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ΜΕΤΑΠΤΥΧΙΑΚΗ ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

"Intracoronary Thrombolysis facilitated Primary Percutaneous Coronary Intervention in ST-Segment Elevation Myocardial Infarction patients: An Updated Meta-Analysis of Randomized Controlled Trials"

"Πρωτογενής Διαδερμική Στεφανιαία Παρέμβαση υποβοηθούμενη από Ενδοστεφανιαία Θρομβόλυση σε ασθενείς με Έμφραγμα του Μυοκαρδίου με Ανάσπαση του Διαστήματος ST: Μια Επικαιροποιημένη Μετα-ανάλυση Τυχαιοποιημένων Ελεγχόμενων Κλινικών Δοκιμών"

Τριμελής Συμβουλευτική Επιτροπή: Δαρδιώτης Ευθύμιος

Στεφανίδης Ιωάννης

Δοξάνη Χρυσούλα

Επιβλέπων Καθηγητής: Δαρδιώτης Ευθύμιος

Συγγραφή: Αλεξίου Σοφία

Α.Μ: 00299

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1.1 Περίληψη

Υπόβαθρο: Η Πρωτογενής Διαδερμική Στεφανιαία Παρέμβαση (ΠΔΣΠ) αποτελεί την κλασική μέθοδο επαναιμάτωσης στο έμφραγμα του μυοκαρδίου με ανάσπαση του διαστήματος ST (STEMI). Ωστόσο, η επιτυχία της συχνά παρακωλύεται από την μικροαγγειακή απόφραξη. Η Ενδοστεφανιαία Θρομβόλυση (ΕΘ) μπορεί να περιορίσει το θρομβωτικό φορτίο. Πραγματοποιήσαμε τη μεγαλύτερη μετα-ανάλυση για την ΕΘ ως επικουρική θεραπεία στην ΠΔΣΠ.

Μέθοδοι: Η παρούσα μετα-ανάλυση διεξήχθη σύμφωνα με τις κατευθύνσεις του PRISMA. Όλες οι μελέτες εντοπίστηκαν με αναζήτηση στο PubMed, Scopus, Cochrane Library και Web of Science, χωρίς χρονικό ή γλωσσικό περιορισμό. Υπολογίστηκε ο λόγος πιθανοτήτων (OR) και η μέση διαφορά (MD) με διάστημα εμπιστοσύνης (ΔΕ) 95%. Οι μελέτες περιλάμβαναν ασθενείς με STEMI που υπεβλήθησαν σε ΠΔΣΠ και έλαβαν επικουρικά ΕΘ.

Results: Συμπεριλήφθηκαν δεκατρείς Τυχαιοποιημένες Ελεγχόμενες Κλινικές Δοκιμές στις οποίες συμμετείχαν συνολικά 1876 ασθενείς (1014 στην ομάδα ενδοστεφανιαίας θρομβόλυσης και 862 στην ομάδα του εικονικού φαρμάκου). Σε σύγκριση με την ομάδα ελέγχου, η ΕΘ σε ασθενείς με STEMI θα μπορούσε να μειώσει τη συχνότητα εμφάνισης Μειζόνων Ανεπιθύμητων Καρδιακών Συμβάντων (ΜΑΚΣ; OR 0.65, 95% CI, 0.48-0.86, P=0.003) και να βελτιώσει το κλάσμα εξώθησης της αριστερής κοιλίας στους 6 μήνες (MD 3.78, 95% CI, 1.53-6.02, P=0.0010). Ενδείξεις βελτιωμένης μικροκυκλοφορίας στο

μυοκάρδιο ήταν πιο έκδηλες στην ομάδα θρομβόλυσης [βαθμός μυοκαρδιακής αιμάτωσης (ΒΜΑ) 2/3 (OR 1.76; 95% CI, 1.16-2.69, P=0.008)] και πλήρης υποχώρηση των ανασπάσεων του διαστήματος ST στο ηλεκτροκαρδιογράφημα 60-90 λεπτά μετά την ΕΘ (OR 1.97; 95% CI, 1.33-2.91, P=0.0007). Το ποσοστό των μειζόνων αιμορραγιών ήταν συγκρίσιμο μεταξύ των 2 ομάδων (OR 1.27, 95% CI, 0.61-2.63, P=0.53).

Συμπεράσματα: Η ενδοστεφανιαία θρομβόλυση συνδέθηκε με βελτίωση των μειζόνων ανεπιθύμητων καρδιαγγειακών συμβαμάτων και της μικροκυκλοφορίας του μυοκαρδίου σε ασθενείς με STEMI που υποβλήθηκαν σε ΠΔΣΠ, χωρίς καμία σημαντική αύξηση στις μείζονες αιμορραγίες.

Λέξεις-κλειδιά

θρομβόλυση, ενδοστεφανιαία, έμφραγμα του μυοκαρδίου με ανάσπαση του διαστήματος ST, μείζονα ανεπιθύμητα καρδιακά συμβάματα, μικροκυκλοφορία, αιμορραγία

1.2 Abstract

Background: Primary percutaneous coronary intervention (PPCI) is the standard evidence-based method for reperfusion in ST-segment elevation myocardial infarction (STEMI). However, the success of PPCI is often limited by microvascular obstruction. Intracoronary thrombolysis (ICT) may mitigate thrombotic burden. We conducted the largest meta-analysis of ICT as adjuvant therapy to PPCI.

Methods: The meta-analysis was conducted according to the PRISMA statement. All relevant studies were identified by searching the PubMed, Scopus, Cochrane Library, and Web of Science, with no time or language limitation. The odds ratio (OR) and standardized mean difference (SMD) with a 95% confidence interval (CI) were calculated. Studies included STEMI patients undergoing PPCI receiving ICT. Both safety and efficacy outcomes were analyzed. Data were combined using a random-effects model.

Results: Thirteen randomized controlled trials (RCTs) involving a total of 1876 (1014 ICT and 862 IC placebo) patients were included. Compared with the control group, ICT in patients with STEMI could reduce the incidence of major adverse cardiac events (MACE; OR 0.65, 95% CI, 0.48-0.86, P=0.003) and improve 6 months left ventricular ejection fraction (MD 3.78, 95% CI, 1.53-6.02, P=0.0010). Indices of enhanced myocardial microcirculation were more common with ICT [Post PCI corrected thrombolysis in myocardial infarction (TIMI) frame count (MD -3.57; 95% CI, -5.00 to -2.14, P<0.00001); myocardial

blush grade (MBG) 2/3 (OR 1.76; 95% CI, 1.16-2.69, P=0.008), and complete ST-segment resolution (OR 1.97; 95% CI, 1.33-2.91, P=0.0007). The incidence rate of major bleeding was comparable between the 2 groups (OR 1.27; 95% CI, 0.61-2.63, P=0.53).

Conclusions: Intracoronary thrombolysis was associated with improved MACE and myocardial microcirculation in patients with STEMI undergoing PPCI, without any significant increase in major bleeding. Our meta-analysis suggests a targeted IC thrombolytic approach is safe and potentially effective to improve PPCI. However, these findings deserve confirmation in a contemporary large randomized controlled trial.

Keywords

thrombolysis, intracoronary, ST-segment elevation myocardial infarction, major adverse cardiac events, microcirculation, bleeding

2. Introduction

Primary percutaneous coronary intervention (PPCI) is the standard evidence-based revascularization treatment of ST-segment elevation myocardial infarction (STEMI) [1]. However, thrombus formation in STEMI patients can lead to embolization of the microvasculature within the culprit artery [2], and one third of patients treated by PPCI result in the no-reflow (NR) phenomenon, a condition characterized by poor myocardial perfusion despite patent epicardial arteries [3]. The presence of NR has been associated with larger infarct size (IS), poor left ventricular (LV) function, heart failure and death following PPCI [3]. Several methods have been employed to mitigate thrombus embolization during PPCI and include intracoronary delivery of antiplatelet and vasodilator drugs and manual thrombus aspiration [4, 5]. Facilitated PCI using systemic thrombolysis followed by immediate PCI was presented as an alternative approach of reperfusion, though several studies have resulted in increased mortality and morbidity, due to bleeding events [6].

Nonetheless, the use of low dose intracoronary thrombolysis (ICT) during PPCI has showed improved myocardial perfusion without increasing the risk of bleeding events [7], decreased long-term IS, with improved LV volumes and function [8]. On the other hand, successive studies with different drugs and regimens have displayed conflicting results [9,10]. Currently, new randomized controlled trials (RCTs) have contributed to the revival of the data [11, 12]. We therefore performed the largest updated meta-analysis of RCTs evaluating the efficacy and safety of ICT as compared to standard treatment among patient with STEMI undergoing PPCI.

3. Methods

3.1 Search Strategy

We conducted a systematic search of electronic databases (PubMed, Scopus, Web of Science and Cochrane Library) from the outset to September 2021, without language limitations, investigating the role of ICT alongside PPCI in comparison to standard treatment (PPCI alone or intracoronary placebo/saline with PPCI). In addition to our computerized search, we manually reviewed the reference lists and related articles of all retrieved studies to complete our search. The keywords used for the systematic search were: ((ST-segment elevation myocardial infarction) OR (STEMI)) AND (intracoronary) AND ((thrombolysis) OR (streptokinase) OR (urokinase) OR (prourokinase) OR (alteplase) OR (reteplase) OR (tenecteplase) OR (anistreplase)). The meta-analysis was guided by the principles of the PRISMA Statement [13].

3.2 Study selection and data extraction

Prespecified inclusion criteria for the studies were the following: RCTs, without date or language restriction, comparing ICT additional to PPCI versus standard treatment in STEMI recording the ensuing primary and secondary outcomes: major adverse cardiac events (MACE defined as a composite of cardiovascular death, nonfatal myocardial infarction, heart failure, angina pectoris, malignant arrhythmias and target vessel revascularization), left ventricular ejection fraction (LVEF) at 6 months, Thrombolysis in Myocardial Infarction (TIMI) flow grade 2/3 in the culprit vessel (TFG defined as a grading scale for the

semiquantitative evaluation of myocardial perfusion before and after coronary reperfusion therapies), myocardial blush grade 2/3 (MBG defined as a visual angiographic assessment of myocardial perfusion in the infarct area), complete ST-segment resolution (STR, used as an important predictor of infarct-related artery patency and effective microcirculatory perfusion), Corrected TIMI Frame Count (CTFC defined as the number of cineframes required for contrast to reach a standardized distal coronary landmark in the culprit vessel), troponin peak value and degree of major and minor bleeding. Duplicates, reviews, observational studies, case reports/series and previous meta-analyses were excluded. The study selection process is shown in the flow diagram outlined in Figure 1. Unpublished data was not searched or used for this meta-analysis. The study data were extracted by 2 authors (S.A. and D.P.) who worked independently and reached a final agreement. Discrepancies between the two reviewers were resolved by consensus and consultation by a senior reviewer (G.K). The following data were extracted: i) source of data and study design; ii) publication details: first author and publication year; iii) characteristics of the population studied including sample size, gender, age, pharmacotherapy of interest and major co-morbidities (hypertension, dyslipidemia, diabetes mellitus etc); iv) safety and efficacy outcomes as described below and v) follow-up duration. We preferred data from intention-to-treat (ITT) analyses, if made available by the researchers of each eligible study.
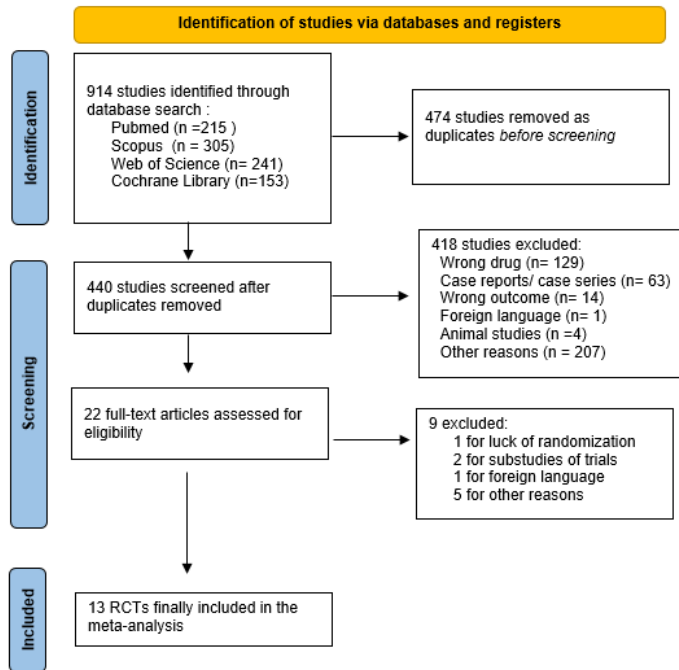
Figure 1. Flow diagram of study selection

3.3 Statistical Analysis

The estimate used for categorical variables was the odds ratio (OR) with 95% confidence interval (CI) in a Mantel-Haenszel (M-H) random-effects model. As for continuous variables, they were presented as mean difference (MD) with 95% CI. Statistical heterogeneity among studies was assessed by using I^2 statistics [14], with I^2 value ≥50% considered as evidence of substantial heterogeneity. All analyses were performed at the 0.05 significance level, while they were undertaken with RevMan 5.4.1 software [15].

4. Results

Thirteen RCTs [7-12, 16-22] involving a total of 1876 (1014 ICT and 862 IC placebo) patients were included in the current meta-analysis. Data from ITT analyses were utilized for every eligible trial. The baseline characteristics of the enlisted studies are compiled in Table 1.

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Study	Year	IC thrombolytic used	Sample size, n (intervention/ standard care)	Age in years, mean ± SD or median (IQR) (intervention/ standard care)	Male sex, n (intervention/ standard care)	Hypertension, n (intervention/ standard care)	Diabetes, n (intervention/ standard care)
Sezer et al. [7]	2007	Streptokinase	21/20	51 ± 6/52 ± 11	21/19	4/7	2/3
Sezer et al. [8]	2009	Streptokinase	51/44	53 ± 9/58 ± 11	45/38	17/16	4/10
Greco et al. [14]	2013	Urokinase	51/51	61 ± 15/59 ± 12	38/34	24/28	8/9
Geng et al. [12]	2018	Prourokinase	118/112	54 ± 11/55 ± 10	77/70	84/69	26/22
Fu et al. [11]	2019	Prourokinase	20/19	63 ± 11/63 ± 11	16/15	11/10	4/5
Gibson et al. [10]	2019	Tenecteplase	20/16	57(49,60)/59(55,62)	15/13	13/6	2/3
Ibrahim et al. [16]	2019	Alteplase	53/49	55 ± 7/55 ± 7	38/35	26/19	29/22
Xiao et al. [15]	2019	NR	38/33	65 ± 13/62 ± 16	28/27	20/24	15/11
McCartney et al. [9]	2019	Alteplase	289/151	60 ± 10 [a]/61 ± 11 61 ± 10[b]/61 ± 11	247/127	94/47	37/19
Wang et al. [18]	2020	Prourokinase	92/90	61 ± 11/59 ± 11	76/73	54/46	20/22
Wu et al. [17]	2020	Prourokinase	25/25	60 ± 14/61 ± 13	21/22	17/19	8/6
Huang et al. [19]	2021	Prourokinase	111/117	59 ± 10/59 ± 10	100/105	52/58	21/21
Jiang et al. [20]	2021	Prourokinase	125/135	54 ± 6/55 ± 7	77/88	62/69	32/35

Table 1. Baseline characteristics of Included Studies (1), IC: intracoronary, NR: not reported, a: Alteplase 10mg group, b: Alteplase 20mg group

Dyslipidemia, n (intervention/ standard care)	Smoking, n (intervention/ standard care)	Thrombus aspiration, n	Oral antiplatelet therapy	GPI, n	Unfractionated heparin	Follow-up period
12/14	17/14	NR	Aspirin & clopidogrel	21/20	100 U/kg	6 months
18/20	38/27	NR	Aspirin & clopidogrel	51/44	100 U/kg	6 months
22/25	30/32	51/51	Aspirin & clopidogrel	NR	100 U/kg	6 months
44/47	50/58	NR	Aspirin & ticagrelor	NR	70 U/kg	6 months
9/9	13/9	20/19	Aspirin & ticagrelor/clopidogrel	NR	NR	3 months
10/6	11/12	NR	Aspirin & clopidogrel	17/15	70 U/kg	1 month
21/16	12/18	NR	Aspirin & ticagrelor	NR	60 U/kg	6 months
17/16	21/17	38/33	Aspirin & ticagrelor	NR	50-70 U/kg	12 months
60/42	134/75	82/37	Aspirin & ticagrelor/clopidogrel/prasugrel	48/13	10000 U / 10000 U	3 months
19/14	51/55	92/90	Aspirin & ticagrelor	17/12	Guided by ACT (250-300 sec)	6 months
8/5	12/13	25/25	Aspirin & ticagrelor	18/14	Guided by ACT (250-300 sec)	3 months
71/89	67/75	58/58	Aspirin & ticagrelor/clopidogrel	Separate group	70-100 U/kg	1 month
39/44	69/77	10/8	Aspirin & ticagrelor	NR	100 U/kg	6 months

Table 1. Baseline characteristics of Included Studies (2), GPI: glycoprotein IIb/IIIa inhibitors, ACT: activated clotting time

4.1 Primary outcomes

Compared with the control group, ICT in patients with STEMI undergoing PPCI could significantly reduce the incidence of MACE at the end of follow-up period, which ranged from 1 to 12 months (OR 0.65, 95% CI, 0.48-0.86, P=0.003, I^2=0%, Figure 2). ICT also resulted in an improvement of LVEF at 6 months (MD 3.78, 95% CI, 1.53-6.02, P=0.0010, I^2=60%, Figure 3).

4.2 Secondary outcomes

Indicators of enhanced myocardial microcirculation were more common with ICT as stands for the decrease in post-PCI CTFC (MD -3.57; 95% CI, -5.00 to -2.14, P<0.00001, I^2=11%, Figure 4) and the significant improvement of MBG 2/3 (OR 1.76; 95% CI, 1.16-2.69, P=0.008, I^2=50%, Figure 5). Likewise, a greater proportion of complete STR was noted in the ICT group (OR 1.97; 95% CI, 1.33-2.91, P<0.0007, I^2=60%, Figure 6), alongside with a lower peak level of cardiac troponin I in study group (MD -1.90; 95% CI, -3.16 to -0.64, P=0.003, I^2=46%, Figure 7). Notwithstanding it did not accomplish the statistical significance, it appeared to be a tendency showing a higher rate of post procedural TIMI flow grade 2/3 in the culprit vessel in the ICT group (OR 1.50; 95% CI, 0.82-2.76, P=0.19, I^2=3%, Figure 8).

4.3 Safety outcomes

There was no difference noted in the rate of major bleeding (OR 1.27; 95% CI, 0.61-2.63, P=0.53, I^2=0%, Figure 9) and minor bleeding (OR 1.64; 95% CI, 0.99-2.71, P=0.05, I^2=0%, Figure 10) between the 2 groups.

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5. Discussion

This meta-analysis, involving a total of 1876 STEMI patients undergoing PPCI, proves that the adjuvant use of ICT compared with IC placebo could significantly lessen the rate of MACE and improve 6 months LVEF, without overcoming the bleeding events. Moreover, indices of enhanced myocardial microcirculation such as MBG, CTFC, and complete STR rate, were more noted with ICT.

To reduce the damage from reperfusion, efforts have been made to find appropriate techniques and treatments, as adjuvant to PPCI. Yet, these methods of therapy in practice have a limited use so far [23]. The utilization of aspiration thrombectomy did not seem to be effective [24-26]. The use of upstream GP IIb/IIIa inhibitors in patients in comparison to in-hospital administration led to increased bleeding without further improvement in reperfusion [27, 28]. IC administration of GP IIb/IIIa inhibitors does not prove superiority over the systemic use of them [29]. Also, adenosine as an adjunct therapy in the non-reflow phenomenon in STEMI is still into investigation [5]. Thus, more research in therapies that help the treatment of distal embolization must be done. According to Sezer et al. [8], the administration of low-dose streptokinase (SK) after the conduction of PPCI resulted in a reduction of microvascular obstruction. In studies performed by Greco et al [16], Fu et al. [11] and Geng et al. [12], it is noted that post-PPCI coronary flow was improved due to the administration of IC thrombolytics before manual thrombectomy

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Unlike the previous meta-analyses, our meta-analysis included another 5 latest RCTs [17-19, 21, 22], enlarging the number of included patients (1876), thus further improving the outcome of MACE and myocardial microcirculation indicators.

To our knowledge, three clinical trials are underway testing the use of ICT in PPCI, as shown in Table 2.

Ongoing clinical trials (ID Number)	NCT Number	Patients enrolled, n	Study Arms	Study Phase	Randomization	Masking	Primary Outcomes
STRIVE.2018	NCT03335839	200	Intracoronary tPA (10mg, 20mg) vs placebo	3	Yes	Triple	-Post-procedural MBG 0/1 or Distal Embolization
RESTORE-MI	NCT03998319	506	Intracoronary tenecteplase vs placebo	3	Yes	Double	-24-month mortality - MI size and intramyocardial bleeding rates at 6 months post-PCI.
OPTIMAL-01	NCT02894138	80	Intracoronary alteplase vs placebo	3	Yes	Double	-Ratio of myocardial infarct size to area at risk assessed by MRI

Table 2. Ongoing clinical trials for ICT in PPCI

6. Limitations

The current meta-analysis has some limitations. Although different types of thrombolytics were utilized in the studies, we omitted to conduct the subgroup analyses. Moreover, McCartney et al. [9], which was a well-designed study as concerns to randomization and masking (randomized, double-blinded), showed a negative result with regard to obstruction in the microcirculatory or MACE in the ICT group. The majority of the other studies was single-blinded, open-label, or unclear, thus enhancing the possibility of introducing a statistical type 1 (false-positive) error. Besides, the meta-analysis incorporated studies with different thrombolytic agents, dose of them, follow-up periods and patients' baseline characteristics, something that would affect the clinical applicability and generalizability of the retrieved evidence. Therefore, further research should be done for more reliable results. Still, this is the largest meta-analysis performed to address the use of ICT as an adjuvant to PPCI.

7. Conclusion

Intracoronary thrombolysis improved MACE and myocardial microcirculatory in STEMI patients undergoing PPCI, without any significant increase in major bleeding. Our meta-analysis suggests a targeted IC thrombolytic approach is safe and potentially effective to improve PPCI. Nonetheless, the conduction of new RCTS is recommended for the verification of the above results.
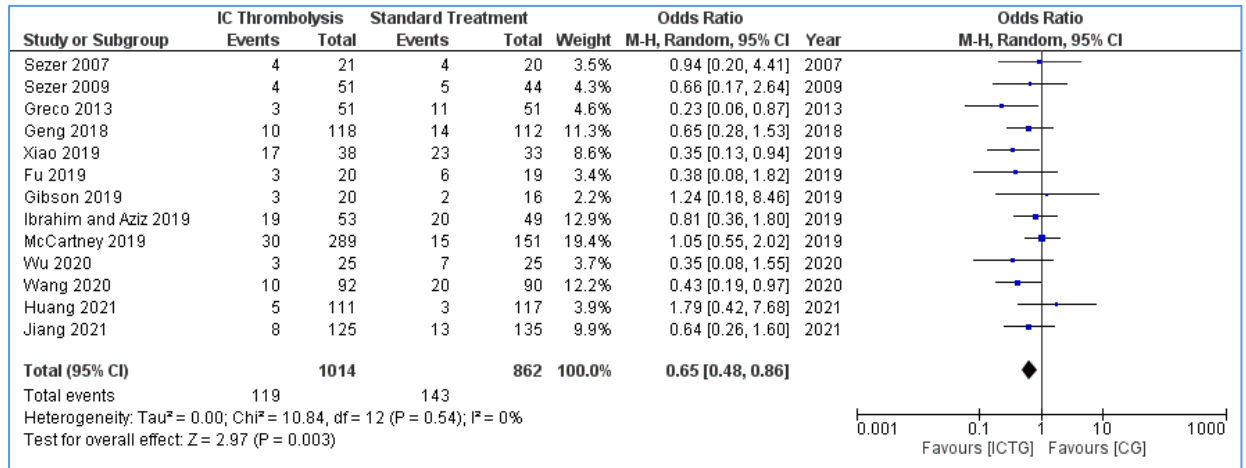
Figure 2. Forest plot for major adverse cardiac events (MACE). ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group
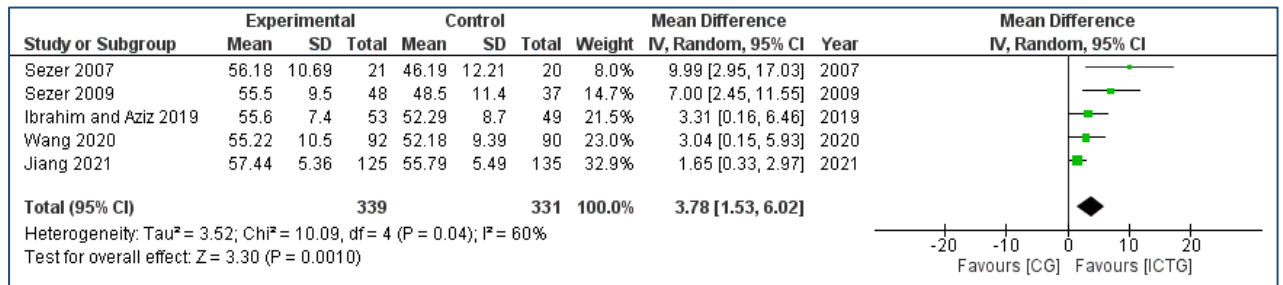
Figure 3. Forest plot for 6-month LVEF. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group
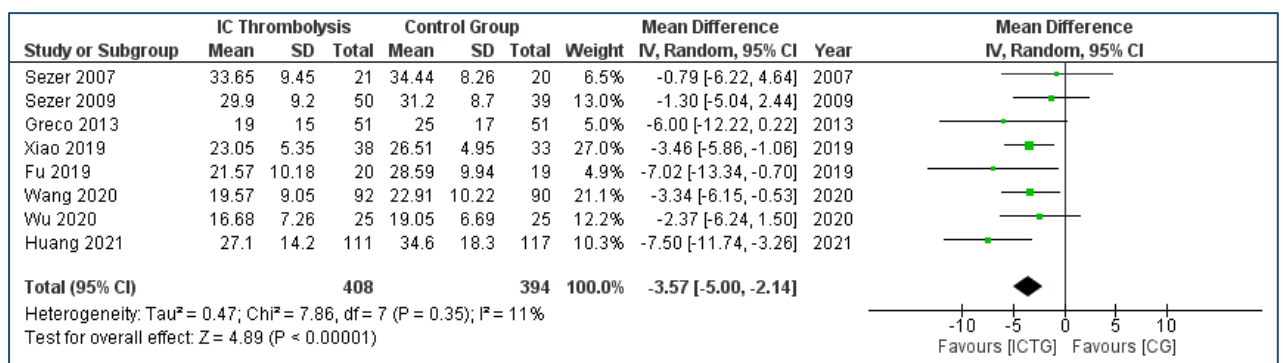
Figure 4. Forest plot for CTFC post-PPCI. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group, CTFC: corrected Thrombolysis in Myocardial Infarction frame count, PPCI: primary percutaneous coronary intervention

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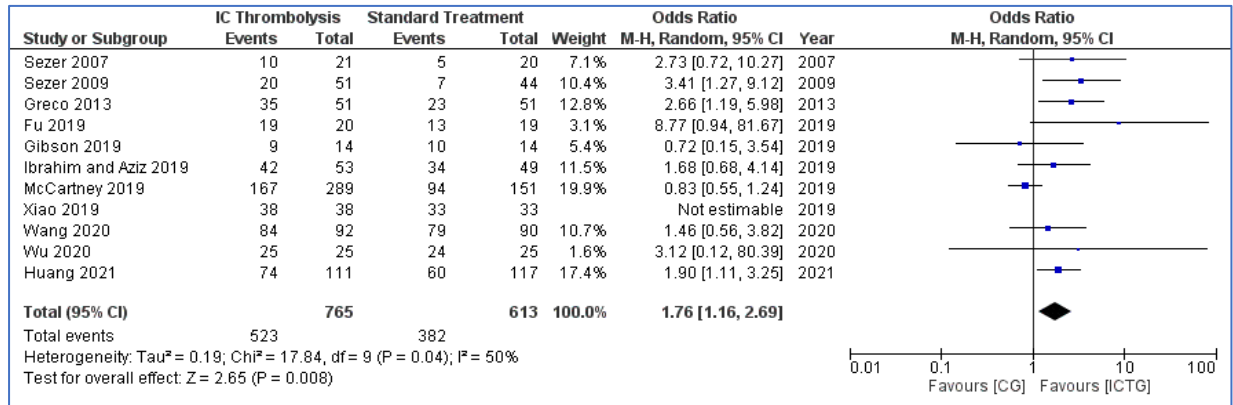
Figure 5. Forest plot for MBG 2/3 post-PPCI. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group, MBG: Myocardial Blush Grade, PPCI: primary percutaneous coronary intervention
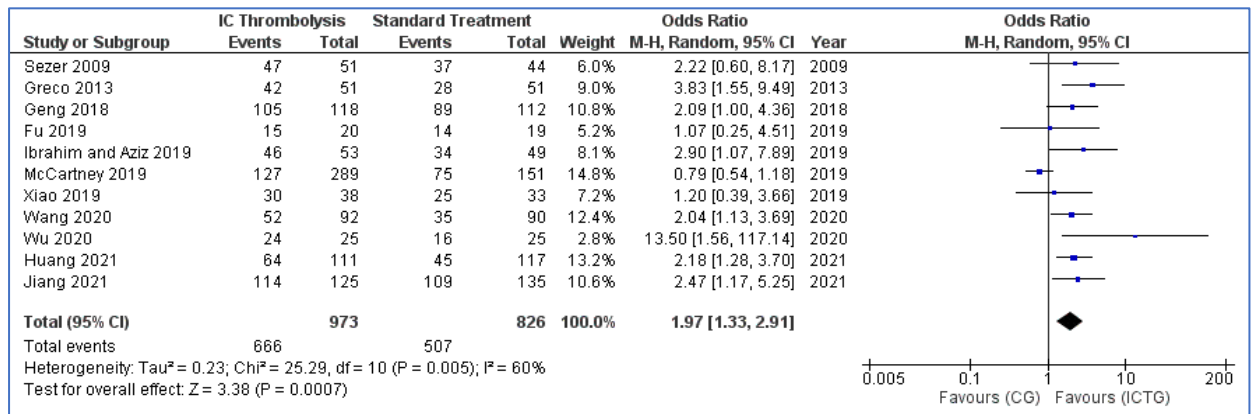
Figure 6. Forest plot for Complete STR post-PPCI. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group, STR: ST-segment resolution, PPCI: primary percutaneous coronary intervention

Figure 7. Forest plot for cTnI peak value. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group, cTnI: cardiac troponin I

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Study or Subgroup	IC Thrombolysis Events	Total	Standard Treatment Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
Sezer 2007	21	21	20	20		Not estimable	2007	
Sezer 2009	51	51	44	44		Not estimable	2009	
Greco 2013	49	51	45	51	13.1%	3.27 [0.63, 17.02]	2013	
Geng 2018	117	118	111	112	4.7%	1.05 [0.07, 17.06]	2018	
McCartney 2019	278	289	145	151	32.8%	1.05 [0.38, 2.89]	2019	
Xiao 2019	38	38	33	33		Not estimable	2019	
Fu 2019	19	20	12	19	7.4%	11.08 [1.21, 101.68]	2019	
Gibson 2019	17	20	15	16	6.5%	0.38 [0.04, 4.03]	2019	
Wang 2020	90	92	86	90	12.1%	2.09 [0.37, 11.72]	2020	
Wu 2020	25	25	25	25		Not estimable	2020	
Huang 2021	106	111	111	117	23.5%	1.15 [0.34, 3.87]	2021	
Jiang 2021	125	125	135	135		Not estimable	2021	
Total (95% CI)		961		813	100.0%	1.50 [0.82, 2.76]		
Total events	936		782					

Heterogeneity: Tau² = 0.02; Chi² = 6.21, df = 6 (P = 0.40); I² = 3%
Test for overall effect: Z = 1.31 (P = 0.19)

Favours (CG)   Favours (ICTG)

Figure 8. Forest plot for TFG 2/3 post-PPCI. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group, TFG: TIMI flow grade, PPCI: primary percutaneous coronary intervention

Study or Subgroup	IC Thrombolysis Events	Total	Standard Treatment Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
Sezer 2007	0	21	0	20		Not estimable	2007	
Sezer 2009	0	51	0	44		Not estimable	2009	
Greco 2013	0	51	0	51		Not estimable	2013	
Geng 2018	1	118	3	112	10.3%	0.31 [0.03, 3.03]	2018	
Fu 2019	0	20	0	19		Not estimable	2019	
Gibson 2019	0	20	0	16		Not estimable	2019	
Ibrahim and Aziz 2019	0	53	0	49		Not estimable	2019	
McCartney 2019	2	289	0	151	5.8%	2.63 [0.13, 55.23]	2019	
Xiao 2019	0	38	0	33		Not estimable	2019	
Wang 2020	4	92	3	90	22.9%	1.32 [0.29, 6.06]	2020	
Wu 2020	0	25	0	25		Not estimable	2020	
Huang 2021	3	111	0	117	6.0%	7.58 [0.39, 148.45]	2021	
Jiang 2021	9	125	8	135	55.0%	1.23 [0.46, 3.30]	2021	
Total (95% CI)		1014		862	100.0%	1.27 [0.61, 2.63]		
Total events	19		14					

Heterogeneity: Tau² = 0.00; Chi² = 3.10, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.63 (P = 0.53)

Favours [ICTG]   Favours [CG]

Figure 9. Forest plot for Major Bleeding. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group

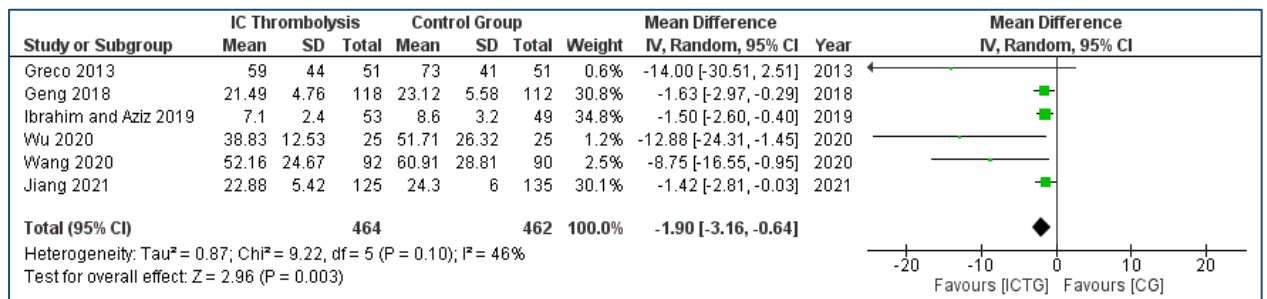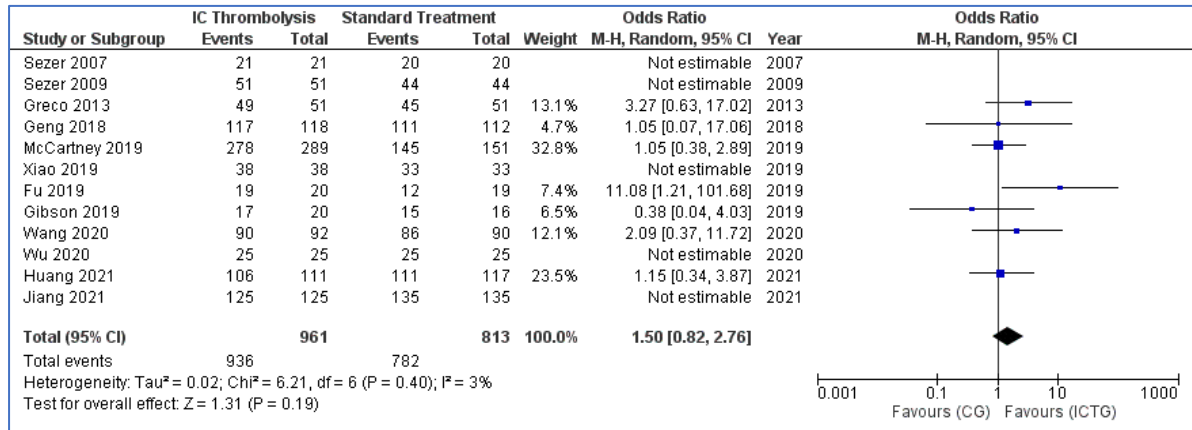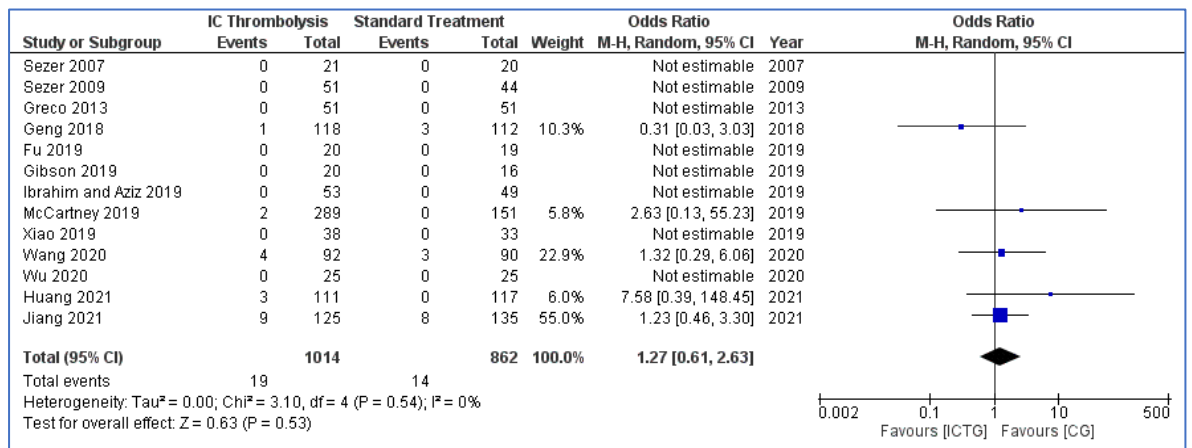| Study or Subgroup	IC Thrombolysis Events	Total	Standard Treatment Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year	Odds Ratio M-H, Random, 95% CI
Sezer 2007	1	21	0	20	2.4%	3.00 [0.12, 78.04]	2007	
Sezer 2009	0	51	0	44		Not estimable	2009	
Greco 2013	0	51	0	51		Not estimable	2013	
Geng 2018	7	118	4	112	16.1%	1.70 [0.48, 5.98]	2018	
Fu 2019	4	20	3	19	9.3%	1.33 [0.26, 6.94]	2019	
Gibson 2019	0	20	0	16		Not estimable	2019	
Ibrahim and Aziz 2019	6	53	4	49	14.3%	1.44 [0.38, 5.43]	2019	
McCartney 2019	0	289	0	151		Not estimable	2019	
Xiao 2019	9	38	3	33	12.9%	3.10 [0.76, 12.62]	2019	
Wu 2020	3	25	1	25	4.6%	3.27 [0.32, 33.84]	2020	
Wang 2020	9	92	6	90	21.9%	1.52 [0.52, 4.46]	2020	
Huang 2021	2	111	1	117	4.3%	2.13 [0.19, 23.81]	2021	
Jiang 2021	4	125	5	135	14.2%	0.86 [0.23, 3.28]	2021	
Total (95% CI)		1014		862	100.0%	1.64 [0.99, 2.71]		
Total events	45		27					

Heterogeneity: Tau² = 0.00; Chi² = 2.33, df = 8 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.92 (P = 0.05)
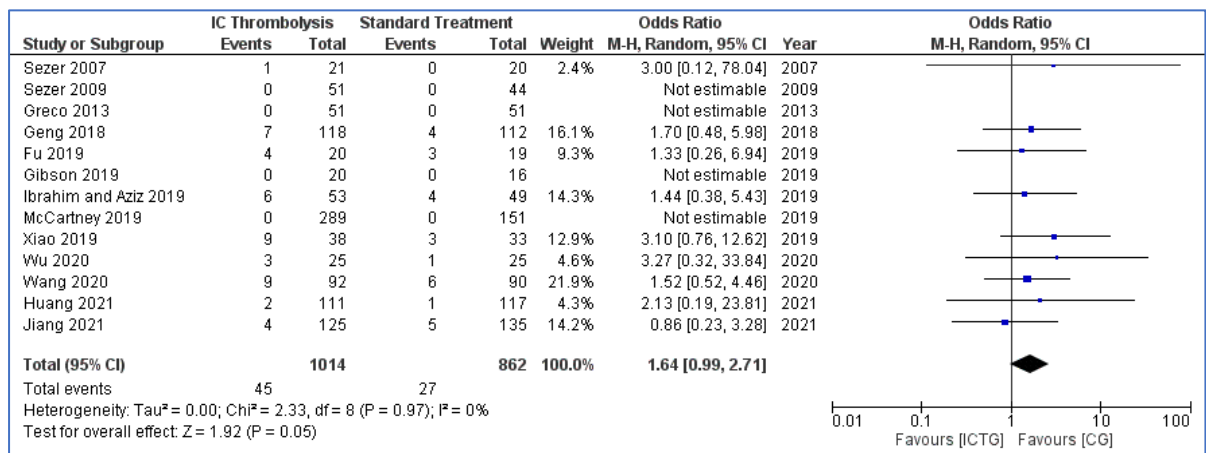
Favours [ICTG]   Favours [CG]

Figure 10. Forest plot for Minor Bleeding. ICTG: Intracoronary Thrombolysis Treatment Group, CG: Control Group

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