Adjunctive Thrombectomy in Primary Percutaneous Intervention for Acute Myocardial Infarction

François-Pierre Mongeon[1,2], Otávio Rizzi Coelho-Filho[1], Otávio Rizzi Coelho[3], Stéphane Rinfret[4]

Cardiovascular Division, Brigham and Women's Hospital[1], Boston MA - USA; Noninvasive Cardiology Service, Montreal Heart Institute, Université de Montréal[2], Montréal QC, Canada; Faculdade de Ciências Médicas, Univesidade Estadual de Campinas - UNICAMP[3], Campinas, SP - Brazil; Institut Universitaire de Cardiologie et de Pneumologie de Québec (Quebec Heart and Lung Institute)[4], Quebec City - Canada

Abstract

Primary percutaneous coronary intervention (PCI) has become the favored reperfusion strategy in acute ST-segment elevation myocardial infarction. Lower post-PCI myocardial perfusion grade, no-reflow and even drug-eluting stent thrombosis have been related to the presence of intracoronary thrombus. Adjunctive thrombectomy refers to procedures and devices that remove thrombotic material from the infarction-related artery, in theory, before distal embolization can occur. There is substantial variability between randomized controlled trials of thrombectomy in primary PCI with regards to tested devices, procedural characteristics, adjuvant medical regimen and examined outcomes. As a general statement, improvements in myocardial perfusion endpoints do not translate into reductions in clinical outcomes. Yet, an increasing number of trials with a longer follow-up reported benefits arising late after the index myocardial infarction. Simple aspiration catheters may also produce better outcomes than devices that fragment the thrombus before aspirating debris. Clinical or angiographic variables which best predict benefits from the use of thrombectomy remain to be defined. The aim of this review is to provide perspective on the conclusions of available trials and meta-analysis of adjunctive thrombectomy in acute myocardial infarction. Targets for future studies are discussed.

Introduction

The goal of reperfusion therapy in acute ST segment elevation myocardial infarction (MI) is to achieve patency of the epicardial infarct-related artery and to restore myocardial tissue perfusion. In randomized controlled trials (RCT), primary percutaneous coronary intervention (PCI) leads to lower mortality, less reinfarction and fewer strokes than thrombolysis[1]. When readily available, primary PCI has become the favored reperfusion strategy in acute MI. However, suboptimal results in primary PCI, such as lower TIMI (thrombolysis in myocardial infarction) myocardial perfusion grade (TMPG) or myocardial blush grade (MBG), no-reflow and even drug-eluting stent thrombosis have been related to the presence of intracoronary thrombus. Angiography, myocardial contrast echocardiography (MCE) and cardiovascular magnetic resonance (CMR) provide evidence that microvascular obstruction is prevalent after primary PCI[2-4].

Thrombectomy, or mechanically removing thrombus from the coronary artery, may improve prognosis after MI as it can, in theory, prevent distal embolization of thrombus and its dismal consequences. Observational studies have shown favorable outcomes with adjunctive thrombectomy, such as implantation of a stent that is shorter than the original lesion with its thrombus[5]. With flow restoration following thrombectomy, it is often possible to perform direct stenting, without balloon dilatation[6]. Several small to moderate-sized RCTs have been published in the recent years. They yielded inconsistent results on the impact of adjunctive thrombectomy on reperfusion surrogate and clinical endpoints. Therefore, the role of adjunctive thrombectomy in primary PCI is debatable[7]. Operators are left with an armada of devices, high hopes to improve the results of primary PCI, but conflicting data on which to base their practice. The aim of this review is to provide perspective on the conclusions of available RCTs and meta-analysis of adjunctive thrombectomy in acute MI.

Keywords

Thrombosis; thrombectomy; angioplasty,balloon,coronary; myocardial infarction.

Mailing address: François-Pierre Mongeon •
Noninvasive Cardiology Service - Montreal Heart Institute - Université de Montréal 5000 Bélanger St - Montréal, QC, Canada H1T 1C8
E-mail: francois.pierrre.mongeon@umontreal.ca
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Assesment of myocardial reperfusion

The underlying hypothesis for using thrombectomy is that thrombus removal may protect the myocardial microcirculation. Microvascular obstruction appears on imaging studies as myocardium which fails to uptake contrast material[8]. Selected RCTs of adjunctive thrombectomy have used MCE[3,9], Tc-99m sestamibi gated single photon emission computed tomography (SPECT)[10-14] and late gadolinium enhancement by CMR[4]. Yet, most RCTs have relied on validated angiographic or electrocardiographic surrogate markers or myocardial perfusion[15]. De Luca et al[15] reported that TMPG, corrected TIMI frame count (cTFC) and residual cumulative ST segment deviation all showed a linear relationship with peak creatine kinase MB (CK-MB), considered as gold standard for infarction size. Patients with the combined presence of a residual ST segment deviation of 0-2 mm, cTFC $\leq$ 14 and TMPG 3 had a very small infarction and good post-discharge left ventricular ejection fraction (LVEF). TMPG is an independent predictor of 30-day mortality after MI. There is

a stepwise improvement in outcome with better TMPG and it allows further risk stratification than flow evaluation alone[16]. There is also a stepwise increase in infarction size by SPECT or CK-MB with lower TMPG[17]. ST segment resolution identifies candidates for rescue PCI, is indicative of tissue level perfusion after reperfusion therapy, and is available at the bedside[18]. Post-MI mortality, congestive heart failure, infarction size and LVEF are related to the extent of ST segment resolution[17,19]. Overall, there is strong evidence to support that if adjunctive thrombectomy can lead to improvements in these surrogate endpoints, clinical benefit would logically follow.

Intracoronary thrombus in PCI

There is good evidence that the presence of thrombus leads to suboptimal results in PCI. Thrombus dislodgment leads to macro or microembolization. Macroembolization, defined as a distal filling defect with an abrupt cutoff in one of the peripheral coronary artery branches of the infarction-related vessel, distal to the site of angioplasty, is reported to occur in 15.2% of primary PCI[20]. It has been associated with lower TIMI 3 flow, less residual stenosis < 50%, lower MBG, lower ST segment resolution, larger enzymatic infarction size, lower LVEF at discharge, left ventricular remodeling and higher long-term mortality[3,20].

Microembolization results in microvascular dysfunction assessed by MCE in the area at risk after primary PCI. It is associated with left ventricular dilatation at 6 months and is a predictor of cardiac death, reinfarction and heart failure[21]. A large thrombus burden was found to predict the occurrence of adverse cardiovascular events after primary PCI, possibly because the thrombus in the infarction-related artery prevents complete stent apposition and promotes stent thrombosis[22]. Embolization with subsequent microvascular dysfunction is among the possible mechanisms resulting in absence of epicardial flow despite a reopened artery (no-reflow)[8].

Yip et al[23] identified thrombus characteristics in the pre-revascularization angiogram, which independently predicted the occurrence of no-reflow in a cohort of patients treated with primary PCI without glycoprotein IIb/IIIa inhibitors and without stenting in their earliest experience[23]. In that study, a thrombus length greater than 3 times the lumen diameter and floating or accumulated thrombus proximal to the artery occlusion appeared at higher risk for slow flow or no-reflow[23].

Adjunctive thrombectomy

Adjunctive thrombectomy refers to procedures and devices that remove thrombotic material from the infarction-related artery, in theory, before distal embolization can occur. This review will focus on thrombectomy performed as the first step during emergent PCI for ST elevation MI, immediately after crossing the culprit lesion with a guidewire. Thrombectomy in acute MI has also been tested in combination with a distal protection device destined to capture thrombus fragment that would have escaped aspiration[24]. The large EMERALD RCT was negative and this strategy has not gained acceptance.

The substantial variability among available thrombectomy devices can make comparison between trials difficult. Devices differ in mechanisms of action, catheter size and performance at thrombus removal. Table 1 lists the devices that have been tested in RCTs. Bavry et al[25] have proposed to distinguish between devices that simply aspirate the thrombus from the artery (aspiration thrombectomy) and devices that fragment the thrombus before aspirating the debris (mechanical thrombectomy). Simple, less bulky, aspiration devices have been tested in a larger sample of patients than mechanical thrombectomy devices. The widespread use of aspiration devices has been advocated based on the ATTEMPT pooled analysis[26,27]. In another meta-analysis, we did not find a substantial advantage to aspiration thrombectomy[28]. The recently published and positive JETSTENT trial, which tested the AngioJet rheolytic thrombectomy device in nearly 500 patients, may revive the interest for mechanical thrombectomy[14]. A recent study also found that the single or multicenter study design has a significant impact on outcomes in trials examining the efficacy of adjunctive devices in acute MI[29].

The cost-effectiveness of adjunctive thrombectomy has been relatively unexplored. Mechanical devices are expected to cost more than simple aspiration catheters. Ideally, the incremental cost should be justified by improved outcomes. Very limited data suggest that thrombectomy does not cost more than standard therapy in the setting of acute MI[30]. Rheolytic thrombectomy improved clinical outcomes and reduced overall medical care costs in comparison to urokinase in patients with extensive thrombus in vein grafts[31].

Studies of adjunctive thrombectomy in primary PCI

Inclusion and exclusion criteria

The typical eligibility criterion for RCTs of adjunctive thrombectomy was ST-segment elevation MI referred for primary or rescue PCI within 12 hours of symptoms onset. The maximal time after symptoms onset was 6 hours in one trial[32], 9 hours in another[4], 24 hours in one trial[33]and 48 hours in one trial[13]. An angiographically visible thrombus was required in 6 trials (Table 2 and 3)[4,14,34-37]. Patients in shock, requiring intra-aortic balloon counterpulsation or mechanical ventilation were excluded from 10 trials[4,10,11,13,34, 37-41] and patients with previous coronary artery bypass were excluded from 9 trials[4,12,13,33,34,39-42]. Only 2 RCTs specifically excluded patients with a LVEF below 30%[10,38]. Six trials reported crossovers from the control to the thrombectomy group (range 3-18 patients)[6,10,11,39,41,43]. One trial recruited only anterior MIs[34]. Some trials required an infarction-related artery minimal reference diameter of at least 2.5 mm[4,11,14,24,33,35,37,38,41] or 2 mm[10]. Patients with left main coronary stenosis were excluded from 6 trials[4,12,33,35,40,42] and those with excessively calcified and tortuous arteries were excluded from one trial[38]. Overall, RCTs mostly included low to moderate-risk MI patients without hemodynamic compromise or high risk coronary anatomy.

Randomized controlled trials of aspiration thrombectomy

The majority of aspiration thrombectomy RCTs found a statistically significant improvement in one or a combination of surrogate markers of myocardial reperfusion (Table 2). This

Table 1 - Thrombectomy devices studied in randomized trials

Aspiration thrombectomy devices			
Device	**Maker**	**Description**	**Reference**
Diver CE	Invatec, Brescia, Italy	Rapid exchange, 6F compatible, thrombus aspirating-catheter. It has a central aspiration lumen running through its full length and a soft, flexible, 0.026-inch, non-traumatic tip with multiples holes communicating with the central lumen. A 30 mL luer lock syringe is connected to the hub in the proximal end for blood aspiration and clot removal.	(34, 43)
Pronto	Vasc.solutions, Minneapolis, MN	Dual-lumen, monorail design, 6F compatible catheter. The smaller lumen is designed to accommodate a standard 0.014-inch guidewire. The larger extraction lumen allows the removal of the thrombus, which is aspirated in a 30-mL locking vacuum syringe. The catheter has a rounded distal tip designed to maximize thrombus aspiration and to protect the vessel while advancing and during aspiration.	(39)
Export	Medtronic	6F catheter (crossing profile 0.068 in) which crosses the target lesion over a floppy guidewire and aspirates the thrombus into a 20-mL syringe. The aspiration lumen is 0.041 in and the aspiration rate is >30 cc of fluid per minute. The total employable length is 145 cm.	(6, 41)
TVAC	Nipro, Japan	Single lumen rapid-exchange aspiration shaft compatible with 7F guiding catheters with a dedicated vacuum pump.	(33)
Rescue	Boston Scientific/ Scimed, Inc, Maple Grove MN	4.5F polyethylene aspiration catheter advanced over a guidewire through a 7F guiding catheter. The proximal end of the catheter has an extension tube connected to a vacuum pump (0.8 bar) with a collection bottle. The catheter is slowly advanced and pulled back through the thrombus, while continuous suction is applied.	(12)
Mechanical thrombectomy devices			
Device	**Maker**	**Description**	**Reference**
AngioJet	Possis Medical Inc, Minneapolis MN	Rheolytic thrombectomy system consisting of a drive unit, a disposable pump set and rheolytic thrombectomy catheter. The dual-lumen catheter tracks over a guidewire. High velocity saline jets are directed back into the catheter, creating a low-pressure zone at the distal tip (Bernoulli principle), which results in suction, break-up and removal of thrombus through the outflow lumen. Single pass anterograde technique is encouraged.	(14, 55)
X-Sizer	eV3, White Bear Lake, MN	Two-lumen over-the-wire system (available diameters 1.5 and 2.0 mm) with a helical shape cutter at its distal tip. The cutter rotates at 2100 rpm driven by a hand-held battery motor unit. One catheter lumen is connected to a 250 mL vacuum bottle, and aspirated debris is collected in an in-line filter. Two or three passages across the lesion are performed.	(38)

finding appears consistent with all available devices. On the contrary, none of the trials found that adjunctive thrombectomy reduced major adverse cardiovascular events (MACE) at a follow-up varying from the hospital stay to 6 months after MI (Table 2). Even in the largest trial (TAPAS), which is the most likely to be adequately powered, no difference in early clinical outcomes was found[6]. The definition of MACE consistently included mortality and nonfatal reinfarction. The select RCTs that extended patient follow-up until 8 to 24 months after MI all reported a lower occurrence of MACE in patients treated with aspiration thrombectomy[4,33,44,45]. The mechanism for this late improvement in clinical outcomes is not defined. If one believes that aspiration thrombectomy favors positive ventricular remodeling, it is plausible that benefits only become apparent at late follow-up or when negative remodeling has had time to occur in patients treated with PCI alone.

Data about infarction size in thrombectomy treated patients at more than 6 months after MI are very limited[3]. Only 2 RCTs were able to demonstrate a reduction in infarction size with thrombectomy[9,11] (Table 4) and among them, one used aspiration thrombectomy. Most RCTs yielded neutral results for that outcome, if they did not find that thrombectomy increased infarction size (Table 4). Thus, it seems unlikely that aspiration thrombectomy improves clinical outcomes by preventing ventricular dysfunction or arrhythmias arising from a large scar area. Little insight can be gained by examining the causes of MACE in RCTs that report a benefit. In the VAMPIRE trial[33], the reduction in MACE is largely due to a reduction in target lesion revascularization with thrombectomy. This supports the hypothesis that thrombus is associated with poorer PCI results at the level of the lesion as suggested by Sianos et al[22]. The causes of death at 9 months in the EXPIRA trial and at 1 year in the TAPAS trial have not been reported[4,45]. The causes of the 6 deaths at 2 years in the PCI alone group of the EXPIRA trial are evenly split between ventricular fibrillation (3), heart failure (2) and reinfarction (1)[44]. To summarize, aspiration thrombectomy improves myocardial perfusion and late clinical outcomes, but this benefit cannot be explained by a reduction in infarction size.

Randomized controlled trials of mechanical thrombectomy

The conclusions of mechanical thrombectomy RCTs are similar to those of aspiration thrombectomy RCTs (Table 3). The JETSTENT trial[14] stands out as the only one to demonstrate a reduction in MACE at 1 month after MI, which is sustained at 6 months. This finding is remarkable given that the AIMI trial[10], which also used the AngioJet, found poorer myocardial perfusion, increased infarction size and more MACE in patients treated with thrombectomy. Investigators in JETSTENT[14] where careful to use a single pass anterograde technique to avoid diffusion of thrombus fragments in the artery. They also only recruited patients with a substantial thrombus burden after wiring of the infarction-related artery and did not exclude high risk patients (4% of patients in cardiogenic shock). The

Table 2 - Randomized controlled trials of aspiration thrombectomy in primary percutaneous coronary intervention

First author, year, acronym	n	Device	Thrombus required	Delay to PCI (min)	Primary outcomes	Results	Clinical events
Burzotta, 2005, REMEDIA[43]	99	Diver CE	No	274 *vs* 300 p = 0.28*	post PCI MBG ≥ 2	OR 2.6 95% CI 1.2-5.9, p = 0.020	No difference in MACE at 30 days.
					post PCI STR ≥ 70%	OR 2.4 95% CI 1.1-5.3, p = 0.034	
De Luca, 2006[34]	76	Diver CE	Yes	432 *vs* 456†	LV volumes at 6 months	ESV: 82 *vs* 75 ml, p < 0.0001 EDV: 153 *vs* 138 ml, p < 0.0001	No difference in MACE at 6 months.
Dudek, 2007, PIHRATE[32]	196	Diver CE	NR	258 *vs* 236†	STR > 70% at 60 min	50 *vs* 23%, p = 0.28	No difference in in-hospital MACE.
Chao, 2008[40]	74	Export	No	312 *vs* 331‡ p = 0.657	ΔMBG post PCI	2.3 ± 1.1 *vs* 1.0 ± 1.5, p < 0.001	No difference in MACE at 6 months.
					ΔTIMI flow post PCI	2.2 ± 1.1 *vs* 1.5 ± 1.3, p = 0.014	
Chevalier, 2008, EXPORT[41]	249	Export	No	322 *vs* 271§ p = 0.53	combined rate of MBG 3 and/or STR > 50%	85.0 *vs* 71.9%, p = 0.025	No difference in MACE at 30 days.
Svilaas, 2008, TAPAS[6]	1,071	Export	No	28 *vs* 26// p = 0.92	MBG 0 or 1	17.1 *vs* 26.3%, p < 0.001	No difference in MACE at 30 days: risk ratio 0.72, 95% CI 0.48-1.08, p = 0.12
Vlaar, 2008, TAPAS[45]	1,060	Export	No	NA	cardiac death or reinfarction at 1 year	5.6 *vs* 9.9% (HR 1.81 95% CI 1.16–2.84, p = 0.009)	Reduction in cardiac death or non fatal reinfarction at 1 year.
Sardella, 2009, EXPIRA[4]	175	Export	Yes	372 *vs* 366† p = 0.642	post PCI MBG ≥ 2	88 *vs* 60%, p = 0.001	Lower cardiac mortality in the Tx group at 9 months (0 *vs* 4.6%, log-rank test p = 0.02).
					STR > 70% at 90 min	64 *vs* 39%, p = 0.001	
Sardella, 2009, EXPIRA[44]	175	Export	Yes	NA	MACE at 2 years	4.5 *vs* 13.6% (HR 3.105 95% CI 1.002-9.629, p = 0.050)	Reduction in MACE and cardiac death (0 *vs* 6.8%, HR 6.657 95% CI 1.642-8.457, p = 0.0001) at 2 years.
Liistro, 2009[9]	111	Export	NR	189 *vs* 209†	STR ≥ 70% at 90 min	OR 3.7 95% CI 1.7-8.3, p = 0.001	No difference in MACE at 6 months.
Silva-Orrego, 2006, DEAR-MI[39]	148	Pronto	No	206 *vs* 199†	MBG 3	88 *vs* 44%, p < 0.0001	No difference in in-hospital MACE.
					STR > 70% at 90 min	68 *vs* 50%, p = 0.041	
Dudek, 2004[37]	72	Rescue	Yes	236 *vs* 258† NS	post PCI TIMI 3 flow, cTFC, TMPG 3	86 *vs* 85% NS, 19 *vs* 21 NS, 38 *vs* 54% NS	NR
					post PCI complete STR	68 *vs* 25%, p = 0.005	
					LVEF at 3 months	55.3 *vs* 60.3%, NS	
Kaltoft, 2006[12]	215	Rescue	No	242 *vs* 208†	myocardial salvage by sestamibi SPECT at 30 days	median 13 *vs* 18%, p = 0.12	No difference in MACE at 30 days.
Andersen, 2007[42]	172	Rescue	NR	NR	LV volumes and function at 30 days	No difference in volumes, systolic and diastolic function.	NR
Ikari, 2008, VAMPIRE[56]	355	TVAC	NR	106 *vs* 115¶ p = 0.27	slow flow or no-reflow during primary PCI	12.4 *vs* 19.4%, p = 0.07	No difference in in-hospital MACE. Reduction in MACE at 8 months due to lower TLR rates in Tx group.

*All data are presented as thrombectomy group versus PCI alone group. *Symptom onset to angiography time. †Symptom onset to balloon time. ‡Symptom onset to catheterization laboratory time. §Symptom onset to randomization time. //Door-to balloon time. ¶Door to TIMI 2-3 flow time. PCI - percutaneous coronary intervention, Tx - thrombectomy, MBG - myocardial blush grade, OR- odds ratio, CI - confidence interval, MACE - major adverse cardiovascular events, STR - ST segment resolution, LV- left ventricular, ESV - end-systolic volume, EDV - end-diastolic volume, NR - not reported, TIMI - Thrombolysis in Myocardial Infarction, NA - not applicable, HR- hazard ratio, cTFC - corrected TIMI frame count, TMPG - TIMI myocardial perfusion grade, LVEF - left ventricular ejection fraction, SPECT - single photon emission computed tomography, TLR - target lesion revascularization.*

Table 3 - Randomized controlled trials of mechanical thrombectomy in primary percutaneous coronary intervention

First author, year, acronym	n	Device	Thrombus required	Delay to PCI (min)	Primary outcomes	Results	Clinical events
Antoniucci, 2004[11]	100	AngioJet	NR	234 *vs* 264* p = 0.295	STR ≥ 50% at 30 min	90 *vs* 72%, p = 0.022	No difference in MACE at 30 days.
Ali, 2006, AIMI[10]	480	AngioJet	No	162 *vs* 150† p = 0.61	TIMI flow 3, TIMI blush score 3, STR	91.8 *vs* 97% p < 0.02; 30.6 *vs* 36.8%; 60 *vs* 68% p = 0.14	30-day MACE was higher in the adjunct Tx group.
Beran, 2002[36]	61	X-Sizer	Yes	291 *vs* 279* p = 0.81	cTFC	18.3 ± 10.2 *vs* 24.7 ± 14.1, p < 0.05	No difference in MACE at 30 days.
Migliorini, 2010, JETSTENT[14]	501	AngioJet	Yes	34 *vs* 31‡ p = 0.727	STR ≥ 50% at 30 min	85.8 *vs* 78.8%, p = 0.043	Reduction in MACE at 1 (3.1 *vs* 6.9%, p = 0.050) and 6 months (12.0 *vs* 20.7%, p = 0.012).
Napodano, 2003[35]	92	X-Sizer	Yes	238 *vs* 204 *§	MBG 3	71.7 *vs* 36.9%, p = 0.006	No difference in MACE at 30 days.
Lefèvre, 2005, X AMINE ST[38]	201	X-Sizer	NR	251 *vs* 264* NS	Magnitude of STR and STR > 50%	7.5 *vs* 4.9 mm, p = 0.033; 68 *vs* 53%, p = 0.037	No difference in MACE at 6 months

*All data are presented as thrombectomy group versus PCI alone group. * Symptom onset to balloon time. †Emergency room presentation to randomization time. ‡Emergency room to arterial puncture time. §Delay calculated from data in published manuscript. Abbreviations as in Table 2.*

design and results of JETSTENT[14] raise the question whether adjunctive thrombectomy is best used selectively in higher risk patients with a large thrombus burden. The differences in outcomes between aspiration and mechanical devices may fade with appropriate patient selection.

Meta-analyses and pooled analyses

There is significant heterogeneity in design between individual RCTs, which is an inherent limitation for meta-analyses and pooled analyses. In addition to inclusion and exclusion criteria and tested devices, several procedural variables, such as lesion predilatation, are left to the discretion of the operator. Nevertheless, meta-analyses further confirm that adjunctive thrombectomy leads to improved myocardial perfusion (Table 5). In the meta-analysis by Bavry et al[25], the authors were the first to suggest that simple aspiration devices carried a mortality advantage over bulkier mechanical thrombectomy devices, which were found to increase mortality. A similar trend was observed by Tamhane et al[46]. This finding was reinforced by the ATTEMPT pooled analysis[26], which found that a mortality benefit was confined to patients treated with manual (aspiration) devices. Another important finding of the ATTEMPT study[26] is that thrombectomy improved survival in patients treated with glycoprotein IIb/IIIa inhibitors, suggesting that they should be used routinely in primary PCI, if adjunctive thrombectomy is performed. The strength of the ATTEMPT study is the use of patient level data with an extended follow-up to 1 year[26]. It is limited by the absence of 6 of 17 eligible RCTs, to which the principal investigators did not grant access to the database[26]. Mongeon et al[28] found that adjunctive thrombectomy may be one of the few preventive measures against no-reflow, but did not find substantially different results with aspiration thrombectomy compared with thrombectomy by any device[28]. Tamhane et al[46] observed an increased risk of stroke with thrombectomy. This novel finding is exploratory, but plausible, given the need for more intravascular manipulations to perform thrombectomy. Stroke should be routinely assessed in outcomes of future RCTs or registries of thrombectomy.

Discussion

The improvement in surrogate markers of reperfusion does not translate into clinical benefits

Absence of improvement in short-term clinical outcomes, despite consistent improvements in surrogate markers of myocardial reperfusion with thrombectomy, has been noted in the majority of RCTs (Table 2 and 3). First, the clinical benefits of thrombectomy may arise later after MI and studies with longer follow-up have consistently reported a reduction in 6 to 24-month MACE with thrombectomy (Table 2 and 3). Second, most RCTs had small sample sizes, making them underpowered to detect a difference in clinical outcome, especially in the low to moderate risk MI patients included in trials. The combined incidence of death, MI or stroke at 30 days was below 5% in thrombectomy and PCI alone groups[28]. Third, most studies excluded patients in cardiogenic shock or with left main coronary artery disease, who may derive a greater benefit from this technique. Fourth, is it possible that the use of thrombectomy induces a delay in reperfusion that offsets any benefit?

Delay to reperfusion

No RCT reported a statistically significant difference in delay to PCI between thrombectomy and control groups (Tables 2 and 3). Different time intervals are reported from trial to trial. On average, symptom onset-to-balloon times are shorter in thrombectomy-treated patients compared with patients undergoing PCI alone, but this difference is not statistically significant[28]. Benefits in clinical outcomes with thrombectomy cannot be explained by a shorter time to treatment[4,6,14,33,44].

Table 4 - Assessment of infarction size in randomized controlled trials of adjunctive thrombectomy

First author, year, acronym	n	Device	Method for assessment of infarct size	Time after MI	Infarction size		p
					Thrombectomy	PCI alone	
Ali, 2006, AIMI[10]	480	AngioJet	Tc-99m sestamibi gated SPECT	14-28 days	12.5 ± 12.13%	9.8 ± 10.92%	0.03
Antoniucci, 2004[11]	100	AngioJet	Tc-99m sestamibi gated SPECT	30 days	13.0 ± 11.6%	21.2 ± 18%	0.01
Migliorini, 2010, JETSTENT[14]	415	AngioJet	Tc-99m sestamibi gated SPECT	30 days	11.8%	12.7%	0.398
Kaltoft, 2006[12]	215	Rescue	Tc-99m sestamibi gated SPECT	30 days	15%	7,5%	0.004
Galiuto, 2006, REMEDIA[3]	50	Diver-CE	Myocardial contrast echocardiography	24 h, 1 week and 6 months	At each time point, contrast score index and contrast defect length and contrast defect length/left ventricular length are significantly reduced in Tx group.		
Liistro, 2009[9]	111	Export	Myocardial contrast echocardiography	Immediately	85% of myocardial segments with homogenous myocardial contrast	64% of myocardial segments with homogenous myocardial contrast	< 0.0001
Lipiecki, 2009[13]	40	Export	Tc-99m sestamibi gated SPECT	6 days	30.6 ± 15.8%	28.5 ± 17.9%	0.7
Sardella, 2009, EXPIRA[4]	75	Export	Contrast-enhanced MRI	3-5 days	14 ± 12%	13 ± 6.7%	0.6
				3 months	9 ± 4.5%	11 ± 8.7%	0.2

All data are presented as thrombectomy group versus *PCI alone group. Abbreviations as in Table 2. MI - myocardial infarction; MRI - magnetic resonance imaging.*

Likewise, delays to PCI were not longer in thrombectomy groups of negative RCTs[10,12]. Of note, the door-to-balloon times in the TAPAS trial were very short and may be difficult to reproduce outside a study setting[6]. Overall, current data do not support that thrombectomy induces clinically relevant delays to treatment, acknowledging that thrombus aspiration with simpler devices is more readily available and easier to set up than more complex devices such as the AngioJet. It is possible that thrombectomy has a distinct capacity to remove thrombus that has been formed for fewer hours[40]. In one study, TIMI flow and MBG were better in thrombectomy-treated patients compared with PCI alone only when the symptom onset-to-catheterization laboratory time was between 4 to 8 hours[40]. No significant difference in myocardial perfusion markers was found for patients treated less than 4 hours after symptom onset[40]. Thus, adjunctive thrombectomy may be less relevant in patients presenting very early after symptom onset.

Infarction size

Most trials found no difference in infarction size with thrombectomy (Table 4). Embolization may occur at times when thrombectomy cannot prevent it: prior to arrival to the catheterization laboratory, with contrast injection or with wire or device crossing of the culprit lesion (distal to proximal technique with activation of the device after crossing the lesion[10]). Impaired microvascular perfusion may also be related to other mechanisms such as necrosis, edema, reperfusion injury and endothelial dysfunction[8].

Two trials, one using a mechanical device[10] and one using an aspiration device[12], found larger infarctions in thrombectomy-treated patients. The JETSTENT investigators advocated the single anterograde technique to avoid promoting distal embolization, but no infarction size reduction was found in that trial[14]. Antoniucci et al[11] found a reduction in infarction size with the AngioJet in a previous trial, but the thrombectomy technique was not detailed. Liistro et al. found better myocardial perfusion by MCE in patients treated with the Export aspiration catheter[9]. Aspiration was started before crossing the lesion and maintained until catheter withdrawal[9]. Comparisons between RCTs must take into account that infarction size measurement is sensitive to the time delay after the index MI and that difference exists between imaging techniques.

The presence of thrombus

Adjunctive thrombectomy is unlikely to be helpful in the absence of intracoronary thrombus and may even be hazardous. A visual semiquantitative method for the assessment of intracoronary thrombus has been described[47]. Because the thrombus is not always visible in the angiography, most RCTs tested a strategy of systematic thrombectomy in primary PCI and thrombus presence in the baseline angiography was an inclusion criterion in only 6 RCTs (Tables 2 and 3)[4,14,34-37]. All of them found that thrombectomy improved surrogate markers of myocardial reperfusion and 2 reported a reduction in clinical events[4,14]. An alternative way to account for the presence of thrombus is to examine the material retrieved by the thrombectomy device, which was noted in 5 RCTs[6,33,35,39,41]. All these trials also yielded positive results for their respective primary outcome. Macroscopic debris was retrieved in 72.9% to 95% of patients[6,33,39]. The value of the presence of thrombus on angiography to select patients who can benefit from adjunctive thrombectomy is further

Table 5 - Meta-analysis of adjunctive thrombectomy in primary percutaneous coronary intervention

First author, year	Number of trials	Surrogate markers of reperfusion	Clinical outcomes
De Luca, 2007[57]	13	Tx devices were associated with higher rate of post PCI TIMI 3 flow (90.5 *vs* 87.3%, OR 1.43 95% CI 0.99-2.06, p = 0.05), MBG 3 (46.6 *vs* 31.8%, OR 2.64 95% CI 1.35-5.16, p = 0.005) and distal embolization (5.8 *vs* 10.6%, OR 0.52 95% CI 0.32-0.85, p = 0.009).	Tx devices were not associated with significant benefits in terms of 30-day mortality (2.6 *vs* 2%, OR 1.32 95% CI 0.76-2.31, p = 0.33).
Kunadian, 2007[58]	10	MBG 3 and complete STR were more common when Tx or embolic protection devices where used.	Tx devices did not improve the clinical outcome of death or reinfarction at 30 days (4.4 *vs* 4.2%, OR 0.98 CI 0.53-1.83, p = 0.95).
Burzotta, 2008[59]	12	Use of Tx devices was associated with significantly less distal embolization, TIMI flow < 3, MBG < 3 and failure to achieve STR.	Tx devices were not associated with a reduction in death and MI at 30 days (OR 1.07 95% CI 0.50–2.32).
Bavry, 2008[25]	18	Aspiration Tx devices, but not mechanical Tx devices, were associated with significantly more post PCI TIMI blush grade 3 (RR 1.69 95% CI 1.26-2.28, p < 0.0001) and STR (RR 1.41 95% CI 1.21-1.64, p < 0.0001).	Over a weighted mean follow-up of 6.2 months, in thrombus aspiration studies, mortality was 2.7% for the adjunctive device group *vs* 4.4% for PCI alone (p = 0.018). For mechanical thrombectomy studies, mortality was 5.3% for the adjunctive device group *vs* 2.8% for PCI alone (p = 0.050) at a mean follow-up of 4.6 months.
Burzotta, 2009, ATTEMPT[26]	11		Tx was associated with lower all-cause mortality (p = 0.049). Tx is associated to improved survival in patients treated with IIb/IIIa-inhibitors (p = 0.045) and the survival benefit is confined to patients treated in manual Tx trials (p = 0.011). Median follow-up was 365 days.
Mongeon, 2010[28]	21	Tx yielded substantially less no-reflow (OR 0.39 95% CrI 0.18-0.69), less distal embolization (OR 0.46 95% CrI 0.28-0.70), more STR ≥ 50% (OR 2.22 95% CrI 1.60-3.23) and more TIMI/myocardial perfusion grade 3 (OR 2.50 95% CrI 1.48-4.41). Simple aspiration Tx devices were, in addition, associated with more post PCI TIMI 3 flow (OR 1.49 95% CrI 1.14-1.99).	There was no evidence for a decrease in death at ? (OR 0.94 95% CrI 0.47-1.80) and in death, recurrent MI, or stroke at 30 days (OR 1.07 95% CrI 0.63-1.92) with Tx. Restriction of the analysis to trials that used simple aspiration Tx devices did not yield substantially different results.
Tamhane, 2010[46]	17	Tx was associated with a greater likelihood of TIMI 3 flow (OR 1.41, p = 0.007), MBG 3 (OR 2.42, p < 0.001), STR > 70% (OR 2.30, p < 0.001).	There was no difference in risk of 30-day mortality (OR 0.84 95% CI 0.54-1.29) and reinfarction (0.59 95% CI 0.29-1.22) with Tx. Tx was associated with a higher risk of stroke (OR 2.88 95% CI 1.06-7.85, p = 0.04). There were trends towards lower mortality with manual aspiration Tx (OR 0.59 95% CI 0.35-1.01, p = 0.05) and towards higher mortality with mechanical Tx devices (OR 2.07 95% CI 0.95-4.48, p = 0.07).

All data are presented as thrombectomy group versus PCI alone group. Abbreviations as in Table 2. RR - risk ratio, CrI - credible interval.

supported by a subgroup analysis of the REMEDIA trial, which found more post-PCI MBG ≥ 2 and ST segment resolution ≥ 70% in patients with a baseline TIMI thrombus score 3-4[47] treated with thrombectomy[43]. Other subgroup analyses, however, yielded opposite results. In the TAPAS trial, there was no significant difference in risk ratio for post-PCI MBG 0-1 with aspiration thrombectomy *versus* PCI alone, according to the baseline thrombus score[6]. In the AIMI trial, thrombectomy did not reduce infarction size in the subgroup of patients with visible thrombus at baseline[10]. In the study by Kaltoft et al[12], infarction size was larger in patients with baseline thrombus, as it was for the whole thrombectomy group.

Anti-platelet therapy

Contemporary management of ST-segment elevation MI involves the use of various antithrombotic agents[48]. Based on the ATTEMPT pooled analysis[26], the use of glycoprotein IIb/IIIa inhibitors is associated with a survival benefit in patients treated with adjunctive thrombectomy and these glycoprotein IIb/IIIa inhibitors were used in more than 75% of patients included in adjunctive thrombectomy RCTs[28]. Practice guidelines rather encourage the use of dual anti-platelet therapy with aspirin and thienopyridine with heparin or bivalirudin[48]. The use of glycoprotein IIb/IIIa inhibitors is not supported as a routine therapy, but in selected cases with a large thrombus burden or without adequate thienopyridine loading dose[48]. Moreover, a loading dose of 600 mg of clopidogrel is often used and dual anti-platelet therapy is continued for 12 months or more after primary PCI[48]. Prasugrel may also be used. Assuming that these recommendations are followed, some patients may undergo thrombectomy with an antithrombotic regimen that is slightly different from the one largely tested. The pre-PCI loading dose of clopidogrel was 300 mg in most trials that reported it[4,10,12,13,40,42,43] and it was given for one month after PCI when this information was available[10,11,34,36,43]. Selected RCTs used a 600 mg loading dose[6,9,14] or maintained its use for 3 to 12 months[4,12,40,42]. As the adjunctive medical regimen evolves, the outcomes of adjunctive thrombectomy will require reappraisal in RCTs more closely reflecting the contemporary practice. It remains unknown if more potent antithrombotic drugs given at the time of primary PCI will improve or offset the benefits of adjunctive thrombectomy. At least, intracoronary administration of abciximab, even at higher dosage, did not result in benefits over the usual intravenous regimen in one small trial[49].

Are aspiration devices better than mechanical devices?

Aspiration thrombectomy has gained increasing popularity and acceptance over mechanical thrombectomy based on meta-analyses[25,26], which suggested that aspiration devices were more beneficial as a class. The JETSTENT trial will likely force the reconsideration of the role of mechanical thrombectomy (Table 3)[14]. Mongeon et al[28] did not find thrombectomy with an aspiration device to yield substantially different results compared to thrombectomy with any device[28]. Vlaar et al[50] compared the Diver and Export aspiration devices (Table 1) and found that a larger internal lumen diameter did not result in retrieval of larger thrombotic particles, nor did it improve angiographic or electrocardiographic outcomes[50]. The RETAMI trial found that the Export catheter removed more thrombotic material and was associated with better myocardial perfusion that the Diver device[51]. We can at least say that thrombus aspiration is easier to set up, and usually a cheaper strategy that does not rely on an expensive console to work. As a result, it has gained popularity over the recent years.

Recommendations

The fact that adjunctive thrombectomy yielded benefits on myocardial perfusion endpoints and that it is sound to remove the thrombus for the infarction-related artery have led to its enthusiastic acceptance in primary PCI. Upon review of the available RCTs (Tables 2 and 3) and summary studies (Table 5), one can choose arguments either to justify or reject the use of this technique. Aspiration thrombectomy has appeared as the favored technique in recent studies (Tables 2 and 4).

What we know

In the more recent trials (Tables 2 and 3), adjunctive thrombectomy, either by aspiration or mechanical device, performed in unselected acute MI patients undergoing primary PCI was not shown to increase adverse events or costs[30]. Adjunctive thrombectomy consistently improves surrogate markers of myocardial reperfusion and can reduce the occurrence of late MACE. It is probably best to use adjunctive thrombectomy in conjunction with glycoprotein IIb/IIIa inhibitors[26] and in patients with an intermediate symptom onset-to-catheterization laboratory time delay[40].

What we do not know

The body of favorable evidence is much larger with aspiration thrombectomy (Table 2) than with mechanical thrombectomy (Table 3). Until the JETSTENT trial[14], aspiration thrombectomy was the only technique shown to reduce MACE after MI. The superiority of aspiration thrombectomy remains controversial, but its technical simplicity cannot be ignored. It is still unclear if there are patients who should undoubtedly receive thrombectomy. Subgroup analysis and review of RCTs inclusion criteria do not allow us to use the baseline thrombus burden as an indication for adjunctive thrombectomy. The benefits of a routine thrombectomy approach compared with a more selective use of these devices are also unknown. An appropriately powered trial to study clinical outcomes would need a very large number of patients, as differences in clinical event rates between thrombectomy and control arms are below 1% in selected trials[28]. A large trial with a planned enrolment of 4,000 patients and reporting outcomes at 6 months is being planned[52]. In addition, future trials should focus on high risk patients, routinely assess the presence of thrombus and report long-term outcomes, as clinical benefits appear to arise later.

Practice guidelines

The American College of Cardiology/American Heart Association 2009 update in the management of ST segment elevation MI gives aspiration thrombectomy a class IIa recommendation. The guidelines committee carefully observes that "*it is reasonable to assume that* [aspiration thrombectomy] *can be useful in* [ST-elevation MI] *patients with short ischemic times and large thrombus burden. It may not be helpful in* [ST-elevation MI] *patients with long ischemic times, side branches with small infarction territories, or lesions with low thrombus burden*"[48]. The European Society of Cardiology guidelines for management of ST-segment elevation MI gave also a class IIa recommendation for manual thrombus aspiration for prevention of no-reflow, but a class IIb recommendation as a reperfusion procedure[53]. Finally, one must keep in mind that thrombectomy RCTs were carried out in high-volume centers by experienced operators. It is recommended that operators ensure sufficient proficiency in the manipulation of thrombectomy devices to use them during emergency PCI[54].

Conclusions

Adjunctive thrombectomy in primary PCI for acute ST segment elevation MI improves myocardial reperfusion. Evidence emerges to suggest that this technique may also improve late clinical outcomes. Based on current practice guidelines, experienced operators should consider the use of adjunctive thrombectomy. Whether it should be routinely performed or selectively used in patients at higher risk or with a large thrombus burden remains to be defined.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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