Christian Hamm

1. How does TAPAS TASTE? Thrombus aspiration in daily practice

Percutaneous interventions in acute coronary syndromes are highly effective in reducing mortality. The challenge of such procedures is the intracoronary thrombus burden that is characteristic, particularly in STEMI. Background antithrombotic therapy is efficient in reducing the risk of low flow or no-reflow in our most critical cases. However, pharmacological therapy has limitations and cannot not remove heavy thrombus load completely. Therefore, mechanical aspiration of thrombus seems a reasonable approach. So is this rather crude approach really the answer? While TAPAS says yes, TASTE says no, is there TOTAL confusion now? No, not really; without going into details with respect to study designs and limitations, daily practice can offer us some crucial insights.

As always in life: the truth is usually somewhere in the middle. In many cases, straight forward stenting gives us excellent results, while the mechanical approach often appears too simplistic. From the clinical trial data, it appears to be very clear from current evidence that *routine* use of aspiration is not the answer. Interestingly, this was already acknowledged by operators who frequently perform primary PCI. However, the same clinicians also recognise that removal of thrombus helps in individual cases whereby the patient has a heavy thrombotic burden. While the efficacy of thrombus aspiration remains dependent on patient circumstances, it is reassuring that all study data to date have demonstrated the favourable safety profile of the intervention and that we will do no harm in using it. Therefore, the door has been left open for individual decision making.

Although, I am a strong believer in evidence from randomized controlled trials, I am convinced that we need personalized approaches, particularly when we have our back against the wall in trying to provide optimal care to patients. And this is how many of us interpret the diverging results in our daily practice; we are happy to have these instruments as tools in our arsenal, but we are also relieved that we retain the decision as to when to employ them. Common sense often remains a good guide for clinicians.

In this issue of *Confluence,* Dr Shuvy and Prof. Lotan give a critical overview of all mechanical approaches to remove thrombus. It is good that he reminds us of the limitations of this technique and reminds us not to get carried away – your patient, undergoing primary PCI, wants you to treat him based not only on the best scientific knowledge available but also as an individual. Therefore, at the end of the day, their care depends on your expertise and skills in judging the optimal treatment pathway.

Address for correspondence
Prof. Dr. Christian Hamm,
Kerckhoff-Klinik gGmbH
Herz- und Thoraxzentrum
Benekestrasse 2-8, D-61231
Bad Nauheim
Germany

c.hamm@kerckhoff-klinik.de

DISCLOSURES: CH has no relevant disclosures to declare.

Chaim Lotan

Mony Shuvy

2. Protection from distal embolization and role of aspiration in ACS

Background

Acute coronary syndrome (ACS) is characterized by rupture of an atherosclerotic plaque, which initiates thrombus formation at the site of plaque rupture.[1] Activation of thrombin and the coagulation cascade, and the central role of activated platelets, result in clot formation, which impair blood flow to the peripheral circulation of the coronary vessel.[2] Persistent and complete thrombotic occlusion of a coronary artery results in ST elevation myocardial infarction (STEMI), while incomplete occlusion may cause non-ST elevation myocardial infarction (NSTEMI). Current guidelines recommend a comprehensive approach that combines pharmacological treatment with reperfusion therapy.[3,4]

In this article we provide an overview of pharmacological therapy and revascularization in ACS. We then discuss the role of mechanical intervention and review the data associated with different thrombectomy devices.

Pharmacological therapy

Since the thrombotic burden plays an important role in ACS pathogenesis, most treatment options target the different mechanisms involved in thrombus formation. Therapy needs to include anticoagulant drugs as well as antiplatelet therapy. All ACS patients should receive anticoagulant therapy, with it being started as soon as possible.[3] Such agents include low molecular weight heparin, fondaparinux and in some centres direct thrombin inhibitors such as bivalirudin. Aspirin therapy should be given to all patients with ACS[5,6], and the Guidelines recommend dual antiplatelet therapy with either one of the thienopyridins (clopidogrel or prasugrel) or ticagrelor. These combinations are essential in ACS treatment regimen. Glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) should be considered for patients with a large thrombus burden or in those who are suffering thrombotic complications during PCI.[7]

Revascularization therapy

Coronary reperfusion after STEMI improves outcome; reperfusion can be achieved by fibrinolytic therapy or by percutaneous coronary intervention (PCI). PCI is the preferred strategy, as it provides better coronary perfusion and better clinical outcomes compared with fibrinolytic therapy alone, although it may not be superior in certain circumstances to the pharmaco-invasive strategy. In patients undergoing primary PCI, pharmacological treatment forms the mainstay of treatment in decreasing thrombus burden. However, despite aggressive antithrombotic/antiplatelet therapy, PCI only restores normal (distal, micro-vascular) myocardial perfusion in approximately two thirds of ACS patients.[8] Several risk factors are associated with non-optimal primary PCI results including: age, diabetes, longer time to reperfusion and low ejection fraction.[9]

It is clear that an important feature of the pathology and natural history of ACS is the presence of thrombus; large thrombus burden is related to distal embolization, which causes microvascular obstruction despite adequate epicardial perfusion (no-reflow).[10] The no-reflow phenomenon is in turn related to increased risk of stent thrombosis and mortality.[11] A recent study followed 1,406 patients with STEMI treated by primary PCI and showed that the no-reflow phenomenon is a strong predictor of 5-year mortality. Interestingly, the no-reflow phenomenon was associated with worse prognosis, independent of infarct size.[9] In order to decrease thrombus burden and no-reflow, several interventions have been suggested and are described below.

Mechanical interventions

Mechanical interventions during PCI include proximal and distal protection devices, as well as aspiration devices; all of these are designed to prevent/attenuate the potential harmful effects of the thrombus. Some are deployed at the distal side of the target lesion, such as the distal protection device.

Distal protection devices have failed to show immediate, short-, or intermediate-term benefits of the adjunctive device.[12,13] Further, the DEDICATION (Drug Elution and DIstal proteCtion in Acute

myocardial infarcTION) trial results suggested that routine use of distal protection increased the incidence of stent thrombosis and TLR.[14] Current recommendations support the use of distal protection devices only during PCI in saphenous vein grafts.[3]

Thrombectomy, performed in the initial phase of PCI, is another potential approach to improving reperfusion in patients with STEMI, through mitigation of thrombus effects. Thrombectomy can be carried out using manual thrombus aspiration or mechanical thrombectomy devices. Thrombectomy devices are designed to aspirate thrombus to reduce the risk of embolisation, generally prior to stent deployment.

Active thrombectomy devices include the AngioJet rheolytic thrombectomy system (Possis Medical Inc, Minneapolis, Minn) and the X-Sizer (ev3 Inc, Plymouth, Minn) catheters. The beneficial effects of these devices have been demonstrated in several studies. However, while the devices may improve early markers of reperfusion, they do not improve 30-day post-MI mortality, re-infarction and stroke.[15] These devices should be used only in selected patients with large caliber vessels and heavy thrombus burden, such that their routine use is not supported.[16]

Devices involving manual aspiration have had more favourable results, including a mortality benefit, as demonstrated in the TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarctionS) study[8], a single-centre all-comers study that enrolled 1,071 STEMI patients. It showed that aspiration improved myocardial blush, ST resolution and significantly improved the 1-year mortality. Following the results of this study, the European Society of Cardiology gave a 2A recommendation for routine thrombus aspiration during treatment of STEMI.[3]

However, meta-analyses have since failed to show absolute benefit from routine thrombus aspiration.[15] Furthermore, the recently published INFUSE AMI trial, which enrolled 452 patients with STEMI randomized to thrombus aspiration versus no aspiration, failed to show any advantage of routine aspiration.[17]

Results from the Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial have been published recently. TASTE was a multicentre, prospective, randomized, controlled, open-label trial that evaluated whether thrombus aspiration during primary PCI reduces mortality in patients with STEMI. In total, 7,244 patients from Sweden, Denmark and Iceland were randomly assigned either to conventional PCI or to thrombus aspiration followed by conventional PCI. The mortality rate at 30 days post-procedure was not statistically different between the groups. Similarly, there was no difference between the two groups for secondary endpoints, including risk of MI, stroke and complications related to the treatment. Even high-risk groups such as smokers, patients with diabetes or patients with large clots had similar results with either approach.[18]

At present, there are clearly conflicting efficacy and safety data surrounding mechanical interventions. However, a further large-scale clinical trial – the TOTAL (ThrOmbecTomy with PCI versus PCI Alone) trial – is currently in progress and will provide further valuable evidence in this field. This study will randomize patients to PCI with or without manual aspiration thrombectomy and is designed to enroll 10,700 patients. The primary endpoint of the trial is a composite of cardiovascular death, recurrent MI, cardiogenic shock, or new or worsening New York Heart Association (NYHA) class IV heart failure at 6 months. TOTAL study is due to report in 2014.

Summary

While PCI is the primary treatment for STEMI, the presence of thrombus in the infarct-related vessel is associated with worse outcome due to embolic micro-vascular damage. Several approaches have been developed to improve PCI outcome. The pharmacological approach combines anticoagulation, oral antiplatelet therapies and possibly parenteral glycoprotein IIb/IIIa inhibitors. However, despite aggressive pharmacological therapy, clinical results after PCI in patients with ACS are still not optimal. Aspiration devices in general failed to show benefit, and some of them may even be harmful. While there have been positive data on the use of proximal manual aspiration devices, additional studies are required to define the role of these devices in ACS treatment, hopefully to define the subpopulations that may benefit from such devices.

Address for correspondence
Prof. Chaim Lotan,
Heart Institute
Hadassah Medical Center,
PO Box 12000
Jerusalem 91120
Israel

REFERENCES:

1. Falk E, et al. *Circulation* 1995;92(3):657-71.
2. Fuster V, et al. *New Engl J Med* 1992;326(5):310-8.
3. Task Force on Myocardial Revascularization of the European Society of Cardiology, et al. *Eur Heart J* 2010;31(20):2501-55.
4. Writing Committee M. *Circulation* 2012;126(7):875-910.
5. Lewis HD, et al. *New Engl J Med* 1983;309(7):396-403.
6. Cairns JA, et al. *New Engl J Med* 1985;313(22):1369-75.
7. Hanna EB, et al. *JACC Cardiovascular interventions* 2010;3(12):1209-19.
8. Vlaar PJ, et al. *Lancet* 2008;371(9628):1915-20
9. Ndrepepa G, et al. *J Am Coll Cardiol* 2010;55(21):2383-9.
10. Rezkalla SH and Kloner RA. *Circulation* 2002;105(5):656-62.
11. Cura FA, et al. *Am J Cardiol* 2001;88(2):124-8.
12. Stone GW, et al. *JAMA* 2005;293(9):1063-72.
13. Gick M, et al. *Circulation* 2005;112(10):1462-9.
14. Kaltoft A, et al. *J Am Coll Cardiol* 2010;55(9):867-71.
15. Mongeon FP, et al. *Circ Cardiovasc Interv* 2010;3(1):6-16.
16. Costopoulos C, et al. *Int J Cardiol* 2011;163(3):229-41
17. Stone GW, et al. *JAMA* 2012;307(17):1817-26.
18. Fröbert O, et al. *New Engl J Med* 2013;369:1587-97.

DISCLOSURES: CL is Medical Director of InspireMD Ltd. MS has no relevant disclosures to declare.

Sanjit Jolly

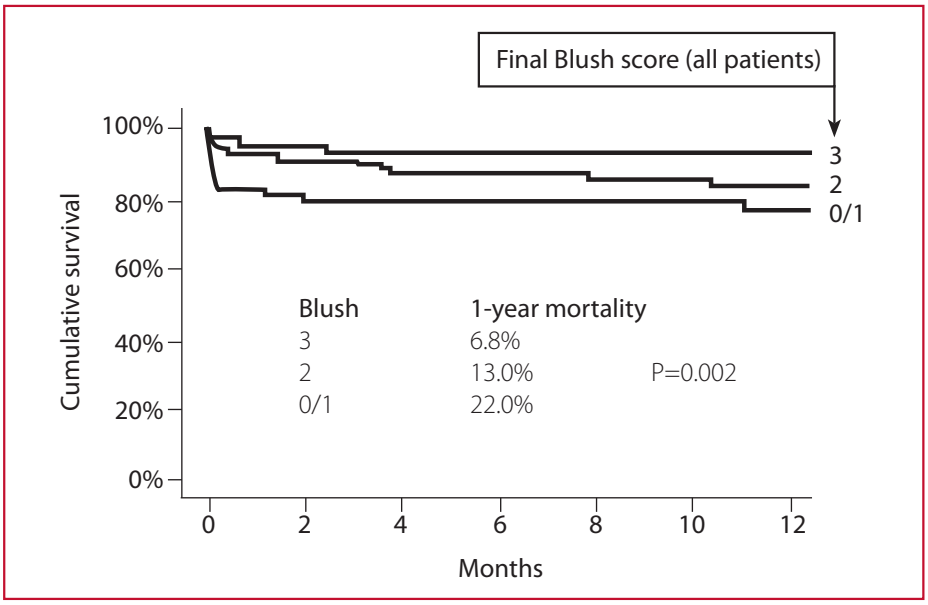
3. Perspectives on thrombectomy on clinical practice

Primary percutaneous coronary intervention (PCI) has become the dominant reperfusion method for ST elevation myocardial infarction (STEMI) across most of Europe and North America. However, a significant limitation of primary PCI is the inability to achieve reperfusion or normalized flow at the microvascular level. Up to a third of patients who have undergone primary PCI have impaired microvascular flow, as measured by myocardial blush grade, and these patients have a marked increased risk of mortality (fig. 1).[1]

Thrombectomy has the potential to reduce distal embolization and improve microvascular perfusion during PCI for STEMI. Meta-analyses of largely small trials have shown that manual thrombectomy improved myocardial blush grade, reduced distal embolization and no reflow.[2,3] Enthusiasm for thrombectomy grew with the results of the TAPAS trial, a single center trial (N=1,071) that showed improvement in the primary outcome of myocardial blush, but more importantly, a reduction in mortality at 1 year.[4,5] However, recently, a much larger randomized trial, the TASTE trial (N=7,244), showed no different in all-cause mortality with manual thrombectomy.[6] An important caveat to the interpretation of the TASTE trial results is that the trial had a much lower than expected mortality and so the trial was not powered to detect modest but important reductions in mortality (i.e., 20–30%). In this issue of *Confluence*, Dr Shuvy and Professor Lotan describe the conflicting data and correctly determine that the efficacy of routine manual thrombectomy in STEMI remains uncertain.

fig. 1

Relationship of Myocardial Blush Grade and Mortality after PPCI[1]



Ongoing Trials: TOTAL trial

The ongoing TOTAL trial (N=10,700) is a randomized trial of routine manual thrombectomy plus PCI vs. PCI alone during primary PCI for STEMI, on a 1:1 basis.[7] The trial is the largest trial to examine this area and will have appropriate power because it is an event driven trial. It is clear with mortality rates of 2–3% that trials utilizing mortality as the primary outcome are impractical because they would require in excess of 30,000 patients. As a result, the TOTAL trial is using a primary outcome that is a composite of cardiovascular death, myocardial infarction, cardiogenic shock or new or worsening NYHA class IV heart failure up to 180 days. The hypothesis of the trial is that thrombectomy i) can prevent distal embolization and no reflow and thus prevent shock, heart failure and death and ii) thrombectomy can reduce thrombus surrounding the stent and thereby reduce risk of stent thrombosis and thus myocardial infarction. The TOTAL trial has recently been revised to be powered to detect a relative risk reduction of 20%, which would put the treatment effect thrombus aspiration on par with other recognized therapies, such as aspirin.[7] The TOTAL trial will provide important new information on the clinical benefit of thrombectomy during STEMI. Results are expected from the trial in 2014.

Implications for Practice

Until further evidence, operators should use clinical judgement to selectively choose cases where thrombectomy may be useful (i.e., large thrombus burden). At the current time, thrombectomy is simply another tool in the PCI toolkit to help operators achieve an optimal angiographic result.

Address for correspondence
Sanjit S. Jolly
Rm. C3-118 DBCSVRI Building
Hamilton General, Hospital
237 Barton St. East, Hamilton
On, Canada, L8L 2X2

Tel: 905-524-2712
Fax: 905-523-8352

sanjit.jolly@phri.ca

REFERENCES:

1. Stone GW, et al. *J Am Coll Cardiol* 2002;39(4):591-7.
2. Mongeon FP, et al. *Circ Cardiovasc Interv*;3(1):6-16.
3. Bavry AA, et al. *Eur Heart J* 2008;29(24):2989-3001.
4. Svilaas T, et al. *N Engl J Med* 2008;358(6):557-67.
5. Vlaar PJ,et al. *Lancet* 2008;371(9628):1915-20.
6. Frobert O, et al. *N Engl J Med* 2013;369(17):1587-97.
7. Jolly SS, et al. *Am Heart J* 2014;167(3):315-321 e1.

DISCLOSURES: SJ has received grant support from Medtronic, Inc., and speaker's honoraria from Astra Zeneca.

Call for case studies!

Case reports should be no more than 1,000 words and submitted to **confluence@axon-com.com**. On the final page of this issue you can find a submission template for case studies. Alternatively, please visit **www.confluencejournal.com** to download the template and submit your case.