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Pre-hospital ticagrelor in ST-segment elevation myocardial infarction in the French ATLANTIC population☆

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ABSTRACT

Background: ATLANTIC was a randomized study comparing pre- and in-hospital treatment with a ticagrelor loading dose (LD) in ongoing ST-segment elevation myocardial infarction (STEMI). We sought to compare patient characteristics and clinical outcomes in France with other countries participating in ATLANTIC.
Methods: The population comprised 1862 patients, 660 (35.4%) from France and 1202 from 12 other countries. The main endpoints were reperfusion (≥70% ST-segment elevation resolution) and TIMI flow grade 3 before (co-primary endpoints) and after percutaneous coronary intervention (PCI). Other endpoints included a composite ischaemic endpoint (death/myocardial infarction/stroke/urgent revascularization/definite stent thrombosis) and bleeding events at 30 days.
Results: In France, median times from first LD to angiography and between first and second LDs were 49 and 35 min, respectively, and were similar to other countries. French patients were younger (mean 58.7 vs 61.9 years, $p < 0.0001$) and characterized by a higher rate of radial access (89.9% vs 54.8%, $p < 0.0001$), more frequent use of pre-hospital glycoprotein (GP) IIb/IIIa inhibitors (14.1% vs 3.1%, $p < 0.0001$) and intravenous enoxaparin (57.3% vs 10.1%, $p < 0.0001$). In France, as in other countries, the co-primary endpoints did not differ between the two randomization groups. The composite ischaemic endpoint was numerically lower in France (3.3% vs 5.1%, $p = 0.07$), with a lower mortality (1.4% vs 3.3%, $p = 0.01$). PLATO major bleeding was numerically less frequent in France (1.8% vs 3.2%, $p = 0.07$).
Conclusions: The French population appears to have better outcomes than the rest of the study population, and seems related to differences in demographics and management characteristics.
Trial registry: ClinicalTrials.gov (NCT01347580).

1. Introduction

ATLANTIC (Administration of Ticagrelor in the cathLab or in the Ambulance for New ST elevation myocardial infarction to open the Coronary artery; NCT01347580) was an international, randomized, placebo-controlled, double-blind study comparing the effects of pre-

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their interpretation.

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hospital (in the ambulance) vs in-hospital (in the catheterization laboratory) treatment with ticagrelor 180 mg loading dose (LD) on coronary artery reperfusion in patients with ongoing ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) [1]. The results of the ATLANTIC study showed that pre-hospital treatment with ticagrelor was safe in terms of bleeding risk, but did not improve pre-PCI reperfusion compared with in-hospital treatment with ticagrelor. Pre-hospital ticagrelor did, however, achieve a reduction in rates of definite stent thrombosis [1] and ischaemic events in the first 24 h after PCI [2].

France is characterized by a well-organized nationwide pre-hospital system that includes an emergency physician, a nurse and a first-aid–trained driver in each mobile intensive care unit (MICU), with direct access to the catheterization laboratory as a default strategy. France also has distinctive features regarding procedural management of STEMI: the rate of the transradial approach is very high, and enoxaparin is used preferentially as the anticoagulant [3], both of which have been associated with a reduction in bleeding and cardiovascular events in primary PCI [4,5]. Recent data from the FAST-MI (French registry of Acute ST elevation or non-ST-elevation Myocardial Infarction) registry confirmed an important reduction in mortality from 1995 to 2010 associated with greater use of reperfusion therapy and recommended medications in France [6].

The objective of this post-hoc analysis was to compare patient baseline characteristics and clinical outcomes in patients enrolled in France vs other countries participating in ATLANTIC.

2. Methods

Patients with STEMI of >30-min' but <6-h' duration were randomized 1:1 in the ambulance to receive pre- or in-hospital treatment with ticagrelor 180 mg LD or matching placebo, followed by ticagrelor 90 mg twice daily for 30 days. Most patients also received open-label aspirin (intravenous [IV] or oral LD followed by oral maintenance treatment). Use of glycoprotein (GP) IIb/IIIa inhibitors had to be identified as either a strategy of choice by the ambulance staff or physician, or as bail-out treatment during PCI. Evaluations included reperfusion in the culprit artery, assessed as ≥70% ST-segment elevation resolution and Thrombolysis In Myocardial Infarction (TIMI) grade 3 flow, before (co-primary endpoints) and after PCI. Rates of major adverse cardiovascular events, including the composite of death/myocardial infarction/stroke/urgent revascularization/definite stent thrombosis, as well as definite stent thrombosis and bleeding events were analysed at 30 days. Efficacy was evaluated in the modified intention-to-treat population, defined as all patients who underwent randomization and received at least one dose of study drug.

The trial design and protocol were approved by the national regulatory authorities in all the participating countries and by the local ethics committee or institutional review board at each participating site. All the patients provided written informed consent.

2.1. Statistical analysis

Comparisons between France and other countries (Algeria, Australia, Austria, Canada, Denmark, Germany, Hungary, Italy, Netherlands, Spain, Sweden, United Kingdom) for patient characteristics and medical management factors were performed using chi-square tests or the Wilcoxon rank test, as appropriate. Association between country (France vs others) and endpoints was calculated from a logistic regression or a Cox proportional hazards model, without and with explanatory variables.

Most of the results by country and treatment groups and their interaction did not show significance, so the two treatment groups were combined and treatment group was added as an explanatory variable, together with multiple patient characteristics (age, sex, previous myocardial infarction, history of hypertension, diabetes mellitus, and TIMI score ≤6/>6) and medical management factors (time from onset of index event to

Table 1
Patient baseline characteristics, index procedure and medication use.

	French patients ($n = 660$)	Non-French patients ($n = 1202$)	p value
Age, years, mean (SD)	58.7 (12.3)	61.9 (12.4)	<0.0001
≥75 years, *n* (%)	88 (13.3)	216 (18.0)	0.0096
Women, *n* (%)	102 (15.5)	267 (22.2)	0.0005
BMI, kg/m^2, mean (SD)	26.6 (4.4)	27.1 (4.7)	0.0374
TIMI risk score, *n* (%)			<0.0001
0–2	443 (67.1)	682 (56.7)	
3–6	209 (31.7)	493 (41.0)	
>6	8 (1.2)	27 (2.2)	
Diabetes mellitus, *n* (%)	76 (11.5)	177 (14.7)	0.0531
Hypertension, *n* (%)	255 (38.6)	540 (44.9)	0.0087
Prior myocardial infarction, *n* (%)	37 (5.6)	122 (10.1)	0.0008
First medical contact, *n* (%)			<0.0001
Primary transfer[a]	459 (69.5)	953 (79.3)	
Secondary transfer[b]	201 (30.5)	249 (20.7)	
Time from onset of index event to pre-hospital ECG, min, median (IQR)	82 (49-155)	69 (39-128)	<0.0001
Coronary angiography, *n* (%)	651 (98.6)	1176 (97.8)	
Radial access (% of those undergoing coronary angiography)	585 (89.9)	644 (54.8)	<0.0001
Primary PCI, *n* (%)			
With drug-eluting stent	298 (45.2)	648 (53.9)	0.0003
With bare-metal stent	257 (38.5)	360 (30.0)	<0.0001
Thromboaspiration, *n* (%)	372 (56.4)	569 (47.3)	0.0002
Antiplatelet therapy			
Aspirin LD, *n* (%)	613 (92.9)	1035 (86.1)	<0.0001
Oral/IV[c] (% of those who received LD)	5.9/95.4	70.7/30.0	<0.0001
GP IIb/IIIa inhibitors, *n* (%)	277 (42.0)	436 (36.3)	0.016
Timing, *n* (% of all subjects)			
Before angiography	93 (14.1)	37 (3.1)	<0.0001
After angiography and before start of PCI	140 (21.2)	263 (21.9)	0.74
Bail-out	44 (6.7)	134 (11.1)	0.0017
IV anticoagulants during hospitalization, *n* (%)	625 (94.7)	1017 (84.6)	<0.0001
Heparin	372 (56.4)	889 (74.0)	
Enoxaparin	378 (57.3)	122 (10.1)	
Bivalirudin	71 (10.8)	294 (24.5)	
Fondaparinux	60 (9.1)	54 (4.5)	
Combination therapy	228 (34.5)	332 (27.6)	

BMI: body mass index; ECG: electrocardiogram; IQR: interquartile range; TIMI: Thrombolysis In Myocardial Infarction. GP: glycoprotein; IV: intravenous; LD: loading dose; PCI: percutaneous coronary intervention.

[a] Transfer by ambulance from site of symptom onset.

[b] Transfer from other location.

[c] Some patients received both IV and oral aspirin.

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