Routine Manual Thrombus Aspiration in ST Elevation Myocardial Infarction: End of the Taste After Totality of Data

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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 due to publishing an additional large randomized clinical trial.

Materials and Method: Sixteen studies in which primary percutaneous coronary intervention ((PPCI) (n=10440) versus PPCI + TA (n=10434)) were 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/lesion revascularization (TVR/TLR), stent thrombosis (ST) and stroke. Our assumptions for TSA included two-sided testing, 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% CI: 0.797 – 1.005, p=0.060), Re-MI (2.1% versus 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). The TSA indicating that sufficient evidence exist to draw a firm conclusion regarding death, re-MI and TVR/TLR.

Conclusion: This updated meta-analysis included over 20000 patients showed that routine manual TA did not reduce the rate of all cause mortality, re-MI, TVR/TLR and ST. The risk of stroke might be increased in TA.

Keywords: Aspiration thrombectomy, ST segment elevation myocardial infarction, meta-analysis, primer percutaneous coronary intervention

ST Elevasyonlu Miyokard Infarktüsünde Rutin Trombüs Aspirasyonunun Yeri

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ÖZET

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

Hastalar ve Metod: Bu metaanalize içinde primer perkütan koroner girişim(PPKG) uygulanan çalışmalar dahil edildi. Tüm nedenlere bağlı ölüm, tekrarlayan enfarktüs (Re-MI), hedef damar/lezyon revaskülarizasyon(TVR/TLR), stent trombozu(ST), ve inme gibi klinik sonuçlar için risk oranı (RR) hesaplandı. Ayrıca metanaliz için klinik sıralı analiz uyguladık. 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'nun inme riskini bir miktar artırdığı gözlendi. (0.8% vs 0.5%, RR= 1.535, 95% CI: 1.003 – 2.351, p=0.049)

Sonuç: 20000'den fazla hastanın dahil edildiği güncellenmiş bu metaanaliz rutin manual trombüs aspirasyonun Tüm nedenlere bağlı ölüm, tekrarlayan enfarktüs (Re-MI), hedef damar/lezyon revaskülarizasyonu ve stent trombozunu azaltmadığını gösterdi. Trombüs aspirasyonu ile inme riski artıyor olabilir.

Anahtar Kelimeler: Aspirasyon trombektomi, ST elevasyonlu miyokard infarktüsü, primer perkütan koroner girişim, metaanaliz

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Introduction:

There is a considerable debate on the role of adjunctive manual thrombus aspiration (TA) for percutaneous treatment of ST elevated myocardial infarctions. Manual TA with a relatively increasing use after the "Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study-TAPAS" in Europe and United States had become questionable following the "thrombus aspiration for myocardial infarction-TASTE" study[1, 2]. We as well conducted a meta-analysis, which has been published recently, also using one-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 as compared to PPCI alone, however it had no effect on the 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 about all cause death; however, TSA showed a lack of sufficient evidence of TA on re-MI, TVR/TLR, stroke and ST. In recently published "Randomized trial of primary PCI with or without routine manual thrombectomy-TOTAL" which is the largest trial to date revealed that, routine manual TA, as compared with PPCI alone, did not reduce the risk of cardiovascular death, recurrent myocardial infarction, TVR and ST within 180 days but was associated with an increased rate 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 underwent to adjunctive manual TA vs PPCI alone.

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 using the terms "thrombectomy, thromboaspiration, aspiration thrombectomy and myocardial infarction" were made.

We chose the studies in which the patients admitting within 24 hours of STEMI were randomized as PPCI+TA or PPCI alone. We excluded the studies which does 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 assessed only cardiovascular death, we accepted cardiovascular death as a all cause mortality. The secondary end-points were Re-MI, TVR/TLR, ST and stroke.

Trial sequential analysis (TSA): We applied TSA to all RCTs included to meta-analysis. TSA was performed according to the monitoring boundaries approach[5, 6] for outcome measures. 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%, 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 or inferiority or futility were determined according to the O'Brien–Fleming alpha- spending function. All calculations were carried out 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 fixed-effects model was used. The Q value, resulting degrees of freedom(df), Tau^2 and I^2 statistic were used to evaluate heterogeneity. 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 <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 TA+PPCI arm and 10,434 in PPCI alone arm) were included in this meta-analysis. We excluded a trial in our previous meta-analysis since it did not include clinical outcomes[8] and updated database research revealed one additional trial[4] (TOTAL) and one trial with extended follow-up[9].

Follow-up duration of the patients was between 1 to 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% versus 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 PPCI alone (0.8% vs 0.5%, RR= 1.535, 95% CI: 1.003 – 2.351, p=0.049) (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), 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 <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 TA+PPCI arm still had no effect on all cause mortality (table-1).

In TSA, the required information size was meet for all cause mortality and TVR/TLR (required information size 8911 and 10945, respectively). Despite the required information size was not meet for re-MI (required information size 31474), the cumulative Z-curve crossed the TSA boundary and ended in futility zone. Thereby, the TSA indicating that sufficient evidence exist to draw a firm conclusion regarding death, re-MI and TVR/TLR. However, TSA showed a lack of sufficient evidence of TA for reduction ST (required information size 52111) or increasing stroke (required information size 164800). We summarized our results comparing with some other meta-analyses results in Table-2.

Discussion

In our meta-analysis, which is the largest that consists of 16 RCTs including over 20,000 patients and which reported TSA results first time; we observed that TA+PPCI did not reduce the rate of death, Re-MI, TVR/TLR and ST. The risk of stroke was higher in TA compared with PPCI alone. We also demonstrated that the TSA indicated sufficient evidence to say a firm conclusion regarding death, re-MI and TVR/TLR. However, TSA showed that there was a no sufficient evidence of TA for reduction in ST or increase in stroke.

Recently, we conducted a meta-analysis also including 1-year outcomes of the TASTE trial[3]. We previously demonstrated that routine manual thrombus aspiration improved epicardial flow assessed by TIMI flow and myocardial perfusion assessed by MBG and STR compared to PPCI alone, 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 the data from TASTE trial. In addition, we achieved information size necessary for death and 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 they analyzed using 30-day outcomes and the number of RCTs was relatively less than RCTs included in to present study. As the consequence, data from TOTAL study also support the previous meta-analysis conducted by us. TOTAL study is the largest RCT that compare TA and PPCI alone[4]. Moreover, the most significant difference from other studies, also including TASTE, is determining sample size by taking 20% RRR into account. After this study has been published, we planned to update our previous meta-analysis considering that it would be the stronger evidence. The incidences of endpoints (death, re-MI, TVR/TLR and ST) except for stroke were similar in TA and PPCI groups. Interestingly, the risk of stroke was significantly higher in TA group. Also in a previous meta-analysis, De-Luca et al. reported that stroke risk was higher in TA group[11]. In conclusion, our meta-analysis demonstrated that routine manual TA did not change incidence of death, re-MI, TVR/TLR and ST, but might increase stroke risk in follow-ups.

The trials conducted on the manual routine TA and obtained neutral outcomes in the recent years, 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 the end of line for routine TA in STEMIs. However, effect of TA in selected patient groups such as patients with high thrombus burden or effect of bailout TA after stenting or effect of TA that would be performed with different TA devices on clinical outcomes are not clear. TASTE and TOTAL studies, which are two large RCTs conducted until today, have left these questions unanswered. For example, TASTE study suggested that 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 in contrast to the previous data. TOTAL trial also reported that 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 TASTE nor TOTAL study has not 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 the previous meta-analysis with the current meta-analysis is shown in Table 2.

Conclusions: 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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Figure Legends:

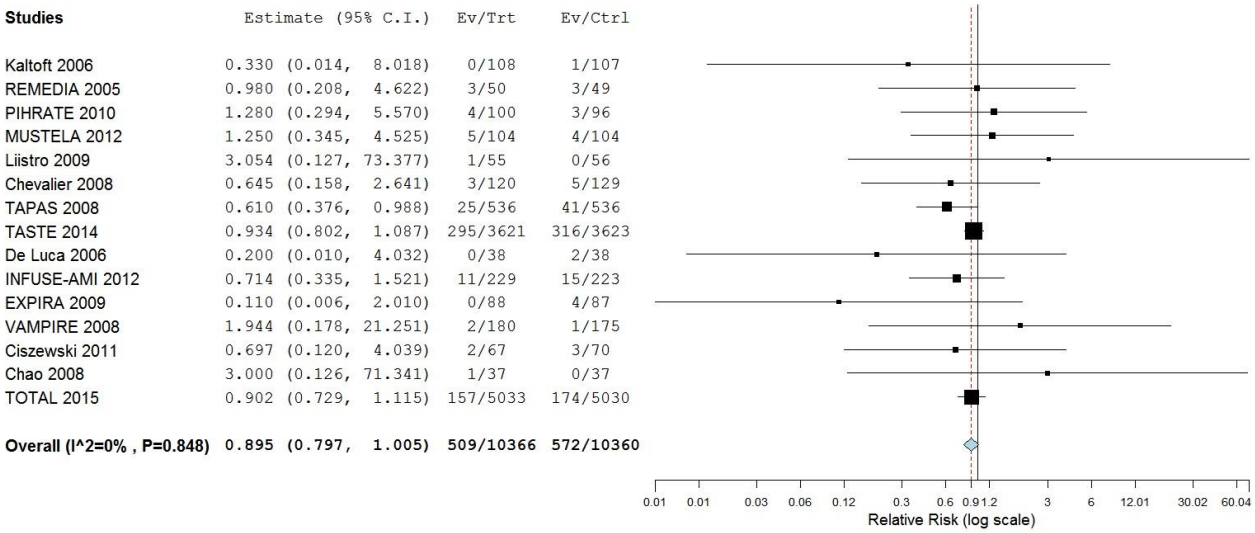

Figure-1: Summary forest plot of all cause death

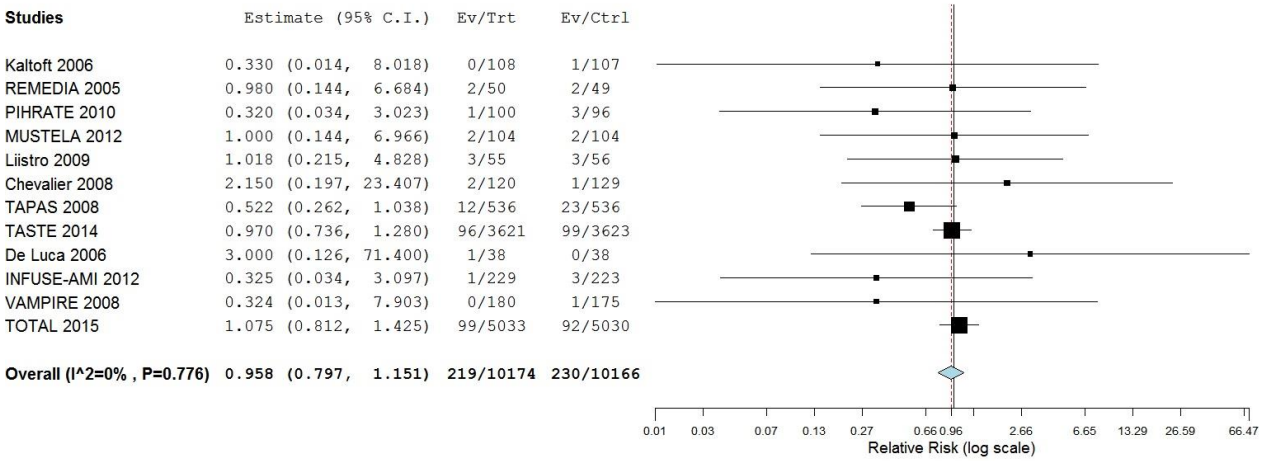

Figure-2: Summary forest plot of recurrent myocardial infarction

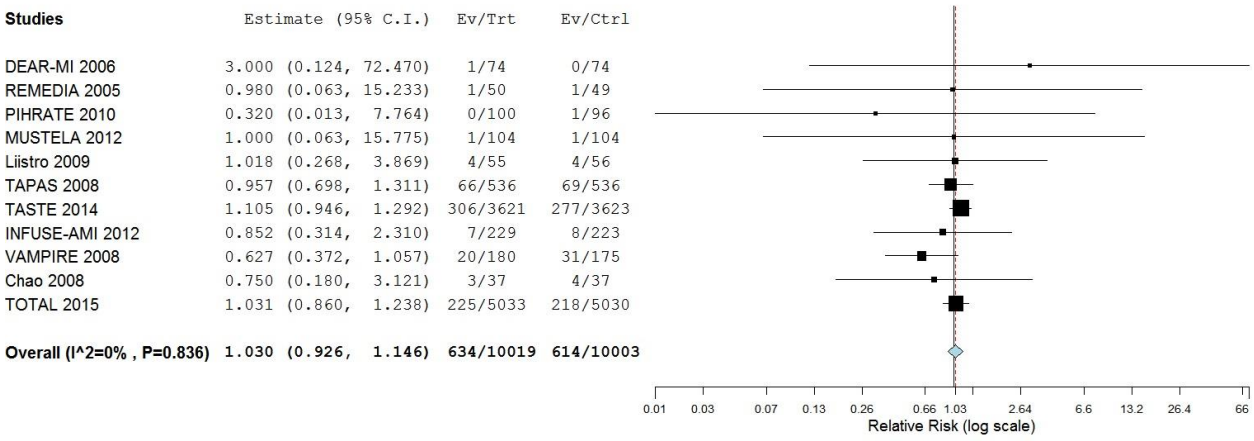

Figure-3: Summary forest plot of target vessel and/or target lesion revascularization

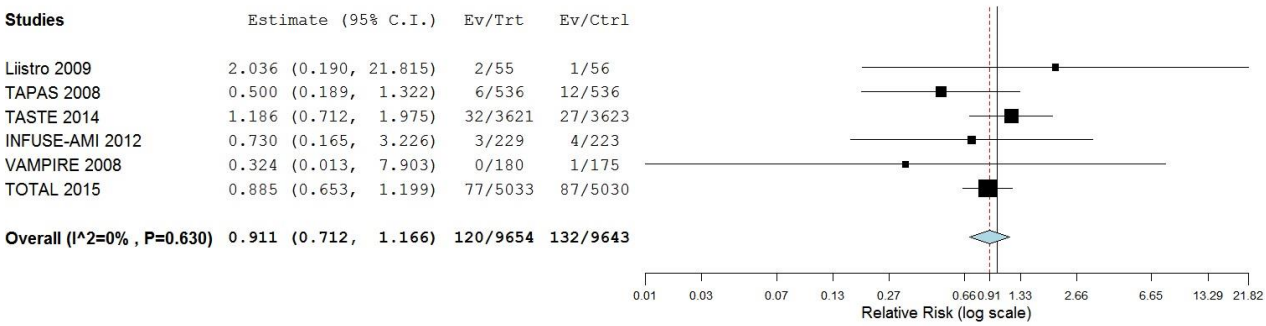

Figure-4: Summary forest plot of stent thrombosis

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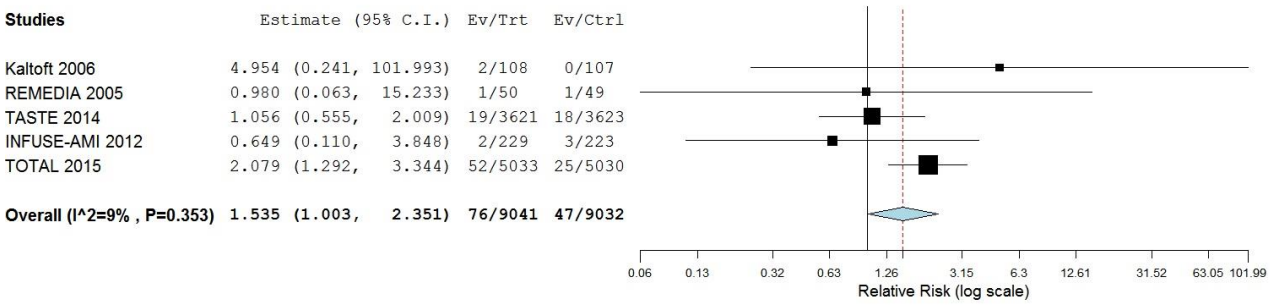

Figure-5: Summary forest plot of stroke

 DOI: 10.5578/khj.34240

Table-1: Meta-regression analysis for all cause death

Variable	Exp(b)	95% CI	SE	p value
Publication year	-0.050	-0.132 to 0.032	0.042	0.233
Mean follow-up (months)	0.012	-0.026 to 0.051	0.020	0.535
Mean age (year)	0.003	-0.046 to 0.051	0.025	0.912
Sex (males)	-0.000	-0.000 to 0.000	<0.001	0.467
Sample size (<100 vs ≥100 in each arm)	-0.078	-0.871 to 0.714	0.404	0.847
Diabetes	-0.000	-0.000 to 0.000	<0.001	0.522
Gp IIb/IIIa antagonist	-0.000	-0.000 to 0.000	<0.001	0.687
Paint o balloon time (min)	-0.000	-0.006 to 0.005	0.003	0.826
Preprocedural TIMI flow II and III	-0.000	-0.000 to 0.000	<0.001	0.433
TIMI thrombus grade IV and V	-0.000	-0.000 to 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	10518	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	20853	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	11943	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	20960	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	20874	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; Kumbhani, Bavry, Tanboğa, Barkagan, Spitzer and Islam et al. used RR in their meta-analysis