

# Manual Thrombectomy in Myocardial Infarction: Aspiring for Better

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Advances in stent technology, procedural technique, and interventional processes of care have contributed to step-wise improvement in outcomes after primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).<sup>1</sup> Beyond early restoration of epicardial blood flow, limiting distal embolization and preserving micro-circulatory integrity have been major goals of recent adjunctive device development. The introduction of mechanical thrombectomy devices showed considerable initial promise in meeting these standards. An upfront strategy of thrombus aspiration appeared to facilitate certain aspects of stent deployment by allowing for more-optimal visualization of the culprit lesion, increasing rates of direct stenting, and minimizing postdilatation.<sup>2</sup> These technical advantages were coupled with improvement in surrogate markers of myocardial reperfusion and ventricular function with manual thrombectomy.<sup>3</sup> However, despite its strong theoretical and intuitive basis for incremental value, results from pivotal trials and “real-world” registries of manual thrombectomy have not consistently demonstrated clinical benefits over standard PCI.

## The TOTALity of Evidence

The rigorous comparison of manual thrombectomy with conventional PCI alone has been the subject of over 20 randomized, controlled clinical trials in the last several years.<sup>4–6</sup> The majority of studies enrolled fewer than 500 STEMI patients with mean age  $\approx$ 60 to 65 years presenting within 6 hours of symptom onset. Most trials evaluated the Export<sup>®</sup> catheter with 1 to 6 months of follow-up.

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Periprocedural thienopyridine dosing, frequency of glycoprotein IIb/IIIa inhibitor utilization, and rates of direct stenting varied considerably across studies.<sup>4–6</sup>

Three landmark trials have shaped the current landscape of our understanding of the risks and benefits of this adjunctive approach. First, TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study), a single-center study, showed lower rates of unfavorable myocardial blush grade with the addition of manual thrombectomy in 1071 patients presenting with STEMI undergoing PCI.<sup>7</sup> Manual thrombectomy reduced the absolute risk of major adverse cardiac events by 2.6% at 30 days and cardiovascular (CV) mortality (CVM) by 3.1% at 1-year follow-up, although these clinical endpoints were not prespecified in TAPAS.<sup>8</sup> Despite this encouraging signal, TASTE (Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia) was subsequently published and reported conflicting results. TASTE was a multicenter, registry-based, randomized trial of 7244 patients with STEMI and failed to show a difference in all-cause mortality at 1 year between the thrombus-aspiration and PCI-only arms (5.3% vs. 5.6%, respectively).<sup>9</sup> Most recently, TOTAL (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI) was an international, multicenter trial representing the largest randomized experience of manual thrombectomy conducted to date (n=10 732).<sup>10</sup> At 180 days, routine manual thrombectomy did not reduce the composite primary endpoint of CV death, recurrent myocardial infarction (RMI), cardiogenic shock, or heart failure with advanced functional class compared with PCI alone.<sup>10</sup>

Interval meta-analyses of available randomized studies of manual thrombectomy, including TAPAS<sup>4,5</sup> and TASTE,<sup>6</sup> suggested that aspiration thrombectomy was associated with an overall reduction in major adverse cardiac events, all-cause mortality, stent thrombosis, and RMI at 6- to 12-month follow-up. The reasons underlying the discrepancy in pooled historical results, compared with the larger, more-recent clinical trials, are not entirely clear. It is plausible that smaller, regionally conducted manual thrombectomy trials were overly heterogeneous, influencing the findings of pooled analyses. Standard PCI practice has evolved such that faster door-to-balloon times, newer-generation drug-eluting stents,<sup>11,12</sup> better oral antiplatelet therapy, and other contemporary advances may attenuate the added benefit conferred by manual thrombectomy. In fact, a

prospective substudy of 214 patients enrolled in TOTAL showed that pre-stent culprit lesion thrombus burden, independently quantified by optical coherence tomography in blinded fashion, was not significantly reduced by manual thrombectomy compared with conventional PCI.<sup>13</sup>

## Concerning Safety Signal

The procedure itself appears to be generally well tolerated. Early meta-analyses<sup>5,14</sup> revealed a trend toward higher stroke risk with aspiration thrombectomy compared with PCI alone, although overall events were limited in number. Subsequent meta-analyses,<sup>5</sup> TAPAS,<sup>7</sup> and TASTE<sup>9</sup> did not substantiate this excess safety hazard. TOTAL was the first trial to prespecify and adjudicate stroke as a key safety outcome. In this trial, manual thrombectomy increased risk of stroke, compared with conventional PCI, at 30- (0.7% vs. 0.3%) and 180-day follow-up (1.0% vs. 0.5%).<sup>10</sup> The mechanisms driving these cerebrovascular events have not been well defined. Although there is a theoretical risk of stroke secondary to retrograde embolization of aspirated material or entrainment of air after manual thrombectomy, continued stroke hazard between 30 and 180 days observed in TOTAL<sup>10</sup> is not entirely consistent with these hypotheses.

## The Future of Manual Thrombectomy

In this issue of the *Journal of the American Heart Association (JAHA)*, 2 very interesting and informative studies<sup>15,16</sup> aim to clarify the contemporary role of manual thrombectomy in clinical practice. Perhaps, one might hope, manual thrombectomy may require longer-term follow-up to show clinical benefit or may have utility in certain high-risk subgroups.

Data from real-world, unselected patients may help refine any potential benefit of manual thrombectomy. Watanabe et al.<sup>15</sup> report 5-year clinical outcome data from a large, registry-based Japanese observational study. The investigators analyzed 3536 STEMI patients who presented within 12 hours of symptom onset, of whom 63% ultimately underwent PCI with manual thrombectomy. Although mortality was lower in patients who received manual thrombectomy compared with PCI alone, multivariate analyses did not reveal an independent survival benefit of this adjunctive device. Similarly, no risk-adjusted differences were observed in CVM, RMI, stroke, or target-lesion revascularization between the 2 groups.<sup>15</sup> It is possible that the subtle myocardial perfusion changes conferred by upfront manual thrombectomy may require longer-term follow-up beyond 1 year (as reported in definitive trials) to translate into clinical benefit. Robust follow-up was a major strength of the current study<sup>15</sup> with complete information available at 1 and 3 years in over 95% of

patients. Late follow-up, however, did not uncover a clinical benefit of routine manual thrombectomy. Despite including a large cohort of consecutively enrolled PCI patients, cautious interpretation of these observational Japanese data are required given regional variation in PCI practices and newer clinical developments since the 2005–2007 study time frame. Absence of clinical benefit of manual thrombectomy has, however, also been demonstrated across a number of other large, recent observational experiences.<sup>17–20</sup>

The neutral outcome effect in all patients undergoing PCI may mask heterogeneity in particular subgroups. To better characterize this, in the second study, Fröbert et al.<sup>16</sup> report 1-year outcomes of manual thrombectomy in individual subsets of the TASTE study. The investigators found no heterogeneity in the efficacy of manual thrombectomy based on aspiration catheter or stent type, direct stenting, or postdilatation.<sup>16</sup> It is possible that certain high-risk subgroups may be excluded from clinical trials, but benefit from manual thrombectomy. However, Watanabe et al. demonstrated that even elderly patients and those presenting in cardiogenic shock do not appear to derive benefit from adjunctive manual thrombectomy.<sup>15</sup>

## The Bottom Line

At this juncture, routine intracoronary manual thrombectomy cannot be recommended in all-comers presenting with STEMI undergoing primary PCI. The current clinical practice guidelines state that manual thrombectomy is “reasonable” for this indication (class IIa; level of evidence B),<sup>1</sup> but this will likely need to be reconsidered given recent robust neutral clinical trial data. There may be a role for manual thrombectomy in specific cases of very large visible thrombus or complications after primary PCI (such as development of occlusive thrombus and degradation of coronary flow), but even this would not be evidence-based practice. The stroke signal is somewhat concerning and requires further investigation. If this hazard is substantiated by more-detailed analyses from TOTAL, then use of manual thrombectomy should be restricted to bail-out indications alone.

The narrative of manual thrombectomy reinforces the enduring necessity for large, definitive, randomized, clinical trials to determine whether interventions that improve surrogate or intermediate endpoints translate into favorable clinical outcomes. Manual thrombectomy has become widely adopted in contemporary clinical practice and is utilized in ≈60% of primary PCI cases.<sup>17–20</sup> Even beyond modifying national and international guidelines, the strong pathophysiological basis and convenience of its use will pose major inherent barriers to curbing the widespread uptake of this costly device that provides no benefit on clinical endpoints from routine use in contemporary practice.

## Disclosures

Dr Bhatt discloses the following relationships: advisory board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; board of directors: Boston VA Research Institute and Society of Cardiovascular Patient Care; chair: American Heart Association Get With The Guidelines Steering Committee; data monitoring committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute (including for the TOTAL trial); honoraria: American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), and WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor); research funding: Amarin, AstraZeneca, Biotronik, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, St. Jude Medical, and The Medicines Company; trustee: American College of Cardiology; Unfunded Research: FlowCo, PLx Pharma, and Takeda.

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## References

- O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX, Anderson JL, Jacobs AK, Halperin JL, Albert NM, Brindis RG, Creager MA, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Kushner FG, Ohman EM, Stevenson WG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force on Practice G. 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–e425.
- Fernandez-Rodriguez D, Regueiro A, Brugaletta S, Martin-Yuste V, Masotti M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tsepili M, den Heijer P, Bethencourt A, Vazquez N, Serruys PW, Sabate M; EXAMINATION Investigators. Optimization in stent implantation by manual thrombus aspiration in ST-segment-elevation myocardial infarction: findings from the EXAMINATION trial. *Circ Cardiovasc Interv*. 2014;7:294–300.
- Liistro F, Grotti S, Angioli P, Falsini G, Ducci K, Baldassarre S, Sabini A, Brandini R, Capati E, Bolognese L. Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. *Circ Cardiovasc Interv*. 2009;2:376–383.
- Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Bhatt DL. Role of aspiration and mechanical thrombectomy in patients with acute myocardial infarction undergoing primary angioplasty: an updated meta-analysis of randomized trials. *J Am Coll Cardiol*. 2013;62:1409–1418.
- Bavry AA, Kumbhani DJ, Bhatt DL. Role of adjunctive thrombectomy and embolic protection devices in acute myocardial infarction: a comprehensive meta-analysis of randomized trials. *Eur Heart J*. 2008;29:2989–3001.
- Kumbhani DJ, Bavry AA, Desai MY, Bangalore S, Byrne RA, Jneid H, Bhatt DL. Aspiration thrombectomy in patients undergoing primary angioplasty: totality of data to 2013. *Catheter Cardiovasc Interv*. 2014;84:973–977.
- Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. Thrombus

- aspiration during primary percutaneous coronary intervention. *N Engl J Med*. 2008;358:557–567.
- Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, de Smet BJ, van den Heuvel AF, Anthonio RL, Jessurun GA, Tan ES, Suurmeijer AJ, Zijlstra F. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. *Lancet*. 2008;371:1915–1920.
  - Lagerqvist B, Frobert O, Olivecrona GK, Gudnason T, Maeng M, Alstrom P, Andersson J, Calais F, Carlsson J, Collste O, Gotberg M, Hardhammar P, Ioanes D, Kallryd A, Linder R, Lundin A, Odenstedt J, Ormerov E, Puskar V, Todt T, Zellerroth E, Ostlund O, James SK. Outcomes 1 year after thrombus aspiration for myocardial infarction. *N Engl J Med*. 2014;371:1111–1120.
  - Jolly SS, Cairns JA, Yusuf S, Meeks B, Pogue J, Rokoss MJ, Kedev S, Thabane L, Stankovic G, Moreno R, Gershlick A, Chowdhary S, Lavi S, Niemela K, Steg PG, Bernat I, Xu Y, Cantor WJ, Overgaard CB, Naber CK, Cheema AN, Welsh RC, Bertrand OF, Avezum A, Bhindi R, Pancholy S, Rao SV, Natarajan MK, ten Berg JM, Shestakovska O, Gao P, Widimsky P, Dzavik V; TOTAL Investigators. Randomized trial of primary PCI with or without routine manual thrombectomy. *N Engl J Med*. 2015;372:1389–1398.
  - Bhatt DL. EXAMINATION of new drug-eluting stents—top of the class! *Lancet*. 2012;380:1453–1455.
  - Sabate M, Cequier A, Iniguez A, Serra A, Hernandez-Antolin R, Mainar V, Valgimigli M, Tsepili M, den Heijer P, Bethencourt A, Vazquez N, Gomez-Hospital JA, Baz JA, Martin-Yuste V, van Geuns RJ, Alfonso F, Bordes P, Tebaldi M, Masotti M, Silvestro A, Backx B, Brugaletta S, van Es GA, Serruys PW. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet*. 2012;380:1482–1490.
  - Bhindi R, Kajander OA, Jolly SS, Kassam S, Lavi S, Niemela K, Fung A, Cheema AN, Meeks B, Alexopoulos D, Kocka V, Cantor WJ, Kaivosoja TP, Shestakovska O, Gao P, Stankovic G, Dzavik V, Sheth T. Culprit lesion thrombus burden after manual thrombectomy or percutaneous coronary intervention-alone in ST-segment elevation myocardial infarction: the optical coherence tomography sub-study of the TOTAL (Thrombectomy versus PCI ALone) trial. *Eur Heart J*. 2015; doi: <http://dx.doi.org/10.1093/eurheartj/ehv176> [Epub ahead of print].
  - Tamhane UU, Chetcuti S, Hameed I, Grossman PM, Moscucci M, Gurm HS. Safety and efficacy of thrombectomy in patients undergoing primary percutaneous coronary intervention for acute ST elevation MI: a meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2010;10:10.
  - Watanabe H, Shiomi H, Nakatsuma K, Morimoto T, Taniguchi T, Furukawa Y, Nakagawa Y, Horie M, Kimura T. The clinical efficacy of thrombus aspiration on five-year clinical outcomes in patients with ST-segment elevation acute myocardial infarction undergoing percutaneous coronary intervention. *J Am Heart Assoc*. 2015;4:e001962 doi: 10.1161/JAHA.114.001962.
  - Fröbert O, Calais F, James SK, Lagerqvist B. ST-elevation myocardial infarction, thrombus aspiration and different invasive strategies. A TASTE trial substudy. *J Am Heart Assoc*. 2015;4:e001755 doi: 10.1161/JAHA.114.001755.
  - Puymirat E, Aissaoui N, Cottin Y, Vanzetto G, Carrie D, Isaaz K, Valy Y, Tchetché D, Schiele F, Steg PG, Simon T, Danchin N. Effect of coronary thrombus aspiration during primary percutaneous coronary intervention on one-year survival (from the FAST-MI 2010 registry). *Am J Cardiol*. 2014;114:1651–1657.
  - Kilic S, Ottervanger JP, Dambrink JH, Hoorntje JC, Koopmans PC, Gosselink AT, Suryapranata H, van't Hof AW; Zwolle Myocardial Infarction Study Group. The effect of thrombus aspiration during primary percutaneous coronary intervention on clinical outcome in daily clinical practice. *Thromb Haemost*. 2014;111:165–171.
  - Jones DA, Rathod KS, Gallagher S, Jain AK, Kalra SS, Lim P, Crake T, Ozkor M, Rakhit R, Knight CJ, Iqbal MB, Dalby MC, Malik IS, Whitbread M, Mathur A, Redwood S, MacCarthy PA, Weerackody R, Wragg A. Manual thrombus aspiration is not associated with reduced mortality in patients treated with primary percutaneous coronary intervention: an observational study of 10,929 patients with ST-segment elevation myocardial infarction from the London Heart Attack Group. *JACC Cardiovasc Interv*. 2015;8:575–584.
  - Siudak Z, Mielecki W, Dzierwicz A, Rakowski T, Legutko J, Bartus S, Bryniarski KL, Partyka L, Dudek D. No long-term clinical benefit from manual aspiration thrombectomy in ST-elevation myocardial infarction patients. Data from NRDES registry. *Catheter Cardiovasc Interv*. 2015;85:E16–E22.

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