Impact of presentation and transfer delays on complete ST-segment resolution before primary percutaneous coronary intervention: insights from the ATLANTIC trial

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KEYWORDS

- adjunctive pharmacotherapy
- clinical research
- clinical trials
- ST-elevation myocardial infarction (STEMI)

Abstract

Aims: The aim of this study was to identify predictors of complete ST-segment resolution (STR) pre-primary percutaneous coronary intervention (PCI) in patients enrolled in the ATLANTIC trial.

Methods and results: ECGs recorded at the time of inclusion (pre-hospital [pre-H]-ECG) and in the catheterisation laboratory before angiography (pre-PCI-ECG) were analysed by an independent core laboratory. Complete STR was defined as ≥70%. Complete STR occurred pre-PCI in 12.8% (204/1,598) of patients and predicted lower 30-day composite MACCE (OR=0.10, 95% CI: 0.002-0.57, p=0.001) and total mortality (OR=0.16, 95% CI: 0.004-0.95, p=0.035). Independent predictors of complete STR included the time from index event to pre-H-ECG (OR=0.94, 95% CI: 0.89-1.00, p=0.035), use of heparins before pre-PCI-ECG (OR=1.75, 95% CI: 1.25-2.45, p=0.001) and time from pre-H-ECG to pre-PCI-ECG (OR=1.09, 95% CI: 1.03-1.16, p=0.005). In the pre-H ticagrelor group, patients with complete STR had a significantly longer delay between pre-H-ECG and pre-PCI-ECG compared to patients without complete STR (median 53 [44-73] vs. 49 [38.5-61] mins, p=0.001); however, this was not observed in the control group (in-hospital ticagrelor) (50 [40-67] vs. 49 [39-61] mins, p=0.258).

Conclusions: Short patient delay, early administration of anticoagulant and ticagrelor if a long transfer delay is expected may help to achieve reperfusion prior to PCI. Pre-H treatment may be beneficial in patients with longer transfer delays, allowing the drug to become biologically active. ClinicalTrials.gov Identifier: NCT01347580.

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Abbreviations

BMI	body mass index
CABG	coronary artery bypass graft
CI	confidence interval
GP	glycoprotein
MACCE	major adverse cardiac and cerebrovascular events
OR	odds ratio
PCI	percutaneous coronary intervention
pre-H	pre-hospital
STEMI	ST-segment elevation myocardial infarction
STR	ST-segment elevation resolution

Introduction

In the randomised, double-blind, placebo-controlled ATLANTIC trial, pre-hospital (pre-H) administration of ticagrelor in patients with acute ST-segment elevation myocardial infarction (STEMI) appeared to be safe but did not improve pre-percutaneous coronary intervention (PCI) ST-segment elevation resolution (STR) and/or TIMI 3 flow in the culprit artery[1]. However, it is possible that the brief time interval from study drug administration in the ambulance to catheterisation laboratory (cathlab) may have limited the potential benefit of pre-H ticagrelor administration.

Since achievement of early myocardial reperfusion is one of the main goals in STEMI patients for improving prognosis, the identification of factors related to this objective may provide further insights into the optimisation of pre-hospital STEMI patient management. Therefore, we undertook an exploratory analysis describing the predictors, and clinical significance, of complete STR before PCI in STEMI patients enrolled in the ATLANTIC trial.

Methods

STUDY DESIGN AND PROCEDURES

The ATLANTIC trial was an international study that randomised 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-hospital (in cathlab), in addition to aspirin and standard of care.

The trial design and main results have been published[1,2]. Briefly, eligible patients were identified by ambulance personnel for inclusion in the study following diagnosis of STEMI of more than 30 minutes' but less than six hours' duration, and with an expected time from qualifying ECG to first balloon inflation of less than 120 minutes. Randomisation 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 cathlab. 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 the physicians' discretion.

ELECTROCARDIOGRAPHIC ANALYSIS, DEFINITIONS AND ENDPOINTS USED

ST-segment analysis was performed on ECGs recorded pre-H (at the time of inclusion) and in the cathlab before angiography. The degree of STR was assessed by an independent core laboratory (eResearch Technology, Peterborough, United Kingdom), blinded to study treatment. The STR was calculated as the mean ST-segment elevation pre-H minus the mean ST-segment elevation pre-PCI divided by the mean ST-segment elevation pre-H and expressed as a percentage, i.e., STR=(ST pre-hospital−ST pre-PCI]/STpre-hospital)×100. Complete STR was defined as ≥70% STR.

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

Safety endpoints analysed included major or minor bleeding (excluding coronary artery bypass graft [CABG]-related bleeding) within 48 hours of first dose and after 48 hours and up to the last study visit, using the Study of Platelet Inhibition and Patient Outcomes (PLATO) definitions, or major, minor and minimal bleeding up to the last study visit, using TIMI, and Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients (STEEPLE) definitions[2]. 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 case of Gaussian distribution, or median, interquartile ranges, and Mann-Whitney's p-value in case of non-Gaussian distribution. For categorical variables, number, percent and chi-square test p-value are presented, or Fisher's test p-value is presented in case of low numbers of events.

Ischaemic endpoint analyses were performed in the modified intention-to-treat population, i.e., those patients who underwent randomisation received at least one dose of the study drug and had complete data for STR pre-PCI. For each endpoint, the two groups (complete STR group and incomplete STR group) were compared with the use of a logistic regression model. The 95% confidence intervals for the odds ratio were calculated and results were also presented as survival curves using Kaplan-Meier estimates.

Potential predictors of complete STR before 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 and major determinants of STR, including age, sex, body mass index, diabetes mellitus (DM), prior coronary intervention and prior MI, with a p-value <0.05 threshold for significance.

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

Results

A complete descriptive analysis of patients with pre-PCI complete STR compared to incomplete STR is shown in **Table 1.**

PATIENT CHARACTERISTICS

A total of 1,598 patients with both pre-H and pre-PCI-ECGs available were included in the present analysis. Complete STR pre-PCI

Table 1. Descriptive analysis.

Characteristic		Incomplete STR pre-PCI (<70%) (n=1,394)	Complete STR pre-PCI (≥70%) (n=204)	Total (n=1,598)	*p*-value
Age, years; median [q1;q3]		59 [52;70]	59 [51.5;67]	59 [52;69]	0.3685
Age ≥75 years, n (%)		225 (16.1)	25 (12.3)	250 (15.6)	0.1536
Female, n (%)		269 (19.3)	41 (20.1)	310 (19.4)	0.7870
Weight, kg; median [q1;q3]		80 [70;89.5]	76 [66;88]	80 [70;89.5]	0.0139
BMI ≥30 kg/m^2, n (%)		279 (20.0)	29 (14.2)	308 (19.3)	0.0499
Diabetes mellitus, n (%)		187 (13.4)	25 (12.3)	212 (13.3)	0.6483
TIMI risk score group, n (%)	0–2	843 (60.5)	128 (62.8)	971 (60.8)	0.8036
	3–6	526 (37.7)	73 (35.8)	599 (37.5)	
	>6	25 (1.8)	3 (1.5)	28 (1.8)	
Prior cardiac history, n (%)	Prior MI	105 (7.5)	19 (9.3)	124 (7.8)	0.3744
	Prior PCI	86 (6.2)	21 (10.3)	107 (6.7)	0.0277
	Prior CABG	5 (0.4)	3 (1.5)	8 (0.5)	0.0705
	Prior haemorrhagic stroke	4 (0.3)	0 (0)	4 (0.3)	1.0000
	Prior ischaemic stroke	10 (0.7)	2 (1.0)	12 (0.8)	0.6583
	Prior TIA	19 (1.4)	1 (0.5)	20 (1.3)	0.4997
Other medical history, n (%)	COPD	56 (4.0)	8 (3.9)	64 (4.0)	0.9481
	Chronic renal failure	24 (1.7)	3 (1.5)	27 (1.7)	1.0000
Killip class I, n (%)		1,271 (91.2)	187 (91.7)	1,458 (91.2)	0.8171
Location of care at time of randomisation, n (%)[a]	In ambulance (primary transfer)	1,043 (74.8)	160 (78.4)	1,203 (75.3)	0.2642
	In emergency unit before ambulance transfer (secondary transfer)	351 (25.2)	44 (21.6)	395 (24.7)	
Study medication	1st loading dose	1,393 (99.9)	204 (100)	1,597 (99.9)	1.0000
	2nd loading dose	1,354 (97.1)	198 (97.1)	1,552 (97.1)	0.9544
	Maintenance dose	1,224 (87.8)	181 (88.7)	1,405 (87.9)	0.7063
Actual pre-H ticagrelor, no morphine		319 (22.9)	67 (32.8)	386 (24.2)	0.0019
Actual pre-H ticagrelor, use of morphine		353 (25.3)	36 (17.7)	389 (24.3)	0.0170
Actual in-H ticagrelor, no morphine		365 (26.2)	47 (23.0)	412 (25.8)	0.3376
Actual in-H ticagrelor, use of morphine		357 (25.6)	54 (26.5)	411 (25.7)	0.7928
Aspirin use	Use before pre-PCI-ECG	1,114 (79.9%)	166 (81.4%)	1,280 (80.1%)	0.6260
	Use in the 24 hrs before index event	418 (30.0%)	58 (28.4%)	476 (29.8%)	0.6503
Other antithrombotic medication for index event	Use of GP IIb/IIIa inhibitors before pre-PCI-ECG	42 (3%)	11 (5.4%)	53 (3.3%)	0.0763
	Intravenous anticoagulant during hospitalisation	1,236 (88.7)	192 (94.1)	1,428 (89.4)	0.0183
	Use of heparin before pre-PCI-ECG	870 (62.4%)	151 (74.0%)	1,021 (63.9%)	0.0013
Time from index event to pre-H-ECG (min) [q1;q3]		73 [42;140]	66 [38;114.5]	71 [42;138]	0.0321
Time from index event to 1st loading dose (min) [q1;q3]		90 [60;159]	85 [55;135]	90 [60;155]	0.0598
Time from pre-H-ECG to pre-PCI-ECG (min) [q1;q3]		49 [39;61]	52 [42;70.5]	49 [39;62]	0.0021
Time from 1st loading dose to 2nd loading dose (min) [q1;q3]		30 [21;42.5]	32 [23;48]	30 [21;43]	0.1002
Time from 1st loading dose to pre-PCI-ECG (min) [q1;q3]		31 [22;42]	33.5 [25;48]	31 [22;43]	0.0083
Procedures for index event, n (%)	Coronary angiography	1,382 (99.1)	203 (99.5)	1,585 (99.2)	1.0000
	Thrombus aspiration	748 (53.7)	86 (42.2)	834 (52.2)	0.0021
	PCI	1,239 (88.9)	186 (91.2)	1,425 (89.2)	0.3243
	With stent	1,166 (83.6)	175 (85.8)	1,341 (83.9)	0.4371
	Without stent	73 (5.2)	11 (5.4)	84 (5.3)	0.9260
	CABG	13 (0.9)	8 (3.9)	21 (1.3)	0.0028

CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; GP: glycoprotein; in-H: in-hospital; MI: myocardial infarction; PCI: percutaneous coronary intervention; pre-H: pre-hospital; TIA: transient ischaemic attack

occurred in 12.8% (n=204/1,598) of patients. Patients with complete STR were less frequently obese (weight: median [q1;q3], 76 [66;88] vs. 80 [70;89.5] kg, p=0.014; body mass index [BMI] ≥30 kg/m², 14.2% vs. 20%, p=0.0499) compared with incomplete STR. Patients with a prior PCI more often had complete STR (10.3% vs 6.2%, p=0.028). No other patient demographic characteristics were significantly different between the two groups.

PRE-HOSPITAL PHARMACOLOGICAL TREATMENT

Use of aspirin before pre-PCI-ECG (80.1%) or its use in the 24 hours before the index event (29.8%) as well as the use of GP IIb/IIIa inhibitors before pre-PCI-ECG (3.3%) was not different between the complete STR and incomplete STR groups. Conversely, the use of heparin (any type) before pre-PCI-ECG was more frequent in the complete STR group (74% vs. 62.4%, p=0.001).

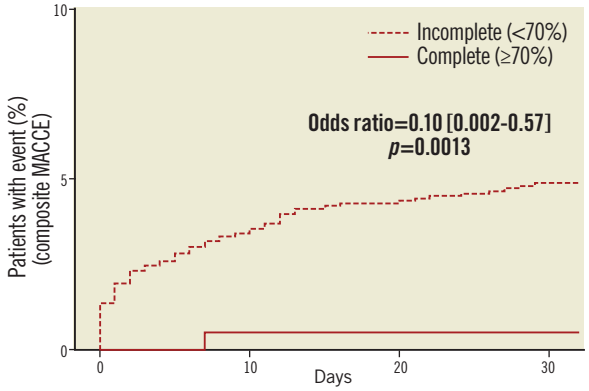
Moreover, the complete STR group more frequently received pre-H ticagrelor administration without concomitant morphine use, compared with the incomplete STR group (32.8% vs. 22.9%, p=0.002). Conversely, the concomitant use of morphine and pre-H ticagrelor was more frequent in the incomplete STR group compared with the complete STR group (25.3% vs. 17.7%, p=0.017). The use of in-H ticagrelor with or without concomitant use of morphine was similar in the complete vs. incomplete STR group.

PRE-HOSPITAL INTERVAL TIMES

Interestingly, the complete STR group exhibited a shorter time interval from the index event to pre-H-ECG (median [q1;q3], 66 [38;114.5] vs. 73 [42;140] mins, p=0.032); conversely, a longer time interval from pre-H-ECG to pre-PCI-ECG (median [q1;q3], 52 [42;70.5] vs. 49 [39;61] mins, p=0.002) and a longer time interval from the first loading dose to the pre-PCI-ECG (median [q1;q3], 33.5 [25;48] vs. 31 [22;42] mins, p=0.008).

CLINICAL SIGNIFICANCE OF PRE-PCI COMPLETE ST RESOLUTION

On logistic regression analysis, complete STR predicted both lower composite MACCE (OR=0.10, 95% CI: 0.002-0.57, p=0.001) and total mortality (OR=0.16, 95% CI: 0.004-0.95, p=0.035) but not definite stent thrombosis **(Table 2)**. Kaplan-Meier curves are shown in **Figure 1** and **Figure 2.** There was no association between complete STR and increased bleeding risk, with the exception of minor non-CABG-related bleeding events (PLATO definition) within 48 hours of first dose **(Table 3)**.

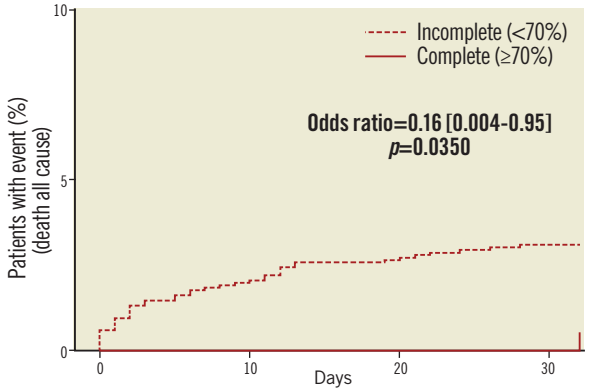


	Patients with event no. (%)	Total no. of patients
Complete ST resolution pre-PCI	1 (0.5%)	204
Incomplete ST resolution pre-PCI	67 (4.8%)	1,394

Figure 1. *Composite MACCE Kaplan-Meier curves in relation to complete and incomplete STR.*

PREDICTORS OF PRE-PCI COMPLETE ST RESOLUTION

Univariate and multivariate analysis of pre-PCI complete STR is presented in **Table 4.** At multivariate adjusted analysis (with age, sex, BMI, diabetes, prior PCI and prior myocardial infarction as variables forced into the model), modifiable independent predictors



	Patients with event no. (%)	Total no. of patients
Complete ST resolution pre-PCI	1 (0.5%)	204
Incomplete ST resolution pre-PCI	42 (3.0%)	1,394

Figure 2. *Total mortality Kaplan-Meier curves in relation to complete and incomplete STR.*

Table 2. ST-segment resolution and ischaemic endpoints*, logistic regression analysis.

Ischaemic endpoints	Incomplete STR pre-PCI (<70%) (n=1,394)	Complete STR pre-PCI (≥70%) (n=204)	Odds ratio¶	*p*-value¶
Composite of death, MI, stroke and urgent revascularisation, n (%)	67 (4.8%)	1 (0.5%)	0.10 [0.002;0.57]	0.0013
Definite stent thrombosis, n (%)	11 (0.8%)	0 (0%)	0.44 [0;2.14]	0.3777
Death (all-cause), n (%)	42 (3.0%)	1 (0.5%)	0.16 [0.004;0.95]	0.0350

*Events occurring up to the date of the last study visit (≤32 days) are included in the Table. ¶exact if n<5 in one group.

Table 3. ST-segment resolution and non-CABG-related bleeding events*, logistic regression analysis.

Non-CABG-related bleeding events			Incomplete STR pre-PCI (<70%) (n=1,394)	Complete STR pre-PCI (≥70%) (n=204)	Odds ratio [CI]¶	*p*-value¶
PLATO definition						
Within 48 hrs of first dose	Major		23 (1.7)	2 (1.0)	0.59 [0.07;2.42]	0.7611
	Minor		9 (0.7)	5 (2.5)	3.87 [1.28;11.66]	0.0163
	Composite of major and minor		32 (2.3)	7 (3.4)	1.51 [0.66;3.47]	0.3294
After 48 hrs and up to 30 days*	Major		17 (1.2)	2 (1.0)	0.80 [0.09;3.42]	1.0000
	Minor		10 (0.7)	1 (0.5)	0.68 [0.02;4.84]	1.0000
	Composite of major and minor		27 (1.9)	3 (1.5)	0.76 [0.15;2.49]	1.0000
TIMI and STEEPLE definition						
Up to 30 days*	TIMI	Major	19 (1.4)	2 (1.0)	0.72 [0.08;3.01]	1.0000
		Minor	32 (2.3)	6 (2.9)	1.29 [0.53;3.12]	0.5724
		Minimal	9 (0.7)	1 (0.5)	0.76 [0.02;5.52]	1.0000
	STEEPLE	Major	37 (2.7)	3 (1.5)	0.55 [0.11;1.76]	0.4696
		Minor	19 (1.4)	5 (2.5)	1.82 [0.67;4.92]	0.2395
		Unknown	4 (0.3)	1 (0.5)	1.71 [0.04;17.40]	1.0000

*Events occurring up to the date of the last study visit (≤32 days) are included in the Table. ¶exact if n<5 in one group.

for complete STR were the time interval (mins) from index event (onset of symptoms) to pre-H-ECG (OR=0.94, 95% CI: 0.89-1.00, p=0.035), which may represent "patient delay" time, the time from pre-H-ECG to pre-PCI-ECG (OR=1.09, 95% CI: 1.03-1.16, p=0.005), which may represent the transfer delay from ambulance to cathlab, and lastly the use of heparin before pre-PCI-ECG (OR=1.75, 95% CI: 1.25-2.45, p=0.001). Further independent predictors, but non-modifiable in relation to the early management of patients, were BMI <30 kg/m^2 (OR=1.56, 95% CI: 1.02-2.39, p=0.039) and prior PCI status (OR=2.15, 95% CI: 1.07-4.35, p=0.033).

EFFECT OF PRE-HOSPITAL TICAGRELOR ON ST RESOLUTION PRE-PCI

There was no significant difference between the pre-H group and the in-H group in terms of the proportion of patients who had complete STR before PCI (13.2% vs. 12.4%, OR=1.07,

Table 4. Clinical predictors of complete ST resolution before PCI.

Variables§		No.	Univariate		Multivariate n=1,571		Multivariate adjusted* n=1,571	
			Odds ratio [CI]	*p*-value	Odds ratio [CI]	*p*-value	Odds ratio [CI]	*p*-value
Time from index event to 1st loading dose	≤1 vs. >3 hrs	1,582	1.69 [1.07;2.69]	0.0751¶				
	>1-3 vs. >3 hrs		1.30 [0.86;1.99]					
	≤1 vs. >1-3 hrs		1.30 [0.92;1.83]					
Time from index event to pre-H-ECG (min)		1,597	0.95 [0.89;1.00]	0.0448¶	0.94 [0.89;1.00]	0.0354	0.94 [0.89;1.00]	0.0346
Time from pre-H-ECG to pre-PCI-ECG (min)		1,598	1.04 [1.00;1.09]	0.0554¶	1.09 [1.03;1.16]	0.0041	1.09 [1.03;1.16]	0.0051
Sex (female vs. male)		1,598	1.05 [0.73;1.52]	0.7870			1.25 [0.84;1.85]	0.2747
Age		1,598	0.99 [0.98;1.01]	0.3401				
Age (≥65 vs. <65 years)		1,598	0.85 [0.62;1.16]	0.3081			0.80 [0.57;1.11]	0.1758
Body mass index (<30 vs. ≥30 kg/m^2)		1,572	1.53 [1.01;2.31]	0.0459¶	1.55 [1.02;2.35]	0.0406	1.56 [1.02;2.39]	0.0389
Prior myocardial infarction (yes vs. no)		1,598	1.26 [0.76;2.11]	0.3751			0.83 [0.41;1.71]	0.6190
Prior PCI (yes vs. no)		1,598	1.75 [1.06;2.88]	0.0295¶	1.82 [1.08;3.05]	0.0241	2.15 [1.07;4.35]	0.0328
Prior CABG (yes vs. no)		1,598	4.14 [0.64;21.47]	0.0705¶				
Diabetes mellitus (yes vs. no)		1,598	0.90 [0.58;1.41]	0.6485			1.00 [0.63;1.58]	0.9831
Use of heparin before pre-PCI-ECG (yes vs. no)		1,598	1.72 [1.23;2.39]	0.0014¶	1.72 [1.23;2.41]	0.0015	1.75 [1.25;2.45]	0.0011
Use of GP IIb/IIIa inhibitors before pre-PCI-ECG (yes vs. no)		1,598	1.84 [0.93;3.62]	0.0806¶				

*The multivariate adjusted analysis is the multivariate analysis with variables forced in the model: age, sex, BMI, diabetes, prior PCI, prior MI. §variables with *p*-value <0.10 in univariate analysis or forced into the multivariate adjusted analysis. ¶variables with *p*-value <0.10 in univariate analysis.

95% CI: 0.8-1.44, p=0.63, respectively). In the pre-H ticagrelor group, patients with complete STR had a significantly longer delay between pre-H-ECG and pre-PCI-ECG compared to patients without complete STR (median 53 [44-73] vs. 49 [38.5-61] mins, p=0.00); this was not observed in the control group (in-hospital ticagrelor) (50 [40-67] vs. 49 [39-61] mins, p=0.258) **(Table 5)**.

Discussion

The ATLANTIC ST-segment resolution substudy represents, in the primary PCI era, the largest prospective cohort of STEMI patients focusing on early myocardial reperfusion expressed as complete STR during patient transportation for primary PCI.

Because achieving early myocardial reperfusion is the main goal in STEMI patients, this study evaluated the possible factors influencing early coronary reperfusion before primary PCI. The fact that a longer delay during patient transportation (the time from pre-H-ECG to pre-PCI-ECG) emerged as an independent predictor of complete STR suggests that pre-H antithrombotic treatment may become effective when there is a longer transfer time, allowing the drug to become biologically active. Moreover, it was only in the pre-H ticagrelor group that patients with complete STR had a significantly longer transportation delay compared to patients without complete STR; conversely, this was not observed in the control group (in-H ticagrelor), thus suggesting a possible effect of pre-H ticagrelor administration in patients with longer transfer delay. The possible efficacy of pre-treatment with antiplatelet agents should be viewed in the perspective of an early or delayed access to coronary angiography and revascularisation[3]. Short medical contact-to-balloon times may explain the absence of a detectable benefit of in-ambulance ticagrelor before the PCI procedure[1]. However, whereas the short time to PCI achieved in the ATLANTIC study[1] represents excellent practice, it may not reflect routine practice. Despite remarkable improvement[4], the timeliness of reperfusion therapy for STEMI patients transferred for primary PCI is often prolonged, with a significant proportion of transferred patients not achieving a guideline-recommended[5,6] door-to-balloon time of less than 90 minutes[4,7]. It is evident, therefore, that, in the real world, early administration of potent antiplatelet therapy may represent an opportunity for improving pre-PCI myocardial reperfusion[8]. This analysis provides further support for a pre-H ticagrelor strategy in STEMI patients, especially for those who still present with a long transfer time. Although this finding can only be considered as hypothesis-generating, the potential benefit of pre-H ticagrelor administration should not be denied, especially considering its proven safety[1]. This is in line with the last ESC Guidelines which recommend giving $P2Y_{12}$ inhibitors at "the time of first medical contact"[9], a recommendation which is more specific as compared to the 2013 ACCF/AHA Guidelines which state that $P2Y_{12}$ inhibitors "should be given as early as possible or at time of primary PCI"[6].

A new opportunity to accelerate the onset of action of the antiplatelet effect could be the use of crushed or chewed rather than whole tablets[10,11]; conversely, the use of morphine was shown to delay the absorption and onset of action of ticagrelor[1,12]. Moreover, the possible delay in ticagrelor absorption in the setting of STEMI cannot be overcome by increasing loading dose regimens[13]. Pre-H administration of a fast-acting antiplatelet agent, such as cangrelor[14], may represent a new strategy to be tested in order to improve pre-PCI reperfusion.

The importance of in-ambulance treatment is also suggested by the fact that early use of heparin (before pre-PCI-ECG) was an independent predictor of complete pre-PCI STR. This suggests that the earlier heparin is instituted, the greater the therapeutic benefit. This is in line with current guidelines that strongly recommend, despite the paucity of evidence[15,16], early administration of an anticoagulant at the time of diagnosis, and also with the common practice among many European emergency medical services to give an anticoagulant as soon as possible, including in the pre-H setting.

Interestingly, complete STR was more frequent in patients with lower weight and BMI, and BMI <30 kg/m^2 emerged as an independent predictor of complete STR. This may reflect the possible influence of BMI on the efficacy of antithrombotic therapy[17]; however, ticagrelor efficacy is not influenced by BMI[18].

Another independent predictor of complete STR was short "patient delay" (the time from index event to pre-H-ECG). This emphasises, once more[19,20], that the delay between symptom onset and diagnosis (first ECG) should be minimised as much as possible. The early period after symptom onset represents a golden opportunity for antithrombotic therapy, because the platelet content of the fresh coronary thrombus is maximal and more susceptible to powerful antiplatelet agents[21]. Moreover, early reperfusion after symptom onset has the maximal life-saving potential, through myocardial salvage. Patient education is an important component in reducing this delay[22], and it is interesting that, in this analysis, prior PCI status was another independent predictor of complete STR. One might speculate that these patients recognised the symptoms of acute myocardial infarction and took timely action to seek medical help.

Table 5. Transfer time and ST-segment resolution in in-hospital and pre-hospital ticagrelor groups.

Variable	Group	No.	Pre-PCI STR	Median [q1;q3]	*p*-value
Time from pre-H-ECG to pre-PCI-ECG (min)	In-hospital ticagrelor group	722	Incomplete (<70%)	49 [39;61]	0.2581
		102	Complete (≥70%)	50 [40;67]	
	Pre-hospital ticagrelor group	672	Incomplete (<70%)	49 [38.5;61]	0.0013
		102	Complete (≥70%)	53 [44;73]	

The ATLANTIC ST-segment resolution analysis highlights the elements that may help to achieve reperfusion before primary PCI. This is particularly relevant considering that this substudy confirmed[19,23,24] the prognostic importance of electrocardiographic assessments of early reperfusion, showing that pre-PCI complete STR represents a valid surrogate marker for cardiovascular clinical outcomes, namely MACCE and death **(Figure 1, Figure 2)**.

Finally, the reduction in ischaemic complications associated with pre-PCI complete STR was not associated with an excess of major bleeding. This result was consistent across all the definitions and types of bleeding adjudicated by the clinical endpoint committee, with the exception of a signal for more early minor bleeding.

Limitations

First, this analysis was a *post hoc* analysis and therefore should be viewed as hypothesis-generating. Second, continuous ST-segment monitoring was not used, thereby precluding the identification of dynamic changes that may be observed during the acute phase of STEMI. Third, 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 STR are likely to have a patent infarct artery[25]. Moreover, STR can be considered a surrogate for tissue-level reperfusion[23] and, in the fibrinolytic era, STR showed a prognostic power that persists even after accounting for the effects of epicardial blood flow[26]. Overall, there was a small difference between the different time intervals that have been considered; however, this study identified clear independent predictors of outcome with clinical applicability. Finally, the possibility of unaccounted confounding related to the non-randomised administration of heparin cannot be excluded; therefore, the potential benefit of early heparin administration requires confirmation in future studies.

Conclusions

Pre-PCI complete STR is a valid surrogate marker for cardiovascular clinical outcomes. Short patient delay, early administration of an anticoagulant and ticagrelor if a long transfer delay is expected may help to achieve reperfusion prior to PCI. The fact that a longer delay during patient transportation emerged as an independent predictor of complete STR suggests that pre-H treatment may be beneficial in patients with longer transfer delays, allowing the drug to become biologically active.

Impact on daily practice

In patients with STEMI being transported for primary percutaneous coronary intervention, pre-hospital treatment with an anticoagulant and ticagrelor in addition to aspirin if a long transfer delay is expected may help to achieve reperfusion prior to PCI. This provides support for a pre-hospital strategy treatment for those who still present with a long transfer time.

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Conflict of interest statement

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