and reduces rates of nonfatal reinfarction and stroke. However, current recommendations regarding the maximal acceptable time delay related to PPCI that still provides a superior mortality benefit compared with thrombolysis are mainly based on analysis of older registries.[18,19] The present study revealed that the superior mortality benefit of PPCI compared with optimal thrombolysis appeared to be offset when the DBT exceeded 60 minutes. More large-scale registries will be needed to redefine this maximal acceptable PCI-related time delay, but according to our data, this appears to be shorter than the previously estimated 90 to 120 minutes.

The results of this study should be considered in view of the following limitations. Our evaluation of treatment differences focused only on short-term mortality. Although other outcome parameters, such as reinfarction rate, stroke, or long-term mortality, may provide a more complete picture of the benefits of PPCI vs thrombolysis, previous studies have shown that short-term mortality is a reliable and representative parameter for global outcome; indeed, up to 50% of episodes of reinfarction and stroke are fatal, and the major differential effect of 2 different treatment strategies is mainly seen in the early postinfarction phase.[20-22]

Although the study design called for consecutive enrollment of STEMI patients, underreporting cannot be excluded and may have created a selection bias. We tried to minimize this effect by organizing audits in each of the participating hospitals and focusing the analysis on relative risk reductions across different risk profiles. In addition, the average mortality rate of 6% in our study population is in concordance with mortality rates of STEMI patients from other recent nationwide registries.[2,14] In conclusion, the present study showed that modern thrombolytic strategies as advocated in the recent STEMI guidelines have substantially attenuated the superior mortality benefit of PPCI compared with thrombolysis, particularly in non–high-risk patient groups.

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