Circulation

RESPONSE TO LETTER TO THE EDITOR

Response by Ibrahim et al to Letter Regarding Article, "Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention: The PACIFY Randomized Clinical Trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl)"

Khalil Ibrahim, MD
Rohan Shah, MD
John W. McEvoy, MBBCh, MEHP, MHS

In Response:

We appreciate the letter submitted by Dr Kikkert and colleagues regarding our randomized trial,[1] which demonstrated that fentanyl administration during percutaneous intervention (PCI) impairs ticagrelor absorption and delays the platelet inhibition effects of this oral $P2Y_{12}$ inhibitor. We agree with the authors that this newly described drug interaction could have the most negative impact on patients presenting with ST-segment–elevation myocardial infarction for the reasons outlined. However, we also feel that this drug interaction may be important in patients presenting with non–ST-segment–elevation myocardial infarction and elective PCI, particularly in US catheterization labs where fentanyl is often routinely and prophylactically administered for cardiac procedures (in contrast to Europe).[2]

We thank Kikkert and colleagues for the opportunity to describe the patient population of our trial in more detail than was possible in our research letter, which had a tight word limit. These details are also published in the rationale and design paper that was referenced in our original research letter.[3] In addition, the full report of the PACIFY trial has now been published and includes the full complement of results from this study.[4] Our sample was entirely composed of patients undergoing elective PCI. There were no patients presenting with ST-segment–elevation myocardial infarction or in cardiogenic shock. Although it would be a logistical challenge, we agree that this is an important patient population to study in further trials. The mean total dose of fentanyl was 96.3 micrograms in the fentanyl arm. Two participants in the no-fentanyl arm crossed over to the fentanyl arm; however, this had little impact on the results because both intention-to-treat and as-treated analyses demonstrated statistically significant results for the primary end point. The standard anticoagulant in our catheterization laboratory is unfractionated heparin, which all participants received. The authors suggest that unfractionated heparin given during PCI would provide adequate antithrombotic protection for the 2 hours after PCI; however, our data show that ticagrelor drug concentration and platelet inhibition did not become equivalent between the 2 groups until 4 hours on average, with some in the fentanyl group having even longer delays to platelet inhibition. The higher troponin levels after PCI in the fentanyl group may be explained by this gap in antithrombotic coverage.

Finally, we would argue that our randomized trial actually answered the hypothesis it was designed to test[3–5] and is hypothesis-generating only in so far as it raises additional questions regarding clinical implications that will require further study in larger samples.

ARTICLE INFORMATION

Affiliation

Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

Disclosures

None.

REFERENCES

1. McEvoy JW, Ibrahim K, Kickler TS, Clarke WA, Hasan RK, Czarny MJ, Keramati AR, Goli RR, Gratton TP, Brinker JA, Chacko M, Hwang CW, Johnston PV, Miller JM, Trost JC, Herzog WR, Blumenthal RS, Thiemann DR, Resar JR, Schulman SP. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: the PACIFY randomized clinical trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl). *Circulation*. 2018;137:307–309. doi: 10.1161/CIRCULATIONAHA.117.031678.
2. Shah R, Kirtane AJ, McEvoy JW. Opiate use in the cath lab. *Eur Heart J*. 2018;39:642–645. doi: 10.1093/eurheartj/ehy016.
3. Ibrahim K, Goli RR, Shah R, Resar JR, Schulman SP, McEvoy JW. Effect of intravenous fentanyl on ticagrelor absorption and platelet inhibition among patients undergoing percutaneous coronary intervention: design, rationale, and sample characteristics of the PACIFY randomized trial. *Contemp Clin Trials*. 2018;64:8–12. doi: 10.1016/j.cct.2017.11.011.
4. Ibrahim K, Shah R, Goli RR, Kickler TS, Clarke WA, Hasan RK, Blumenthal RS, Thiemann DR, Resar JR, Schulman SP, McEvoy JW. Fentanyl delays the platelet inhibition effects of oral ticagrelor: full report of the PACIFY randomized clinical trial. *Thromb Haemost*. 2018. doi: 10.1055/s-0038-1666862.
5. McCarthy CP, Mullins KV, Sidhu SS, Schulman SP, McEvoy JW. The on- and off-target effects of morphine in acute coronary syndrome: a narrative review. *Am Heart J*. 2016;176:114–121. doi: 10.1016/j.ahj.2016.04.004.

Response by Ibrahim et al to Letter Regarding Article, ''Effect of Intravenous Fentanyl on Ticagrelor Absorption and Platelet Inhibition Among Patients Undergoing Percutaneous Coronary Intervention: The PACIFY Randomized Clinical Trial (Platelet Aggregation With Ticagrelor Inhibition and Fentanyl)''

Khalil Ibrahim, Rohan Shah and John W. McEvoy

Circulation. 2018;138:216-217
doi: 10.1161/CIRCULATIONAHA.118.034741
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539