

CLINICAL RESEARCH

CORONARY

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-H²⁴ Analysis



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ABSTRACT

OBJECTIVES The aim of this landmark exploratory analysis, ATLANTIC-H²⁴, was to evaluate the effects of pre-hospital ticagrelor during the first 24 h after primary percutaneous coronary intervention (PCI) in the ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial infarction to open the Coronary artery) study.

BACKGROUND The ATLANTIC trial in patients with ongoing ST-segment elevation myocardial infarction showed that pre-hospital ticagrelor was safe but did not improve pre-PCI coronary reperfusion compared with in-hospital ticagrelor. We hypothesized that the effect of pre-hospital ticagrelor may not have manifested until after PCI due to the rapid transfer time (31 min).

METHODS The ATLANTIC-H²⁴ analysis included 1,629 patients who underwent PCI, evaluating platelet reactivity, Thrombolysis In Myocardial Infarction flow grade 3, ≥70% ST-segment elevation resolution, and clinical endpoints over the first 24 h.

RESULTS Following PCI, largest between-group differences in platelet reactivity occurred at 1 to 6 h; coronary reperfusion rates numerically favored pre-hospital ticagrelor, and the degree of ST-segment elevation resolution was significantly greater in the pre-hospital group (median, 75.0% vs. 71.4%; $p = 0.049$). At 24 h, the composite ischemic endpoint was lower with pre-hospital ticagrelor (10.4% vs. 13.7%; $p = 0.039$), as were individual endpoints of definite stent thrombosis ($p = 0.0078$) and myocardial infarction ($p = 0.031$). All endpoints except death (1.1% vs. 0.2%; $p = 0.048$) favored pre-hospital ticagrelor, with no differences in bleeding events.

CONCLUSIONS The effects of pre-hospital ticagrelor became apparent after PCI, with numerical differences in platelet reactivity and immediate post-PCI reperfusion, associated with reductions in ischemic endpoints, over the first 24 h, whereas there was a small excess of mortality. (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial infarction to open the Coronary artery [ATLANTIC, [NCT01347580](https://clinicaltrials.gov/ct2/show/study/NCT01347580)]) (J Am Coll Cardiol Intv 2016;9:646-56) © 2016 by the American College of Cardiology Foundation.

In the randomized, double-blind, placebo-controlled ATLANTIC (Administration of Ticagrelor in the cath Lab or in the Ambulance for New ST elevation myocardial infarction to open the Coronary artery) study, in-ambulance administration of the P2Y₁₂ antagonist ticagrelor shortly before percutaneous coronary intervention (PCI) did not improve pre-PCI reperfusion of the culprit artery compared with in-catheterization laboratory administration, as measured by the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 on the

angiogram and $\geq 70\%$ ST-segment elevation resolution on the electrocardiogram (1). The

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median times from randomization to angiography and between the 2 ticagrelor loading doses (i.e., pre-hospital vs. in-hospital) were only 48 and 31 min, respectively. These short intervals may explain the absence of a detectable benefit of in-ambulance ticagrelor on coronary reperfusion evaluated before

ABBREVIATIONS AND ACRONYMS

MI = myocardial infarction
PCI = percutaneous coronary intervention
PRU = platelet reactivity unit
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

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the PCI procedure (2). Pre-hospital administration of ticagrelor was, however, associated with a reduction in the risk of stent thrombosis at 30-day follow-up. We hypothesized that the effect of earlier administration of ticagrelor did not become manifest until after the procedure because of the short delay in transfer to the catheterization laboratory. We therefore examined more closely all the data available during the first 24 h after the primary PCI, including platelet function analysis, coronary reperfusion, ischemic endpoints, and safety outcomes, in an exploratory analysis (the ATLANTIC-H²⁴ analysis).

METHODS

STUDY DESIGN AND PROCEDURES. ATLANTIC was an international study that randomized patients presenting with ongoing ST-segment elevation myocardial infarction (STEMI) to receive double-blind treatment with a 180-mg loading dose of ticagrelor, either pre-hospital (in-ambulance) or in-hospital (in the catheterization laboratory), in addition to aspirin and standard of care (3). The coordinating center was the ACTION Study Group at Pitié-Salpêtrière Hospital in Paris. The full list of ATLANTIC investigators is shown in the [Online Appendix](#).

The trial design and main results have been reported (1). Briefly, eligible patients were identified by ambulance personnel for inclusion in the study after diagnosis of STEMI of >30-min but <6 h-duration and with expected time from the qualifying electrocardiogram to first balloon inflation of <120 min. Randomization and first loading dose of ticagrelor or matching placebo took place immediately after the diagnosis of STEMI was confirmed by electrocardiography. Patients were then transferred to undergo coronary angiography and PCI, and the second loading dose was administered in the catheterization laboratory. All patients then received maintenance treatment with ticagrelor 90 mg twice daily for at least 30 days to a maximum of 12 months.

In-ambulance use of glycoprotein IIb/IIIa inhibitors was discouraged, but left to physicians' discretion. Post-angiography, in-laboratory use of glycoprotein IIb/IIIa inhibitors had to be identified as either the strategy of choice or bail-out treatment during PCI. The reasons for bail-out use of glycoprotein IIb/IIIa inhibitors in the catheterization laboratory were recorded by the investigators.

A pharmacodynamic substudy was conducted at 5 participating centers to assess platelet inhibition during the first 24 h of the study after pre-hospital or in-hospital initiation of ticagrelor therapy. VerifyNow P2Y₁₂ platelet reactivity units (PRUs) were measured

immediately after PCI and at 1, 6, and 12 h post-PCI before the first maintenance dose of ticagrelor.

The ATLANTIC study was performed in accordance with the ethical principles that have been laid down in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization/Good Clinical Practice guidelines and applicable regulatory requirements.

STUDY ENDPOINTS. Although the primary aim of the main ATLANTIC study was to evaluate coronary reperfusion on admission to the catheterization laboratory with pre- versus in-hospital ticagrelor, with 30-day follow-up for clinical outcomes, the landmark ATLANTIC-H²⁴ analysis focused on endpoints during the first 24 h after PCI in patients who underwent PCI. All the endpoints of this ATLANTIC-H²⁴ analysis evaluated the combined effect of the ticagrelor strategy tested and the revascularization procedure. Thus, the landmark analysis began at the start of the PCI procedure and continued up to 24 h later. Coronary reperfusion endpoints were the following: 1) ST-segment elevation resolution measured as the percentage of patients achieving $\geq 70\%$ ST-segment elevation resolution 1 h after PCI and the average degree of ST-segment elevation resolution 1 h after PCI (median %); and 2) TIMI flow measured as the percentage of patients reaching TIMI flow grade 3 in the infarct-related artery at the end of PCI. ST-segment elevation resolution was calculated as the combination of 2 electrocardiographic variables (ST-segment elevation at the index electrocardiogram and 1 h after PCI). Clinical endpoints evaluated over the first 24 h after PCI included the composite endpoint evaluating death and myocardial ischemic events of myocardial infarction (MI), definite stent thrombosis, urgent revascularization, or per-procedure bail-out use of a glycoprotein IIb/IIIa inhibitor (defined as any use of glycoprotein IIb/IIIa inhibitor after the start of PCI and not including any that were given after coronary angiography but before PCI), and each individual parameter of this composite endpoint. Definitions of new MI are summarized in [Online Table 1](#). Safety endpoints included major, life-threatening or minor bleeding (excluding coronary artery bypass graft-related bleeding) within the first 24 h using the PLATO (Study of Platelet Inhibition and Patient Outcomes), TIMI, STEEPLE (Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients), GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries), and Bleeding Academic Research Consortium (BARC) bleeding definitions.

For comparative purposes, all endpoints were also evaluated in the global population of all patients who

TABLE 1 Baseline Demographics, Clinical Characteristics, and Treatment of Patients Included in the ATLANTIC-H²⁴ Analysis

	PCI Population			Angiography-Only Population		
	Pre-Hospital Ticagrelor (n = 799)	In-Hospital Ticagrelor (n = 830)	p Value	Pre-Hospital Ticagrelor (n = 90)	In-Hospital Ticagrelor (n = 107)	p Value
Age, yrs	60.9 ± 12.1	60.9 ± 12.0	0.901	57.5 ± 13.8	61.9 ± 15.5	0.040
Female	150 (18.8)	159 (19.20)	0.844	20 (22.2)	34 (31.8)	0.134
BMI, kg/m ²	27.1 ± 4.7	26.9 ± 4.4	0.509	26.9 ± 4.4	25.6 ± 4.3	0.045
Diabetes mellitus	98 (12.3)	116 (14.0)	0.307	15 (16.7)	19 (17.8)	0.840
TIMI risk score						
0-2	489 (61.2)	511 (61.6)	0.883	52 (57.8)	53 (49.5)	0.232
3-6	296 (37.0)	307 (37.0)		33 (36.7)	51 (47.7)	
>6	14 (1.8)	12 (1.4)		5 (5.6)	3 (2.8)	
Killip class I	722 (90.4)	767 (92.4)	0.141	83 (92.2)	89 (83.2)	0.058
First medical contact						
Ambulance	612 (76.6)	637 (76.7)	0.874	61 (67.8)	73 (68.2)	0.651
Emergency/casualty department	129 (16.1)	135 (16.3)		20 (22.2)	23 (21.5)	
Specialty ward/floor	4 (0.5)	4 (0.5)		0	0	
Acute care/general hospital	42 (5.3)	37 (4.5)		5 (5.0)	9 (8.4)	
General medicine/medical floor	12 (1.5)	17 (2.0)				
MI location						
Anterior	361 (45.2)	417 (50.2)	0.041	65 (72.2)	69 (64.5)	0.246
Inferior/unknown	438 (54.8)	413 (49.8)		25 (27.8)	38 (35.5)	
Time from onset of index event to PCI, min	157 (59-6,345)	161 (50-4,231)	0.111			
Procedure for index event						
Sheath insertion site						
Femoral	247 (30.9)	271 (32.7)	0.452	32 (35.6)	38 (35.5)	0.995
Radial	547 (68.5)	556 (67.0)		57 (63.3)	69 (64.5)	
Unknown	5 (0.6)	3 (0.4)		1 (1.1)	0	
Thromboaspiration	470 (58.8)	470 (56.6)	0.370*	N/A	N/A	
PCI with stent	759 (95.0)	776 (93.5)	0.194*	N/A	N/A	
Any drug-eluting stent	466 (58.3)	479 (57.7)	0.802*	N/A	N/A	
Any bare-metal stent	305 (38.2)	312 (37.6)	0.809*	N/A	N/A	
CV drug use in PCI patients						
Aspirin LD	721 (90.2)	737 (88.8)	0.342	N/A	N/A	
Started aspirin maintenance	777 (97.2)	811 (97.7)	0.550	N/A	N/A	
Glycoprotein IIb/IIIa inhibitor before start of PCI	269 (33.7)	255 (30.7)	0.204	N/A	N/A	
Abciximab	148 (18.5)	128 (15.4)	0.095	N/A	N/A	
Eptifibatide	72 (9.0)	61 (7.3)	0.221	N/A	N/A	
Tirofiban	49 (6.1)	66 (8.0)	0.152	N/A	N/A	
IV anticoagulant during hospitalization						
Heparin	541 (67.7)	579 (69.8)	0.372	N/A	N/A	
Enoxaparin	224 (28.0)	223 (26.9)	0.598	N/A	N/A	
Bivalirudin	172 (21.5)	184 (22.2)	0.754	N/A	N/A	
Fondaparinux	45 (5.6)	59 (7.1)	0.223	N/A	N/A	
Statin use post-qualifying ECG/pre-PCI	78 (9.8)	105 (12.7)	0.065	N/A	N/A	

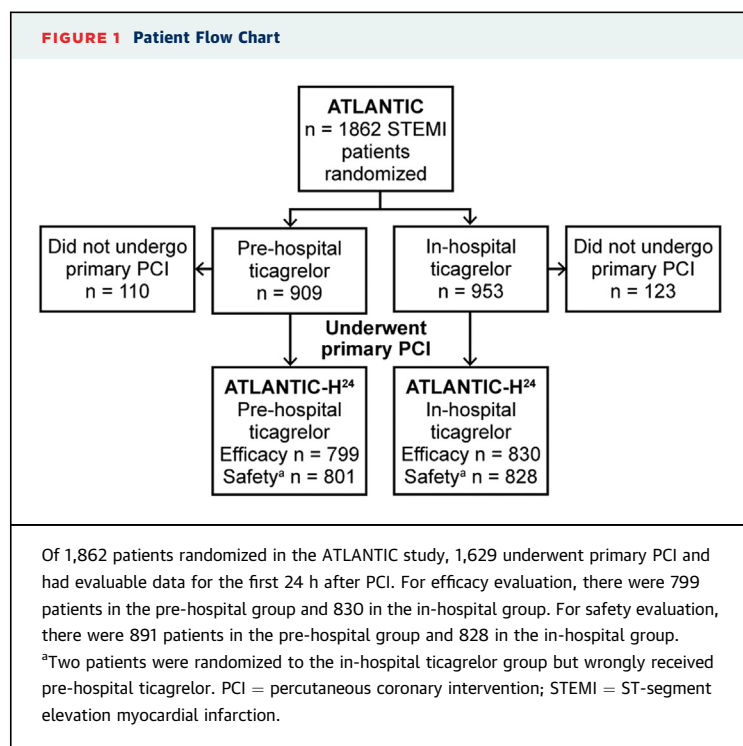
Values are mean ± SD, n (%), or median (range). *p Value for the characteristic, yes versus no.
BMI = body mass index; CV = cardiovascular; ECG = electrocardiogram; IV = intravenous; LD = loading dose; MI = myocardial infarction; N/A = not applicable; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

underwent coronary angiography followed by PCI and those who underwent coronary angiography but not PCI.

Blinded review of angiographic data and electrocardiographic recordings was performed centrally by Cardialysis core laboratory services (Rotterdam, the Netherlands) and ERT (eResearch Technology Inc.,

Peterborough, United Kingdom), respectively. An independent adjudication committee conducted a blind review of all clinical endpoints (except deaths and minimal bleeding events) (1).

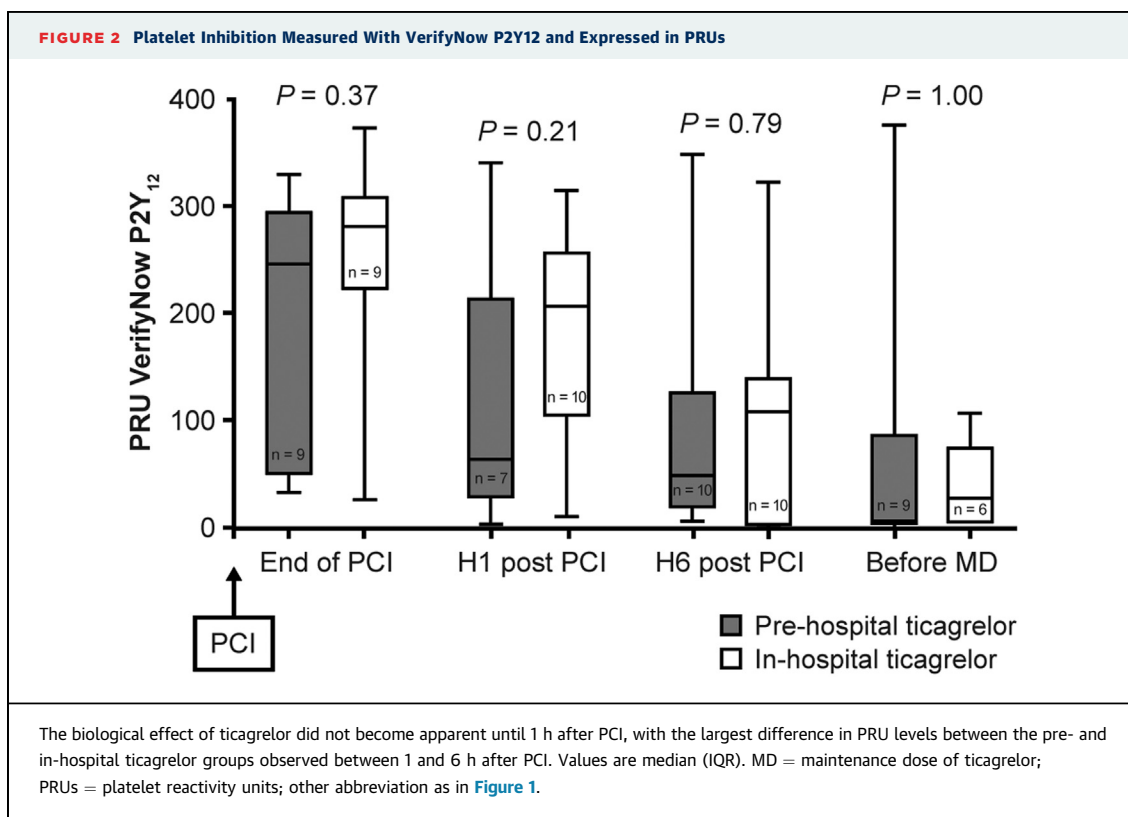
STATISTICAL ANALYSIS. The present ATLANTIC-H²⁴ analysis of data acquired during the first 24 h after



PCI is a posthoc analysis that was not pre-specified in the study protocol. It was conducted as an exploratory analysis, and the findings cannot be considered as definitive.

Efficacy analyses were performed on the modified intent-to-treat population, defined as all randomized patients who received at least 1 dose of the study drug. Patients missing either ST-segment elevation measurements or TIMI flow grade were excluded from analysis of these endpoints. Kaplan-Meier estimates of clinical endpoints were produced for the period of 0 to 24 h after PCI and compared using the hazard ratio obtained from a Cox proportional hazards model. Because no pre-specified hypothesis was made, statistical testing of all secondary variables, including the clinical endpoints, was considered exploratory by nature, and there was no statistical correction for multiple comparisons. Odds ratios 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. Where comparisons included no events in 1 group, p values were calculated using Fisher's exact test.

The safety analysis included all patients who received at least 1 dose of the study drug. Adjudicated bleeding events were summarized separately according to the protocol definition (PLATO) and



other pre-specified definitions (1). The p values for between-group differences for the PLATO bleeding categories were calculated using the chi-square test.

RESULTS

STUDY POPULATION. A total of 1,862 consenting patients were randomized to receive either pre- or in-hospital ticagrelor. Of these, 1,629 patients underwent primary PCI, received study treatment, and had evaluable data for the first 24 h after PCI, 799 in the pre-hospital group and 830 in the in-hospital group, and were included in the present analysis (Table 1, Figure 1). A total of 197 patients underwent coronary angiography but no PCI (Table 1), giving a total of 1,826 patients for the global PCI/angiography population.

PLATELET FUNCTION SUBSTUDY. The platelet function substudy was performed in a small subset of the population (n = 37) recruited at 5 centers. PRU levels showing the biological effect of ticagrelor did not become apparent until 1 h after PCI (Figure 2). The largest (but nonsignificant) difference in mean PRU level between the 2 strategies (pre-hospital vs. in-hospital) was observed 1 to 6 h after PCI.

PER-PROCEDURE THROMBOTIC GLYCOPROTEIN IIB/IIIA INHIBITOR BAIL-OUT USE. Bail-out use of glycoprotein IIB/IIIA inhibitors was numerically lower with pre-hospital versus in-hospital administration of ticagrelor (9.4% vs. 12.0%, respectively; odds ratio: 0.76; 95% confidence interval: 0.55 to 1.04), an absolute (nonsignificant) difference of 2.6%. The difference was mostly driven by a decrement of coronary flow, ischemia, or physician choice during the procedure, all of which occurred more frequently in the in-hospital ticagrelor group (Table 2). In contrast, distal embolization was identified as the reason for bail-out glycoprotein IIB/IIIA inhibitor use more frequently in the pre-hospital ticagrelor group.

POST-PROCEDURE CORONARY REPERFUSION. There were no significant differences between the pre- and in-hospital ticagrelor groups in terms of either post-PCI TIMI flow grade 3 or $\geq 70\%$ ST-segment elevation resolution at 1 h (Table 3). However, both endpoints showed numerical differences in favor of the pre-hospital group. ST-segment elevation resolution $\geq 70\%$ measured 1 h after PCI occurred in 57.5% of patients in the pre-hospital group and in 52.5% of patients in the in-hospital group (p = 0.055). The degree of ST-segment elevation resolution after PCI was significantly different between the 2 groups (median of 75.0% in the pre-hospital group vs. 71.4% in the in-hospital group, p = 0.049).

TABLE 2 Thrombotic Bail-Out Use of Glycoprotein IIB/IIIA Inhibitors During the PCI Procedure

Endpoint	Pre-Hospital Ticagrelor (n = 799)	In-Hospital Ticagrelor (n = 830)	Odds Ratio (95% CI)	p Value
Patients with thrombotic bail-out with glycoprotein IIB/IIIA inhibitors	75 (9.4)	100 (12.0)	0.756 (0.551-1.038)	0.084
Reason				
Decrement in TIMI flow grade or abrupt closure	8 (1.0)	20 (2.4)		
No reflow	8 (1.0)	8 (1.0)		
Side-branch closure	2 (0.3)	1 (0.1)		
Dissection with decreased flow	2 (0.3)	3 (0.4)		
Distal embolization	15 (1.9)	9 (1.1)		
Clinical instability due to ischemia/prolonged ischemia during the procedure	7 (0.9)	11 (1.3)		
Other (physician's decision)	33 (4.1)	48 (5.8)		

Values are n (%) unless otherwise indicated.
CI = confidence interval; other abbreviations as in Table 1.

Similar results were observed in the global population for pre- versus in-hospital ticagrelor for post-PCI/angiography TIMI flow grade 3 (82.1% vs. 80.4%; p = 0.389), ST-segment elevation resolution $\geq 70\%$ (54.5% vs. 50.1%; p = 0.080), and degree of ST-segment elevation resolution (median, 73.3% vs. 70.0%; p = 0.045).

CLINICAL OUTCOMES UP TO 24 h. At 24 h, the composite myocardial ischemic endpoint of death, MI, urgent revascularization, definite stent thrombosis, or bail-out glycoprotein IIB/IIIA inhibitor use was significantly lower proportionally by 27% with pre- versus in-hospital administration of ticagrelor (10.4% vs. 13.7%; p = 0.039) (Table 4, Figure 3). On exclusion of bail-out glycoprotein IIB/IIIA inhibitor use from the

TABLE 3 Coronary Reperfusion After PCI: TIMI Flow Grade 3 Immediately After PCI, and ST-Segment Elevation Resolution $\geq 70\%$ 1 h Post-PCI

Endpoint	Pre-Hospital Ticagrelor	In-Hospital Ticagrelor	Odds Ratio (95% CI)	p Value
No. of subjects*	760	784		
TIMI flow grade 3 of MI culprit vessel post-PCI	625 (82.2)	630 (80.4)	1.132 (0.876-1.462)	0.344
No. of subjects*	713	743		
ST-segment elevation resolution $\geq 70\%$ post-PCI	410 (57.5)	390 (52.5)	1.225 (0.996-1.506)	0.055
No. of subjects*	713	743		0.049†
Degree of ST-segment elevation resolution 1 h post-PCI, %	66.7 $\pm$ 36.8, 75.0	63.9 $\pm$ 34.3, 71.4		

Values are n (%) or mean $\pm$ SD, median. *Subjects with a PCI performed for the index event and available data on TIMI flow grade or ST-segment elevation. †p Value from nonparametric Wilcoxon test.
Abbreviations as in Tables 1 and 2.

TABLE 4 Clinical Endpoints Within 24 h of the Index PCI

Endpoint	Pre-Hospital Ticagrelor (n = 799)	In-Hospital Ticagrelor (n = 830)	Odds Ratio (95% CI)	p Value
Composite of death/new MI/urgent revascularization/definite stent thrombosis/bail-out glycoprotein IIb/IIIa inhibitor use	83 (10.4)	114 (13.7)	0.728 (0.539–0.984)	0.039
Composite of death/new MI/urgent revascularization/definite stent thrombosis	10 (1.3)	17 (2.0)	0.606 (0.276–1.332)	0.213
New MI or definite acute stent thrombosis	0 (0.0)	13 (1.6)	0.027 (0.017–0.184)*	<0.001*
New MI	0 (0.0)	6 (0.7)	0.058 (0.032–0.541)†	0.031*
Definite stent thrombosis	0 (0.0)	8 (1.0)	0.044 (0.025–0.357)†	0.008*
Bail-out glycoprotein IIb/IIIa inhibitor use	75 (9.4)	100 (12.0)	0.756 (0.551–1.038)	0.084
Urgent revascularization	1 (0.1)	5 (0.6)	0.207 (0.024–1.774)	0.151
Stroke (ischemic)	1 (0.1)	0 (0)	3.558 (0.303–9.545)†	0.491*
All-cause mortality	9 (1.1)	2 (0.2)	4.716 (1.016–21.896)	0.048

Values are n (%) unless otherwise indicated. *p Value from the Fisher exact test. †Estimated odds ratio calculated using the modified Median Unbiased Estimators for event probability, with a bootstrap CI calculated using a conservative method.

composite endpoint, the difference remained in favor of pre-hospital ticagrelor but was no longer significant (1.3% vs. 2.0%; $p = 0.212$) (Figure 4). However, the 2 individual endpoints of definite stent thrombosis and

new MI were significantly lower in the pre-hospital group. Interestingly, all except 1 MI occurred in patients who did not present with stent thrombosis: these were additional events unrelated to the stented lesions. The double endpoint of new MI or stent thrombosis was also significantly lower with pre-hospital ticagrelor administration, and all events occurred in the in-hospital group over this 24-h period, most within the first 4 h (Figure 5, Online Figure 1). As shown in Online Table 2, the culprit vessel for the index event was the left anterior descending or right coronary artery in all 6 patients with recurrent MI and in 7 of 8 patients with stent thrombosis, and most were treated with anticoagulants but few were treated with glycoprotein IIb/IIIa inhibitors. The other ischemic endpoints (urgent revascularization, bail-out glycoprotein IIb/IIIa inhibitor use) also trended in favor of the pre-hospital group. However, all-cause deaths during the 24 h after PCI, although infrequent, occurred more often in the pre-hospital than the in-hospital ticagrelor group (9 vs. 2 patients, respectively; $p = 0.048$) (Online Figure 2).

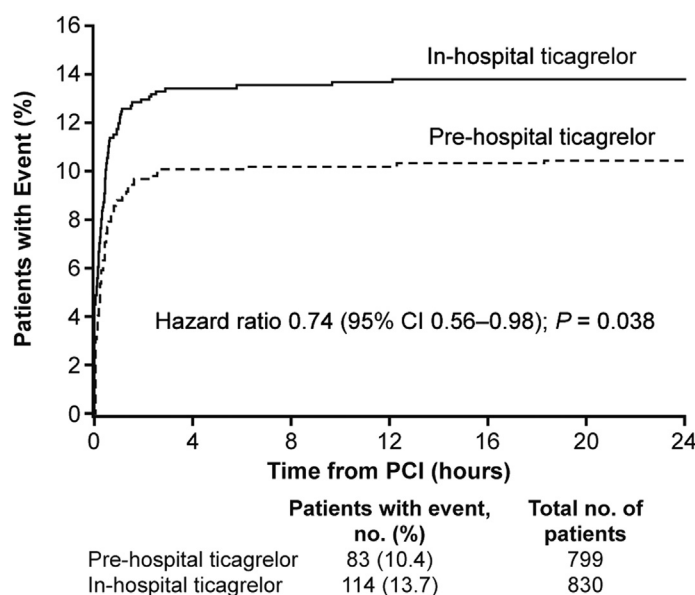
Clinical endpoints at 24 h for pre- versus in-hospital ticagrelor in the global population (PCI and angiography) were comparable to those in the PCI population for the composite of death, MI, and urgent revascularization (1.1% vs. 1.3%; $p = 0.761$), and MI alone (0% vs. 0.6%; $p = 0.031$), but the difference in all-cause mortality was no longer statistically significant (9 [1.0%] vs. 3 [0.3%] patients; $p = 0.083$).

As shown in Online Table 3, there were no significant differences in terms of clinical endpoints for those who did or did not receive pre-PCI glycoprotein IIb/IIIa inhibitors.

The causes of death during this period are shown in Online Table 4 and included cardiogenic shock ($n = 4$), cardiac arrest ($n = 3$), mechanical complications ($n = 3$), and heart failure ($n = 1$). Five additional deaths occurred immediately after randomization and before the procedure (3 in the pre-hospital group due to cardiac arrest, ventricular fibrillation, and heart failure and 2 in the in-hospital group due to cardiac arrest and hemothorax) and were not counted in the present landmark analysis starting at the time of PCI.

Among the characteristics of the 11 patients who died during the 24 h after PCI, the mean age was much older than that of the 1,618 patients who survived the first 24 h ($p < 0.0001$), and higher proportions of female and diabetic patients died than survived ($p = 0.025$ and $p = 0.022$, respectively) (Online Table 5). A numerically greater percentage of patients who died had an anterior MI compared with those who survived. Significantly more patients who

FIGURE 3 Composite of Death/MI/Urgent Revascularization/Definite Stent Thrombosis/Bail-Out Glycoprotein IIb/IIIa Inhibitor Use Within 24 h of Index PCI



At 24 h, the composite endpoint was significantly lower with pre- versus in-hospital ticagrelor (10.4% vs. 13.7%; $p = 0.04$). The hazard ratio from the Cox model is shown. CI = confidence interval; PCI = percutaneous coronary intervention.

died had a TIMI risk score >6 compared with survivors ($p < 0.0001$), with an average TIMI score of 5.2 versus 2.0, respectively ($p < 0.0001$), and Killip class >1 was reported in 27.3% versus 4.6% ($p = 0.001$). Patients who died were more likely to have had femoral sheath insertion than those who did not ($p = 0.023$) and were less likely to have received a drug-eluting stent ($p = 0.038$).

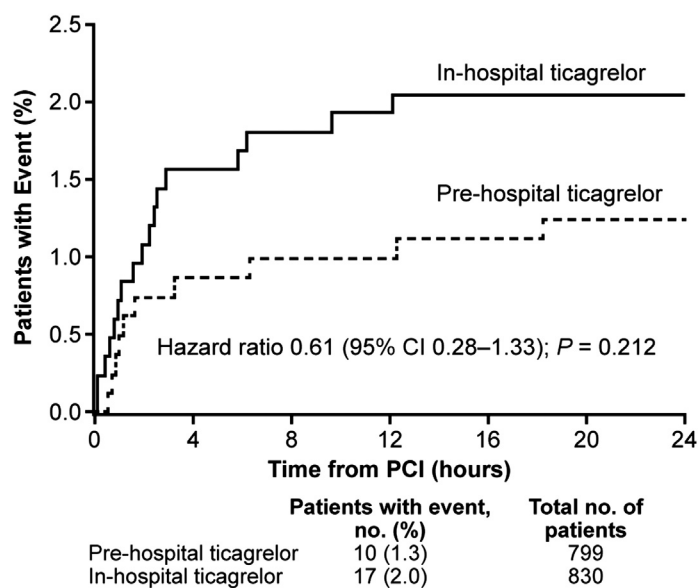
SAFETY. Non-coronary artery bypass graft-related bleeding event rates within 24 h of PCI are shown in Table 5. There were no statistically significant differences between the 2 treatment groups in terms of major or minor bleeding complications. The results were consistent across all definitions and types of bleeding adjudicated by the Clinical Endpoint Committee.

DISCUSSION

The main results of the ATLANTIC study showed no difference between the pre- and in-hospital ticagrelor treatment groups in terms of pre-PCI coronary reperfusion, as measured with ST-segment elevation resolution and TIMI flow grade 3 at the time of admission to the catheterization laboratory (1). However, an early reduction in stent thrombosis was observed in the pre-hospital group. We hypothesized that this finding may not be the play of chance but more likely the result of an effect of the pre-hospital administration of ticagrelor, potentially leading to earlier post-PCI maintenance of infarct-related artery and microvascular patency. Indeed, considering the onset of action of ticagrelor, the unexpectedly brief time difference of 31 min between the 2 strategies appeared too short to provide a benefit in terms of pre-PCI reperfusion (4). The present analysis explored the first 24 h after the start of primary PCI to see whether there was any impact of the pre-hospital strategy on coronary patency endpoints after PCI. Later events occurring up to 30 days of follow-up may be less related to the initial treatment strategy, thereby lessening any initial positive effect.

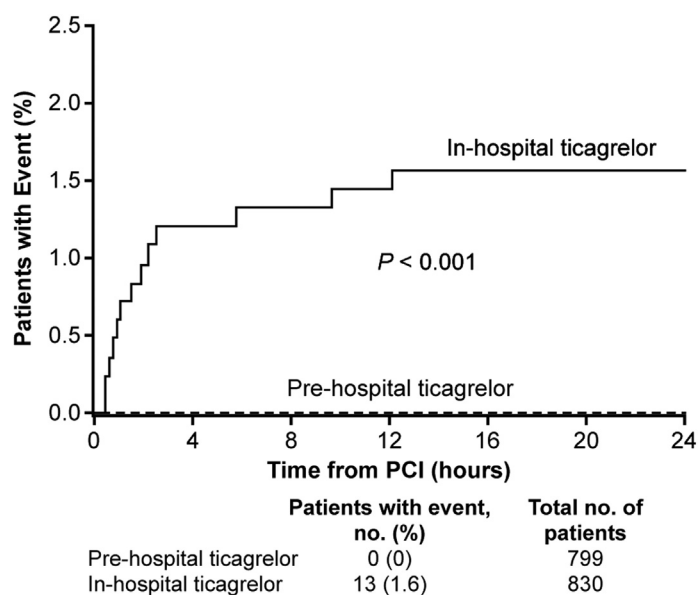
The present analysis shows that the largest difference in platelet aggregation between the 2 strategies occurred immediately after PCI (with no measurements being made during PCI), and the largest difference in ST-segment elevation resolution was observed 1 h after PCI. These findings are consistent with previously reported vasodilator-stimulated phosphoprotein phosphorylation assay-platelet reactivity index levels with pre-hospital ticagrelor (average 2.3 h to $<50\%$ platelet reactivity) (5) and those reported in the ATLANTIC study, which included pre-PCI levels (1).

FIGURE 4 Composite of Death/MI/Urgent Revascularization/Definite Stent Thrombosis Within 24 h of Index PCI



At 24 h, the composite endpoint excluding bail-out glycoprotein IIb/IIIa inhibitor use with pre- and in-hospital ticagrelor was 1.3% versus 2.0% ($p = 0.21$). The hazard ratio from the Cox model is shown. Abbreviations as in Figure 3.

FIGURE 5 Myocardial Infarction or Definite Stent Thrombosis Within 24 h of Index PCI



At 24 h, the double endpoint of new MI or definite stent thrombosis was significantly lower with pre- versus in-hospital ticagrelor (0% vs. 1.6%; $p < 0.001$). PCI = percutaneous coronary intervention.

TABLE 5 Non-CABG-Related Bleeding Events Up to 24 h After the Index PCI

Definition and Bleeding Category	With Bleeding Event*		p Value
	Pre-Hospital Ticagrelor (n = 801)	In-Hospital Ticagrelor (n = 828)	
PLATO			
Major	13 (1.6)	8 (1.0)	0.240
Minor	7 (0.9)	9 (1.1)	0.663
Composite of major and minor	20 (2.5)	17 (2.1)	0.548
STEEPLE			
Major	14 (1.7)	7 (0.8)	0.107
Minor	5 (0.6)	10 (1.2)	0.218
Unknown	2 (0.2)	1 (0.1)	0.544
TIMI			
Major	7 (0.9)	3 (0.4)	0.186
Minor	13 (1.6)	11 (1.3)	0.622
Minimal	1 (0.1)	4 (0.5)	0.191
GUSTO			
Severe or life-threatening	7 (0.9)	3 (0.4)	0.186
Moderate	2 (0.2)	2 (0.2)	0.974
Mild	12 (1.5)	13 (1.6)	0.906
BARC type			
0	0	0	
1	1 (0.1)	1 (0.1)	0.981
2	8 (1.0)	11 (1.3)	0.535
3	11 (1.4)	6 (0.7)	0.198
3a	4 (0.5)	3 (0.4)	0.672
3b	6 (0.7)	3 (0.4)	0.292
3c	1 (0.1)	0	
4	0	0	
5	1 (0.1)	0	
5a	0	0	
5b	0	0	
Unknown	0	0	

Values are n (%). *Subjects with a PCI performed for the index event. Patients may be included in more than 1 bleeding event category.

CABG = coronary artery bypass graft; BARC = Bleeding Academic Research Consortium; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; PLATO = Study of Platelet Inhibition and Patient Outcomes; STEEPLE = Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients; other abbreviations as in Table 1.

During the procedure, bail-out use of glycoprotein IIb/IIIa inhibitors by the investigators, who were blinded to the ticagrelor strategy, was an endpoint reflecting thrombotic complications or concerns. A smaller number of patients required the use of glycoprotein IIb/IIIa inhibitors during the procedure in the pre-hospital group. The composite myocardial ischemic endpoint of death, MI, urgent revascularization, definite stent thrombosis, and bail-out glycoprotein IIb/IIIa inhibitor use was significantly lower at 24 h in the pre-hospital group. This classic composite endpoint reflects coronary complications of PCI leading to stent thrombosis, rescue use of glycoprotein IIb/IIIa inhibitors, or urgent revascularization after the index PCI. Stent thrombosis and

MI were also significantly lower with pre-hospital ticagrelor. Interestingly, all but 1 of the MI events were unrelated to a simultaneous stent thrombosis, suggesting that the pre-hospital group was better protected against coronary occlusion that might also occur in a nonculprit artery when patients have multivessel disease (6). When stent thrombosis events were combined with recurrent MI events, all occurred in the late ticagrelor administration group during the 24 h after PCI (Figure 4), suggesting potential protection during the post-procedural period with earlier administration of the drug. The present results are in line with those of the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction 28) study, which showed a clear benefit of clopidogrel compared with placebo on overall coronary artery patency and clinical outcome in STEMI patients initially treated with fibrinolytics, suggesting that at least some of the benefit of P2Y₁₂ antagonism may be derived (or observed) after reperfusion (7,8). There are also similarities with the results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) study, in which there was a higher risk of early stent thrombosis in patients treated with bivalirudin compared with those treated with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (9). All patients also received a clopidogrel or ticlopidine loading dose before catheterization, and the authors considered the higher rate of early stent thrombosis in the bivalirudin group to be likely related to adenosine diphosphate-induced platelet activation before maximal blockade of the P2Y₁₂ receptor or to residual thrombin activity after discontinuation of bivalirudin (at completion of angiography or PCI). Finally, the benefit observed with early ticagrelor in our study is in line with that observed with the rapidly acting cangrelor in patients undergoing PCI (10,11).

Safety over the first 24 h was comparable in the 2 study groups for both major and minor bleeding complications, despite the higher use of bail-out glycoprotein IIb/IIIa inhibitors in the in-hospital ticagrelor group. These findings were consistent across the various definitions used.

The numerical trend observed in the overall ATLANTIC study for higher mortality with pre-hospital ticagrelor administration was already evident during the first 24 h after PCI. This finding contrasts with the lower rates of nonfatal ischemic events and comparable rates of bleeding complications with the pre- versus the in-hospital strategy. Analysis of the specific causes of death suggests also that these deaths were not related to either ischemic or bleeding events but to the

severity of the initial MI more frequently leading to mechanical complications and shock. The patients who died were generally much older than those who survived, were more often women, patients with diabetes, or patients presenting with heart failure, a higher TIMI risk score, and mechanical complications or shock that developed rapidly after PCI. There was also less use of drug-eluting stents and radial access in the group of patients who died. The timing of these deaths also suggests they were unrelated to pre- or in-hospital ticagrelor administration because several deaths occurred very early, before ticagrelor was biologically effective. The hypothesis of an immediate mortality effect of ticagrelor, observed only in the pre-hospital group and with a difference of only 31 min between the 2 treatment groups, is not very plausible. More likely explanations are the play of chance and the imbalance between the 2 treatment groups in terms of severity of the event, leading to more early cardiogenic shock, cardiac arrest, or cardiac rupture in the pre-hospital group. It should be noted, however, that this study was underpowered to compare the patient groups in terms of mortality and particularly for those who died versus those who did not.

Overall, the present exploratory analysis is consistent with the main findings of the ATLANTIC study and demonstrates further that the first hours after PCI are a vulnerable period, with potential benefits of pre-hospital use of ticagrelor in STEMI patients undergoing primary PCI. Our results suggest also that there is room left for intravenous antiplatelet agents during this early period when the full effect of oral P2Y₁₂ antagonists is not yet obtained (10–16). It has also been reported that administration of crushed ticagrelor tablets may allow earlier platelet inhibition compared with whole tablets (17).

STUDY LIMITATIONS. Limitations of the ATLANTIC-H²⁴ analysis include the exploratory nature of this post-hoc study. As in the overall ATLANTIC study, there is also a limitation related to the sample size, particularly for the platelet function substudy. Our findings should be interpreted with caution as numbers were small and the differences were not statistically significant for all the endpoints. The ATLANTIC-H²⁴ analysis did, however, attempt to address the previously cited (1) limitation of the short interval between the 2 treatment strategies and between diagnosis and PCI.

CONCLUSIONS

The effects of pre-hospital ticagrelor became apparent after PCI, with numerical differences in

platelet reactivity and immediate post-PCI reperfusion, associated with reductions in ischemic endpoints, including stent thrombosis, over the first 24 h, while there was a small excess of mortality.

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PERSPECTIVES

WHAT IS KNOWN? As pre-hospital antiplatelet therapy, administration of glycoprotein IIb/IIIa inhibitors has been shown to improve coronary reperfusion before PCI in STEMI patients, the ATLANTIC study was designed to evaluate the potential effects of pre-hospital oral antiplatelet therapy with ticagrelor. The results showed no significant difference in pre-PCI coronary reperfusion with a pre- versus in-hospital ticagrelor loading dose, but the transfer time was very short, resulting in a median between-loading dose difference of only 31 min, and previous evidence suggests that the antiplatelet effects of ticagrelor may not have manifested until after this time.

WHAT IS NEW? The ATLANTIC-H²⁴ exploratory analysis in patients undergoing primary PCI confirmed that maximal inhibition of platelet reactivity with pre-hospital ticagrelor did not occur until 1 h after PCI. There were also significant differences in favor of the pre-hospital ticagrelor group in terms of the degree of ST-segment elevation resolution and the composite ischemic endpoint.

WHAT IS NEXT? Observation of the effects of pre- versus in-hospital oral antiplatelet therapy in STEMI patients in a real-world context, where transfer delays are likely longer than we observed, would provide further evidence as would pharmacodynamic studies in a larger patient population.

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KEY WORDS myocardial infarction, platelets, reperfusion, stents, thrombosis

APPENDIX For the full list of ATLANTIC investigators and supplemental tables and figures, please see the online version of this article.