Editorial

SECURE PCI: how important can a subgroup analysis be?

Mathieu Kerneis, Megan K. Yee, C. Michael Gibson

Division of Cardiovascular Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
Correspondence to: Prof. C. Michael Gibson, MS, MD. Beth Israel Deaconess Medical Center, Cardiovascular Division, 20 Overland Street, Boston, MA 02215, USA. Email: mgibson@bidmc.harvard.edu.
Provenance: This is an invited Editorial commissioned by the Section Editor Hai-Long Dai (Department of Cardiology, Yan'an Affiliated Hospital of Kunming Medical University, Kunming, China).
Comment on: Berwanger O, Santucci EV, de Barros E Silva PGM, *et al.* Effect of loading dose of atorvastatin prior to planned percutaneous coronary intervention on major adverse cardiovascular events in acute coronary syndrome: the SECURE-PCI randomized clinical trial. JAMA 2018;319:1331-40.

Submitted May 02, 2018. Accepted for publication May 22, 2018.
doi: 10.21037/jtd.2018.05.155
View this article at: http://dx.doi.org/10.21037/jtd.2018.05.155

Among acute coronary syndrome (ACS) and stable coronary artery disease patients, the effect of a loading dose of statin, prior to revascularization, has been assessed in several observational studies and randomized controlled trials (1-3). A high dose of statin before percutaneous or surgical revascularization was associated with a decreased risk of periprocedural myocardial infarction (MI), contrast induced—acute kidney injury and, finally, improved clinical outcomes (4,5). The underlying mechanism was hypothesized to be related to the complex pleiotropic effects of statins which improve endothelial function, stabilize the atherosclerotic plaque, and decrease the vascular inflammation (6).

European and American Guidelines recommend the administration of statins in all patients with acute MI, irrespective of cholesterol concentration at presentation. In addition, lipid-lowering treatment should be started as early as possible (class I in European Guidelines, IIa in American Guidelines) and given as a high-intensity treatment (class I in both guidelines) (7,8). However, the efficacy of a high dose of statin, as a pretreatment, was evaluated in trials with small sample size and soft endpoints (9).

The SECURE-PCI study was an ambitious, multicenter, randomized controlled trial designed to address the limitations of previous studies. The trial had a large sample size (N=4,191), and strong methodology (10). Nevertheless, Berwanger *et al*. failed to demonstrate that two separate loading doses of 80 mg of atorvastatin administered among ACS patients was superior in the reduction of major adverse cardiovascular events (MACE) compared to placebo at 30 days (11). Since P of the primary endpoint comparison are too often translated into a 'positive' or 'negative' result (12), the SECURE PCI Trial was mainly reported as a 'negative' trial.

It might be unfair, however, to dismiss the SECURE PCI trial based on its primary endpoint alone analysis alone for three main reasons: (I) a prespecified and powered analysis among patients who underwent PCI demonstrated a 2.2% absolute reduction in the occurrence of the composite ischemic endpoint (P for interaction =0.04) mainly driven by a decreased rate of periprocedural MI and unplanned coronary revascularization, (II) the prior data and the rationale for the efficacy early high dose statin among patients undergoing revascularization is robust, (III) this strategy did not increase the occurrence of serious adverse events.

Indeed, the subgroup of patients who underwent PCI was a pre-specified sensitivity analyses in the protocol (10). Further, the sample size calculation for the trial was performed to maintain approximately 80% power for this analysis, though it should be noted the observed overall event rate was nearly half the estimated rate. Still, a significant result was observed (P=0.02, NNT =46) and a significant interaction was observed (P=0.04), indicating PCI status modulated the treatment effect of the loading dose of statin.

In daily practice, the vast majority of the ACS patients are already treated with a high dose of statin administered within the first 24 hours. This 'routine care' will likely not be influenced by the primary endpoint analysis of the SECURE

PCI trial. More than 12 randomized studies, previously demonstrated the consistent benefit of a pretreatment with statin among patients undergoing PCI (9). Instead of only considering the scientific result of the primary endpoint analysis in one trial, physicians often take into account the pathophysiology, previous results, and the balance of benefit/risk to guide their decisions.

Of importance in the SECURE-PCI trial, no cases of rhabdomyolysis or hepatic failure were reported in the atorvastatin group. The safety of an early treatment strategy which will inevitably be given to the patient chronically counterbalances the lack adjustments for multiple testing or sequential order for the secondary analyses that may limit our conclusion (if a simple Bonferroni correction was applied to the subgroup analysis, the significance of the P would be lower)

While such an approach is safe, and the totality of the data suggests it is effective, it should not delay therapy in ACS patients, particularly STEMI patients. It is obvious, in particular, that the lack of administration of a loading dose of statin should never delay a transfer to the Cath lab or the administration of an antithrombotic regimen. However, in the Cath lab for STEMI patients, or in the coronary care unit for non-ST elevated ACS patients, giving a loading dose of statin seems easy, economic, harmless and may reduce the ischemic risk.

Acknowledgements

None.

Footnote

Conflicts of Interest: M Kerneis has received research grant support from French federation of Cardiology, Institut Servier, consulting fees or honorarium from Bayer and AstraZeneca. CM Gibson has received research grant support from Angel Medical Corporation, Bayer Corp, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson Corporation, and Portola Pharmaceuticals; and has received modest consulting monies from Amarin Pharma, Amgen, Arena Pharmaceuticals, Bayer Corporation, Boehringer Ingelheim, Boston Clinical Research Institute, Cardiovascular Research Foundation, Chiesi, CSL Behring, Eli Lilly, Gilead Sciences, Inc., Janssen Pharmaceuticals, Johnson & Johnson Corporation, The Medicines Company, Merk & Co, Inc., Novo Nordisk, Pfizer, Pharma Mar, Portola Pharmaceuticals, Sanofi, Somahlution, St. Francis Hospital, Verson Corporation, and Web MD. Another author has no conflicts of interest to declare.

References

1. Dotani MI, Elnicki DM, Jain AC, et al. Effect of preoperative statin therapy and cardiac outcomes after coronary artery bypass grafting. Am J Cardiol 2000;86:1128-30, A6.
2. Kim JS, Kim J, Choi D, et al. Efficacy of high-dose atorvastatin loading before primary percutaneous coronary intervention in ST-segment elevation myocardial infarction: the STATIN STEMI trial. JACC Cardiovasc Interv 2010;3:332-9.
3. Patti G, Pasceri V, Colonna G, et al. Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention: results of the ARMYDA-ACS randomized trial. J Am Coll Cardiol 2007;49:1272-8.
4. Benjo AM, El-Hayek GE, Messerli F, et al. High dose statin loading prior to percutaneous coronary intervention decreases cardiovascular events: a meta-analysis of randomized controlled trials. Catheter Cardiovasc Interv 2015;85:53-60.
5. Lee JM, Park J, Jeon KH, et al. Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomized controlled trials. PLoS One 2014;9:e111397.
6. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. Circulation 2004;109:III39-43.
7. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
8. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-425.
9. Patti G, Cannon CP, Murphy SA, et al. Clinical benefit of statin pretreatment in patients undergoing percutaneous coronary intervention: a collaborative patient-level meta-analysis of 13 randomized studies. Circulation

2011;123:1622-32.
10. Berwanger O, de Barros E Silva PGM, Dall Orto FTC, et al. Rationale and design of the Statins Evaluation in Coronary procedUres and REvascularization: The SECURE-PCI Trial. Am Heart J 2018;198:129-34.
11. Berwanger O, Santucci EV, de Barros E Silva PGM, et al. Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial. JAMA 2018;319:1331-40.
12. Pocock SJ, McMurray JJV, Collier TJ. Making Sense of Statistics in Clinical Trial Reports: Part 1 of a 4-Part Series on Statistics for Clinical Trials. J Am Coll Cardiol 2015;66:2536-49.

Cite this article as: Kerneis M, Yee MK, Gibson CM. SECURE PCI: how important can a subgroup analysis be? J Thorac Dis 2018;10(Suppl 17):S2032-S2034. doi: 10.21037/jtd.2018.05.155