Impact of vomiting on P2Y12 platelet inhibition in patients with ST-elevation myocardial infarction: A prespecified subanalysis of the ON-TIME 3 trial

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Vomiting is associated with lower levels of ticagrelor concentration and higher platelet reactivity in the early hours of ST-elevation myocardial infarction. These results support reloading with a ticagrelor loading dose and/or treatment with intravenous platelet inhibitors when patients vomit. (Am Heart J 2022;243:39–42.)

Optimal antiplatelet therapy is one of the cornerstones in the treatment of patients with ST-elevation myocardial infarction (STEMI). Nausea and vomiting are both symptoms of STEMI, but they can also result from adverse effects of opioids, which are currently recommended for pain relief in STEMI.[1,2] This prespecified subanalysis of the ON-TIME 3 trial[3] aims to show the impact of vomiting on platelet inhibition in the early hours of STEMI.

Methods

In brief, patients with STEMI and a pain score of 4 or higher on a 10-step numeric rating pain score who were planned to undergo a primary PCI, were enrolled and randomized to intravenous (iv) fentanyl or iv acetaminophen in a prehospital setting in the ON-TIME 3 trial. All patients were treated with crushed ticagrelor, aspirin and heparin in the ambulance. In the current analysis patients who vomited after randomization, either prehospitally or during coronary angiography or primary PCI, were compared with patients who did not vomit.

Pharmacodynamics were assessed by a VerifyNow $P2Y_{12}$ point of care test (Accriva, San Diego, CA) for measurement of platelet reactivity units (PRU) at 4 time points: before angiography (T1), immediately after primary PCI (or 1 hour after angiography) (T2), 1 hour after primary PCI (or 2 hours after angiography) (T3) and 6 hours after primary PCI (or 7 hours after angiography) (T4). High on-treatment platelet reactivity (HPR) was defined as PRU >208.[4] At similar time points the plasma levels of ticagrelor were analyzed using liquid chromatography-mass spectrometry.

Continuous variables were compared with Students *t*test or Mann Whitney U test, and categorical variables with Pearson's χ^2 test or Fisher exact test. Univariable and multivariable (using nonlinear quantile regression including a model with gender and study arm) analyses were performed for all time points. A P value below .05 was considered statistically significant. All analyses were performed with R version 3.6.0 and SPSS version 27. The ON-TIME 3 trial was conducted with an unrestricted grant from AstraZeneca. However, AstraZeneca was not involved in the analysis and writing of this subanalysis. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Results

All 195 patients included in the ON-TIME 3 trial were included in the current analysis, of which 17 patients vomited (8.7%) and 178 did not (91.3%). Patients who vomited were more frequently randomized to fentanyl (82.4% vs 46.6%; $P = .01$) and received more often a glycoprotein IIb/IIIa inhibitor (GPI) (41.2% vs 16.3%; $P = .02$). Cardiovascular risk factors as well as the time from randomization and administration of the loading dose of crushed ticagrelor to each timepoint of pharmacodynamic and -kinetic measurements, were balanced

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between patients who vomited and those who did not (Table).

In patients who vomited, higher levels of platelet reactivity were seen immediately after primary PCI (229 [212-236] vs 135 [37-213], $P = .003$), at 1 hour after primary PCI (143 [68-181] vs 38 [6-97], $P = .01$), and at 6 hours after primary PCI (55 [27-94] vs 8 [4-32], $P = .004$, Figure). Moreover, vomiting was associated with HPR measured immediately after primary PCI (47.1% vs 24.7%; $P = .005$). If patients received GPI, then an interaction with the VerifyNow assay occurred and this was presented as an error (missing value). However, in most patients that received GPI, the first and often the second measurements could be performed as blood was taken before infusion of GPI. The results were consistent in sensitivity analyses using multiple imputation for missing values and in patients without use of GPI (Supplementary file).

Furthermore, vomiting was associated with lower levels of plasma concentrations of ticagrelor up to 1 hour after primary PCI (before primary PCI 23 [16-68] vs 98 [18-407], $P = .03$; immediately after primary PCI 67 [34-89] vs 226 [60-544], $P = .02$; at 1 hour after primary PCI 105 [64-267] vs 444 [251-778], $P = .003$).

Also, in multivariable analyses, vomiting was significantly associated with higher levels of platelet reactivity and lower levels of ticagrelor concentration (both $P < .001$).

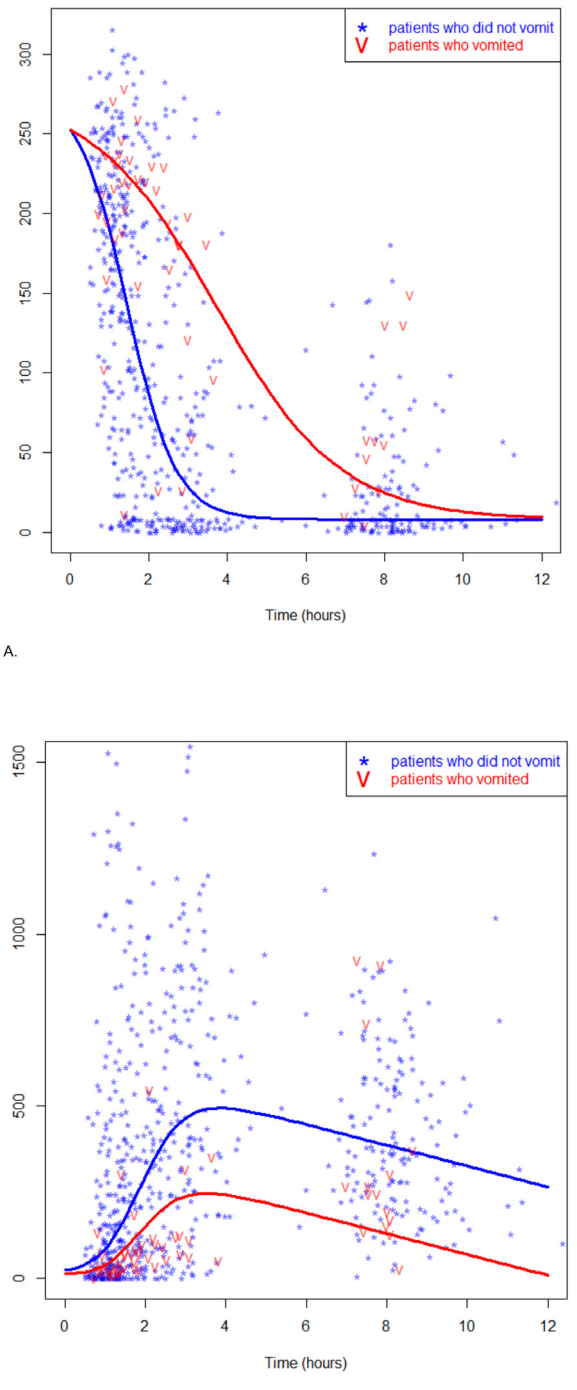
Discussion

This analysis presented that vomiting in the early hours of STEMI was associated with lower plasma levels of ticagrelor and higher levels of platelet reactivity. This analysis supports reloading with a ticagrelor loading dose and/or treatment with intravenous platelet inhibitors, such as cangrelor or GPIs, in STEMI patients who vomit.

As vomiting is a common adverse effect of opioids, and moreover, opioids are associated with reduced platelet inhibition,[3,5,6] this analysis supports the search for alternative pain relievers for opioids in the acute phase of STEMI. Acetaminophen may be a suitable alternative, as presented in the main analysis of the ON-TIME 3 trial.[3] If opioids are still being considered (eg, persistent pain despite adequate treatment), use of metoclopramide might help to limit the adverse effects of opioids on platelet inhibition.[7]

Some limitations need to be acknowledged. Although this subanalysis was prespecified, a nonrandomized comparison was performed, and confounding might still be present despite multivariable analyses. Since the number of patients who vomited was small, no specific comparison could be made between patients who vomited and were treated with fentanyl and patients who vomited and were treated with acetaminophen. Moreover, the

Figure



Vomiting vs no vomiting. **A**, Platelet reactivity units (PRU) in patients who vomited and those who did not, shown over time. **B**, Ticagrelor plasma concentrations in patients who vomited and those who did not, shown over time.

Table. Baseline and angiographic characteristics

General baseline characteristics	Vomiting $N = 17$	No vomiting $N = 178$	*P* value
Study arm			.01
Acetaminophen (%)	3 (17.6)	95 (53.4)	
Fentanyl (%)	14 (82.4)	83 (46.6)	
Age (mean, SD)	65.4 (11.1)	63.2 (11.4)	.55
Female (%)	4 (23.5)	54 (30.3)	.76
Diabetes mellitus (%)	2 (11.8)	32 (18.0)	.74
Hypertension (%)	5 (29.4)	72 (40.4)	.53
Hypercholesterolemia (%)	4 (23.5)	53 (29.8)	.78
Smoking			.40
Nonsmoker (%)	10 (58.8)	67 (37.6)	
In the past (%)	2 (11.7)	34 (19.1)	
Current (%)	5 (29.4)	77 (43.3)	
Family history of CAD (%)	9 (53.9)	83 (46.6)	.76
Peripheral artery disease (%)	0 (0.0)	4 (2.2)	1.00
Prior myocardial infarction (%)	1 (5.9)	18 (10.1)	1.00
Prior PCI (%)	2 (11.8)	20 (11.2)	1.00
Prior CABG (%)	0 (0.0)	1 (0.6)	1.00
Renal function based on creatinine μmol/L (median, IQR)	78 (75-100)	81 (69-94)	.37
Killip class I (%)	16 (94.1)	173 (97.2)	.43
Pain score at randomisation (median, IQR)	7 (6-8)	7 (6-8)	.34
Time from randomisation to T1 in mins (median, IQR)	68 (56-80)	65 (52-78)	.32
Time from randomisation to T2 in mins (median, IQR)	104 (89-112)	100 (83-120)	.79
Time from randomisation to T3 in mins (median, IQR)	173 (150-186)	181 (153-203)	.37
Time from randomisation to T4 in mins (median, IQR)	480 (453-486)	490 (454-522)	.12

Angiographic characteristics	Vomiting $N = 17$	No vomiting $N = 178$	*P* value
Radial access site (%)	15 (88.2)	167 (93.8)	.32
Type of procedure			1.00
CAG only (%)	1 (5.9)	18 (10.1)	
POBA only (%)	1 (5.9)	10 (5.6)	
Primary PCI (%)	15 (88.2)	150 (84.3)	
Culprit			1.00
LAD (%)	6 (35.3)	58 (32.6)	
RCA (%)	9 (52.9)	90 (50.6)	
RCx (%)	2 (11.8)	19 (10.7)	
LM (%)	0 (0.0)	2 (1.1)	
Other/no culprit (%)	0 (0.0)	9 (0.0)	
Thrombus aspiration (%)	3 (17.6)	37 (20.8)	1.00
Distal embolization (%)	0 (0.0)	11 (6.2)	.60
TIMI flow grade preprocedure (%)			.47
0	10 (58.8)	83 (46.6)	
1	1 (5.9)	17 (9.6)	
2	4 (23.5)	27 (15.2)	
3	1 (5.9)	33 (18.5)	
Unknown	1 (5.9)	18 (10.1)	
Glycoprotein IIb/IIIa inhibitor (%)			.02
None	10 (58.8)	149 (83.7)	
6 hours infusion	6 (35.3)	17 (9.6)	
12 hours infusion	1 (5.9)	8 (4.5)	
24 hours infusion	0 (0.0)	4 (2.2)	

CAG, coronary angiography; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IQR, interquartile range; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; POBA, plain old balloon angiography; RCA, right coronary artery; RCx, ramus circumflex artery; SD, standard deviation; T1, before primary PCI; T2, immediately after primary PCI; T3, 1-hour after primary PCI; T4, 6 hours after primary PCI; TIMI, thrombolysis in myocardial infarction.

number of patients was too small to assess effects on clinical outcome.

Conclusion

Vomiting in the early hours of STEMI was associated with lower plasma levels of ticagrelor and higher levels of platelet reactivity.

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Disclosures

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.08.011.

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