Thrombus aspiration and prehospital ticagrelor administration in ST-elevation myocardial infarction: Findings from the ATLANTIC trial

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Background The potential interactions between prehospital (pre-H) ticagrelor administration and thrombus aspiration (TA) in patients with ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI) have never been studied. Therefore, we evaluated the potential benefit of TA and pre-H ticagrelor treatment in patients enrolled in the ATLANTIC trial (NCT01347580).

Methods This analysis included 1,630 patients who underwent primary PCI. Multivariate analysis was used to explore the potential association of TA and pre-H treatment to clinical outcomes. Potential interactions between TA and pre-H ticagrelor were also explored.

Results A total of 941 (57.7%) patients underwent TA. In adjusted multivariate logistic model, pre-H ticagrelor treatment was significantly associated with less frequent new MI or definite stent *thrombosis (ST) (odds ratio [OR] 0.43, 95% CI 0.20-0.92, $P = .031$), or definite ST (OR 0.26, 95% CI 0.07-0.91, $P = .036$) at 30 days. Patients treated with TA had higher frequency of Thrombolysis in Myocardial Infarction (TIMI) flow 0-1 compared with no-TA group (80.7% vs 51.9%, $P < .0001$). TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bailout use of glycoprotein IIb/IIIa inhibitors (OR 1.72, 95% CI 1.18-2.50, $P = .004$) and more frequent 30-day TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, $P = .032$). No significant interactions between TA and pre-H ticagrelor were present for the explored end points.

Conclusions TA when left to physicians' discretion was used in high-risk patients, was associated with bailout use of glycoprotein IIb/IIIa inhibitors and TIMI major bleeding, and had no impact on 30-day clinical outcomes. Conversely, pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI without interaction with TA. (Am Heart J 2018;196:1-8.)

Acute coronary syndromes are usually precipitated by an acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, causing a sudden and critical reduction in blood flow. The most important treatment for patients with ST-elevation myocardial infarction (STEMI) is early recovery of the infarct-related artery blood flow.[1-4] However, reduced flow due to distal embolization of thrombus is associated with an increased infarct size, reduced recovery of ventricular function, and increased mortality.[3,5] The high frequency of suboptimal myocardial reperfusion after primary percutaneous coronary intervention (PCI) has resulted in the development of devices that evacuate coronary thrombus to limit distal embolization and to protect the microcirculation; moreover, large interest has focused on the prehospital (pre-H) administration of pharmacological therapy.

Clinical trials focusing on manual thrombus aspiration (TA) in primary PCI have generally shown improved myocardial reperfusion. However, no reduction in hard clinical end points was seen when compared with conventional PCI in large clinical trials.[3,6]

In the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial

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Infarction to Open the Coronary Artery (ATLANTIC) trial, pre-H administration of ticagrelor in patients with STEMI appeared to be safe but did not improve coronary or myocardial reperfusion before primary PCI[4]; however, the effects of pre-H ticagrelor became apparent immediately after PCI.[7]

Because both TA and pre-H pharmacological treatment are potential options to improve myocardial reperfusion and post-PCI clinical outcomes in patients with STEMI treated with primary PCI, we evaluate the potential benefit of TA and pre-H ticagrelor treatment in patients enrolled in the ATLANTIC trial.

Methods

Study design and patients

The ATLANTIC study was an international, randomized, double-blind study (NCT01347580). Patients were randomly assigned to receive either pre-H (in the ambulance) or in-hospital (in the catheterization laboratory) treatment with ticagrelor, in addition to aspirin and standard care. The trial design has been previously published.[8]

Study procedures

In the pre-H group, patients received a 180-mg loading dose of ticagrelor before transfer and then a matching placebo in the catheterization laboratory. Patients in the in-hospital group received a placebo before transfer and then a 180-mg loading dose of ticagrelor in the catheterization laboratory. All the patients subsequently received ticagrelor at a dose of 90 mg twice daily for 30 days, with a recommendation that treatment be continued for a total of 12 months. In-ambulance use of glycoprotein IIb/IIIa inhibitors (GPI) was discouraged but was left to the physician's discretion. In-laboratory use of GPI had to be identified as either a strategy of choice or a bailout treatment during PCI. Coronary angiography was performed via the radial or femoral artery. Manual TA was performed at the discretion of the operator as per the standard protocol followed by conventional PCI to the culprit vessel.

Study end points

Clinical end points, evaluated up to date of the last study visit (≤32 days), included death, new myocardial infarction (MI), stent thrombosis (ST), urgent revascularization, bailout GPI use, stroke, Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 at the end of the procedure, and complete (≥70%) resolution of ST-segment elevation at 60 minutes after PCI. Safety end point included major bleeding up to the last study visit using TIMI definitions.

Centralized, blinded reviews of angiographic data and ECG recordings were conducted by Cardialysis Core Laboratory services (Rotterdam, the Netherlands) and eResearch Technology (Peterborough, United Kingdom), respectively. An independent adjudication committee, whose members were unaware of the treatment assignments, reviewed the clinical end points, except deaths and minimal bleeding events.

Statistical analysis

Statistics. Subjects were classified according to TA subgroup. Continuous variables are presented as mean and SD or median (interquartile range), and compared using Student *t* test's *P* value in case of Gaussian distribution or Mann-Whitney's *P* value in case of non-Gaussian distribution. Categorical variables are presented as number and percentages and compared using χ^2 test *P* value or Fisher test *P* value in case of low numbers of events. The association between TA subgroup and clinical end points was assessed by fitting logistic regression model with TA as the only covariate. Odds ratios (ORs) and *P* values for pre- versus in-hospital ticagrelor were calculated using a logistic regression model with study treatment group as the only explanatory variable. The interaction between TA and study treatment group was tested by using a multivariate logistic regression model. For testing the association between pre-H ticagrelor and end points, a multivariate adjusted analysis was performed with variables forced in the model: age (<75, ≥75 years), sex, body mass index (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischemic attack, nonhemorrhagic stroke, stent, drug-eluting stent, bare metal stent, hypertension, arterial access, and GPI before PCI. The same variables forced in the model plus TIMI flow 0-1 were used to evaluate the association between TA subgroup and clinical end points. The 2-sided significance level was fixed at 5%. All tests were performed with SAS version 9.4 (SAS Institute Inc, Cary, NC).

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Results

Patient and procedure characteristics

One thousand six hundred thirty patients enrolled in the trial and who underwent primary PCI were included in the analysis.

A total of 941 (57.7%) patients underwent TA. Patients treated with TA were younger (60 ± 12 vs 62 ± 12 years, *P* < .0001), were more frequently men (83% vs 78.4%, *P* = .019), less frequently had a previous MI (6.6% vs 9.6%, *P* = .027) or transient ischemic attack (0.4% vs 1.5%, *P* = .026), and more frequently had radial access (70.4% vs 64.7%, *P* = .015). Patients treated with TA had

Table I. Baseline characteristics and procedural characteristics between patients with and without TA

	TA			
	TA n = 941	No TA n = 689	Overall N = 1630	*P* value
Age				
Mean ± SD	59.9 ± 11.9	62.3 ± 12.1	60.9 ± 12.1	<.0001
Age group (<75, ≥75), n (%)				
≥75 y	126 (13.4%)	132 (19.2%)	258 (15.8%)	.0016
Sex, n (%)				
Female	160 (17.0%)	149 (21.6%)	309 (19.0%)	.0187
Weight (kg)				
Mean ± SD	80.8 ± 15.3	79.5 ± 16.1	80.3 ± 15.6	.0797
Body mass index group (kg/m^2), n (%)				
≥30 kg/m^2	193 (20.5%)	130 (18.9%)	323 (19.8%)	.4113
Diabetes mellitus, n (%)	127 (13.5%)	87 (12.6%)	214 (13.1%)	.6077
TIMI risk score category, n (%)				
0-2	601 (63.9%)	400 (58.1%)	1001 (61.4%)	.0535
3-6	327 (34.8%)	276 (40.1%)	603 (37.0%)	
>6	13 (1.4%)	13 (1.9%)	26 (1.6%)	
TIMI flow grade, n (%)				
0-1	744 (80.7%)	349 (51.9%)	1093 (68.5%)	<.0001
2-3	178 (19.3)	324 (48.1%)	502 (31.5%)	
Myocardial infarction, n (%)	62 (6.6%)	66 (9.6%)	128 (7.9%)	.0266
PCI, n (%)	55 (5.8%)	61 (8.9%)	116 (7.1%)	.0196
Coronary artery bypass graft, n (%)	4 (0.4%)	5 (0.7%)	9 (0.6%)	.5061
Chronic obstructive pulmonary disease, n (%)	38 (4.0%)	27 (3.9%)	65 (4.0%)	.9030
Chronic renal disease, n (%)	10 (1.1%)	14 (2.0%)	24 (1.5%)	.1085
Hypertension, n (%)	374 (39.7%)	303 (44.0%)	677 (41.5%)	.0868
Congestive heart failure, n (%)	6 (0.6%)	7 (1.0%)	13 (0.8%)	.3963
Dyslipidemia including hypercholesterolemia, n (%)	328 (34.9%)	247 (35.8%)	575 (35.3%)	.6787
Transient ischemic attack, n (%)	4 (0.4%)	10 (1.5%)	14 (0.9%)	.0265
Hemorrhagic stroke, n (%)	4 (0.4%)	0 (0.0%)	4 (0.2%)	.1425
Nonhemorrhagic stroke, n (%)	6 (0.6%)	10 (1.5%)	16 (1.0%)	.0997
Killip class I, n (%)	857 (91.1%)	632 (91.7%)	1489 (91.3%)	.6427
Arterial access, n (%)				
Radial	659 (70.4%)	444 (64.7%)	1103 (68.0%)	.0154
Femoral	277 (29.6%)	242 (35.3%)	519 (32.0%)	
Stent, n (%)				
With stent	877 (93.2%)	659 (95.6%)	1536 (94.2%)	.0363
Drug-eluting stent, n (%)	513 (54.5%)	433 (62.8%)	946 (58.0%)	.0008
Bare-metal stent, n (%)	377 (40.1%)	240 (34.8%)	617 (37.9%)	.0315
1st loading dose, n (%)	939 (99.8%)	689 (100.0%)	1628 (99.9%)	.5117
2nd loading dose, n (%)	922 (98.0%)	668 (97.0%)	1590 (97.5%)	.1848
Maintenance dose, n (%)	889 (94.5%)	640 (92.9%)	1529 (93.8%)	.1896

(continued on next page)

Table I (*continued*)

	TA			
	TA n = 941	No TA n = 689	Overall N = 1630	*P* value
Aspirin use, n (%)	939 (99.8%)	685 (99.4%)	1624 (99.6%)	.2484
GPI before PCI, n (%)	350 (37.2%)	175 (25.4%)	525 (32.2%)	<.0001
Intravenous anticoagulant during hospitalization, n (%)	843 (89.6%)	621 (90.1%)	1464 (89.8%)	.7193

higher frequency of TIMI flow 0-1 compared with no-TA group (80.7% vs 51.9%, $P < .0001$). The rate of bailout use of GPI was more frequent in the TA group than in the PCI-alone group (37.2% vs 25.4%, $P < .0001$). Stenting was lower in the TA group (93.2% vs 95.6%, $P = .036$) (Table I).

Pre-H treatment and TA as potential predictors of clinical outcomes

At multivariate and adjusted multivariate analysis, pre-H ticagrelor emerged as a predictor of lower incidence of new MI or definite ST (OR 0.43, 95% CI 0.20-0.92, $P = .031$), or definite ST (OR 0.26, 95% CI 0.07-0.91, $P = .036$) at 30 days (Table III).

TA when also adjusted for TIMI flow 0-1 showed significant association only for higher bailout use of GPI (OR 1.72, 95% CI 1.18-2.50, $P = .004$) and higher 30-day TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, $P = .032$) (Table IV).

Importantly, TA was not associated with the occurrence of stroke at 30 days (Table IV).

No significant interactions between TA and pre-H ticagrelor were present for the explored end points or composite end points (Table II).

Pre-H treatment and TA as potential predictors of electrocardiographic and angiographic outcomes

TA and pre-H treatment did not emerge as significant predictors of electrocardiographic and angiographic outcomes (Table IV). No significant interactions between TA and pre-H ticagrelor were present for the explored end points.

Pre-H treatment and TA as potential predictors of bleeding events

TA was strongly associated with TIMI major bleeding (OR 2.92, 95% CI 1.10-7.76, $P = .032$) (Tables II and IV).

Conversely, pre-H treatment showed no significant associations with both major and minor TIMI bleeding (Tables II and III).

Discussion

We evaluated the potential benefit of TA and pre-H ticagrelor treatment in a large cohort of STEMI patients enrolled in the ATLANTIC trial, and for the first time, we evaluated the potential synergy effect of pre-H ticagrelor treatment and TA on post-PCI myocardial reperfusion and clinical outcomes.

Interestingly, TA, when left to physicians' discretion, was not associated with improvement in myocardial reperfusion and clinical outcomes. Conversely, pre-H treatment emerged as an independent predictor of lower incidence of composite 30-day new MI or definite acute ST and definite ST and showed a favorable trend for myocardial reperfusion expressed as complete ST resolution post-PCI, highlighting a potential benefit of pre-H pharmacological treatment in STEMI patients.

Despite the use of pre-H treatment together with the use of TA (aimed to reduce thrombotic burden and to improve coronary flow)[9] and consequently clinical outcomes,[10] this analyses showed no significant interactions between TA and pre-H ticagrelor treatment for all the explored end points. However, this analysis showed that TA was frequently used in high-risk patients presenting with TIMI flow 0-1 and TA was a strong predictor of bailout use of GPI.

The absence of interaction between pre-H treatment and TA, however, is in line with the INFUSE-AMI trial[11] where patients were randomized in a 2 × 2 factorial design to bolus intracoronary abciximab versus no abciximab and to TA versus no TA. No interaction was present between the 2 randomization groups for the 30-day infarct size end point, although median infarct size was lowest in the intracoronary abciximab plus TA group compared with the other 3 groups combined. However, it has to be noted that the INFUSE-AMI trial randomized both GPI and TA, whereas the ATLANTIC trial randomized only pre-H ticagrelor versus in-hospital ticagrelor.

This analysis provided further insights regarding the use of TA in the current era of STEMI reperfusion. Indeed, in STEMI patients who received early antithrombotic treatment and fast transportation to the catheterization laboratory,[4] 57.7% received TA treatment; we observed a lower rate of stenting in patients treated with TA, which may suggest, in some cases, a patency of infarct-related artery after manual TA that enabled the interventional cardiologist to leave the artery unstented. It should be

Table II. Multivariate logistic model for the study clinical outcomes and interaction

		Multivariate logistic model* N = 1630	
End points	Predictors	OR (95% CI)	*P* value
30-d composite of death/new MI/urgent revascularization and definite ST	Pre-H vs in-hospital ticagrelor	1.04 (0.64-1.68)	.8741
	TA vs NO TA	0.92 (0.57-1.49)	.7247
	Interaction†		.9602
30-d new MI or definite acute ST	Pre-H vs in-hospital ticagrelor	0.39 (0.16-0.95)	.0375
	TA vs NO TA	1.11 (0.46-2.70)	.8174
	Interaction†		.7006
30-d new MI	Pre-H vs in-hospital ticagrelor	0.72 (0.27-1.92)	.5124
	TA vs NO TA	0.84 (0.32-2.24)	.7318
	Interaction†		.8424
30-d definite ST	Pre-H vs in-hospital ticagrelor	0.20 (0.04-1.02)	.0526
	TA vs NO TA	2.12 (0.42-10.85)	.3661
	Interaction†		.5448
30-d urgent revascularization	Pre-H vs in-hospital ticagrelor	0.60 (0.19-1.88)	.3810
	TA vs NO TA	1.27 (0.41-3.96)	.6799
	Interaction†		.3810
30-d stroke (ischemic)	Pre-H vs in-hospital ticagrelor	4.07 (0.45-37.09)	.2137
	TA vs NO TA	0.95 (0.10-8.63)	.9609
	Interaction†		.8516
Bailout use of GPI	Pre-H vs in-hospital ticagrelor	0.74 (0.52-1.04)	.0845
	TA vs NO TA	1.86 (1.32-2.63)	.0004
	Interaction†		.9113
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	Pre-H vs in-hospital ticagrelor	0.89 (0.69-1.16)	.3964
	TA vs NO TA	1.26 (0.96-1.63)	.0903
	Interaction†		.6830
Absence of ST-segment elevation resolution ≥70% post-PCI	Pre-H vs in-hospital ticagrelor	0.82 (0.66-1.01)	.0606
	TA vs NO TA	0.84 (0.68-1.04)	.1076
	Interaction†		.8163

* Multivariate analysis without covariables testing association between ticagrelor groups, TA groups, and clinical end point and their interactions.
† Interaction between treatment group and TA.

noted that more than half of patients underwent TA despite randomized trials and meta-analyses that tested the effect of TA leading to conflicting results.[3,11-23] Indeed, the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS) trial showed improvement in perfusion indices and significant reduction of mortality and reinfarction after 1 year,[14] but this trial has been criticized for lack of statistical power to prove reduced mortality. Conversely, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial showed no benefit of TA use in 30-day clinical outcomes (all-cause mortality, reinfarction, ST, or revascularization), and follow-up at 1 year did not show increased survival compared with patients who underwent conventional PCI. However, the TASTE trial was powered to demonstrate only a large survival benefit. This shortcoming was addressed in the Trial of Routine Aspiration Thrombectomy With Percutaneous Coronary Intervention (PCI) Versus PCI Alone in Patients With ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary PCI (TOTAL) trial. The use of TA in the TOTAL trial showed reduced angiographic distal embolization and improved ST-segment resolution,[3,6] but there was no improvement in outcomes of TIMI flow, myocardial blush grade, or the incidence of no reflow, and the trial showed a neutral result on its primary efficacy outcome (180-day cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association class IV), and outcomes at 1 year were largely similar.[22] The trial findings, however, raised safety concerns because an increased risk of 30-day stroke was noted with TA with the excess risk already apparent within the first 48 hours after the procedure.[24] Interestingly, in our analysis, TA was not associated with the occurrence of stroke at 30 days, supporting that possibility that the excess risk of stroke could not be fully attributed to TA; indeed, reasonable explanations for increased risk, other than the role of chance associated with the relatively small sample size, are lacking.

Finally, TA was associated to increased risk for major TIMI bleeding, whereas pre-H ticagrelor was not. Again, the possible concomitant use of TA and GPI may explain the higher incidence of bleeding events in TA groups. However, there was no interaction between TA and pre-H ticagrelor for bleeding events, suggesting the potential safety of pre-H ticagrelor administration and subsequent use of TA.

Table III. Pre-H ticagrelor and study clinical outcomes, adjusted multivariate logistic model

Predictors pre-H vs in-hospital ticagrelor	Adjusted multivariate logistic model§ n = 1622	
End points	OR (95% CI)	*P* value
30-d composite of death/new MI/urgent revascularization and definite ST	1.11 (0.67-1.83)	.6823
30-d new MI or definite acute ST	0.43 (0.20-0.92)	.0307
30-d new MI	0.70 (0.31-1.58)	.3885
30-d definite ST	0.26 (0.07-0.91)	.0357
30-d urgent revascularization	0.82 (0.31-2.16)	.6899
30-d stroke (ischemic)	3.96 (0.95-16.46)	.0582
Bailout use of GPI	0.79 (0.56-1.13)	.1952
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	0.89 (0.68-1.16)	.3812
Absence of ST-segment elevation resolution ≥70% post-PCI	0.82 (0.66-1.02)	.0693
TIMI major bleeding	1.04 (0.41-2.68)	.9309
TIMI minor bleeding	0.95 (0.54-1.69)	.8712

§ The multivariate adjusted analysis is the multivariate analysis with variables forced in the model: age (<75, ≥75), sex, body mass index (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischemic attack, nonhemorrhagic stroke, stent, DE stent, BM stent, hypertension, arterial access, and GPI before PCI.

Table IV. TA and study clinical outcomes, adjusted multivariate logistic model

Predictors TA vs NO TA	Adjusted multivariate logistic model§ n = 1622	
End points	OR (95% CI)	*P* value
30-d composite of death/new MI/urgent revascularization and definite ST	0.84 (0.49-1.44)	.5334
30-d new MI or definite acute ST	0.92 (0.41-2.07)	.8488
30-d new MI	0.77 (0.33-1.81)	.5499
30-d definite ST	1.56 (0.46-5.32)	.4790
30-d urgent revascularization	0.83 (0.31-2.24)	.7110
30-d stroke (ischemic)	0.96 (0.23-4.08)	.9539
Bailout use of GPI	1.72 (1.18-2.50)	.0045
Absence of TIMI flow grade 3 of MI culprit vessel post-PCI	1.09 (0.82-1.46)	.5390
Absence of ST-segment elevation resolution ≥70% POST PCI	0.87 (0.69-1.09)	.2157
TIMI major bleeding	2.92 (1.10-7.76)	.0321
TIMI minor bleeding	1.46 (0.79-2.69)	.2264

§ The multivariate adjusted analysis is the multivariate analysis with variables forced in the model: age (<75, ≥75), sex, BMI (<30 kg/m^2, ≥30 kg/m^2), prior MI, prior PCI, transient ischemic attack, nonhemorrhagic stroke, stent, DE stent, BM stent, hypertension, arterial access, GPI before PCI, and TIMI flow 0-1.

Limitations

Several limitations of the present analysis should be considered. This analysis was a post hoc analysis and therefore should be viewed as hypothesis generating. We cannot fully exclude the possibility of confounding as a result of baseline factors that we did not study. The possibility of unaccounted confounding related to the nonrandomized use of TA cannot be excluded; therefore, the potential benefit of TA together with pre-H treatment requires to be evaluated in future studies.

Conclusion

TA when left to physician's discretion was used in high-risk patients, was associated with bailout use of GPI and TIMI major bleeding, and was not associated with improvement in 30-day clinical outcome. Conversely, pre-H ticagrelor treatment predicted lower 30-day rates of ST or new MI as well as definite ST without significant interaction with TA.

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