Clinical impact and predictors of complete ST segment resolution after primary percutaneous coronary intervention: A subanalysis of the ATLANTIC Trial

Enrico Fabris[1,2], Arnoud van 't Hof[1,3,4], Christian W Hamm[5], Frédéric Lapostolle[6], Jens F Lassen[7], Shaun G Goodman[8], Jurriën M ten Berg[9], Leonardo Bolognese[10], Angel Cequier[11], Mohamed Chettibi[12], Christopher J Hammett[13], Kurt Huber[14,15], Magnus Janzon[16,17], Béla Merkely[18], Robert F Storey[19], Uwe Zeymer[20], Warren J Cantor[21], Anne Tsatsaris[22], Mathieu Kerneis[23], Abdourahmane Diallo[24], Eric Vicaut[24] and Gilles Montalescot[23], for the ATLANTIC investigators

Abstract

Background: In the ATLANTIC (Administration of Ticagrelor in the catheterization laboratory or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) trial the early use of aspirin, anticoagulation, and ticagrelor coupled with very short medical contact-to-balloon times represent good indicators of optimal treatment of ST-elevation myocardial infarction and an ideal setting to explore which factors may influence coronary reperfusion beyond a well-established pre-hospital system.

Methods: This study sought to evaluate predictors of complete ST-segment resolution after percutaneous coronary intervention in ST-elevation myocardial infarction patients enrolled in the ATLANTIC trial. ST-segment analysis was performed on electrocardiograms recorded at the time of inclusion (pre-hospital electrocardiogram), and one hour after

[1]Cardiology Department, Isala Heart Center, the Netherlands
[2]Cardiovascular Department, University of Trieste, Italy
[3]Department of Cardiology, Maastricht University Medical Center, the Netherlands
[4]Department of Cardiology, Zuyderland Hospital, the Netherlands
[5]Kerckhoff Heart and Thorax Center, Germany
[6]SAMU 93, Hôpital Avicenne, France
[7]Department of Cardiology B, Aarhus University Hospital, Denmark
[8]Canadian Heart Research Centre, University of Toronto, Canada
[9]Department of Cardiology, St Antonius Hospital Nieuwegein, the Netherlands
[10]Cardiovascular and Neurological Department, Azienda Ospedaliera Arezzo, Italy
[11]Heart Disease Institute, University of Barcelona, Spain
[12]Centre Hospito-universitaire Frantz Fanon, Algeria
[13]Department of Cardiology, Royal Brisbane and Women's Hospital, Australia
[14]Cardiology and Intensive Care Medicine, Wilhelminen Hospital, Austria
[15]Sigmund Freud Private University, Austria
[16]Department of Cardiology, Linköping University, Sweden
[17]Department of Medical and Health Sciences, Linköping University, Sweden
[18]Heart and Vascular Center, Semmelweis University, Hungary
[19]Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, UK
[20]Klinikum Ludwigshafen and Institut für Herzinfarktforschung, Germany
[21]Southlake Regional Health Centre, University of Toronto, Canada
[22]AstraZeneca, UK
[23]ACTION Study Group, Sorbonne Université Paris 6, France
[24]ACTION Study Group, Hospital Lariboisiere, France

Corresponding author:
Arnoud van 't Hof, Maastricht University Medical Center, Department of Cardiology, PO Box 5800, 6202 AZ Maastricht, the Netherlands.
Email: awjhof@xs4all.nl

percutaneous coronary intervention (post-percutaneous coronary intervention electrocardiogram) by an independent core laboratory. Complete ST-segment resolution was defined as ≥70% ST-segment resolution.
Results: Complete ST-segment resolution occurred post-percutaneous coronary intervention in 54.9% (n=800/1456) of patients and predicted lower 30-day composite major adverse cardiovascular and cerebrovascular events (odds ratio 0.35, 95% confidence interval 0.19–0.65; p<0.01), definite stent thrombosis (odds ratio 0.18, 95% confidence interval 0.02–0.88; p=0.03), and total mortality (odds ratio 0.43, 95% confidence interval 0.19–0.97; p=0.04). In multivariate analysis, independent negative predictors of complete ST-segment resolution were the time from symptoms to pre-hospital electrocardiogram (odds ratio 0.91, 95% confidence interval 0.85–0.98; p<0.01) and diabetes mellitus (odds ratio 0.6, 95% confidence interval 0.44–0.83; p<0.01); pre-hospital ticagrelor treatment showed a favorable trend for complete ST-segment resolution (odds ratio 1.22, 95% confidence interval 0.99–1.51; p=0.06).
Conclusions: This study confirmed that post-percutaneous coronary intervention complete ST-segment resolution is a valid surrogate marker for cardiovascular clinical outcomes. In the current era of ST-elevation myocardial infarction reperfusion, patients' delay and diabetes mellitus are independent predictors of poor reperfusion and need specific attention in the future.

Keywords

ST-elevation myocardial infarction, ST segment resolution, ticagrelor,

reperfusion Accepted: 2 August 2017

Introduction

In the randomized, double-blind, placebo-controlled ATLANTIC (Administration of Ticagrelor in the catheterization laboratory or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery) trial, pre-hospital (pre-H) administration of ticagrelor in patients with acute ST elevation myocardial Infarction (STEMI) appeared to be safe but did not improve coronary or myocardial reperfusion before percutaneous coronary intervention (PCI).[1] It is possible that the brief interval time from ambulance to catheterization laboratory (cath lab) may explain the absence of a detectable benefit of pre-H administration before PCI, however the effects of pre-hospital ticagrelor became apparent after PCI.[2]

In the ATLANTIC trial the frequent early use of aspirin and anticoagulation and the early use of ticagrelor coupled with very short medical contact-to-balloon times represent good indicators of optimal treatment of STEMI patients.[3] Since achieving myocardial reperfusion is the main goal in STEMI patients for improving prognosis, this setting is ideal to explore which factors may influence myocardial reperfusion beyond a well-established pre-H system.

Therefore, we undertook an exploratory analysis describing the predictors, and clinical significance, of complete ST resolution (STR) post PCI in STEMI patients enrolled in the ATLANTIC trial.

Methods

Study design and procedures

ATLANTIC was an international study that randomized patients presenting with ongoing STEMI to receive double-blind treatment with a 180 mg loading dose of ticagrelor either pre-H (in-ambulance) or in-H (in- catheterization laboratory), in addition to aspirin and standard of care.

The trial design and main results have been published.[1,4] Briefly, eligible patients were identified by ambulance personnel for inclusion in the study following diagnosis of STEMI of more than 30 min but less than 6 h duration, and with expected time from qualifying electrocardiogram (ECG) to first balloon inflation of less than 120 min. Randomization and first loading dose of ticagrelor or matching placebo took place immediately after ECG confirmed the diagnosis of STEMI. Patients were then transferred to undergo coronary angiography and PCI, and the second loading dose was administered in the cath lab. All patients then received maintenance treatment with ticagrelor 90 mg twice daily for at least 30 days, up to a maximum of 12 months. In-ambulance use of glycoprotein (GP) IIb/IIIa inhibitors was discouraged, but left to physicians' discretion.

Electrocardiographic analysis, definitions and endpoints used

ST-segment analysis was performed on ECGs recorded pre-H (at the time of inclusion) and one hour after PCI (post-PCI ECG). The degree of STR was assessed by an independent core laboratory (eResearch Technology, Peterborough, UK) blinded to study treatment. The STR was calculated as the mean ST-segment elevation pre-H minus the mean ST-segment elevation post-PCI divided by the mean ST-segment elevation pre-H and expressed as a percentage, i.e.

$$STR=((ST_{pre\text{-}hospital}-ST_{post\text{-}PCI})/ST_{pre\text{-}hospital})\times 100$$

Complete STR was defined as ≥70% STR.[5]

Clinical endpoints, evaluated up to the date of the last study visit (≤32 days), included composite major adverse cardiovascular clinical events (MACCE; defined as death, myocardial infarction, stroke or urgent revascularization), definite stent thrombosis, and total mortality.

Safety endpoints analyzed included major or minor bleeding (excluding coronary artery bypass graft (CABG)-related bleeding) within 48 h of first dose and after 48 h and up to the last study visit using the Platelet Inhibition and Patient Outcomes (PLATO) study definitions; or major, minor and minimal bleeding up to the last study visit using Thrombolysis in Myocardial Infarction (TIMI), and Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) definitions.[4] An independent adjudication committee conducted a blinded review of all clinical endpoints (except deaths and minimal bleeding events).

Statistical analysis

For continuous variables, mean, standard deviation and Student's t-test *p*-value are presented in cases of Gaussian distribution, or median, interquartile ranges and Mann-Whitney's or Wilcoxon test *p*-value in cases of non-Gaussian distribution. For categorical variables, number, percentage and chi-square test *p*-value are presented or Fisher's test *p*-value is presented in cases of low numbers of events. Ischemic endpoints analyses were performed in the modified intention-to-treat population, i.e. those patients who underwent randomization, received at least one dose of the study drug and had complete data for STR post-PCI. For each endpoint, the two groups (complete STR and incomplete STR) were compared with the use of a logistic regression model. The 95% confidence interval (CI) for the odds ratio (OR) was calculated. Potential predictors of complete STR post-PCI were first identified as those variables with a *p*-value<0.10 in univariate analyses; these were then introduced in the multivariate analysis adjusted for baseline characteristics, with a *p*-value<0.05 threshold for significance.

All tests had a two-sided significant level of 5% and were performed with the use of SAS software, version 9.4 (SAS Institute).

Results

Complete descriptive analysis of patients with post-PCI complete STR compared to incomplete STR is shown in Table 1.

Patient characteristics

In the ATLANTIC trial, 1862 consenting patients were randomized to receive either pre-H or in-H ticagrelor. Of these, a total of 1456 patients who underwent PCI and had both pre-H and post-PCI ECGs available were included in the present analysis. Patients received pre-H ticagrelor and in-H ticagrelor in 49% (713) and in 51% (743), respectively. Complete STR post-PCI occurred in 54.9% (*n*=800/1456) of patients. Patients with complete STR were younger (59 (51–68 years) vs 61 (52–71 years), *p*=0.01), were less frequently diabetics (9.6% vs 16.5%, *p*<0.01) and had lower TIMI risk scores (see Table 1) compared with incomplete STR. Patients with complete STR had shorter interval time from symptom onset to pre-H ECG (69 (41–122) vs 76 (42–150) min, *p*=0.03) or from symptom onset to first loading dose of study medication (85 (60–142) vs 96 (60–166) min, *p*=0.02). No other patient demographic characteristics were significantly different between the two groups.

The use of heparin (any type) pre-PCI was more frequent in the complete STR group compared with incomplete STR (62.9 vs 58.2%, *p*=0.07). Use of aspirin (99.6%) was not different between complete STR and incomplete STR group as well as the use of GP IIb/IIIa inhibitors (GPIs) (32.1%). It has to be noted that in-ambulance use of GPI was discouraged and GPI was used only in 3.3% during patients' transfer to the catheterization lab.

Effect of pre-hospital ticagrelor on ST resolution post-PCI

Post-PCI complete STR occurred in 57.5% of patients in the pre-H ticagrelor group and in 52.5% of patients in the control group (*p*=0.055). The degree of STR was significantly greater in the pre-H group (median, 75.0% vs 71.4%, *p*=0.049).

Clinical significance of post-PCI complete ST resolution

On logistic regression analysis, post-PCI complete STR predicted both lower 30 days composite MACCE (OR 0.35, CI 0.19–0.65) *p*<0.01), definite stent thrombosis (OR 0.18, 95% CI 0.02–0.88; *p*=0.03) and total mortality (OR 0.43, 95% CI 0.19–0.97; *p*=0.04) (Table 2, Figures 1 and 2). Complete STR predicted both lower major (OR 0.31, 0.11–0.88, *p*=0.03) and a composite of major and minor (OR 0.48, CI 0.24–0.998, *p*=0.049) non-CABG-related bleeding events according to PLATO definition (Table 3).

Predictors of post-PCI complete ST resolution

The results of univariate and multivariate analysis of post-PCI complete STR are presented in Table 4. At multivariate analysis, independent negative predictors of complete STR were time from symptoms to pre-H ECG (OR=0.91, 95% CI 0.85–0.98, *p*<0.01) and diabetes mellitus (OR=0.6, CI 0.44–0.83, *p*<0.01); pre-H ticagrelor treatment showed a

Table 1. Descriptive analysis.

Characteristic	ST resolution post-PCI incomplete (<70%) (*n*=656)	ST resolution post-PCI complete (≥70%) (*n*=800)	Total (*n*=1456)	*p*-Value
Age, years; median (Q1–Q3)	61 (52–71)	59 (51–68)	60 (52–69)	**0.0070**
Age≥75 years, %	113 (17.2)	106 (13.3)	219 (15.0)	**0.0347**
Female, *n* (%)	122 (18.6)	150 (18.8)	272 (18.7)	0.9408
Weight, kg; median (Q1–Q3)	80 (70–88)	80 (70–90)	80 (70–90)	0.8466
BMI ≥30 kg/m^2, *n* (%)	121 (18.5)	164 (20.5)	285 (19.6)	0.3255
Diabetes mellitus, *n* (%)	108 (16.5)	77 (9.6)	185 (12.7)	**<0.0001**
TIMI risk score group, *n* (%)				**0.0076**
0–2	379 (57.8)	516 (64.5)	895 (61.5)	
3–6	264 (40.2)	278 (34.8)	542 (37.2)	
>6	13 (2.0)	6 (0.8)	19 (1.3)	
Prior cardiac history, *n* (%)				
Prior MI	54 (8.2)	56 (7.0)	110 (7.6)	0.3762
Prior PCI	50 (7.6)	49 (6.1)	99 (6.8)	0.2589
Prior CABG	3 (0.5)	4 (0.5)	7 (0.5)	1.0000
Prior hemorrhagic stroke	2 (0.3)	2 (0.3)	4 (0.3)	1.0000
Prior ischemic stroke	9 (1.4)	5 (0.6)	14 (1.0)	0.1462
Prior TIA	9 (1.4)	4 (0.5)	13 (0.9)	0.0784
Other medical history, *n* (%)				
COPD	30 (4.6)	29 (3.6)	59 (4.1)	0.3613
Chronic renal failure	14 (2.1)	8 (1.0)	22 (1.5)	0.0776
Killip class I, *n* (%)	597 (91.0)	736 (92.0)	1333 (91.6)	0.4975
Procedures for index event, *n* (%)				
Thrombo-aspiration	369 (56.3)	485 (60.6)	854 (58.7)	0.0917
PCI	656 (100)	800 (100)	1456 (100)	
Without stent	41 (6.3)	42 (5.3)	83 (5.7)	0.4129
With stent	615 (93.8)	758 (94.8)	1373 (94.3)	
DES	391 (59.6)	444 (55.5)	835 (57.4)	0.1152
BMS	237 (36.1)	325 (40.6)	562 (38.6)	0.0795
Study medication				
Aspirin use				
Any use	653 (99.5)	797 (99.6)	1450 (99.6)	1.0000
Maintenance dose	641 (97.7)	787 (98.4)	1428 (98.1)	0.3604
Pre-PCI ECG use	500 (76.2%)	620 (77.5%)	1120 (76.9%)	0.5639
Use in the 24 h before index event	201 (30.6%)	234 (29.3%)	435 (29.9%)	0.5642
Other antithrombotic medication for index event				
GP IIb/IIIa inhibitor	205 (31.3)	262 (32.8)	467 (32.1)	0.5418
Intravenous anticoagulant during hospitalization	584 (89.0)	720 (90)	1304 (89.6)	0.5447
Use of heparin before pre-PCI ECG	382 (58.2%)	503 (62.9%)	885 (60.8%)	0.0710
Time from symptoms to Pre-H ECG (min)	76 (42–150)	69 (41–122)	71 (42–135)	**0.0332**
Time from symptoms to 1st loading dose (min)	96 (60–166)	85 (60–142)	90 (60–151)	**0.0195**
Time from pre-H ECG to pre-PCI ECG (min)	50 (39–62)	49 (38–61)	49 (39– 61)	0.5687

BMI: body mass index; BMS: bare metal stent; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; DES: drug eluting stent; ECG: electrocardiogram; GP: glycoprotein; MI: myocardial infarction; PCI: percutaneous coronary intervention; pre-H: pre-hospital; TIA: transient ischemic attack.

Table 2. Post-percutaneous coronary intervention (PCI) ST-segment resolution and ischemic endpoints,[a] logistic regression analysis.

Ischemic endpoints	ST resolution post-PCI incomplete (<70%) (*n*=656)	ST resolution post-PCI complete (≥70%) (*n*=800)	Odds ratio[b] (CI)	*p*-Value[b]
Composite of death, MI, stroke and urgent revascularization - *n*, (%)	34 (5.2%)	15 (1.9%)	0.35 (0.19–0.65)	**0.0008**
Definite stent thrombosis - *n*, (%)	9 (1.4%)	2 (0.3%)	0.18 (0.02–0.88)	**0.0282**
Death (all-cause) - *n*, (%)	17 (2.6%)	9 (1.1%)	0.43 (0.19–0.97)	**0.0410**

CI: confidence interval; MI: myocardial infarction.
[a]Events occurring up to the date of the last study visit (≤32 days) are included in the table; [b]exact if *n*<5 in one group.

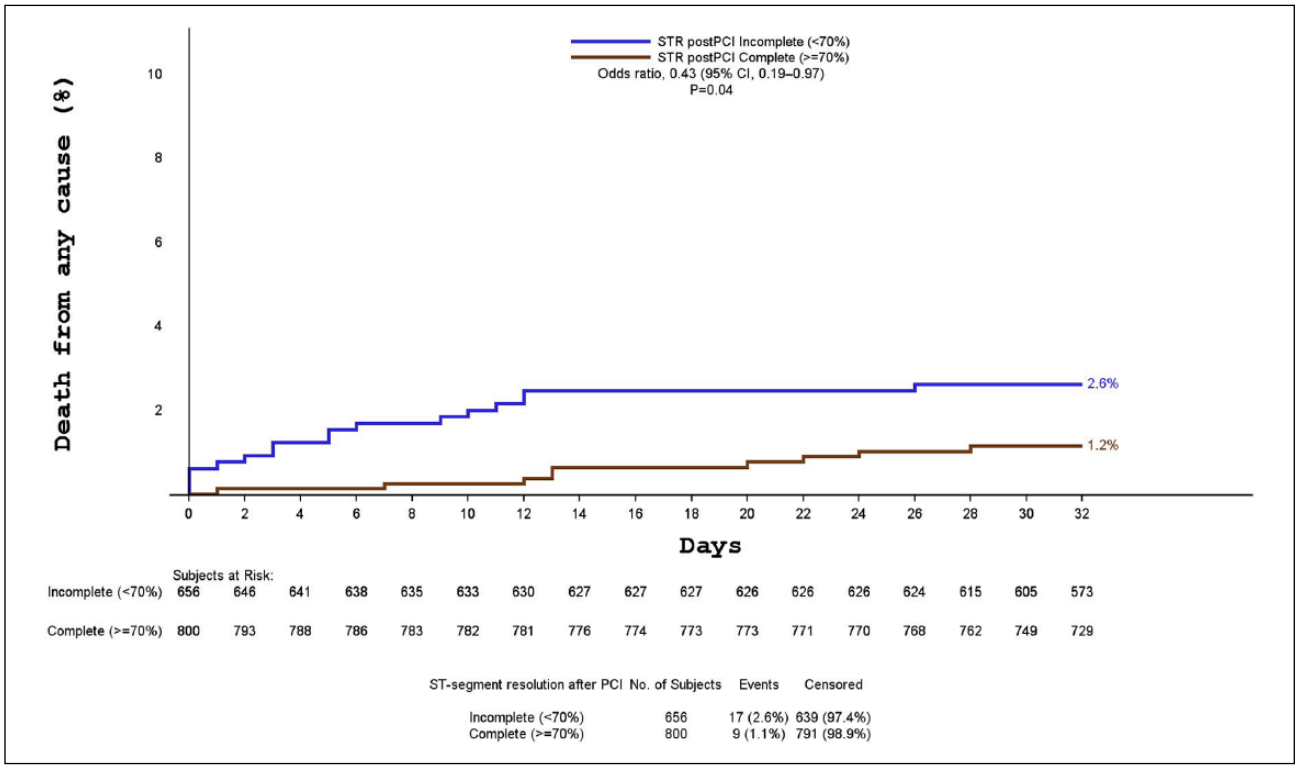

Figure 1. Total mortality curves in relation to complete and incomplete ST-segment resolution (STR). CI: confidence interval: PCI: percutaneous coronary intervention.

favorable trend for complete STR (OR 1.22, 95% CI 0.99–1.51; *p*=0.06).

Discussion

This ATLANTIC trial sub-analysis evaluated a large prospective cohort of STEMI patients focusing on myocardial reperfusion expressed as post-PCI complete STR. In this cohort of patients who received early antithrombotic treatment and fast transportation to the cath lab we found that patient delay and diabetes mellitus were independent predictors of reduced myocardial reperfusion after PCI. These findings provide further insights into the potential optimization of STEMI management in the current era of STEMI reperfusion, and are particularly important because they clearly identify patient subtypes who need particular attention.

Interestingly, the time from pre-H ECG to pre-PCI ECG was not different in the two groups (complete vs incomplete STR). However, in our study this time was very short, and when time to PCI is as brief as it was in the ATLANTIC trial, it might blunt the risk associated with patients' transfer delay, and at the same time it may suggest that when a well-established pre-hospital system has optimal performance further efforts to reduce time to PCI time (i.e. the system-of-care-dependent time (system delay)) might not further improve outcomes. Therefore, these data may suggest that other additional strategies are needed to improve outcomes in the STEMI population. Indeed, despite the efforts to reduce door-to-balloon time over the past decade,

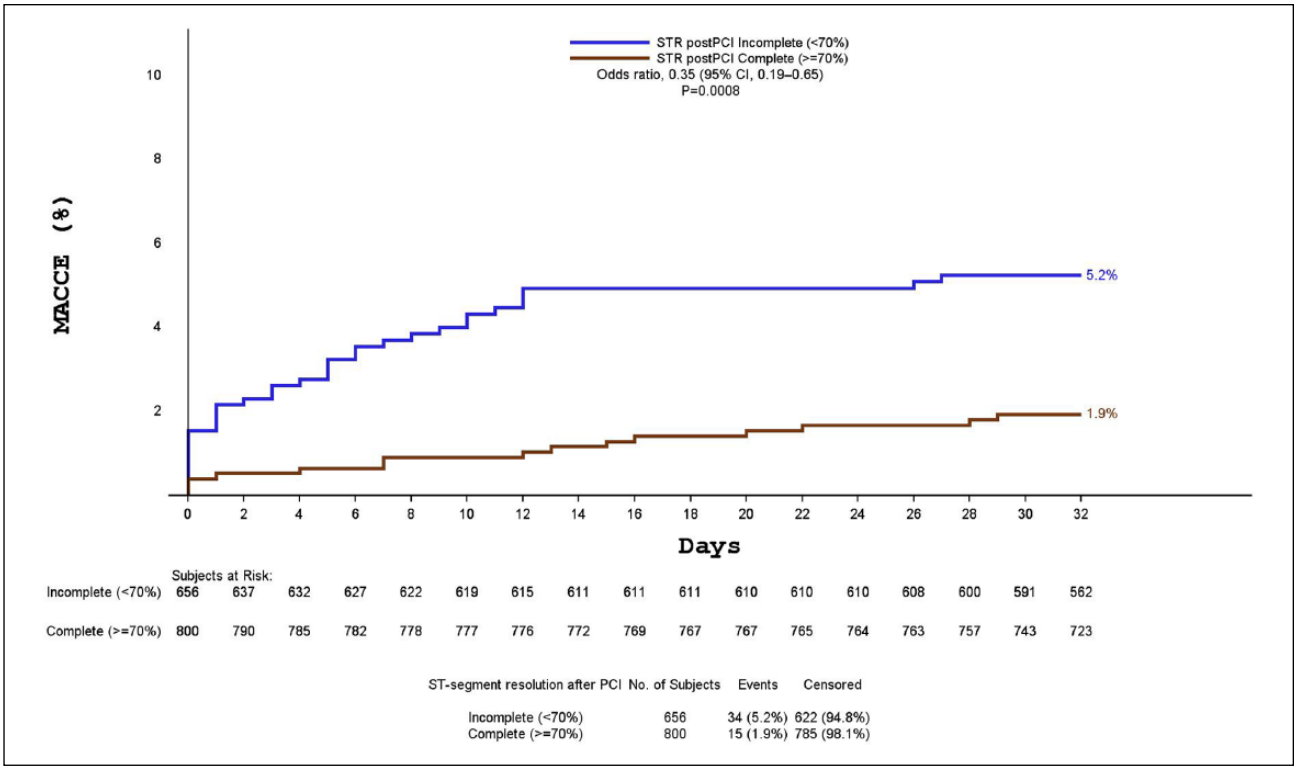

Figure 2. Composite major adverse cardiovascular clinical events (MACCE) curves in relation to complete and incomplete ST-segment resolution (STR) post-percutaneous coronary intervention (PCI). CI: confidence interval.

Table 3. Post-percutaneous coronary intervention (PCI) ST-segment resolution and non-coronary artery bypass graft (CABG)-related bleeding events,[a] logistic regression analysis.

Bleedings events	ST resolution post-PCI incomplete (<70%) (*n*=656)	ST resolution post-PCI complete (≥70%) (*n*=800)	Odds ratio[b] (CI)	*p*-Value[b]
Non-CABG-related bleeding events (PLATO definition)				
Within 48 h of first dose				
Major	13 (2.0)	5 (0.6)	0.31 (0.11–0.88)	**0.0273**
Minor	7 (1.1)	7 (0.9)	0.82 (0.29–2.35)	0.7091
Composite of major and minor	20 (3.1)	12 (1.5)	0.48 (0.24–0.998)	**0.0494**
After 48 h and up to 30 days[a]				
Major	10 (1.5%)	5 (0.6%)	0.41 (0.14–1.20)	0.1017
Minor	4 (0.6%)	7 (0.9%)	1.44 (0.36–6.73)	0.7631
Composite of major and minor	14 (2.1%)	12 (1.5%)	0.70 (0.32–1.52)	0.3657
Non-CABG-related bleeding events up to 30 days[a] (TIMI and STEEPLE definitions)				
TIMI				
Major	9 (1.4%)	6 (0.8%)	0.54 (0.19–1.53)	0.2493
Minor	20 (3.1%)	16 (2.0%)	0.65 (0.33–1.26)	0.2030
Minimal	4 (0.6%)	3 (0.4%)	0.61 (0.09–3.64)	0.7076
STEEPLE				
Major	21 (3.2%)	10 (1.3%)	0.38 (0.18–0.82)	**0.0133**
Minor	10 (1.5%)	11 (1.4%)	0.90 (0.38–2.13)	0.8121
Unknown	2 (0.3%)	4 (0.5)	1.64 (0.24–18.21)	0.6960

CI: confidence interval; PLATO: Platelet Inhibition and Patient Outcomes; STEEPLE: Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients; TIMI: Thrombolysis in Myocardial Infarction.

[a]Events occurring up to the date of the last study visit (≤32 days) are included in the table; [b]exact if *n*<5 in one group.

Table 4. Univariate and multivariate analysis of predictors of complete ST resolution post-percutaneous coronary intervention (PCI).

Variables	Univariate logistic model[a]			Multivariate logistic model[b]		
	n	Odds-ratio (95% CI)	*p*-Value	*n*	Odds-ratio (95% CI)	*p*-Value
Ticagrelor pre-H vs ticagrelor in-H	1456	1.22 (1.00–1.51)	0.0547	1455	1.22 (0.99–1.51)	0.0609
Age	1456	0.99 (0.98–1.00)	0.0054			
Age (Group ≥75 Years vs <75 Years)	1456	0.73 (0.55–0.98)	0.0352	1455	0.94 (0.66–1.34)	0.7507
Chronic renal disease (yes vs no)	1456	0.46 (0.19–1.11)	0.0847	1455	0.57 (0.23–1.40)	0.2229
Diabetes mellitus (yes vs no)	1456	0.54 (0.40–0.74)	0.0001	1455	**0.60 (0.44–0.83)**	**0.0018**
Use of heparin before pre PCI ECG (yes vs no)	1456	1.21 (0.98–1.50)	0.0711	1455	1.17 (0.95–1.46)	0.1416
Sex (female vs male)	1456	1.01 (0.77–1.32)	0.9408			
TIMI risk score category (0–2 vs >6)	1456	2.95 (1.11–7.83)	0.0099	1455	2.32 (0.82–6.50)	0.0851
TIMI risk score category (3–6 vs >6)	1456	2.28 (0.85–6.09)	0.2812	1455	2.01 (0.73–5.50)	0.2985
Time from symptoms to 1st LD (≤1 vs >3 h)	1445	1.36 (0.99–1.86)	0.2299			
Time from symptoms to 1st LD (>1–3 vs >3 h)	1445	1.35 (1.03–1.78)	0.1587			
Time from symptoms to pre-H ECG (min)[c]	1455	0.89 (0.83–0.96)	0.0016	1455	**0.91 (0.85–0.98)**	**0.0078**
Transient ischemic attack (yes vs no)	1456	0.36 (0.11–1.18)	0.0915	1455	0.37 (0.11–1.24)	0.1079

CI: confidence interval; ECG: electrocardiogram; in-H: in-hospital; LD: loading dose; pre-H: pre-hospital; TIMI: Thrombolysis in Myocardial Infarction. [a]The univariate logistic model; [b]multivariate logistic model: variables with *p*-value<0.10 in univariate analysis; [c]unit=60 for Time from symptoms to pre-H ECG.

a recent analysis from the Cath-PCI registry[6] questioned the usefulness of decreasing door-to-balloon times in the contemporary era. However, that study did not collect information regarding the ischemic time determined by the time from symptom onset to ECG thus suggesting that additional factors also need to be targeted in contemporary treatment. Indeed the prognostic importance of short ECG-to-PCI times[7,8] is likely to be modulated by the duration of ischemia until diagnostic ECG is performed.[9] This is relevant considering that a significant proportion of patients still continue to delay seeking medical care voluntarily or not.[10] Moreover, considering that the education profile of patients is an important component in reducing delay,[11] considerable efforts should still be made to educate the general public about the positive effects of an early and adequate first emergency call.

Patient delay is crucial, in fact the early period after symptom onset represents a golden opportunity for antithrombotic therapy,[12] because the platelet content of the fresh coronary thrombus is maximal and more susceptible to powerful antiplatelet agents;[13] and early reperfusion has the maximal life-saving potential, through myocardial salvage.

Although a slight decrease in patient delay during the years has been reported, effort should be made especially in those at higher risk of prolonged patient delays, such as elderly patients, diabetics, female and those who have symptoms presentation during the night.[14,15]

Although the known worse outcome observed in diabetic patients may be partially related due to the longer time delay to presentation, diabetes has been associated with abnormal coronary endothelial function, diminished coronary flow reserve, and impaired ischemic preconditioning,[16–18] all of which may result in abnormal myocardial perfusion. This study confirmed that diabetes is an independent predictor of impaired myocardial perfusion after primary PCI.[19–21] Indeed, these patients may cumulate both the additional risk of being diabetic and a longer delay from chest pain to emergency call due a higher pain threshold or a more atypical clinical presentation. Additional research is required to develop further approaches to enhance microcirculatory function after primary PCI,[22] which may improve clinical outcomes. This should be considered a high priority because diabetes is an increasing international health burden and its prevalence continues to rise.[23]

Interestingly, myocardial reperfusion rates numerically favored pre-H ticagrelor treatment, and although pre-H treatment did not reach statistical significance as an independent predictor of myocardial reperfusion, pre-H ticagrelor showed a favorable trend. The possible efficacy of pre-treatment with antiplatelet agents should be viewed from the perspective of early or delayed access to coronary angiography and revascularization, and pre-H ticagrelor administration may help to achieve early (pre-PCI) myocardial reperfusion in patients with longer transfer delays[24] and may help to reduce ischemic endpoints, over the first 24 h.[2] This may be particularly pertinent in patients who do not receive pre-H opiate treatment, which might counteract the time advantage of pre-H administration of oral $P2Y_{12}$ inhibitors.[25] Although the routine pre-H initiation of a high-bolus dose of GPIs has been showed to improve STR,[26] in this analysis GPIs did not emerge as a predictor of STR; however, in the ATLANTIC trial, ambulance use of GPIs was discouraged and therefore GPIs were used in a very small percentage during patients' transfer (3.3%) and were frequently used for bailout situations. Thus this setting may conceal the potential effect of GPI administration.

Pre-H administration of a fast-acting antiplatelet agent, such as cangrelor, may represent a new strategy to be tested in order to improve myocardial reperfusion. Because cangrelor is administered intravenously and has rapid onset, it could offer particular advantages in the STEMI primary PCI setting, especially where there is little opportunity for pretreatment as in patients who are intubated or in cardiogenic shock or those experiencing nausea and vomiting. In a pooled analysis of patient-level data from the three CHAMPION trials,[27] cangrelor compared to control (clopidogrel or placebo), reduced PCI periprocedural thrombotic complications, at the expense of increased bleeding, however only 12% of STEMI where included in these studies.[27]

This analysis highlighted the key factors that in the current era of STEMI treatment may influence reperfusion post-primary PCI expressed as STR. This is relevant considering that this study confirmed the prognostic importance of electrocardiographic assessments of early reperfusion,[28] showing that post-PCI complete STR still represents a valid surrogate marker for cardiovascular clinical outcomes at 30 days. Finally, the lower ischemic complications associated with post-PCI complete STR was associated with lower major non-CABG-related bleeding events according to the PLATO and STEEPLE definitions. This could be related to the fact that patients with early optimal reperfusion may require less frequent use of more potent post-PCI antithrombotic regimens, including prolonged GPI administration, however it is also possible that patients with complete STR were at lower risk of bleeding because of other factors.

Limitations

This analysis was a post-hoc analysis and therefore should be viewed as hypothesis-generating. This analysis considered only STR as a marker of myocardial reperfusion and did not consider TIMI 3 flow in the culprit artery. However, patients with complete STR are likely to have a patent infarct artery;[29] moreover, STR can be considered as a surrogate for tissue-level reperfusion[30] and, in the fibrinolytic era, STR showed a prognostic power that persists even after accounting for the effects of epicardial blood flow.[31]

Conclusions

Post-PCI complete STR is confirmed to be a valid surrogate marker for cardiovascular clinical outcomes. In the current era of STEMI reperfusion, patients' delay and diabetes are independent predictors of poor reperfusion and would need specific attention in the future.

Short key messages

What is already known on this subject?

The achievement of early myocardial reperfusion in patients with ST-elevation myocardial infarction (STEMI) improves prognosis. In the current era of STEMI treatment, which factors may influence myocardial reperfusion beyond the well-established pre-hospital (pre-H) system is poorly known.

What might this study add?

This study which evaluated a large cohort of STEMI patients who received early antithrombotic treatment during the pre-H phase coupled with fast transportation to the cath lab, showed that diabetes mellitus and patients' delay are independent predictors of poor myocardial reperfusion.

How might this impact on clinical practice?

These findings provide further insights into the potential optimization of STEMI treatment. In the current era of STEMI reperfusion characterized by early pre-H drug administration and fast transportation, diabetic patients are still a subgroup of patients who require further approaches for improving outcomes, and additional strategies are needed also to improve patient's delay.

Conflict of interest

L Bolognese reports personal fees from Daiichy Sankyo, Eli Lilly, Menarini Ind Farma, Abbott, AstraZeneca, Iroko Cardio International, outside the submitted work; WJ Cantor reports personal fees from AstraZeneca, outside the submitted work; A Cequier reports research grants from AstraZeneca, Abbott, Medtronic, Spanish Society of Cardiology, and consulting fees from AstraZeneca, Abbott, Boston Scientific, Medtronic, and lecture fees from AstraZeneca, Abbott, Boston Scientific, and Medtronic; M Chettibi reports personal fees from AstraZeneca, during the conduct of the study; SG Goodman reports Research Grant and personal support from AstraZeneca Canada, during the conduct of the study; grants and personal fees from AstraZeneca, Eli Lilly, Sanofi, outside the submitted work; CW Hamm reports grants and personal fees from AstraZeneca, during the conduct of the study; personal fees from DaiichiSankyo Lilly, SanofiAventis, Boehringer Ingelheim, outside the submitted work; CJ Hammett reports grants from AstraZeneca, during the conduct of the study; personal fees from AstraZeneca, Eli Lilly, Bayer Healthcare, Boehringer Ingelheim, Amgen, The Medicines Company, outside the submitted work; M Janzon reports personal fees from AstraZeneca, during the conduct of the study; F Lapostolle reports grants, personal fees and non-financial support from AstraZeneca, grants, Boehringer Ingelheim, grants, Bayer, Lilly, Correvio Daiichi-Sankyo, The Medicines Company, during the conduct of the study; grants, personal fees and non-financial support from Merck-Serono, Roche, outside the submitted work; JF Lassen reports personal fees from AstraZeneca, outside the submitted work; G Montalescot reports grants from ADIR, Amgen, AstraZeneca, Bayer Boehringer Ingelheim, Bristol-Myers Squibb, Celladon, Daiichi-Sankyo, Eli-Lilly, ICAN, Fédération Française de Cardiologie, Medtronic, MSD, Pfizer, Sanofi-Aventis, The Medicines Company, personal fees from Amgen, AstraZeneca, from Bayer, Berlin Chimie AG, Boehringer Ingelheim, Bristol-Myers Squibb, Beth Israel Deaconess Medical, Brigham Women's Hospital, Cardiovascular Research Foundation, CME Resources Daiichi-Sankyo, from Eli-Lilly,

Europa, Elsevier, Fondazione Anna Maria Sechi per il Cuore, Gilead, Janssen, Lead-Up, Menarini, MSD, Pfizer, Sanofi-Aventis, The Medicines Company, TIMI Study Group, WebMD, outside the submitted work; RF Storey reports grants from AstraZeneca, during the conduct of the study; grants and personal fees from AstraZeneca, personal fees from The Medicines Company, grants and personal fees from PlaqueTec, personal fees from ThermoFisher Scientific, personal fees from Bristol-Myers Squibb/Pfizer alliance; personal fees from Bayer; personal fees from Avacta, outside the submitted work; JM ten Berg reports grants from Astra, personal fees from MSD, Daichi Sankyo Ely Lilly, Boehringer Ingelheim, outside the submitted work; A Tsatsaris is an employee of AstraZeneca, Luton, UK; A van 't Hof reports grants, personal fees and non-financial support from AstraZeneca, during the conduct of the study; grants from Medtronic, Daiichi Sankyo, personal fees from Iroko Cardio, outside the submitted work; E Vicaut reports grants from Boehringer, during the conduct of the study; personal fees from Pfizer, Sanofi, LFB, Abbott, Fresenius, Medtronic, Hexacath, CERC, personal Novartis, Elli Lilly, grants from Sanofi, outside the submitted work; U Zeymer reports personal fees from AstraZeneca, during the conduct of the study; personal fees from AstraZeneca, grants and personal fees from Daiichi Sankyo, Eli Lilly, personal fees from Bayer Healthcare, The Medicines Company, grants and personal fees from Sanofi, Novartis, personal fees from Boehringer Ingelheim, MSD, outside the submitted work; other authors have nothing to disclose.

Funding

This study was supported by AstraZeneca. Clinical trial registration: ClinicalTrials.gov identifier: NCT01347580.

References

1. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014; 371: 1016–1027.
2. Montalescot G, van 't Hof AW, Bolognese L, et al. Effect of pre-hospital ticagrelor during the first 24 h after primary percutaneous coronary intervention in patients with st-segment elevation myocardial infarction: The ATLANTIC-H(2)(4) Analysis. *JACC Cardiovasc Interv* 2016; 9: 646–656.
3. Schiele F, Gale CP, Bonnefoy E, et al. Quality indicators for acute myocardial infarction: A position paper of the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care* 2017; 6: 34–59.
4. Montalescot G, Lassen JF, Hamm CW, et al. Ambulance or in-catheterization laboratory administration of ticagrelor for primary percutaneous coronary intervention for ST-segment elevation myocardial infarction: Rationale and design of the randomized, double-blind Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial Infarction to open the Coronary artery (ATLANTIC) study. *Am Heart J* 2013; 165: 515–522.
5. 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: 384–391.
6. Menees DS, Peterson ED, Wang Y, et al. Door-to-balloon time and mortality among patients undergoing primary PCI. *N Engl J Med* 2013; 369: 901–909.
7. Terkelsen CJ, Sorensen JT, Maeng M, et al. System delay and mortality among patients with STEMI treated with primary percutaneous coronary intervention. *JAMA* 2010; 304: 763–771.
8. Puymirat E, Caudron J, Steg PG, et al. Prognostic impact of non-compliance with guidelines-recommended times to reperfusion therapy in ST-elevation myocardial infarction. The FAST-MI 2010 registry. *Eur Heart J Acute Cardiovasc Care* 2017; 6: 26–33.
9. De Luca G, Suryapranata H, Zijlstra F, et al. Symptom-onset-to-balloon time and mortality in patients with acute myocardial infarction treated by primary angioplasty. *J Am Coll Cardiol* 2003; 42: 991–997.
10. Nguyen HL, Saczynski JS, Gore JM, et al. Age and sex differences in duration of prehospital delay in patients with acute myocardial infarction: A systematic review. *Circ Cardiovasc Qual Outcomes* 2010; 3: 82–92.
11. Heo JY, Hong KJ, Shin SD, et al. Association of educational level with delay of prehospital care before reperfusion in STEMI. *Am J Emerg Med* 2015; 33: 1760–1769.
12. Savonitto S, De Luca G, Goldstein P, et al. Antithrombotic therapy before, during and after emergency angioplasty for ST elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2017; 6: 173–190.
13. Silvain J, Collet JP, Nagaswami C, et al. Composition of coronary thrombus in acute myocardial infarction. *J Am Coll Cardiol* 2011; 57: 1359–1367.
14. Jager B, Farhan S, Rohla M, et al. Clinical predictors of patient related delay in the VIENNA ST-elevation myocardial infarction network and impact on long-term mortality. *Eur Heart J Acute Cardiovasc Care* 2017; 6: 254–261.
15. Nielsen CG, Laut KG, Jensen LO, et al. Patient delay in patients with ST-elevation myocardial infarction: Time patterns and predictors for a prolonged delay. *Eur Heart J Acute Cardiovasc Care*. Epub ahead of print 7 November 2016. DOI: 10.1177/2048872616676570.
16. Ishihara M, Inoue I, Kawagoe T, et al. Diabetes mellitus prevents ischemic preconditioning in patients with a first acute anterior wall myocardial infarction. *J Am Coll Cardiol* 2001; 38: 1007–1011.
17. Nahser PJ Jr, Brown RE, Oskarsson H, et al. Maximal coronary flow reserve and metabolic coronary vasodilation in patients with diabetes mellitus. *Circulation* 1995; 91: 635–640.
18. Nitenberg A, Valensi P, Sachs R, et al. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes* 1993; 42: 1017–1025.
19. Timmer JR, van der Horst IC, de Luca G, et al. Comparison of myocardial perfusion after successful primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction with versus without diabetes mellitus. *Am J Cardiol* 2005; 95: 1375–1377.
20. Prasad A, Stone GW, Stuckey TD, et al. Impact of diabetes mellitus on myocardial perfusion after primary angioplasty in patients with acute myocardial infarction. *J Am Coll Cardiol* 2005; 45: 508–514.
21. Antoniucci D, Valenti R, Migliorini A, et al. Impact of insulin-requiring diabetes mellitus on effectiveness of reperfusion and outcome of patients undergoing primary

percutaneous coronary intervention for acute myocardial infarction. *Am J Cardiol* 2004; 93: 1170–1172.
22. Niccoli G, Scalone G, Lerman A, et al. Coronary microvascular obstruction in acute myocardial infarction. *Eur Heart J* 2016; 37: 1024–1033.
23. Shaw JE, Sicree RA and Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010; 87: 4–14.
24. Fabris E, van 't Hof A, Hamm CW, et al. Impact of presentation and transfer delays on complete ST segment resolution before primary percutaneous coronary intervention: Insights from the ATLANTIC trial. *EuroIntervention* 2017; 13: 69–77.
25. Silvain J, Storey RF, Cayla G, et al. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. *Thromb Haemost* 2016; 116: 369–378.
26. Van 't Hof AW, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): A multicentre, double-blind, randomised controlled trial. *Lancet* 2008; 372: 537–546.
27. Steg PG, Bhatt DL, Hamm CW, et al. Effect of cangrelor on periprocedural outcomes in percutaneous coronary interventions: A pooled analysis of patient-level data. *Lancet* 2013; 382: 1981–1992.
28. Van 't Hof AW, Liem A, de Boer MJ, et al. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial Infarction Study Group. *Lancet* 1997; 350: 615–619.
29. Zeymer U, Schroder R, Tebbe U, et al. 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: 769–775.
30. Bainey KR, Fu Y, Wagner GS, et al. Spontaneous reperfusion in ST-elevation myocardial infarction: Comparison of angiographic and electrocardiographic assessments. *Am Heart J* 2008; 156: 248–255.
31. 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.