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Clinical impact of thrombectomy in acute ST-elevation myocardial infarction: an individual patient-data pooled analysis of 11 trials

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Aims Thrombectomy in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) is associated to better myocardial reperfusion. However, no single trial was adequately powered to asses the impact of thrombectomy on long-term clinical outcome and to identify patients at higher benefit. Thus, we sought to assess these issues in a collaborative individual patient-data pooled analysis of randomized studies (study acronym: ATTEMPT, number of registration: NCT00766740).

Methods and results Individual data of 2686 patients enrolled in 11 trials entered the pooled analysis. Primary endpoint of the study was all-cause mortality. Major adverse cardiac events (MACE) were considered as the occurrence of all-cause death and/or target lesion/vessel revascularization and/or myocardial infarction (MI). Subgroups analysis was planned according to type of thrombectomy device (manual or non-manual), diabetic status, IIb/IIIa-inhibitor therapy, ischaemic time, infarct-related artery, pre-PCI TIMI flow. Clinical follow-up was available in 2674 (99.6%) patients at a median of 365 days. Kaplan–Meier analysis showed that allocation to thrombectomy was associated with significantly lower all-cause mortality ($P = 0.049$). Thrombectomy was also associated with significantly reduced MACE ($P = 0.011$) and death + MI rate during the follow-up ($P = 0.015$). Subgroups analysis showed that thrombectomy is associated to improved survival in patients treated with IIb/IIIa-inhibitors ($P = 0.045$) and that the survival benefit is confined to patients treated in manual thrombectomy trials ($P = 0.011$).

Conclusion The present large pooled analysis of randomized trials suggests that thrombectomy (in particular manual thrombectomy) significantly improves the clinical outcome in patients with STEMI undergoing mechanical reperfusion and that its effect may be additional to that of IIb/IIIa-inhibitors.

Keywords ST-elevation myocardial infarction • Thrombectomy • Primary PCI • Long-term clinical outcome

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Introduction

Primary percutaneous coronary intervention (PCI) has been shown to provide mortality benefit compared with thrombolysis, mainly because of better and sustained optimal coronary perfusion.[1] However, despite epicardial recanalization with TIMI 3 flow, myocardial reperfusion is not achieved in a relevant percentage of ST-elevation myocardial infarction (STEMI) patients, with a significant impact on long-term survival.[2–4] Accordingly, a series of adjunctive devices with different design and mechanism of action have been developed and tested in clinical studies with conflicting results.[5] A meta-analysis of prospective randomized trials[6] suggested that the use of thrombectomy devices, but not of distal protection devices, is associated with a significant reduction of angiographically evident distal embolization and no-reflow (as assessed by post-procedural myocardial blush grade (MBG) and ST-segment resolution). As angiographic and electrocardiographic markers of myocardial reperfusion are well-known predictors of late clinical events,[3,7–10] the use of thrombectomy may also translate into improved clinical outcome. Unfortunately, no published study was specifically designed and adequately powered to asses long-term clinical outcome. Yet, recent data from a large single-centre trial showed an advantage of thrombus-aspiration use in terms of mortality at 1 year follow-up[11] and a recent meta-analysis of nine randomized trials showed an advantage of thrombus-aspiration in terms of early (up to 30 days) mortality.[12] As such promising observations deserve further evaluations,[13] we have designed and performed a pooled analysis of the individual patient data of prospective randomized trials comparing standard PCI with or without thrombectomy to evaluate the impact of thrombectomy use on clinical outcome.

Methods

The study protocol has been registered in the clinicaltrials.gov website (number of registration: NCT00766740), has been drafted and submitted for publication before the first analysis was undertaken and has been published in details in a study design manuscript.[14]

A systematic MEDLINE database search (www.ncbi.nlm.nih.gov) for studies comparing PCI with thrombectomy with standard PCI was conducted according to a modified Robinson and Dickersin strategy.[15] Keywords were 'STEMI', 'randomized', 'thrombus aspiration', and 'thrombectomy'. Furthermore, the TCT (http://www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (http://www.americaheart.org), and ESC (www.escardio.org) websites were searched for pertinent abstracts and expert slides presentations between October 2003 and February 2008. No language restriction was applied.

Inclusion criteria for selected studies were: (i) comparison of thrombectomy with standard PCI in patients with STEMI; (ii) randomized treatment allocation. Exclusion criteria were: (i) equivocal treatment allocation processes.

Fifteen studies were published as full papers[16–30] and two additional studies[31–32] were reported as abstract[31] or expert slides presentation.[32]

The 15 principal investigators of these 17 identified studies were contacted by mail or by fax to participate into the ATTEMPT study (pooled Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual PatienT data). The study flowchart is depicted in *Figure 1*. Each principal investigator who agreed to participate into the study was asked to complete a structured patient-level database including a series of key baseline clinical and angiographic data as well as the longest available clinical outcome data of each patient previously enrolled in the corresponding trial. The modality of follow-up update was not defined in the study protocol.

The requested dataset included: sex (male or female), age (years), diabetes (yes or no), rescue PCI (yes or no), usage of IIb/IIIa-inhibitors (yes or no), infarct-related artery [left anterior descending artery (LAD), left circumflex artery (LCX), or right coronary artery (RCA)], multivessel disease (yes or no), baseline TIMI flow 0 or 1 (yes or no), time from symptoms to balloon/cath-lab (minutes), thrombectomy device used (name of the device), device efficacy (device able to reach and treat the culprit lesion), and long-term clinical follow-up [death for any cause, time to death, myocardial infarction (MI), time to MI, target lesion/vessel revascularization (TLR/TVR), time to TLR/TVR]. Such individual patient data have been sent to the study coordinator (M.D.V.) who was responsible for data consistency checking (matching against previous publication of the trials as well as coherence controls) and for final pooling in a single database. A statistical expert in the field of meta-analysis (G.B.Z.) was responsible for statistical analyses.

Sample size calculation

A meta-analysis of randomized trials comparing thrombectomy with standard PCI in patients with STEMI[6] showed a rate of post-procedural MBG 3 significantly higher in the thrombectomy group with an OR estimate of 2.3. Moreover, van't Hof *et al.* demonstrated that post-PCI MBG is a strong predictor of long-term mortality in patients with STEMI treated with primary PCI. In particular, they reported a long-term total mortality rate of 3% in patients with post-PCI MBG 3 and of 29% in patients with post-PCI MBG <3.[3] Considering these results, we anticipated a sample size of 1350 patients (675 for each randomization arm) to demonstrate, with an alpha risk of 5% and a beta risk of 20%, a survival advantage at 1 year using thrombectomy compared with standard PCI.

Primary endpoint

The primary endpoint of the study was the comparison of all-cause mortality between patients randomized to thrombectomy or standard PCI.

Secondary endpoints

Secondary endpoints of the study were survival free from MI, TLR or TVR, major adverse coronary events (MACE: death + MI + TLR/TVR) and death + MI between patients randomized to thrombectomy or standard PCI.

Pre-defined subgroup analyses

The comparison of all-cause mortality between patients randomized to thrombectomy and standard PCI was performed according to the following pre-defined subgroups:[14]

(1) treated by manual thrombectomy devices or non-manual thrombectomy devices
(2) with or without diabetes mellitus
(3) undergoing primary PCI or rescue PCI (after failed thrombolysis)
(4) treated or not treated with IIb/IIIa-inhibitors
(5) different ischaemic time (pre-defined time intervals: ≤ 3, $>3 \leq 6$, >6 h)
(6) infarct-related artery (LAD, LCX, or RCA)
(7) pre-PCI TIMI flow (TIMI 0–1 or TIMI 2–3)

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation or median (first to third quartiles) and categorical variables as *n* (%),

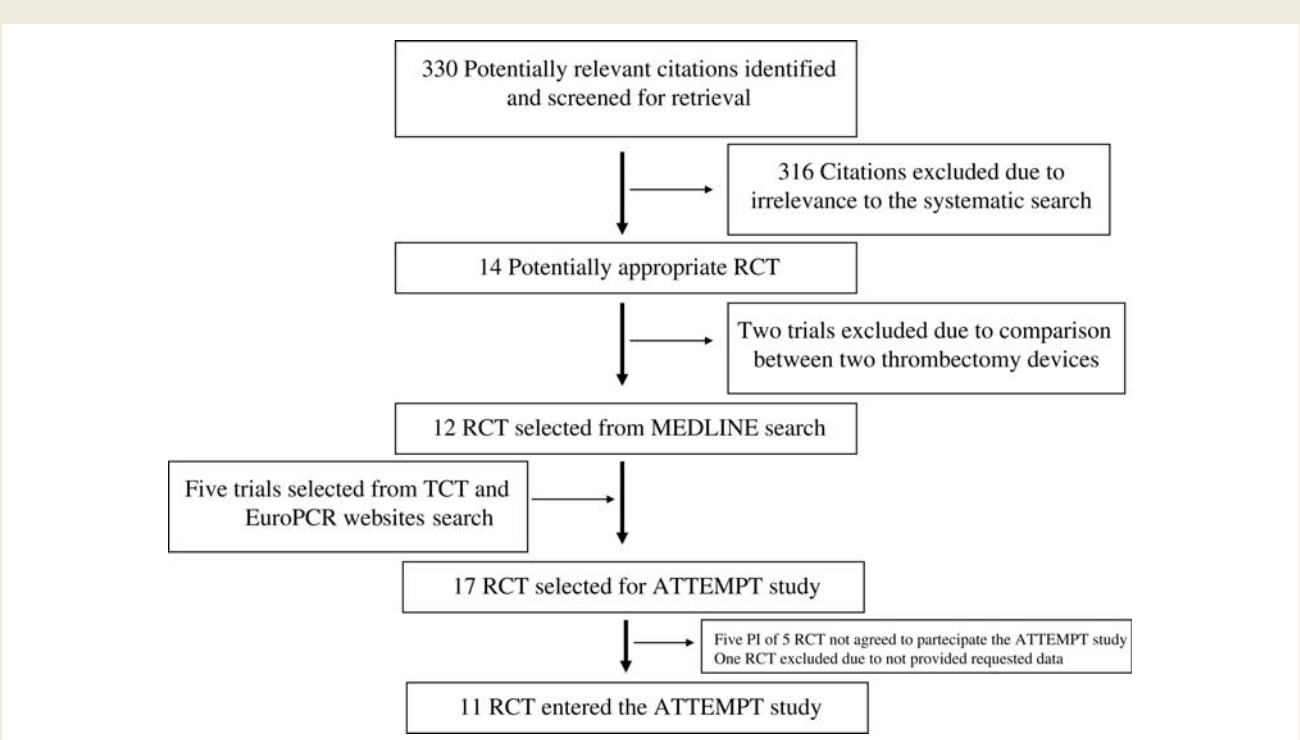

Figure 1 Flow-chart of the systematic search process (RCT, randomized controlled trials; PI, principal investigator).

unless otherwise stated. Statistical pooling has been performed with the Peto fixed effect method for patient-level analysis (according to event counts reported at the longest available follow-up) as well as with a random effect method with generic inverse variance weighting (according to risk estimates obtained with Cox proportional hazard analysis). Thus, we have been able to compute pooled odds ratios (OR) with their corresponding 95% confidence intervals. Kaplan–Meier curves have been computed for survival and event-free survival analyses, both crude and stratified by study, with statistical testing based on log-rank test. A two-tailed *P*-value of 0.05 was chosen as cut-off for statistical significance at hypothesis testing, whereas statistical inconsistency was appraised by means of I^2, with values more than 50% identifying subsets with at least moderate heterogeneity. The internal validity and quality of the individual studies entering the pooled analysis have been performed according to the Cochrane collaboration's tool for risk of bias assessment.[33] Publication bias has been appraised by means of funnel plot inspection and Egger test.[34]

Results

Study population

Ten principal investigators who authored 11 of 17 eligible randomized studies agreed to participate into the study and provided the requested data for each patient enrolled in the corresponding trial.

A total of 2686 patients entered the present pooled analysis: 1347 (50.1%) subjects randomized to PCI with thrombectomy device use and 1339 (49.9%) randomized to standard PCI.

The key protocol characteristics of the 11 randomized studies are summarized in *Table 1*. As shown in *Table 1*, the updated clinical follow-up available for the present analysis was significantly extended compared with that previously published for the majority of the studies. As a result, from a total of 2686 patients clinical follow-up was available in 2674 (99.6%) patients at a median of 365 days (first to third quartiles 232–365; mean 380 ± 272 days; follow-up time interval: 6–1594 days). In particular, clinical follow-up was available in 2470 patients at 6 months, in 1896 patients at 9 months, in 1685 patients at 12 months, in 374 patients at 18 months, in 296 patients at 24 months, and in 281 patients at more than 24 months.

The clinical and angiographic data collected in the pooled ATTEMPT population were similar between patients randomized to thrombectomy or standard PCI (*Table 2*).

The assessment of internal validity and quality for each study included in the analysis is reported in *Table 3*.

Primary endpoint

Kaplan–Meier analysis at the longest available follow-up, either crude (*Figure 2*) or stratified by study (which provided similar results for direction and magnitude of statistical significance), showed that allocation to thrombectomy was associated with reduced all-cause mortality (log-rank $P = 0.049$). A similar result was provided by Peto fixed effect analysis, showing that thrombectomy was associated with significantly fewer deaths (OR = 0.71, 95% CI 0.49–1.00; $P = 0.05$) when compared with standard PCI. Notably, no evidence of heterogeneity (P for heterogeneity >0.10), statistical inconsistency ($I^2 < 50\%$), or small study bias (Egger test >0.05) was evident (*Figure 3*). The result was similar in the analysis performed excluding the two studies not yet published as full paper.

Table 1 Key characteristics of the trials entered the ATTEMPT study and ATTEMPT FU length

Study	Design	Thrombectomy device	Timing of randomization	Angiographic inclusion criteria	Main exclusion criteria	Number of patients		Stenting rate	Complications of thrombectomy device use	Longest published clinical FU (days)	FU length (days) for ATTEMPT study (median, 1st–3rd quartiles)
						SP	T				
Antoniucci *et al.*[18]	Single centre	Non-manual T (Angiojet)	After coronary angiography	IRA diameter ≥2.5 mm	Ischaemic time >12 h Previous MI Rescue PCI	50	50	98%	Not reported	30	180 (180–180)
REMEDIA[20]	Single centre	Manual T (Diver CE)	Before coronary angiography	None	Ischaemic time >12 h	49	50	100%	None	30	371 (212–516)
X-AMINE ST[21]	Multicentre	Non-manual T (X-Sizer)	After coronary angiography	*De novo* lesion Single V disease baseline TIMI flow 0–1 Thrombus containing lesion IRA diameter ≥2.5 mm Absence of tortuosity or severe calcification in IRA	Ischaemic time >12 h Previous PCI in IRA Rescue PCI Killip class ≥3	101	100	99%	One case of coronary arterio-venous fistola at angio-FU	180	180 (180–180)
Noel *et al.*[31]	Single centre	Manual T (Export)	After coronary angiography	Baseline TIMI flow <3	Ischaemic time >12 h	26	24	100%	Not reported	In hospital	6 (6–6)
DEAR-MI[22]	Single centre	Manual T (Pronto)	Before coronary angiography	None	Ischaemic time >12 h Cardiogenic shock Previous MI Contraindication to Gp IIb/IIIa-inhibitors	74	74	98%	Not reported	In hospital	657 (429–862)
VAMPIRE[28]	Multicentre	Non-manual T (TVAC)	Before coronary angiography	Absence of LM disease IRA diameter ≥2.5 and ≤5 mm	Ischaemic time >24 h Rescue PCI Cardiogenic shock Previous CABG LM disease	175	180	94%	Not reported	240	895 (239–1192)
Kaltoft *et al.*[23]	Single centre	Non-manual T (Rescue)	After coronary angiography	Absence of LM disease IRA suitable for thrombectomy according to treating physician	Ischaemic time >12 h Previous CABG Rescue PCI LM disease Cardiogenic shock	107	108	96%	None	30	365 (365–365)

De Luca *et al.*[24]	Single centre	Manual T (Diver CE)	After coronary angiography	Identifiable thrombus on IRA Culprit vessel LAD 3 V disease Baseline TIMI flow 0–1	Ischaemic time >12 h Previous MI Previous CABG Severe valvular heart disease	38	38	100%	One case of coronary dissection	180	468 (384–520)
PIHRATE[32]	Multicentre	Manual T (Diver CE)	After coronary angiography	Baseline TIMI flow 0–1	Ischaemic time >6 h ST-elevation >3 mm in one lead	96	100	98%	Not reported	180	180 (180–180)
EXPIRA[30]	Single centre	Manual T (export)	After coronary angiography	IRA diameter >2.5 mm TS>3 Baseline TIMI flow 0–1 *De novo* lesion Absence of LM or 3 V disease	Ischaemic time >12 h Previous MI Previous CABG Rescue PCI LM/3 V disease Cardiogenuic shock Contraimdication to Gp IIb/IIIa-inhibitors Severe valvular heart disease	87	88	100%	Not reported	270	270 (270–270)
TAPAS trial[27]	Single centre	Manual T (Export)	Before coronary angiography	None	Ischaemic time >12 h Rescue PCI Life expectancy <6 month	536	535	92%	None	365	365 (365–365)
ATTEMPT study population	—	—	—	—	—	1339	1347	—		—	365 (232–365)

Table 2 Baseline key clinical and angiographic characteristics of the ATTEMPT study population

	ATTEMPT thrombectomy ($n = 1347$)	ATTEMPT standard PCI ($n = 1339$)	*P*-value
Age (mean ± SD)	63 ± 12	63 ± 12	1.0
Sex (M), *n* (%)	891 (66%)	894 (67%)	0.73
Diabetes, *n* (%)	183 (13%)	185 (14%)	0.86
Failed TL, *n* (%)	16 (1%)	14 (1%)	0.72
IIb/IIIa-inhibitors, *n* (%)	907 (67%)	880 (66%)	0.37
Time to reperfusion (min) (mean ± SD)	269 ± 184	281 ± 212	0.09
MVD, *n* (%)	555 (41%)	566 (42%)	0.57
Baseline TIMI flow 0–1, *n* (%)	944 (70%)	968 (72%)	0.20
Culprit vessel			
LAD, *n* (%)	578 (43%)	600 (45%)	0.32
LCX, *n* (%)	181 (13%)	167 (12%)	0.45
RCA, *n* (%)	462 (34%)	461 (34%)	0.94
Crossover	105 (7.7%)	29 (2.2%)	
FU length (median; 1st–3rd quartiles) (mean ± SD)	365 (197–365) 384 ± 275	365 (180–365) 376 ± 269	0.43

PCI, percutaneous coronary intervention; SD, standard deviation; TL, thrombolysis; MVD, multi-vessels disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; FU, follow-up.

Secondary endpoints

Kaplan–Meier analyses at the longest follow-up available, either crude or stratified by study (which provided similar results for direction and magnitude of statistical significance), showed that allocation to thrombectomy was associated with significantly fewer MACE (log-rank $P = 0.011$) (*Figure 4*) and death + MI (log-rank $P = 0.015$), but non-significant differences in MI (log-rank $P = 0.126$) or in TLR/TVR (log-rank $P = 0.126$). Similar results were provided by Peto fixed effect analysis, showing that thrombectomy was associated with significantly fewer MACE (OR = 0.80, 95% CI 0.65–0.98; $P = 0.03$) and death + MI (OR = 0.70, 95% CI 0.52–0.93; $P = 0.02$) when compared with standard PCI, whereas there were non-significant differences in MI (OR = 0.72, 95% CI 0.47–1.10; $P = 0.13$) or TLR/TVR (OR = 0.87, 95% CI 0.67–1.12; $P = 0.27$). No evidence of heterogeneity (all *P* for heterogeneity >0.10), statistical inconsistency (all $I^2 < 50\%$), or small study bias (all *P* at Egger test >0.05) was evident in any of the analyses.

Subgroups analysis

Type of thrombectomy device

The ATTEMPT study population was divided into two groups considering the type of thrombectomy device used: manual thrombectomy group (1815 patients enrolled in trials with use of Diver CE, Pronto, and Export catheters) and non-manual thrombectomy group (871 patients enrolled in trials with use of X-Sizer, Angiojet, Rescue, and TVAC devices).

In the manual thrombectomy group, Kaplan–Meier analyses at the longest follow-up available showed that allocation to thrombectomy was associated with significantly fewer deaths (log-rank $P = 0.011$) (*Figure 5A*), whereas in the non-manual thrombectomy group, the allocation to thrombectomy was associated to similar mortality compared with standard PCI (log-rank $P = 0.481$) (*Figure 5B*).

Clinical and angiographic subgroups

There was no qualitative difference in mortality when splitting the study population according to the presence or absence of diabetes, to shorter, intermediate or longer time-to-reperfusion, to type of culprit artery (left anterior descending or circumflex artery or RCA) and to pre-PCI TIMI flow (0–1 or 2–3).

Conversely, subgroup analysis according to administration of IIb/IIIa-inhibitors showed that randomization to thrombectomy was associated to a survival benefit in the subgroup of patients treated with IIb/IIIa-inhibitors (1787 patients; log-rank $P = 0.045$; HR 0.61, 95% CI 0.38–0.90) and not in those not receiving this drugs (899 patients; log-rank $P = 0.843$; HR 0.93, 95% CI 0.48–1.80).

Discussion

The failure to achieve myocardial tissue reperfusion is known to be the main complication limiting the early and long-term clinical benefit of mechanical reperfusion in patients with STEMI. Among the different strategies to limit the 'no reflow phenomenon', reducing distal embolization by thrombectomy devices use is a promising one.[13] The present pooled analysis on 2686 individual patients data (from 11 randomized trials) shows that the adjunct of thrombectomy during mechanical reperfusion is associated to a detectable improvement of survival at follow-up with an estimated number needed to treat to prevent one death at 1 year of 62. Moreover, we found that the survival advantage of thrombectomy is confined to patients treated by simple manual thrombectomy catheters with an estimated number needed to treat to prevent one death at 1 year of 34.

Such findings extend the recently published single-centre TAPAS trial results[11] which showed a significantly lower cardiac mortality at 12 months in the group of patients treated with manual thrombectomy. However, the TAPAS trial was not specifically designed

Table 3 Appraisal of internal validity and quality of included studies

Study	Adequate sequence generation	Allocation concealment used	Blinding	Incomplete outcome data addressed in the published FU	Incomplete outcome data addressed in the extended FU	Losses to follow-up <10% in published and extended FU	Uniform and explicit outcome definitions	Free of selective published outcome reporting	Free of selective extended outcome reporting	Free of other bias	Overall risk of bias
Antoniucci *et al.*[18]	Yes (computer generated)	Yes (sealed envelopes)	Yes (angiogram, EKG, SPECT and clinical outcome assessors)	No	Yes (1 patient lost to FU)	Yes	Yes	Yes	Unclear	Yes	Low
REMEDIA[20]	Yes (computer generated)	Yes	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (two patients lost to FU)	Yes	Yes	Yes	Yes	Yes	Low
X-AMINE-ST[21]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Moderate
Noel *et al.*[31]	Unclear	Unclear	Unclear	No	Yes	Yes	No	Unclear	Unclear	Unclear	High
DEAR-MI[22]	Unclear	Unclear	Yes (angiogram, and EKG assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Moderate
VAMPIRE[28]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (eight patients lost to FU)	Yes	Yes	Yes	Unclear	Yes	Moderate
Kaltoft *et al.*[23]	Yes (computer generated)	Yes (external personnel)	Yes (angiogram, EKG, SPECT and clinical outcome assessors)	No	No	Yes	No	Unclear	Unclear	Yes	Moderate
De Luca *et al.*[24]	Unclear	Unclear	Yes (angiogram, EKG, echo and clinical outcome assessors)	No	No	Yes	Yes	Yes	Unclear	Yes	Low
PIHRATE[32]	Yes (computer generated)	Yes (sealed envelopes)	Yes (angiogram, EKG and clinical outcome assessors)	No	Yes (1 patient lost to FU)	Yes	Yes	Unclear	Unclear	Yes	Low
EXPIRA[30]	Unclear	Unclear	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Yes	Yes	Low
TAPAS[27]	Yes (computer generated)	Yes (computerized voice–response system)	Yes (angiogram, EKG and clinical outcome assessors)	No	No	Yes	Yes	Yes	Yes	Yes	Low

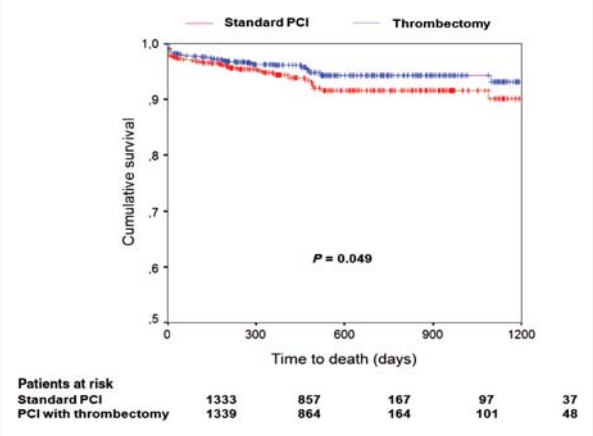

Figure 2 Kaplan–Meier curves for cumulative survival; log-rank $P = 0.049$.

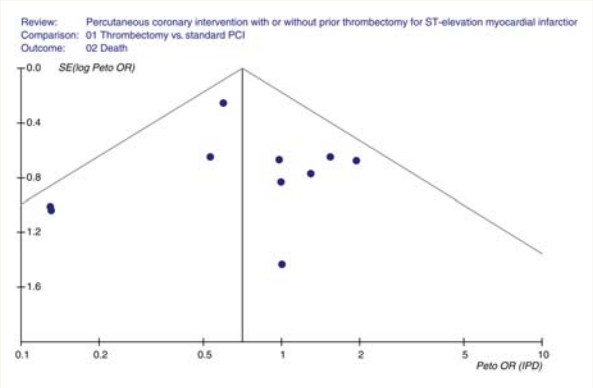

Figure 3 Funnel plot graph for mortality.

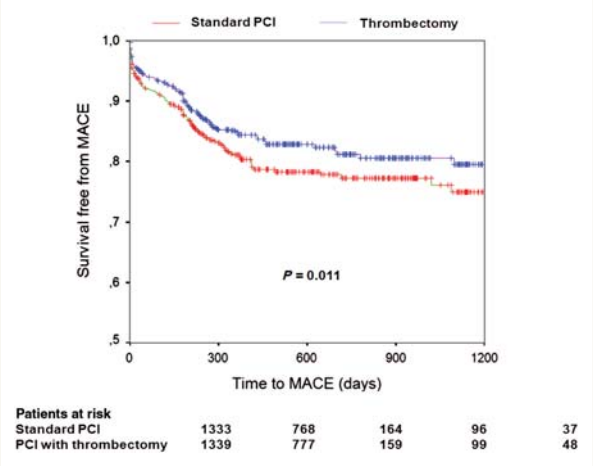

Figure 4 Kaplan–Meier curves for MACE-free survival; log-rank $P = 0.011$.

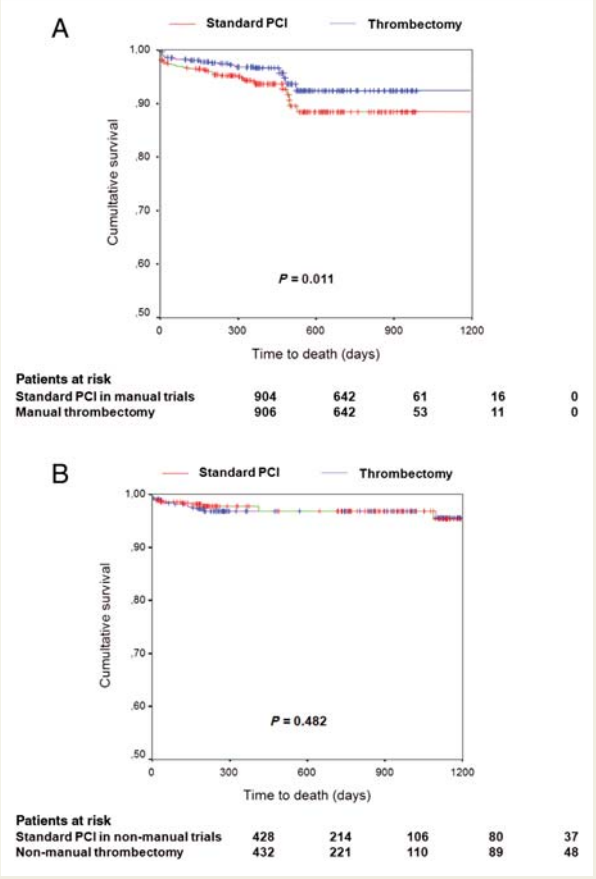

Figure 5 (*A*) Kaplan–Meier curves for cumulative survival in the manual thrombectomy group and corresponding control group; log-rank $P = 0.011$. (*B*) Kaplan–Meier curves for cumulative survival in the non-manual thrombectomy group and corresponding control group; log-rank $P = 0.481$.

and powered to assess the difference between thrombectomy and standard PCI at the long-term clinical follow-up.[35] In the absence of large, multicentre trials adequately powered to assess long-term outcome in patients with STEMI treated with PCI and thrombectomy, the best way to evaluate the role of this treatment is pooling individual patient data collected by different investigators in different randomized studies of standard PCI vs. PCI with thrombectomy. Indeed, pooled analyses of randomized trials using individual patient data are known to provide more accurate results compared with simple meta-analyses,[36] so that they have been used to answer the key questions in the field of cardiovascular medicine like the benefit of prolonged anti-platelet therapy,[37] the benefit of beta-blockade after MI,[38] the impact of mechanical over pharmacological reperfusion in STEMI[39] and the safety of drug-eluting stents in selected patients with coronary artery disease.[40] Thus, we designed and carried out this collaborative study, which allowed not only to collect a large number of patients, pooling the majority of available randomized trials, but also to significantly extend the clinical follow-up of some of the studies previously published with a short clinical follow-up. As a consequence, the number of patients with at least 1 year follow-up (i.e. 1685)

was larger than the calculated sample size for a reliable assessment of the primary endpoint. Moreover, as the very late outcome of patients treated by thrombectomy was not previously investigated, the present study provides novel information on a subgroup of patients with follow-up extended beyond 1 year. In keeping with the hypothesis of a long-lasting thrombectomy-induced benefit, the survival curves of thrombectomy-treated patients continued to differ from that of control patients throughout the study period.

Large studies are also needed to assess if subgroups of patients have more to gain from the application of this novel treatment. Thus, we planned to collect data allowing a series of pre-defined clinical and angiographic subgroup analyses. Interestingly, the benefit of thrombectomy was more evident in patients who received IIb/IIIa-inhibitors thus suggesting a possible additive benefit of thrombectomy in patients treated with IIb/IIIa-inhibitors. It might be speculated that pharmacological and mechanical thrombus remodelling are synergic to obtain the best myocardial reperfusion and, consequently, the best clinical outcome. Indeed, in the ATTEMPT study, patients treated by both thrombectomy and IIb/IIIa-inhibitors had the lower mortality rate, those who had none of these treatments had the higher mortality rate, patients receiving only one of these therapies exhibiting intermediate outcome (*Figure 6*). Accordingly, such observations seem to support the last release of the ESC guidelines on the management of patients with STEMI which recommends the use of both IIb/IIIa-inhibitors and thrombus-aspiration to prevent no-reflow.[41]

Finally, once the use of thrombectomy to reduce distal embolization is accepted, the issue of device selection emerges. More complex (non-manual) devices are probably more effective than manual thrombus-aspiration catheters in extracting atherothrombotic particles from the coronary arteries. Yet, they are bulky, require longer learning curves and selected coronary anatomies. Conversely, manual thrombus-aspirating catheters are user-friendly, not associated with specific complications, and suitable for most coronary anatomies. In the absence of large studies comparing the simple manual thrombectomy catheters with the more complex non-manual thrombectomy devices, the present study does not support the routine use of non-manual thrombectomy. Possible benefits of complex non-manual thrombectomy devices might be confined to selected subgroups of patients with larger thrombus burden and device-favourable coronary anatomy and need to be tested in *ad hoc* prospective studies.

Study limitations

The results obtained in the present study may have been influenced by the quality of each original trial. In particular, no further quality control has been performed nor any restriction in trial size, publication status, and updated clinical follow-up length or modality of assessment have been applied. All these limitations were anticipated[14] and have been accepted in the effort to achieve the goal to collect in a single database the largest number of patients randomized in thrombectomy trials. Moreover, the validated statistical analyses applied allowed to show no evidence of heterogeneity, statistical inconsistency, or small study bias in any of the analyses.

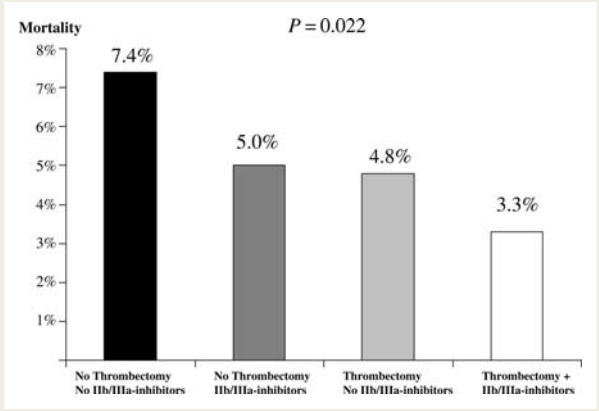

Figure 6 Mortality rates observed in the ATTEMPT database according to thrombectomy and to administration of IIb/IIIa-inhibitors. Comparison between four treatment subgroups performed by Fisher test.

Another limitation of the present study is the exclusion of six eligible trials (accounting for 1019 patients) due to lack of agreement by the principal investigators to participate the study. As a consequence, the participation was unbalanced in favour of manual thrombectomy trials (indeed 88% of studies testing manual thrombectomy were included when compared with 44% of studies testing non-manual thrombectomy). Thus, the hypothesis that the overall positive result may have been driven by manual thrombectomy studies cannot be discarded.

The subgroup analysis generated small subgroups of patients so that the survival analyses were underpowered. Yet, as no large assessment of clinical benefit of thrombectomy according to the key angiographic and clinical parameters has previously been conducted, the present results should be considered as hypothesis-generating and deserve further evaluations.

Finally, the different endpoint definitions for MI, TVR, or TLR adopted in the trials included may have limited the strength of the secondary endpoints analysis. However, the presence of such possible heterogeneity cannot have influenced the primary endpoint which was the unequivocal all-cause mortality.

Conclusions

The pooled analysis of patients with STEMI enrolled in 11 randomized trials showed that the adjunct of thrombectomy (in particular manual thrombectomy) during mechanical reperfusion improves late clinical outcome and that this benefit is evident in patients receiving IIb/IIIa-inhibitors.

Conflict of interest: none declared.

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CARDIOVASCULAR FLASHLIGHT

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Critical aortic stenosis in combination with an aorto-left ventricular tunnel: a rare congenital malformation[111]

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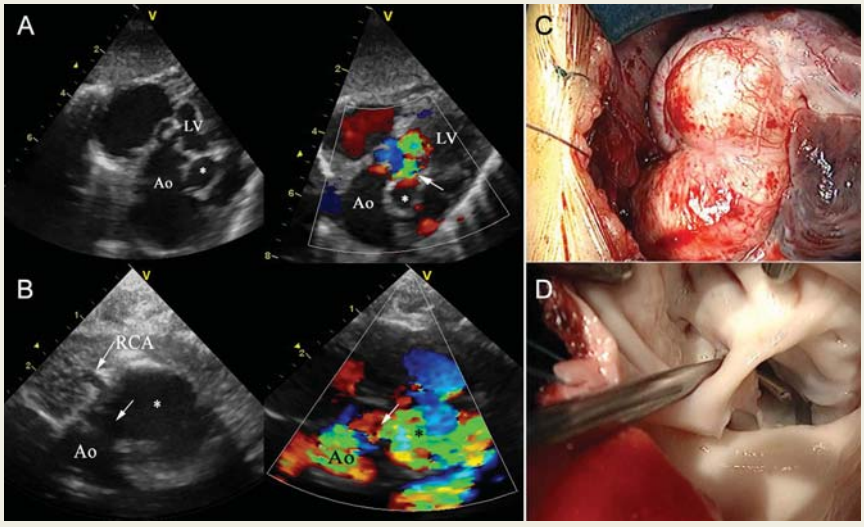

On the first day of live, a female newborn with a three out of six systolic murmur on the right sternal border showed signs of heart failure: dyspnoea, tachypnoe, low blood pressure. On echocardiography, the diagnosis of a critical aortic stenosis with a pin whole ostium was established and a prostaglandin infusion was started.

The aortic valve appeared tricommissural with an opening from the right sinus of valsalva to a lateral and anterior extra-aortic tunnel (*Panel A*), the right coronary artery only few millimetre separate. In subcostal echo views, the tunnel could be demonstrated in a more longitudinal axis from its beginning lateral of the aorta (Ao) to its end in the left ventricular outflow tract (*Panel B*). The flow through this tunnel was antegrade from the left ventricle (LV) to the aorta in systole with a backflow Ao–LV in diastole. The maximum systolic instantaneous gradient on CW Doppler as measured through the stenotic aortic valve was 95 mmHg, mean Doppler gradient 42 mmHg.

On the fourth day of live, a ballon valvuloplasty was performed and the pressure gradient dropped to maximum 48 and mean 28 mmHg on Doppler with a mild aortic regurgitation through the valve. Seven months later aortic stenosis became again clinically relevant (101/46 mmHg maximum and mean gradients).

At operation, the enlarged aortic root bulging towards the pulmonary trunk was found (*Panel C*). The dysplastic aortic valve was excised (see Supplementary material online, *Movie S1*). The aortic annulus was incised towards the mouth of the tunnel (*Panel D*). Thus, the aortic annulus was enlarged to accommodate the smallest available mechanical heart valve prosthesis. The aortic root was augmented with a patch. The post-operative course was uneventful.

An aorto-left ventricular tunnel is a rare congenital malformation where a channel connects the ascending Ao above the sinotubular junction to the cavity of the LV. Associated lesions of the aortic valve occur in ~20%, ranging from bicuspid valves without obstruction to dysplasia and even atresia. Usually, after adequate tunnel closure, the aortic valvar mechanism is not a clinical problem during follow-up. However, in some patients, aortic insufficiency may increase. In our described case, a severe dysplasia required early valve replacement.

Supplementary material is available at *European Heart Journal* online.

Panel A Transthoracic echocardiography, subcostal view: demonstrating the connection of the LV with the Ao via the stenotic aortic valve and the left ventricular aortic tunnel (asterisk). Colour Doppler shows the regurgitation from the Ao to the LV through the left ventricular aortic tunnel (arrow).

Panel B Transthoracic echocardiography, parasternal short axis: shows the connection of the left ventricular aortic tunnel (asterisk) with the Ao in the region of the right aortic coronary cusp. Colour Doppler proves blood flow across this connection (arrow). RCA indicates the right coronary artery.

Panel C At operation, a prominent area of the ascending aorta just above the tunnel was found.

Panel D Surgeons' view from the aorta. Depiction of the tunnel (probe through the tunnel).