Simple aspiration in acute myocardial infarction: too simple to be true?

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This editorial refers to ‘Impact of thrombus aspiration during primary percutaneous coronary intervention on mortality in ST-segment elevation myocardial infarction’†, by A. Noman et al., on page 3054

Primary percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) has contributed to dramatic declines in cardiovascular mortality over the last three decades. Nonetheless, normal myocardial perfusion is not restored in approximately one-third of patients after primary PCI, prompting investigation of novel drugs, technologies, and approaches to improve reperfusion success further. While numerous mechanisms may contribute to reperfusion failure, distal embolization of thrombus and friable atheromatous debris is believed to be ubiquitous during primary PCI, and results in microvascular obstruction. Preventing embolization is therefore intuitive, and theoretically should result in improved reperfusion success as measured angiographically (better epicardial and myocardial blood flow), electrocardiographically (increased ST-segment resolution (STR)), functionally (greater myocardial salvage with reduced infarct size), and clinically (enhanced survival free from heart failure events).

Four types of devices have been developed to prevent embolization during PCI: distal embolic protection catheters; ‘active’ vacuum-type thrombectomy systems; manual aspiration; and microneedle mesh-covered stents (the latter of which is currently undergoing investigation). Despite their innate appeal, in randomized trials distal embolic protection devices and active thrombectomy systems have surprisingly not been shown to be beneficial. In contrast, outcomes with ‘simple’ aspiration systems in which intracoronary thrombus is extracted through a hollow catheter prior to stent implantation have been more favourable, although not uniformly so. In TAPAS, the largest such randomized trial to date, aspiration resulted in modestly better rates of myocardial blush [without improving TIMI (Thrombolysis in Myocardial Infarction) flow or preventing macroscopic coronary thrombo-emboli] and STR, with a trend toward improved 30-day survival which became significant by 1 year.4,5 However, other trials have reported conflicting or negative results, and even meta-analyses cannot agree on whether clinical outcomes with aspiration thrombectomy are improved (greater survival), neutral, or even worsened (increased stroke). Indeed, one meta-analysis determined that adjunctive devices to prevent distal embolization improved STR and survival in single-centre but not multicentre trials, questioning the role of patient selection, bias, and/or operator technique. Regardless, the results of aspiration from single-centre studies cannot be considered generalizable until they are broadly replicated.

Were the results of TAPAS too good to be true? In this regard, it is essential to understand the pitfalls inherent in undersized trials. Given the excellent outcomes currently achieved with primary PCI, very large randomized trials are required to demonstrate incremental reductions in mortality. Powering a trial requires accurate estimates of treatment effects and control event rates. What is a reasonable estimate of a likely treatment effect for aspiration? By markedly improving TIMI flow from 30–55% with fibrinolytic therapy to ~90% (and avoiding intracranial haemorrhage, etc.), primary PCI reduced mortality by a relative 27% (absolute mortality reduction 2.3%) in 23 randomized trials performed 15–20 years ago. It would not be reasonable to expect anything close to this treatment effect with aspiration thrombectomy as an adjunct to primary PCI. However, even assuming a 25% treatment effect, for a trial to have 80% power to reduce 30-day mortality in an all-comers cohort from 3% (as seen in recent large-scale ‘all-comer’ STEMI trials) to 2.25%, 14 794 patients would need to be randomized. If the control event rates are increased to 4% by restricting enrolment to only high-risk patients, or even to 6% by extending follow-up duration, 10 988 and 7204 patients would need to be enrolled, respectively, for adequate power. In the 1071 all-comers TAPAS trial (markedly underpowered by these standards), the 1-year observed rates of mortality were (a surprisingly high) 7.6% with control and 4.7% with aspiration, representing 40% relative and 2.9% absolute reductions. The magnitude of these differences, larger than those observed with primary PCI compared with fibrinolysis, is thus unrealistic, and raises concerns of type I errors.

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error (a spuriously large effect size that would be attenuated in an adequately powered trial). Thus even the largest randomized trial performed to date is woefully underpowered to conclude confidently that aspiration improves survival.

Given the challenge of performing adequately powered mortality trials, infarct size would appear to be the most direct and appropriate surrogate for STEMI studies of aspiration. In the absence of a demonstrable reduction in infarct size (or stent thrombosis, which has not been suggested in any study), it is difficult to hypothesize a mechanism through which thrombectomy might improve survival. In this regard, two early trials using Tc-99m sestamibi imaging failed to demonstrate a reduction in infarct size with aspiration. Moreover, infarct size measured by cardiac enzyme release was not reduced with aspiration in TAPAS, again questioning the mechanism and validity of the marked improvement in survival observed in this single-centre study.

The discordance between improved myocardial reperfusion (enhanced rates of myocardial blush and STR) without infarct size reduction may be explained by the fact that transmural infarction is completed within several hours of coronary occlusion. Thus, in the absence of well-formed coronary collaterals or spontaneous recanalization, infarct artery reperfusion must occur rapidly to salvage myocardium. Furthermore, substantially more myocardium is jeopardized by occlusion of the left anterior descending (LAD) than either the left circumflex or right coronary arteries. By including significant proportions of patients with inferior STEMI and/or late presentation, demonstrating a reduction in infarct size with aspiration in most previous trials may have been (nearly) impossible, assuming such a benefit exists (type II error). Also, clinical benefit should only be expected in patients in whom infarct size is substantially reduced.

The multicentre, randomized INFUSE-AMI trial, which enrolled a highly selected group of 452 patients with STEMI due to proximal or mid LAD occlusion presenting early (median 2.5 h from symptom onset to device), was designed to overcome these limitations. Nonetheless, despite ideal conditions to demonstrate myocardial salvage (early reperfusion in patients with a large amount of myocardium at risk), the powered endpoint of infarct size at 30 days by cardiac magnetic resonance imaging (MRI) was nearly identical in the aspiration and control arms, as were TIMI flow, myocardial blush, STR, and clinical outcomes including mortality and heart failure.

One reason why simple aspiration may be too good to be true is that thrombectomy is inefficient. Optical coherence tomography has demonstrated that substantial amounts of residual thrombus are still present in most patients after aspiration, even if not angiographically evident. Aspiration catheters have relatively small inner diameters, and may fail to retrieve thrombus from diffusely diseased vessels or distally located lesions, or if coronary perfusion pressure is reduced or the thrombus partially organized.

Finally, Noman and colleagues have analysed the outcomes of primary PCI in 2567 STEMI patients at a single centre, 43% of whom were treated with aspiration per physician discretion. As expected, numerous differences in baseline demographic and angiographic characteristics were present between the aspiration and no aspiration groups. In a propensity score- and covariate-adjusted multivariable model, aspiration use was associated with lower mortality at mean follow-up of ∼10 months [hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.19–0.97, P = 0.04]. Aspiration was of benefit only in patients with total ischaemic time <3 h, consistent with the window of opportunity based on the temporal evolution of myocardial necrosis. Do these data tip the scales in favour of aspiration? Unfortunately, the best available statistical models are unable to adjust for differences in unmeasured confounders between non-randomized groups which may affect choice of therapies. For example, numerous large-scale registries have reported substantial mortality reductions with drug-eluting stents (DES) compared with bare metal stents (BMS), whereas randomized trials uniformly found no such benefit. Which finding represents the truth? Examining the hazard curves from propensity-matched groups reveals that most of the apparent survival benefit in the non-randomized studies occurred before 30 days, a time period during which there are no known benefits of DES relative to BMS. This finding probably represents the impact of unmeasured confounders, i.e. DES were selected for less ill patients for reasons not recorded in an administrative database. Comparative effectiveness decisions should not be strongly influenced by non-randomized trials.

Anecdotally, aspiration appears to be useful in selected cases of STEMI with massive amounts of thrombus. For routine use during primary PCI, however, the 2012 European Society of Cardiology (ESC) guidelines reasonably provide a class IIa recommendation with level of evidence B, reflecting uncertainty in clinical benefit of aspiration. Fortunately, two large-scale, ‘simple’ randomized trials each enrolling ≥4000 patients are underway to determine whether survival is indeed improved by use of aspiration thrombectomy during primary PCI in STEMI (ClinicalTrials.gov identifiers NCT01093404 and NCT01149044). Pending these results, there may be little downside to performing aspiration thrombectomy, other than the cost of the device (although the spectre of stroke remains to be disproven). As a scientist who believes in pathophysiology- and evidence-based medicine, I will not be surprised if these definitive trials demonstrate that simple aspiration is too simple and too good to be true. I hope to be proven wrong!

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References


