

Individual patient-data meta-analysis comparing clinical outcome in patients with ST-elevation myocardial infarction treated with percutaneous coronary intervention with or without prior thrombectomy. ATTEMPT study: A pooled Analysis of Trials on Thrombectomy in acute Myocardial infarction based on individual Patient data

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Background: Available data from randomized trials on thrombectomy in patients with ST-elevation myocardial infarction (STEMI) have shown favorable trends in myocardial reperfusion. However, few data are available on the effect of thrombectomy on clinical outcome. Thus we have designed a collaborative individual patient-data meta-analysis which aimed to assess the long-term clinical outcome in STEMI patients randomized to percutaneous coronary intervention (PCI) with or without thrombectomy.

Method: After a thorough database search, the principal investigators of randomized trials comparing thrombectomy with standard PCI in patients with STEMI were contacted. Principal investigators as authors of 11 randomized studies agreed to participate and were asked to complete a structured database by providing a series of key pre-PCI clinical and angiographic data as well as the longest available clinical outcome of the patients enrolled in the corresponding trial. The primary end-point of this pooled analysis is the comparison of overall survival rates between patients randomized to PCI with thrombectomy or PCI without thrombectomy. The secondary end-points are survival free from myocardial infarction (MI), target lesion revascularization (TLR), major adverse coronary events (MACE: death + MI + TLR) and death + MI between patients randomized to PCI with thrombectomy or PCI without thrombectomy. A pre-defined subgroup analysis is planned considering the following variables: type of thrombectomy device used, diabetes, rescue PCI, IIB/IIIa-inhibitors use, time-to-reperfusion, infarct-related artery, and pre-PCI TIMI flow.

Implications: This study will provide useful data on the effect of the reported improved myocardial perfusion associated with thrombectomy on the long-term clinical outcome in patients with STEMI.

Keywords: ST elevation myocardial infarction, thrombectomy, primary PCI

Introduction

Primary percutaneous coronary intervention (PCI) has been shown to provide mortality benefits in comparison with thrombolysis, mainly because of better and sustained optimal coronary perfusion.¹ However, despite epicardial recanalization with Thrombolysis in Myocardial Infarction Trial 3 (TIMI 3) flow, myocardial reperfusion is not achieved in up to 40% of patients, with a significant effect on their long-term survival.^{2,3} Atherothrombotic embolization is considered to play an important role in the pathogenesis of this “no-reflow phenomenon.”⁴ Accordingly, a series of adjunctive devices with different

antiembolic properties (thrombectomy or distal protection) has been developed and tested in clinical studies with conflicting results. Nevertheless, a meta-analysis of prospective randomized trials⁵ suggests that the use of thrombectomy devices, but not distal protection devices, may be associated with a significant reduction of angiographically evident distal embolization and with higher rates of myocardial blush grade (MBG) 3 and ST-segment resolution.

Because angiographic and electrocardiographic markers of myocardial reperfusion are well known predictors of late clinical outcome,^{3,6-9} the use of thrombectomy may also translate to a clinical advantage. Unfortunately, most of the trials on thrombectomy have been based on a small sample size and short follow-up for reliable assessment of clinical benefit. Only one, recently published, single-center trial conducted on 1071 patients with ST-elevation myocardial infarction (STEMI), showed an advantage of thrombus-aspiration use in terms of mortality at one year follow-up.¹⁰

To extend the investigation on this issue to a larger population, we have designed a pooled analysis of the individual patient data of prospective randomized trials comparing standard PCI with or without thrombectomy, to evaluate the influence of thrombectomy use on clinical outcome.

Design and method

Study design

Individual patient data meta-analysis. The study protocol was initiated in October 2007 (by FB, MDV, and FC) and the first final manuscript design drafting was completed on January 10th, 2008.

Method

A systematic MEDLINE database search (see <http://www.ncbi.nlm.nih.gov/>) for studies comparing standard PCI with thrombectomy (T) with standard PCI only (SP) was conducted according to a modified Robinson and Dickersin strategy.¹¹ Keywords were “STEMI,” “randomized,” “thrombus aspiration,” and “thrombectomy.” The TCTMD (see <http://www.tctmd.com/>), EuroPCR (see <http://www.europcr.com/>), American College of Cardiology (see <http://www.acc.org/>), America Heart (see <http://www.americaheart.org/>), and European Society of Cardiology (see <http://www.escardio.org/>) websites were searched for pertinent abstracts and expert slide presentations between October 2003 and February 2008. No language restriction was applied.

Inclusion criteria for selected studies were: 1. comparison of T with SP in patients with STEMI; 2. randomized

treatment allocation. The exclusion criterion was the equivocal treatment allocation process.

Thirteen studies published as full papers¹²⁻²⁴ and four additional studies²⁵⁻²⁸ published as abstracts and/or slide presentations (Noel B,²⁸ from the EuroPCR 2005 meeting; the PIHRATE trial;²⁵ the expert slide presentation from the TCTMD 2007 meeting; the EXPIRA trial;²⁶ expert slide presentations on the Transcatheter Cardiovascular Therapeutics website (see <http://www.tct2007.com/>); and the Export study²⁷ expert slide presentations on the Transcatheter Cardiovascular Therapeutics website were identified.

The 15 principal investigators of these 17 identified studies were contacted by mail or fax to participate in the ATTEMPT study (meta-Analysis of Trials on ThrombEctomy in acute Myocardial infarction based on individual Patient data), a meta-analysis based on individual patient data to compare the long-term clinical outcome between thrombectomy and standard PCI in patients with STEMI enrolled in the selected randomized trials.

All 10 principal investigators who agreed to participate were asked to complete a structured database including standard baseline clinical and angiographic data as well as the longest available clinical outcome data of each patient previously enrolled in the corresponding trial.

This individual patient data will be sent to the study coordinator (MDV) who will be responsible for the final pooling in a single database.

A statistical expert (GBZ) will be responsible for statistical analyses. All the principal investigators will be informed about the status of the project by regular newsletters.

End points

The primary end-point of the study will be to compare rates of overall survival in patients randomized to T or SP. Secondary end-points will be survival free from myocardial infarction (MI), target lesion revascularization (TLR), major adverse coronary events (MACE: death + MI + TLR) and death + MI between patients randomized to T or SP.

Pre-defined subgroup analyses

The comparison of clinical outcome between patients randomized to T and SP will be performed according to:

1. Type of thrombectomy device (manual thrombus aspiration devices versus non-manual thrombectomy devices)
2. Presence or absence of diabetes mellitus
3. Rescue PCI or primary PCI

4. Administration or no administration of IIb/IIIa-inhibitors
5. Time-to-reperfusion (≤ 3 h or between 3 h and 6 h or >6 h)
6. Infarct-related artery (LAD or LCX or RCA)
7. Pre-PCI TIMI flow (TIMI 0–1 or TIMI 2–3)

Sample size calculation and study feasibility

A meta-analysis of randomized trials comparing thrombectomy with standard PCI in patients with STEMI⁵ showed a rate of myocardial blush grade 3 (MBG 3) significantly higher in the thrombectomy group: odds ratio [OR] 2.32 (1.28–4.21). Moreover, van't Hof and colleagues demonstrated that the post-PCI MBG is a strong predictor of long-term mortality in patients with STEMI treated with primary PCI. In particular they reported, after a mean follow-up of 1.9 ± 1.7 years, a total mortality rate of 3% in patients with post-PCI MBG 3 and of 29% in patients with post-PCI MBG < 3 .³ Given these results, we anticipated a sample size of 1350 patients to demonstrate an advantage in terms of mortality at one year using thrombectomy, with an alpha risk of 5% and a beta risk of 20%.

Study population

To date, 10 principal investigators of 11 randomized studies agreed to participate in the ATTEMPT study and provided the requested data. The key characteristics of these 11 randomized studies are summarized in Table 1.

The ATTEMPT study population will comprise all the patients enrolled in the randomized studies entered in this single patient data meta-analysis. The key characteristics of the study populations recruited in the 11 studies are summarized in Table 2.

Statistical analysis

Continuous variables will be reported as mean \pm standard deviation or median (1st–3rd quartiles), and categorical variables as n (%), unless otherwise stated. Statistical pooling will be based on the Peto fixed effect method for patient-level analysis (according to event counts reported at the longest available follow-up), and a random effect method with generic inverse variance weighting (according to risk estimates obtained with Cox proportional hazard analysis). In this way we can compute pooled OR and hazard ratios (HR) with their corresponding 95% confidence intervals. Kaplan–Meier curves will be computed for survival and event-free survival analyses, both crude and stratified by study, with statistical testing based on log-rank test. Multivariable analyses, logistic or proportional hazard as appropriate will also be conducted by clustering patients according to each study. A two-tailed p value of 0.05 was chosen as the cut-off for statistical significance at hypothesis testing, whereas we plan to appraise statistical inconsistency by means of I^2 , with values $> 50\%$ identifying subsets with at least moderate heterogeneity. Finally, publication bias will be appraised by means of funnel plot inspection and Egger test.

Table 1 Key characteristics of the trials entered in the ATTEMPT study

Study	Design	Thrombectomy device	Number of patients		Pre-coronary time limit (hours)	Longest published clinical FU
			SPT	T		
VAMPIRE ¹⁹	Multicenter	TVAC	175	180	<24	In hospital
X-AMINE ST ¹⁷	Multicenter	X-Sizer	101	100	<12	Six months
DEAR-MI (19)	Single center	Pronto	74	74	<12	In hospital
Antoniucci et al ¹⁴	Single center	Angiojet	50	50	<6	30 days
REMEDIA ¹⁶	Single center	Diver CE	50	49	<12	In hospital
Noel et al ²⁸	Single center	Export	26	24	<12	In hospital
Kaltoft et al ²⁰	Single center	Rescue	107	108	<12	30 days
De Luca et al ²¹	Single center	Diver CE	38	38	<12	Six months
PIHRATE ²⁵	Multicenter	Diver CE	94	102	<6	Six months
EXPIRA ²⁶	Single center	Export	87	88	<12	Nine months
TAPAS trial ²⁴	Single center	Export	536	535	<12	One year
ATTEMPT study population	–	–	1338	1348	–	–

Abbreviations: FU, follow-up; NA, not available; PCI percutaneous coronary intervention; SP, standard PCI; T, thrombectomy device treatment.

Table 2 Key characteristics of the study population in the 11 trials entered in the ATTEMPT study

Study	Age (mean)	Diabetes (%)	IIB/IIIa inhibitors (%)	Failed TL (%)	Anterior MI ¶(%)	Mean symptom-to balloon time (minutes)	Baseline TIMI flow 0–1 (%)
VAMPIRE ¹⁹	63	26	0	0	51	291*	75
X-AMINE ST ¹⁷	61	22	51	0	52	257	100
DEAR-MI ¹⁸	59	18	100	0	47	130	78
Antoniucci et al ¹⁴	65	17	98	0	40	249	78
REMEDIA ¹⁶	60	21	69	38	45	280§	88
Noel et al ²⁸	60	13	NA	34	44	282	NA
Kaltoft et al ²⁰	64	7	95	0	44	225	69
De Luca et al ²¹	65	21	100	0	100	438	100
PIHRATE ²⁵	60	10	62	0	NA	200	100
EXPIRA ²⁶	66	17	75	0	100	390	100
TAPAS study ²⁴	63	12	92	0	43	187	57

Abbreviations: MI, myocardial infarction; TS, thrombolysis; ¶, in the studies with missing anterior MI rate patients with left anterior descending artery as culprit artery where considered to have anterior MI; §, symptom to angiography time; *, symptom to hospital admission time; NA, not available.

Discussion

The clinical data from a meta-analysis of 18 trials on adjunctive devices in patients with STEMI show that use of thrombectomy devices is associated with better myocardial reperfusion, which does not translate, however, to a lower rate of mortality or MI at 30 days.⁵ This short follow-up time might be insufficient to show a clinical benefit. Of note, two recent non-randomized studies comparing Angio-jet with SP in STEMI patients with a high thrombus burden reported a significant reduction of long-term mortality.^{29,30} Moreover, very recent data from the randomized EXPIRA trial (Sardella, personal communication at TCT 2007 meeting) and the randomized TAPAS trial showed respectively a strong trend toward lower mortality at nine months²⁶ and a significantly lower mortality at 12 months in the group of patients treated with thrombectomy.¹⁰ Therefore the available data support the possible advantage of thrombectomy on long-term clinical outcome. Because angiographic analyses have shown that thrombectomy may have different efficacy in different patients,³¹ the clinical benefit of thrombectomy use may be more pronounced in some subgroups of patients. Thus previous studies showed a greater advantage using thrombectomy for reperfusion in patients with baseline TIMI flow 0–1, baseline thrombus score 3–4 or angiographically evident thrombus-containing lesions.^{16,22} For these reasons, the design of the present study planned for subgroup analyses of patients stratified according to a series of key clinical, angiographic, and procedural variables.

In conclusion the aim of the ATTEMPT study is to assess if thrombectomy, by improving myocardial reperfusion,

can influence the long-term clinical outcome in particular in some high risk subgroups of STEMI patients such as those with a higher thrombus burden or a large amount of myocardium at risk.

Expected study limitations

As a consequence of the ATTEMPT study design, the quality of the results will be influenced by the quality of the design of each original trial. In particular, no quality control has been planned so that each participant principal investigator will be completely responsible for the quality control of the data entered in the ATTEMPT database. No restriction in trial size, publication status (full paper or abstract presentation) and length of updated clinical follow-up has been applied. Consequently, some of the trials included are single-center and/or small-sized, and the length of patient follow-up will be not uniform.

All these anticipated limitations have been accepted in an effort to achieve the goal of wide participation in the study. Such extensive collaboration was sought to better summarize the available data obtained to date by the scientific community. Thus publication bias assessment has been planned according to validated statistical techniques.

Another possible limitation may arise from the fact that different definitions may have been adopted across the trials included in the analysis. In particular, the definition of device failure differed across the studies so that a reliable pooled estimate of device efficacy will not be possible. Nevertheless, the planned primary “intention-to-treat” analysis selected for the

present study is not expected to be influenced by such factors. Moreover, the presence of (minor) heterogeneity among some clinical end-point (like myocardial infarction, target vessel, or target lesion revascularization) definitions adopted across the trials will not influence the primary end-point analysis which is focused on the univocal all-cause mortality.

Disclosure

The authors declare no conflicts or competing interests in this work.

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