

LETTER TO THE EDITOR

Response by Montone et al to Letter Regarding Article, “Optimized Treatment of ST-Elevation Myocardial Infarction”

It's the Time to Move Towards Powered Trials Evaluating Multitargeted Therapeutic Strategies

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In Response:

We appreciate the interest of Jones et al¹ in our review article about microvascular obstruction (MVO) as a therapeutic target to further improve prognosis in patients with ST-elevation myocardial infarction.² The authors reported the interesting data of the NITRITE-AMI trial (Intra-Coronary Nitrite During Acute Myocardial Infarction), a randomized, placebo-controlled trial, evaluating the intracoronary injection of sodium nitrite in 80 patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention.³ They found a trend for reduced infarct size and a significantly improved myocardial salvage index assessed by cardiac magnetic resonance as well as a reduced occurrence of major adverse cardiac events at 3 years. Of interest, they also demonstrated a trend for reduction of cardiac magnetic resonance-detected MVO. Moreover, in a subgroup of 66 patients with thrombolysis in myocardial infarction flow ≤ 1 , they showed significant reductions in cardiac magnetic resonance-infarct size (20%, $P=0.03$), and a further greater reduction in MVO (48% reduction, $P=0.015$), suggesting that MVO may represent a possible target for inorganic nitrite. A major limitation of this interesting study, however, is the small sample size (80 patients randomized in 2 groups) that did not allow for performing multiple comparisons and, at the end, a powered statistical analysis. Thus, further larger studies are needed to confirm these exploratory results. However, along with findings deriving from the administration of a single drug (often from small sized and unpowered studies), in our review, we highlighted the importance of a multitargeted therapeutic approach to target MVO. Indeed, MVO is a complex phenomenon, involving multiple pathogenic mechanisms, and probably therapeutic strategies addressing these multiple pathogenic players

should be tested in future trials adequately powered to detect differences in clinical end points, along with cardiac magnetic resonance end points.^{4–6}

ARTICLE INFORMATION

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Disclosures

None.

REFERENCES

1. Jones DA, Mathur A, Ahluwalia A. Letter by Jones et al regarding article, “Optimized treatment of ST-elevation myocardial infarction.” *Circ Res*. 2019;125:e29. doi: 10.1161/CIRCRESAHA.119.315692
2. Niccoli G, Montone RA, Ibanez B, Thiele H, Crea F, Heusch G, Bulluck H, Hausenloy DJ, Berry C, Stiermaier T, et al. Optimized treatment of ST-elevation myocardial infarction. *Circ Res*. 2019;125:245–258. doi: 10.1161/CIRCRESAHA.119.315344
3. Jones DA, Pellaton C, Velmurugan S, Rathod KS, Andiapan M, Antoniou S, van Eijl S, Webb AJ, Westwood MA, Parmar MK, et al. Randomized phase 2 trial of intracoronary nitrite during acute myocardial infarction. *Circ Res*. 2015;116:437–447. doi: 10.1161/CIRCRESAHA.116.305082
4. Stiermaier T, Jensen JO, Rommel KP, de Waha-Thiele S, Fuernau G, Desch S, Thiele H, Eitel I. Combined intrahospital remote ischemic preconditioning and postconditioning improves clinical outcome in ST-elevation myocardial infarction. *Circ Res*. 2019;124:1482–1491. doi: 10.1161/CIRCRESAHA.118.314500
5. Hausenloy DJ, Yellon DM. Combination therapy to target reperfusion injury after ST-segment-elevation myocardial infarction: a more effective approach to cardioprotection. *Circulation*. 2017;136:904–906. doi: 10.1161/CIRCULATIONAHA.117.029859
6. Davidson SM, Ferdinandy P, Andreadou I, Botker HE, Heusch G, Ibáñez B, Ovize M, Schulz R, Yellon DM, Hausenloy DJ, et al; CARDIOPROTECTION COST Action (CA16225). Multitarget strategies to reduce myocardial ischemia/reperfusion injury: JACC review topic of the week. *J Am Coll Cardiol*. 2019;73:89–99. doi: 10.1016/j.jacc.2018.09.086