

# THE RISE AND FALL OF ROUTINE MANUAL THROMBECTOMY FOR ST-ELEVATION MYOCARDIAL INFARCTION

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## ABSTRACT

Manual thrombectomy (MT) with an aspiration catheter is frequently used in primary percutaneous coronary intervention (PPCI) for acute myocardial infarction with ST-segment elevation (STEMI). It is used to reduce the thrombus burden and the risk of no-reflow in the infarct related artery. This article summarises a chronological overview of the available evidence for its routine use in PPCI. An early series of small randomised controlled trials (RCTs) have shown a benefit of PPCI with MT over percutaneous coronary intervention alone, mainly when considering intermediate endpoints reflecting myocardial reperfusion. However, a recent series of large multicentre RCTs failed to corroborate the initial enthusiasm for MT, showing no improved benefit on hard endpoints such as mortality when compared with PPCI without MT. Furthermore, the largest RCT to date raised safety concerns after reporting an increased stroke risk after MT. We review the background, value, and implications of the current evidence before concluding that the routine use of MT in PPCI for STEMI should not be encouraged.

**Keywords:** ST-elevation myocardial infarction (STEMI), manual thrombectomy (MT).

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## INTRODUCTION

Over the last few decades, primary percutaneous coronary intervention (PPCI) has become the preferred treatment to reduce mortality of acute myocardial infarction with ST-segment elevation (STEMI).<sup>1</sup> Despite successful recanalisation of the infarct related artery (IRA) with balloon angioplasty and coronary stents, restoration of coronary flow and myocardial perfusion is often incomplete. This 'no-reflow' phenomenon is associated with larger infarct size and increased mortality.<sup>2</sup> One of the causes of no-reflow is the distal embolisation of a thrombus, which is ubiquitous to STEMI culprit lesions. Manual thrombectomy (MT) with dedicated aspiration catheters was conceived as a strategy to reduce thrombus burden prior to coronary stenting and became part of the standard treatment strategy in PPCI, being used in 30–60% of real-world practice.<sup>3,4</sup> Although the principles of MT are intuitively beneficial, clinical research designed to determine the clinical value of routine MT in PPCI has provided conflicting results. We will

review the available evidence for the use of the MT in PPCI.

## EARLY RANDOMISED CONTROLLED TRIALS

Initial enthusiasm for MT came from a couple of small randomised controlled trials (RCTs) that demonstrated a reduction of immediate no-reflow. The REMEDIA trial randomised 100 consecutive patients presenting with STEMI to either standard percutaneous coronary intervention (PCI) or PCI with manual thrombus aspiration.<sup>5</sup> This study showed that the use of MT was associated with significantly better myocardial blush grade (MBG) and ST-segment resolution (STR). These angiographic and electrocardiographic derived parameters were surrogate indicators of better microvascular reperfusion and less no-reflow. De Luca et al.<sup>6</sup> reported the same observations in 76 consecutive patients with anterior STEMI. These authors also reported a lower incidence of adverse left ventricular (LV) remodelling on transthoracic

echocardiography at 6 months in the MT group. The multicentre PIHRATE, EXPORT, and VAMPIRE trials reported similar improvement in no-reflow in 196, 249, and 355 patients with STEMI, randomised to MT compared with standard PCI alone, respectively.<sup>7-9</sup> However, none of these trials were adequately powered to answer whether MT improved clinical outcomes.

### The TAPAS Study

One example of a larger, high profile RCT reporting the clinical benefit of MT is the TAPAS trial.<sup>10</sup> This single-centre study randomised 1,071 patients to PPCI with MT or to conventional PPCI alone without MT. This study demonstrated better immediate MBG and STR in the MT group that appeared to translate to a clinical benefit of optimised reperfusion: the MT group had significantly less mortality and re-infarction at 30 days and less mortality at 1 year after the index STEMI;<sup>11</sup> however, the TAPAS trial was not powered to address these secondary endpoints. A subsequent meta-analysis of 18 clinical trials randomising patients with STEMI to an adjuvant MT device prior to PCI compared with PCI alone, including TAPAS, concluded that MT was beneficial in reducing mortality compared with PCI alone.<sup>12</sup> Based on these encouraging results, the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) guidelines initially recommended MT as adjunctive therapy during PPCI (Class IIa - level of evidence: A in ESC guidelines, B in ACC/AHA).<sup>13,14</sup>

## RECENT MULTICENTRE RANDOMISED CONTROLLED TRIALS

Whereas the early trial evidence favoured the use of routine MT in PPCI for STEMI, this consensus now needs to be revised after the results of a series of large multicentre RCTs, which demonstrated a neutral effect of MT on hard clinical endpoints. The INFUSE-AMI trial enrolled 452 patients with a large anterior STEMI and compared MT versus no MT and intracoronary (IC) abciximab versus no IC abciximab in a 2x2 factorial design.<sup>15</sup> This trial reported that MT was not effective in reducing major adverse cardiac events (MACE) at 30 days, whereas IC abciximab did reduce MACE. The TASTE trial included 7,244 patients with STEMI undergoing PPCI. These patients were randomly assigned to MT followed by PCI or to PCI only.<sup>16</sup> This multicentre, prospective, open-label, clinical RCT, enrolled patients from the national comprehensive Swedish

Coronary Angiography and Angioplasty Registry (SCAAR). The authors reported no reduction of 30-day mortality with routine thrombus aspiration before PCI as compared with PCI alone. Finally, the multicentre TOTAL trial randomly assigned 10,732 patients with STEMI to undergo PPCI with routine upfront MT versus PPCI alone.<sup>17</sup> This very large study concluded that routine MT, as compared with PCI alone, did not reduce the 180-day risk of cardiovascular death, recurrent myocardial infarction, cardiogenic shock, or New York Heart Association (NYHA) Class IV heart failure.<sup>18</sup> Two recent meta-analyses gathered the data together, including the TASTE and TOTAL data, comprised of over 20,000 patients, and confirmed that routine MT before PPCI was not associated with significant benefit on mortality or re-infarction.<sup>19,20</sup> Meta-regression analysis did not identify any benefit of MT even when combined with glycoprotein IIb/IIIa inhibitors.

### Safety Concerns due to Stroke Risk

The TOTAL trial has yielded concerning results regarding the safety of MT. In light of earlier meta-analyses that identified a potentially higher stroke incidence after MT, TOTAL was the first trial pre-specifying stroke as a safety endpoint.<sup>21</sup> In TOTAL, routine MT was associated with an increased rate of stroke within 30 days of the procedure. The absolute numbers remain small (33/5,033 patients in MT versus 16/5,030 in the PCI alone, hazard ratio [HR] 2.06,  $p=0.02$ ) but require consideration given the lack of benefit of routine MT. The 1-year follow-up results of the TOTAL trial confirmed a higher stroke risk (1.2% versus 0.7%, HR 1.66,  $p=0.015$ ).<sup>18</sup> The mechanistic cause of increased cerebrovascular event risk in MT remains unclear, but could be attributed to embolisation of the thrombus and air after the retrieval of the aspiration catheter. In agreement with this hypothesis, a sub-analysis of the TOTAL trial confirmed that the majority of excess strokes occurred within the first 48 hours of the procedure.<sup>22</sup> The stroke risk between the two groups remained similar beyond the first 48 hours. There was primarily an increase in ischaemic strokes but also in haemorrhagic strokes and strokes of varying severity. After multivariate regression using the traditional risk factors for stroke, MT was determined to be an independent predictor of stroke.

### Does Thrombectomy Remove Thrombus?

The evidence provided by TOTAL is counterintuitive; we speculate that technical issues may prevent

the translation of the mechanical removal of a thrombus from the IRA into an improvement in prognosis after STEMI. It is known that the currently used MT aspiration catheters are often unable to remove a substantial load of thrombus. The TROFI trial compared optical frequency domain imaging (OFDI) in 141 patients randomised to PPCI with or without MT and showed that approximately 80% of the total clot burden quantified by OFDI remains in the IRA following MT.<sup>23</sup> In a sub-study of the TOTAL trial, the thrombus burden at the culprit lesion was compared in 243 patients treated with thrombectomy versus PCI alone using optical coherence tomography. This study concluded that MT did not reduce culprit lesion pre-stent thrombus burden compared with PCI alone and that both strategies were associated with low thrombus burden at the lesion site post-PPCI. This suggests that the effect of an aspiration catheter may not be much greater than dottering with a predilatation balloon. Development of more effective aspiration catheters evacuating all the thrombus safely may still be beneficial and worthy of further research.

### **Does Thrombectomy Harm Microvascular Function?**

Another consideration is whether the device used in the IRA causes microvascular injury rather than preventing it. To assess the impact of device therapy on microvascular function during PPCI procedure, our group set up the IMPACT trial.<sup>24</sup> We performed serial measurements of the index of myocardial resistance (IMR) in 41 PPCI patients randomised to MT or balloon angioplasty (BA) followed by stenting. IMR is a wire-based, invasive measure of microcirculatory function that can predict final infarct size and LV function in patients with STEMI.<sup>25</sup> Our data showed that in patients with partial restoration of flow in the IRA after passage of a guide wire, both MT and BA result in similar final IMR values. In a predefined sub-group with low IMR at baseline (IMR <32), both MT and BA prior to stenting resulted in a highly significant increase in IMR. This suggests that in patients with preserved microvascular function, instrumentation of the culprit vessel contributes to, rather than prevents, further acute microcirculatory injury. Hypothetically, the relatively large bore thrombus aspiration catheters could even cause more injury than a predilatation balloon.

### **Do We Blame the Technique or the Device?**

Another question is why the results from early, single-centre RCTs (TAPAS) are contradicted by the

more recent, larger, multicentre RCTs (TASTE and TOTAL). TAPAS was a trial conducted in a single, high volume PPCI centre with short door-to-balloon times. Could it be considered that more diverse operator skill, PCI techniques, and patient populations of multicentre trials account for the neutral effect of MT observed in TASTE and TOTAL? A TASTE trial sub-study showing no difference in mortality, recurrent myocardial infarction, or stent thrombosis between the type of aspiration catheter used, the stent type used, the practice of direct stenting, or the use of post-dilatation balloons seems to suggest this is not the case.<sup>26</sup>

### **Is There Any Group That Might Benefit from Manual Thrombectomy?**

Sub-group analyses of TASTE and TOTAL did not identify any specific sub-group (e.g. anterior myocardial infarction or high thrombus burden) that benefitted from routine MT. MT may improve visualisation, particularly in those patients with a poor Thrombolysis In Myocardial Infarction flow where it has been shown to result in fewer and more appropriately sized stents implanted by direct stenting, which do not require further post-dilatation. However, these procedural differences did not impact clinical outcomes, at a relatively short clinical follow-up of 2 years.<sup>27</sup> Many of the trials suffer from selection bias; they did not randomise patients with extremely heavy clot burden, a group where MT may still have a role. In addition, improved visibility following MT may make the intervention easier and provisional use of MT if there is persistent clotting despite PCI may still be warranted. Therefore, selective or bail-out MT still receives a Class IIb recommendation, level of evidence: C in the updated ACC/AHA/SCAI guidelines.<sup>28</sup>

### **Do We Need to Wait Longer to See the Benefits?**

The aforementioned RCTs do not report follow-up beyond a year. One may suggest that the observed improvements in MBG and STR in the MT sub-groups may take more time to turn into a clinical advantage. However, this is not confirmed by the results of two recently published large observational cohort studies. Jones et al.<sup>4</sup> reported on the outcomes of 10,929 STEMI patients treated with PPCI. One-third (32.7%) underwent MT during PPCI. MT was used more frequently in younger patients and patients with a worse post-infarct LV ejection fraction. MT was associated with a higher procedural success rate and a lower risk of

in-hospital MACE. The median follow-up duration was 3 years (interquartile range: 1.2–4.6). However, after multivariate analysis and propensity matching, the use of MT was not associated with an improvement in long-term mortality.<sup>4</sup> Similar results were reported by Watanabe et al.<sup>29</sup> in a cohort study of 5,429 STEMI patients in Japan. These registries suggest that the results of the RCTs can be extrapolated to a ‘real-world’ population.

## CONCLUSION

In the past, MT with a dedicated aspiration catheter was often attempted to improve visualisation and the ease of PPCI for STEMI. Although early evidence from RCTs revealed improvement in surrogate markers of microvascular reperfusion, large, multicentre RCTs have not been able to confirm significant clinical benefit from routine MT

in PPCI. The potential for harm with a higher incidence of stroke after MT compared to PCI alone now clearly discourages the routine use of MT in PPCI. This is reflected in the focussed update on primary PCI for patients with STEMI guidelines recently published by ACC/AHA/SCAI, where routine MT received a Class III, no benefit, level of evidence: A, indication.<sup>28</sup> However, it may still have a role in selected situations e.g. particularly large thrombus burden, to improve visualisation, and as a bail-out. Enthusiasm for MT may be reinvigorated when more sophisticated and effective catheters are conceived in the future. The rise and fall of the use of MT confirms, once more, that the findings of small studies using intermediate endpoints must be substantiated by large RCTs assessing meaningful clinical endpoints before wider adoption is endorsed.

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