Aspiration thrombectomy in 2015: a TOTAL defeat?

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Primary percutaneous coronary intervention (pPCI) is the treatment of choice for ST-elevation myocardial infarction (STEMI), but in a relevant proportion of cases it fails to achieve restoration of perfusion at the level of microcirculation, due to the "no reflow" phenomenon (1). Distal thrombotic embolization has a role among the mechanisms of no reflow, and intracoronary aspiration thrombectomy (AT) was conceived several years ago as an adjunct to pPCI to address this problem (2). Over the last 15 years, AT has been thoroughly investigated in clinical trials, but its clinical value is still debated. In fact, initial studies reported that routine use of AT impacted favourably on surrogate end points such as myocardial blush grade or ST-segment elevation resolution (STR) after pPCI; in addition, the randomized TAPAS trial (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study), although not powered for clinical endpoints, reported a benefit on 1-year mortality (3,4). Therefore, the 2012 guidelines on STEMI of the European Society of Cardiology (ESC) stated that "routine AT should be considered" (class IIa recommendation) (5). However, the larger TASTE trial (Thrombus Aspiration in STEMI in Scandinavia) failed to prove a significant advantage of routine AT in terms of early and medium-term mortality (6,7), leading to a downgrade of AT to class IIb in 2014 ESC guidelines on myocardial revascularization (8). Most recently, the TOTAL trial (Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI), enrolling 10,732 patients, confirmed the lack of mortality benefit with routine AT (9).

In this scenario, the updated meta-analysis by Elgendy and coworkers, involving 17 trials for a total of 20,960 patients, appears of particular interest (10). The main results of this meta-analysis confirm the lack of benefit with routine AT in terms of reduction of mortality and MACCE, while highlighting a non-significant increase in the incidence of stroke in the AT group. In particular, at a weighted mean follow-up of 3.7±2.7 months, routine AT was associated with a nonsignificant reduction in the incidence of all-cause mortality [2.8% *vs.* 3.2%; relative risk (RR) 0.89; 95% confidence interval (CI) 0.76–1.04; P=0.13] and of the composite of mortality or reinfarction (4.1% *vs.* 4.6%; RR 0.90; 95% CI 0.79–1.02; P=0.11). In addition, AT was associated with a significantly higher incidence of complete STR (68% *vs.* 64%; RR 1.17; 95% CI 1.08–1.28; P<0.0001), and final myocardial blush grade ≥2 (59% *vs.* 43%; RR 1.39; 95% CI, 1.19–1.62; P<0.0001). The reverse of the coin was a nonsignificant increase in the risk of stroke (0.6% *vs.* 0.4%; RR 1.45; 95% CI 0.96–2.21; P=0.08).

Importantly, the authors address through meta-regression analyses two additional issues, i.e., the effect of co-administration of intravenous glycoprotein IIb/IIIa inhibitors (GPIs), and the role of ischemic time. Thrombosis has a pivotal role in STEMI, and the anti-thrombotic regimen is therefore crucial. The only randomized trial designed to evaluate contemporarily the role of AT and of a potent anti-thrombotic agent, abciximab, was the INFUSE-Anterior Myocardial Infarction (INFUSE-AMI) trial, which randomized in 2×2 factorial design 452 patients with anterior STEMI to intracoronary abciximab *vs.* no abciximab and to AT *vs.* no AT (11). Although small, this trial was very well designed and relevant information has been derived from its results. Intralesional abciximab, but not AT, was associated with a reduction in 30-day infarct size, as assessed by cardiac magnetic resonance imaging (MRI); 1-year results showed that intralesional abciximab, AT, or both compared with no active therapy resulted in lower mortality (4.5% *vs.* 10.4%; P=0.03), severe heart

failure (4.2% *vs.* 10.3%; P=0.02), and stent thrombosis (0.9% *vs.* 3.8%; P=0.046) (12). In particular, AT was associated with significantly lower rates of new-onset severe heart failure (0.9% *vs.* 4.5%; P=0.02) and of rehospitalization for heart failure (0.9% *vs.* 5.4%; P=0.0008), and with numerically lower mortality between 30 days and 1 year (1.9% *vs.* 4.5%; P=0.12) (12). In the absence of a significant reduction in infarct size with AT, the pathophysiologic mechanisms of such potential clinical benefit remains unclear. The meta-analysis by Elgendy has the strength of the number of patients analyzed, but also the intrinsic weakness of pooling together markedly heterogeneous studies, notwithstanding the results of formal heterogeneity testing. In fact, anti-thrombotic drug treatment was quite different among trials, in terms of both GPI and ADP antagonists. Surprisingly, in the meta-regression GPI use did not influence any end point, both clinical and surrogate; the authors were not able to conduct separate meta-regression analysis using the difference in GPI use between AT versus no AT arm. Conversely, in another recent meta-regression analysis of AT trials, Bajaj and coworkers observed a marginal benefit on 30-day mortality with higher GPI use (P=0.047), being more evident in the AT arm compared with the control arm (P=0.01) (13). Regarding the effect of ischemic time, Elgendy and coworkers could not demonstrate a significant impact on any end point considered, an unreliable and contradictory finding that highlights the limits of meta-analyses when researchers try to extract information which go beyond the primary end point of the trials.

In our opinion, there are still a few issues to address, following the latest publications on AT: (I) is it reasonable to expect a reduction in mortality with routine AT in future trials? (II) is it reasonable to design future trials imposing routine use of AT, rather than selective use in patients with angiographic evidence of thrombus? (III) can we accept a benefit on "softer" end points, such as reduction in infarct size and hospitalizations due to heart failure, as a reasonable evidence to support the use of AT? (IV) is the increase in stroke rate a real issue with AT?

(I)   Regarding the first question, we believe that a reduction in mortality by any adjunctive treatment will be extremely difficult to prove in randomized trials, given the dramatic improvement in the management of STEMI over the last 20 years. It is also evident that AT with currently available devices has a very limited potential to impact on mortality, if any. Other factors impact on mortality, as shown by the INFUSE-AMI trial, such as the location of the occlusion in the proximal vs mid left anterior descending artery (14), and a delay to reperfusion >3 hours (15);

(II) In randomized trials imposing routine AT in all STEMI patients, the potential benefit obtained in patients with high thrombotic burden is diluted among patients who may only get the risks of AT without any reasonable advantage. In the MUSTELA (MUltidevice Thrombectomy in Acute ST-Segment ELevation Acute Myocardial Infarction) randomized trial we previously failed to demonstrate that AT could reduce infarct size, even when used only in patients with high thrombotic burden (16). However, AT was associated with significantly higher rate of STR (57.4% *vs.* 37.3%; P=0.004), of final myocardial blush 3 (68.3% *vs.* 52.9%; P=0.03), and with lower rate of microvascular obstruction (11.4% *vs.* 26.7%; P=0.02). Although the benefit of AT on infarct size was smaller than expected, leading to the failure of the primary end point, we still believe that a larger patient population might have allowed for the detection of a significant benefit. In our opinion, future thrombectomy trials should focus exclusively on patients with high thrombotic burden, also reflecting the attitude of physicians in everyday practice, where AT is performed only in the presence of angiographically relevant thrombus;

(III) If AT cannot save lives, at least it can help saving muscle. In our opinion, the available evidence demonstrates that AT improves surrogate end points of successful myocardial reperfusion, such as higher STR, myocardial blush grade 3, and lower distal embolization (4,10,16,17). The INFUSE-AMI and MUSTELA trials failed to prove a reduction in infarct size at MRI with AT, showing that other factors (ischemic time, amount of jeopardized myocardium) have a prevalent effect. Nevertheless, the benefit of AT appears intuitive to whoever retrieved large amounts of thrombotic material from a coronary artery during pPCI; a tight similarity exist with the use of embolic protection devices for carotid artery stenting, whose clinical benefit is still unproven, but whose necessity is self-evident to most interventionists;

(IV) No intervention is risk-free, and AT is no exception. The TOTAL trial reported for the first

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time a safety issue with AT, since stroke occurred more frequently (0.7% *vs.* 0.3%; hazard ratio 2.06; 95% CI 1.13–3.75; P=0.02) (17). However, if the mechanism of stroke were embolization of thrombus or air due to manipulation of the thrombectomy catheter, it is difficult to explain why stroke continued to occur more frequently in the AT arm between 30 and 180 days (1.0% *vs.* 0.5%; hazard ratio 2.08; 95% CI 1.29–3.35; P=0.002), possibly reflecting the play of chance. In the meta-analysis by Elgendy, the increase in the risk of stroke with AT was nonsignificant (0.6% *vs.* 0.4%; RR 1.45; 95% CI 0.96–2.21; P=0.08) (10). In our opinion, if a meta-analysis on >20,000 patients cannot rule out a chance finding, this question will hardly find a definitive answer. Nevertheless, AT requires expertise and its complexity should not be underestimated by the physician; in particular, extreme caution should be applied when performing AT in the left main trunk, and in the ostial segment of the left anterior descending, circumflex and right coronary artery, as thrombus may be dislodged in the aorta during advancement and retrieval of the thrombectomy catheter. Moreover, continuous suction should always be applied to the catheter during its retrieval from the coronary artery into the guiding catheter.

In conclusion, AT remains an important tool in the hands of the interventional cardiologist when dealing with extensive coronary thrombus during pPCI; if performed correctly, it can prevent distal embolization and the entailed myocardial damage, although it does not reduce mortality. Expertise is required in order to minimize the risk of brain embolization during maneuvering of the aspiration catheter.

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None.

Footnote

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