Routine Manual Thrombus Aspiration in ST Elevation Myocardial Infarction: End of the TASTE after TOTALity of Data

Selim Topcu

Atatürk University Faculty of Medicine, Department of Cardiology, Erzurum, Turkey

ABSTRACT

Introduction: We aimed to update our meta-analysis that investigated the effects of routine manual thrombus aspiration (TA) on clinical outcomes in patients with ST elevation myocardial infarction by publishing an additional large randomized clinical trial.

Patients and Metods: Sixteen studies in which primary percutaneous coronary intervention [(PPCI) (n= 10.440) vs. TA + PPCI (n= 10.434)] was performed were included to this meta-analysis. We calculated the risk ratio (RR) for clinical outcome, such as all cause death, recurrent infarction (Re-MI), target vessel revascularization/target lesion revascularization (TVR/TLR), stent thrombosis (ST), and stroke. In addition, we performed trial sequential analysis (TSA) to differentiate conclusive vs inconclusive results and to demonstrate the presence or absence of futility. Our assumptions for TSA included two-sided testing were type 1 error= 5%, power= 80%, and 20% relative risk reduction (RRR).

Results: There were no significant differences between TA + PPCI and PPCI alone arms in terms of all cause mortality [4.9% vs. 5.5%, RR= 0.895, 95% confidence interval (CI): 0.797-1.005, p= 0.060], Re-MI (2.1% vs. 2.2%, RR= 0.958, 95% CI: 0.797–1.151, p= 0.647), TVR/TLR (6.3% vs. 6.1%, RR= 1.030, 95% CI: 0.926-1.146, p= 0.586), and ST (1.2% vs. 1.4%, RR= 0.911, 95% CI: 0.712-1.166, p= 0.459). However, TA slightly increased the risk of stroke (0.8% vs. 0.5%, RR= 1.535, 95% CI: 1.003-2.351, p= 0.049). TSA indicates that sufficient evidence exists to draw a firm conclusion regarding death, re-MI, and TVR/TLR. However, TSA showed a lack of sufficient evidence that TA resulted in a reduction in the incidence of ST or increased the risk of stroke.

Conclusion: This updated meta-analysis including over 20.000 patients showed that routine manual TA did not reduce the incidence of all cause mortality, re-MI, TVR/TLR, and ST. The risk of stroke might be increased in TA.

Key Words: Aspiration thrombectomy; ST segment elevation myocardial infarction; primary percutaneous coronary intervention; meta-analysis

ST Elevasyonlu Miyokart İnfarktüsünde Rutin Trombüs Aspirasyonunun Yeri

ÖZET

Giriş: Bu çalışmada, büyük bir randomize kontrollü klinik çalışma yayınlanması nedeniyle, daha önce yayınladığımız ST elevasyonlu miyokart infarktüsü olan hastalarda rutin trombüs aspirasyonunun (TA) etkilerini inceleyen meta-analizimizi güncellemeyi amaçladık.

Hastalar ve Yöntem: Bu meta-analize primer perkütan koroner girişim (PPKG) uygulanmış hastaların alındığı çalışmalar dahil edildi. Tüm nedenlere bağlı ölüm, tekrarlayan infarktüs (Re-MI), hedef damar/lezyon revaskülarizasyon (TVR/TLR), stent trombozu (ST) ve inme gibi klinik sonuçlar için risk oranı (RR) hesaplandı. Ayrıca klinik sıralı analiz uygulandı. Klinik sıralı analiz için varsayımlarımız: tip 1 hata = %5, güç = %80 ve relatif risk azalması %20 idi.

Bulgular: TA + PPKG ve PPKG kolları arasında tüm nedenlere bağlı ölüm (%4.9 vs. %5.5, RR= 0.895, %95 CI: 0.797-1.005, p= 0.060), Re-MI (%2.1 vs. %2.2, RR= 0.958, %95 CI: 0.797-1.151, p= 0.647), TVR/TLR (%6.3 vs. %6.1, RR= 1.030, %95 CI: 0.926-1.146, p= 0.586) ve ST (%1.2 vs. %1.4, RR= 0.911, %95 CI: 0.712-1.166, p= 0.459) bakımından anlamlı fark yoktu. Bununla beraber TA'nın inme riskini bir miktar artırdığı gözlendi (%0.8 vs. %0.5, RR= 1.535, %95 CI: 1.003-2.351, p= 0.049).

Sonuç: Yirmi binden fazla hastanın dahil edildiği güncellenmiş bu meta-analiz rutin manual trombüs aspirasyonunun tüm nedenlere bağlı ölüm, tekrarlayan infarktüs (Re-MI), hedef damar/lezyon revaskülarizasyonu ve stent trombozunu azaltmadığını gösterdi. Fakat trombüs aspirasyonu ile inme riski artıyor olabilir.

Anahtar Kelimeler: Aspirasyon trombektomi; ST elevasyonlu miyokart infarktüsü; primer perkütan koroner girişim; meta-analiz

Correspondence

Selim Topcu

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INTRODUCTION

There is a considerable debate on the role of adjunctive manual thrombus aspiration (TA) in percutaneous treatment of ST elevated myocardial infarctions. The relatively increasing use of manual TA after the "Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS)" in Europe and the United States had become questionable following the "thrombus aspiration for myocardial infarction (TASTE)" study[1,2]. We conducted a meta-analysis, which has been published recently using 1-year outcome data of the TASTE study[3]. Our analysis included 16 randomized control trials (RCT) (n= 10.518). Adjunctive manual TA in combination with primary percutaneous coronary intervention (PPCI) improved epicardial and myocardial perfusion compared with that with PPCI alone; however, it had no effect on clinical endpoints such us death, recurrent myocardial infarction (re-MI), TVR/TLR, ST, and stroke. In an additional analysis (trial sequential analysis–TSA), our results indicated that meta-analysis allowed us to draw a firm conclusion with respect to all cause death; however, TSA showed a lack of sufficient evidence of the effects of TA on re-MI, TVR/TLR, stroke, and ST. A recently published "Randomized trial of primary PCI with or without routine manual thrombectomy (TOTAL)," which is the largest trial to date, revealed that compared with PPCI alone, routine manual TA did not reduce the risk of cardiovascular death, recurrent myocardial infarction, TVR, and ST within 180 days but was associated with an increased incidence of stroke within 30 days[4]. We aimed to perform this updated meta-analysis and TSA to draw a firm conclusion about clinical outcomes in patients who underwent adjunctive manual TA vs those in patients who underwent PPCI alone.

PATIENTS and METHODS

We searched the MEDLINE and Cochran Library for randomized controlled trials (RCT) published from January 1996 to March 2015 in the English language and in humans. A computerized search was performed using the terms "thrombectomy," "thromboaspiration," "aspiration thrombectomy," and "myocardial infarction".

We chose the studies in which patients who were admitted within 24 h of STEMI were randomized as TA + PPCI or PPCI alone. We excluded the studies which did not have clinical outcomes and/or myocardial perfusion symptoms and the studies in which mechanical thrombectomy was used. The primary end-point of the study was all cause mortality. All cause mortality was defined as death from any cause in most trials. In trials in which only cardiovascular death assessed, we accepted cardiovascular death as all cause mortality. The secondary endpoints were Re-MI, TVR/TLR, ST, and stroke.

TSA: We applied TSA to all RCTs included in our meta-analysis. TSA was performed according to the monitoring boundaries approach for outcome measures[5,6]. TSA is a statistical method that combines a priori information size calculation for a meta-analysis with adaptation of monitoring boundaries to evaluate the accumulating evidence[7]. Our assumptions included two-sided testing were type 1 error = 5% and power = 80%. We chose a 20% relative risk reduction (RRR) for outcome measures. The main result of TSA was expressed through a cumulative Z-curve graph; the boundaries in this graph for concluding superiority, inferiority, or futility were determined according to the O'Brien-Fleming alpha spending function. All calculations were performed using specific statistical software of TSA version 0.9 beta (TSA, User Manual for TSA, Copenhagen Trial Unit 2011, www.ctu.dk/tsa).

Statistical Analyses

Summary risk ratio (RR) and 95% confidence interval (CI) were calculated between TA + PPCI and PPCI alone regarding the clinical outcome using fixed- and random-effects model. The random-effect model was indicated in outcomes with significant heterogeneity ($I^2 > 25\%$). In others, the fixed-effects model was used. The Q value, resulting degrees of freedom (df), Tau^2, and I^2 statistic were used to evaluate heterogeneity[2]. Furthermore, we investigated possible reasons for heterogeneity using a meta-regression by evaluating the impact of prespecified covariates, such as publication year, follow-up duration, age, sex, sample size > 100 vs sample size < 100, diabetes, pain to balloon time, administration of GP2b3a antagonists, preprocedural TIMI flow grade 2-3, and high thrombus burden (TIMI thrombus grade 4-5). Statistical significance was defined as $p< 0.05$ (two-tailed tests). Statistical analysis was performed using an Open Meta-analyst software version 4.16.12, Tufts University, U.S for all analyses.

RESULTS

A total of 16 RCTs (n= 20.874 patients; 10.440 patients in the TA + PPCI arm and 10.434 in the PPCI alone arm) were included in this meta-analysis. We excluded a trial in our previous meta-analysis because it did not include clinical outcomes and updated database research revealed one additional trial (TOTAL) and one trial with extended follow-up[4,8,9].

Follow-up duration of the patients was between 1 and 12 months. There were no significant differences between TA + PPCI and PPCI alone arms in terms of all cause mortality (4.9% vs. 5.5%, RR= 0.895, 95% CI: 0.797-1.005, p= 0.060) (Figure 1) despite borderline statistical significance, Re-MI (2.1% vs. 2.2%, RR= 0.958, 95% CI: 0.797-1.151, p= 0.647) (Figure 2), TVR/TLR (6.3% vs. 6.1%, RR= 1.030, 95% CI: 0.926-1.146, p= 0.586) (Figure 3), and ST (1.2% vs. 1.4%, RR= 0.911, 95% CI: 0.712-1.166, p= 0.459) (Figure 4). However, the risk of stroke in TA + PPCI was significantly higher than that in PPCI alone (0.8% vs. 0.5%, RR= 1.535, 95% CI: 1.003-2.351, p= 0.049)

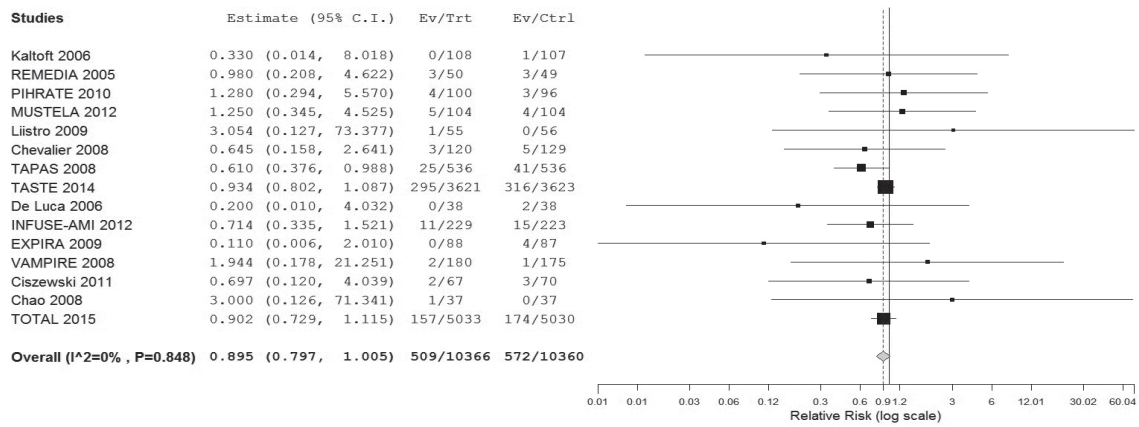

Figure 1. Summary forest plot of all cause death.

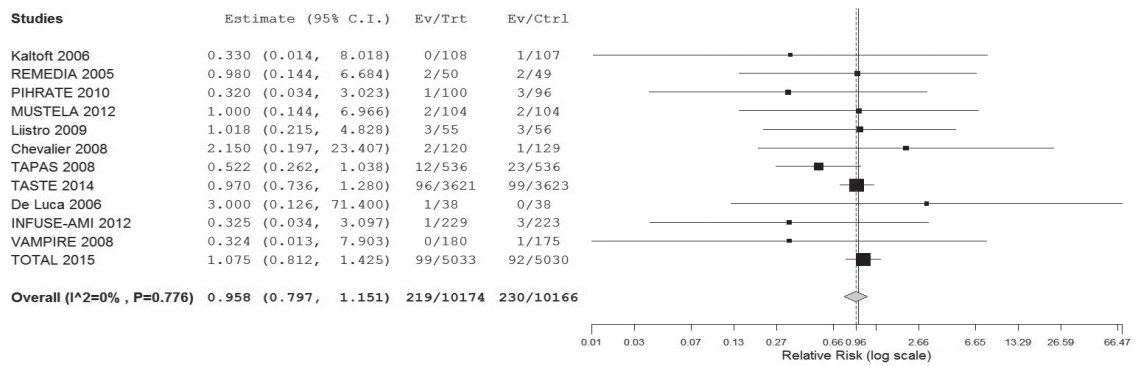

Figure 2. Summary forest plot of recurrent myocardial infarction.

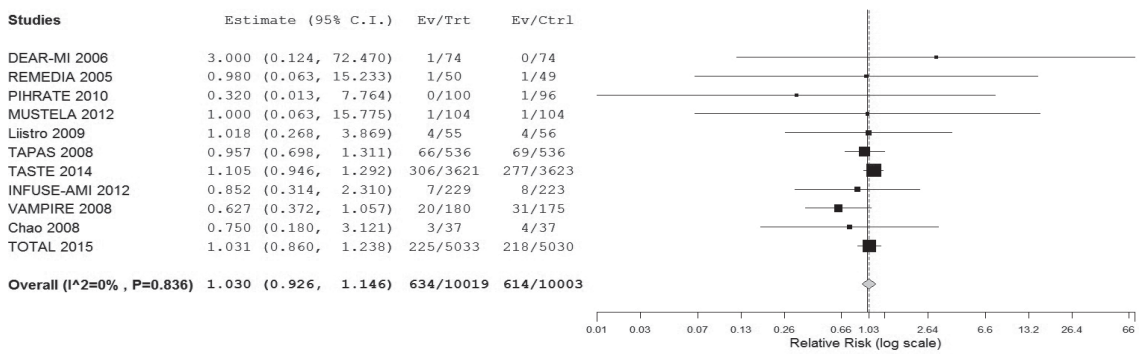

Figure 3. Summary forest plot of target vessel and/or lesion revascularization.

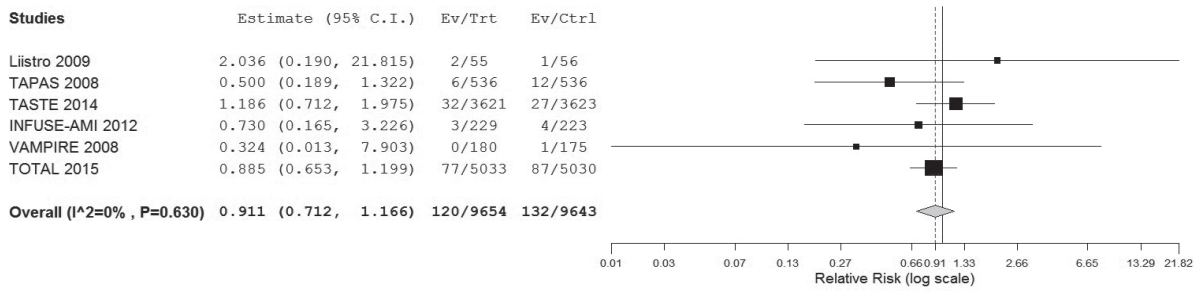

Figure 4. Summary forest plot of stent thrombosis.

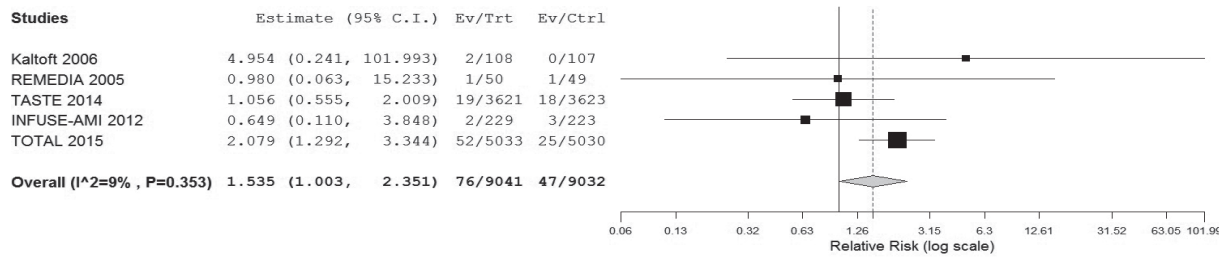

Figure 5. Summary forest plot of stroke.

Table 1. Meta-regression analysis for all cause death

Variable	Exp (b)	95% CI	SE	p value
Publication year	–0.050	–0.132-0.032	0.042	0.233
Mean follow-up (months)	0.012	–0.026-0.051	0.020	0.535
Mean age (year)	0.003	–0.046-0.051	0.025	0.912
Sex (males)	–0.000	–0.000-0.000	< 0.001	0.467
Sample size (< 100 vs. ≥ 100 in each arm)	–0.078	–0.871-0.714	0.404	0.847
Diabetes	–0.000	–0.000-0.000	< 0.001	0.522
Gp IIb/IIIa antagonist	–0.000	–0.000-0.000	< 0.001	0.687
Paint o balloon time (min)	–0.000	–0.006-0.005	0.003	0.826
Preprocedural TIMI flow II and III	–0.000	–0.000-0.000	< 0.001	0.433
TIMI thrombus grade IV and V	–0.000	–0.000-0.000	< 0.001	0.799

Table 2. Comparison of meta-analyses in patients with STEMI who used manual aspiration thrombectomy

	No. of RCT	No. of pts.	Death	Re-MI	TVR/TLR	Stroke	ST
Kumbhani[10]	18	3941	0.71 (0.51-1.00)	0.68 (0.42-1.10)	0.78 (0.61-1.01)	1.31 (0.30-5.79)	NA
Costopoulos[12]	11	2293	0.57 (0.33-0.97)	NA	NA	NA	NA
Bavry[13]	13	3026	0.63 (0.43-0.93)	0.65 (0.37-1.12)	0.83 (0.64-1.08)	3.43 (0.85-14.0)	NA
De Luca[11]	11	2311	0.65 (0.39-1.09)	0.78 (0.39-1.58)	NA	3.1 (0.62-15.5)	NA
Mongeon[14]	16	3365	0.58 (0.28-1.22)	NA	NA	NA	NA
Tamhane[15]	8	1902	0.59 (0.35-1.01)	NA	NA	2.84 (0.51-15.6)	NA
Tanboğa[3]	16	10.518	0.86 (0.69-1.06)	0.63 (0.43-0.92)	0.79 (0.66-0.95)	1.07 (0.58-1.96)	0.58 (0.33-1.02)
Barkagan[16]	17	20.853	0.88 (0.75-1.04)	0.96 (0.80-1.15)	NA	1.56 (1.09-2.25)	0.84 (0.65-1.07)
Spitzer[17]	26	11.943	0.88 (0.74-1.04)	0.85 (0.67-1.08)	0.86 (0.73-1.00)	1.03 (0.57-1.86)	0.76 (0.49-1.16)
Islam[18]	17	20.960	0.89 (0.76-1.04)	0.93 (0.73-1.17)	NA	1.45 (0.96-2.21)	0.82 (0.62-1.08)
Present meta-analyses	16	20.874	0.89 (0.79-1.00)	0.95 (0.79-1.15)	1.03 (0.92-1.14)	1.53 (1.00-2.35)	0.91 (0.71-1.16)

NA: Not available, RCT: Randomized controlled trials, Re-MI: Recurrent myocardial infarction, ST: Stent thrombosis, STEMI: ST elevation myocardial infarction, TLR: Target lesion revascularization, TVR: Target vessel revascularization.
* De Luca, Tamhane, Costopoulos, and Mongeon et al. used OR in their meta-analysis and Kumbhani, Bavry, Tanboğa, Barkagan, Spitzer, and Islam et al. used RR in their meta-analysis.

(Figure 5). There was mild significant heterogeneity for all cause mortality (Tau^2: 0.000 Q(df)= 8.7, I^2= 0%, p= 0.848). However, there was no significant heterogeneity for re-MI [Tau^2: 0.000 Q(df)= 7.2, I^2= 0%, p= 0.776], Tau^2 TVR/TLR [Tau^2: 0.000 Q(df)= 5.7, I^2= 0%, p= 0.836], ST [Tau^2: 0.000 Q(df)= 3.4, I^2= 0%, p= 0.630], and stroke [Tau^2: 0.027 Q(df)= 4.4, I^2= 9%, p= 0.353]. After adjusting for baseline covariates [publication year, follow-up duration, age, sex, sample size > 100 vs. sample size < 100, diabetes, pain to balloon time, administration of GP2b3a antagonists, preprocedural TIMI flow grade 2-3, and high thrombus burden (TIMI thrombus grade 4-5)], we determined that the TA + PPCI arm still had no effect on all cause mortality (Table 1).

In TSA, the required information size was met for all cause mortality and TVR/TLR (required information size 8911 and 10.945, respectively). Although the required information size was not met for re-MI (required information size 31.474), the cumulative Z-curve crossed the TSA boundary and ended in the futility zone. Thereby, TSA indicated that sufficient evidence exists to draw a firm conclusion regarding death, re-MI, and TVR/TLR. However, TSA showed a lack of sufficient evidence that TA resulted in a reduction in the incidence of ST (required information size 52.111) or increased the risk of stroke (required information size 164.800). We summarized our results by comparing with some other meta-analyses results in Table 2.

DISCUSSION

In our meta-analysis, which is the largest and consists of 16 RCTs including over 20.000 patients and which to the best of our knowledge, reported TSA results for the first time, we observed that TA + PPCI did not reduce the incidence of death, Re-MI, TVR/TLR, and ST. The risk of stroke was higher with TA than with PPCI alone. We also demonstrated that TSA indicated sufficient evidence to provide a firm conclusion regarding death, re-MI, and TVR/TLR. However, TSA showed that there was a no sufficient evidence that TA resulted in a reduction in the incidence of ST or increased the risk of stroke.

Recently, we conducted a meta-analysis that also included 1-year outcomes of the TASTE trial[3]. We previously demonstrated that compared with PPCI alone, routine manual TA improved epicardial flow, assessed by TIMI flow, and myocardial perfusion, assessed by MBG and STR; however, the incidence of clinical outcomes such as death, re-MI, TVR/TLR, ST, and stroke were similar in both groups. Moreover, we obtained similar results when we repeated the analysis after excluding data from TASTE trial. In addition, we achieved information size necessary for death; therefore, this allowed us to draw a firm conclusion in TSA analysis. However, we determined that we could not achieve adequate IS for re-MI

and TVR/TLR, but cumulative Z-curve ended in the futility area suggesting that the outcome would probably not be changed with increased sample size. In a recent meta-analysis, Kumbhani et al. reported that TA has a favorable effect on the clinical outcomes that continued when repeated even after exclusion of the TASTE trial[10]. This difference might have resulted from the facts that their analysis used 30-day outcomes and the number of RCTs was relatively less than those included in the present study. Therefore, data from the TOTAL study also support our previous meta-analysis. The TOTAL study is the largest RCT that compares TA and PPCI alone[4]. Moreover, the most significant difference among other studies, also including TASTE, is determining the sample size by taking 20% RRR into account. After this study has been published, we plan to update our previous meta-analysis considering that it would be stronger evidence. The incidences of endpoints (death, re-MI, TVR/TLR, and ST), except for stroke, were similar in the TA and PPCI groups. The risk of stroke was significantly higher in the TA group. Also, in a previous meta-analysis, De-Luca et al. reported that the risk of stroke was higher in the TA group[11]. In conclusion, our meta-analysis demonstrated that routine manual TA did not change the incidence of death, re-MI, TVR/TLR, and ST, but might increase the risk of stroke in follow-ups.

The trials conducted on routine manual TA and obtained neutral outcomes in the recent years have led to confusion among cardiologists[2,4,9]. Even many interventional cardiologists may believe that manual TA is at the end of the line. Recent evidences strongly indicate routine manual TA as an end of line for STEMIs. However, the effect of TA in selected patient groups, such as patients with high thrombus burden; the effect of bailout TA after stenting; or the effect of TA performed with different TA devices on clinical outcomes are not clear. TASTE and TOTAL studies, which are two large RCTs conducted till date, have left these questions unanswered. For example, the TASTE study suggested that the effect of TA on clinical events is not associated with thrombus burden[2]. However, the number of patients with high thrombus burden is significantly low in the present study compared with previous data. The TOTAL trial also reported that the effect of TA on the clinical events was not related to thrombus burden[4]. Nevertheless, contrary to many studies, thrombus burden was calculated before wire crossing in this trial. In conclusion, neither the TASTE study nor the TOTAL study has provided comprehensive information about the role of TA in patients with high thrombus burden. Therefore, we believe that TA is not end of road and can be still considered as an option in selected patients until comprehensive data are obtained. The comparison of data of the previous meta-analysis with the data of current meta-analysis is shown in Table 2.

CONCLUSION

In patients with STEMI, TA did not reduce the frequency of death, re-MI, TVR/TLR, and ST. However, TA might increase the risk of stroke. These results do not support the routine use of TA in patients with STEMI.

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CONFLICT of INTEREST

The author reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: ST
Analysis/Interpretation: ST
Data Acquisition: ST
Writing: ST
Critical Revision: ST
Final Approval: ST

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