

# Thrombus Removal in STEMI Patients With Large Thrombus Burden

A look at the current data on the optimum treatment for this high-risk patient subset.

BY CAROL LINDEKE, MPH

The recently reported early results of the TASTE trial<sup>1</sup> have raised some questions about the current practice guidance recommendations<sup>\*2,3</sup> regarding the viability of manual thrombus aspiration (MA) as a thrombectomy device in ST-segment elevation myocardial infarction (STEMI) patients.<sup>4-7</sup>

## CONTEMPORARY ASPIRATION DATA

The TASTE trial was designed to confirm the findings of an earlier randomized controlled trial (RCT)—the TAPAS trial.<sup>8,9</sup> TAPAS met the primary endpoint in achieving a significantly higher rate of myocardial blush grade 0 to 1 with MA over primary percutaneous coronary intervention (PCI). In addition, TAPAS reported a significant reduction in the 1-year mortality and major adverse cardiac event (MACE) rates.

TASTE was a registry-based RCT with more than 6,000 patients enrolled and is the largest trial to date evaluating outcomes of MA in STEMI patients. The TASTE trial failed to demonstrate that routine adjunctive use of MA significantly reduced the rate of 30-day mortality over patients treated with PCI (MA, 2.8%; PCI, 3%;  $P = .63$ ). A trend toward lower rates of recurrent MI ( $P = .09$ ) and stent thrombosis ( $P = .06$ ) in the MA arm was observed.

A meta-analysis evaluating the outcomes for adjunctive MA versus primary PCI was recently updated to include the results of the TASTE trial.<sup>10</sup> The experience of 11,321 patients in the 20 RCTs considered in this analysis continues to support current guidance recommendations.\*

The 6- to 12-month mortality data, to which TASTE contributes minimally, were significantly reduced in patients

treated with adjunctive MA (3.3%) over that observed for patients treated with primary PCI (5.2%;  $P = .016$ ).

The composite MACE endpoint and its components (defined as reinfarction, stent thrombosis, and target vessel revascularization [TVR]) continue to support the value of adjunctive thrombus removal over primary PCI (MACE: 5.6% vs 6.9%,  $P = .006$ ; reinfarction: 0.8% vs 1.3%,  $P = .017$ ; stent thrombosis: 0.4% vs 0.8%,  $P = .021$ ; TVR: 3.2% vs 3.9%,  $P = .06$ ).

The authors noted that the clinical benefit with aspiration thrombectomy may be dependent on the duration of follow-up, consistent with the findings of the TAPAS trial. The upcoming TASTE2 results and the results of the large TOTAL trial are anticipated to provide data on longer follow-up after treatment.

A difference in the patient population of the TASTE trial may provide an explanation for the differing results between it and the previous MA studies. More than half of the patients (56%) included in the TASTE trial had a TIMI thrombus grade<sup>†11,12</sup> of  $\geq 3$ .<sup>†</sup> The presence of angiographically visible thrombus has been shown to be associated with failure to achieve final TIMI 3 flow, reduced post-PCI myocardial blush, as well as distal embolization,<sup>12</sup> resulting in an increased risk of MACE events. In an editorial response to recently published data from the DEFER-STEMI trial, David Antonucci, MD, states that manual aspiration is ineffective in retrieving macroscopic debris from approximately one-third of patients<sup>13</sup> and that OCT shows a large, residual thrombus burden in a majority of patients (see Figures 3A and 3B in sidebar).<sup>14</sup>

\*Current practice guidelines for the management of acute myocardial infarction in STEMI patients recommend that MA “should be considered”<sup>2</sup> or “is reasonable”<sup>3</sup> for patients undergoing PCI.

<sup>†</sup> TIMI thrombus grades<sup>†9</sup>—grade 0: no angiographic characteristics of thrombus present; grade 1: possible thrombus present; grade 2: definite thrombus, with largest dimension  $\leq$  half the vessel diameter; grade 3: definite thrombus, with largest linear dimension  $>$  half but  $<$  2 X vessel diameter; grade 4: definite thrombus, with the largest dimension  $\geq$  2 vessel diameters; grade 5: total occlusion.

Sponsored by Bayer HealthCare

## MANUAL ASPIRATION



Figure 1A. In a manual aspiration device, the maximum negative pressure is created at the syringe, but that is quickly reduced by frictional forces in the tubing so that at the catheter tip, only a fraction of the negative pressure remains.

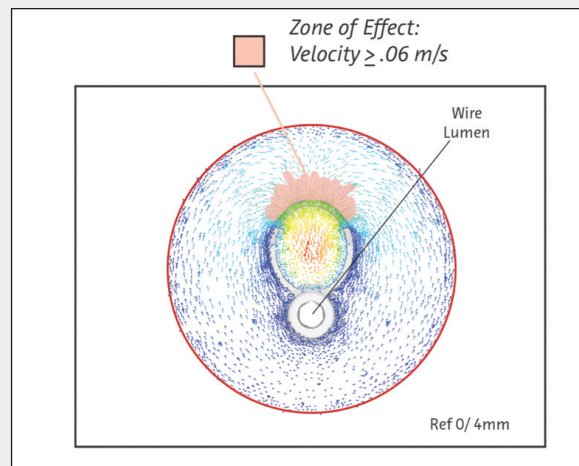


Figure 2A. As illustrated in this computational fluid dynamics (CFD) analysis, due to the much lower inter-catheter negative pressure, a manual aspiration device has a much smaller zone of effect around the catheter tip, allowing it to affect only the thrombus in close proximity to the catheter opening.

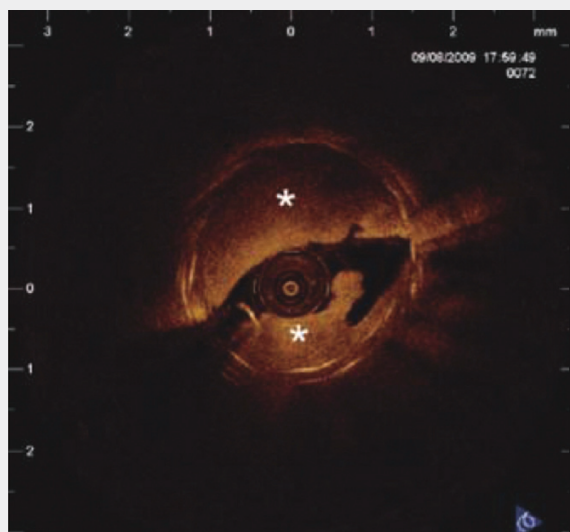


Figure 3A. After treating a coronary artery with manual aspiration, optical coherence tomographic (OCT) imaging shows a considerable remaining thrombus burden (asterisks).

## ANGIOJET THROMBECTOMY



Figure 1B. In the AngioJet Thrombectomy System, an entirely unique technology utilizes high-pressure water jets and the Bernoulli effect to create maximum negative pressure at the catheter tip.

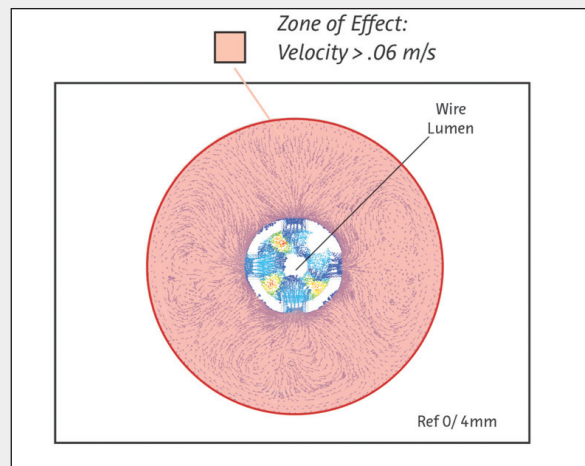


Figure 2B. An AngioJet Thrombectomy Catheter, with a much greater negative pressure at the tip, uses multiple inflow and outflow windows to create fluid flow within the vessel, resulting in a much larger zone of effect, drawing in and capturing the thrombus from a wider area of the vessel being treated.

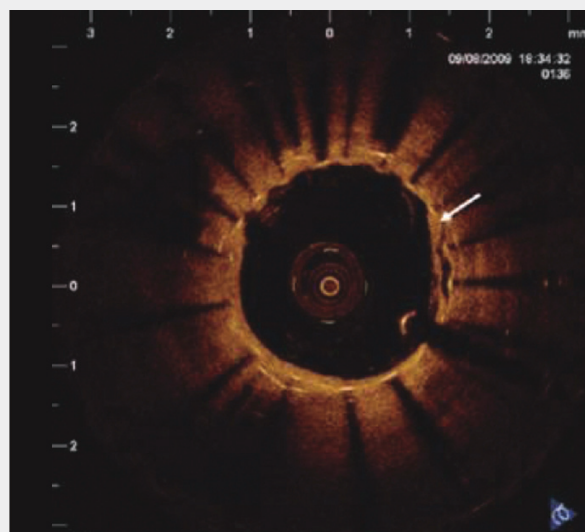


Figure 3B. In the same vessel, after treating with AngioJet Thrombectomy, OCT imaging confirms a significant reduction of LTB with only minimal residual mural thrombus (white arrow).

## BROADER VIEW OF THROMBECTOMY DATA

A recent meta-analysis<sup>15</sup> comparing the literature on MA versus mechanical thrombectomy suggests that the benefits of mechanical thrombectomy over MA are seen in patients with a large thrombus burden (LTB). Analysis of only trials predominately composed of patients with LTB indicates that mechanical thrombectomy resulted in a significant reduction in recurrent MI ( $P < .001$ ) and stroke ( $P = .04$ ) over MA.<sup>\*</sup> In patients with a small thrombus burden, MA appears to effectively remove sufficient thrombus for clinical benefit. However, in patients with LTB, MA may not remove enough thrombus to affect vessel revascularization or revascularization to micro-/macrovasculatures; or possibly, the passage of the manual aspiration device may result in microembolization. Either mechanism could result in an increased risk of adverse coronary events.

Although the benefit of adjunctive MA over primary PCI in STEMI patients is generally accepted,<sup>2,3</sup> the evidence supporting AngioJet (AJ) thrombectomy is not as clear.<sup>16</sup> To date, there have been four RCTs evaluating AJ thrombectomy—AiMI, JETSTENT, MUSTELA, and SMART PCI. The AiMI trial<sup>17</sup> randomized 480 patients (all-comers) to AJ thrombectomy or primary PCI. With a primary endpoint of infarct size, routine use of AJ thrombectomy failed to show benefit over PCI alone.

The subsequent JETSTENT trial,<sup>18</sup> which randomized 501 STEMI patients to AJ thrombectomy or direct stenting (PCI), included only patients with TIMI thrombus grades<sup>8,9</sup> of  $\geq 3$  (LTB). The study required that either both of the coprimary endpoints of ST-segment reduction (STR) at 30-minutes and 1-month infarct size achieve an  $\alpha < 0.05$  or one of the primary endpoints meet an  $\alpha < 0.025$  level for study success. Although the STR for the AJ thrombectomy group was significantly higher than that of the control/direct stenting arm ( $P = .043$ ), the infarct size was comparable between treatment groups; therefore, the JETSTENT trial failed to meet its defined statistical requirements for success. However, the significance of clinical outcomes in JETSTENT is supported by multivariate analysis, which showed randomization to AJ thrombectomy to be an independent predictor of both improved STR and MACE rates. In addition, STR was strongly associated with both mortality and MACE. Lower rates of MACE events (driven by lower TVR and mortality) were observed at 30 days (AJ, 3.1%; PCI, 6.9%;  $P = .05$ ). The difference between MACE rates increased further over time through 12 months ( $P = .009$ ).

The MUSTELA trial<sup>19</sup> randomized 208 patients with a LTB (TIMI thrombus grade  $\geq 3$ ) to primary PCI or throm-

bectomy using either MA or the AJ catheter. The thrombectomy group again demonstrated a significantly higher rate of STR over primary PCI (thrombectomy, 57% vs PCI, 37%;  $P = .004$ ), but did not differ with respect to infarct size—the primary study endpoint. Although the study was not powered to compare MA and AJ thrombectomy, a comparison of outcomes of the two thrombectomy devices suggests that AJ thrombectomy was more effective than MA in removing thrombus. There was a higher rate of complete thrombus removal with AJ thrombectomy over MA (AJ, 94.4% vs MA, 78%;  $P = .02$ ). There were no statistical differences in primary or secondary endpoints for the two devices, but there was a trend toward smaller infarct size with the AJ thrombectomy over MA ( $P = .10$ ). However, these improved measures of reperfusion did not translate into differences in MACE events at 1 year.

The SMART PCI<sup>20</sup> trial further substantiates the observations of the JETSTENT and MUSTELA trials. Eighty patients with predominately TIMI thrombus grades of 3 to 5 were randomized to adjunctive AJ thrombectomy or MA, followed by PCI (direct stenting). For the primary endpoint, a reduction in the residual thrombus burden (measured by optical coherence tomography), there was a trend of less residual thrombus in the AJ thrombectomy group ( $P = .083$ ). In addition, surrogate measures of thrombus removal and reperfusion further support this trend:

- Lower residual thrombus grade ( $P = .003$ ).
- Higher rate of STR ( $P = .06$ ).
- TIMI blush grade 3 and TIMI flow grade 3 were more frequently attained ( $P = .039$  and  $.043$ , respectively).
- TVR was less frequent ( $P = .044$ ), which drove a significantly lower 6-month MACE rate ( $P = .034$ ).

## SUMMARY

In patients with smaller thrombus burden, data support the use of MA, which appears to remove sufficient thrombus for clinical benefit. However, when patients with larger thrombus burden are added to the data, as in the TASTE trial, the benefit of routine use of MA is less clear. Although RCTs evaluating AJ thrombectomy do not support the routine use of AJ thrombectomy, there is a consistent trend that AJ thrombectomy effectively removes thrombus in STEMI patients with LTB, resulting in improvements in measures of reperfusion and improved late outcomes. Because this is a patient subgroup at greatest risk of adverse cardiac events, consideration of the thrombus burden should be a factor in selecting between manual aspiration and AJ thrombectomy devices for thrombus removal. ■

<sup>\*</sup> No mechanical thrombectomy device is cleared or approved by the US Food and Drug Administration to treat, cure, prevent, mitigate, or diagnose recurrent myocardial infarction or stroke.

Sponsored by Bayer HealthCare

*Carol Lindeke, MPH, is President of Lindeke Research, LLC, and is a consultant to Bayer HealthCare. Ms. Lindeke may be reached at [lindekeresearch@comcast.net](mailto:lindekeresearch@comcast.net).*

1. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369:1587-1597.
2. Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Euro Heart J*. 2012;33:2569-2619.
3. 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. *J Am Coll Cardiol*. 2013;61:e78-140.
4. Byrne RA, Kastrati A. Unmet aspirations—where to now for catheter thrombectomy? *N Engl J Med*. 2013;369:1649-1650.
5. Berry C, Lee M, Ahmed N. Thrombus aspiration during myocardial infarction. *N Engl J Med*. 2014;370:674.
6. Parodi G, Migliorini A, Rodriguez AE. Thrombus aspiration during myocardial infarction. *N Engl J Med*. 2014;370:675.
7. Diletti R, Serruys PW. Thrombus aspiration during myocardial infarction. *N Engl J Med*. 2014;370:675.
8. Svilaas T, Vlaar PJ, van der Horst IC, et al. Thrombus aspiration during primary percutaneous coronary intervention. *N Engl J Med*. 2008;358:557-567.
9. Vlaar PJ, Svilaas T, van der Horst IC, et al. 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.
10. Kumbhani DJ, Bavry AA, Desai MY, et al. Aspiration thrombectomy in patients undergoing primary angioplasty:

totality of data to 2013 [published online ahead of print April 30, 2014]. *Cathet Cardiovasc Interv*. doi: 10.1002/ccd.25532.

11. Gibson CM, de Lemos JA, Murphy SA, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation*. 2001;103:2550-2554.
12. Sianos G, Papafakis MI, Daemen J, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. *J Am Coll Cardiol*. 2007;50:573-583.
13. Antonucci A. Put off till tomorrow what you can do today. *J Am Coll Cardiol*. 2014;63:2099-2100.
14. Parodi G, Valenti R, Migliorini A, et al. Comparison of manual thrombus aspiration with rheolytic thrombectomy in acute myocardial infarction. *Circulation Cardiovasc Interv*. 2013;6:224-230.
15. Navarese EP, Tarantini G, Musumeci G, et al. Manual vs mechanical thrombectomy during PCI for STEMI: a comprehensive direct and adjusted indirect meta-analysis of randomized trials. *Am J Cardiovasc Dis*. 2013;3:146-157.
16. Costopoulos C, Gorog DA, Di Mario C, Kukreja N. Use of thrombectomy devices in primary percutaneous coronary intervention: a systematic review and meta-analysis. *Int J Cardiol*. 2013;163:229-241.
17. Ali A, Cox D, Dib N, et al. Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. *J Am Coll Cardiol*. 2006;48:244-252.
18. Migliorini A, Stabile A, Rodriguez AE, et al. Comparison of AngioJet rheolytic thrombectomy before direct infarct artery stenting with direct stenting alone in patients with acute myocardial infarction. The JETSTENT trial. *J Am Coll Cardiol*. 2010;56:1298-1306.
19. De Carlo M, Aquaro GD, Palmieri C, et al. A prospective randomized trial of thrombectomy versus no thrombectomy in patients with ST-segment elevation myocardial infarction and thrombus-rich lesions: MUSTELA (Multidevice Thrombectomy in Acute ST-Segment Elevation Acute Myocardial Infarction) trial. *JACC Cardiovasc Interv*. 2012;5:1223-1230.
20. Parodi G, Valenti R, Migliorini A, et al. Comparison of manual thrombus aspiration with rheolytic thrombectomy in acute myocardial infarction. *Circulation Cardiovasc Interv*. 2013;6:224-230.

#### **General Indications/Contraindications**

AngioJet System peripheral indications include: breaking up and removing thrombus from infra-inguinal peripheral arteries, upper and lower extremity peripheral arteries, upper extremity peripheral veins, iliofemoral, infra-iliac and lower extremity veins, A-V access conduits, and for use with the AngioJet Power Pulse Kit for the control and selective infusion of physician specified fluids, including thrombolytic agents, into the peripheral vascular system. AngioJet System coronary indications include: removing thrombus in the treatment of patients with symptomatic coronary artery or saphenous vein graft lesions prior to balloon angioplasty or stent placement. Do not use in patients: who are contraindicated for intracoronary or endovascular procedures, who cannot tolerate contrast media, and in whom the lesion cannot be accessed with the wire guide.

#### **General Warnings and Precautions**

The System has not been evaluated for treatment of pulmonary embolism in the US and some other countries or for use in the carotid or cerebral vasculature. Some AngioJet devices have not been evaluated for use in coronary vasculature. Operation of the catheter may cause embolization of some thrombus and/or thrombotic particulate debris. Cardiac arrhythmias may occur and cardiac rhythm should be monitored during catheter use and appropriate management employed, if needed. Systemic heparinization is advisable to avoid pericatheterization thrombus and acute rethrombosis. Operation of the System causes transient hemolysis. Large thrombus burdens may result in significant hemoglobinemia, which should be monitored. Consider hydration, as appropriate. Before coronary AngioJet treatment, verify the presence of thrombus because routine use of AngioJet in every STEMI patient, without proper selection for thrombus, has been associated with increased mortality risk. Do not use the system in the coronary vasculature without placing a temporary pacing catheter to support the patient through hemodynamically significant arrhythmias which may occur.

#### **Potential Adverse Events**

Potential adverse events (in alphabetical order), which may be associated with use of the system, are similar to those associated with other interventional procedures and include, but are not limited to, the following: abrupt closure of treated vessel, acute myocardial infarction, acute renal failure, arrhythmias (including VF and VT), bleeding from access site, death, dissection, embolization (proximal or distal), emergent CABG, hematoma, hemolysis, hemorrhage requiring transfusion, hypotension/hypertension, infection at access site, myocardial ischemia, pain, pancreatitis, perforation, pseudoaneurysm, reactions to contrast medium, stroke/CVA, thrombosis/occlusion, total occlusion of treated vessel, vascular aneurysm, vascular spasm, vessel wall or valve damage.

Caution: Federal (US) law restricts this device to sale by or on the order of a physician.

Indications, operating specifications and availability may vary by country. Check with local product representation and country-specific Information for Use for your country.

Bayer, the Bayer Cross and AngioJet may be registered trademarks of Bayer in the US and other countries.

Bayer © 2014 4531-001 06/14