Accepted: 15 September 2018

Pre-hospital administration of ticagrelor in diabetic patients with ST-elevation myocardial infarction undergoing primary angioplasty: A sub-analysis of the ATLANTIC trial

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Abstract

Objective: We investigated, in the contemporary era of ST-elevation myocardial infarction (STEMI) treatment, the influence of diabetes mellitus (DM) on cardiovascular outcomes, and whether pre-hospital administration of ticagrelor may affect these outcomes in a subgroup of STEMI patients with DM.

Background: DM patients have high platelet reactivity and a prothrombotic condition which highlight the importance of an effective antithrombotic regimen in this high-risk population.
Methods: In toal 1,630 STEMI patients enrolled in the ATLANTIC trial who underwent primary percutaneous coronary intervention (PCI) were included. Multivariate analysis was used to explore the association of DM with outcomes and potential treatment-by-diabetes interaction was tested.
Results: A total of 214/1,630 (13.1%) patients had DM. DM was an independent predictor of poor myocardial reperfusion as reflected by less frequent ST-segment elevation resolution (≥70%) after PCI (OR 0.59, 95% CI 0.43–0.82, $P < 0.01$) and was an independent predictor of the composite 30-day outcomes of death/new myocardial infarction (MI)/urgent revascularization/definite stent thrombosis (ST) (OR 2.80, 95% CI 1.62–4.85, $P < 0.01$), new MI or definite acute ST (OR 2.46, 95% CI 1.08–5.61, $P = 0.03$), and definite ST (OR 10.00, 95% CI 3.54–28.22, $P < 0.01$). No significant interaction between pre-hospital ticagrelor vs in-hospital ticagrelor administration and DM was present for the clinical, electrocardiographic and angiographic outcomes as well as for thrombolysis in myocardial infarction major bleeding.
Conclusions: DM remains independently associated with poor myocardial reperfusion and worse 30-day clinical outcomes. No significant interaction was found between pre-hospital vs in-hospital ticagrelor administration and DM status. Further approaches for the treatment of DM patients are needed.
CLINICAL TRIAL REGISTRATION: clinicaltrials.gov identifier: NCT01347580.

KEYWORDS
antithrombotic drug, diabetes mellitus, STEMI, ticagrelor

1 | INTRODUCTION

Although the prognosis of ST-segment elevation myocardial infarction (STEMI) patients has improved with the implementation of reperfusion strategies, patients with diabetes mellitus (DM) remain an high-risk group.[1] Indeed patients with DM, when compared with those without, have consistently been shown to have higher platelet reactivity,[2,3] which highlights the importance of aggressive antithrombotic drug regimens to manage this population.[4] Ticagrelor is an oral non-thienopyridine $P2Y_{12}$-inhibiting agent with a reversible and direct action on the receptor that provides rapid and consistent platelet inhibition.[5] The ATLANTIC (Administration of Ticagrelor in the Cath Lab or in the Ambulance for New STEMI to Open the Coronary Artery) trial was a randomized study comparing pre-Hospital (pre-H) vs in-Hospital (in-H) treatment with ticagrelor loading dose in acute STEMI.[6] In the trial, the frequent early use of aspirin and anticoagulation and the early use of ticagrelor, coupled with very short medical contact-to-balloon times,[6] represent contemporary treatment of STEMI patients and an ideal setting to explore the influence of DM on clinical outcomes. Moreover, whether there are differences in clinical outcomes according to randomized treatment (pre-H vs in-H) and DM status is unknown. Therefore, we performed a subgroup analysis of the ATLANTIC trial, investigating the potential association of DM with clinical outcomes and the potential interaction between randomized treatment group and DM.

2 | METHODS

2.1 | Study design and study procedures

The ATLANTIC trial was an international study that randomized patients presenting with acute STEMI to receive double-blind treatment with a 180-mg loading dose of ticagrelor either pre-H (in-ambulance) or in-H (in catheterization laboratory), in addition to aspirin and standard of care. The trial design has been published.[7] Briefly, eligible patients (aged ≥18 years) were identified by ambulance personnel for inclusion in the study following diagnosis of STEMI of >30 min but <6 h duration. Immediately after diagnosis, patients were randomized to pre-H administration of ticagrelor 180 mg followed by matching placebo administered in-H, or pre-H administration of placebo followed by ticagrelor 180 mg administered in-H. 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 IIb/IIIa inhibitors (GPI) was discouraged but left to physicians' discretion. In the catheterization laboratory, use of GPI had to be identified as either a planned upfront strategy or a bailout treatment during percutaneous coronary intervention (PCI). PCI techniques, including access site, thrombusaspiration and direct stenting were left to the discretion of the operator.

2.2 | Study end points

Clinical endpoints, evaluated up to date of the last study visit (≤32 days), included the following: death, new myocardial infarction (MI), urgent revascularization, definite stent thrombosis (ST); bail-out GPI use, stroke (ischemic); and reperfusion endpoints consisting of thrombolysis in myocardial infarction (TIMI) flow grade 3 at the end of the procedure and ≥ 70% ST-segment elevation resolution (STR) at 60 min after PCI. Pre-PCI STR and pre-PCI TIMI flow grade 3 were also evaluated. Safety endpoints included major bleeding up to the last study visit using TIMI definition.

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.

2.3 | Statistics

Subjects were classified according to presence or absence of DM at baseline. 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 Chi square test *P*-value or Fisher's test *P*-value in case of low numbers of events.

The association between DM and clinical endpoints was assessed by fitting logistic regression model with DM as the only covariate. A multivariate-adjusted analysis was performed with variables forced in the model: Age, sex, BMI (<30 and ≥30 kg/m^2), TIMI risk score, MI, previous PCI, coronary artery bypass graft (CABG), chronic renal disease, hypertension, dyslipidaemia including hypercholesterolemia, and stent type (drug-eluting (DES) or bare-metal (BMS)). The same variables were forced in the model plus arterial access for bleeding events.

The interaction between DM and study treatment group was tested by using a multivariate logistic regression model. A multivariate-adjusted analysis was performed with variables forced in the model: MI, previous PCI and chronic obstructive pulmonary disease (COPD).

In case of zero cells we performed a Firth's penalized likelihood approach. The two-sided significance level was fixed at 5%. All tests were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

Patients enrolled in the trial and who underwent primary PCI (1,630 patients) were included in the analysis. A total of 214 (13.1%) patients had DM. DM patients compared with non-DM patients were older (64.3 ± 11.6 vs 60.4 ± 12.1 years, $P < 0.01$), with a higher body weight (84.7 ± 15.0 vs 79.6 ± 15.6 kg, $P < 0.01$) and more frequently a body mass index (BMI) ≥30 kg/m^2 (36.4% vs 17.3%, $P < 0.01$). DM patients, compared with non-DM patients, more frequently exhibited

TABLE 1 Baseline characteristics and procedural characteristics between patients with and without diabetes

	Overall (*N* = 1,630)	Diabetes (*N* = 214)	No diabetes (*N* = 1,416)	*P*-Value
Age				
Mean ± sd	60.9 ± 12.1	64.3 ± 11.6	60.4 ± 12.1	
Median (Q1–Q3)	60.0 (52.0–70.0)	64.0 (57.0–73.0)	59.0 (51.0–69.0)	**<0.01**[a]
Age group (≥75)—No. (%)	258 (15.8%)	47 (22.0%)	211 (14.9%)	**<0.01**
Sex—No. (%)				
Female	309 (19.0%)	39 (18.2%)	270 (19.1%)	0.77[b]
Weight (kg)				
Mean ± sd	80.3 ± 15.6	84.7 ± 15.0	79.6 ± 15.6	
Median (Q1–Q3)	80.0 (70.0–90.0)	84.0 (75.0–95.0)	80.0 (70.0–89.0)	**<0.01**[a]
Body mass index group (kg/m2) ≥30 kg/m^2—No. (%)	323 (19.8%)	78 (36.4%)	245 (17.3%)	**<0.01**[b]
Hypertension—No. (%)	677 (41.5%)	153 (71.5%)	524 (37.0%)	**<0.01**[b]
Dyslipidaemia including Hypercholesterol—No. (%)	575 (35.3%)	118 (55.1%)	457 (32.3%)	**<0.01**[b]
Chronic renal disease—No. (%)	24 (1.5%)	10 (4.7%)	14 (1.0%)	**<0.01**[c]
MI—No. (%)	128 (7.9%)	25 (11.7%)	103 (7.3%)	**0.03**[b]
PCI—No. (%)	116 (7.1%)	24 (11.2%)	92 (6.5%)	**0.01**[b]
Coronary artery bypass graft—No. (%)	9 (0.6%)	4 (1.9%)	5 (0.4%)	**0.02**[c]
Chronic obstructive pulmonary disease—No. (%)	65 (4.0%)	9 (4.2%)	56 (4.0%)	0.86[b]
Congestive heart failure—No. (%)	13 (0.8%)	1 (0.5%)	12 (0.8%)	1.00[c]
Transient Ischaemic attack—No. (%)	14 (0.9%)	3 (1.4%)	11 (0.8%)	0.41[c]
Haemorrhagic stroke—No. (%)	4 (0.2%)	0 (0.0%)	4 (0.3%)	1.00[c]
Non-haemorrhagic stroke—No. (%)	16 (1.0%)	3 (1.4%)	13 (0.9%)	0.46[c]
Killip class I—No. (%)	1,489 (91.3%)	192 (89.7%)	1,297 (91.6%)	0.36[b]
TIMI risk score category—No. (%)				
0–2	1,001 (61.4%)	100 (46.7%)	901 (63.6%)	**<0.01**[c]
3–6	603 (37.0%)	107 (50.0%)	496 (35.0%)	
>6	26 (1.6%)	7 (3.3%)	19 (1.3%)	
GP IIb/IIIa inhibitor before PCI—No. (%)	525 (32.2%)	64 (29.9%)	461 (32.6%)	0.44[b]

[a] Mann Whitney *U* test/Wilcoxon Sum Rank test.
[b] Pearson's chi-square test.
[c] Fisher's exact test.
bold text for the p-value means p-value with statistical significance

cardiovascular risk factors including history of hypertension (71.5 vs 37.0%, $P < 0.01$), dyslipidemia (55.1 vs 32.3%, $P < 0.01$) and chronic renal disease (4.7 vs 1.0%, $P < 0.01$). DM patients more frequently had a history of previous MI (11.7 vs 7.3%, $P < 0.01$), previous PCI (11.2 vs 6.5%, $P < 0.01$) and CABG (1.9 vs 0.4%, $P = 0.02$). Finally, DM patients had a higher TIMI risk score category compared with non-DM patients (see Table 1). Baseline characteristics of DM according to randomization (pre-H ticagrelor vs in-H ticagrelor administration) are showed in Table 2. The two cohorts were well balanced with the exception of previous MI and COPD, which were less frequent in patients randomized to pre-H treatment compared with in-H treatment (6.1 vs 16.4%, $P = 0.02$, and 0 vs 7.8%, $P < 0.01$, respectively). No other significant differences were noted between pre-H vs in-H ticagrelor in the DM patient subgroup.

3.2 | Diabetes as potential predictors of myocardial reperfusion

At multivariate analysis, DM was a significant predictor of poor myocardial reperfusion expressed as ≥70% ST-STR post-PCI (odds ratio [OR] 0.59, 95% CI 0.43–0.82, $P < 0.01$) but was not significantly associated with TIMI flow grade 3 of the culprit vessel post-PCI (OR 0.98, 95% CI 0.67–1.44, $P = 0.92$) (Table 3).

3.3 | Diabetes as potential predictors of clinical outcomes

At multivariate analysis, DM was a significant predictor of a composite outcome of 30-day death/new MI/urgent revascularization/definite ST (OR 2.80 CI 1.62–4.85, $P < 0.01$) (Table 3). Kaplan-Meier (KM) curves for the composite outcome in patients with or without DM are reported in Figure 1. DM was also a significant independent predictor of a composite of 30-day new MI or definite acute ST (OR 2.46 95% CI 1.08–5.61, $P = 0.03$) and 30-day definite ST (OR 10.00, 95% CI 3.54–28.22, $P < 0.01$) (Table 3). KM-curves for definite ST in patients with or without DM are reported in Figure 2.

3.4 | Interaction between the treatment group and diabetes status

Clinical outcomes according to randomized treatment (pre-H vs in-H) and DM status are presented in Table 4. Multivariate analysis for all previous outcomes was performed using variables forced in the model (previous MI, previous PCI and COPD) (Table 4).

TABLE 2 Baseline characteristics of patients with diabetes by randomized treatment

	Overall (*N* = 214)	Ticagrelor in-Hosp (*N* = 116)	Ticagrelor pre-Hosp (*N* = 98)	P-Value
Age				
Mean ± sd	64.3 ± 11.6	63.5 ± 11.5	65.2 ± 11.6	0.30[a]
Median (Q1–Q3)	64.0 (57.0–73.0)	64.0 (54.5-72.5)	63.5 (57.0-74.0)	
Age group (≥75 years)—No. (%)	47 (22.0%)	23 (19.8%)	24 (24.5%)	0.41[b]
Sex—No. (%)				
Female	39 (18.2%)	19 (16.4%)	20 (20.4%)	0.45[b]
Weight (kg)				
Mean ± sd	84.7 ± 15.0	84.1 ± 14.0	85.5 ± 16.2	
Median (Q1–Q3)	84.0 (75.0–95.0)	82.0 (75.0–93.5)	84.0 (76.0–95.0)	0.48[c]
Body mass index group (≥ 30 kg/m^2)—No. (%)	78 (36.4%)	45 (38.8%)	33 (33.7%)	0.44[b]
Hypertension—No. (%)	153 (71.5%)	79 (68.1%)	74 (75.5%)	0.23[b]
Dyslipidaemia—No. (%)	118 (55.1%)	65 (56.0%)	53 (54.1%)	0.77[b]
Chronic renal disease—No. (%)	10 (4.7%)	3 (2.6%)	7 (7.1%)	0.19[d]
MI—No. (%)	25 (11.7%)	19 (16.4%)	6 (6.1%)	**0.02**[b]
PCI—No. (%)	24 (11.2%)	17 (14.7%)	7 (7.1%)	**0.08**[b]
Coronary artery bypass graft—No. (%)	4 (1.9%)	3 (2.6%)	1 (1.0%)	0.63[d]
Chronic obstructive pulmonary disease—No. (%)	9 (4.2%)	9 (7.8%)	0 (0.0%)	**<0.01**[d]
Congestive heart failure—No. (%)	1 (0.5%)	1 (0.9%)	0 (0.0%)	1.00[d]
Transient Ischaemic attack—No. (%)	3 (1.4%)	1 (0.9%)	2 (2.0%)	0.59[d]
Non-haemorrhagic stroke—No. (%)	3 (1.4%)	1 (0.9%)	2 (2.0%)	0.59[d]
Killip class I—No. (%)	192 (89.7%)	107 (92.2%)	85 (86.7%)	0.19[b]
TIMI risk score category—No. (%)				
0–2	100 (46.7%)	56 (48.3%)	44 (44.9%)	0.79[d]
3–6	107 (50.0%)	57 (49.1%)	50 (51.0%)	
>6	7 (3.3%)	3 (2.6%)	4 (4.1%)	
GP IIb/IIIa inhibitor before PCI—No. (%)	64 (29.9%)	36 (31.0%)	28 (28.6%)	0.69[b]

[a] Two-Sample T-test.
[b] Pearson's chi-square test.
[c] Mann Whitney U test/Wilcoxon Sum Rank test.
[d] Fisher's exact test.

TABLE 3 Association between outcomes and diabetes

	Univariate logistic Model[a]					Multivariate logistic Model[b]		
	Diabetes	No diabetes	N	Odds-ratio (95% CI)	*P*-value	N	Odds-ratio (95% CI)	*P*-value
30 days composite of death/ new MI/urgent revascularization and definite ST	22/214 (10.3%)	48/1,415 (3.4%)	1,629	3.26 (1.93;5.53)	<0.01	1,629	2.80 (1.62;4.85)	**<0.01**
30 days new MI or definite acute ST	7/214 (3.3%)	19/1,415 (1.3%)	1,629	2.48 (1.03;5.98)	0.04	1,629	2.46 (1.08;5.61)	**0.03**
30 days new MI	1/214 (0.5%)	16/1,415 (1.1%)	1,629	0.41 (0.05;3.11)	0.39	1,629	0.52 (0.13;2.12)	0.36
30 days definite ST	7/214 (3.3%)	6/1,415 (0.4%)	1,629	7.94 (2.64;23.86)	<0.01	1,629	10.00 (3.54;28.22)	**<0.01**
30 days urgent revascularization	3/214 (1.4%)	10/1,415 (0.7%)	1,629	2.00 (0.55;7.32)	0.30	1,629	2.15 (0.72;6.41)	0.17
30 days stroke (ischemic)	1/214 (0.5%)	2/1,415 (0.1%)	1,629	3.32 (0.30;36.74)	0.33	1,629	1.63 (0.39;6.83)	0.50
TIMI flow grade 3 of MI culprit vessel pre-PCI	27/206 (13.1%)	220/1,388 (15.9%)	1,594	0.80 (0.52;1.23)	0.31	1,594	0.90 (0.57;1.42)	0.66
ST-STR ≥70% pre-PCI	23/179 (12.8%)	163/1,246 (13.1%)	1,425	0.98 (0.61;1.56)	0.93	1,425	1.01 (0.61;1.67)	0.97
TIMI flow grade 3 of MI culprit vessel post-PCI	152/195 (77.9%)	1,103/1,349 (81.8%)	1,544	0.79 (0.55;1.14)	0.20	1,544	0.98 (0.67;1.44)	0.92
ST-STR ≥70% post PCI	77/185 (41.6%)	723/1,271 (56.9%)	1,456	0.54 (0.40;0.74)	<0.01	1,456	0.59 (0.43;0.82)	**<0.01**
Bail-out use of glycoprotein IIb/IIIa inhibitors	20/214 (9.3%)	155/1,416 (10.9%)	1,630	0.84 (0.51;1.37)	0.48	1,630	0.91 (0.55;1.51)	0.72
TIMI major bleeding[c]	3/214 (1.4%)	18/1,415 (1.3%)	1,629	1.10 (0.32;3.78)	0.88	1,621	1.48 (0.50;4.39)	0.47
TIMI minor bleeding[c]	11/214 (5.1%)	37/1,415 (2.6%)	1,629	2.02 (1.01;4.02)	0.05	1,621	1.36 (0.67;2.78)	0.40

[a] Univariate Logistic regression.
[b] Multivariate Logistic regression with variables forced in the model[a]: Age, sex, BMI (<30 kg/m^2, ≥30 kg/m^2), TIMI Risk Score, MI, Previous PCI, Coronary Artery Bypass Graft, Chronic Renal Disease, Hypertension, Dyslipidaemia including Hypercholesterol, DES and BMS.
[c] Multivariate Logistic regression with variables forced in the model[a]: Age, sex, BMI (<30 kg/m^2, ≥ 30 kg/m^2), TIMI Risk Score, Myocardial Infarction, Previous PCI, Coronary Artery Bypass Graft, Chronic Renal Disease, Hypertension, Dyslipidaemia including Hypercholesterol, DES, BMS and Arterial access.
bold text for the p-value means p-value with statistical significance

No significant interaction between pre-H ticagrelor vs in-H ticagrelor administration and DM was present for the clinical, electrocardiographic and angiographic outcomes as well as for TIMI-major bleeding.

4 | DISCUSSION

This ATLANTIC trial subgroup analysis evaluated in a prospective cohort of STEMI patients, the current influence of DM on early clinical outcomes and, for the first time, the potential interaction between pre-H vs in-H ticagrelor administration and DM.

In this cohort of >1,600 patients who received early antithrombotic treatment and rapid transportation to the catheterization laboratory, we found that DM, in the present era of coronary reperfusion with primary PCI, remains an independent predictor of poor clinical outcomes, associated with a >2-fold increase risk for clinically important ischemic events. DM was also an independent predictor of poor myocardial reperfusion expressed as complete STR (≥70%) post PCI, a surrogate endpoint that is consistently associated with poor prognosis in this group of patients.[8] Interestingly, DM was not a predictor of TIMI III flow. Thus, DM patients in particular experience poor tissue-level reperfusion due to coronary microvascular dysfunction despite prompt epicardial recanalization of the infarct-related artery.[9] Indeed, the adverse outcomes associated with DM may be partly attributable to their higher baseline risk profile, including higher age and higher prevalence of other cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and chronic renal disease. However, DM patients are further characterized by non-classical risk factors such as endothelial dysfunction, alterations in coagulation and alteration in platelet reactivity which creates a prothrombotic state.[10] Given this prothrombotic condition and reduced responsiveness to antiplatelet therapy,[3] which increases risk for subsequent coronary events,[11] DM patients appear to be ideal candidates to realize the potential clinical benefits of early, potent $P2Y_{12}$ receptor inhibitor therapy. Therefore we explored whether the early administration of ticagrelor in the pre-H setting compared with in-H administration may influence clinical and myocardial reperfusion outcomes in DM subgroup population. However, this subgroup analysis did not demonstrate any significant interaction between treatment group and DM status for all the clinical, electrocardiographic, and angiographic outcomes explored. It is possible that the brief interval time from study drug administration in the ambulance to catheterization laboratory may have limited the potential benefit of pre-H ticagrelor administration in this subgroup of patients. However, the absence of an apparent treatment-by-diabetes interaction for major bleeding suggests that pre-H ticagrelor administration should not be denied to DM patients.

Ticagrelor exhibits a faster and more potent antithrombotic effect than clopidogrel in DM patients[12] and was shown to reduce adverse events in the PLATO trial.[13] The benefits of ticagrelor vs clopidogrel in the DM subgroup were consistent with the overall results, without a significant treatment-by-diabetes interaction.[14] The identification of DM patients as potential candidates who may benefit to a greater extent from antithrombotic therapy has been showed for some

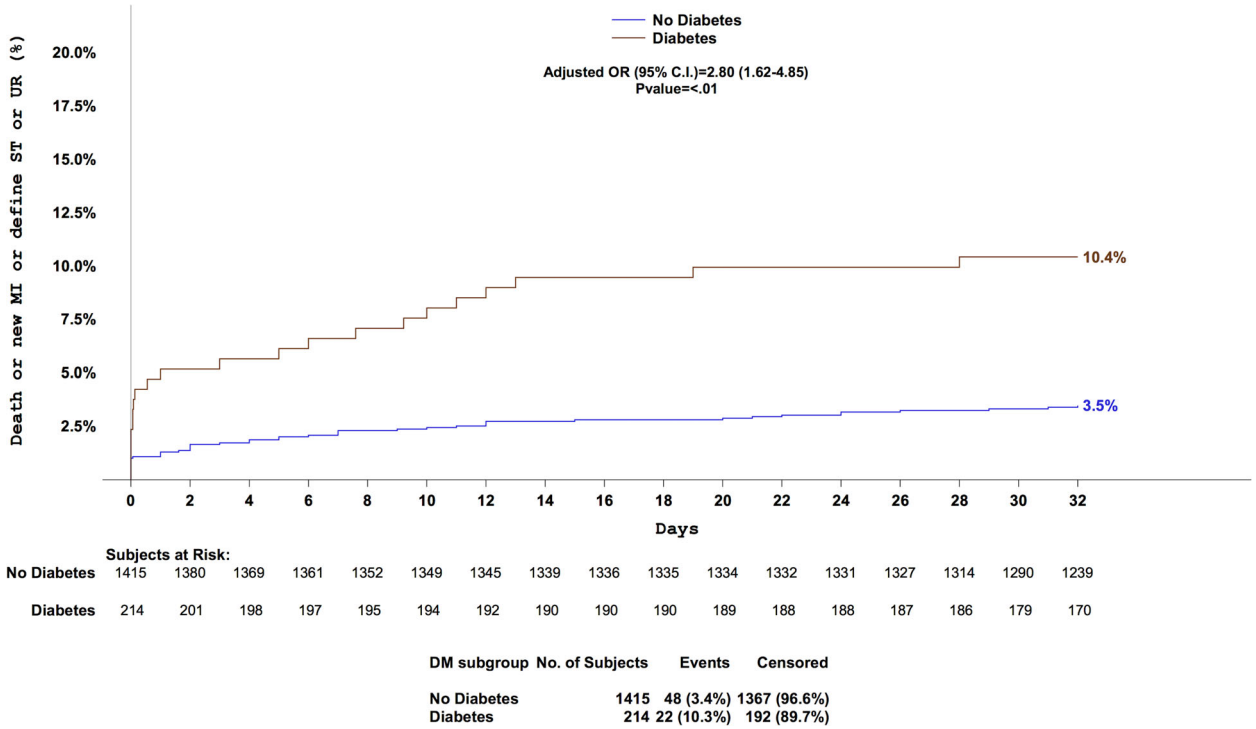

FIGURE 1 KM curves for the composite end point of death, new MI, urgent revascularization, define ST, in patients with or without diabetes [Color figure can be viewed at wileyonlinelibrary.com]

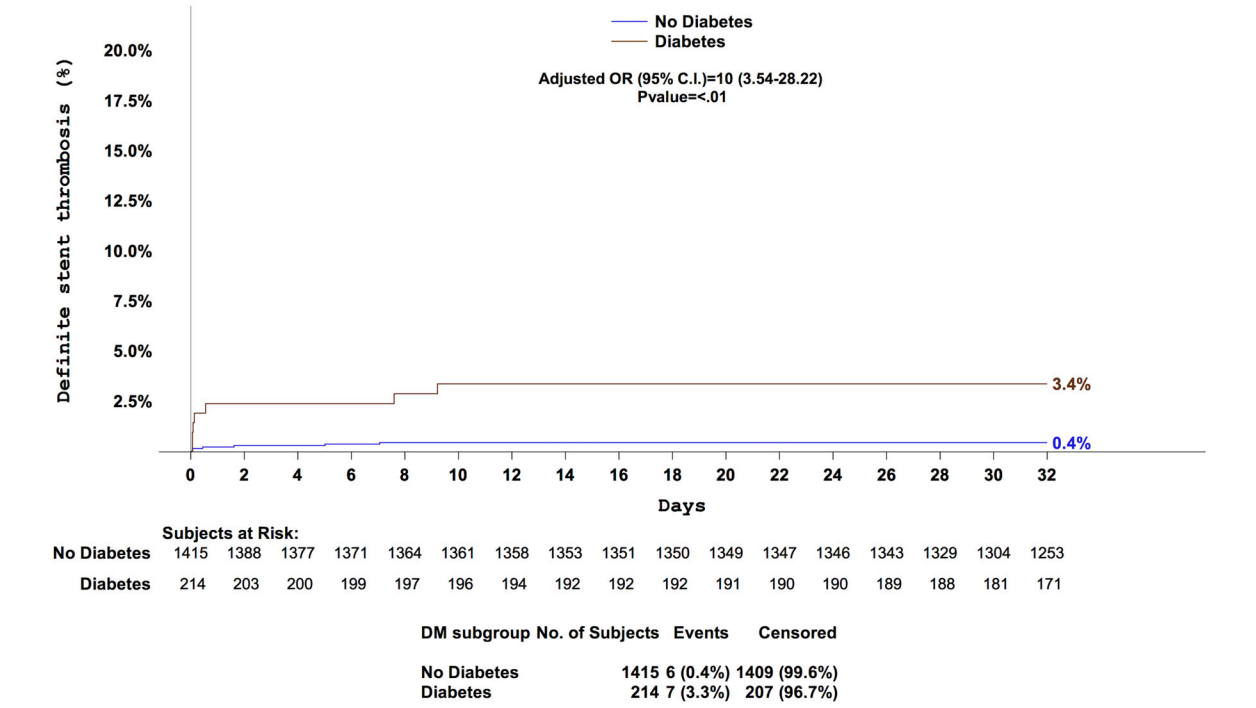

FIGURE 2 KM curves for define ST in patients with or without diabetes [Color figure can be viewed at wileyonlinelibrary.com]

adjuvant therapies, including an intracoronary bolus of abciximab[15] and early high-dose tirofiban administration.[16] Because the mechanisms of the potential increased benefit of potent and rapid antiplatelet therapy in DM patients was centered on increased platelet reactivity with DM, additional research is required to develop further approaches to enhance myocardial perfusion and improve clinical outcomes in this high-risk subset of patients. Indeed, DM is an increasing international health burden and its prevalence continues to rise.[17]

TABLE 4 Outcomes according to randomized treatment (pre-H vs in-H) and diabetes status

		Univariate logistic model[a]				Multivariate logistic model[b]	
Outcomes		**Pre hospital ticagrelor**	**In hospital ticagrelor**	**Odds-ratio (95% CI)**	***P*-value***	**Odds-ratio (95% CI)**	***P*-value***
30 days composite of death/new MI/ urgent revascularization and definite ST	Diabetes	11/98 (11.2%)	11/116 (9.5%)	1.21 (0.50;2.92)	0.75	1.17 (0.48;2.85)	0.80
	No diabetes	24/701 (3.4%)	24/714 (3.4%)	1.02 (0.57;1.81)		1.02 (0.57;1.81)	
30 days new MI or definite acute ST	Diabetes	0/98 (0.0%)	7/116 (6.0%)	0.07 (0.00;1.33)	0.17	0.07 (0.00;1.18)	0.15
	No diabetes	7/701 (1.0%)	12/714 (1.7%)	0.61 (0.24;1.51)		0.60 (0.25;1.48)	
30 days new MI	Diabetes	0/98 (0.0%)	1/116 (0.9%)	0.39 (0.02;9.86)	0.68	0.40 (0.02;9.14)	0.68
	No diabetes	7/701 (1.0%)	9/714 (1.3%)	0.80 (0.31;2.10)		0.80 (0.32;2.04)	
30 days definite ST	Diabetes	0/98 (0.0%)	7/116 (6.0%)	0.07 (0.00;1.33)	0.23	0.07 (0.00;1.15)	0.20
	No diabetes	2/701 (0.3%)	4/714 (0.6%)	0.56 (0.12;2.66)		0.56 (0.12;2.52)	
30 days urgent revascularization	Diabetes	1/98 (1.0%)	2/116 (1.7%)	0.59 (0.05;6.58)	0.92	0.62 (0.05;7.12)	0.95
	No diabetes	4/701 (0.6%)	6/714 (0.8%)	0.68 (0.19;2.41)		0.68 (0.19;2.42)	
30 days stroke (ischemic)	Diabetes	1/98 (1.0%)	0/116 (0.0%)	3.58 (0.14;90.29)	0.88	6.52 (0.30;140.45)	0.90
	No diabetes	2/701 (0.3%)	0/714 (0.0%)	5.10 (0.24;106.69)		5.03 (0.37;68.75)	
TIMI flow grade 3 of MI culprit vessel pre-PCI	Diabetes	15/94 (16.0%)	12/112 (10.7%)	1.58 (0.70;3.57)	0.28	1.51 (0.67;3.42)	0.33
	No diabetes	108/687 (15.7%)	112/701 (16.0%)	0.98 (0.74;1.31)		0.98 (0.73;1.31)	
ST-STR ≥70% pre- CI	Diabetes	10/79 (12.7%)	13/100 (13.0%)	0.97 (0.40;2.35)	0.71	1.01 (0.42;2.47)	0.77
	No diabetes	86/617 (13.9%)	77/629 (12.2%)	1.16 (0.83;1.61)		1.17 (0.84;1.63)	
TIMI flow grade 3 of MI culprit vessel post-PCI	Diabetes	73/91 (80.2%)	79/104 (76.0%)	1.28 (0.65;2.54)	0.69	1.25 (0.63;2.49)	0.74
	No diabetes	552/669 (82.5%)	551/680 (81.0%)	1.10 (0.84;1.46)		1.11 (0.84;1.46)	
ST-STR ≥70% post PCI	Diabetes	40/85 (47.1%)	37/100 (37.0%)	1.51 (0.84;2.73)	0.44	1.47 (0.81;2.66)	0.49
	No diabetes	370/628 (58.9%)	353/643 (54.9%)	1.18 (0.94;1.47)		1.18 (0.94;1.47)	
Bail-out use of glycoprotein IIb/IIIa inhibitors	Diabetes	10/98 (10.2%)	10/116 (8.6%)	1.20 (0.48;3.02)	0.29	1.17 (0.46;2.95)	0.31
	No diabetes	65/702 (9.3%)	90/714 (12.6%)	0.71 (0.50;0.99)		0.71 (0.50;0.99)	
TIMI major bleeding	Diabetes	3/98 (3.1%)	0/116 (0.0%)	8.54 (0.43;169.58)	0.18	9.62 (0.56;166.79)	0.14
	No diabetes	9/701 (1.3%)	9/714 (1.3%)	1.02 (0.41;2.52)		1.02 (0.42;2.46)	
TIMI minor bleeding	Diabetes	3/98 (3.1%)	8/116 (6.9%)	0.43 (0.11;1.65)	0.13	0.44 (0.11;1.74)	0.15
	No diabetes	21/701 (3.0%)	16/714 (2.2%)	1.35 (0.70;2.60)		1.36 (0.70;2.62)	

[a] Univariate Logistic regression.
[b] Multivariate Logistic regression with variables forced in the model[a]: MI, Previous PCI and Chronic Obstructive Pulmonary Disease.
*The *P*-value is from the test statistic for testing the interaction between the treatment group and Diabetes group.

Pre-H administration of a new fast-acting antiplatelet agent, such as cangrelor (a direct-acting and reversible $P2Y_{12}$ receptor inhibitor), or use of crushed Ticagrelor or Prasugrel may represent additional strategies to be tested in order to improve myocardial reperfusion and outcomes in DM patients. However, despite the use of dual antiplatelet therapy with aspirin and a fast-acting $P2Y_{12}$ blocker, multiple other signaling pathways, known to be upregulated in DM patients,[18] remain uninhibited, highlighting the need for new potent antithrombotic treatment strategies to tackle the thrombotic burden of patients with DM. Moreover, there is a reciprocal interplay between DM and inflammation in promoting vascular events,[19] the modulation of inflammatory mechanisms in diabetic patients may represent a further strategy to improve outcomes, indeed in patients who have a chronic inflammatory state, anti-inflammatory therapy has recently showed to significantly reduce the rate of recurrent cardiovascular events.[20] Finally, in diabetic patients the presence of endothelial dysfunction is implicated in the induction of proatherothrombotic mechanisms,[21] thus the development of novel therapeutic approaches targeting endothelial dysfunction could be helpful to ameliorate prognosis in these high risk patients.

4.1 | Limitations

This study was a subgroup analysis of the ATLANTIC trial with its inherent limitations.[6] Moreover, it was a post-hoc analysis and therefore should be viewed as hypothesis-generating. The subgroup analysis focused on DM patients but information about the duration and type of therapy for DM was not available. Thus, whether the efficacy of pre-H ticagrelor administration differed among DM patients managed with or without insulin remains unknown. Moreover, baseline levels of glucose and HbA1c were not available. Finally, randomization was not stratified by DM status, although the main baseline characteristics for DM patients were balanced between the randomized groups.

5 | CONCLUSIONS

In an era of rapid STEMI reperfusion treatment with primary PCI and potent antiplatelet therapy, DM remains independently associated with poor myocardial reperfusion and worse 30-day clinical outcomes. No significant interaction was found between pre-H vs in-H ticagrelor administration and DM status for the explored endpoints. Further approaches for the treatment of DM patients are needed.

ACKNOWLEDGMENT

This study was supported by Astrazeneca.

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