

Format for ANSWERING REVIEWERS



June 20, 2014

Dear Editors (Giuseppe De Luca MD, PhD; Jian-Ju Li MD, PhD and Nathan D. Wong MD, PhD);

Please find enclosed the edited manuscript in Word format (file name: 10957-review.doc).

Title: Does manual thrombus aspiration help optimize stent implantation in ST-segment elevation myocardial infarction?

Author: Diego Fernández-Rodríguez, MD; Luis Alvarez-Contreras, MD; Victoria Martín-Yuste, MD, PhD; Salvatore Brugaletta, MD, PhD; Ignacio Ferreira, MD, PhD; Marta De Antonio, MD; Montserrat Cardona, MD; Vicens Martí, MD; Juan García-Picart, MD; Manel Sabaté, MD, PhD.

Name of Journal: World Journal of Cardiology

ESPS Manuscript NO: 10957

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated. We have also included the Comment Sections (1 *Background*; 2 *Research frontiers*; 3 *Related publications*; 4 *Innovations and breakthroughs*; 5 *Applications*; 6 *Terminology*; 7 *Peer review*)

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer #00225343:

Excellent.

We thank the reviewer his/her comment about our work.

(2) Reviewer #02745062:

In this study, Diego et al reported that the thrombus aspiration therapy in patients with AMI were associated with high procedure success and contributed to optimize the implantation of stents. As a non-randomized, prospective registry study, it provides us some new insights about the use of thrombus aspiration in the real world. Some concern needs to be further clarify before it merit to publication.

We thank the reviewer for the suggestions, which allows us to improve our manuscript. We have modified the paper according to reviewer's comments.

1. The authors need clarify the basis of thrombus aspiration use in their center.

According to the reviewer, we have clarified the use of thrombus aspiration in our institution.

Procedure

Manual TA; using the 6-French Pronto V3® aspiration catheter (Vascular Solutions Inc, Minneapolis, MN) and the 6-French Export® aspiration catheter (Medtronic, Minneapolis, MN), was performed according to the operator's choice; and patients were thereafter classified in TA group and non-thrombus aspiration (NTA) group.

Manual TA technique was performed as follows. The aspiration was started 2-centimetres before the culprit lesion and the aspiration catheter was advanced very slowly, crossing the lesion with continuous aspiration. The catheter was removed under aspiration even into the guiding catheter, with generous backflow after retrieving the thrombectomy device. At least two or three passages were performed. Manual TA was especially considered in case of high thrombus burden and initial slow TIMI flow. (Page 5, paragraph 6 of the revised paper).

2. How to explain the relative low rate of multivessel disease in TA group, whether the factor was related to TA use by physician decision?

One of the limitations of our study is its observational nature. Because the condition of non-randomized study, there were differences in clinical and angiographic baseline characteristics (including the presence of a low rate of multivessel disease in patients who underwent manual TA) leading to a worse risk profile in conventional PCI group compared with manual TA group. Nevertheless, a multivariate analysis was performed in order to exclude confounding factors in primary end-point (angiographic success).

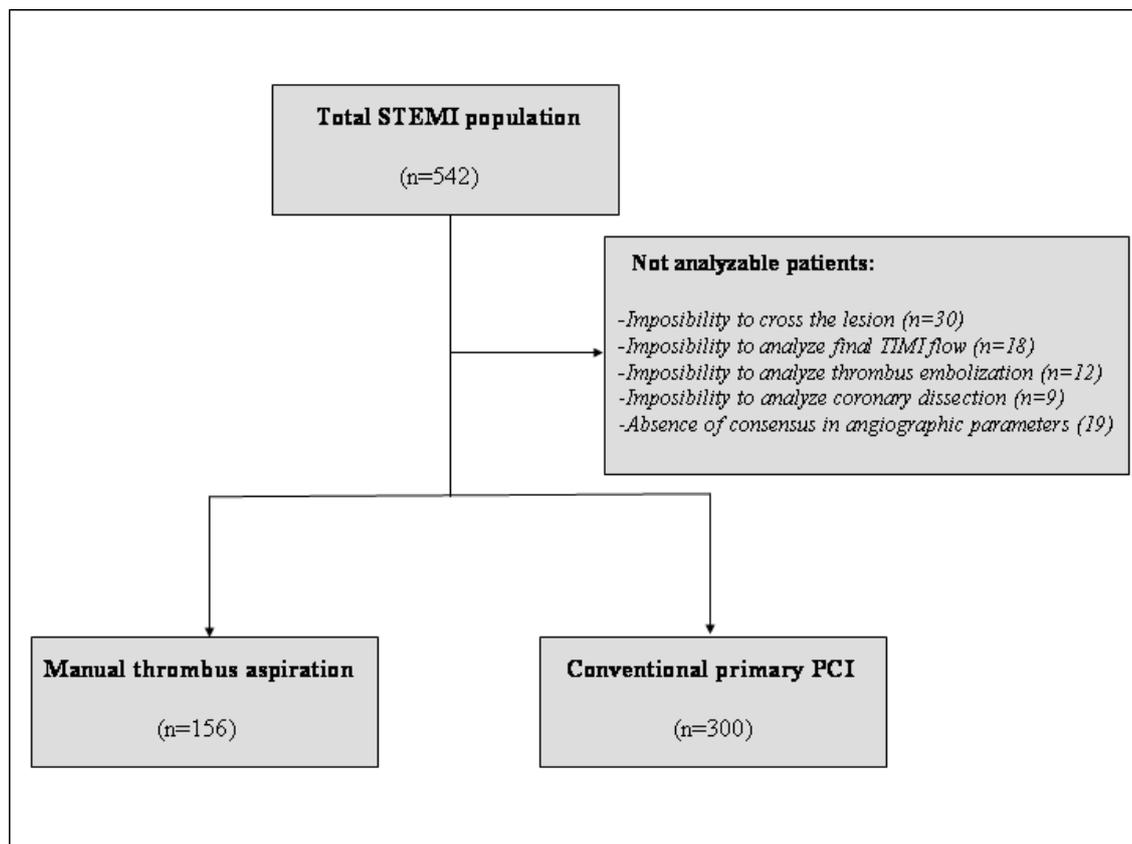
Furthermore, the condition of prospective and non-randomized registry was also highlighted in the limitation section of our study, explaining that differences in baseline clinical and angiographic characteristics may have introduced confounding factors and bias into the analysis

3. For 56 cases who were not subjected to angiographic analysis, what is the detailed reason?

Angiographic analysis was the key point of our study. Both the primary endpoint (angiographic success) as several of the secondary endpoints of the study were related to angiographic parameters. In order to perform an angiographic analysis of high quality, this was done by consensus of two independent experienced interventional cardiologists.

In 37 of the 56 patients, the evaluators were unable to assess comprehensively angiographic aspects as the final TIMI flow, thrombus embolization and coronary dissection. In the remaining 19 patients, the independent evaluators did not reach a consensus on angiographic parameters.

To detail the specific causes of impossibility in angiographic analysis, we have modified the study flow-chart (Page 15, Figure 1 of the revised paper).



4. In multivariable logistic regression, how to explain the GPIIb/IIIa inhibitors was associated to the lower angiographic success. How many patients taken GPIIb/IIIa inhibitor before angiography?

We agree with the reviewer that it is not plausible that the use of I Ib/IIIa inhibitors is associated with lower angiographic success. To clarify the manuscript, if the reviewer agrees, we would like to eliminate the use of I Ib/IIIa inhibitors in Table 3 (Multivariate analysis of angiographic success).

Table 3. Multivariate analysis of angiographic success. (Page 20, Table 3 of the revised paper).

	HR (95% CI)	p
Thrombus aspiration	2.3 (1.2-4.3)	0.007
Primary PCI	4.4 (2.1-9)	<0.001
Active smoking	1.76 (0.9-3.4)	0.093
Age	1.031 (1.001-1.063)	0.044
GP I Ib/IIIa inhibitors	0.52 (0.27-0.98)	0.044
Initial TIMI flow=0	0.46 (0.25-0.84)	0.012

The glycoprotein I Ib/IIIa inhibitors are used in our institution, as bailout therapy, in case of significant thrombus, slow or non-reflow of thrombotic complications. For this reason, any patient is referred for primary PCI under pre-treatment with I Ib/IIIa inhibitors. To clarify this point, we have also described in the text the conditions of use of I Ib/IIIa in our institution.

Procedure

Patients treated with primary PCI were pretreated with aspirin (300 mg), clopidogrel loading dose (300 mg) and unfractionated heparin adjusted to weight. The use of glycoprotein (GP) I Ib/IIIa inhibitors was left at the discretion of the operators “in case of significant thrombus, slow or non-reflow of thrombotic complications”.

(Page 5, paragraph 5 of the revised paper).

(3) **Reviewer #02639698:**

The present investigation was aimed at evaluating the impact of TA on procedural outcomes in a real-world STEMI registry. In their series, TA was performed in the 34%. TA was more often used in primary PCI, in presence of initial TIMI flow <3, and with concomitant use of GP IIb/IIIa inhibitors in comparison with NTA group. According to the results of the present investigation, the use of TA resulted in more efficient procedure leading to the implantation of less number of stents per lesion of shorter lengths and larger sizes.

We thank the reviewer for his/her suggestions. We have modified the manuscript according to reviewer's comments.

1. We suggest that recent papers on this topic should be cited and discussed (Kumbhani et al Catheter Cardiovasc Intervent 2014; Ahn et al Yonsei Med J 2014, Jolly et al Am Heart J 2014, In particular, controversies on the clinical impact of TA should be more extensively discussed.

According to the reviewer, we have cited and discussed the papers of Kumbhani, Ahn and Jolly and expanded the "Introduction", "Optimization of angiographic outcomes and stent implantation by manual TA in real-world" and "Clinical outcomes of thrombus aspiration in real-world" sections.

The randomized clinical trial (RCT) TAPAS, in particular, showed that manual thrombus aspiration (TA) improved myocardial reperfusion and reduced mortality in STEMI patients at 1-year follow-up^{5,6}. These results, confirmed by other studies⁷⁻¹⁰, including a meta-analysis¹¹ of 11,321 patients from 20 RCT showing lower rates of late mortality, reinfarction and stent thrombosis in patients underwent manual TA compared with conventional primary PCI, led to a recommendation class IIa for manual TA in patients undergoing primary PCI for STEMI¹². Nevertheless, the use of the thrombectomy devices is still controversial and not routine in STEMI patients,

especially because some studies have shown no impact on clinical outcome¹³⁻²⁰, such as the TASTE trial²¹ (Page 4, paragraph 3 of the revised paper).

According to clinical trials and real-world registries, our work confirms that manual TA is more often used in the presence of high thrombus burden, such as in patients with initial low TIMI flow (0-1) or primary PCI indication. This registry confirms as well that use of TA achieves better angiographic results than conventional PCI, with greater reduction in thrombus burden and higher rate of final TIMI flow 3. Of note is the recent article by Ahn et al. which showed that the addition of IIb/IIIa inhibitors (Abciximab) to manual TA improves the index of microcirculatory resistance and the microvascular obstruction assessed by cardiac magnetic resonance. This leads us to hypothesize that the optimal strategy to optimize myocardial perfusion would be the synergistic use of these two therapeutic options. (Page 11, paragraph 4 of the revised paper).

“This interesting controversy will continue until the publication of the results of the TOTAL trial³³. The TOTAL trial is a multicenter, prospective, open, international, randomized trial with blinded assessment of outcomes which will recruit 10,700 STEMI patients to compare routine manual TA with the Export aspiration catheter vs. conventional primary PCI alone. The primary outcome will be the composite of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or new or worsening New York Heart Association class IV heart failure up to 180 days”.

(Page 13, paragraph 3 of the revised paper).

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Cardiology*.

Sincerely yours,

A handwritten signature in black ink, enclosed in a rectangular box. The signature is cursive and appears to read 'Diego'. It features a large, stylized 'D' at the beginning, followed by 'iego', and a long horizontal line extending to the right.

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