ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2026) **12**, 25–34
https://doi.org/10.1093/ehjcvp/pvaf085

ORIGINAL ARTICLE
Acute coronary syndromes

Intracoronary adjunctive therapies for ST-elevation myocardial infarction: a network meta-analysis of trials

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Received 22 August 2025; revised 4 November 2025; accepted 2 December 2025; online publish-ahead-of-print 9 December 2025

Aims

This network meta-analysis of randomized controlled trials (RCTs) evaluates the comparative safety and efficacy of intra-coronary (IC) pharmacological and procedural treatments—on top of balloon angioplasty and stent placement—on clinical outcomes and surrogate endpoints of coronary microvascular obstruction (CMVO) in patients with ST-elevation myocardial infarction (STEMI).

Methods and results

Two electronic databases were searched for eligible studies. Primary efficacy endpoints included all-cause mortality, non-fatal myocardial infarction (MI), and heart failure (HF) hospitalization. Primary safety endpoints included peri-procedural arrhythmias including atrioventricular blocks (AVBs) and ventricular fibrillation/sustained ventricular tachycardia (VF/SVT), any bleeding, and stroke. Secondary efficacy endpoints included the occurrence of post-procedural thrombolysis in myocardial infarction (TIMI) flow grade 0–2 and ST-segment resolution. A total of 64 RCTs involving 27 243 patients were included. In mixed comparisons, no treatment significantly reduced the incidence of primary efficacy endpoints compared to conventional primary PCI during a mean follow-up of 8 months. Several treatments significantly reduced the occurrence of post-PCI TIMI 0–2 flow grade [adenosine: 0.40 (odds ratio), (95% Confidence Interval 0.24–0.68); verapamil: 0.22 (0.07–0.69); tirofiban: 0.43 (0.27–0.71); manual thrombus aspiration (TA): 0.61 (0.45–0.82); fibrinolytic + manual TA: 0.24 (0.12–0.48); tirofiban + manual TA: 0.32 (0.14–0.75)], compared to conventional primary PCI. IC administration of tirofiban increased the risk of any bleeding [incidence rate ratio: 1.65 (1.11–2.45)], while IC adenosine increased the risk of peri-procedural AVBs [OR: 2.80 (1.14–6.84)]. Nicorandil reduced the incidence of peri-procedural VF/SVT [OR: 0.31 (0.12–0.81)].

Conclusion

Adjunctive IC treatments during primary PCI do not influence hard clinical outcomes compared to conventional therapy within a mean 8-month follow-up, although several of them lead to an improvement in surrogate endpoints of CMVO.

Study registration number

CRD42023468559

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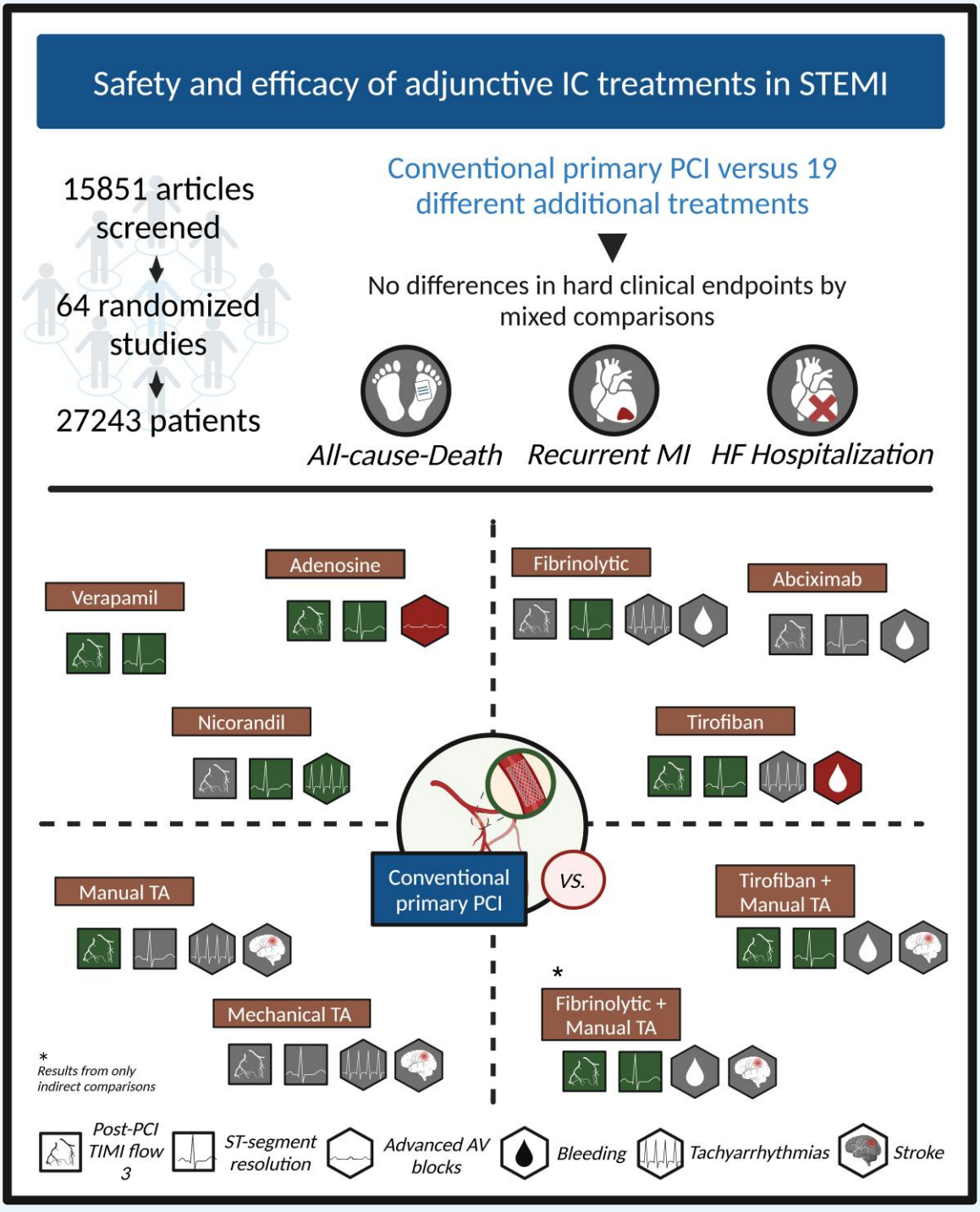
Graphical abstract



Abbreviations: AVB, atrio-ventricular block; CMVO, coronary microvascular obstruction; HF, heart failure; IC, intra-coronary; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TA, thrombus aspiration; TIMI, Thrombolysis in Myocardial Infarction.

Keywords ST-elevation myocardial infarction • Coronary microvascular obstruction • Intra-coronary • Adjunctive therapies

Introduction

Percutaneous coronary intervention (PCI) represents the cornerstone therapy for the reduction of myocardial damage and adverse clinical events in patients with ST-segment elevation myocardial infarction (STEMI), especially if performed within the time windows recommended by current guidelines.[1] Nevertheless, a sizeable proportion of patients, ranging from 5%–60%, fails to achieve complete myocardial reperfusion despite the restoration of the epicardial flow.[2] This phenomenon, defined as coronary microvascular obstruction (CMVO), involves multiple pathophysiological mechanisms and is strongly associated with mortality and hospitalization for heart failure (HF) within one year in patients with STEMI.[2,3] Therefore, over the past 30 years, a variety of strategies, both pharmacological and procedural have been tested alone, or in combination, by using different routes and timing of administration to overcome this clinically relevant issue with inconsistent results.[3] The intra-coronary (IC) route of administration may offer the optimal trade-off between safety and efficacy as it delivers the drug directly to the coronary microcirculation faster and at higher concentrations, while minimizing the risk of systemic adverse events.[3] Randomized controlled trials (RCTs) performed so far showed intrinsic limitations, being limited in size, and lacking the statistical power to detect differences in hard endpoints.[2] A large number of pairwise meta-analyses comparing various experimental treatments targeting CMVO vs. conventional PCI, defined as coronary balloon angioplasty followed by stent placement only[4,5] led to heterogeneous results, failing to show a clear benefit in terms of hard clinical outcomes but rather raising safety concerns for some of the strategies tested. They also suffer from the inherent limitation of not being able to test many therapeutic options simultaneously.[6] Therefore, despite numerous trials and pairwise meta-analyses, a comprehensive summary of the efficacy and safety of various IC strategies remains lacking, rendering CMVO an unmet clinical need.[2] To overcome this clinical conundrum, a network meta-analysis, considering all available IC strategies simultaneously through direct and indirect comparisons, might represent an appropriate methodological approach to gather evidence and to establish a hierarchy of treatments for the outcomes of interest.[6,7] Therefore, we aimed to perform a network meta-analysis to comprehensively assess the safety and efficacy of all investigated IC strategies, including their possible combinations, as adjuncts to conventional PCI in patients with STEMI.

Methods

This network meta-analysis was conducted according to the Cochrane Collaboration recommendations, Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA) report, and PRISMA extension statement for network meta-analyses.[8,9]

Protocol and registration

The study was registered through PROSPERO (identification code: CRD42023468559) and the protocol was conceived before extracting the dataset and beginning data analysis. The reference PRISMA checklist is reported in Supplementary Material.

Study search strategy

Pubmed and Scopus databases were searched systematically, as well as the references of eligible studies and recent reviews. Full electronic search strategy is reported in Supplementary Method *S1*. Five different investigators (RL, EB, GC, SF, and DAP) independently reviewed the studies to determine whether they met the inclusion criteria. The electronic search was supplemented with a manual review of the references cited in the shortlisted articles.

Data extraction and quality assessment

Data extraction on baseline characteristics, sample size, events, and follow-up duration of each study was performed by five independent authors (RL, EB, GC, SF, DAP) using a structured data collection form. Events were considered at the longest follow-up time. When possible, data were extracted from the intention-to-treat analysis. The Cochrane Risk of Bias Assessment Tool 2 (RoB2) scale was used to assess the risk of bias of the included studies, by two reviewers (RL, DAP).[10]

Efficacy endpoints

Primary efficacy endpoints comprehended the following: 'all-cause death', 'recurrent myocardial infarction (MI)', and 'HF hospitalization'. Secondary efficacy endpoints included also the rate of 24 h ST-segment resolution (i.e. >50% or >70% resolution compared to baseline) and the rate of thrombolysis in myocardial infarction (TIMI) flow grade 0–2 at the end of revascularization procedure.

Safety endpoints

The incidence of any bleeding, stroke, and peri-procedural arrhythmias—further distinguished into advanced atrio-ventricular blocks (AVB) and sustained ventricular tachycardia/ventricular fibrillation (SVT/VF)—were considered as safety endpoints. Further details on endpoint definitions are available in Supplementary Method *S2*.

Selection criteria

All the inclusion and exclusion criteria are reported in Supplementary Method *S3*.

Statistical analysis

The current network meta-analysis was conducted using the frequentist methods with restricted maximum likelihood estimation to quantify network heterogeneity and to assume a common heterogeneity estimate within a network. Statistical analyses were performed using Stata 18.[9] The inconsistency was globally assessed with a Wald test and then each loop was tested for inconsistency by the node-splitting technique, listing the differences between direct and indirect comparisons for each one of them.[9] Briefly, in network meta-analysis, loops are formed when three or more treatments are compared directly (head-to-head comparisons) and indirectly (indirect comparisons between trials sharing a common comparator) across different trials, and inconsistency occurs when the results of direct and indirect comparisons within a loop are not in agreement.[9] Global inconsistency refers to the overall disagreement between direct evidence and indirect evidence (derived from trials connected through a common comparator) across the entire network of treatments.[9] Inconsistency at both the global and single loops level is considered statistically significant when the *P* value is <0.05, suggesting disagreement between direct and indirect evidence; in such cases, potential sources of inconsistency should be explored through sensitivity analyses.[9] All the *P* values were two-sided. Effect sizes were reported as Incidence Rate Ratio (IRR) using a patient-month approach for efficacy and safety clinical endpoints (i.e. all-cause death, HF hospitalization, recurrent MI, stroke, bleeding), to account for different follow-up times. Odds ratios (OR) were used as effect measure for peri-procedural outcomes (i.e. TIMI flow grade, ST resolution, and arrhythmias). Rankograms with surface under the cumulative ranking curve (SUCRA) were reported to provide a comparative hierarchy of the different outcomes for each intervention.[9] SUCRA expressed as a percentage would be 100% when a treatment is certain to be the best, and 0% if a treatment is certain to be the worst.[11] Network maps were performed to visualize the quality of evidence for each comparison, based on the RoB 2 scale. The three colors [i.e. green (low risk), yellow (some concern), and red (high risk)] were used to represent the quality level assigned to most of the studies (> 50%) involved in the node. Inter-study heterogeneity was quantified using the I2 statistic. Cochran's Q method and Pearson chi-squared *P* values were also reported. Three pre-specified sensitivity analyses were conducted for the primary efficacy endpoints by excluding: (i) studies where bare metal stents (BMS) were employed; (ii) studies in which the mean ischemic time was higher than 6 h; (iii) studies where patients underwent rescue PCIs.

Results

The PRISMA flow chart of the study analysis was depicted in *Figure 1*. Out of 15 851 potentially relevant articles initially screened, 64 RCTs met the inclusion criteria, with a total of 27 243 patients involved. The reference list of studies included in the meta-analysis is reported in Supplementary Reference. A total of 19 treatments were compared: adenosine, diltiazem, epinephrine, fibrinolytic, fibrinolytic + manual thrombus aspiration (TA), anisodamine, eptifibatide, tirofiban, nicorandil, mechanical TA, nitroprusside, conventional PCI, manual TA, urapidil, verapamil, abciximab + manual TA, abciximab, tirofiban + manual TA, abciximab + mechanical TA. The alphabetic codes used for each treatment during the analysis are reported in Supplementary Method *S4*. The mean follow-up was weighted for the sample size of each study and was 8.2 ± 6.8 months (median follow-up: 6 months; interquartile range: 1–12). The mean age of the studied population was 62·4 years, Male patients were 17 061 (i.e. 76%) and 3068 (i.e. 11·2%) had diabetes. The mean total ischemic time across the studies was 224 min. In 49% of the patients involved, the left anterior descending artery was the site of the culprit lesion, and a stent was implanted in 98.7% of patients. The main characteristics of the included studies were summarized in Supplementary material online, *Table S1*.

Regarding all-cause mortality, a total of 24 790 patients from 47 RCTs were involved with a weighted mean follow-up of 6·1 (95%CI 2.1–10.1) months. None of the adjunctive treatments showed a statistically significant reduction in all-cause mortality compared with conventional PCI (*Table 1*), and among the experimental strategies considered, none was shown to be significantly superior to the others (see Supplementary material online, *Figure S1*). The network map was reported in *Figure 2A*. The ranking probability of being the best and

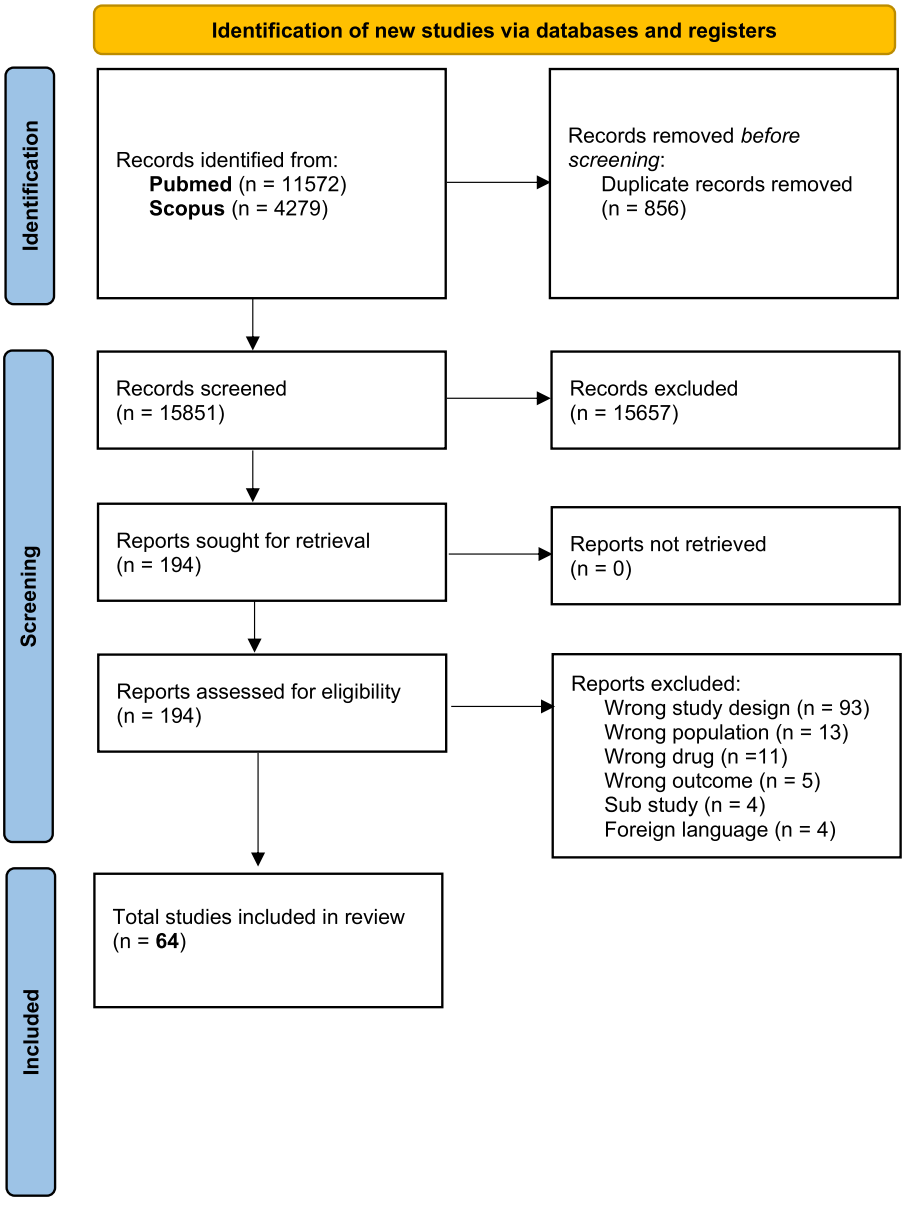


Figure 1 PRISMA flow-chart for the study analysis.

Table 1 Estimated IRR of direct and mixed comparison for all-cause-death

Comparison	IRR with 95% CI for direct comparison	IRR with 95% CI for mixed comparison	95% PI	Studies involved in direct comparison
Contrasts with direct comparison				
Adenosine vs. cPCI	0.86 (0.33–2.22)	0.86 (0.33–2.23)	0.31–2.37	Desmet et al. Grygier et al. Tian et al. Naghshtabrizi et al. Garcia-Dorado et al. Darahim et al.
Fibrinolytic vs. cPCI	2.18 (0.67–7.12)	1.25 (0.56–2.75)	0.54–2.89	Huang et al. CM Gibson et al. McCartney et al. Geng et al.
Anisodamine vs. cPCI	0.35 (0.01–8.12)	0.31 (0.01–6.73)	0.01–8.11	Chen et al.
Tirofiban vs. cPCI	0.65 (0.32–1.35)	0.77 (0.40–1.51)	0.38–1.57	Huang et al. Liu et al. Akpek et al. Liu et al. Ji et al. Wang et al.
Nicorandil vs. cPCI	1.01 (0.23–4.40)	0.88 (0.23–3.40)	0.21–3.69	Chen et al. Qi et al. Lee et al. Miyazawa et al. Nameki et al.
Mechanical TA vs. cPCI	1.60 (0.75–3.42)	1.63 (0.78–3.41)	0.75–3.57	Lefèvre et al. Ali et al. Napodano et al. Hamza et al. Ciszewski et al.
Nitroprusside vs. cPCI	0.98 (0.21–4.66)	1.11 (0.25–4.85)	0.23–5.31	Qi et al. Amit et al.
Manual TA vs. cPCI	0.93 (0.80–1.08)	0.89 (0.70–1.13)	0.69–1.14	Liu et al. De Luca et al. Stone et al. Ikari et al. Dudek et al. Svilaas et al. Y. Onuma et al. Bulum et al. Burzotta et al. Rezq et al. Haeck et al. Frobert et al. Jolly et al.
Urapidil vs. cPCI	1 (0.02–48.6)	1 (0.02–50.4)	0.02–64	Dao Kuo et al.
Abciximab + manual TA vs. cPCI	1.56 (0.38–6.37)	1.60 (0.48–5.33)	0.45–5.74	Stone et al.
Abciximab vs. cPCI	1.01 (0.23–4.38)	0.86 (0.27–2.80)	0.25–3	Bertrand et al. Stone et al.
Tirofiban + manual TA vs. cPCI	0.82 (0.02–41.18)	0.47 (0.08–2.59)	0.08–2.87	Liu et al.

Continued

Table 1 *Continued*

Comparison	IRR with 95% CI for direct comparison	IRR with 95% CI for mixed comparison	95% PI	Studies involved in direct comparison
Contrasts with only indirect comparison				
Manual TA + Fibrinolytic vs. cPCI	[a]	0.50 (0.14–1.75)	0.13–1.89	[a]
Abciximab + mechanical TA vs. cPCI	[a]	0.18 (0.01–3.74)	0.01–4.5	[a]

CI, confidence interval; cPCI, conventional percutaneous coronary intervention; IRR, Incidence Rate Ratio; PI, predictive interval; TA, thrombus aspiration.
[a]All the evidence about these contrasts comes from indirect comparison.

the SUCRA percentages for each treatment were reported in Supplementary material online, *Figure S2*.

Regarding recurrent MI, a total of 18 460 patients from 49 RCTs were involved. Detailed definition of this endpoint was provided in Supplementary material online, *Table S2.1*. By pooled mixed comparisons, no adjunctive treatment significantly reduced the incidence of recurrent MI compared to conventional PCI (see Supplementary material online, *Table S2.3*). By indirect comparison, the combination of fibrinolytic and manual TA was the only adjunctive treatment that significantly reduced the incidence of recurrent MI compared to conventional PCI (IRR 0·47, 95% CI 0·22–0·99, $P = 0·047$; Predicted interval PI: 0·21–1·04), (see Supplementary material online, *Table S2.3*). Manual TA alone had a significantly higher rate of recurrent MI compared to the combination of fibrinolytic and manual TA (IRR 2·12, 95% CI 1·04–4·36; PI: 0·99–4·57), (see Supplementary material online, *Figure S3*). The ranking probability of being the best and the SUCRA percentages for each treatment were reported in Supplementary material online, *Table S2.3* and Supplementary material online, *Figure S4*. The network map integrated with the studies' quality grading was reported in *Figure 2B*.

Regarding HF hospitalization, a total of 12 577 patients from 19 RCTs were involved with a weighted mean follow-up of 10·8 (95%CI 9·2–12·4) months. By pooled mixed comparisons, no adjunctive treatment significantly reduced the incidence of HF compared to conventional PCI (see Supplementary material online, *Table S2.4*). By indirect comparison, the combination of fibrinolytic and manual TA was the only adjunctive treatment that significantly decreased the incidence of HF hospitalization compared to conventional PCI (IRR 0·40, 95% CI 0·16–0·98, $P = 0·045$; PI:0·05–2·88), (see Supplementary material online, *Table S2.4*, Supplementary material online, *Figure S5*). The ranking probability of being the best and the SUCRA percentages for each treatment were reported in Supplementary material online, *Table S2.4* and in Supplementary material online, *Figure S6*. The network map integrated with the studies' quality grading was reported in *Figure 2C*.

Regarding post-PCI TIMI flow grade, a total of 19 609 patients from 59 RCTs were involved. Various treatments significantly reduced the rate of post-PCI TIMI 0–2 flow grade compared to conventional PCI (fibrinolytic + manual TA: OR 0·24, 95% CI 0·12–0·48, $P < 0·001$; adenosine: OR 0·40, 95% CI 0·24–0·68, $P = 0·001$; manual TA: OR 0·61, 95% CI 0·45–0·82, $P = 0·001$; verapamil: OR 0·22, 95% CI 0·07–0·69, $P = 0·009$; tirofiban: OR 0·43, 95% CI 0·27–0·71, $P = 0·001$; tirofiban + manual TA: OR 0·32, 95% CI 0·14–0·75, $P = 0·009$), (*Figure 3*). Furthermore, both manual TA and mechanical TA showed a significantly higher incidence of post-procedural TIMI 0–2 flow grade compared to the combination of fibrinolytic and manual TA (OR 2·51, 95% CI 1·35–4·66; OR 4·46, 95% CI 1·9–10·4, respectively), (see Supplementary material online, *Figure S7*). The ranking probability of being the best and SUCRA percentages of each treatment for post-procedural TIMI 0–2 flow grade were reported in Supplementary material online, *Figure S8*. The network map integrated with the studies' quality grading was reported in Supplementary material online, *Figure S9*.

Regarding ST-segment resolution, a total of 17 791 patients from 46 RCTs were involved. Different treatments significantly increased the rate of ST-segment resolution compared to conventional PCI (fibrinolytic + manual TA; fibrinolysis; adenosine; manual TA; diltiazem; verapamil; nicorandil; tirofiban; tirofiban + manual TA), (*Figure 3*). The ranking probability of being the best and SUCRA percentages of each treatment for ST-segment resolution were reported in Supplementary material online, *Figure S11*. The network map integrated with the studies' quality grading was reported in Supplementary material online, *Figure S12*.

Regarding any bleeding, a total of 4 744 patients from 23 RCTs were involved. Detailed definition of this endpoint was provided in Supplementary material online, *Table S2.2*. The use of tirofiban significantly increased the incidence of any bleeding compared to conventional PCI (IRR 1·65, 95% CI 1·11–2·45, $P = 0·013$; PI: 0·94–2·89), (*Figure 3*, Supplementary material online, *Figure S13*). The ranking probability of being the best and SUCRA percentages of each treatment is reported in Supplementary material online, *Figure S14*. The network map integrated with the studies' quality grading was reported in Supplementary material online, *Figure S15*. As consistency analysis, the 99% CI of the multivariable meta-regression coefficient for the increase in bleeding events following tirofiban treatment was performed, with a P of 0·013 (see Supplementary material online, *Figure S34*).

Regarding stroke, a total of 18 RCTs were involved, including 20, 084 patients. No adjunctive treatment significantly increased the incidence of stroke compared to conventional PCI, nor did any of them differ significantly from each other (*Figure 3*, Supplementary *S16*). The ranking probability of being the best and SUCRA percentages of each treatment were reported in Supplementary material online, *Figure S17*. The network map integrated with the studies' quality grading was reported in Supplementary material online, *Figure S18*.

Regarding arrhythmias, a total of 2, 187 patients from 18 RCTs were involved. The use of nicorandil was associated with a significant reduction in both any-type arrhythmia and VF/SVT compared to conventional PCI (OR 0·31, 95% CI 0·12–0·81, $P = 0·016$; PI: 0·04–2·54), (*Figure 3*). The interval plot with all the mixed results from direct and indirect comparisons was reported in Supplementary material online, *Figure S19*. In the secondary analysis considering only bradyarrhythmia, adenosine was the only treatment that significantly increased the incidence of peri-procedural AVBs (OR 2·80, 95% CI 1·14–6·84, $P = 0·02$), (see Supplementary material online, *Figure S20*). The ranking probability of being the best and SUCRA percentages of each treatment was reported in Supplementary material online, *Figure S21*. The network map integrated with the studies' quality grading was reported in Supplementary material online, *Figure S22*.

Between studies heterogeneity for direct comparisons was reported for all the endpoints of interest in Supplementary material online, *Tables S3–S10*. Moderate heterogeneity was detected in the direct comparison of conventional PCI vs. fibrinolytic (Q test $P = 0·09$, $I^2 = 50·32$), manual TA vs. Abciximab + manual TA

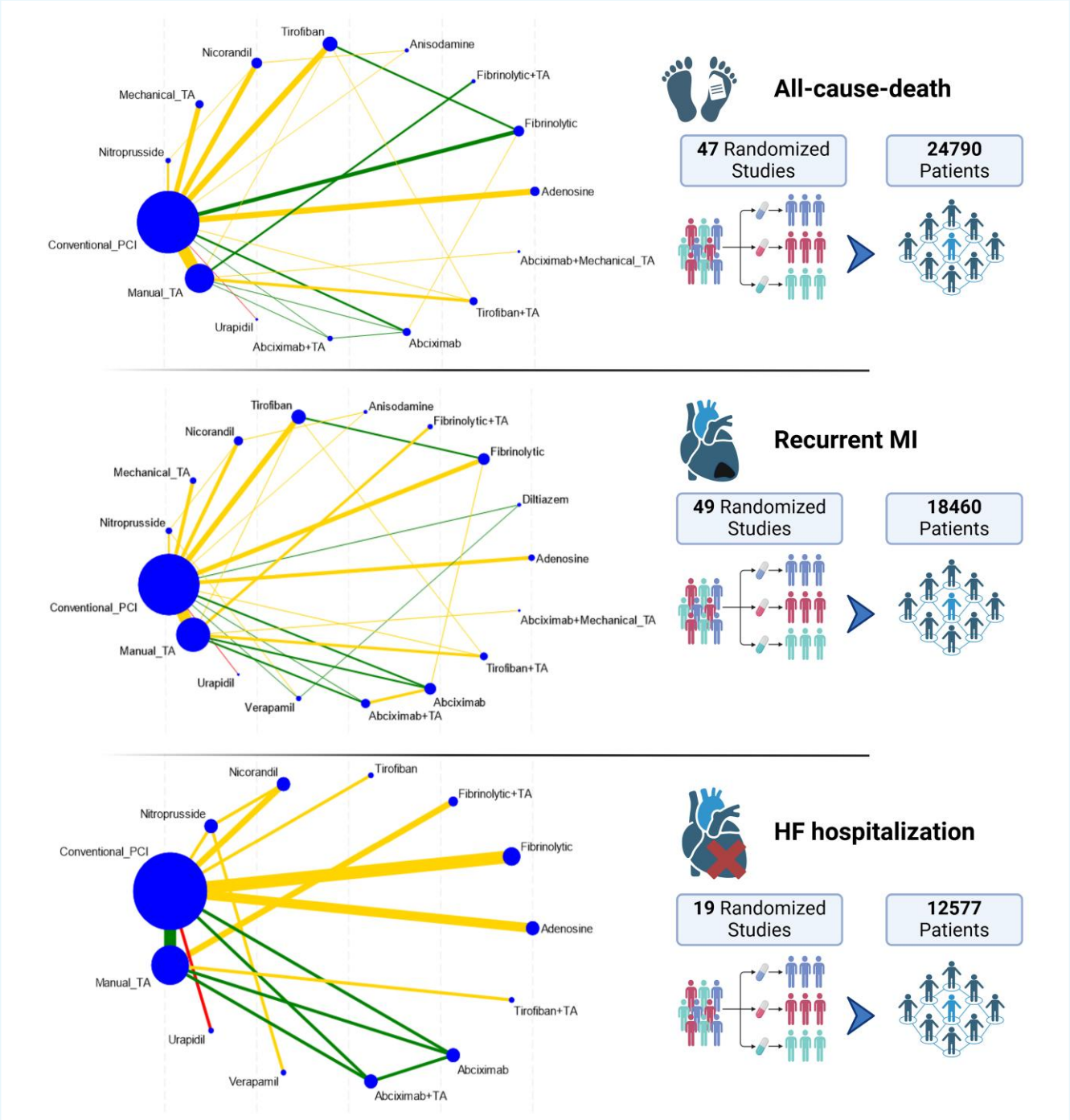


Figure 2 Network maps integrated with quality grading for each node. PCI, percutaneous coronary intervention; TA, thrombus aspiration.

(Q test $P = 0{\cdot}11$, $I^2 = 61{\cdot}78$) and Abciximab + manual TA vs. Abciximab (Q test $P = 0{\cdot}08$, $I^2 = 67{\cdot}10$) for post-procedural TIMI flow 0–2 grade analyses. Node splitting tables reporting potential statistical inconsistency between direct and indirect comparisons were reported in Supplementary material online, *Tables S11–S18*. Since significant inconsistency was detected in the comparison between conventional PCI and the combination treatment of abciximab and manual TA, a secondary analysis was performed excluding this comparison and confirming the primary analysis results; the interval plot for the secondary analysis was reported in Supplementary material online, *Figure S23*. The result was inconsistent in the pre-specified sensitivity analyses after excluding studies where BMS whereas it was maintained after excluding studies where rescue PCIs were employed (see Supplementary material online, *Figures S24* and *S25*). Forest plots for all the endpoints of interests are reported in Supplementary material online, *Figures S26–S33*.

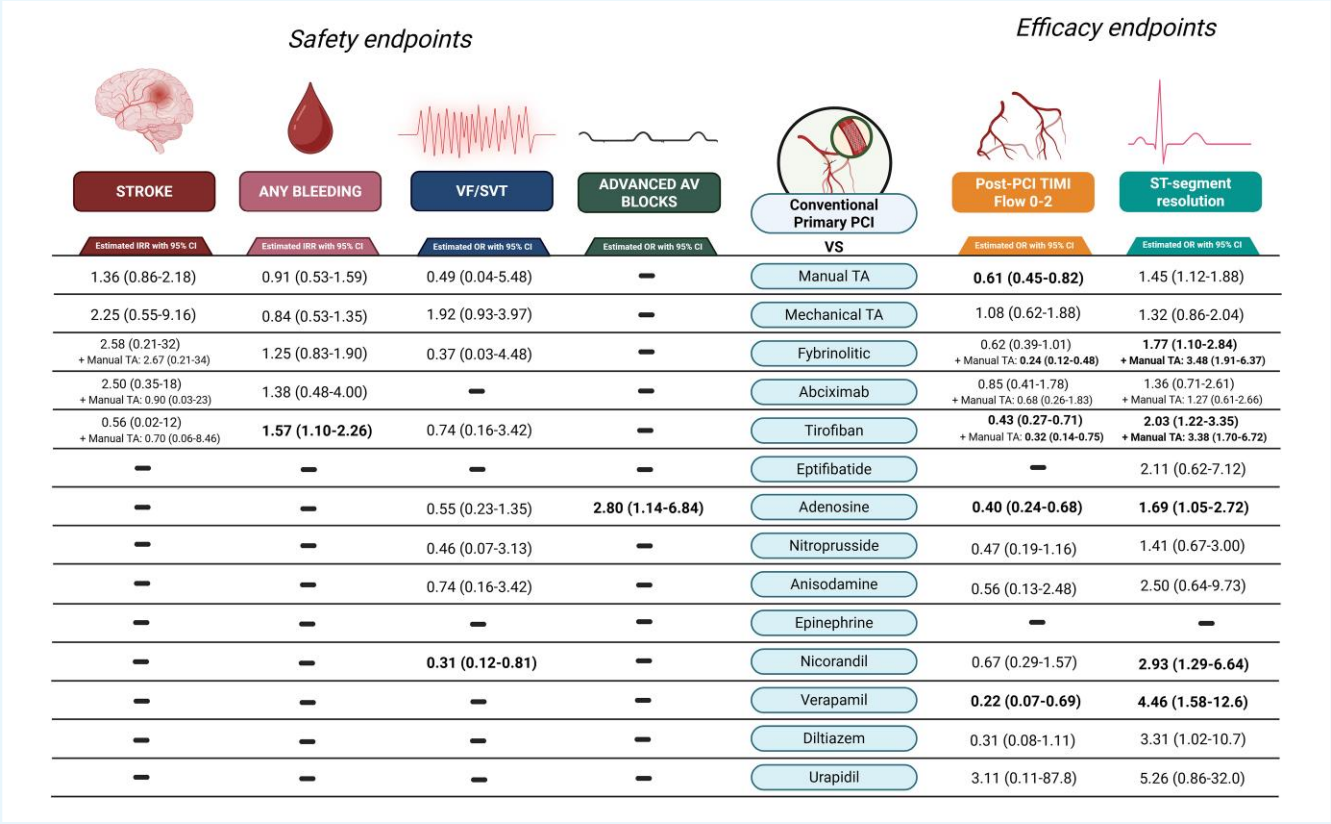


Figure 3 Summary of all the mixed effect of the treatments of interest on safety and efficacy endpoints compared to conventional PCI. AV, atrio ventricular; CI, confidence interval; IRR, Incidence Rate Ratio; OR, odds ratio; PCI, percutaneous coronary intervention; PI, predictive interval; TA, thrombus aspiration; TIMI, thrombolysis in myocardial infarction; VF/SVT, ventricular fibrillation/sustained ventricular tachycardia.

Discussion

The main findings of the current network meta-analysis, involving 27, 243 patients from 64 RCTs, are summarized as follows: (i) in a broad population of patients presenting with STEMI, a routinary use of adjunctive IC treatments do not significantly affect the incidence of hard clinical outcomes in a mid-term follow-up; (ii) adjunctive IC nicorandil seems to reduce the rate of peri-procedural malignant ventricular arrhythmias compared to conventional PCI; (iii) IC adenosine increases the rate of AVBs; (iv) additional IC tirofiban enhances the occurrence of any bleeding; (v) based on indirect comparisons, the combination of manual TA and IC fibrinolysis may reduce the incidence of both HF hospitalization and recurrent MI. (*Graphical abstract*).

Current guidelines do not recommend any strategies for the prevention or treatment of CMVO in STEMI patients, and the present network meta-analysis further confirms this gap in recommendations.[1] It is also noteworthy that promising strategies beyond adjunctive IC treatments have been proposed to improve coronary perfusion and clinical outcomes and are currently under investigation in large RCTs (e.g. left ventricular unloading before reperfusion, administration of supersaturated oxygen delivery).[12-15] A recent pairwise meta-analysis, investigating the impact of manual TA on post-infarction left ventricular remodeling, revealed a significant correlation between the effect size, measured as left ventricular ejection fraction at follow-up, and the duration of the follow-up period.[16] Therefore, an inadequately follow-up duration in the included studies may be a key factor explaining the lack of significant clinical benefits with adjunctive IC treatments.[16] However, through indirect comparisons only, our study suggests that combining manual TA with IC fibrinolysis may effectively reduce the incidence of HF hospitalizations and recurrent MI. IC fibrinolytic agents may act synergistically with TA by targeting the microscopic components of the thrombus, thereby promoting more complete thrombus resolution and reducing distal embolization. At the culprit lesion site, incomplete clearance of thrombotic material may impair optimal stent expansion and act as a proliferative and pro-inflammatory stimulus, thereby heightening the risk of future MI events.[17,18] However, this finding should be regarded as hypothesis-generating and requires validation through adequately powered RCTs, as it is based on indirect comparisons of small-scale studies.

Various single and combined strategies are associated with a higher incidence of ST-segment resolution and TIMI flow grade 3 after PCI, although only the combination of manual TA and IC fibrinolysis has been shown to improve prognosis. Conflicting results on their prognostic value have been reported in both RCTs or registry studies, questioning their accuracy and predictive power.[19,20] This is probably due to the inconsistency of methods and lack of standardization between and within the different studies, further exacerbated by the vasodilatory and rheological effects of certain treatments under investigation (i.e. adenosine, anisodamine, diltiazem, verapamil, nicorandil, nitroprusside, urapidil, epinephrine).[3] Therefore, caution is warranted when evaluating the efficacy of these treatments solely based on surrogate measures of CMVO, and not on cardiac magnetic resonance. Moreover, the potential benefit of intracoronary drugs in limiting CMVO after STEMI is inherently influenced by the variable response of the downstream microcirculation and myocardial cells to acute ischemia, which depends on several patient-specific factors such as the ischemic preconditioning, the degree of local inflammatory activation, and the

thrombotic burden.[2] This high degree of individual variability might explain the absence of a significant benefit at the population level and underscores one of the main limitations of such studies.

A common issue with prevention strategies is that some patients receive treatment unnecessarily, as only a subset ultimately develops the complication. Consequently, ensuring the safety of such interventions is a critical concern. The prognostic role of tachy- and brady-arrhythmias has been well established in STEMI patients.[11,21] In our network meta-analysis, IC nicorandil was shown to reduce the risk of ventricular arrhythmias, while IC adenosine increased the risk of AVBs. Apart from timely and effective revascularization, there are no recommended therapies to prevent the occurrence of ventricular arrhythmic events in STEMI patients.[1] Nicorandil, acting as a K-ATP channel opener, has the potential to dilate resistance arterioles, to reduce the production of reactive oxygen species upon re-oxygenation, to attenuate ischemia/reperfusion-induced activation of neutrophils via nitric oxide donation, and to act as a key mediator of ischemic preconditioning.[22,23] Conversely, the risk of AVBs with adenosine was already known and our results are consistent with a previous meta-analysis.[4] The occurrence of bleeding is also associated with a poor prognosis in STEMI patients.[24] Both minor and major bleeding can worsen prognosis through several direct and indirect mechanisms, such as increased inflammatory response as a consequence of blood transfusion or unplanned interruption of life-saving drugs (i.e. anti-platelet therapies, statins, or beta-blockers).[24] The adjunctive administration of IC tirofiban is the only treatment that increases the risk of any bleeding, compared to conventional PCI. Compared to tirofiban and eptifibatide, the abciximab molecule is a chimeric molecule with a higher mass and, consequently, a longer action time.[25] As a result, an intravenous maintenance dose of tirofiban or eptifibatide was additionally administered in most of the included RCTs, increasing the overall dose and drug exposure. Indeed, the exclusion of RCTs using an additional intravenous maintenance dose of tirofiban after an IC bolus, abolished the increase in bleeding risk. Finally, TA alone or in combination with other treatments have been shown to be safe, with no significant increase in stroke occurrence compared to conventional PCI.[26]

Limitations

The results of this meta-analysis should be interpreted given the following limitations. First, although we exclude RCTs in which one of the treatments of interest is administered intravenously by default, in some of the included studies a certain percentage of patients receives an additional treatment at the operator's discretion. Second, some combinations of treatments and other approaches, such as ischemic conditioning and deferral PCI, not fulfilling the above inclusion criteria, have not been evaluated in the current network meta-analysis. Third, the dosage and the timing of administration for some of the drugs tested varied between trials. Fourth, the absence of a significant benefit at the population level should be interpreted as an expression of the considerable patient-level variability—both between and within studies—rather than as definitive evidence of inefficacy.

Fifth, RCTs included in this meta-analysis are performed over approximately 20 years, which may imply differences in background therapy, type of stent used, and revascularization techniques. The lack of patient-level data hinders the assessment of baseline clinical and procedural characteristics, such as thrombus burden, that may potentially impact safety and efficacy outcomes.

Conclusions

The IC strategies tested to date in the context of primary PCI have not demonstrated a significant improvement in clinical outcomes, aligning with current guidelines that do not recommend their routine implementation in daily clinical practice.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Acknowledgements

Nothing to declare.

Author contributions

R.L., E.B., D.D.A., and F.B. conceived and designed the study. R.L., E.B., G.C., D.A.P., S.F. independently assessed the studies for possible inclusion and collected the data. R.L. and E.B. analyzed the data. R.L., D.D.A., E.B., and F.B. produced the first draft of the manuscript. P.S., F.C., M.G., G.P., C.T., and G.B.Z. critically revised the manuscript for important intellectual content. All authors revised and approved the final version of the manuscript.

Funding

There was no funding source for this study.

Conflict of interest: G.B-Z. has consulted for Abiomed, Advanced Nanotherapies, Aleph, Amarin, Balmed, Cardionovum, Crannmedical, Endocore Lab, Eukon, Guidotti, Innovheart, Meditrial, Menarini, Microport, Opsens Medical, Terumo, and Translumina, outside the present work. G.S. reports grants and personal fees from CSL Vifor, Boehringer Ingelheim, AstraZeneca, Servier, Novartis, Cytokinetics, Pharmacosmos, Medtronic, Bayer, and personal fees from Roche, Abbott, Edwards Lifescience, TEVA, INTAS, Menarini, Hikma, and grants from Boston Scientific, Merck, all outside the submitted work. The remaining authors have no conflicts of interest to declare for the present work.

Data availability

The data underlying this article are available in the individual trials included in the analysis and have been fully reported in the article and in its online supplementary material.

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