ST segment resolution in patients with tenecteplase-facilitated percutaneous coronary intervention versus tenecteplase alone: Insights from the Combined Angioplasty and Pharmacological Intervention versus Thrombolysis ALone in Acute Myocardial Infarction (CAPITAL AMI) trial

Derek YF So MD FRCPC, Andrew CT Ha MD FRCPC, Richard F Davies MD FRCPC PHD,
Michael Froeschl MD FRCPC, George A Wells PHD, Michel R Le May MD FRCPC

DYF So, ACT Ha, RF Davies, M Froeschl, GA Wells, MR Le May. ST segment resolution in patients with tenecteplase-facilitated percutaneous coronary intervention versus tenecteplase alone: Insights from the Combined Angioplasty and Pharmacological Intervention versus Thrombolysis ALone in Acute Myocardial Infarction (CAPITAL AMI) trial. *Can J Cardiol* 2010;26(1):e7-e12.

BACKGROUND: Compared with fibrinolysis alone, fibrinolysis followed by immediate percutaneous coronary intervention (PCI) reduced clinical events in the Combined Angioplasty and Pharmacological Intervention versus Thrombolysis ALone in Acute Myocardial Infarction (CAPITAL AMI) study. It is unclear whether the benefits go beyond achieving epicardial reperfusion.

OBJECTIVES: To determine the differences in ST segment resolution (STR) among patients treated with tenecteplase (TNK)-facilitated PCI compared with patients treated with TNK alone.

METHODS AND RESULTS: A formal ST segment analysis was conducted on the 170 patients with ST elevation myocardial infarction in the CAPITAL AMI trial: 86 patients treated with TNK-facilitated PCI were compared with 84 patients who were treated with TNK alone. Epicardial flow measured by percentage with Thrombolysis In Myocardial Infarction (TIMI) 3 flow improved from 52% (pre-PCI) to 89% (post-PCI) in those assigned to facilitated PCI. ST segment resolution was stratified by complete (70% or greater), partial (less than 70% to 30%) or no (less than 30% to 0%) resolution. The baseline mean ST segment elevation was 11.3 ± 7.5 mm in the facilitated PCI patients and 11.8 ± 7.1 mm in patients with TNK alone ($P=0.66$). Complete STR in the facilitated PCI patients versus the TNK-alone patients was present in 55.6% versus 54.6%, respectively ($P=0.58$) at 180 min and 62.0% versus 55.3% ($P=0.64$), respectively at day 1. The mean STR at 180 min and day 1 were similar in patients who experienced death, reinfarction, recurrent unstable ischemia or stroke at six months compared with patients who remained event free: 56.3% versus 64.6% at 180 min ($P=0.40$); and 67.7% versus 67.6% at day 1 ($P=0.99$), respectively.

CONCLUSIONS: TNK-facilitated PCI did not demonstrate differences in ST segment resolution compared with TNK alone, despite improvement in epicardial flow after PCI. Further studies are required to clarify these findings.

Key Words: Facilitated PCI; ST elevation myocardial infarction; ST segment resolution

La résolution du segment ST chez les patients ayant subi une intervention coronaire percutanée facilitée par le ténecteplase par rapport au ténecteplase seul : Aperçus de l'essai CAPITAL AMI sur l'angioplastie combinée et l'intervention pharmacologique par rapport à la thrombolyse seule en cas d'infarctus aigu du myocarde

HISTORIQUE : Par rapport à la fibrinolyse seule, la fibrinolyse suivie d'une intervention coronaire percutanée (ICP) immédiate réduisait les événements cliniques dans le cadre de l'essai CAPITAL AMI sur l'angioplastie combinée et l'intervention pharmacologique par rapport à la thrombolyse seule en cas d'infarctus aigu du myocarde. On ne sait pas si les bienfaits vont au-delà d'une reperfusion épicardique.

OBJECTIFS : Déterminer les différences de résolution du segment ST (RST) chez les patients traités au moyen d'une ICP facilitée par le ténecteplase (TNK) par rapport à ceux traités au moyen de TNK seul.

MÉTHODOLOGIE ET RÉSULTATS : On a effectué une analyse officielle du segment ST auprès de 170 patients ayant eu un infarctus du myocarde avec élévation du segment ST dans le cadre de l'essai CAPITAL AMI : les 86 patients traités par ICP facilitée par le TNK ont été comparés aux 84 patients traités par TNK seul. Le débit épicardique mesuré en pourcentage au moyen de la thrombolyse dans l'infarctus du myocarde à triple flux est passé de 52 % (avant l'ICP) à 89 % (après l'ICP) chez les patients faisant partie de l'ICP facilitée. La résolution du segment ST était stratifiée selon la résolution complète (70 % ou plus), partielle (moins de 70 % à 30 %) ou inexistante (moins de 30 % à 0 %). L'élévation moyenne du segment ST de départ était de $11,3 \pm 7,5$ mm chez les patients ayant eu une ICP facilitée et de $11,8 \pm 7,1$ mm chez ceux prenant seulement le TNK ($P=0,66$). On constatait une RST complète chez 55,6 % des patients ayant eu une ICP facilitée par rapport à 54,6 % de ceux prenant seulement le TNK ($P=0,58$) au bout de 180 minutes et de 62 % par rapport à 55,3 % ($P=0,64$), respectivement, le jour 1. La RST moyenne à 180 minutes et le jour 1 était similaire chez les patients qui sont décédés ou ont eu un nouvel infarctus, une ischémie instable récurrente ou un accident vasculaire cérébral au bout de six mois par rapport à ceux qui n'en avaient pas subi, soit 56,3 % par rapport à 64,6 % à 180 minutes ($P=0,40$) et 67,7 % par rapport à 67,6 % le jour 1 ($P=0,99$), respectivement.

CONCLUSIONS : L'ICP facilitée par le TNK n'entraînait pas de différence entre la RST et le TNK seul, malgré une amélioration du débit épicardique après l'ICP. D'autres études s'imposent pour clarifier ces constatations.

University of Ottawa Heart Institute, Ottawa, Ontario

Correspondence and reprints: Dr Derek YF So, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario K1Y 4W7.

Telephone 613-761-5387, fax 613-761-4338, e-mail dso@ottawaheart.ca

Received for publication May 22, 2008. Accepted May 26, 2009

Recent studies have tried to define the role of new reperfusion strategies for patients with ST elevation myocardial infarction (STEMI) (1-7). These trials and subsequent qualitative reviews have provided insights into the three primary modalities: primary percutaneous coronary intervention (PCI), fibrinolysis-facilitated PCI and fibrinolysis alone (8,9). Primary PCI performed in a timely fashion has been shown to be superior to facilitated PCI and fibrinolysis (2,6,10). Lack of on-site catheterization or long transfer delays may make primary PCI unrealistic (11). The options then include fibrinolysis with a wait-and-see approach or immediate transfer for PCI after initiating fibrinolysis. Contemporary randomized trials comparing fibrinolysis-facilitated PCI and fibrinolysis alone demonstrated that early systematic PCI after fibrinolysis decreased adverse outcomes (1,3-5,7,8). This benefit may be due to earlier and more complete restoration of an 'open artery', and consequently, increased myocardial salvage (12). The basis of this rationale has not been fully elucidated and the advantages provided with early epicardial reperfusion have not been confirmed to improve microvascular perfusion (13).

Analysis of ST segment resolution (STR) on electrocardiograms (ECGs) provides a simple means to document the success of epicardial reperfusion, and predict the short- and long-term prognosis of patients after STEMI (14-23). Resolution of ST segment elevation has also been used as a tool to evaluate microvascular- and tissue-level perfusion (24-26). Persistent elevation of ST segments after restoration of epicardial flow may be indicative of incomplete myocardial reperfusion and confers a poorer prognosis (27,28).

The Combined Angioplasty and Pharmacological Intervention versus Thrombolysis ALone in Acute Myocardial Infarction (CAPITAL AMI) trial provided the opportunity to compare STR in patients treated with facilitated PCI and fibrinolysis alone. The trial randomly assigned 170 high-risk patients with STEMI to a strategy of tenecteplase (TNK)-facilitated PCI or TNK alone. The primary end point was a composite of death, reinfarction, recurrent unstable ischemia or stroke at six months. All patients received full-dose TNK with weight-adjusted unfractionated heparin. Patients in the TNK-alone arm were brought for acute cardiac catheterization if persistent ST segment elevation existed after 90 min or more, or if there was hemodynamic deterioration. The rate of rescue for patients treated with fibrinolysis alone was 9.5%. The results of the CAPITAL AMI trial demonstrated a reduction in the primary end point from 24.4% in the fibrinolysis-alone arm to 11.6% in the facilitated PCI arm.

The aim of the present substudy of CAPITAL AMI was to evaluate the differences in STR in patients receiving TNK-facilitated PCI compared with those receiving TNK alone. Improved STR in patients receiving TNK-facilitated PCI may infer better epicardial and microvascular reperfusion. Analysis of STR may also provide insights into the long-term prognosis of patients receiving fibrinolysis-facilitated PCI.

METHODS

All patients enrolled in the CAPITAL AMI trial were reviewed and only patients with a complete set of ECGs (ie, baseline, within 4 h of reperfusion therapy, and day 1) were included. ECGs with features confounding proper ST segment evaluation, such as left bundle branch block, accelerated idioventricular rhythm and missing leads, were excluded from the analysis. Two investigators blinded to the clinical outcomes analyzed all available ECGs. ST segment analysis was conducted according to previously validated criteria (20,21). ST segments were measured 20 ms after the end of the QRS complex and the TP segment was used as the isoelectric reference baseline. The sum of ST segment elevation was measured for anterior STEMI (V1 to V6, I and aVL) and inferior STEMI (II, III, aVF, V5 and V6) (22). For measurement of total ST segment deviation, leads with 1 mm or greater depression were added to the sum of ST segment elevation for anterior STEMI (leads II, III and aVF) and inferior STEMI (leads V1 to V4). ST elevation in the single lead with the highest ST elevation was also measured. Measurement of the corrected Thrombolysis In Myocardial Infarction frame count (CTFC) was performed as described by Gibson et al (29).

The protocols of the CAPITAL AMI trial and the present substudy were approved by the institutional review boards of each hospital involved in the study. Informed consent was obtained from all patients.

Stratification of STR and CTFC

As per previous studies, the extent of STR was calculated by comparison with the baseline ECG (20,22). The results were divided into three prognostic groups. Complete STR was defined as 70% or greater; partial STR as less than 70% to 30%; and no resolution as less than 30% to 0% or greater. For the 180 min ECG, a time window of 120 min to 240 min was allowed, as per previous studies (20,22). The day 1 ECG was the first ECG recorded more than 24 h and less than 48 h after random assignment.

The CTFC was divided into two groups based on a previous analysis (30) demonstrating a correlation with left ventricular recovery and long-term outcomes after myocardial infarction. Patients with a CTFC of 27 or less were defined as low CTFC, while those with a CTFC of greater than 27 were defined as high CTFC (30).

Statistical analysis

Analysis was performed according to an intention-to-treat principle. Categorical variables are reported as percentages using a Fisher's exact test or χ^2 test. For continuous variables, a Student's *t* test was used for normally distributed variables and Wilcoxon's rank-sum test was used for non-normal data. ST segment resolution was considered categorical (complete, partial and no resolution) as well as continuous. All significant tests were two-sided with statistical significance predefined as $P < 0.05$. Statistical analysis was conducted using Systat 11.0 (Systat Software Inc, USA).

RESULTS

In patients randomly assigned to the TNK-facilitated PCI group, epicardial flow was assessed using Thrombolysis In Myocardial Infarction (TIMI) flow grades. At baseline angiography, the rate of patency (TIMI 2 or 3) was 84% and the TIMI 3 flow was 52%. After PCI, the rate of patency improved to 97%, with 89% achieving TIMI 3 flow. A complete ECG data set was available for analysis in 169 of the 170 randomized patients. One patient was excluded because of an underlying left bundle branch block. The two treatment groups were well matched in baseline ECG parameters (Table 1).

STR comparison between TNK-facilitated PCI and TNK alone

Using the sum of ST segment elevation criteria at 180 min, the distribution of STR (complete, partial and no resolution, respectively) was 54.6%, 32.5% and 13.0% in the facilitated PCI group, and 55.6%, 26.4% and 18.1% in the TNK-alone group ($P = 0.58$). Similarly, at day 1, STR distributions were 55.3%, 29.4% and 15.3%, respectively, in the facilitated group, and 62.0%, 26.6% and 11.4%, respectively, in the TNK-alone group ($P = 0.64$). Table 2 summarizes the differences in achieving complete STR using several validated ECG criteria between the facilitated PCI group and the TNK-alone group. Quantile plots of STR of ST elevation further demonstrate no discrepancy in the distribution of STR between the two treatment groups (Figure 1).

Correlation of STR with CTFC in patients with facilitated PCI

Among patients in the facilitated PCI group, 71 had complete data for the analysis of both CTFC and STR. Of this group, 30 patients (42.3%) had a CTFC of greater than 27 (high CTFC), versus 41 (57.7%) with a CTFC of 27 or less (low CTFC). Analysis of STR at 180 min demonstrated that patients with a low CTFC had a higher mean STR than those with a high CTFC (Figure 2).

Correlation of STR with clinical outcomes

By sum of ST elevation, the average STR at 180 min was 56.3% in patients with a primary end point and 64.6% in those without a primary end point ($P = 0.40$). The day 1 ECG also revealed no differences in STR between those with and without primary end

TABLE 1
Baseline electrocardiogram parameters in patients receiving tenecteplase (TNK)-facilitated percutaneous coronary intervention (PCI) compared with those receiving TNK alone

Characteristics	TNK-facilitated PCI (n=86)	TNK alone (n=84)	P
Anterior wall myocardial infarction, %	52.3	49.3	0.70
Leads with ST segment elevation, n	4.4±1.5	4.4±1.6	0.97
Total ST segment elevation, mm	11.3±7.5	11.8±7.1	0.66
ST segment elevation in the lead with the highest elevation, mm	3.9±2.0	4.1±1.9	0.56
Leads with ST segment deviation, n	6.4±1.9	6.4±1.8	0.96
Total ST segment deviation, mm	14.4±7.9	15.5±8.6	0.41

Data presented as mean ± SD unless otherwise indicated

TABLE 2
Percentage of patients achieving complete ST segment resolution* receiving tenecteplase (TNK)-facilitated percutaneous coronary intervention (PCI) compared with those receiving TNK alone at 180 min and at day 1

Criteria	TNK-facilitated PCI (n=86), %	TNK alone (n=84), %	P
ST elevation resolution at 180 min	55.6	54.6	0.58
ST elevation resolution at day 1	62.0	55.3	0.64
ST deviation resolution at 180 min	57.8	58.7	0.80
ST deviation resolution at day 1	65.4	54.8	0.36
ST segment elevation resolution in highest lead at 180 min	54.3	50.1	0.45
ST segment elevation resolution in highest lead at day 1	61.5	50.0	0.27

*Complete ST segment resolution defined as ≥70% compared with baseline

Figure 1 A Quantile plot of ST segment elevation (STE) resolution in tenecteplase (TNK)-facilitated percutaneous coronary intervention (PCI) versus TNK alone at 180 min. B Quantile plot of STE resolution in TNK-facilitated PCI versus TNK alone at day 1

points (67.7% versus 67.6%, respectively; $P=0.99$). At 30 days, eight patients in the TNK-facilitated PCI group suffered a primary outcome, compared with 15 in the TNK-alone group. The distribution of STR within the group was 42.9%, 42.9% and 14.3% for complete, partial and no STR, respectively, at 180 min ($P=0.27$).

DISCUSSION

The present study was the first to compare STR in patients treated with fibrinolysis-facilitated PCI versus fibrinolysis alone. Despite improvements in TIMI flow grades in patients who underwent TNK-facilitated PCI, we found no difference in early STR between patients with STEMI who were treated with TNK-facilitated PCI compared with TNK alone. These results suggest that the reduction in clinical ischemic events in the CAPITAL AMI study was not related to STR.

The extent of STR is a powerful tool in the evaluation of reperfusion therapy in patients with STEMI (23). In both fibrinolytic therapy and primary PCI trials, complete STR after the procedure has been correlated with decreased mortality (20,23,27,31). Epicardial flow, as measured by TIMI flow grade, has been demonstrated to correlate with STR (32). Furthermore, STR has been demonstrated to predict perfusion at a microvascular level (23). Studies have also shown that STR correlates with higher myocardial salvage and a better left ventricular ejection fraction (23,33).

Figure 2 Mean percentage ST segment resolution (STR) at 180 min in patients with facilitated percutaneous coronary intervention divided by high (left bar) versus low (right bar) corrected Thrombolysis In Myocardial Infarction frame count (CTFC). High CTFC is >27 and low CTFC is ≤27

The expected outcome of the present study would be that STR improved in patients assigned to TNK-facilitated PCI because better epicardial flows were achieved after PCI. The lack of differences in

STR between the two randomized groups warrants further explanation. A likely possibility may be an ongoing compromise in microvascular reperfusion. This is further supported by the absence of a difference in left ventricular ejection fraction improvement at 30 days between the two groups (1). In the TIMI-14 study, patients with persistent ST segment elevation were at increased risk despite a patent infarct-related artery; the investigators attributed this finding to impaired microvascular perfusion and tissue damage (32). The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) study (16) included patients with glycoprotein IIb/IIIa-facilitated PCI. Despite achievement of TIMI 3 flow in 96.1% of patients in the trial, only 17.4% of patients had normal myocardial perfusion as assessed by blush grade (34).

Corrected TIMI frame count has also been correlated with microvascular reperfusion and myocardial salvage (30,35,36). Because of the CAPITAL AMI study design, CTFC was not possible in patients randomly assigned to the TNK-alone arm. Analysis of the CTFC in patients receiving facilitated PCI demonstrated that those with a low CTFC had a better percentage STR. Because CTFC is an alternate measure of microvascular flow and myocardial recovery, this observed correlation of low CTFC with improved STR would support the hypothesis of ongoing microvascular impairment in patients with TNK-facilitated PCI.

If microvascular perfusion was compromised in patients with TNK-facilitated PCI, the mechanisms may be a result of several causes. Mechanical intervention on a ruptured plaque during facilitated PCI may cause microembolization of thrombus into the distal bed, thereby compromising microvascular flow (28,37,38). Restoration of flow may also result in hemorrhagic injury, which may be especially detrimental in patients presenting later after symptom onset (31). Finally, delays from symptom onset to treatment may already have caused irreversible damage, where myocardial salvage is minimal despite restoration of flow in the epicardial vessel (12,39).

Other explanations may contribute to the lack of differences in STR if impaired microvascular reperfusion is not the cause. First, rescue performed in 9.5% of patients in the TNK-alone group may have diminished the actual differences in STR. Previous studies have suggested that STR may worsen in some patients undergoing PCI after fibrinolysis (31). Although this was not observed in the overall cohort in our study, it is conceivable that this phenomenon in a small group of patients may dilute the overall STR effect within the TNK-facilitated arm.

The clinical benefits observed with TNK-facilitated PCI are likely due to an improvement in epicardial patency coupled with prevention of reocclusion in the infarct-related artery. A similar parallel can be drawn from the CADILLAC trial, where primary stenting reduced ischemic events at six months compared with balloon angioplasty alone, despite no significant difference in the rates of TIMI 3 flow and TIMI blush scores (34).

Primary PCI has been definitively proven to be a better strategy if conducted in an expedient manner (2). For geographical regions where fibrinolysis remains the initial modality of treatment, further strategies may be required for high-risk patients who may be receiving a pharmacoinvasive approach. A substudy of TIMI-14 demonstrated that in patients initially treated with fibrinolysis, those who also received abciximab during subsequent facilitated PCI had better STR than those with fibrinolysis-facilitated PCI alone (23,40,41). The recently published Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI) (7) showed half-dose reteplase plus glycoprotein IIb/IIIa (abciximab) with immediate transfer for PCI to be superior to this regimen without immediate PCI. The Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) (42), however, demonstrated that, when feasible, primary PCI is better than facilitated PCI with glycoprotein IIb/IIIa, or IIb/IIIa in conjunction with fibrinolysis. Thus, the role of glycoprotein IIb/IIIa

receptor inhibitors in the presence of fibrinolysis needs further elucidation.

Use of thrombectomy or distal protection devices has been shown to improve STR in smaller preliminary studies (43,44). Previously, these devices have failed to limit infarct size or improve clinical outcomes (45,46). The recently published Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) (28) randomly assigned 1071 patients, and demonstrated clear improvements in STR and blush score with routine aspiration. A one-year follow-up reported mortality reduction in patients who received aspiration during primary PCI. The use of an aspiration device may be a strategy to improve the extent of STR in patients receiving TNK-facilitated PCI.

Limitations

The improvement in epicardial patency in the facilitated PCI arm coupled with an almost identical degree of STR between the two arms would suggest that even if differences in STR exist, a very large study would be needed to prove the difference. Because of the study design, patients in the TNK-alone group did not receive immediate cardiac catheterization; therefore, comparison of TIMI flow grade or TIMI blush scores relative to the facilitated PCI group was not possible. Because the present study was a randomized trial, the assumption would be that patients receiving TNK alone would have had the same epicardial flow as the pre-PCI flow of those in the facilitated arm. Because the use of STR as a gauge of microvascular perfusion has been validated (23), ongoing impairment in microvascular perfusion would be a possible assumption for the findings of the present study. The correlation of lower CTFC with better STR in patients with facilitated PCI would substantiate this hypothesis. To definitively delineate the status of the microvasculature in patients with TNK-facilitated PCI would require a prospective study that incorporates a modality to measure myocardial perfusion in both arms of the study.

The small sample size and low event rates may be confounding variables for definitive conclusions to be drawn between STR and clinical outcomes in the present study. Also, the primary outcome of CAPITAL AMI was a composite of death, reinfarction, recurrent unstable ischemia or stroke. ST segment resolution may not be reflective of all components within this primary outcome, especially if it is primarily driven by recurrent ischemia. Irrespective of the exact mechanisms behind the lack of differences in STR, our study suggests that new strategies should be considered when treating these high-risk patients.

CONCLUSIONS

Percutaneous coronary intervention performed immediately after fibrinolysis did not improve ST segment resolution compared with fibrinolysis alone, despite improvements in epicardial patency after facilitated PCI. Further studies are required to explain these observations.

ACKNOWLEDGEMENTS: The parent CAPITAL AMI study was supported by a peer review grant from the Canadian Institutes of Health Research (CIHR), and a CIHR Industry-Partnered Program with Hoffmann La-Roche Limited Canada and Guidant Corporation Canada.

REFERENCES

1. Le May MR, Wells GA, Labinaz M, et al. Combined angioplasty and pharmacological intervention versus thrombolysis alone in acute myocardial infarction (CAPITAL AMI study). *J Am Coll Cardiol* 2005;46:417-24.
2. Primary versus tenecteplase-facilitated percutaneous coronary intervention in patients with ST segment elevation acute myocardial infarction (ASSENT-4 PCI): Randomised trial. *Lancet* 2006;367:569-78.

3. Armstrong PW. A comparison of pharmacologic therapy with/without timely coronary intervention vs. primary percutaneous intervention early after ST elevation myocardial infarction: The WEST (Which Early ST elevation myocardial infarction Therapy) study. *Eur Heart J* 2006;27:1530-8.
4. Scheller B, Hennen B, Hammer B, et al. Beneficial effects of immediate stenting after thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 2003;42:634-41.
5. Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST segment elevation (GRACIA-1): A randomised controlled trial. *Lancet* 2004;364:1045-53.
6. Andersen HR, Nielsen TT, Rasmussen K, et al. A comparison of coronary angioplasty with fibrinolytic therapy in acute myocardial infarction. *N Engl J Med* 2003;349:733-42.
7. Di Mario C, Dudek D, Piscione F, et al. Immediate angioplasty versus standard therapy with rescue angioplasty after thrombolysis in the Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction (CARESS-in-AMI): An open, prospective, randomised, multicentre trial. *Lancet* 2008;371:559-68.
8. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: A multiple meta-analyses approach according to the type of strategy. *J Am Coll Cardiol* 2006;48:1326-35.
9. Keeley EC, Boura JA, Grines CL. Comparison of primary and facilitated percutaneous coronary interventions for ST elevation myocardial infarction: Quantitative review of randomised trials. *Lancet* 2006;367:579-88.
10. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.
11. Angeja BG, Gibson CM, Chin R, et al. Predictors of door-to-balloon delay in primary angioplasty. *Am J Cardiol* 2002;89:1156-61.
12. Gersh BJ, Stone GW, White HD, Holmes DR Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: Is the slope of the curve the shape of the future? *JAMA* 2005;293:979-86.
13. Roe MT, Ohman EM, Maas AC, et al. Shifting the open-artery hypothesis downstream: The quest for optimal reperfusion. *J Am Coll Cardiol* 2001;37:9-18.
14. Zeymer U, Schroder R, Tebbe U, Molhoek GP, Wegscheider K, Neuhaus KL. Non-invasive detection of early infarct vessel patency by resolution of ST segment elevation in patients with thrombolysis for acute myocardial infarction: results of the angiographic substudy of the Hirudin for Improvement of Thrombolysis (HIT)-4 trial. *Eur Heart J* 2001;22:769-75.
15. Tomaszuk-Kazberuk A, Musial WJ, Dobrzycki S. ST segment resolution predicts clinical outcome and response to dobutamine testing after primary percutaneous transluminal coronary angioplasty. *Can J Cardiol* 2005;21:153-8.
16. McLaughlin MG, Stone GW, Aymong E, et al. Prognostic utility of comparative methods for assessment of ST segment resolution after primary angioplasty for acute myocardial infarction: The Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. *J Am Coll Cardiol* 2004;44:1215-23.
17. Brodie BR, Stuckey TD, Hansen C, et al. Relation between electrocardiographic ST segment resolution and early and late outcomes after primary percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2005;95:343-8.
18. De Luca G, Maas AC, van't Hof AW, et al. Impact of ST segment depression resolution on mortality after successful mechanical reperfusion in patients with ST segment elevation acute myocardial infarction. *Am J Cardiol* 2005;95:234-6.
19. French JK, Andrews J, Manda SO, Stewart RA, McTigue JJ, White HD. Early ST segment recovery, infarct artery blood flow, and long-term outcome after acute myocardial infarction. *Am Heart J* 2002;143:265-71.
20. Schroder R, Wegscheider K, Schroder K, Dissmann R, Meyer-Sabellek W. Extent of early ST segment elevation resolution: A strong predictor of outcome in patients with acute myocardial infarction and a sensitive measure to compare thrombolytic regimens. A substudy of the International Joint Efficacy Comparison of Thrombolytics (INJECT) trial. *J Am Coll Cardiol* 1995;26:1657-64.
21. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST segment elevation resolution: A simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol* 1994;24:384-91.
22. Schroder R, Zeymer U, Wegscheider K, Neuhaus KL. Comparison of the predictive value of ST segment elevation resolution at 90 and 180 min after start of streptokinase in acute myocardial infarction. A substudy of the hirudin for improvement of thrombolysis (HIT)-4 study. *Eur Heart J* 1999;20:1563-71.
23. de Lemos JA, Braunwald E. ST segment resolution as a tool for assessing the efficacy of reperfusion therapy. *J Am Coll Cardiol* 2001;38:1283-94.
24. Feldman LJ, Coste P, Furber A, et al. Incomplete resolution of ST segment elevation is a marker of transient microcirculatory dysfunction after stenting for acute myocardial infarction. *Circulation* 2003;107:2684-9.
25. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST segment elevation recovery after successful primary angioplasty: Real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. *Circulation* 2002;106:313-8.
26. Sezer M, Nisanci Y, Ummann B, et al. New support for clarifying the relation between ST segment resolution and microvascular function: Degree of ST segment resolution correlates with the pressure derived collateral flow index. *Heart* 2004;90:146-50.
27. Matetzky S, Novikov M, Gruberg L, et al. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. *J Am Coll Cardiol* 1999;34:1932-8.
28. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med* 2008;358:557-67.
29. Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: A quantitative method of assessing coronary artery flow. *Circulation* 1996;93:879-88.
30. French JK, Ellis CJ, White HD. The corrected TIMI frame count. The new gold standard? *Aust N Z J Med* 1998;28:569-73.
31. McDonald MA, Fu Y, Zeymer U, et al. Adverse outcomes in fibrinolytic-based facilitated percutaneous coronary intervention: Insights from the ASSENT-4 PCI electrocardiographic substudy. *Eur Heart J* 2008;29:871-9.
32. de Lemos JA, Antman EM, Giugliano RP, et al. ST segment resolution and infarct-related artery patency and flow after thrombolytic therapy. Thrombolysis in Myocardial Infarction (TIMI) 14 investigators. *Am J Cardiol* 2000;85:299-304.
33. Dong J, Ndrepepa G, Schmitt C, et al. Early resolution of ST segment elevation correlates with myocardial salvage assessed by Tc-99m sestamibi scintigraphy in patients with acute myocardial infarction after mechanical or thrombolytic reperfusion therapy. *Circulation* 2002;105:2946-9.
34. Costantini CO, Stone GW, Mehran R, et al. Frequency, correlates, and clinical implications of myocardial perfusion after primary angioplasty and stenting, with and without glycoprotein IIb/IIIa inhibition, in acute myocardial infarction. *J Am Coll Cardiol* 2004;44:305-12.
35. Li CM, Zhang XH, Ma XJ, Zhu XL. Relation of corrected thrombolysis in myocardial infarction frame count and ST segment resolution to myocardial tissue perfusion after acute myocardial infarction. *Catheter Cardiovasc Interv* 2008;71:312-7.
36. Kunadian V, Harrigan C, Zorkun C, et al. Use of the TIMI frame count in the assessment of coronary artery blood flow and microvascular function over the past 15 years. *J Thromb Thrombolysis* 2009;27:316-28.
37. Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. *Eur Heart J* 2002;23:1112-7.
38. Topol EJ, Yadav JS. Recognition of the importance of embolization in atherosclerotic vascular disease. *Circulation* 2000;101:570-80.
39. De Luca G, van't Hof AW, de Boer MJ, et al. Time-to-treatment significantly affects the extent of ST segment resolution and myocardial blush in patients with acute myocardial infarction treated by primary angioplasty. *Eur Heart J* 2004;25:1009-13.

40. de Lemos JA, Antman EM, Gibson CM, et al. Abciximab improves both epicardial flow and myocardial reperfusion in ST elevation myocardial infarction. Observations from the TIMI 14 trial. *Circulation* 2000;101:239-43.
 41. de Lemos JA, Gibson CM, Antman EM, et al. Abciximab and early adjunctive percutaneous coronary intervention are associated with improved ST segment resolution after thrombolysis: Observations from the TIMI 14 Trial. *Am Heart J* 2001;141:592-8.
 42. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST elevation myocardial infarction. *N Engl J Med* 2008;358:2205-17.
 43. Antoniucci D, Valenti R, Migliorini A, et al. Comparison of rheolytic thrombectomy before direct infarct artery stenting versus direct stenting alone in patients undergoing percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2004;93:1033-5.
 44. Limbruno U, Micheli A, De Carlo M, et al. Mechanical prevention of distal embolization during primary angioplasty: Safety, feasibility, and impact on myocardial reperfusion. *Circulation* 2003;108:171-6.
 45. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST segment elevation myocardial infarction: A randomized controlled trial. *JAMA* 2005;293:1063-72.
 46. Gick M, Jander N, Bestehorn HP, et al. Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST segment elevation. *Circulation* 2005;112:1462-9.
-