Editorial

Fine-tuning treatment for patients with ST-elevation myocardial infarction

Feng Qian, Edward L. Hannan

University at Albany-State University of New York, Albany, NY, USA

Correspondence to: Feng Qian, MD, PhD, Assistant Professor. Department of Health Policy, Management & Behavior, School of Public Health, University at Albany-State University of New York, GEC Room 169, One University Place, Rensselaer, NY 12144, USA. Email: fqian@albany.edu.

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As the most severe type of heart attack, ST-elevation myocardial infarction (STEMI) is a life-threatening medical emergency and calls for a rapid response. In the United States, it is estimated that 30% of patients with myocardial infarction have STEMI and that 50% of STEMI patients have multivessel disease (1,2). Literature suggests that compared with STEMI patients with single vessel disease, STEMI patients with multivessel disease have worse clinical outcomes (3). The optimal strategy for the treatment of patients with STEMI and multivessel disease is of increasing interest and practice guidelines continue to evolve with new data (4). Also, the safety and effectiveness of adjunctive aspiration thrombectomy in percutaneous coronary intervention (PCI) are in doubt although it was initially perceived to be an effective therapy to reduce distal embolization (5-7).

Summary of changes in the 2015 focused update

Recently, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines ("Task Force") issued a Guideline Focused Update 2015 ACC/AHA/society for cardiac angiography and interventions (SCAI) focused update on Primary PCI for Patients with STEMI) in response to new findings from important new studies on multivessel PCI and aspiration thrombectomy (1). The Guideline Writing Committee (GWC) composed of national experts and leading physicians made recommendations after reviewing four recently published randomized controlled trials (RCTs) on culprit artery-only versus multivessel PCI [preventive angioplasty in acute myocardial infarction (PRAMI) trial, Complete Versus Culprit-Lesion Only Primary PCI (CvLPRIT) trial, third Danish study of optimal acute treatment of patients with ST-segment elevation myocardial infarction (DANAMI 3 PRIMULTI) trial, and primary angioplasty in patients transferred from general community hospitals to specialized PTCA units with or without emergency thrombolysis (PRAGUE-13) trial] and three multicenter RCTs on aspiration thrombectomy [i.e., Intracoronary Abciximab and aspiration thrombectomy in patients with large anterior myocardial infarction (INFUSE-AMI) trial, thrombus aspiration during ST-segment elevation myocardial infarction (TASTE) trial, and Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients with STEMI (TOTAL) trial] (8-15).

In a nutshell, the 2015 Focused Update recommends that "PCI of a non-infarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure [class of recommendation (COR): IIb; level of evidence (LOE): B-randomized]" The previous [2013] recommendation was that "PCI should not be performed in a non-infarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable (COR: III-harm; LOE: B) (1,16).

The COR represents the strength of recommendation and the LOE indicates the quality of scientific evidence. There are four levels of COR (I-strong, benefit >>> risk; IIa-moderate, benefit >> risk; IIb-weak, benefit ≥ risk; III-no benefit, benefit = risk; and III-harm, risk > benefit) and five levels of LOE (A, B-randomized, B-nonrandomized, C-limited data, and C-expert opinion) in descending order.

The ACC and AHA use both COR and LOE to articulate the recommendations (17). Therefore, the 2015 Focused Update has upgraded "PCI of a non-infarct artery" from COR III-harm to COR IIb and stated specifically that "PCI of a non-infarct artery may be considered" either at the time of primary PCI or as a staged procedure. Furthermore, the 2015 Focused Update has recommended that "Routine aspiration thrombectomy before primary PCI is not useful (COR: III-no benefit; LOE: A)" and "The usefulness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI is not well established (COR: IIb; LOE: C-limited data)" from previous 2011/2013 Recommendations' "Manual aspiration thrombectomy is reasonable for patients undergoing primary PCI (COR: IIa; LOE: B)." In other words, the 2015 Focused Update has downgraded "use of manual aspiration thrombectomy" from COR IIa to COR III-no benefit and concluded that "routine use of manual aspiration thrombectomy is now not recommended". Moreover, the 2015 Focused Update has downgraded "selective and bailout usefulness of manual aspiration thrombectomy" to COR IIb-weak (not well established).

How to treat patients with STEMI and multivessel disease?

The newest recommendations of the 2015 Focused Update reflect the existing controversies and evolving knowledge of the optimal strategy to treat patients with STEMI and multivessel disease. Currently, there are three approaches to PCI in STEMI patients with multivessel disease: (I) culprit vessel–only PCI; (II) multivessel PCI at the time of primary PCI; and (III) culprit vessel-only primary PCI and planned, staged PCI of nonculprit vessels. The approach of multivessel PCI at the time of primary PCI was once thought to make intuitive sense in the hope of improving hemodynamic stability and clinical outcomes. Unexpectedly, findings from observational studies using cardiac registries and randomized controlled trials suggested that patients who underwent immediate multivessel PCI experienced worse outcomes relative to patients who underwent culprit vessel-only PCI (18-20). Therefore, the 2013 practice guidelines recommended against PCI of nonculprit vessels at the time of primary PCI in hemodynamically stable STEMI patients largely due to safety concerns (16). Recently, four randomized trials of PCI strategies (i.e., PRAMI, CvLPRIT, DANAMI 3 PRIMULTI, and PRAGUE-13) provided new data suggesting that multivessel PCI, either at the time of primary PCI or as a planned, staged procedure, might be safe and beneficial in hemodynamically stable STEMI patients with multivessel disease (1). Based on these results, the 2015 Focused Update made corresponding recommendations by upgrading nonculprit vessel PCI from COR III-harm to COR IIb.

It is worth noting that these four randomized trials differed from each other with respect to study design and patient populations. PRAMI was a multicenter trial with 465 STEMI patients enrolled in the United Kingdom to compare outcomes between multivessel primary PCI of all stenoses ≥50% and culprit vessel-only PCI (patients randomized in a 1:1 fashion) (10). CvLPRIT was a multicenter trial including 296 STEMI patients randomized in a 1:1 fashion to evaluate multivessel PCI of all stenoses >70% during the index hospitalization (72% underwent multivessel primary PCI) versus culprit vessel-only PCI (9). DANAMI 3 PRIMULTI was a Danish trial which enrolled 627 STEMI patients with multivessel disease to assess angiography and fractional flow reserve (FFR)-guided multivessel staged PCI before discharge versus culprit vessel-only PCI (8). PRAGUE-13 was a multicenter randomized trial including 214 STEMI patients from Czech Republic to compare outcomes between patients undergoing staged PCI (3 to 40 days after the index procedure) of ≥70% diameter stenosis nonculprit vessels and patients receiving culprit vessel-only PCI (11). Three trials, namely, PRAMI, CvLPRIT, and DANAMI 3 PRIMULTI, showed that STEMI patients with multivessel disease treated with a strategy of multivessel PCI (either at the time of primary PCI or as a planned staged procedure) had significantly better outcomes. However, PRAGUE-13 trial failed to detect significant differences in outcomes between the two PCI approaches over a follow-up period of 38 months. Also, the reported benefits of staged multivessel PCI from DANAMI 3 PRIMULTI trial echoed the findings from a previous more comprehensive observational study using all-inclusive audited New York State cardiac registries (18). In that population-based study, Hannan *et al*. demonstrated that STEMI patients treated with staged multivessel PCI within 60 days after the index procedure were associated with better 1-year outcomes relative to patients treated with culprit vessel-only PCI.

Several challenging issues on this topic still remain open for researchers. First, studies are needed to determine whether multivessel PCI is better than culprit vessel only PCI regardless of the vessels and degree of stenosis of the nonculprit vessels. Second, how to appropriately evaluate

the lesion severity of nonculprit vessels during primary PCI is uncertain as diagnostic testing such as FFR has practical difficulties at the time of primary PCI (21). Third, the optimal timing of non-culprit vessel PCI (i.e., during primary PCI *vs.* staged PCI during index admission *vs.* staged PCI within certain days of the index admission) remains unclear in contemporary practice because of the limited scope and small sample size of the four recent clinical trials. Fourth, the use of composite outcome measures (e.g., a composite of cardiac-cause mortality, or non-fatal myocardial infarction, or refractory angina) in existing literature does not reflect the relevant importance of each outcome measure. Larger well-designed RCTs would be helpful as there would be no need for composite outcome measures. Another alternative would be to focus on those composite measures that are restricted to the most important and relevant outcomes to see if the findings are robust. Fifth, conflicting findings from different types of studies (randomized clinical trials vs large observational studies using registries) with different patient populations and variable definitions exist and interpreting and aggregating those results is very challenging. Thus, we believe that larger well-designed randomized controlled trials along with observational studies using high-quality cardiac registries are needed to confirm results from the four recent clinical trials and clarify which patient subgroups would benefit most from different multivessel PCI strategies.

How to evaluate aspiration thrombectomy?

The newest recommendations of the 2015 Focused Update downgrade routine aspiration thrombectomy to a Class III recommendation and conclude that routine use of manual aspiration thrombectomy is now not recommended (1). These recommendations were made based on findings from three recent randomized clinical trials, namely, Intracoronary Abciximab and Aspiration Thrombectomy in Patients With Large Anterior Myocardial Infarction (INFUSE-AMI) trial, Thrombus Aspiration During ST-Segment Elevation Myocardial Infarction (TASTE) trial, and Trial of Routine Aspiration Thrombectomy With PCI Versus PCI Alone in Patients With STEMI) (TOTAL) (12-15). Previously, aspiration thrombectomy was considered to be an intuitively valid strategy and a relatively simple technique to reduce distal embolization. Findings from an earlier large single-center clinical trial (n=1,071), Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial, suggested that compared with patients receiving PCI alone, patients receiving adjunctive aspiration thrombectomy had better 1-year outcomes (6). As a result, adjunctive aspiration thrombectomy became rapidly deployed in practice for patients undergoing primary PCI. However, the recent INFUSE-AMI trial failed to demonstrate any significant benefit in terms of infarct size reduction by aspirational thrombectomy before primary PCI (12). Similarly, the TASTE trial with a much larger sample size (n=7,244) and the TOTAL trial with even more patients (n=10,732) both failed to detect significant difference with regard to clinical outcomes between the group of adjunctive aspirational thrombectomy and the group of primary PCI only (13-15). The TOTAL trial and a subsequent meta-analysis study even reported that patients in aspiration thrombectomy treatment group experienced a slightly increased risk of stroke (15,22). The findings from these three recent randomized controlled trials were consistent with results from several earlier studies (23,24). Moreover, subgroup analyses from the two largest trails (TASTE and the TOTAL) suggested that there was no relative benefit from routine aspiration thrombectomy before primary PCI in STEMI patients who had increased thrombus burden, or initial Thrombolysis in Myocardial Infarction (TIMI) flow grade 0–1, or left anterior descending artery/anterior infarction (13,15). On the basis of these findings, routine aspiration thrombectomy has been downgraded from a prior COR IIa to current COR III-no benefit in the 2015 Focused Update. Additionally, the 2015 Focused Update states that "the usefulness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI is not well established" as the evidence-base to inform the use of such strategies is recognized as insufficient.

The rise and fall of routine aspirational thrombectomy in treating STEMI patients is an excellent example of using newer and better-quality evidence to guide real practice (5). Although there were differences in study design and patient populations across the three recent clinical trials, the negative findings from all of them suggest that initial exuberance about aspirational thrombectomy might not translate into benefits in real-world settings. The two largest trials (TASTE and TOTAL) on this topic also underscore the important role of large and rigorous randomized controlled trials in addressing challenging research questions. At the same time, observational studies using all-inclusive high-quality registries should be considered to provide comprehensive and useful evidence

due to their comparative advantages over randomized clinical trials (larger sample sizes, more diverse patient populations, fewer exclusion) (25). This may be particularly important to fill the knowledge gap of the effectiveness of selective and bailout aspiration thrombectomy in patients undergoing primary PCI.

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Footnote

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