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## Supplementary appendix

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# Supplementary appendix

**Comparative efficacy and safety of Reperfusion Therapy with Fibrinolytic Agents in Patient with ST-segment Elevation Myocardial Infarction: A Systematic Review and Network Meta-analysis.**

Jinatongthai P, Kongwatcharapong J, Foo CY, Phrommintikul A, Nathisuwan S, Thakkinstian A, Reid CM, Chaiyakunapruk N.

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# Appendix 1 Additional methods

Type of studies

All randomized controlled trials (RCTs) will be included if they investigated the efficacy and safety of reperfusion therapy with fibrinolytic agents, whether given alone or in combination with adjunctive antithrombotic therapy, comparing with each other, treatment with antithrombotic therapy only, placebo, or no treatment in adult patients with STEMI. No language restriction will be applied. Non-control study such as pre-post study, non-RCT, observational or cross-sectional study will be excluded. Study established to determine non-clinical outcome will be included if the clinical outcomes of interest are reported. Studies with PCI as a facilitation of fibrinolytic therapy or in comparison with fibrinolytic agents will be excluded. Trials investigating adjunctive antithrombotic therapy after reperfusion with fibrinolytic agents will also be excluded if the results of the studies are not stratified by each fibrinolytic agent or distribution of patients between each of the treatment regimen are not equal.

Types of participants

Studies investigating adults 18 years or older with a diagnosis of STEMI will be considered to be included in this review. Patients will be included if they were diagnosed with STEMI (new ST elevation at the J point in at least 2 contiguous leads of ≥2 mm [0.2 mV] in men or ≥1.5 mm [0.15 mV] in women in leads V2–V3 and/or of ≥1 mm [0.1mV] in other contiguous chest leads or the limb leads) or STEMI equivalent (new or presumably new LBBB) and were candidate of reperfusion therapy with fibrinolytic agents according to clinical practice guidelines recommendation.[1,2] Studies investigating patients with ST depression will be considered if it is suspected to be a true posterior (inferobasal) MI or if it is associated with ST elevation in lead aVR. Patients with other types of ACS (other than STEMI, such as non-ST segment elevation myocardial infarction, NSTEMI; or unstable angina) will be excluded. Study with mixed population other than STEMI will also be excluded.

Types of interventions

Randomized controlled trials investigating one or more of the following fibrinolytic agents administered in intravenous form, whether given alone or in combination with adjunctive antithrombotic therapy: streptokinase, alteplase (separate into 2 type based on administration regimen, accelerated and non-aceerelated infusion alteplase), lanoteplase, tenecteplase, and reteplase.

If the including studies were identified, they will be considered to be included in the network meta-analysis after determining their comparability with the pre-specified set of competing treatment options. The findings for these treatment options and the conclusions of the review will be reported. For a randomized trial that have investigated the efficacy of adjunctive antithrombotic treatment with fibrinolytic agents (for example, streptokinase plus unfractionated heparin versus accelerated infusion alteplase plus enoxaparin), the treatment comparison will be coded as each type of fibrinolytic agent plus the group of adjunctive antithrombotic treatment based on its pharmacological property regardless of the dosage regimen (coded as streptokinase plus parenteral anticoagulants [PAC] versus accelerated infusion alteplase plus PAC). Trial with similar coding of treatment comparison will not be considered in the network meta-analysis.

Only treatment options using approved dosing regimens will be considered. Adjunctive antithrombotic treatment that are not available or not approved in the current practice will be excluded, except for the combination regimen with Glycoprotein IIb/IIIa. Treatment regimens of fibrinolytic agents in combination with glycoprotein IIb/IIIa were included in the network meta-analysis in order to test the efficacy and safety of the addition of glycoprotein IIb/IIIa into the regimen. Treatment regimen with Glycoprotein IIb/IIIa was grouped similarly. Data on dose confirmation study from phase II clinical trials are also included. When studies compare more than 2 intervention arms with assumed equal distribution of patients in each arm, only the intervention meeting the above criteria will be included if it remains at least two interventions in each study.

Outcome measures

**Primary efficacy outcomes:** All-cause mortality within 30-35 days (including inhospital mortality)

**Primary safety outcome:** Major bleeding (as a report of significant bleeding [major bleeding, serious bleeding, severe bleeding] as per the definition of each trial, or a composite of bleeding event reporting as intracranial hemorrhage, cardiac tamponade, intraocular bleed, retroperitoneal bleed, or bleeding associated with dropping hemoglobin/hematocrit, or bleeding requiring intervention)

**Secondary efficacy outcomes:**

1. All-type stroke (as report in trials)

2. Recurrent myocardial infarction (as report in trials)

3. Another cardiovascular outcome such as death from cardiovascular causes or combined cardiovascular outcomes will also be assessed for the possibility to perform the analysis

**Secondary safety outcomes:** hemorrhagic stroke or intracranial hemorrhage (as reported in trials)

The definition of major bleeding included are tabulated.

*Search methods for identification of studies*

The following databases will be used to search for original research articles from inception to May 2016: Medline (Pubmed), Embase OVID, Cochrane Central Register of Control Trials, ClinicalTrials.gov, WHO International Clinical Trials Registry (WHO ICTR). A combination of medical subject headings (MeSH) and keywords were used to design the search strategy.The MeSH and keywords contain “plasminogen activator”, “fibrinolytic agent”, “acute coronary syndrome”, “myocardial infarction”, “heart infarction”, “ST segment elevation myocardial infarction”, name of fibrinolytic agents (streptokinase, tenecteplase, alteplase, reteplase, and lanoteplase), and synonymous words. References derived from full text review were screened to identify potential studies not indexed in the above databases. No language restriction was applied. See the Appendix 2 for search terms used in strategies of this review.

*Data collection and analysis*

A calibration exercise was conducted. Two reviewers independently screened the titles and abstracts. Assessment of non-English studies was performed after electronic translation. Conflicts were resolved by discussion. The same process was adopted in data extraction and methodological quality appraisal using the Cochrane Risk of Bias Tool.[3] Two independent reviewers (PJ, JK) extracted the necessary data using a standard extraction form. The form was developed through a consensus process involving all reviewers.

Data extracted include:

1) Characteristics of the study such as year, country, number of arms, study design, period of study, period of follow up, center of study.

2) Characteristic of participant such as age, gender, number of patients included in analysis, population of analysis (intention to treat, per protocol, other), type of ECG, time from an onset of symptoms, a sub-classification of STEMI severity (such as Killip classification).

3) Type of intervention and type of comparator(s) such as dosing strategy, drug category (fibrin/non-fibrin specific fibrinolytic agents), concomitant medication (adjunctive antithrombotic drugs and other pharmacologic intervention), time to reperfusion.

4) Outcome measures such as time to outcome measure, outcomes of interest as stated above including primary and secondary outcomes, composite outcomes, and net clinical outcome.

*Risk of bias assessment*

The quality of individual studies was assessed using Cochrane's Risk of Bias Tool[3] on selection bias, attrition bias, performance bias, detection bias and reporting bias. Each studies was judged to be at high, low or unclear risk of bias based on their adequacy of sequence generation, allocation concealment, blinding, and method of addressing incomplete data, selective reporting, and other biases. Quality assessment was undertaken by one reviewer and checked by a second reviewer. Disagreements were resolved by consensus, or by consulting a third party.

*Measures of treatment effect*

<u>Relative treatment effects</u>

All outcomes are dichotomous and the relevative effect were measured by the risk ratio (RR). Presentation of the treatment effect estimated by the network meta-analysis are summarized as relative effect sizes for each possible pair of treatments.

Relative treatment ranking

The ranking probabilities of being at each possible have been estimated for all treatment options. A treatment hierarchy is obtained by using the surface under the cumulative ranking curve (SUCRA) and mean ranks. SUCRA is shown as a percentage and can be interpreted as the percentage of efficacy/safety of a treatment that would be ranked first without uncertainty.[4]

*Data synthesis*

The overall effect (summary measure) was estimated using both fixed effect models (MantelHaenszel) and random effects models (DerSimonian and Laird). The choice between the two models was based on the presence (or absence) of heterogeneity diagnosed using the Cochran Q test and the I2 statistic. Network meta-analysis allowing for indirect comparisons was performed. Direct meta-analysis was performed using a random effects model. Publication bias was examined using funnel plot and Egger's regression test. We modeled the comparative efficacy of any two treatments as a function of each treatment relative to the placebo. This approach assumes "consistency" of treatment effects across all included trials – that is, the direct and indirect estimates are the same effects. Network inconsistency was evaluated by comparing the direct estimates to the indirect estimates. The GRADE approach was used to rate the quality of evidence of the estimates derived from network meta-analysis.

Standard Pairwise and Network Meta-Analysis was performed using STATA version 14 (StataCorp, College Station, Texas, USA) and a programmed STATA routines for network meta-analysis available at http://www.mtm.uoi.gr/index.php/stata-routines-for-network-meta-analysis.

*Sensitivity and subgroup analyses*

The benefit of reperfusion therapy with fibrinolytic agents among the patients with higher risk of bleeding were assessed using subgroup analysis technique. The rationale for this assessment was based on the hypothesis that patients who are at higher risk of bleeding may gain less benefit from reperfusion therapy with fibrinolytic agents.Elderly, female gender, patients with low body weight, and Asian participants are factors consideredto be related to increase risk of bleeding[5-8]. Other subgroup analyses included Killip classification.

Sensitivity analyses were conducted on the primary outcomes in order to determine the sources of heterogeneity or inconsistency and to assess applicability of the findings. This included restricting the analyses to: trials that have included ASA in the trial treatment protocol; excluding trials that have reported mortality of less than 30 days; trials with clearly reported major bleeding definition; trials that have investigated fibrinolytics with PAC; excluding trials with small sample size (<25$^{th}$ and <75th percentiles); and excluding trials with inadequate concealed allocation. We also have conducted a restrictive analysis that have excluded trials conducted in China. This is due to the raising concerns of data fabrication in Chinese clinical trials reported recently.[9]

*Differences between protocol and review*

We have also conducted a net clinical benefit analysis in order to determine the value of fibrinolytic therapy taking into consideration of both the risk and benefit. See the Appendix 11 for detials.

We have also decided to exclude lanoteplase from the original inclusion criteria because this agent has been withdrawn from the market as we learnt along the conduct of this study.

We updated the search until the end of February 2017.

In order to minimize the heterogeneity of the definition of major bleeding across the included studies, bleeding events was matched agaist the standardized bleeding end-point definitions adopted by Bleeding Academic Research Consortium (BARC).[10] We defined major bleeding in this study according to BARC type 3a, 3b, or 3c. Table below provides an example of the matching process between major bleeding by the Thrombolysis in Myocardial Infarction (TIMI) bleeding and the Global Use of Strategies to Open Occluded Arteries (GUSTO) with BARC definition.

| BARC bleeding definition | | TIMI major bleeding | GUSTO severe or life-threatening |
|---|---|---|---|
| **Type 0** | No bleeding | | |
| **Type 1** | Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional | | |
| **Type 2** | Any overt, actionable sign of hemorrhage that does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation | | |
| **Type 3a** | Overt bleeding plus Hb drop of 3 to <5 g/dL | | Resulting in substantial hemodynamic compromise requiring treatment |
| | Any transfusion with overt bleeding | | |
| **Type 3b** | Overt bleeding plus Hb drop ≥5 g/dL | Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL | |
| | Cardiac tamponade | | |
| | Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) | | |
| | Bleeding requiring intravenous vasoactive agents | | |
| **Type 3c** | Intracranial hemorrhage | Any intracranial bleeding | Intracerebral hemorrhage |
| | Subcategories confirmed by autopsy or imaging or lumbar puncture | | |
| | Intraocular bleed compromising vision | | |
| **Type 4** | CABG-related bleeding | | |
| **Type 5** | Fatal bleeding | Fatal bleeding | |

# Appendix 2 Search strategies

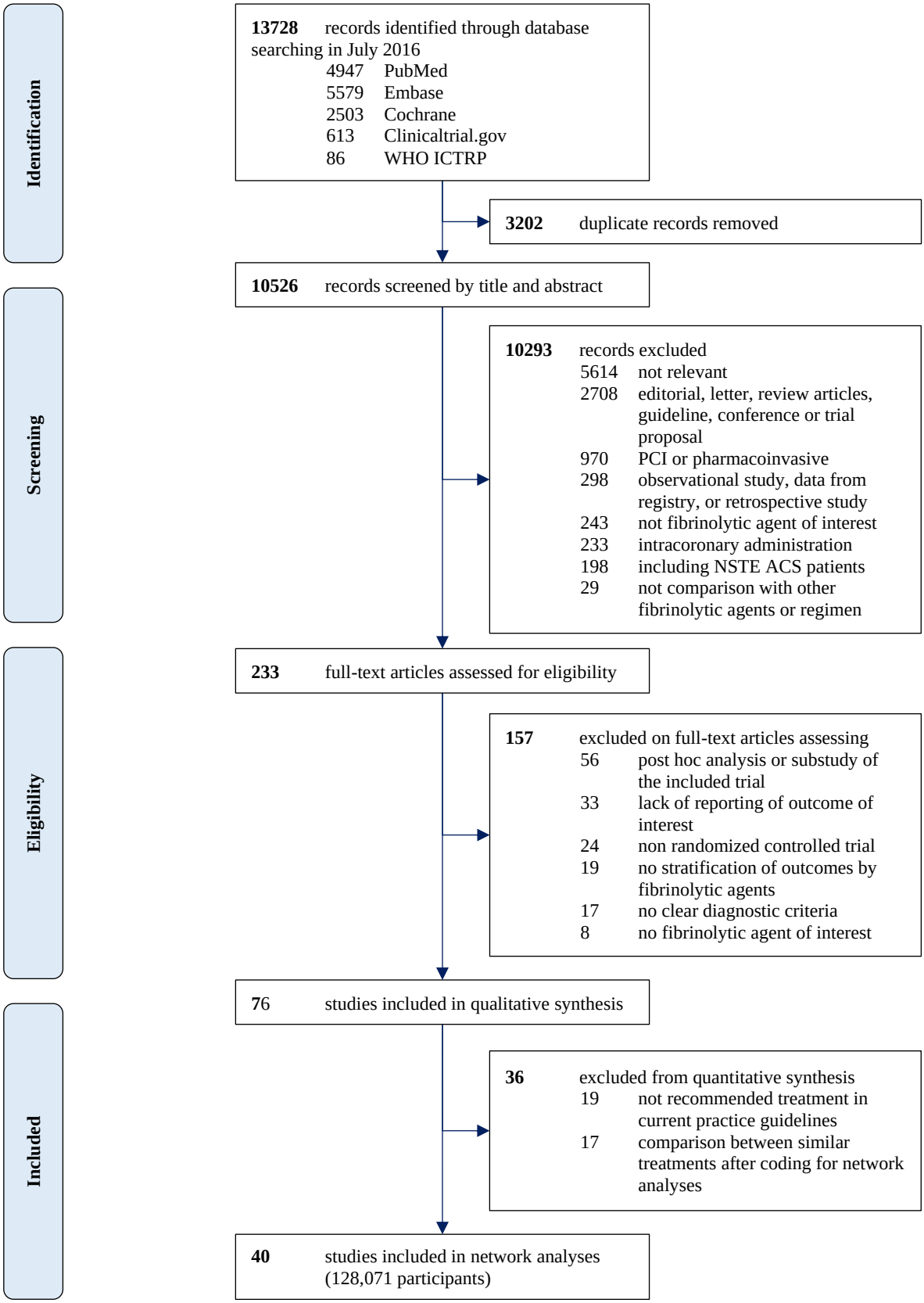
**eTable 2.1 Search algorithms.**

| Database | Step | Search algorithm | Items found |
|---|---|---|---|
| **PubMed** | #1 | streptokinase | 11198 |
| | #2 | tenecteplase | 515 |
| | #3 | alteplase | 27605 |
| | #4 | reteplase | 447 |
| | #5 | lanoteplase | 59 |
| | #6 | plasminogen activator | 54383 |
| | #7 | fibrinolytic agent | 163486 |
| | #8 | acute coronary syndrome | 24933 |
| | #9 | myocardial infarction | 219989 |
| | #10 | ST segment elevation myocardial infarction | 17516 |
| | #11 | ((((#1) OR #2) OR #3) OR #4) OR #5 | 37087 |
| | #12 | ((#11) OR #6) OR #7 | 189121 |
| | #13 | ((#8) OR #9) OR #10 | 234072 |
| | #14 | (#12) AND #13 | 19650 |
| | #15 | ((#12) AND #13) Filters: Clinical Study | 4249 |
| | #16 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial | 4249 |
| | #17 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I | 4249 |
| | #18 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II | 4249 |
| | #19 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV | 4249 |
| | #20 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Controlled Clinical Trial | 4249 |
| | #21 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Controlled Clinical Trial; Meta-Analysis | 4615 |
| | #22 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Controlled Clinical Trial; Meta-Analysis; Multicenter Study | 4952 |
| | #23 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Controlled Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial | 4952 |
| | #24 | ((#12) AND #13) Filters: Clinical Study; Clinical Trial; Clinical Trial, Phase I; Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Controlled Clinical Trial; Meta-Analysis; Multicenter Study; Randomized Controlled Trial; Humans | 4947 |
| **Embase** | #1 | streptokinase | 20548 |
| | #2 | tenecteplase | 2288 |
| | #3 | alteplase | 16539 |
| | #4 | reteplase | 1962 |
| | #5 | lanoteplase | 322 |
| | #6 | plasminogen activator | 93126 |
| | #7 | blood clot lysis | 39084 |
| | #8 | reperfusion | 111392 |

| Database | Step | Search algorithm | Items found |
|---|---|---|---|
| | #9 | fibrinolytic agent | 122964 |
| | #10 | fibrinolysis | 78571 |
| | #11 | acute coronary syndrome | 52410 |
| | #12 | heart infarction | 344220 |
| | #13 | 1 or 2 or 3 or 4 or 5 | 35116 |
| | #14 | 6 or 13 | 94460 |
| | #15 | 9 or 14 | 139797 |
| | #16 | ST segment elevation myocardial infarction | 35285 |
| | #17 | 15 and 16 | 2098 |
| | #18 | 11 or 12 or 16 | 370793 |
| | #19 | 6 or 7 or 8 or 9 or 10 or 13 | 278282 |
| | #20 | 18 and 19 | 52997 |
| | #21 | 1 or 2 or 3 or 4 or 5 or 6 or 9 | 139797 |
| | #22 | 18 and 21 | 21607 |
| | #23 | 22 | 21607 |
| | #24 | limit 23 to human | 20305 |
| | #25 | limit 24 to ((clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) and (conference abstract or conference paper or conference proceeding or "conference review" or journal)) | 5579 |
| **Cochrane** | #1 | streptokinase | 1453 |
| | #2 | tenecteplase | 187 |
| | #3 | alteplase | 799 |
| | #4 | reteplase | 149 |
| | #5 | lanoteplase | 32 |
| | #6 | plasminogen activator | 3961 |
| | #7 | fibrinolytic agent | 2889 |
| | #8 | acute coronary syndrome | 4129 |
| | #9 | myocardial infarction | 23222 |
| | #10 | ST segment elevation myocardial infarction | 3311 |
| | #11 | #1 or #2 or #3 or #4 or #5 | 2295 |
| | #12 | #11 or #6 or #7 | 6944 |
| | #13 | #8 or #9 or #10 | 25181 |
| | #14 | #12 and #13 | 2503 |
| **Clinicaltrail.gov** | #1 | streptokinase | 22 |
| | #2 | tenecteplase | 42 |
| | #3 | alteplase | 338 |
| | #4 | reteplase | 7 |
| | #5 | lanoteplase | 0 |
| | #6 | plasminogen activator | 360 |
| | #7 | reperfusion | 809 |
| | #8 | fibrinolytic agent | 2451 |
| | #9 | acute coronary syndrome | 1597 |
| | #10 | myocardial infarction | 4051 |
| | #11 | ST segment elevation myocardial infarction | 732 |

| Database | Step | Search algorithm | Items found |
|---|---|---|---|
| | #12 | ( streptokinase OR tenecteplase OR alteplase OR reteplase OR lanoteplase OR plasminogen activator OR fibrinolytic agent ) AND ( acute coronary syndrome OR myocardial infarction OR ST segment elevation myocardial infarction ) | 613 |
| **WHO ICTRP** | #1 | streptokinase | 36 |
| | #2 | tenecteplase | 78 |
| | #3 | alteplase | 366 |
| | #4 | reteplase | 5 |
| | #5 | lanoteplase | 0 |
| | #6 | plasminogen activator | 208 |
| | #7 | reperfusion | 518 |
| | #8 | fibrinolytic agent | 80 |
| | #9 | acute coronary syndrome | 1384 |
| | #10 | myocardial infarction | 2934 |
| | #11 | ST segment elevation myocardial infarction | 273 |
| | #12 | streptokinase AND acute coronary syndrome OR streptokinase AND myocardial infarction OR streptokinase AND ST segment elevation myocardial infarction | 19 |
| | #13 | tenecteplase AND acute coronary syndrome OR tenecteplase AND myocardial infarction OR tenecteplase AND ST segment elevation myocardial infarction | 32 |
| | #14 | alteplase AND acute coronary syndrome OR alteplase AND myocardial infarction OR alteplase AND ST segment elevation myocardial infarction | 16 |
| | #15 | reteplase AND acute coronary syndrome OR reteplase AND myocardial infarction OR reteplase AND ST segment elevation myocardial infarction | 4 |
| | #16 | lanoteplase AND acute coronary syndrome OR lanoteplase AND myocardial infarction OR lanoteplase AND ST segment elevation myocardial infarction | 0 |
| | #17 | plasminogen activator AND acute coronary syndrome OR plasminogen activator AND myocardial infarction OR plasminogen activator AND ST segment elevation myocardial infarction | 10 |
| | #18 | fibrinolytic agent AND acute coronary syndrome OR fibrinolytic agent AND myocardial infarction OR fibrinolytic agent AND ST segment elevation myocardial infarction | 14 |
| | #19 | combination of 12-18 (manually combined) | 86 |

**eFigure 2.1 Flow diagram and references of included studies.**



# Appendix 3 General characteristics of treatment options

**eTable 3.1 General characteristics of treatment options.**

| Treatment | Fibrinolytic agents | PAC | GP IIb/IIIa | Definition of abbreviation of intervention |
|---|---|---|---|---|
| No_ATbx | - | - | - | No antithrombotics |
| nPA+UFH | nPA | UFH | - | Lanoteplase+Unfrationated heparin |
| rPA+UFH | rPA | UFH | - | Reteplase+Unfrationated heparin |
| rPA_red+UFH | rPA_red | UFH | - | Reteplase (reduced dose)+Unfrationated heparin |
| rPA_red+UFH+Abx | rPA_red | UFH | Abx | Reteplase (reduced dose)+Unfrationated heparin+Abciximab |
| rSK | rSK | - | - | Streptokinase (recombinant) |
| SK | SK | - | - | Streptokinase |
| SK+Bival | SK | Bival | - | Streptokinase+Bivalirudin (Hirulog) |
| SK+Dalte | SK | Dalte | - | Streptokinase+Dalteparin |
| SK+Efeg | SK | Efeg | - | Streptokinase+Efegatran |
| SK+Enox | SK | Enox | - | Streptokinase+Enoxaparin |
| SK+Ept | SK | - | Ept | Streptokinase+Eptifibatide |
| SK+Fraxi | SK | Fraxi | - | Streptokinase+Fraxiparin |
| SK+Lepi | SK | Lepi | - | Streptokinase+Lepirudin |
| SK+UFH | SK | UFH | - | Streptokinase+Unfrationated heparin |
| SK-tPA_red+UFH | SK-tPA_red | UFH | - | Streptokinase + alteplase (reduced dose)+Unfrationated heparin |
| SK_acc | SK_acc | - | - | Streptokinase (accelerated infusion) |
| SK_acc+UFH | SK_acc | UFH | - | Streptokinase (accelerated infusion)+Unfrationated heparin |
| SK_FL+UFH | SK_FL | UFH | - | Streptokinase (front loaded)+Unfrationated heparin |
| SK_red+UFH | SK_red | UFH | - | Streptokinase (reduced dose)+Unfrationated heparin |
| TNK+Enox | TNK | Enox | - | Tenecteplase+Enoxaparin |
| TNK+UFH | TNK | UFH | - | Tenecteplase+Unfrationated heparin |
| TNK+UFH+Abx | TNK | UFH | Abx | Tenecteplase+Unfrationated heparin+Abciximab |
| TNK_red | TNK_red | - | - | Tenecteplase (reduced dose) |
| TNK_red+Enox+Abx | TNK_red | Enox | Abx | Tenecteplase (reduced dose)+Enoxaparin+Abciximab |
| TNK_red+UFH+Abx | TNK_red | UFH | Abx | Tenecteplase (reduced dose)+Unfrationated heparin+Abciximab |
| TNK_red+UFH+Ept | TNK_red | UFH | Ept | Tenecteplase (reduced dose)+Unfrationated heparin+Eptifibatide |
| tPA | tPA | - | - | Alteplase (non-accelerated infusion) |
| tPA+UFH | tPA | UFH | - | Alteplase (non-accelerated infusion)+Unfrationated heparin |
| tPA_acc+Argat | tPA_acc | Argat | - | Alteplase (accelerated infusion)+Argatroban |
| tPA_acc+Dalte | tPA_acc | Dalte | - | Alteplase (accelerated infusion)+Dalteparin |
| tPA_acc+Efeg | tPA_acc | Efeg | - | Alteplase (accelerated infusion)+Efegatran |
| tPA_acc+Enox | tPA_acc | Enox | - | Alteplase (accelerated infusion)+Enoxaparin |
| tPA_acc+Fonda | tPA_acc | Fonda | - | Alteplase (accelerated infusion)+Fondaparinux |
| tPA_acc+UFH | tPA_acc | UFH | - | Alteplase (accelerated infusion)+Unfrationated heparin |
| tPA_acc+UFH+Ept | tPA_acc | UFH | Ept | Alteplase (accelerated infusion)+Unfrationated heparin+Eptifibatide |
| tPA_DB+UFH | tPA_DB | UFH | - | Alteplase (double bolus)+Unfrationated heparin |
| tPA_red | tPA_red | - | - | Alteplase (reduced dose) |

| Treatment | Fibrinolytic agents | PAC | GP IIb/IIIa | Definition of abbreviation of intervention |
|---|---|---|---|---|
| tPA_red+UFH | tPA_red | UFH | - | Alteplase (reduced dose)+Unfrationated heparin |
| tPA_red+UFH+Ept | tPA_red | UFH | Ept | Alteplase (reduced dose)+Unfrationated heparin+Eptifibatide |
| tPA_red+UFH+Tiro | tPA_red | UFH | Tiro | Alteplase (reduced dose)+Unfrationated heparin+Tirofiban |
| tPA_red_acc+UFH | tPA_red_acc | UFH | - | Alteplase (reduced dosed-accelerated infusion)+Unfrationated heparin |
| tPA_red_acc+UFH+Abx | tPA_red_acc | UFH | Abx | Alteplase (reduced dosed-accelerated infusion)+Unfrationated heparin+Abciximab |
| UFH | - | UFH | - | Unfrationated heparin |

# Appendix 4 Description of included studies

## eTable 4.1 Description of included studies.

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| AMI SK[11] | 2002 | Randomized, placebo controlled | Europe (5) | 496 | - SK (243)<br>- SK+Enox (253) | ≥18 | ST↑ | Not specified | ≤12 | Yes (study protocol) | No (study protocol) | Yes (only intervention group) | No (study protocol) |
| ASSENT-2[12] | 1999 | Randomized, double-blind, double dummy | Africa (1), Asia (1), Europe (20), Latin America (3), North America (2), Oceania (2) | 16949 | - TNK+UFH (8461)<br>- tPA_acc+UFH (8488) | ≥18 | ST↑, LBBB | Not specified | ≤6 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| ASSENT-3[13] | 2001 | Randomized, open-label, active controlled | Africa (1), Asia (1), Europe (18), Latin America (3), North America (2), Oceania (1) | 6095 | - TNK+Enox (2040)<br>- TNK+UFH (2038)<br>- TNK+UFH+Abx (2017) | ≥18 | ST↑, LBBB | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Open (according to local practice) | Open (according to local practice) |
| ASSENT-3 Plus[14] | 2003 | Randomized, open-label, active controlled | Europe (12), North America (2) | 1639 | - TNK+Enox (818)<br>- TNK+UFH (821) | ≥18 | ST↑, LBBB | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Yes (only intervention group) | Open (according to local practice) |
| ASSENT Plus[15] | 2003 | Randomized, open-label, active controlled | Europe (1), North America (1) | 434 | - tPA_acc+Dalte (221)<br>- tPA_acc+UFH (213) | ≥18 | ST↑, LBBB | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Yes (only intervention group) | No (study protocol) |
| BIOMACS-II[16] | 1999 | Randomized, double-blind, placebo controlled | Europe (1) | 101 | - SK (47)<br>- SK+Dalte (54) | ≤80 | ST↑, LBBB | Not specified | ≤12 | Yes (study protocol) | No (study protocol) | Yes (only intervention group) | Not report |
| Bleich[17] | 1990 | Randomized, open-label, active controlled | North America (1) | 84 | - tPA (42)<br>- tPA+UFH (42) | Not specified | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| Central Illinois[18] | 1993 | Randomized, double-blind, active controlled | North America (1) | 253 | - SK_FL+UFH (130)<br>- tPA+UFH (123) | ≤75 | ST↑ | Not specified | ≤4 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Cherng[19] | 1992 | Randomized, open-label, active controlled | Asia (1) | 122 | - SK+UFH (63)<br>- tPA+UFH (59) | <70 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| COBALT[20] | 1997 | Randomized, open-label, active controlled | Africa (1), Asia (1), Europe (19), Latin America (3), Oceania (2) | 7169 | - tPA_acc+UFH (3584)<br>- tPA_DB+UFH (3585) | Not specified | ST↑ | ≥20 | ≤6 | Yes (study protocol) | Yes (study protocol) | Depend on investigator | Depend on investigator |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| CORRETA[21] | 2004 | Randomized, active controlled | Asia (1) | 266 | - TNK+UFH (132)<br>- tPA_acc+UFH (134) | ≥18 | ST↑, LBBB | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Cortadellas[22] | 1989 | Randomized, active controlled | Europe (1) | 214 | - No_ATbx (104)<br>- SK_red+UFH (110) | <70 | ST↑ | ≥30 | Not specified | Not report | Yes (study protocol) | Not report | Not report |
| Curylo[23] | 1997 | Randomized, active controlled | Europe (1) | 86 | - SK+Fraxi (45)<br>- SK+UFH (41) | Not specified | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | | Not report |
| DouBLE[24] | 1998 | Randomized, open-label, active controlled | Europe (1), North America (2) | 461 | - tPA_acc+UFH (237)<br>- tPA_DB+UFH (224) | 18-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Dwivedi[25] | 2000 | Randomized, active controlled | Asia (1) | 47 | - SK+UFH (23)<br>- SK_acc+UFH (24) | Not specified | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| ECSG[26] | 1985 | Randomized, single-blind, active controlled | Europe (4) | 129 | - SK+UFH (65)<br>- tPA+UFH (64) | 21-70 | ST↑ (including Q-wave) | ≥30 | ≤6 | Not report | Yes (study protocol) | Not report | Not report |
| ECSG-6[27] | 1992 | Randomized, double-blind, placebo controlled | Europe (6) | 644 | - tPA (320)<br>- tPA+UFH (324) | 21-70 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| ECSG-tPA[28] | 1988 | Randomized, double-blind, placebo controlled | Europe (7) | 721 | - tPA+UFH (355)<br>- UFH (366) | 21-71 | ST↑ | ≥30 | ≤5 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| ENTIRE TIMI-23[29] | 2002 | Randomized, open-label, active controlled, phase II-dose ranging | Europe (4), North America (2) | 483 | - TNK+Enox (160)<br>- TNK+UFH (82)<br>- TNK_red+Enox+Abx (164)<br>- TNK_red+UFH+Abx (77) | 21-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (only intervention group) | Yes (only intervention group) | Yes (only intervention group) |
| ESCALAT[30] | 1999 | Randomized, active controlled | North America (2) | 178 | - SK+Efeg (116)<br>- tPA_acc+UFH (62) | 21-75 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| FRAMI[31] | 1997 | Randomized, double-blind, placebo controlled | Europe (1) | 776 | - SK (388)<br>- SK+Dalte (388) | All ages | ST↑ with anterior Q wave MI | Not specified | ≤24 | Yes (study protocol) | No (study protocol) | Yes (only intervention group) | No (study protocol) |
| Ghaffari[32] | 2013 | Randomized, active controlled | Asia (1) | 300 | - SK+UFH (100)<br>- SK_acc+UFH (200) | Not specified | ST↑ | ≥30 | Not specified | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| GISSI-2/ ISG[33,34] | 1990 | Randomized, open-label, active controlled | Europe (11), Latin America (1), Oceania (2) | 20768 | - SK±UFH (10396)<br>- tPA±UFH (10372) | Not specified | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| GUSTO-I[35] | 1993 | Randomized, open-label, active controlled | Europe (11), North America (2), Oceania (2) | 41021 | - SK+UFH (20251)<br>- SK-tPA_red+UFH (10374)<br>- tPA_acc+UFH (10396) | Not specified | ST↑ | ≥20 | <6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| GUSTO-III[36] | 1997 | Randomized, open-label, active controlled | Africa (1), Europe (14), North America (2), Latin America (1), Oceania (2) | 15059 | - rPA+UFH (10138)<br>- tPA_acc+UFH (4921) | Not specified | ST↑, BBB | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Depend on investigator | Depend on investigator |
| GUSTO-V[37] | 2001 | Randomized, open-label, active controlled | Africa (1), Europe (14), Latin America (1), North America (2), Oceania (1) | 16588 | - rPA+UFH (8260)<br>- rPA_red+UFH+Abx (8328) | ≥18 | ST↑, LBBB | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Depend on investigator | Yes (only intervention group) |
| HART-II[38] | 2001 | Randomized, open-label, active controlled | Europe (1), North America (2) | 400 | - tPA_acc+Enox (200)<br>- tPA_acc+UFH (200) | ≥18 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| HERO[39] | 1997 | Randomized, double-blind, placebo controlled, dose variation | Europe (4), North America (1), Oceania (2) | 412 | - SK+Bival (272)<br>- SK+UFH (140) | Not specified | ST↑ | Not specified | ≤12 | Yes (study protocol) | Yes (only intervention group) | Not report | Open (according to local practice) |
| HERO-2[40] | 2001 | Randomized, open-label, active controlled | Africa (1), Asia (6), Europe (26), Latin America (7), North America (4), Oceania (2) | 17073 | - SK+Bival (8516)<br>- SK+UFH (8557) | Any age | ST↑, LBBB | >30 | ≤6 | Yes (study protocol) | Yes (only intervention group) | Open (according to local practice) | Open (according to local practice) |
| HIT-4[41] | 1999 | Randomized, double-blind, matching placebo | Europe (7) | 1208 | - SK+Lepi (603)<br>- SK+UFH (605) | 18-75 | ST↑ | Not specified | <6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| IMPACT AMI[42] | 1997 | Randomized, double-blind, placebo controlled, dose confirmation | North America (1) | 48 | - tPA_acc+UFH (13)<br>- tPA_acc+UFH+Ept (35) | 18-75 | ST↑, LBBB | >30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Yes (only intervention group) |
| INJECT[43] | 1995 | Randomized, double-blinded, double-dummy | Europe (9) | 6010 | - rPA+UFH (3004)<br>- SK+UFH (3006) | ≥18 | ST↑, BBB | ≥30 | ≤12 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| INTEGRITI[44] | 2003 | Randomized, open-label, active controlled | Africa (1), Europe (4), North America (2) | 237 | - TNK+UFH (118)<br>- TNK_red+UFH+Ept (119) | 18-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Yes (only intervention group) |
| InTIME[45] | 1998 | Randomized, double-blind, placebo control, phase II-dose ranging | Europe (11), North America (2) | 602 | - nPA+UFH (478)<br>- tPA_acc+UFH (124) | 18-80 | ST↑, LBBB | ≥20 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| InTIME-II[46] | 2000 | Randomized, double-blind, active controlled | Africa (1), Europe (26), Latin America (5), North America (2), Oceania (1) | 15060 | - nPA+UFH (10038)<br>- tPA_acc+UFH (5022) | >18 | ST↑, LBBB | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) |
| INTRO AMI[47] | 2002 | Randomized, open-label, active controlled, phase II, dose confirmation | Africa (1), Europe (2), North America (2) | 299 | - tPA_acc+UFH (100)<br>- tPA_red+UFH+Ept (199) | >18 | ST↑ | ≥20 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Yes (only intervention group) |
| ISAM[48] | 1986 | Randomized, double-blind, double dummy | Europe (2), North America (1) | 1741 | - SK+UFH (859)<br>- UFH (882) | ≤75 | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Janousek[49] | 1988 | Randomized, active controlled | Europe (1) | 57 | - SK+UFH (31)<br>- UFH (26) | ≤65 | ST↑ | Not specified | ≤4 | Not report | Yes (study protocol) | Not report | Not report |
| Jiang[50] | 2005 | Randomized, active controlled | Asia (1) | 184 | - tPA_acc+UFH (93)<br>- tPA_red+UFH (91) | <75 | ST↑, LBBB | ≥30 | <12 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| KAMIT[51] | 1991 | Randomized, active controlled | North America (1) | 216 | - SK-tPA_red+UFH (109)<br>- tPA+UFH (107) | 18-75 | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Kennedy[52] | 1988 | Randomized, active controlled | North America (1) | 368 | - SK+UFH (191)<br>- UFH (177) | ≤75 | ST↑ | ≥20 | ≤6 | Not report | Yes (study protocol) | Not report | Not report |
| Khalilullah[53] | 1984 | Randomized, active controlled | Asia (1) | 30 | - No_ATbx (11)<br>- SK_red+UFH (19) | Not specified | ST↑ | Not specified | Not specified | Not report | Yes (only intervention group) | Not report | Not report |
| LATE[54] | 1993 | Randomised double-blind, placebo controlled | Europe (10), North America (2), Oceania (1) | 5711 | - tPA+UFH (2836)<br>- UFH (2875) | ≥18 | ST↑, BBB | ≥30 | ≤24 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| Li[55] | 2006 | Randomized, active controlled | Asia (1) | 89 | - tPA_acc_30 min+UFH (46)<br>- tPA_acc_45 min+UFH (43) | <75 | ST↑ | >30 | <12 | Yes (study protocol) | Yes (study protocol) | Yes (study protocol) | Not report |
| Lidon[56] | 1994 | Randomized, double-blind, active controlled | North America (1) | 45 | - SK+Bival (30)<br>- SK+UFH (15) | Not specified | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| MINT[57] | 1999 | Randomized, single-blind, active controlled, dose variation | Latin Amarica (2), North America (1) | 125 | - tPA_acc+Argat (85)<br>- tPA_acc+UFH (40) | ≥21 | ST↑ | ≥30 | <6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| NCT00148460[58] | 2005 | Randomized, open-label, active controlled | Asia (3) | 267 | - TNK+UFH (130)<br>- tPA_acc+UFH (137) | 18-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | No (study protocol) | No (study protocol) |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| NHFA[59] | 1988 | Randomized, double-blind, placebo controlled | Oceania (1) | 144 | - tPA+UFH (73)<br>- UFH (71) | ≤75 | ST↑ | Not specified | ≤4 | Not report | Yes (study protocol) | Not report | Not report |
| O'Rourke[60] | 1988 | Randomized, double-blind, placebo controlled | Oceania (1) | 145 | - tPA+UFH (74)<br>- UFH (71) | 21-72 | ST↑ | >30 | <2.5 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| Olson[61] | 1986 | Randomized, active controlled | North America (1) | 52 | - SK_red+UFH (28)<br>- UFH (24) | Not specified | ST↑ | Not specified | ≤12 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| PAIMS[62] | 1989 | Randomized, single blind, active controlled | Europe (1) | 171 | - SK+UFH (85)<br>- tPA+UFH (86) | 20-70 | ST↑ | ≥30 | ≤3 | Not report | Yes (study protocol) | Not report | Not report |
| PENTALYSE[63] | 2001 | Randomized, open-label, active controlled, phase II-dose finding | Europe (6) | 326 | - tPA_acc+Fonda (241)<br>- tPA_acc+UFH (85) | 21-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (only intervention group) | | Not report |
| Plotnikov[64] | 1993 | Not specified | Europe (1) | 80 | - SK_red+UFH (39)<br>- tPA+UFH (41) | 21-70 | ST↑ | ≥30 | ≤6 | Not report | Yes (study protocol) | Not report | Not report |
| PRIME[65] | 2002 | Randomized, single-blind, active controlled, phase II-dose ranging | North America (1) | 321 | - tPA_acc+Efeg (238)<br>- tPA_acc+UFH (83) | 21-75 | ST↑ | Not specified | ≤12 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| RAAMI[66] | 1992 | Randomized, open-label, active controlled | North America (1) | 281 | - tPA+UFH (138)<br>- tPA_acc+UFH (143) | Any age | ST↑ | ≥30 | <6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| RAPID[67] | 1994 | Randomized, open-label, active controlled, dose variation | Europe (2), North America (1), Oceania (1) | 606 | - rPA+UFH (154)<br>- rPA_red+UFH (298)<br>- tPA+UFH (154) | 18-75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| RAPID-II[68] | 1996 | Randomized, open-label, active controlled | Europe (1), North America (1) | 324 | - rPA+UFH (169)<br>- tPA_acc+UFH (155) | >18 | ST↑, LBBB | ≥30 | ≤12 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| Ronner[69] | 2000 | Randomized, double-blind, placebo controlled, phase II-dose ranging | Europe (2) | 181 | - SK (62)<br>- SK+Ept (119) | ≥18 | ST↑ | Not specified | ≤6 | Yes (study protocol) | No (study protocol) | Not report | Yes (only intervention group) |
| Sarullo[70] | 2001 | Randomized, double-blind, active controlled | Europe (1) | 120 | - tPA_acc+UFH (60)<br>- tPA_red+UFH+Tiro (60) | <70 | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| SPEED[71] | 2000 | Randomized, active controlled, dose confirmation | Europe (5), North America (1), Latin America (1), Oceania (1) | 224 | - rPA+UFH (109)<br>- rPA_red+UFH+Abx (115) | ≥18 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (study protocol) | No (study protocol) | No (study protocol) |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| Srimahachota[72] | 2000 | Randomized, active controlled | Asia (1) | 40 | - SK (20)<br>- SK_acc (20) | 15-75 | ST↑ | ≥20 | ≤6 | Open (according to local practice) | Open (according to local practice) | Open (according to local practice) | Open (according to local practice) |
| Strandberg[73] | 1996 | Not specified, dose variation | Europe (1) | 20 | - SK (5)<br>- SK+Dalte (15) | Not specified | ST↑ | ≥30 | ≤12 | No (study protocol) | Not report | Yes (only intervention group) | Not report |
| Tabatabaie[74] | 2009 | Randomized, double-blind, active controlled | Asia (1) | 150 | - SK+Enox (75)<br>- SK+UFH (75) | 18-75 | ST↑ | ≥30 | ≤12 | Not report | Yes (only intervention group) | Yes (only intervention group) | Not report |
| TAMI-3[75] | 1989 | Randomized, active controlled | North America (1) | 134 | - tPA (70)<br>- tPA+UFH (64) | <75 | ST↑ | ≥30 | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| TERIMA[76] | 1999 | Randomized, active controlled | Latin America (1) | 224 | - SK (111)<br>- rSK (113) | ≤70 | ST↑, BBB | ≥30 | ≤12 | Yes (study protocol) | Open (according to local practice) | Not report | Not report |
| Theroux[77] | 1995 | Randomized, double-blind, placebo controlled, phase II-dose ranging | North America (1) | 68 | - SK+Bival (55)<br>- SK+UFH (13) | ≤81 | ST↑, LBBB | Not specified | ≤6 | Yes (study protocol) | Yes (only intervention group) | Not report | Not report |
| TIMI-1[78] | 1987 | Randomized, open-label, active controlled | North America (1) | 290 | - SK+UFH (147)<br>- tPA+UFH (143) | ≤75 | ST↑ | ≥30 | ≤7 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| TIMI-10B[79] | 1998 | Randomized, active controlled, phase II-dose ranging | Europe (3), North America (2) | 837 | - TNK+UFH (526)<br>- tPA_acc+UFH (311) | <80 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |
| TIMI-14[80] | 1999 | Randomized, open-label, active controlled, phase II,dose confirmation | Europe (5), North America (2) | 211 | - tPA_acc+UFH (72)<br>- tPA_red_acc+UFH+Abx (139) | 18-75 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (only intervention group) | Open (according to local practice) | Yes (only intervention group) |
| TIMI-14-rPA[81] | 2000 | Randomized, active controlled, dose variation | Europe (4), North America (2) | 299 | - rPA+UFH (102)<br>- rPA_red+UFH+Abx (197) | 18-75 | ST↑ | ≥30 | ≤12 | Yes (study protocol) | Yes (only intervention group) | Not report | Yes (only intervention group) |
| Verstraete[82] | 1985 | Randomized, double-blind, placebo controlled | Europe (4) | 129 | - tPA+UFH (64)<br>- UFH (65) | <70 | ST↑ (including Q-wave) | ≥30 | ≤6 | Not report | Yes (study protocol) | Not report | Not report |
| White[83] | 1987 | Randomized, double-blind, placebo controlled | Oceania (1) | 219 | - SK_acc+UFH (107)<br>- UFH (112) | <70 | ST↑ | ≥30 | <4 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |

| Study group/ first author | Year | Trial design | Location of trial (country) | n | Treatment (n)* | Inclusion criteria | | | | Aspirin | UFH | LMWH | GP IIb/IIIa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Age (year) | Type of ECG | Duration of chest pain (min) | Duration from chest pain (hour) | | | | |
| White[84] | 1989 | Randomized, double-blind, placebo controlled | Oceania (1) | 270 | - SK+UFH (135)<br>- tPA+UFH (135) | <70 | ST↑ | ≥30 | <3 | Yes (study protocol) | Yes (study protocol) | Not report | Not report |
| Zhai[85] | 2016 | Randomized, single-blind, active controlled | Asia (1) | 251 | - TNK_red (124)<br>- tPA_red (127) | 18-70 | ST↑ | >30 | ≤12 | Open (according to local practice) | Open (according to local practice) | Not report | Not report |
| Zhang[86] | 2010 | Randomized, active controlled | Asia (1) | 54 | - rPA_red+UFH (29)<br>- tPA_red+UFH (25) | >75 | ST↑ | Not specified | ≤6 | Yes (study protocol) | Yes (study protocol) | Open (according to local practice) | Open (according to local practice) |

* Treatment was grouped regardless of dosage. For the details of dosage regimen in each treatment group, please refer to eTable 4.3 Description of treatment interventions of included studies.

**Abbreviation:** BBB, Bundle branch block; ECG, Electrocardiogram; GP IIb/IIIa, Glycoprotein IIb/IIIa inhibitors; LBBB, Left bundle branch block; LMWH, Low molecular weight heparin; n, Number of patient; TIMI, Thrombolysis in myocardial infarction.

**eTable 4.2 Description of participants of included studies.**

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| AMI SK[11] | 2002 | SK | 243 | 62.9±11.9 | Mean | 79.4 | 33.0 | | 40.7 | 43.6 | 14.8 | 31.3 | | | | 2.8 | Median |
| | | SK+Enox | 253 | 62.8±11.7 | Mean | 72.3 | 24.0 | | 40.3 | 39.9 | 17.0 | 32.8 | | | | 3.3 | Median |
| ASSENT-2[12] | 1999 | TNK+UFH | 8461 | 61 (52, 70) | Median | 77.1 | 15.8 | | 44.3 | 37.7 | 16.4 | | 12.0 | 39.4 | | 2.7 (1.9, 3.8) | Median |
| | | tPA_acc+UFH | 8488 | 61 (52, 70) | Median | 76.7 | 16.1 | | 43.7 | 38.5 | 15.7 | | 11.9 | 40.2 | | 2.8 (1.9, 3.9) | Median |
| ASSENT-3[13] | 2001 | TNK+Enox | 2040 | 61±12 | Mean | 77.0 | 14.0 | 6.2 | 44.0 | 41.0 | 19.0 | | 10.3 | 39.0 | | 3.0 | Median |
| | | TNK+UFH | 2038 | 61±13 | Mean | 77.0 | 14.0 | 6.4 | 47.0 | 41.0 | 18.0 | | 12.4 | 38.0 | | 3.1 | Median |
| | | TNK+UFH+Abx | 2017 | 61±12 | Mean | 76.0 | 13.0 | 6.0 | 47.0 | 41.0 | 18.0 | | 11.4 | 39.0 | | 3.1 | Median |
| ASSENT-3 Plus[14] | 2003 | TNK+Enox | 818 | 62±13 | Mean | 76.3 | 14.7 | 7.4 | 41.9 | 35.5 | 14.1 | | 27.0 | 42.0 | | | Median |
| | | TNK+UFH | 821 | 62±13 | Mean | 77.6 | 14.3 | 6.4 | 45.1 | 36.3 | 15.6 | | 27.0 | 43.0 | | | Median |
| ASSENT Plus[15] | 2003 | tPA_acc+Dalte | 221 | 64.1±10.6 | Mean | 71.5 | 12.7 | 3.2 | 35.3 | 28.5 | 13.1 | | 11.9 | 44.8 | | | |
| | | tPA_acc+UFH | 213 | 65.0±10.9 | Mean | 69.5 | 16.4 | 5.2 | 32.1 | 35.7 | 10.8 | | 12.2 | 43.2 | | | |
| BIOMACS-II[16] | 1999 | SK | 47 | 64.0 | Median | 77.0 | 11.0 | | 30.0 | 36.0 | 13.0 | | | | | | |
| | | SK+Dalte | 54 | 68.0 | Median | 65.0 | 17.0 | | 35.0 | 18.0 | 7.0 | | | | | | |
| Bleich[17] | 1990 | tPA | 42 | 56.6 | Mean | 83.0 | | | | | | | | 50.0 | | 2.8 | Mean |
| | | tPA+UFH | 42 | 59.4 | Mean | 79.0 | | | | | | | | 45.0 | | 2.6 | Mean |
| Central Illinois[18] | 1993 | SK_FL+UFH | 130 | 59±11 | Mean | 72.0 | | | | | | | | 36.0 | | 2.5±1.0 | Mean |
| | | tPA+UFH | 123 | 59±10 | Mean | 72.0 | | | | | | | | 44.0 | | 2.4±1.0 | Mean |
| Cherng[19] | 1992 | SK+UFH | 63 | 57.8±9.5 | Mean | 79.4 | | | 71.0 | 41.0 | 33.0 | | | 61.9 | | 4.9 | Mean |
| | | tPA+UFH | 59 | 57.3±9.6 | Mean | 91.5 | | | 78.0 | 39.0 | 22.0 | | | 57.6 | | 5.2 | Mean |
| COBALT[20] | 1997 | tPA_acc+UFH | 3584 | 62 (53, 70) | Median | 76.0 | 16.0 | 2.0 | 44.0 | 37.0 | 13.0 | | 16.0 | 43.0 | | 2.9 (2.0, 4.0) | Median |
| | | tPA_DB+UFH | 3585 | 63 (53, 70) | Median | 77.0 | 17.0 | 2.0 | 45.0 | 38.0 | 13.0 | | 17.0 | 45.0 | | 3.0 (2.0, 4.1) | Median |
| CORRETA[21] | 2004 | TNK+UFH | 132 | 46.0 | Median | | 6.1 | | 59.8 | | | | | 60.0 | | 2.9±0.2 | Mean |
| | | tPA_acc+UFH | 134 | 47.0 | Median | | 7.5 | | 51.5 | | | | | 61.0 | | 3.1±0.2 | Mean |
| Cortadellas[22] | 1989 | No_ATbx | 104 | 54.0 | Median | 97.1 | | | | | | | | 46.2 | | | |
| | | SK_red+UFH | 110 | 54.0 | Median | 92.7 | | | | | | | | 48.2 | | | |
| Curylo[23] | 1997 | SK+Fraxi | 45 | | | | 11.1 | | 77.8 | 22.2 | 13.3 | 28.9 | | 44.4 | | | |
| | | SK+UFH | 41 | | | | 7.3 | | 80.5 | 29.3 | 9.8 | 26.8 | | 46.3 | | | |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DouBLE[24] | 1998 | tPA_acc+UFH | 237 | 57.4±10.5 | Mean | 76.4 | 19.0 | | | 35.0 | 11.0 | | | 34.2 | 66.1 | 2.9±1.4 | Mean |
| | | tPA_DB+UFH | 224 | 58.0±10.3 | Mean | 69.2 | 20.1 | | | 33.9 | 11.2 | | | 35.7 | 57.9 | 2.8±1.5 | Mean |
| Dwivedi[25] | 2000 | SK+UFH | 23 | 53.4±11.6 | Mean | 56.0 | | | 17.0 | 4.0 | 13.0 | | 26.1 | 56.0 | | | |
| | | SK_acc+UFH | 24 | 55.6±10.2 | Mean | 50.0 | | | 12.0 | 0.0 | 17.0 | | 25.0 | 50.0 | | | |
| ECSG[26] | 1985 | SK+UFH | 65 | 54.3 | Median | 83.1 | | | | | | | | 48.4 | | 2.6 | Median |
| | | tPA+UFH | 64 | 55.1 | Median | 81.3 | | | | | | | | 53.1 | | 3.0 | Median |
| ECSG-6[27] | 1992 | tPA | 320 | 56.0 | Median | 88.0 | 5.0 | | 63.0 | 26.0 | | | | 44.0 | 66.4 | 2.5 | Median |
| | | tPA+UFH | 324 | 57.0 | Median | 86.0 | 6.0 | | 62.0 | 24.0 | | | | 40.0 | 75.5 | 2.5 | Median |
| ECSG-tPA[28] | 1988 | tPA+UFH | 355 | 58 (41, 69) | Median | 88.0 | 8.0 | | | | | | 23.0 | 41.0 | | 2.9 (1.4, 4.6) | Median |
| | | UFH | 366 | 58 (43, 69) | Median | 83.0 | 7.0 | | | | | | 26.0 | 36.0 | | 2.8 (1.3, 4.5) | Median |
| ENTIRE TIMI-23[29] | 2002 | TNK+Enox | 160 | 58 (51, 64) | Median | 84.0 | 9.0 | 6.0 | 51.0 | 23.0 | 15.0 | | | 33.0 | 50.0 | 2.9 (2.0, 3.8) | Median |
| | | TNK+UFH | 82 | 56 (50, 66) | Median | 84.0 | 4.0 | 1.0 | 57.0 | 22.0 | 16.0 | | | 39.0 | 52.0 | 3.0 (2.1, 4.0) | Median |
| | | TNK_red+Enox+Abx | 164 | 60 (51, 68) | Median | 81.0 | 15.0 | 9.0 | 53.0 | 31.0 | 14.0 | | | 37.0 | 52.0 | 2.9 (2.3, 3.8) | Median |
| | | TNK_red+UFH+Abx | 77 | 59 (52, 66) | Median | 82.0 | 14.0 | 9.0 | 55.0 | 26.0 | 7.0 | | | 31.0 | 48.0 | 3.0 (2.2, 4.1) | Median |
| ESCALAT[30] | 1999 | SK+Efeg | 116 | 57.0 | Mean | 79.0 | 11.0 | 8.0 | 45.0 | | | | 15.0 | 37.0 | 40.0 | 3.3 | Mean |
| | | tPA_acc+UFH | 62 | 55.6 | Mean | 76.0 | 10.0 | 8.0 | 42.0 | | | | 16.0 | 50.0 | 53.0 | 3.0 | Mean |
| FRAMI[31] | 1997 | SK | 388 | 63.6±11.7 | Mean | 74.2 | 8.2 | | | 16.5 | | | 8.0 | 100.0 | | 4.8±5.5 | Mean |
| | | SK+Dalte | 388 | 63.7±12.1 | Mean | 72.4 | 8.2 | | | 16.2 | | | 8.2 | 100.0 | | 4.3±2.2 | Mean |
| Ghaffari[32] | 2013 | SK+UFH | 100 | 60.1±13.2 | Mean | 75.0 | | | 33.0 | 32.0 | 15.0 | 16.0 | 10.6 | 61.0 | 85.7 | 4.5±2.9 | Mean |
| | | SK_acc+UFH | 200 | 58.7±12.1 | Mean | 81.5 | | | 44.0 | 35.5 | 16.0 | 15.0 | 8.7 | 53.0 | 75.4 | 4.2±2.9 | Mean |
| GISSI-2/ISG[33,34] | 1990 | SK±UFH | 10396 | | | 78.9 | 16.9 | | | | | | 20.6 | | | 63.7% ≤3 hr, 98.5% ≤6 hr | |
| | | tPA±UFH | 10372 | | | 78.2 | 17.4 | | | | | | 20.7 | | | 63.9% ≤3 hr, 98.4% ≤6 hr | |
| GUSTO-I[35] | 1993 | SK+UFH | 9841 | 62 (52, 70) | Median | 75.0 | 16.0 | | 43.0 | 39.0 | 15.0 | | | | | 2.7 (1.9, 3.9) | Median |
| | | SK+UFH | 10410 | 62 (52, 70) | Median | 75.0 | 17.0 | | 43.0 | 38.0 | 15.0 | | | | | 2.8 (2.0, 3.8) | Median |
| | | SK-tPA_red+UFH | 10374 | 61 (52, 70) | Median | 75.0 | 16.0 | | 43.0 | 38.0 | 14.0 | | | | | 2.8 (2.0, 4.0) | Median |
| | | tPA_acc+UFH | 10396 | 62 (52, 70) | Median | 75.0 | 17.0 | | 43.0 | 38.0 | 15.0 | | | | | 2.8 (2.0, 3.8) | Median |
| GUSTO-III[36] | 1997 | rPA+UFH | 10138 | 62.9 (53, 71) | Median | 72.5 | 18.4 | | 41.3 | 39.5 | 15.5 | 34.4 | 14.3 | 47.4 | | 2.7 (1.8, 3.8) | Median |
| | | tPA_acc+UFH | 4921 | 63.0 (53, 72) | Median | 72.8 | 18.4 | | 41.4 | 39.1 | 15.9 | 34.8 | 14.7 | 47.7 | | 2.7 (1.9, 3.9) | Median |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| GUSTO-V[37] | 2001 | rPA+UFH | 8260 | 61.1±12.2 | Mean | 76.0 | 15.0 | | 46.0 | 33.0 | 16.0 | 16.0 | | 37.0 | | 2.9±1.6 | Mean |
| | | rPA_red+UFH+Abx | 8328 | 61.6±12.1 | Mean | 75.0 | 16.0 | | 45.0 | 35.0 | 16.0 | 18.0 | | 38.0 | | 3.1±2.2 | Mean |
| HART-II[38] | 2001 | tPA_acc+Enox | 200 | 61.0 | Mean | 74.0 | 13.5 | | 49.0 | 30.1 | 11.3 | | | | | | |
| | | tPA_acc+UFH | 200 | 59.5 | Mean | 78.0 | 11.0 | | 48.5 | 20.4 | 15.4 | | | | | | |
| HERO[39] | 1997 | SK+Bival | 136 | 61±12 | Mean | 73.5 | 15.0 | | 62.0 | 31.0 | | | | 33.0 | 46.0 | 4.1±3.1 | Mean |
| | | SK+Bival | 136 | 61±12 | Mean | 76.5 | 11.0 | | 65.0 | 32.0 | | | | 32.0 | 48.0 | 3.9±2.7 | Mean |
| | | SK+UFH | 140 | 62±12 | Mean | 75.0 | 16.0 | | 62.0 | 28.0 | | | | 34.0 | 35.0 | 3.9±2.5 | Mean |
| HERO-2[40] | 2001 | SK+Bival | 8516 | 61.8 (52.1, 70.5) | Median | 70.6 | 15.1 | 1.2 | 43.8 | 51.8 | 14.0 | 24.6 | 22.1 | 45.3 | | 3.3 | Median |
| | | SK+UFH | 8557 | 61.8 (51.6, 70.3) | Median | 72.7 | 15.2 | 1.2 | 44.2 | 51.6 | 14.0 | 25.4 | 21.1 | 44.1 | | 3.3 | Median |
| HIT-4[41] | 1999 | SK+Lepi | 603 | 61.1±11.6 | Mean | 76.0 | 12.1 | 4.3 | 43.3 | 39.6 | 12.9 | 25.0 | 12.4 | 38.9 | | 2.9±1.3 | Mean |
| | | SK+UFH | 605 | 61.3±11.9 | Mean | 75.9 | 14.5 | 5.6 | 45.0 | 34.2 | 13.4 | 24.5 | 11.4 | 41.6 | | 2.8±1.3 | Mean |
| IMPACT AMI[42] | 1997 | tPA_acc+UFH | 13 | 61 (53, 68) | Median | 62.0 | 8.0 | | | 42.0 | 15.0 | | | 46.0 | 77.0 | 2.0 (1.5, 2.8) | Median |
| | | tPA_acc+UFH+Ept | 35 | 55 (49, 67) | Median | 83.0 | 23.0 | | | 40.0 | 17.0 | | | 26.0 | 64.0 | 2.4 (1.6, 3.7) | Median |
| INJECT[43] | 1995 | rPA+UFH | 3004 | 61.8±11.5 | Mean | 71.8 | 14.5 | | 44.8 | 34.1 | 11.5 | | | 41.4 | | 4.2±2.8 | Mean |
| | | SK+UFH | 3006 | 61.9±11.7 | Mean | 72.9 | 14.7 | | 45.5 | 32.5 | 11.3 | | | 44.0 | | 4.1±2.4 | Mean |
| INTEGRITI[44] | 2003 | TNK+UFH | 118 | 57 (51, 66) | Median | 76.0 | 8.0 | | 49.0 | 35.0 | 17.0 | | 15.0 | 32.0 | 49.0 | 2.8 (2.1, 4.0) | Median |
| | | TNK_red+UFH+Ept | 119 | 58 (49, 66) | Median | 70.0 | 17.0 | | 48.0 | 34.0 | 13.0 | | 11.0 | 32.0 | 59.0 | 3.0 (2.3, 3.8) | Median |
| InTIME[45] | 1998 | nPA+UFH | 123 | 58.3±10.4 | Mean | 79.0 | 15.4 | | | | | | 8.0 | 15.0 | 47.1 | 3.1±1.3 | Mean |
| | | nPA+UFH | 123 | 59.2±11.3 | Mean | 85.0 | 21.1 | | | | | | 7.0 | 21.0 | 44.0 | 3.0±1.3 | Mean |
| | | nPA+UFH | 123 | 59.4±11.0 | Mean | 80.0 | 13.0 | | | | | | 8.0 | 25.0 | 23.6 | 3.1±1.5 | Mean |
| | | nPA+UFH | 109 | 59.7±10.2 | Mean | 78.0 | 10.1 | | | | | | 7.0 | 24.0 | 29.5 | 3.1±1.3 | Mean |
| | | tPA_acc+UFH | 124 | 59.1±11.3 | Mean | 84.0 | 14.5 | | | | | | 8.0 | 23.0 | 37.4 | 3.2±1.3 | Mean |
| InTIME-II[46] | 2000 | nPA+UFH | 10038 | 62 (52, 70) | Median | 75.4 | 16.3 | | 45.0 | 30.2 | 13.5 | | 12.8 | 42.5 | | 2.8 (2, 4) | Median |
| | | tPA_acc+UFH | 5022 | 61 (52, 70) | Median | 75.1 | 15.5 | | 44.9 | 31.0 | 14.7 | | 12.2 | 41.2 | | 2.9 (2, 4) | Median |
| INTRO AMI[47] | 2002 | tPA_acc+UFH | 100 | 59 (50, 68) | Median | 78.0 | 16.0 | | | 41.0 | 13.0 | | | 33.0 | 47.0 | 3.0 | Median |
| | | tPA_red+UFH+Ept | 100 | 59 (49, 71) | Median | 78.0 | 18.0 | | | 36.0 | 21.0 | | | 36.0 | 59.0 | 3.0 | Median |
| | | tPA_red+UFH+Ept | 99 | 60 (50, 68) | Median | 73.7 | 16.2 | | | 46.5 | 16.2 | | | 37.0 | 46.0 | 2.9 | Median |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ISAM[48] | 1986 | SK+UFH | 859 | 58.3 | Mean | 80.8 | 12.3 | | | 23.5 | 12.9 | | | 42.9 | | 55.5% ≤3 hr | |
| | | UFH | 882 | 58.4 | Mean | 82.4 | 11.6 | | | 23.2 | 10.9 | | | 46.8 | | 52.4% ≤3 hr | |
| Janousek[49] | 1988 | SK+UFH | 31 | 54±9 | Mean | | | | | | | | 3.0 | 35.0 | | 2.5±0.8 | Mean |
| | | UFH | 26 | 55±7 | Mean | | | | | | | | 0.0 | 38.0 | | 2.5±1.0 | Mean |
| Jiang[50] | 2005 | tPA_acc+UFH | 93 | 57.3±8.9 | Mean | 83.9 | 2.2 | | 49.5 | 39.8 | 11.8 | 25.8 | | | | 4.0 | Mean |
| | | tPA_red+UFH | 91 | 57.8±8.8 | Mean | 86.8 | 3.3 | | 56.0 | 42.9 | 13.2 | 22.0 | | | | 3.9 | Mean |
| KAMIT[51] | 1991 | SK-tPA_red+UFH | 109 | 53+11 | Mean | 83.0 | 12.0 | | | | | | | 42.0 | | 2.9±1.2 | Mean |
| | | tPA+UFH | 107 | 55±11 | Mean | 83.0 | 13.0 | | | | | | | 42.0 | | 3.0±1.2 | Mean |
| Kennedy[52] | 1988 | SK+UFH | 191 | 57.0±11.0 | Mean | 82.2 | 13.7 | | | | | | | | 60.8 | 3.5±1.4 | Mean |
| | | UFH | 177 | 57.1±10.1 | Mean | 85.9 | 13.0 | | | | | | | | 37.1 | - | Mean |
| Khalilullah[53] | 1984 | No_ATbx | 11 | | | 100.0 | | | | | | | | 36.4 | 45.5 | | |
| | | SK_red+UFH | 19 | | | 89.5 | | | | | | | | 63.2 | 52.6 | | |
| LATE[54] | 1993 | tPA+UFH | 2836 | 62.5±10.8 | Mean | 71.6 | 21.8 | | 41.0 | 35.3 | 12.5 | | 64.3 | 43.6 | | | |
| | | UFH | 2875 | 62.8±10.8 | Mean | 73.2 | 21.3 | | 40.9 | 35.7 | 13.1 | | 65.4 | 42.9 | | | |
| Li[55] | 2006 | tPA_red_acc+UFH | 46 | | Mean | | | | | | | | | | 47.5 | | |
| | | tPA_red_acc+UFH | 43 | | Mean | | | | | | | | | | 46.6 | | |
| Lidon[56] | 1994 | SK+Bival | 30 | 56.3±10.6 | Mean | 80.0 | 20.0 | 3.3 | 46.7 | 13.3 | 16.7 | 30.0 | 3.3 | 33.3 | 67.0 | 2.5±0.9 | Mean |
| | | SK+UFH | 15 | 55.5±9.4 | Mean | 73.3 | 33.3 | 20.0 | 73.3 | 33.3 | 6.7 | 33.3 | 6.7 | 26.7 | 40.0 | 2.6±1.1 | Mean |
| MINT[57] | 1999 | tPA_acc+Argat | 47 | 56±1.8 | Mean | 85.1 | | | | | | | | | 58.7 | 3.1±0.2 | Mean |
| | | tPA_acc+Argat | 38 | 59±1.7 | Mean | 73.7 | | | | | | | | | 56.8 | 3.0±0.2 | Mean |
| | | tPA_acc+UFH | 40 | 60±1.5 | Mean | 82.5 | | | | | | | | | 42.1 | 2.7±0.2 | Mean |
| NCT00148460[58] | 2005 | TNK+UFH | 130 | 57.3±10.9 | Mean | 76.9 | 1.5 | 57.7 | 50.8 | 46.2 | 18.5 | | 17.0 | 57.7 | 57.9 | 3.6±1.4 | Mean |
| | | tPA_acc+UFH | 137 | 56.1±10.8 | Mean | 82.5 | 5.1 | 53.3 | 49.6 | 49.6 | 14.6 | | 8.7 | 51.1 | 62.1 | 3.5±1.5 | Mean |
| NHFA[59] | 1988 | tPA+UFH | 73 | 59.6±10.1 | Mean | 75.3 | 19.2 | | | 45.2 | 11.0 | | | 46.6 | | 100% ≤4 hr | |
| | | UFH | 71 | 58.5±10.1 | Mean | 67.6 | 12.7 | | | 38.0 | 5.6 | | | 33.8 | | 100% ≤4 hr | |
| O'Rourke[60] | 1988 | tPA+UFH | 74 | 56 (29, 71) | Median | 79.7 | | | | 39.2 | 2.7 | | | 52.7 | | 2.0±0.5 | Mean |
| | | UFH | 71 | 56 (30, 70) | Median | 87.3 | | | | 35.2 | 7.0 | | | 40.8 | | 1.9±0.5 | Mean |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Olson[61] | 1986 | SK_red+UFH | 28 | 56±7.1 | Mean | | 25.0 | | 50.0 | 53.6 | 14.3 | 10.7 | 46.4 | 46.4 | | | |
| | | UFH | 24 | 61±10 | Mean | | 37.5 | | 50.0 | 33.3 | 16.7 | 0.0 | 54.2 | 37.5 | | | |
| PAIMS[62] | 1989 | SK+UFH | 85 | 58±8 | Mean | 77.6 | | | 62.0 | 40.0 | 15.0 | 28.0 | | 43.5 | | 2.1±0.7 | Mean |
| | | tPA+UFH | 86 | 57±8 | Mean | 87.2 | | | 72.0 | 34.0 | 9.0 | 21.0 | | 51.2 | | 2.1±0.7 | Mean |
| PENTALYSE[63] | 2001 | tPA_acc+Fonda | 83 | 59 (49, 67) | Median | 83.0 | 11.0 | | 42.0 | 28.0 | 8.0 | 49.0 | | | 75.9 | 2.6 (2, 3.8) | Median |
| | | tPA_acc+Fonda | 77 | 55 (48, 66) | Median | 83.0 | 8.0 | | 53.0 | 33.0 | 12.0 | 39.0 | | | 93.2 | 3.1 (2.2, 4.3) | Median |
| | | tPA_acc+Fonda | 81 | 61 (53, 68) | Median | 85.0 | 16.0 | | 62.0 | 35.0 | 9.0 | 47.0 | | | 82.3 | 2.8 (2.2, 3.8) | Median |
| | | tPA_acc+UFH | 85 | 55 (48, 65) | Median | 80.0 | 9.0 | | 59.0 | 25.0 | 9.0 | 34.0 | | | 81.0 | 2.7 (2, 3.5) | Median |
| Plotnikov[64] | 1993 | SK_red+UFH | 39 | 52.7±1.5 | Mean | | | | | | | | | 43.6 | | 4.6±0.1 | Mean |
| | | tPA+UFH | 41 | 51.4±1.2 | Mean | | | | | | | | | 43.9 | | 4.2±0.1 | Mean |
| PRIME[65] | 2002 | tPA_acc+Efeg | 117 | 58 (47, 65) | Median | 81.0 | 21.0 | | | | 13.0 | | | 40.0 | 58.0 | 3.0 (1.8, 4.3) | Median |
| | | tPA_acc+Efeg | 121 | 61 (52, 66) | Median | 81.0 | 17.0 | | | | 14.0 | | | 30.0 | 56.0 | 3.0 (1.7, 4.3) | Median |
| | | tPA_acc+UFH | 83 | 58 (52, 66) | Median | 89.0 | 20.0 | | | | 18.0 | | | 33.0 | 54.0 | 2.5 (1.7, 3.8) | Median |
| RAAMI[66] | 1992 | tPA+UFH | 138 | 57.1±9.4 | Mean | 75.0 | 17.0 | | | | | | | 42.0 | | 2.8±1.3 | Mean |
| | | tPA_acc+UFH | 143 | 58.8±10.9 | Mean | 78.0 | 10.0 | | | | | | | 41.0 | | 2.7±1.1 | Mean |
| RAPID[67] | 1994 | rPA+UFH | 154 | 57±10 | Mean | 77.0 | 12.0 | | | | | | | 50.0 | 62.7 | 3.0±1.4 | Mean |
| | | rPA_red+UFH | 152 | 57±10 | Mean | 77.0 | 10.0 | | | | | | | 49.0 | 45.7 | 2.9±1.3 | Mean |
| | | rPA_red+UFH | 146 | 57±10 | Mean | 82.0 | 9.0 | | | | | | | 49.0 | 40.9 | 3.0±1.4 | Mean |
| | | tPA+UFH | 154 | 59±10 | Mean | 73.0 | 13.0 | | | | | | | 45.0 | 49.0 | 3.1±1.3 | Mean |
| RAPID-II[68] | 1996 | rPA+UFH | 169 | 58.0 | Median | 76.0 | 17.0 | | | 49.0 | 15.0 | | | 39.0 | 59.9 | 2.5 | Median |
| | | tPA_acc+UFH | 155 | 62.0 | Median | 81.0 | 8.0 | | | 39.0 | 14.0 | | | 37.0 | 45.2 | 2.4 | Median |
| Ronner[69] | 2000 | SK | 62 | 58.0 | Mean | 76.0 | 5.0 | | 66.0 | 23.0 | 16.0 | | 7.0 | 39.0 | 31.0 | | |
| | | SK+Ept | 45 | 60.0 | Mean | 84.0 | 16.0 | | 71.0 | 20.0 | 18.0 | | 7.0 | 49.0 | 42.0 | | |
| | | SK+Ept | 30 | 62.0 | Mean | 70.0 | 7.0 | | 63.0 | 20.0 | 3.0 | | 7.0 | 27.0 | 45.0 | | |
| | | SK+Ept | 44 | 63.0 | Mean | 77.0 | 5.0 | | 73.0 | 27.0 | 7.0 | | 16.0 | 30.0 | 46.0 | | |
| Sarullo[70] | 2001 | tPA_acc+UFH | 60 | 54±9 | Mean | 68.3 | | | 61.7 | 60.0 | 33.3 | 46.7 | | 38.3 | | | |
| | | tPA_red+UFH+Tiro | 60 | 55±7 | Mean | 70.0 | | | 66.7 | 56.7 | 35.0 | 50.0 | | 36.7 | | | |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| SPEED[71] | 2000 | rPA+UFH | 109 | 60 (51, 71) | Median | 74.0 | 14.0 | | | 31.0 | 14.0 | | | 42.0 | 47.0 | 2.5 (2.0, 3.6) | Median |
| | | rPA_red+UFH+Abx | 115 | 60 (53, 71) | Median | 75.0 | 10.0 | | | 26.0 | 17.0 | | | 44.0 | 54.0 | 2.8 (2.0, 3.9) | Median |
| Srimahachota[72] | 2000 | SK | 20 | 58.2±8.6 | Mean | 75.0 | 20.0 | | 60.0 | 40.0 | 30.0 | 50.0 | 30.0 | 40.0 | | 5.1±1.3 | Mean |
| | | SK_acc | 20 | 54.1±9.0 | Mean | 95.0 | 15.0 | | 65.0 | 15.0 | 35.0 | 15.0 | 20.0 | 45.0 | | 5.0±2.2 | Mean |
| Strandberg[73] | 1996 | SK | 5 | 66.0 | Mean | 80.0 | 20.0 | | 40.0 | 40.0 | 0.0 | | | 60.0 | | 3.0 | Mean |
| | | SK+Dalte | 5 | 59.0 | Mean | 60.0 | 0.0 | | 60.0 | 60.0 | 0.0 | | | 100.0 | | 3.0 | Mean |
| | | SK+Dalte | 5 | 63.0 | Mean | 80.0 | 20.0 | | 40.0 | 20.0 | 0.0 | | | 60.0 | | 4.0 | Mean |
| | | SK+Dalte | 5 | 68.0 | Mean | 80.0 | 0.0 | | 40.0 | 0.0 | 20.0 | | | 60.0 | | 7.0 | Mean |
| Tabatabaie[74] | 2009 | SK+Enox | 75 | 58.9±9.4 | Mean | 66.7 | | | | | | | | | | | |
| | | SK+UFH | 75 | 56.3±9.0 | Mean | 72.0 | | | | | | | | | | | |
| TAMI-3[75] | 1989 | tPA | 70 | 58.0 | Median | 81.0 | 20.0 | | | | | | | | 52.9 | 2.6 | Median |
| | | tPA+UFH | 64 | 55.0 | Median | 84.0 | 11.0 | | | | | | | | 54.0 | 3.0 | Median |
| TERIMA[76] | 1999 | rSK | 113 | 58.8±9.3 | Mean | 100.0 | 11.5 | | | 44.2 | 18.6 | 6.2 | 7.1 | | | 4.2±2.3 | Mean |
| | | SK | 111 | 53.4±9.1 | Mean | 82.9 | 14.4 | | | 46.8 | 10.8 | 11.7 | 8.1 | | | 4.6±2.6 | Mean |
| Theroux[77] | 1995 | SK+Bival | 28 | 60±10 | Mean | 85.7 | 32.1 | | 64.3 | | 14.3 | 50.0 | | 28.6 | 61.0 | 2.5±1.5 | Mean |
| | | SK+Bival | 27 | 60±8 | Mean | 85.2 | 22.2 | | 59.3 | | 11.1 | 40.7 | | 37.0 | 85.0 | 2.1±1.5 | Mean |
| | | SK+UFH | 13 | 63±12 | Mean | 69.2 | 7.7 | | 53.8 | | 23.1 | 15.4 | | 30.8 | 31.0 | 2.6±1.5 | Mean |
| TIMI-1[78] | 1987 | SK+UFH | 147 | 58.0 | Mean | 80.0 | 19.0 | | 56.0 | 38.0 | 13.0 | | | 52.0 | | 4.8 | Mean |
| | | tPA+UFH | 143 | 56.0 | Mean | 80.0 | 17.0 | | 57.0 | 51.0 | 13.0 | | | 44.0 | | 4.8 | Mean |
| TIMI-10B[79] | 1998 | TNK+UFH | 76 | 61 (51, 70) | Median | 73.7 | 15.8 | | 42.1 | | 18.4 | | | 38.2 | 65.8 | 2.9 (2.1, 3.9) | Median |
| | | TNK+UFH | 302 | 59 (51, 70) | Median | 77.2 | 15.2 | | 50.7 | | 14.9 | | | 39.1 | 54.3 | 2.8 (1.9, 4.5) | Median |
| | | TNK+UFH | 148 | 58 (50, 68) | Median | 69.6 | 13.5 | | 50.0 | | 14.9 | | | 41.9 | 62.8 | 2.9 (1.8, 4.3) | Median |
| | | tPA_acc+UFH | 311 | 59 (51, 69) | Median | 78.5 | 14.5 | | 43.7 | | 15.1 | | | 36.9 | 62.7 | 2.9 (2.1, 4.1) | Median |
| TIMI-14[80] | 1999 | tPA_acc+UFH | 72 | 58 (50, 67)§ | Median | 77.0§ | 12.0§ | | 52.0§ | 26.0§ | 13.0§ | | | 37.0§ | 64.0 | 3 (2, 5)§ | Median |
| | | tPA_red_acc+UFH+Abx | 69 | 58 (50, 67)§ | Median | 77.0§ | 12.0§ | | 52.0§ | 26.0§ | 13.0§ | | | 37.0§ | 78.0 | 3 (2, 5)§ | Median |
| | | tPA_red_acc+UFH+Abx | 70 | 58 (50, 67)§ | Median | 77.0§ | 12.0§ | | 52.0§ | 26.0§ | 13.0§ | | | 37.0§ | 69.0 | 3 (2, 5)§ | Median |

| Study group/ first author | Year | Treatment* | n | Age (year)† | | Male (%) | Previous MI (%) | Previous PCI (%) | Current smoker (%) | HTN (%) | DM (%) | DLP (%) | Killip class ≥2 (%) | Anterior location (%) | TIMI 3 flow at 60-90 min (%)‡ | Average time to fibrinolytics (hour)† | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| TIMI-14-rPA[81] | 2000 | rPA+UFH | 102 | 59 (51, 66) | Median | 79.0 | 7.8 | | 50.0 | 28.0 | 13.0 | | | 38.0 | 70.0 | 3.0 (2.0, 4.0) | Median |
| | | rPA_red+UFH+Abx | 63 | 61 (50, 67) | Median | 76.0 | 7.9 | | 48.0 | 33.0 | 18.0 | | | 43.0 | 74.0 | 3.0 (2.0, 6.0) | Median |
| | | rPA_red+UFH+Abx | 42 | 59 (53, 67) | Median | 79.0 | 7.1 | | 45.0 | 29.0 | 12.0 | | | 36.0 | 85.0 | 3.0 (2.0, 5.0) | Median |
| | | rPA_red+UFH+Abx | 42 | 59 (45, 65) | Median | 79.0 | 4.8 | | 62.0 | 24.0 | 5.0 | | | 41.0 | 71.0 | 3.0 (2.0, 6.0) | Median |
| | | rPA_red+UFH+Abx | 50 | 60 (56, 68) | Median | 78.0 | 18.0 | | 36.0 | 30.0 | 8.0 | | | 30.0 | 71.0 | 3.0 (2.0, 6.0) | Median |
| Verstraete[82] | 1985 | tPA+UFH | 64 | 56.4 | Mean | 92.2 | | | | | | | | 49.2 | | 3.4 | Median |
| | | UFH | 65 | 54.9 | Mean | 90.8 | | | | | | | | 47.7 | | 3.3 | Median |
| White[83] | 1987 | SK_acc+UFH | 107 | 56±8.7 | Mean | 72.0 | 26.0 | | 82.0 | 23.0 | 12.0 | | | 38.0 | | 3.0±0.8 | Mean |
| | | UFH | 112 | 55±8.6 | Mean | 80.0 | 17.0 | | 83.0 | 35.0 | 8.0 | | | 38.0 | | 3.0±0.8 | Mean |
| White[84] | 1989 | SK+UFH | 135 | 56±9 | Mean | 79.0 | | | 56.0 | 26.0 | 10.0 | | | 32.0 | | 2.5±0.6 | Mean |
| | | tPA+UFH | 135 | 55±9 | Mean | 81.0 | | | 55.0 | 22.0 | 10.0 | | | 36.0 | | 2.5±0.6 | Mean |
| Zhai[85] | 2016 | TNK_red | 124 | 55.9±9.67 | Mean | 84.7 | 5.7 | 2.4 | 66.1 | 35.5 | 13.7 | 39.5 | 9.7 | 51.6 | 65.6 | 4.5±2.8 | Mean |
| | | tPA_red | 127 | 55.47±9.63 | Mean | 89.8 | 6.3 | 2.4 | 66.9 | 40.9 | 26.0 | 40.9 | 7.9 | 58.3 | 54.0 | 4.4±2.7 | Mean |
| Zhang[86] | 2010 | rPA_red+UFH | 29 | | | | | | | | | | | | | | |
| | | tPA_red+UFH | 25 | | | | | | | | | | | | | | |

* Treatment was grouped regardless of dosage. For the details of dosage regimen in each treatment group, please refer to eTable 4.3 Description of treatment interventions of included studies.

† Data were presented in term of mean±standard deviation (S.D.) or median (interquartile range; IQR).

‡ After treatment with fibrinolytic agents.

§ Data were presented by using the average data from the whole study.

**Abbreviation:** DLP, Dyslipidemia; DM, Diabetes mellitus; HTN, Hypertension; n, Number of patient.

**eTable 4.3 Description of treatment interventions of included studies.**

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| AMI SK[11] | 2002 | SK | 243 | - SK 1.5 MU IV infusion over 1 hr | Yes | Recommended treatment in current practice guidelines | SK |
| | | SK+Enox | 253 | - SK 1.5 MU IV infusion over 1 hr<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| ASSENT-2[12] | 1999 | TNK+UFH | 8461 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | tPA_acc+UFH | 8488 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| ASSENT-3[13] | 2001 | TNK+Enox | 2040 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK+UFH | 2038 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK+UFH+Abx | 2017 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 40 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | TNK+PAC+GP |
| ASSENT-3 Plus[14] | 2003 | TNK+Enox | 818 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | TNK+UFH | 821 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| ASSENT Plus[15] | 2003 | tPA_acc+Dalte | 221 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Dalte 30 IU/kg IV bolus, then 120 IU/kg SC q 12 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+UFH | 213 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| BIOMACS-II[16] | 1999 | SK | 47 | - SK 1.5 MU IV infusion over 1 hr | No | Not recommended treatment in current practice guidelines | - |
| | | SK+Dalte | 54 | - SK 1.5 MU IV infusion over 1 hr<br>- Dalte 100 U/kg SC, then 120 IU/kg SC q 12 hr | No | Not recommended treatment in current practice guidelines | - |
| Bleich[17] | 1990 | tPA | 42 | - tPA 6 mg IV bolus, then 54 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr) | Yes | Recommended treatment in current practice guidelines | tPA |
| | | tPA+UFH | 42 | - tPA 6 mg IV bolus, then 54 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| Central Illinois[18] | 1993 | SK_FL+UFH | 130 | - SK 375,000 U IV bolus over 5 min, then 1,125,000 U infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA+UFH | 123 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| Cherng[19] | 1992 | SK+UFH | 63 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 40 U/kg IV bolus, then 15 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA+UFH | 59 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 40 U/kg IV bolus, then 15 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| COBALT[20] | 1997 | tPA_acc+UFH | 3584 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_DB+UFH | 3585 | - tPA 50 mg IV bolus, then 50 mg (40 mg for BW<60 kg) IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| CORRETA[21] | 2004 | TNK+UFH | 132 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | tPA_acc+UFH | 134 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| Cortadellas[22] | 1989 | No_ATbx | 104 | - Standard therapy | No | Not recommended treatment in current practice guidelines | - |
| | | SK_red+UFH | 110 | - SK 840,000 U IV infusion over 1 hr<br>- UFH 800 mg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| Curylo[23] | 1997 | SK+Fraxi | 45 | - SK 1.5 MU IV infusion over 1 hr<br>- Fraxi 250 U/kg IV for 48 hr, then 250 U/kg SC | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 41 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| DouBLE[24] | 1998 | tPA_acc+UFH | 237 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_DB+UFH | 224 | - tPA 50 mg IV bolus, then 0.6 mg/kg (max 50 mg) IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| Dwivedi[25] | 2000 | SK+UFH | 23 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 10000 U IV bolus, then 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK_acc+UFH | 24 | - SK 1.5 MU IV infusion over 15 min<br>- UFH 10000 U IV bolus, then 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| ECSG[26] | 1985 | SK+UFH | 65 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus | No | Not recommended treatment in current practice guidelines | - |
| | | tPA+UFH | 64 | - tPA 0.75 mg/kg IV infusion over 90 min<br>- UFH 5000 U IV bolus | No | Not recommended treatment in current practice guidelines | - |
| ECSG-6[27] | 1992 | tPA | 320 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr | Yes | Recommended treatment in current practice guidelines | tPA |
| | | tPA+UFH | 324 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| ECSG-tPA[28] | 1988 | tPA+UFH | 355 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| | | UFH | 366 | - UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| ENTIRE TIMI-23[29] | 2002 | TNK+Enox | 160 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK+UFH | 82 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK_red+Enox+Abx | 164 | - TNK 0.27 mg/kg single IV bolus over 5 second<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | TNK+PAC+GP |
| | | TNK_red+UFH+Abx | 77 | - TNK 0.27 mg/kg single IV bolus over 5 second<br>- UFH 40 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | TNK+PAC+GP |
| ESCALAT[30] | 1999 | SK+Efeg | 116 | - SK 1.5 MU IV infusion over 1 hr<br>- Efeg 0.05-0.2 mg/kg IV bolus, then 0.3-1.0 mg/kg/h IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+UFH | 62 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| FRAMI[31] | 1997 | SK | 388 | - SK 1.5 MU IV infusion over 1 hr | No | Not recommended treatment in current practice guidelines | - |
| | | SK+Dalte | 388 | - SK 1.5 MU IV infusion over 1 hr<br>- Dalte 150 U/kg SC q 12 hr | No | Not recommended treatment in current practice guidelines | - |
| Ghaffari[32] | 2013 | SK+UFH | 100 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH Not specified dosage | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK_acc+UFH | 200 | - SK 1.5 MU IV infusion over 20 min<br>- UFH Not specified dosage | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| GISSI-2/ISG[33,34] | 1990 | SK | 5205 | - SK 1.5 MU IV infusion over 1 hr | Yes | Recommended treatment in current practice guidelines | SK |
| | | SK+UFH | 5191 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 12,500 U SC BID | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA | 5202 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr) | Yes | Recommended treatment in current practice guidelines | tPA |
| | | tPA+UFH | 5170 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 12,500 U SC BID | Yes | Recommended treatment in current practice guidelines | tPA+PAC |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| GUSTO-I[35] | 1993 | SK+UFH | 9841 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 12,500 U SC BID | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | SK+UFH | 10410 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | SK-tPA_red+UFH | 10374 | - SK+tPA SK 1.0 MU IV infusion over 1 hr + tPA 0.1 mg/kg IV bolus, then 0.9 mg/kg IV infusion over 60 min (total max 90 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+UFH | 10396 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| GUSTO-III[36] | 1997 | rPA+UFH | 10138 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | tPA_acc+UFH | 4921 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| GUSTO-V[37] | 2001 | rPA+UFH | 8260 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | rPA_red+UFH+Abx | 8328 | - rPA 5 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 60 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| HART-II[38] | 2001 | tPA_acc+Enox | 200 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Enox 30 mg IV bolus, then 1 mg/kg SC q 12 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+UFH | 200 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 4000 U IV bolus (5000 U IV bolus for BW >67 kg), then 15 U/kg/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| HERO[39] | 1997 | SK+Bival | 136 | - SK 1.5 MU IV infusion over 0.5-1 hr<br>- Bival 0.125 mg/kg IV bolus, then 0.25 mg/kg/hr IV infusion for 12 hr, then 0.125 mg/kg/hr IV infusion for 60 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+Bival | 136 | - SK 1.5 MU IV infusion over 0.5-1 hr<br>- Bival 0.25 mg/kg IV bolus, then 0.5 mg/kg/hr IV infusion for 12 hr, then 0.25 mg/kg/hr IV infusion for 60 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 140 | - SK 1.5 MU IV infusion over 0.5-1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| HERO-2[40] | 2001 | SK+Bival | 8516 | - SK 1.5 MU IV infusion over 0.5-1 hr<br>- Bival 0.25 mg/kg IV bolus, then 0.5 mg/kg/hr IV infusion for 12 hr, then 0.25 mg/kg/hr IV infusion for 36 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 8557 | - SK 1.5 MU IV infusion over 0.5-1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion (800 U/hr for BW <80 kg) | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| HIT-4[41] | 1999 | SK+Lepi | 603 | - SK 1.5 MU IV infusion over 1 hr<br>- Lepi 0.5 mg/kg SC BID | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 605 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 12,500 U SC BID | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| IMPACT AMI[42] | 1997 | tPA_acc+UFH | 13 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 40 U/kg IV bolus, then 15 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| | | tPA_acc+UFH+Ept | 35 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 40 U/kg IV bolus, then 15 U/kg/hr IV infusion<br>- Ept 180 mcg/kg IV bolus, then 0.75 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |
| INJECT[43] | 1995 | rPA+UFH | 3004 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | SK+UFH | 3006 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| INTEGRITI[44] | 2003 | TNK+UFH | 118 | - TNK 0.53 mg/kg or weight based IV bolus over 5 sec (0-60 kg 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK_red+UFH+Ept | 119 | - TNK 0.27 mg/kg<br>- UFH 60 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Ept 180 mcg/kg IV bolus 2 doses apart for 10 min, then 2.0 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | TNK+PAC+GP |
| InTIME[45] | 1998 | nPA+UFH | 123 | - nPA 60 kU/kg IV single bolus over 2 or 4 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | nPA+UFH | 109 | - nPA 30 kU/kg IV single bolus over 2 or 4 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | nPA+UFH | 123 | - nPA 15 kU/kg IV single bolus over 2 or 4 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | nPA+UFH | 123 | - nPA 120 kU/kg (max 12,000 kU) IV single bolus over 2 or 4 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+UFH | 124 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| InTIME-II[46] | 2000 | nPA+UFH | 10038 | - nPA 120 kU/kg (max 12,000 kU) IV single bolus over 2 or 4 min<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+UFH | 5022 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| INTRO AMI[47] | 2002 | tPA_acc+UFH | 100 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| | | tPA_red+UFH+Ept | 100 | - tPA 15 mg IV bolus, then 35 mg over 60 min<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion<br>- Ept 180 mcg/kg IV bolus, then 90 mcg/kg IV bolus 30 min apart, then 2.00 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |
| | | tPA_red+UFH+Ept | 99 | - tPA 15 mg IV bolus, then 35 mg over 60 min<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion<br>- Ept 180 mcg/kg IV bolus, then 90 mcg/kg IV bolus 30 min apart, then 1.33 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |
| ISAM[48] | 1986 | SK+UFH | 859 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | UFH | 882 | - UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |
| Janousek[49] | 1988 | SK+UFH | 31 | - SK 1.5 MU IV infusion over 45 min<br>- UFH 500 U/hr IV infusion for 12 hr, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | UFH | 26 | - UFH 10000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |
| Jiang[50] | 2005 | tPA_acc+UFH | 93 | - tPA 8 mg IV bolus, then 1 mg/kg IV infusion over 90 min (min 42 mg, max 92 mg)<br>- UFH 70 U/kg IV bolus, then 12 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_red+UFH | 91 | - tPA 8 mg IV bolus, then 42 mg IV infusion over 90 min<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| KAMIT[51] | 1991 | SK-tPA_red+UFH | 109 | - SK+tPA 10 mg IV bolus, then 40 mg IV infusion over 1 hr + SK 1.5 MU IV infusion over 1 hr<br>- UFH 3000-5000 U IV bolus (with additional 5000-7000 U IV bolus for patient who undergone PTCA | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA+UFH | 107 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 3000-5000 U IV bolus (with additional 5000-7000 U IV bolus for patient who undergone PTCA | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| Kennedy[52] | 1988 | SK+UFH | 191 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | UFH | 177 | - UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| Khalilullah[53] | 1984 | No_ATbx | 11 | - Standard therapy | No | Not recommended treatment in current practice guidelines | - |
| | | SK_red+UFH | 19 | - SK 0.5 MU IV infusion over 0.5 hr<br>- UFH 800 mg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| LATE[54] | 1993 | tPA+UFH | 2836 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| | | UFH | 2875 | - UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |
| Li[55] | 2006 | tPA_red_acc+UFH | 46 | - tPA 8 mg IV bolus, then 42 mg IV infusion over 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_red_acc+UFH | 43 | - tPA 8 mg IV bolus, then 42 mg IV infusion over 45 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| Lidon[56] | 1994 | SK+Bival | 30 | - SK 1.5 MU IV infusion over 45-60 min<br>- Bival 0.5 mg/kg/hr IV infusion for 12 hr, then 0.1 mg/kg/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 15 | - SK 1.5 MU IV infusion over 45-60 min<br>- UFH 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| MINT[57] | 1999 | tPA_acc+Argat | 38 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Argat 100 µg/kg IV LD, then 1.0 µg/kg/min IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+Argat | 47 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Argat 100 µg/kg IV LD, then 3.0 µg/kg/min IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+UFH | 40 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| NCT00148460[58] | 2005 | TNK+UFH | 130 | - TNK 0.53 mg/kg or weight based IV bolus over 10 sec (0.0-49.9 kg 25 mg, 50.0-59.9 30 mg, 60.0-69.9 kg 35 mg, 70.0-79.9 kg 40 mg, 80.0-89.9 kg 45 mg, ≥ 90 kg 50 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | tPA_acc+UFH | 137 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| NHFA[59] | 1988 | tPA+UFH | 73 | - tPA bolus injection of 10 mg of rTPA followed by 50 mg over the next hour and 40 mg over the subsequent 2 h<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| | | UFH | 71 | - UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| O'Rourke[60] | 1988 | tPA+UFH | 74 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then followed immediately by a constant infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| | | UFH | 71 | - UFH 5000 U IV bolus, then followed immediately by a constant infusion | Yes | Recommended treatment in current practice guidelines | PAC |
| Olson[61] | 1986 | SK_red+UFH | 28 | - SK 0.5 MU IV infusion over 15-30 min, then 0.2 MU IV infusion over 2 hr<br>- UFH 15 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | UFH | 24 | - UFH 15 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| PAIMS[62] | 1989 | SK+UFH | 85 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 40 U/kg IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA+UFH | 86 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 40 U/kg IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| PENTALYSE[63] | 2001 | tPA_acc+Fonda | 81 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Fonda 4 mg (6 mg for BW >90kg) IV, then 4 mg (6 mg for BW >90kg) SC OD | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+Fonda | 83 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Fonda 12 mg (10 mg for BW <60kg) IV, then 12 mg (10 mg for BW <60kg) SC OD | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+Fonda | 77 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Fonda 8 mg (6 mg for BW <60kg or 10 mg for BW >90kg) IV, then 8 mg (6 mg for BW <60kg or 10 mg for BW >90kg) SC OD | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | tPA_acc+UFH | 85 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 4000 U IV bolus, then 800 U/hr IV infusion (5000 U IV bolus, then 1000 U/hr IV infusion for BW >67 kg) | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| Plotnikov[64] | 1993 | SK_red+UFH | 39 | - SK 1.0 MU IV infusion over 0.5-1 hr<br>- UFH 5000-10000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA+UFH | 41 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000-10000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| PRIME[65] | 2002 | tPA_acc+Efeg | 121 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Efeg 0.075-0.1 mg/kg IV bolus, then 0.6-0.8 mg/kg/h IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+Efeg | 117 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- Efeg 0.2-0.3 mg/kg IV bolus, then 1.0-1.2 mg/kg/h IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_acc+UFH | 83 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| RAAMI[66] | 1992 | tPA+UFH | 138 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| | | tPA_acc+UFH | 143 | - tPA 15 mg IV bolus, then 50 mg/kg IV infusion over 30 min, then 35 mg/kg IV infusion over 60 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| RAPID[67] | 1994 | rPA+UFH | 154 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | rPA_red+UFH | 152 | - rPA 10 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | rPA_red+UFH | 146 | - rPA 15 U IV bolus<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA+UFH | 154 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| RAPID-II[68] | 1996 | rPA+UFH | 169 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | tPA_acc+UFH | 155 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| Ronner[69] | 2000 | SK | 62 | - SK 1.5 MU IV infusion over 1 hr | Yes | Recommended treatment in current practice guidelines | SK |
| | | SK+Ept | 44 | - SK 1.5 MU IV infusion over 1 hr<br>- Ept 180 mcg/kg IV bolus, then 0.75 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | SK+GP |
| | | SK+Ept | 45 | - SK 1.5 MU IV infusion over 1 hr<br>- Ept 180 mcg/kg IV bolus, then 1.33 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | SK+GP |
| | | SK+Ept | 30 | - SK 1.5 MU IV infusion over 1 hr<br>- Ept 180 mcg/kg IV bolus, then 2.00 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | SK+GP |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| Sarullo[70] | 2001 | tPA_acc+UFH | 60 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 70 U/kg IV bolus (max 5000 U), then subsequent IV infusion (max 1200 U/hr) | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| | | tPA_red+UFH+Tiro | 60 | - tPA 15 mg IV bolus, then 0.5 mg/kg IV infusion over 30 min (max 35 mg)<br>- UFH 60 U/kg IV bolus (max 4000 U), then 7 U/kg/hr IV infusion (max 800 U/hr)<br>- Tiro 0.4 mcg/kg/min IV infusion for 30 min, then 0.1 mcg/kg/min IV infusion | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |
| SPEED[71] | 2000 | rPA+UFH | 109 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 70 U/kg IV bolus with weight-adjusted bolus or continuous infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | rPA_red+UFH+Abx | 115 | - rPA 5 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 40 U/kg IV bolus with weight-adjusted bolus or continuous infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| Srimahachota[72] | 2000 | SK | 20 | - SK 1.5 MU IV infusion over 1 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK_acc | 20 | - SK 1.5 MU IV infusion over 0.5 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| Strandberg[73] | 1996 | SK | 5 | - SK 1.5 MU IV infusion over 1 hr | No | Not recommended treatment in current practice guidelines | - |
| | | SK+Dalte | 5 | - SK 1.5 MU IV infusion over 1 hr<br>- Dalte 100 U/kg SC BID | No | Not recommended treatment in current practice guidelines | - |
| | | SK+Dalte | 5 | - SK 1.5 MU IV infusion over 1 hr<br>- Dalte 50 U/kg SC BID | No | Not recommended treatment in current practice guidelines | - |
| | | SK+Dalte | 5 | - SK 1.5 MU IV infusion over 1 hr<br>- Dalte 75 U/kg SC BID | No | Not recommended treatment in current practice guidelines | - |
| Tabatabaie[74] | 2009 | SK+Enox | 75 | - SK 1.5 MU IV infusion over 1 hr<br>- Enox 40 mg IV bolus, then 1 mg/kg SC q 12 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 75 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 70 U/kg IV bolus with weight-adjusted bolus or continuous infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| TAMI-3[75] | 1989 | tPA | 70 | - tPA 0.1 mg/kg IV bolus, then 0.9 mg/kg IV infusion over 1 hr (max 90 mg for the 1st hr), then 0.5 mg/kg IV infusion over 3 hr (max 45 mg) | Yes | Recommended treatment in current practice guidelines | tPA |
| | | tPA+UFH | 64 | - tPA 0.1 mg/kg IV bolus, then 0.9 mg/kg IV infusion over 1 hr (max 90 mg for the 1st hr), then 0.5 mg/kg IV infusion over 3 hr (max 45 mg)<br>- UFH 10000 U IV bolus concurrent with thrombolytic agents, then 500-1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| TERIMA[76] | 1999 | SK | 111 | - SK 1.5 MU IV infusion over 1 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK | 113 | - rSK 1.5 MU IV infusion over 1 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| Theroux[77] | 1995 | SK+Bival | 28 | - SK 1.5 MU IV infusion over 45-60 min<br>- Bival 0.1 mg/kg/hr IV infusion for 12 hr | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+Bival | 27 | - SK 1.5 MU IV infusion over 45-60 min<br>- Bival 0.5 mg/kg/hr IV infusion for 12 hr, then 0.1 mg/kg/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| | | SK+UFH | 13 | - SK 1.5 MU IV infusion over 45-60 min<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | No | Comparison between similar treatments after re-coding of treatment for network analyses | - |
| TIMI-1[78] | 1987 | SK+UFH | 147 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA+UFH | 143 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| TIMI-10B[79] | 1998 | TNK+UFH | 76 | - TNK 50 mg IV bolus over 5-10 sec<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK+UFH | 148 | - TNK 40 mg IV bolus over 5-10 sec<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | TNK+UFH | 302 | - TNK 30 mg IV bolus over 5-10 sec<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | TNK+PAC |
| | | tPA_acc+UFH | 311 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 5000 U IV bolus, then 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| TIMI-14[80] | 1999 | tPA_acc+UFH | 72 | - tPA 15 mg IV bolus, then 0.75 mg/kg IV infusion over 30 min (max 50 mg), then 0.5 mg/kg IV infusion over 60 min (max to 35 mg)<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA_acc+PAC |
| | | tPA_red_acc+UFH+Abx | 69 | - tPA 15 mg IV bolus, then 35 mg IV infusion over 60 min<br>- UFH 60 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |
| | | tPA_red_acc+UFH+Abx | 70 | - tPA 15 mg IV bolus, then 35 mg IV infusion over 60 min<br>- UFH 30 U/kg IV bolus, then 4 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | tPA+PAC+GP |

| Study group/ first author | Year | Treatment | n | Treatment details | Included in network analyses | Reason of included in network analyses | Coding of treatment for network analyses |
|---|---|---|---|---|---|---|---|
| TIMI-14-rPA[81] | 2000 | rPA+UFH | 102 | - rPA 10 U IV bolus, then 10 U IV bolus apart for 30 min<br>- UFH 70 U/kg IV bolus, then 15 U/kg/hr IV infusion | Yes | Recommended treatment in current practice guidelines | rPA+PAC |
| | | rPA_red+UFH+Abx | 42 | - rPA 5 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 60 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| | | rPA_red+UFH+Abx | 42 | - rPA 10 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 60 U/kg IV bolus, then 7 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| | | rPA_red+UFH+Abx | 50 | - rPA 10 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 30 U/kg IV bolus, then 4 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| | | rPA_red+UFH+Abx | 63 | - rPA 5 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 30 U/kg IV bolus, then 4 U/kg/hr IV infusion<br>- Abx 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min IV infusion for 12 hr | Yes | Treatment regimen with GP IIb/IIIa | rPA+PAC+GP |
| Verstraete[82] | 1985 | tPA+UFH | 64 | - tPA 0.75 mg/kg IV infusion over 90 min<br>- UFH 5000 U IV bolus | No | Not recommended treatment in current practice guidelines | - |
| | | UFH | 65 | - UFH 5000 U IV bolus | No | Not recommended treatment in current practice guidelines | - |
| White[83] | 1987 | SK_acc+UFH | 107 | - SK 1.5 MU IV infusion over 0.5 hr<br>- UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | UFH | 112 | - UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | PAC |
| White[84] | 1989 | SK+UFH | 135 | - SK 1.5 MU IV infusion over 1 hr<br>- UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | SK+PAC |
| | | tPA+UFH | 135 | - tPA 10 mg IV bolus, then 50 mg IV infusion over 1 hr, then 40 mg IV infusion over 2 hr (100 mg over 3 hr)<br>- UFH 1000 U/hr IV infusion | Yes | Recommended treatment in current practice guidelines | tPA+PAC |
| Zhai[85] | 2016 | TNK_red | 124 | - TNK 20 mg IV bolus over 5-10 sec | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_red | 127 | - tPA 8 mg IV bolus, then 42 mg IV infusion over 90 min | No | Not recommended treatment in current practice guidelines | - |
| Zhang[86] | 2010 | rPA_red+UFH | 29 | - rPA 5 U IV bolus, then 5 U IV bolus apart for 30 min<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |
| | | tPA_red+UFH | 25 | - tPA 8 mg IV bolus, then 42 mg IV infusion over 90 min<br>- UFH 60 U/kg IV bolus, then 12 U/kg/hr IV infusion | No | Not recommended treatment in current practice guidelines | - |

**Abbreviation:** n, Number of patient; NMA, Network meta-analysis.

**eTable 4.4 Description of outcomes in studies included in network analyses.**

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| AMI SK[11] | 2002 | ST-segment elevation of 0.1 mV or more in two or more limbs leads or at least 0.2 mV in two or more precordial leads | - 0-18 hr: recurrent symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevation 0.1 mV in ≥2 contiguous leads lasting 30 min<br>- >18 hr: recurrent symptoms of ischaemia at rest lasting 30 min and meeting the ECG criteria, or meeting enzyme criteria | Not specified | No | Yes | ≥5 g/dL | | No | No | Yes | |
| ASSENT-2[12] | 1999 | ST-segment elevations of 0.1 mV or more in two or more limb leads, or 0.2 mV or more in two or more contiguous precordial leads; or have left bundle-branch block | Not specified | Primary haemorrhagic, ischaemic, ischaemic with conversion to haemorrhage, or of unknown cause (if no brain scans or necropsy results were available) | No | No | | | No | Yes | No | - Requiring intervention because of hemodynamic comprise |
| ASSENT-3[13] | 2001 | ST-segment elevation of at least 0.1 mV in two or more limb leads or at least 0.2 mV in two or more contiguous precordial leads, or left bundle-branch block | Reinfarction in the first 18 h was defined as recurrent symptoms of ischaemia at rest accompanied by new or recurrent ST-segment elevations of 0.1 mV or more in at least two contiguous leads, lasting at least 30 min. After 18 h, the definition was: new Q waves in two or more leads, or further increases in concentrations of creatine kinase MB, troponins, or total creatine kinase above the upper limit of normal and increased over the previous value. Refractory ischaemia was defined as symptoms of ischaemia with ST-segment deviation or T-wave inversion persisting for at least 10 min despite medical management and not fulfilling the diagnosis of reinfarction. | Non-cerebral bleeding complications were defined as major (requiring transfusion, intervention because of haemodynamic compromise, or both) or minor. | No | No | | | No | Yes | No | - Requiring intervention because of hemodynamic comprise |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retrope ritoneal | Required transfusion | Cardiac temponade | Other |
| Bleich[17] | 1990 | ST-segment elevation on electrocardiogram of ≥0.1 mV in at least 1 of 3 locations (anterior [≥2 of the 6 precordial leads Vi-V& inferior [≥2 of 3 inferior leads (II, III, aVF)]; or lateral [leads I and aVL]) | clinical reocclusion was defined by recurrence of<br>(1) cardiac-type chest pain similar to that which occurred with the index myocardial infarction lasting 220 minutes, unrelieved by nitroglycerin<br>(2) ECG changes consistent with ischemia (described previously) in the same distribution as the index myocardial infarction<br>(3) deterioration in clinical condition consistent with reinfarction. | Not specified | No | Yes | | | No | Yes | No | - >500 ml blood loss requiring transfusion for augmentation of Hct<br>- Gastrointestinal or other internal bleeding causing hypotension |
| Central Illinois[18] | 1993 | 0.2 mV of ST-segment elevation in >2 contiguous precordial leads (anterior AMI) or 2 of 3 inferior leads (II, III or aVF) (inferior AMI); patients with inferior AMI were also required to have reciprocal ST-segment depression in precordial leads or leads I and aVL | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| Cherng[19] | 1992 | ST segment elevation of 0.1 mV or more in at least two limb leads or 0.2 mV or more in at least two precordial leads | Myocardial reinfarction was recorded if there was a recurrence of typical chest pain with serum enzyme levels rising to twice the upper limit of normal combined with new ECG changes | Not specified for all type of stroke, but intracranial bleeding was documented when a new neurologic deficit occurred and a cranial axial tomographic scan revealed a blood clot. | No | Yes | >5 g/dL | >15% | No | No | No | |
| CORRETA[21] | 2004 | ST-segment elevations of 0.1 mV in 2 electrocardiographic limb leads or 0.2 mV in 2 contiguous precordial electrocardiographic leads, and left bundle branch block | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| ECSG-6[27] | 1992 | at least 0.3 mV ST segment elevation measured at 60 ms after the J point in two precordial leads (VI to V4), and/or 0.2 mV ST elevation in two frontal plane leads or V5 and V6, and/or 0.1 mV ST elevation in two frontal plane leads or V5 and V6 combined with 0.2 mV ST depression in two precordial leads (V1-V4) | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| ECSG-tPA[28] | 1988 | ST segment elevation of at least 2 mm (measured 60 milliseconds after the J point) in two or more limb leads or leads V5 and V6 had to be present or an elevation of 3 mm in two or more precordial leads. Patients with ST segment depression of 2 mm or more in two precordial leads together with ST segment elevation of a least 1 mm in two limb leads or leads V5 and V6, indicating infarction of the posterior wall, were also included | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| ENTIRE TIMI-23[29] | 2002 | exhibited at least 0.1 mV ST-segment elevation in 2 limb leads or 0.2 mV ST-segment elevation in 2 contiguous precordial leads | The definition of recurrent infarction within or after 18 hours of thrombolytic therapy was established on the basis of ECG and enzyme criteria as previously described. Within 18 hours, recurrent ischemic discomfort greater or equal to 30 minutes and new or recurrent STsegment elevation greater or equal to 0.1 mV were required. After 18 hours, a criterion of reelevation of CKMB to above the upper limit of normal and increased by greater or equal to 50% over the previous value was added. If quantitative CKMB was not available, it was required that the total CK be reelevated to more than twice the upper limit of normal and | Not specified | No | Yes | ≥5 g/dL | | No | No | Yes | - Not associated with CABG |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| | | | increased by greater or equal to 25% or greater or equal to 200 U/mL over the previous value; if reelevated to less than twice normal, the CK was required to exceed the upper limit of normal by greater or equal to 50% and the previous value by twofold or greater or equal to 200 U/mL. After coronary angioplasty, the definition of recurrent infarction was new Q waves in two or more leads and reelevation of the CKMB (or total CK if CKMB was not available) to at least twice normal and greater or equal to 50% above the previous value; after coronary artery bypass surgery, the latter criterion was set at a CKMB elevation at least five times normal. | | | | | | | | | |
| GISSI-2/ISG[33,34] | 1990 | ST segment elevation of 1 mm or more in any limb lead and/or of 2 mm or more in any precordial lead | The diagnosis of in-hospital reinfarction was based on the same criteria as definite AMI. AMI required two of the following three criteria: typical ischaemic chest pain; the new appearance of abnormal Q waves with evolutionary ST and T wave changes on serial tracings; total serum creatine kinase twice the upper limit of normal. | Not specified | No | No | | | No | Yes | No | - Requiring transfusion of 2 or more blood units |
| GUSTO-I[35] | 1993 | ≥0.1 mV of ST-segment elevation in two or more limb leads or ≥0.2 mV in two or more contiguous precordial leads | Not specified | Not specified | No | Yes | | | No | No | No | - Bleeding resulted in substantial hemodynamic compromise requiring treatment |
| GUSTO-III[36] | 1997 | ST-segment elevation of at least 1 mm in two or more limb leads, ST-segment elevation of at least 2 mm in the precordial leads, or bundle-branch block | Not specified | Not specified | No | No | | | No | No | No | - Bleeding resulted in substantial hemodynamic compromise requiring treatment. |
| GUSTO-V[37] | 2001 | ≥0.1 mV of ST-segment elevation in two or more limb leads or ≥0.2 mV in two or more contiguous precordial leads | Reinfarction required supportive evidence with either new significant electrocardiographic changes, an increase in cardiac enzyme concentration signifying myocardial necrosis, or both. | Not specified | No | No | | | No | No | No | - Bleeding associated with hemodynamic compromise |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| IMPACT AMI[42] | 1997 | ST-segment depression in leads V1 to V6 consistent with posterior current of injury; ST-segment elevation greater or equal to 0.1 mV (measured 20 ms after the Jpoint) in at least two inferior leads (II, III, or aVF), precordial leads (V1 through V6), or leads I and aVL; or primary STsegment change in the inferior or anterior leads with left bundle-branch block | Not specified | Not specified | No | Yes | | | No | Yes | No | - Bleeding that resulted in hemodynamic compromise requiring intervention |
| INJECT[43] | 1995 | Persistent ST-segment elevation ≥0.1 mV in two of three inferior leads, or in leads I and aVL, or ≥0.2 mV in two contiguous precordial leads, or bundle branch block | Definite myocardial infarction: Either unequivocal new Q waves and peak enzyme levels exceeding the upper limit of normal (as defined locally) or peak enzymes greater than twice the upper limit of normal for local practice with an abnormal ECG as required for entry into the study.<br>Possible myocardial infarction: Qualifying ECG but without the appearance of new Q waves, and peak enzyme levels elevated to less than twice the upper normal level.<br>Ischaemic heart disease: Previous myocardial infarction or angina pectoris but no new permanent ECG or enzyme changes during the index admission.<br>Chest pain of unknown cause: No previous angina or myocardial infarction, no evolution of ECG or enzyme changes, and no other proven cause of chest pain found.<br>Other diagnoses: Irrespective of previous history, no new ECG or enzyme changes, and another proven cause of chest pain found. | strokes and other cardiovascular endpoints | N/A | N/A | | | N/A | N/A | N/A | |
| INTEGRITI[44] | 2003 | along with electrocardiographic criteria of STEMI | Not specified | Not specified | No | Yes | ≥5 g/dL | | No | Yes | No | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| INTRO AMI[47] | 2002 | Not specified | Reinfarction in the first 24 h was diagnosed if ST elevation reoccurred or there was re-elevation of CK-MB (33% for a previous decrease from peak of ≥25% or 100% for a preceding decrease of ≥50%). Reinfarction after 24 h was diagnosed based on CK-MB re-elevation to above 3 times normal (2 times normal after day 7) or new significant Q waves. | Stroke was diagnosed on the basis of an imaging study and an expert neurologist opinion. | No | Yes | ≥5 g/dL | | No | No | Yes | - Intraocular hemorrhage<br>- Any clinical overt hemorrhage associated with drop in Hb<br>- Excluding the number of CABG related bleeding |
| ISAM[48] | 1986 | ST elevations of 1 mm or more were observed in the extremity leads of the electrocardiogram, with elevations of 2 mm or more in the chest leads | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| Janousek[49] | 1988 | either ST elevation greater than 1 mm in two or more leads V1-V4, or at least 1 mm in two or more other leads or patients with a "giant" T waves with a complete history of classic AMI | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| Kennedy[52] | 1988 | ST segment elevation (at least 0.15 mV in V1, V2, or V3 or 0.1 mV in other leads) in two or more leads measured 60 msec beyond the J point, and one or more leads with ST segment elevation without Q waves (40 msec duration or longer) | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| LATE[54] | 1993 | ST elevation ≥1 mm in two or more limb leads or ≥2 mm in two or more chest leads, ST depression ≥2 mm in at least two leads, pathological Q waves, and abnormal T wave inversion in at least two leads and thought to represent a non-Q wave infarct. Patients with old or equivocal ECG changes or bundle-branch block were acceptable if there was evidence of raised cardiac enzymes. | Not specified | Strokes were categorised as haemorrhagic, embolic, or uncertain | No | No | | | No | Yes | No | - Bleeding needed to transfuse 2 or more units of blood |
| NCT00148460[58] | 2005 | ST segment elevation ≥ 0.1 mV in two or more limb leads, or ≥ 0.2 mV in two or more contiguous precordial leads indicative of AMI | In the first 18 hours after the start of study drug administration, recurrent acute myocardial infarction (AMI) is defined as:<br>- Recurrent signs and symptoms of ischemia at rest accompanied by new or recurrent ST segment elevation of ≥0.1 mV in at least two contiguous leads<br>- Signs and symptoms of ischemia and/or ST segment elevation must persist for at least 30 minutes<br>After 18 hours, recurrent AMI is defined as follows:<br>- ECG evidence of recurrent MI: New Q waves in two or more leads Or<br>- ECG evidence of new left branch block<br>- Enzyme evidence<br>Re-elevation of CK-MB to above the upper limit of normal and increased by ≥50% over the previous value. If quantitative CK-MB is not available, the total CK will be evaluated. The total CK must either be re-elevated to ≥2 times the upper limit of normal and increased by ≥25% or to ≥200U/ml over the previous value; if re-elevated to <2 times the upper limit of normal, the total CK must exceed the upper limit of normal by ≥50% and exceed the previous value by 2-fold or to ≥200U/ml.<br>Recurrent AMI after PTCA is defined as follows: | - Stroke is defined as the sudden onset of a focal neurologic deficit that does not resolve spontaneously within 24 hours and is not a temporary result of pharmacologic interventions, e.g., lidocaine or analgesics.<br>- Intracranial hemorrhage is defined as stroke with focal collections of intracerebral blood seen on a brain image (CT or MRI) or on post-mortem examination, not felt to represent hemorrhage conversion (Subarachnoid hemorrhage should be included in this category.) | No | No | | | Yes | Yes | No | - Bleeding that causes hemodynamic compromise requiring intervention and transfusion.<br>- Acute gastrointestinal bleeding or retroperitoneal bleeding causing hemodynamic compromise. |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| | | | - CK-MB (or CK, if MB is not available) >2 times the upper limit of normal and ≥50% greater than the previous value or new Q waves in two or more contiguous leads<br>Recurrent AMI after CABG surgery is defined as follows:<br>- CK-MB (or CK, if CK-MB is not available) of >5 times the upper limit of normal and ≥50% greater than the previous value and new Q waves in two or more contiguous leads. | | | | | | | | | |
| NHFA[59] | 1988 | >2 mm in suspected anterior infarction or >1 mm in suspected inferior infarction | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| O'Rourke[60] | 1988 | ST segment elevation 60 msec after the J point of more than 1 mm in two or more standard leads or V4-V6, or of greater than 2 mm in two or more of leads V1-V3 | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| PAIMS[62] | 1989 | ST segment elevation ≥0.1 mV in two or more standard frontal plane leads or ≥0.2 mV in two or more precordial leads and ST segment depression ≥0.3 mV in two or more precordial leads | Not specified | Not specified | No | Yes | ≥5 g/dL | | No | No | No | |
| RAAMI[66] | 1992 | evidence of infarction with at least 1-mm ST segment elevation in at least two of three inferior leads (II, III or aVF) and at least two contiguous precordial leads (V1 to V6) or lateral leads I and aVL. | Recurrent ischemia: Chest pain with recurrent ST elevation.<br>Recurrent infarction: Recurrent electrocardiographic changes with elevation of creatine kinase levels. | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| RAPID[67] | 1994 | ST-segment elevation of 0.1 mV in the inferior or lateral leads or 0.2 mV in the precordial leads | Not specified | Not specified | No | No | | | No | Yes | No | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| RAPID-II[68] | 1996 | ST-segment elevation of greater or equal to 0.1 mV in two of three inferior or lateral leads or greater or equal to 0.2 mV in at least two contiguous precordial leads or left bundle-branch block | Not specified | Not specified | No | Yes | | | No | Yes | No | - Prolonging the period of hospitalization |
| Ronner[69] | 2000 | ST-elevation of 0.1 mV in two or more standard leads or 0.2 mV in two or more precordial leads | Not specified | Not specified | No | Yes | ≥5 g/dL | ≥15% | No | No | Yes | |
| Sarullo[70] | 2001 | ST-segment elevation involving more than 3 leads, >1 mm in the peripheral leads and/or 2 mm in the precordial leads | Not specified | Not specified | N/A | N/A | | | N/A | N/A | N/A | |
| SPEED[71] | 2000 | exhibited ≥0.1-mV ST-segment elevation in 2 contiguous leads | Not specified | Not specified | No | Yes | >5 g/dL | ≥15% | Yes | No | No | - Clinically overt with a hemoglobin decrease more than Hb/Hct cutpoint<br>- Intraocular |
| TAMI-3[75] | 1989 | ST segment elevation of 1 mm or more in two or more contiguous leads | A second rise in creatine kinase with positive myocardial isoform fraction, accompanied by recurrent clinical signs, defined reinfarction. | Not specified | No | Yes | | | No | Yes | No | - Bleeding with requirement of transfusion of 2 or more units PRC |
| TIMI-1[78] | 1987 | ST segment elevation (0.1 mV) in at least two contiguous electrocardiographic leads | (1) recurrence of chest pain attributable to ischemia of 30 or more minutes duration and unresponsive to nitroglycerin<br>(2) new ST segment elevation (0.1 mV) in at least two contiguous electrocardiographic leads but in no more than seven leads or new Q waves<br>(3) new plasma creatine kinase elevation (accompanied by the appearance of creatine kinase-MB isoenzymes) to 50% above the average of consecutive normal values or 50% above the previous value if the creatine kinase value had not returned to within the normal range | Not specified | No | Yes | >5 g/dL | >15% | No | No | No | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| TIMI-10B[79] | 1998 | ST-segment elevation ≥0.1 mV in ≥2 contiguous leads | Not specified | Not specified | Yes | No | | | No | No | No | - Required or prolonged hospitalization<br>- Resulted in significant disability<br>- necessitated medical or surgical intervention to preclude permanent impairment of a body function or structure |
| TIMI-14[80] | 1999 | exhibited ≥0.1-mV ST-segment elevation in 2 contiguous leads | The definition of recurrent infarction within or after 18 hours of thrombolytic therapy was established on the basis of ECG and enzyme criteria as previously described. Within 18 hours, recurrent ischemic discomfort greater or equal to 30 minutes and new or recurrent STsegment elevation greater or equal to 0.1 mV were required. After 18 hours, a criterion of reelevation of CKMB to above the upper limit of normal and increased by greater or equal to 50% over the previous value was added. If quantitative CKMB was not available, it was required that the total CK be reelevated to more than twice the upper limit of normal and increased by greater or equal to 25% or greater or equal to 200 U/mL over the previous value; if reelevated to less than twice normal, the CK was required to exceed the upper limit of normal by greater or equal to 50% and the previous value by twofold or greater or equal to 200 U/mL. After coronary angioplasty, the definition of recurrent infarction was new Q waves in two or more leads and reelevation of the CKMB (or total CK if CKMB was not available) to at least twice normal and greater or equal to 50% above the previous value; after coronary artery bypass surgery, the latter criterion was set at a CKMB elevation at least five times normal. | Not specified | No | Yes | ≥5 g/dL | | Yes | No | No | - Intraocular hemorrhage<br>- Any clinical overt hemorrhage associated with drop in Hb |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retroperitoneal | Required transfusion | Cardiac temponade | Other |
| TIMI-14-rPA[81] | 2000 | exhibited at least 0.1 mV ST segment elevation in two contiguous leads | The definition of recurrent infarction within or after 18 hours of thrombolytic therapy was established on the basis of ECG and enzyme criteria as previously described. Within 18 hours, recurrent ischemic discomfort greater or equal to 30 minutes and new or recurrent STsegment elevation greater or equal to 0.1 mV were required. After 18 hours, a criterion of reelevation of CKMB to above the upper limit of normal and increased by greater or equal to 50% over the previous value was added. If quantitative CKMB was not available, it was required that the total CK be reelevated to more than twice the upper limit of normal and increased by greater or equal to 25% or greater or equal to 200 U/mL over the previous value; if reelevated to less than twice normal, the CK was required to exceed the upper limit of normal by greater or equal to 50% and the previous value by twofold or greater or equal to 200 U/mL. After coronary angioplasty, the definition of recurrent infarction was new Q waves in two or more leads and reelevation of the CKMB (or total CK if CKMB was not available) to at least twice normal and greater or equal to 50% above the previous value; after coronary artery bypass surgery, the latter criterion was set at a CKMB elevation at least five times normal. | Not specified | No | Yes | ≥5 g/dL | | Yes | No | No | - Intraocular hemorrhage<br>- Any clinical overt hemorrhage associated with drop in Hb |
| White[83] | 1987 | ST-segment elevation of 1 mm or more in precordial Leads V 4 through V 6 or the limb leads of the electrocardiogram, or of 2 mm or more in precordial Leads V 1 through V3 | Reinfarction was indicated by chest pain or electrocardiographic changes associated with a rise in creatine kinase above normal or by the development of a second peak in the creatine kinase curve. | Not specified | N/A | N/A | | | N/A | N/A | N/A | |

| Study group/ first author | Year | ECG criteria | Reinfarction endpoint definition | Stroke endpoint definition | Major bleeding definition | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Fatal bleeding | ICH | Hb cutpoint | Hct cutpoint | Retrope ritoneal | Required transfusion | Cardiac temponade | Other |
| White[84] | 1989 | ST-segment elevation of 1 mm or more in the limb leads or precordial Leads V4 through V6, or 2 mm or more in the precordial Leads V1 through V3. Patients with non-Q-wave infarctions were not included. | Reinfarction was defined as chest pain associated with a rise in the creatine kinase level to twice the upper limit of normal or with the development of new Q waves. | Not specified | N/A | N/A | | | N/A | N/A | N/A | |

**Abbreviation:** AMI, Acute myocardial infarction; CK, Creatine kinase; CKMB, Creatine kinase myocardial band; ECG, Electrocardiogram; Hb, Hemoglobin; Hct, Hematocrit; ICH, Intracranial hemorrhage; N/A, Not available; WHO, World health organization.

**eTable 4.5 Detail of reported concomitant therapies received in the included studies (ordered by year of publication).**

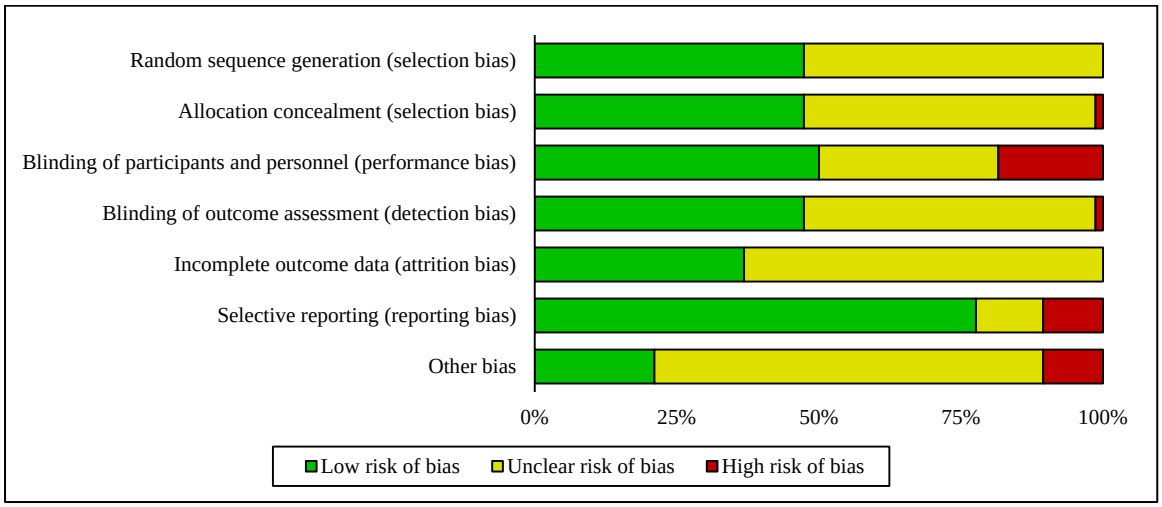
| Study | Year | Treatment (n) | Include in NMA | Other oral antiplatelet agents | | BBs (%) | ACEIs/ ARBs (%) | Statins (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | Detail | (%) | | | |
| Olson[61] | 1986 | - SK_red+UFH (28)<br>- UFH (24) | No | Dipyridamole 75 mg TID in combination with aspirin* | | | | |
| TIMI-1[78] | 1987 | - SK+UFH (147)<br>- tPA+UFH (143) | Yes | Dipyridamole 75 mg TID in combination with aspirin* | | | | |
| White[83] | 1987 | - SK_acc+UFH (107)<br>- UFH (112) | Yes | Dipyridamole 200 mg BID in combination with aspirin* | | 22.2* | | |
| O'Rourke[60] | 1988 | - tPA+UFH (74)<br>- UFH (71) | Yes | Dipyridamole 100 mg TID* | | | | |
| White[84] | 1989 | - SK+UFH (135)<br>- tPA+UFH (135) | Yes | Dipyridamole 200 mg BID in combination with aspirin* | | 13.0* | | |
| Bleich[17] | 1990 | - tPA (42)<br>- tPA+UFH (42) | Yes | Dipyridamole as an alternative to aspirin* | | | | |
| GISSI-2+ISG[33,34] | 1990 | - SK±UFH (10396)<br>- tPA±UFH (10372) | Yes | | | 70.2† | | |
| Lidon[56] | 1994 | - SK+Bival (30)<br>- SK+UFH (15) | No | | | 62.2 | | |
| Theroux[77] | 1995 | - SK+Bival (55)<br>- SK+UFH (13) | No | | | 92.6 | 19.1 | |
| ASSENT-2[12] | 1999 | - TNK+UFH (8461)<br>- tPA_acc+UFH (8488) | Yes | Ticlopidine/clopidogrel | 22.5 | 80.8 | 55.5 | 31.6 |
| BIOMACS-II[16] | 1999 | - SK (47)<br>- SK+Dalte (54) | No | | | 86.6 | 32.1 | 4.5 |
| TERIMA[76] | 1999 | - SK (111)<br>- rSK (113) | No | | | 56.7 | | |
| ASSENT-3[13] | 2001 | - TNK+Enox (2040)<br>- TNK+UFH (2038)<br>- TNK+UFH+Abx (2017) | Yes | Ticlopidine/clopidogrel | 30.0 | 83.7 | 64.7 | 51.0 |
| GUSTO-V[37] | 2001 | - rPA+UFH (8260)<br>- rPA_red+UFH+Abx (8328) | Yes | | | 19.5* | 13.5* | |
| HERO-2[40] | 2001 | - SK+Bival (8516)<br>- SK+UFH (8557) | No | | | 12.8‡ | | |
| Sarullo[70] | 2001 | - tPA_acc+UFH (60)<br>- tPA_red+UFH+Tiro (60) | Yes | | | 31.7§ | | |
| ASSENT-3_Plus[14] | 2003 | - TNK+Enox (818)<br>- TNK+UFH (821) | No | Ticlopidine/clopidogrel | 55.2 | 89.3 | 64.2 | 72.2 |
| CORRETA[21] | 2004 | - TNK+UFH (132)<br>- tPA_acc+UFH (134) | Yes | | | 90.6 | 61.3 | 71.4 |
| NCT00148460[58] | 2005 | - TNK+UFH (130)<br>- tPA_acc+UFH (137) | Yes | Ticlopidine/clopidogrel | 61.8 | 85.8 | 90.3 | 76.1 |
| Li[55] | 2006 | - tPA_acc_30 min+UFH (46)<br>- tPA_acc_45 min+UFH (43) | No | Clopidogrel 300 mg PO, then 75 mg PO daily* | | | | |
| Zhai[85] | 2016 | - TNK_red (124)<br>- tPA_red (127) | No | Clopidogrel | 99.6 | | | |

*Specified in study protocol
†Drug on entry/previous therapy
‡Full dose of beta-blocker during acute phase
§Intravenous beta-blocker
¶Exclusion criteria was set to exclude patients receiving beta-blockers

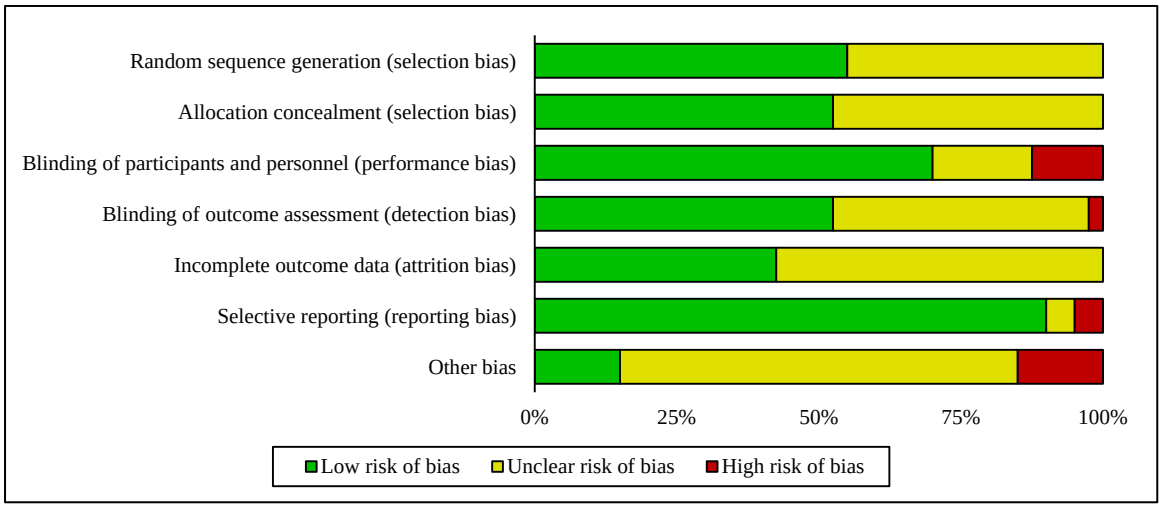
# Appendix 5 Risk of bias assessments

Risk of bias assessments were followed according to the recommended approach for assessing risk of bias in studies included in Cochrane reviews. Specific bias domains have been addressed in this tool including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data and selective outcome reporting. The adjudication for the risk of bias for each item within each study is done by answering pre-specified questions about the methods reported by each study in relation to the risk domain. The conclusion of risk of bias for each item is classified to either low risk of bias, unclear risk of bias or high risk of bias. In overall, the study is considered to be at risk of bias from selective reporting domain when the data for all-cause mortality, or major bleeding were not reported.

**eFigure 5.1 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages for all of included studies (76 studies).**



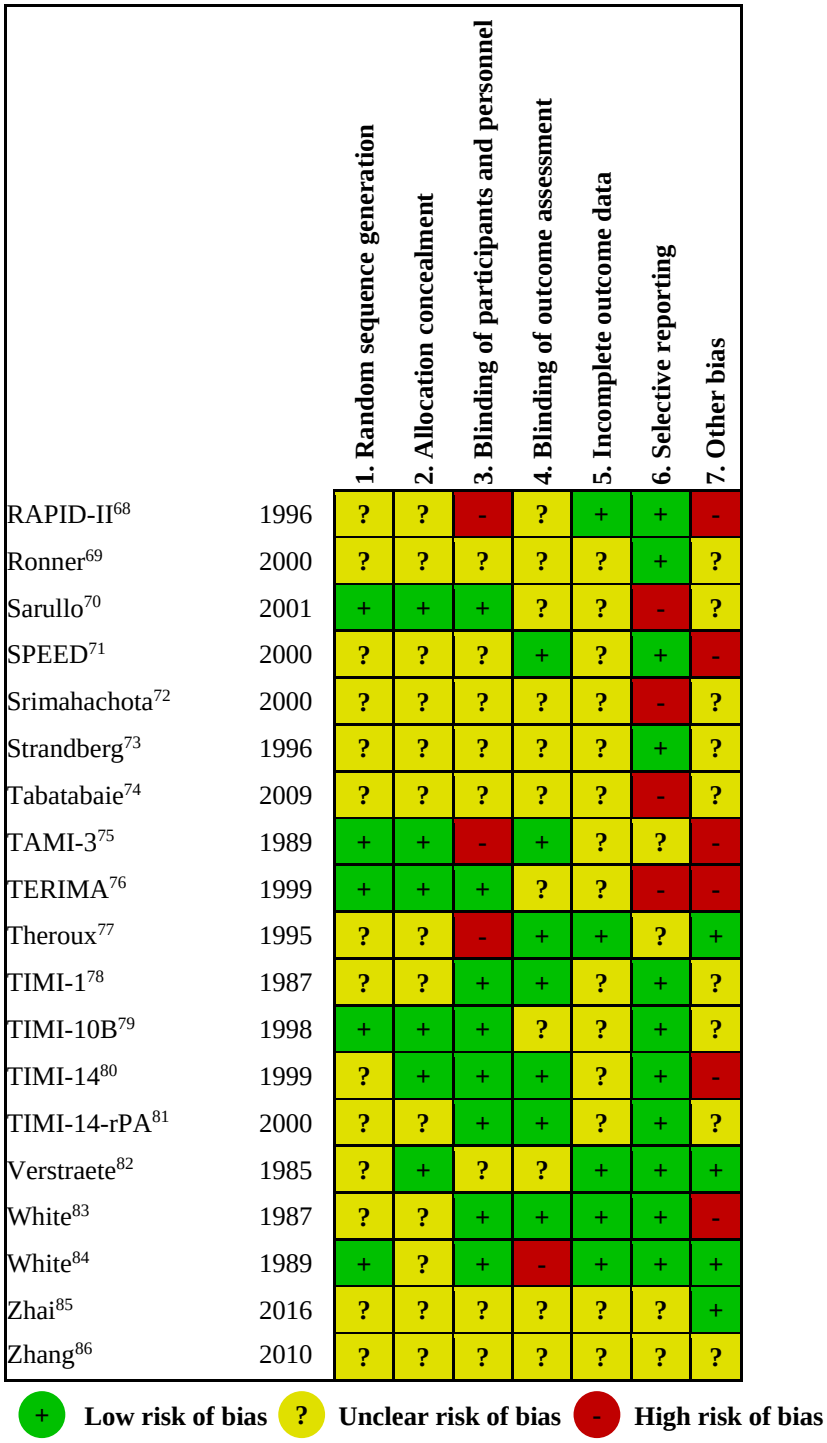

**eFigure 5.2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages for studies including in network analyses (40 studies).**



**eTable 5.2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

| | | 1. Random sequence generation | 2. Allocation concealment | 3. Blinding of participants and personnel | 4. Blinding of outcome assessment | 5. Incomplete outcome data | 6. Selective reporting | 7. Other bias |
|---|---|---|---|---|---|---|---|---|
| AMI SK[11] | 2002 | + | + | + | + | + | + | ? |
| ASSENT-2[12] | 1999 | + | + | + | + | + | + | ? |
| ASSENT-3[13] | 2001 | + | + | + | + | + | + | ? |
| ASSENT-3 Plus[14] | 2003 | + | + | + | ? | + | ? | + |
| ASSENT Plus[15] | 2003 | ? | ? | - | + | + | + | ? |
| BIOMACS-II[16] | 1999 | + | ? | ? | ? | ? | + | ? |
| Bleich[17] | 1990 | + | ? | + | ? | ? | + | ? |
| Central Illinois[18] | 1993 | ? | ? | + | ? | + | + | - |
| Cherng[19] | 1992 | ? | ? | + | ? | + | + | ? |
| COBALT[20] | 1997 | + | + | + | + | + | + | + |
| CORRETA[21] | 2004 | + | ? | ? | ? | ? | + | ? |
| Cortadellas[22] | 1989 | ? | ? | ? | ? | + | + | ? |
| Curylo[23] | 1997 | ? | ? | ? | ? | ? | + | ? |
| DouBLE[24] | 1998 | ? | ? | + | ? | ? | + | ? |
| Dwivedi[25] | 2000 | ? | ? | - | + | ? | - | ? |
| ECSG[26] | 1985 | + | + | - | + | + | ? | + |
| ECSG-6[27] | 1992 | + | + | + | ? | ? | + | ? |
| ECSG-tPA[28] | 1988 | + | + | + | + | + | + | ? |
| ENTIRE TIMI-23[29] | 2002 | ? | + | + | + | ? | + | ? |
| ESCALAT[30] | 1999 | + | + | ? | ? | ? | + | ? |
| FRAMI[31] | 1997 | ? | ? | ? | ? | + | + | ? |
| Ghaffari[32] | 2013 | + | - | - | + | ? | + | ? |
| GISSI-2[33]/ ISG[34] | 1990 | + | + | - | ? | + | + | + |
| GUSTO-I[35] | 1993 | ? | + | + | + | + | + | + |
| GUSTO-III[36] | 1997 | ? | + | + | + | + | + | ? |
| GUSTO-V[37] | 2001 | ? | + | + | + | + | + | + |
| HART-II[38] | 2001 | ? | ? | - | + | ? | + | ? |

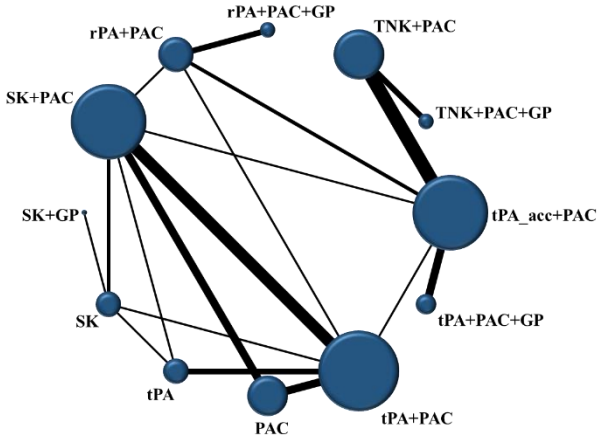
| | | 1. Random sequence generation | 2. Allocation concealment | 3. Blinding of participants and personnel | 4. Blinding of outcome assessment | 5. Incomplete outcome data | 6. Selective reporting | 7. Other bias |
|---|---|---|---|---|---|---|---|---|
| HERO[39] | 1997 | + | + | - | + | ? | + | + |
| HERO-2[40] | 2001 | + | + | - | + | + | + | - |
| HIT-4[41] | 1999 | + | + | + | + | ? | + | ? |
| IMPACT AMI[42] | 1997 | + | ? | ? | ? | + | + | ? |
| INJECT[43] | 1995 | + | + | + | + | + | + | + |
| INTEGRITI[44] | 2003 | + | + | + | + | ? | + | ? |
| InTIME[45] | 1998 | ? | + | + | + | + | + | ? |
| InTIME-II[46] | 2000 | + | + | + | + | + | + | + |
| INTRO AMI[47] | 2002 | ? | ? | + | ? | ? | + | ? |
| ISAM[48] | 1986 | ? | ? | ? | + | ? | + | ? |
| Janousek[49] | 1988 | ? | ? | ? | ? | ? | ? | ? |
| Jiang[50] | 2005 | ? | ? | ? | ? | ? | + | + |
| KAMIT[51] | 1991 | + | + | ? | ? | ? | + | ? |
| Kennedy[52] | 1988 | + | + | + | ? | ? | + | ? |
| Khalilullah[53] | 1984 | ? | ? | ? | ? | ? | ? | ? |
| LATE[54] | 1993 | + | + | + | + | ? | + | ? |
| Li[55] | 2006 | ? | ? | ? | ? | ? | ? | ? |
| Lidon[56] | 1994 | + | + | + | + | ? | - | ? |
| MINT[57] | 1999 | ? | ? | + | ? | ? | + | ? |
| NCT00148460[58] | 2005 | + | ? | + | + | + | + | ? |
| NHFA[59] | 1988 | ? | ? | ? | ? | ? | + | ? |
| O'Rourke[60] | 1988 | + | + | + | ? | ? | - | ? |
| Olson[61] | 1986 | ? | ? | ? | ? | ? | - | ? |
| PAIMS[62] | 1989 | ? | ? | - | ? | ? | + | ? |
| PENTALYSE[63] | 2001 | + | + | + | + | ? | + | ? |
| Plotnikov[64] | 1993 | ? | ? | ? | ? | ? | + | ? |
| PRIME[65] | 2002 | ? | + | - | + | ? | + | + |
| RAAMI[66] | 1992 | + | ? | + | + | ? | + | ? |
| RAPID[67] | 1994 | + | + | + | + | ? | + | ? |


1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias
RAPID-II[68] 1996 ? ? - ? + + -
Ronner[69] 2000 ? ? ? ? ? + ?
Sarullo[70] 2001 + + + ? ? - ?
SPEED[71] 2000 ? ? ? + ? + -
Srimahachota[72] 2000 ? ? ? ? ? - ?
Strandberg[73] 1996 ? ? ? ? ? + ?
Tabatabaie[74] 2009 ? ? ? ? ? - ?
TAMI-3[75] 1989 + + - + ? ? -
TERIMA[76] 1999 + + + ? ? - -
Theroux[77] 1995 ? ? - + + ? +
TIMI-1[78] 1987 ? ? + + ? + ?
TIMI-10B[79] 1998 + + + ? ? + ?
TIMI-14[80] 1999 ? + + + ? + -
TIMI-14-rPA[81] 2000 ? ? + + ? + ?
Verstraete[82] 1985 ? + ? ? + + +
White[83] 1987 ? ? + + + + -
White[84] 1989 + ? + - + + +
Zhai[85] 2016 ? ? ? ? ? ? +
Zhang[86] 2010 ? ? ? ? ? ? ?
+ Low risk of bias
? Unclear risk of bias
- High risk of bias

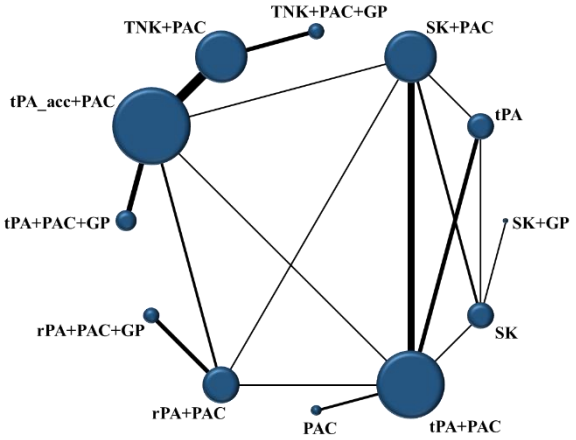
# Appendix 6 Networks of treatment comparisons

The size of each treatment nodes is related to the number of studies of the treatments. Each line represents the direct comparison between treatments, the thickness of the line corresponds is relate to the number of studies of the comparison. Abbreviation for all of the following eFigure: GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

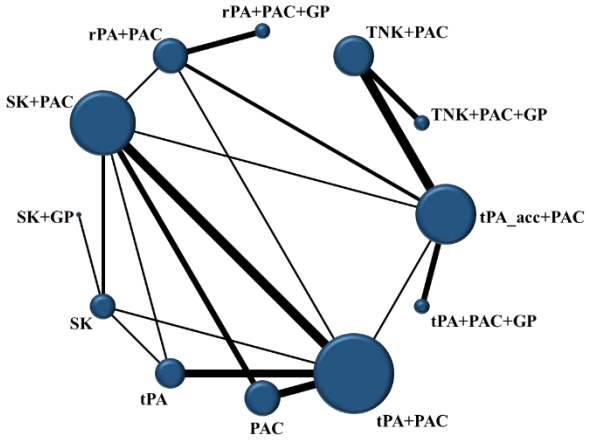
**eFigure 6.1 Networks map of treatment comparisons for each outcomes.**



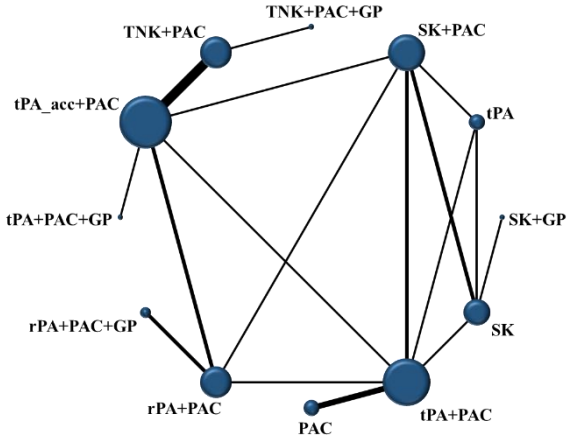

**Mortality within 30-35 days**



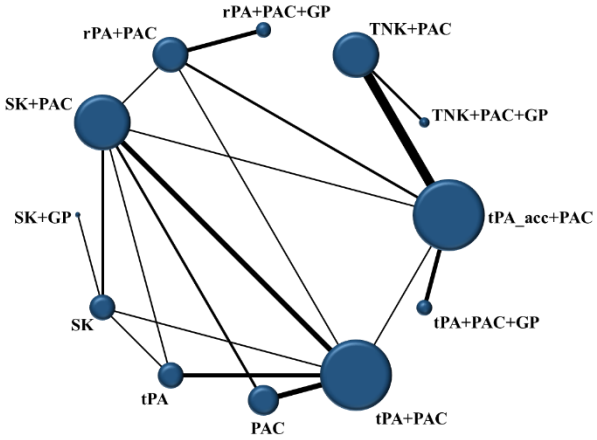

**Major bleeding**




**Recurrent infarction**




**All-type stroke**




**Hemorrhagic stroke**

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion)

# Appendix 7 Assessment of inconsistency for each outcome network

**eTable 7.1 Evaluation of the global inconsistency in networks using the 'design-by-treatment' interaction model for each outcome.**

| Network outcome | Chi-square | P value for test of global inconsistency |
|---|---|---|
| **Primary outcomes** | | |
| • All-cause mortality within 30-35 days | 10.92 | 0.1422 |
| • Major bleeding | 3.89 | 0.6919 |
| **Secondary outcomes** | | |
| • Recurrent infarction | 13.11 | 0.0695 |
| • All-type stroke | 5.87 | 0.3187 |
| • Hemorrhagic stroke | 3.84 | 0.7980 |

GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; SE, Standard error; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion)

# Appendix 8 Results of meta-analyses of direct comparisons of treatment options

**eTable 8.1 Pairwise meta-analysis risk ratio (and 95% CI) for all dichotomous outcomes.**

| Comparisons | | | No. studies | No. of patients | Pairwise meta-analysis risk ratio (95% CI) | | Heterogeneity I2 (variation in RR attributable to heterogeneity) |
|---|---|---|---|---|---|---|---|
| | | | | | Fixed effect | Random effect | |
| **All-cause mortality within 30-35 days** | | | | | | | |
| SK+PAC | vs. | PAC | 4 | 2385 | 1.34 (1.00,1.81) | 1.47 (0.94,2.31) | 27.00% |
| tPA+PAC | vs. | PAC | 4 | 6721 | 1.17 (1.01,1.37) | 1.17 (0.71,1.93) | 43.40% |
| SK+GP | vs. | SK | 1 | 181 | 1.54 (0.43,5.51) | 1.54 (0.43,5.51) | N/A |
| SK+PAC | vs. | SK | 2 | 10892 | 1.17 (1.03,1.32) | 1.17 (1.03,1.32) | 0.00% |
| tPA | vs. | SK | 1 | 10407 | 1.06 (0.94,1.20) | 1.06 (0.94,1.20) | N/A |
| tPA+PAC | vs. | SK | 1 | 10375 | 1.00 (0.89,1.13) | 1.00 (0.89,1.13) | N/A |
| rPA+PAC | vs. | SK+PAC | 1 | 6010 | 1.06 (0.90,1.24) | 1.06 (0.90,1.24) | N/A |
| tPA | vs. | SK+PAC | 1 | 10393 | 0.90 (0.79,1.03) | 0.90 (0.79,1.03) | N/A |
| tPA+PAC | vs. | SK+PAC | 6 | 11467 | 0.89 (0.79,1.01) | 1.15 (0.79,1.66) | 25.80% |
| tPA_acc+PAC | vs. | SK+PAC | 1 | 30647 | 1.16 (1.06,1.27) | 1.16 (1.06,1.27) | N/A |
| TNK+PAC+GP | vs. | TNK+PAC | 3 | 6815 | 0.87 (0.72,1.07) | 0.87 (0.71,1.07) | 0.00% |
| tPA_acc+PAC | vs. | TNK+PAC | 4 | 18338 | 1.01 (0.90,1.13) | 1.03 (0.81,1.31) | 15.00% |
| rPA+PAC+GP | vs. | rPA+PAC | 3 | 17111 | 1.05 (0.93,1.19) | 1.05 (0.93,1.19) | 0.00% |
| tPA+PAC | vs. | rPA+PAC | 1 | 308 | 0.50 (0.13,1.96) | 0.50 (0.13,1.96) | N/A |
| tPA_acc+PAC | vs. | rPA+PAC | 2 | 15383 | 1.02 (0.90,1.15) | 0.82 (0.42,1.60) | 61.10% |
| tPA+PAC | vs. | tPA | 3 | 11150 | 0.96 (0.85,1.08) | 0.96 (0.85,1.08) | 0.00% |
| tPA_acc+PAC | vs. | tPA+PAC | 1 | 281 | 0.60 (0.25,1.49) | 0.60 (0.25,1.49) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC+GP | 4 | 684 | 0.76 (0.39,1.48) | 0.72 (0.36,1.42) | 0.00% |
| **Major bleeding** | | | | | | | |
| tPA+PAC | vs. | PAC | 2 | 5856 | 0.55 (0.28,1.06) | 0.55 (0.29,1.08) | 0.00% |
| SK+GP | vs. | SK | 1 | 181 | 0.06 (0.00,0.95) | 0.06 (0.00,0.95) | N/A |
| SK+PAC | vs. | SK | 2 | 10892 | 0.52 (0.35,0.79) | 0.52 (0.35,0.79) | 0.00% |
| tPA | vs. | SK | 1 | 10407 | 1.37 (0.81,2.32) | 1.37 (0.81,2.32) | N/A |
| tPA+PAC | vs. | SK | 1 | 10375 | 0.82 (0.52,1.30) | 0.82 (0.52,1.30) | N/A |
| rPA+PAC | vs. | SK+PAC | 1 | 6010 | 1.02 (0.81,1.28) | 1.02 (0.81,1.28) | N/A |
| tPA | vs. | SK+PAC | 1 | 10393 | 2.63 (1.65,4.20) | 2.63 (1.65,4.20) | N/A |
| tPA+PAC | vs. | SK+PAC | 5 | 11197 | 1.47 (1.09,1.98) | 1.40 (1.03,1.90) | 0.00% |
| tPA_acc+PAC | vs. | SK+PAC | 1 | 30647 | 1.00 (0.67,1.48) | 1.00 (0.67,1.48) | N/A |
| TNK+PAC+GP | vs. | TNK+PAC | 3 | 6815 | 0.53 (0.42,0.68) | 0.48 (0.31,0.75) | 24.10% |
| tPA_acc+PAC | vs. | TNK+PAC | 4 | 18338 | 0.80 (0.71,0.90) | 0.75 (0.50,1.13) | 20.30% |
| rPA+PAC+GP | vs. | rPA+PAC | 3 | 17111 | 0.47 (0.34,0.65) | 0.47 (0.34,0.65) | 0.00% |
| tPA+PAC | vs. | rPA+PAC | 1 | 308 | 0.86 (0.30,2.49) | 0.86 (0.30,2.49) | N/A |
| tPA_acc+PAC | vs. | rPA+PAC | 2 | 15383 | 0.86 (0.65,1.14) | 0.89 (0.62,1.28) | 27.00% |
| tPA+PAC | vs. | tPA | 3 | 10560 | 0.69 (0.45,1.07) | 0.75 (0.42,1.35) | 21.40% |
| tPA_acc+PAC | vs. | tPA+PAC | 1 | 281 | 0.44 (0.18,1.12) | 0.44 (0.18,1.12) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC+GP | 3 | 684 | N/A | N/A | 0.00% |

| Comparisons | | | No. studies | No. of patients | Pairwise meta-analysis risk ratio (95% CI) | | Heterogeneity I2 (variation in RR attributable to heterogeneity) |
|---|---|---|---|---|---|---|---|
| | | | | | Fixed effect | Random effect | |
| **Recurrent infarction** | | | | | | | |
| SK+PAC | vs. | PAC | 3 | 2017 | 0.47 (0.24,0.93) | 0.48 (0.24,0.94) | 0.00% |
| tPA+PAC | vs. | PAC | 4 | 6721 | 1.23 (0.95,1.58) | 1.23 (0.95,1.58) | 0.00% |
| SK+GP | vs. | SK | 1 | 181 | 0.72 (0.20,2.62) | 0.72 (0.20,2.62) | N/A |
| SK+PAC | vs. | SK | 2 | 10892 | 1.06 (0.86,1.31) | 1.61 (0.53,4.92) | 83.00% |
| tPA | vs. | SK | 1 | 10407 | 1.06 (0.85,1.32) | 1.06 (0.85,1.32) | N/A |
| tPA+PAC | vs. | SK | 1 | 10375 | 1.22 (0.97,1.54) | 1.22 (0.97,1.54) | N/A |
| rPA+PAC | vs. | SK+PAC | 1 | 6010 | 1.08 (0.87,1.34) | 1.08 (0.87,1.34) | N/A |
| tPA | vs. | SK+PAC | 1 | 10393 | 1.08 (0.86,1.34) | 1.08 (0.86,1.34) | N/A |
| tPA+PAC | vs. | SK+PAC | 5 | 11214 | 1.21 (0.99,1.49) | 1.20 (0.98,1.48) | 0.00% |
| tPA_acc+PAC | vs. | SK+PAC | 1 | 30647 | 0.93 (0.82,1.05) | 0.93 (0.82,1.05) | N/A |
| TNK+PAC+GP | vs. | TNK+PAC | 3 | 6815 | 1.53 (1.12,2.08) | 1.50 (0.72,3.10) | 44.90% |
| tPA_acc+PAC | vs. | TNK+PAC | 4 | 18338 | 1.08 (0.93,1.24) | 1.05 (0.78,1.41) | 18.30% |
| rPA+PAC+GP | vs. | rPA+PAC | 3 | 17111 | 1.51 (1.27,1.81) | 1.51 (1.27,1.81) | 0.00% |
| tPA+PAC | vs. | rPA+PAC | 1 | 308 | 0.57 (0.17,1.91) | 0.57 (0.17,1.91) | N/A |
| tPA_acc+PAC | vs. | rPA+PAC | 2 | 15383 | 1.00 (0.85,1.17) | 1.00 (0.85,1.17) | 0.00% |
| tPA+PAC | vs. | tPA | 4 | 11234 | 1.13 (0.91,1.41) | 1.13 (0.91,1.41) | 0.00% |
| tPA_acc+PAC | vs. | tPA+PAC | 1 | 281 | 0.52 (0.05,5.65) | 0.52 (0.05,5.65) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC+GP | 2 | 473 | 1.83 (0.78,4.27) | 1.84 (0.78,4.29) | 0.00% |
| **All-type stroke** | | | | | | | |
| tPA+PAC | vs. | PAC | 3 | 6576 | 0.49 (0.33,0.73) | 0.50 (0.34,0.74) | 0.00% |
| SK+GP | vs. | SK | 1 | 181 | 0.38 (0.02,7.81) | 0.38 (0.02,7.81) | N/A |
| SK+PAC | vs. | SK | 2 | 10892 | 0.91 (0.62,1.33) | 1.49 (0.23,9.57) | 50.50% |
| tPA | vs. | SK | 1 | 10407 | 0.61 (0.42,0.88) | 0.61 (0.42,0.88) | N/A |
| tPA+PAC | vs. | SK | 1 | 10375 | 0.70 (0.48,1.02) | 0.70 (0.48,1.02) | N/A |
| rPA+PAC | vs. | SK+PAC | 1 | 6010 | 0.81 (0.50,1.31) | 0.81 (0.50,1.31) | N/A |
| tPA | vs. | SK+PAC | 1 | 10393 | 0.72 (0.51,1.02) | 0.72 (0.51,1.02) | N/A |
| tPA+PAC | vs. | SK+PAC | 2 | 10614 | 0.82 (0.57,1.16) | 0.82 (0.57,1.16) | 0.00% |
| tPA_acc+PAC | vs. | SK+PAC | 1 | 30647 | 0.85 (0.70,1.03) | 0.85 (0.70,1.03) | N/A |
| TNK+PAC+GP | vs. | TNK+PAC | 1 | 6095 | 1.06 (0.69,1.62) | 1.06 (0.69,1.62) | N/A |
| tPA_acc+PAC | vs. | TNK+PAC | 3 | 18072 | 1.08 (0.87,1.35) | 1.08 (0.87,1.34) | 0.00% |
| rPA+PAC+GP | vs. | rPA+PAC | 2 | 16812 | 0.92 (0.68,1.26) | 0.92 (0.67,1.26) | 0.00% |
| tPA+PAC | vs. | rPA+PAC | 1 | 308 | 0.08 (0.00,1.35) | 0.08 (0.00,1.35) | N/A |
| tPA_acc+PAC | vs. | rPA+PAC | 2 | 15383 | 0.91 (0.71,1.17) | 0.91 (0.71,1.17) | 0.00% |
| tPA+PAC | vs. | tPA | 1 | 10372 | 1.15 (0.82,1.60) | 1.15 (0.82,1.60) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC | 1 | 281 | 3.11 (0.33,29.53) | 3.11 (0.33,29.53) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC+GP | 1 | 48 | 1.17 (0.05,26.97) | 1.17 (0.05,26.97) | N/A |
| **Hemorrhagic stroke** | | | | | | | |
| SK+PAC | vs. | PAC | 1 | 1960 | 0.11 (0.01,2.01) | 0.11 (0.01,2.01) | N/A |
| tPA+PAC | vs. | PAC | 4 | 6721 | 0.22 (0.10,0.49) | 0.24 (0.11,0.52) | 0.00% |
| SK+GP | vs. | SK | N/A | 181 | N/A | N/A | N/A |

| Comparisons | | | No. studies | No. of patients | Pairwise meta-analysis risk ratio (95% CI) | | Heterogeneity I2 (variation in RR attributable to heterogeneity) |
|---|---|---|---|---|---|---|---|
| | | | | | Fixed effect | Random effect | |
| SK+PAC | vs. | SK | 2 | 10892 | 1.56 (0.77,3.17) | 1.55 (0.76,3.16) | 0.00% |
| tPA | vs. | SK | 1 | 10407 | 0.90 (0.48,1.70) | 0.90 (0.48,1.70) | N/A |
| tPA+PAC | vs. | SK | 1 | 10375 | 0.75 (0.41,1.37) | 0.75 (0.41,1.37) | N/A |
| rPA+PAC | vs. | SK+PAC | 1 | 6010 | 0.48 (0.23,0.98) | 0.48 (0.23,0.98) | N/A |
| tPA | vs. | SK+PAC | 1 | 10393 | 0.60 (0.29,1.23) | 0.60 (0.29,1.23) | N/A |
| tPA+PAC | vs. | SK+PAC | 4 | 11006 | 0.46 (0.25,0.87) | 0.47 (0.25,0.88) | 0.00% |
| tPA_acc+PAC | vs. | SK+PAC | 1 | 30647 | 0.72 (0.53,0.96) | 0.72 (0.53,0.96) | N/A |
| TNK+PAC+GP | vs. | TNK+PAC | 2 | 6578 | 0.87 (0.51,1.47) | 0.75 (0.27,2.11) | 28.30% |
| tPA_acc+PAC | vs. | TNK+PAC | 4 | 18338 | 0.99 (0.74,1.33) | 0.99 (0.74,1.33) | 0.00% |
| rPA+PAC+GP | vs. | rPA+PAC | 3 | 17111 | 0.93 (0.64,1.36) | 0.94 (0.64,1.38) | 0.00% |
| tPA+PAC | vs. | rPA+PAC | 1 | 308 | 0.11 (0.01,2.05) | 0.11 (0.01,2.05) | N/A |
| tPA_acc+PAC | vs. | rPA+PAC | 2 | 15383 | 0.97 (0.69,1.38) | 0.97 (0.69,1.38) | 0.00% |
| tPA+PAC | vs. | tPA | 3 | 11150 | 0.81 (0.46,1.42) | 0.82 (0.46,1.45) | 0.00% |
| tPA_acc+PAC | vs. | tPA+PAC | 1 | 281 | 5.18 (0.25,106.93) | 5.18 (0.25,106.93) | N/A |
| tPA_acc+PAC | vs. | tPA+PAC+GP | 3 | 564 | 1.03 (0.29,3.62) | 1.03 (0.29,3.62) | 0.00% |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; SE, Standard error; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion)

# Appendix 9 Results of network meta-analysis

Treatment options are in order of their efficacy or safety ranking. Estimates are presented as risk ratios (RR) and 95% confidence intervals. Treatments are ordered by rankings for each outcome.

Comparisons between treatments should be read from column to row for each outcome (row treatment is reference). For efficacy outcomes, such as clinical and microbiological cure. Risk ratios more than 1 favour the column-defining treatment. To obtain risks ratios for comparisons in the opposite direction, reciprocals should be taken. For safety outcomes, nephrotoxicity, and adverse events. Risk ratios lower than 1 favour the column-defining treatment. To obtain risks ratios for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold and underlined. GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eFigure 9.1 Network estimated risk ratios (95% confidence intervals) of treatment options on all-cause mortality within 30-35 days.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **tPA+PAC +GP** | | | | | | | | | | | |
| 0.72 (0.36,1.46) | **rPA+PAC +GP** | | | | | | | | | | |
| 0.72 (0.36,1.42) | 0.99 (0.84,1.16) | **tPA_acc +PAC** | | | | | | | | | |
| 0.71 (0.35,1.42) | 0.98 (0.81,1.19) | 0.99 (0.88,1.11) | **TNK+PAC** | | | | | | | | |
| 0.85 (0.20,3.64) | 1.17 (0.32,4.27) | 1.18 (0.33,4.29) | 1.20 (0.33,4.35) | **SK+GP** | | | | | | | |
| 0.69 (0.34,1.38) | 0.95 (0.84,1.08) | 0.96 (0.87,1.06) | 0.97 (0.84,1.13) | 0.81 (0.22,2.95) | **rPA+PAC** | | | | | | |
| 0.63 (0.31,1.25) | 0.87 (0.74,1.02) | **0.88 (0.81,0.95)** | 0.89 (0.77,1.02) | 0.74 (0.21,2.68) | 0.91 (0.82,1.02) | **SK+PAC** | | | | | |
| 0.62 (0.30,1.27) | 0.85 (0.65,1.13) | 0.86 (0.69,1.09) | 0.87 (0.71,1.06) | 0.73 (0.20,2.69) | 0.90 (0.70,1.15) | 0.98 (0.77,1.26) | **TNK+PAC +GP** | | | | |
| 0.58 (0.29,1.17) | **0.80 (0.65,0.98)** | **0.81 (0.70,0.94)** | **0.82 (0.68,0.98)** | 0.68 (0.19,2.47) | **0.84 (0.71,0.99)** | 0.92 (0.81,1.04) | 0.94 (0.71,1.23) | **tPA** | | | |
| 0.57 (0.28,1.14) | **0.78 (0.64,0.95)** | **0.79 (0.69,0.91)** | **0.80 (0.67,0.96)** | 0.67 (0.18,2.41) | **0.82 (0.70,0.96)** | 0.90 (0.80,1.01) | 0.92 (0.70,1.20) | 0.98 (0.87,1.10) | **tPA+PAC** | | |
| 0.55 (0.27,1.11) | **0.76 (0.62,0.93)** | **0.77 (0.67,0.89)** | **0.78 (0.65,0.94)** | 0.65 (0.18,2.34) | **0.80 (0.68,0.94)** | **0.88 (0.78,0.99)** | 0.89 (0.68,1.17) | 0.95 (0.84,1.08) | 0.98 (0.87,1.10) | **SK** | |
| **0.48 (0.24,0.98)** | **0.66 (0.53,0.84)** | **0.67 (0.56,0.81)** | **0.68 (0.55,0.84)** | 0.57 (0.16,2.06) | **0.70 (0.57,0.85)** | **0.77 (0.65,0.90)** | 0.78 (0.58,1.04) | **0.83 (0.70,0.99)** | **0.85 (0.74,0.98)** | 0.87 (0.73,1.04) | **PAC** |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).
* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

**eFigure 9.2 Network estimated risk ratios (95% confidence intervals) of treatment options on major bleeding.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PAC** | | | | | | | | | | | |
| 0.83 (0.37,1.85) | **tPA** | | | | | | | | | | |
| 0.69 (0.31,1.52) | 0.83 (0.50,1.37) | **SK** | | | | | | | | | |
| 0.55 (0.28,1.09) | 0.67 (0.43,1.02) | 0.81 (0.53,1.23) | **tPA+PAC** | | | | | | | | |
| **0.44 (0.20,1.00)** | **0.53 (0.29,0.98)** | 0.64 (0.36,1.14) | 0.80 (0.50,1.27) | **TNK+PAC** | | | | | | | |
| **0.40 (0.19,0.85)** | **0.48 (0.30,0.78)** | **0.58 (0.37,0.92)** | 0.72 (0.51,1.01) | 0.90 (0.64,1.29) | **rPA+PAC** | | | | | | |
| **0.38 (0.18,0.79)** | **0.46 (0.30,0.70)** | **0.55 (0.37,0.83)** | **0.68 (0.52,0.91)** | 0.86 (0.58,1.27) | 0.95 (0.76,1.18) | **SK+PAC** | | | | | |
| **0.35 (0.16,0.75)** | **0.42 (0.25,0.70)** | **0.51 (0.31,0.83)** | **0.63 (0.44,0.92)** | **0.79 (0.63,1.00)** | 0.88 (0.69,1.12) | 0.92 (0.70,1.21) | **tPA_acc +PAC** | | | | |
| **0.27 (0.10,0.77)** | **0.33 (0.14,0.78)** | **0.40 (0.17,0.93)** | 0.50 (0.23,1.09) | 0.62 (0.30,1.28) | 0.69 (0.33,1.43) | 0.72 (0.35,1.52) | 0.79 (0.39,1.56) | **tPA+PAC +GP** | | | |
| **0.24 (0.10,0.54)** | **0.29 (0.16,0.52)** | **0.35 (0.20,0.61)** | **0.43 (0.27,0.69)** | **0.54 (0.39,0.73)** | **0.60 (0.41,0.87)** | **0.63 (0.42,0.94)** | **0.68 (0.51,0.91)** | 0.86 (0.41,1.83) | **TNK+PAC +GP** | | |
| **0.19 (0.08,0.43)** | **0.22 (0.12,0.40)** | **0.27 (0.15,0.48)** | **0.34 (0.21,0.54)** | **0.42 (0.26,0.69)** | **0.47 (0.33,0.65)** | **0.49 (0.33,0.73)** | **0.53 (0.35,0.81)** | 0.68 (0.30,1.52) | 0.78 (0.47,1.31) | **rPA+PAC +GP** | |
| **0.04 (0.00,0.73)** | **0.05 (0.00,0.82)** | **0.06 (0.00,0.95)** | 0.07 (0.00,1.21) | 0.09 (0.01,1.56) | 0.10 (0.01,1.69) | 0.10 (0.01,1.77) | 0.11 (0.01,1.94) | 0.14 (0.01,2.69) | 0.17 (0.01,2.90) | 0.21 (0.01,3.71) | **SK+GP** |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

**eFigure 9.3 Network estimated risk ratios (95% confidence intervals) of treatment options on recurrent infarction.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **rPA+PAC +GP** | | | | | | | | | | | |
| 0.93 (0.60,1.43) | **TNK+PAC +GP** | | | | | | | | | | |
| 0.79 (0.56,1.11) | 0.85 (0.54,1.34) | **tPA+PAC** | | | | | | | | | |
| 0.71 (0.48,1.05) | 0.77 (0.47,1.25) | 0.90 (0.69,1.18) | **PAC** | | | | | | | | |
| **0.69 (0.49,0.99)** | 0.75 (0.47,1.18) | 0.88 (0.70,1.09) | 0.97 (0.69,1.37) | **tPA** | | | | | | | |
| **0.66 (0.54,0.80)** | 0.71 (0.48,1.05) | 0.84 (0.63,1.11) | 0.93 (0.66,1.31) | 0.95 (0.71,1.28) | **rPA+PAC** | | | | | | |
| **0.65 (0.50,0.85)** | 0.70 (0.47,1.05) | 0.83 (0.67,1.01) | 0.92 (0.67,1.25) | 0.94 (0.75,1.18) | 0.99 (0.82,1.19) | **SK+PAC** | | | | | |
| **0.63 (0.43,0.91)** | 0.67 (0.42,1.09) | **0.79 (0.62,1.00)** | 0.88 (0.61,1.27) | 0.90 (0.71,1.15) | 0.94 (0.68,1.31) | 0.96 (0.75,1.21) | **SK** | | | | |
| **0.63 (0.49,0.80)** | **0.68 (0.47,0.97)** | 0.79 (0.61,1.02) | 0.88 (0.63,1.22) | 0.90 (0.69,1.19) | 0.95 (0.82,1.10) | 0.96 (0.83,1.11) | 1.00 (0.74,1.36) | **tPA_acc +PAC** | | | |
| 0.45 (0.12,1.73) | 0.48 (0.12,1.93) | 0.57 (0.15,2.12) | 0.63 (0.16,2.43) | 0.65 (0.17,2.42) | 0.68 (0.18,2.58) | 0.69 (0.18,2.56) | 0.72 (0.20,2.62) | 0.72 (0.19,2.71) | **SK+GP** | | |
| **0.59 (0.44,0.79)** | **0.63 (0.46,0.87)** | 0.74 (0.54,1.02) | 0.82 (0.57,1.19) | 0.85 (0.61,1.17) | 0.89 (0.71,1.10) | 0.90 (0.71,1.13) | 0.94 (0.66,1.34) | 0.94 (0.80,1.10) | 1.31 (0.34,4.99) | **TNK+PAC** | |
| **0.37 (0.15,0.87)** | **0.40 (0.16,0.98)** | 0.46 (0.19,1.11) | 0.52 (0.21,1.26) | 0.53 (0.22,1.27) | 0.55 (0.24,1.29) | 0.56 (0.24,1.31) | 0.59 (0.24,1.42) | 0.59 (0.25,1.35) | 0.82 (0.17,3.91) | 0.62 (0.27,1.46) | **tPA+PAC +GP** |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).
* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

**eFigure 9.4 Network estimated risk ratios (95% confidence intervals) of treatment options on all-type stroke.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PAC** | | | | | | | | | | | |
| 0.72 (0.42,1.24) | **SK** | | | | | | | | | | |
| 0.66 (0.39,1.11) | 0.91 (0.62,1.35) | **SK+PAC** | | | | | | | | | |
| 0.60 (0.34,1.08) | 0.84 (0.53,1.34) | 0.92 (0.70,1.20) | **rPA+PAC** | | | | | | | | |
| 0.48 (0.02,11.58) | 0.66 (0.03,15.79) | 0.73 (0.03,16.88) | 0.79 (0.03,18.44) | **tPA+PAC +GP** | | | | | | | |
| 0.55 (0.29,1.08) | 0.77 (0.44,1.35) | 0.84 (0.56,1.27) | 0.92 (0.67,1.26) | 1.16 (0.05,27.51) | **rPA+PAC +GP** | | | | | | |
| **0.56 (0.32,0.97)** | 0.77 (0.50,1.19) | 0.85 (0.71,1.02) | 0.92 (0.74,1.16) | 1.17 (0.05,26.97) | 1.00 (0.68,1.48) | **tPA_acc +PAC** | | | | | |
| 0.55 (0.26,1.14) | 0.76 (0.40,1.45) | 0.83 (0.50,1.39) | 0.90 (0.53,1.54) | 1.14 (0.05,27.42) | 0.98 (0.53,1.83) | 0.98 (0.60,1.59) | **TNK+PAC +GP** | | | | |
| **0.52 (0.29,0.94)** | 0.72 (0.44,1.16) | 0.79 (0.59,1.05) | 0.86 (0.63,1.17) | 1.08 (0.05,25.24) | 0.93 (0.60,1.45) | 0.93 (0.75,1.16) | 0.95 (0.62,1.46) | **TNK+PAC** | | | |
| **0.50 (0.34,0.73)** | **0.69 (0.47,1.00)** | 0.75 (0.53,1.07) | 0.82 (0.53,1.27) | 1.04 (0.04,24.61) | 0.89 (0.52,1.53) | 0.89 (0.60,1.31) | 0.91 (0.49,1.69) | 0.96 (0.61,1.50) | **tPA+PAC** | | |
| 0.27 (0.01,5.90) | 0.38 (0.02,7.81) | 0.42 (0.02,8.77) | 0.45 (0.02,9.65) | 0.57 (0.01,45.76) | 0.49 (0.02,10.67) | 0.49 (0.02,10.40) | 0.50 (0.02,11.02) | 0.53 (0.02,11.28) | 0.55 (0.03,11.59) | **SK+GP** | |
| **0.45 (0.27,0.74)** | **0.62 (0.43,0.90)** | **0.68 (0.48,0.96)** | 0.74 (0.48,1.14) | 0.93 (0.04,22.12) | 0.80 (0.47,1.37) | 0.80 (0.54,1.18) | 0.82 (0.44,1.52) | 0.86 (0.55,1.35) | 0.90 (0.65,1.25) | 1.63 (0.08,34.14) | **tPA** |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).
* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

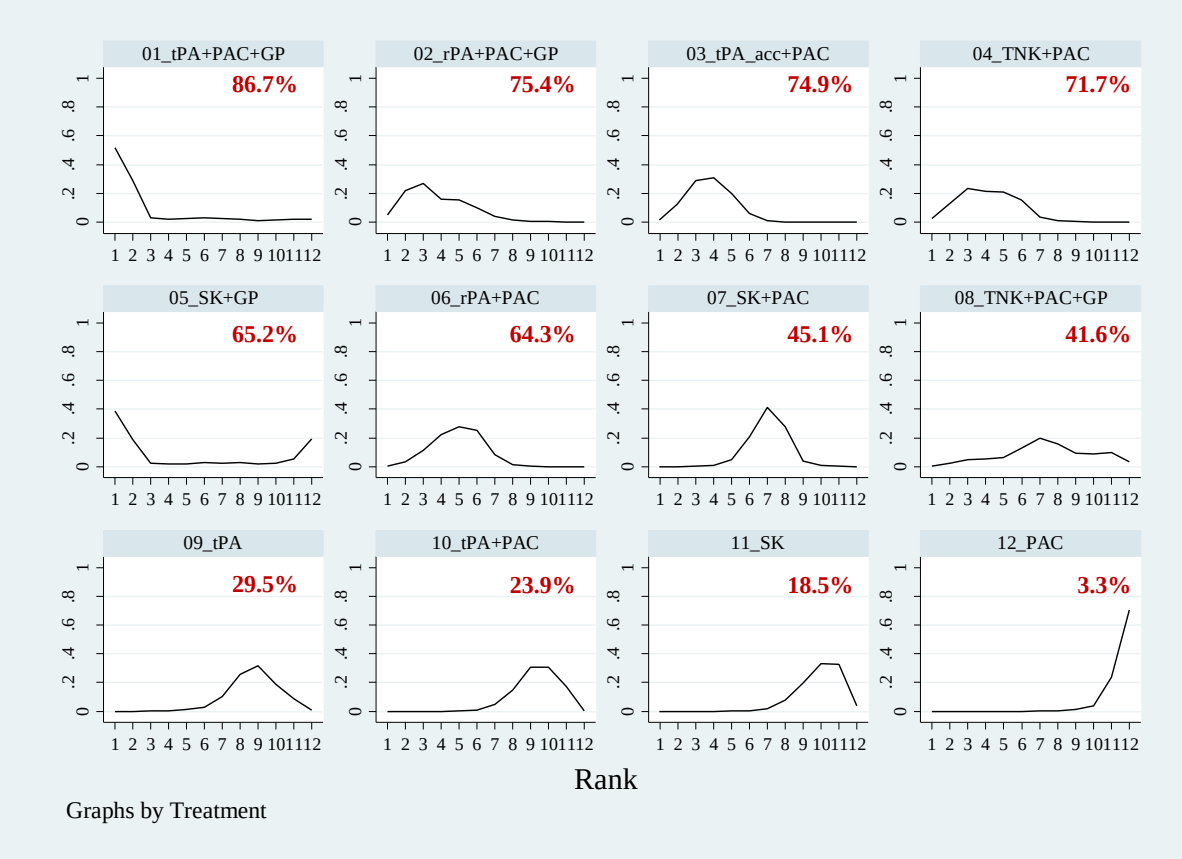
**eFigure 9.5 Network estimated risk ratios (95% confidence intervals) of treatment options on hemorrhagic stroke.**

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **PAC** | | | | | | | | | | | |
| 0.51 (0.20,1.27) | **SK+PAC** | | | | | | | | | | |
| 0.57 (0.01,31.75) | 1.13 (0.02,59.40) | **SK+GP** | | | | | | | | | |
| **0.35 (0.13,0.96)** | 0.70 (0.47,1.05) | 0.62 (0.01,33.42) | **TNK+PAC** | | | | | | | | |
| **0.35 (0.13,0.91)** | **0.69 (0.53,0.91)** | 0.62 (0.01,32.78) | 0.99 (0.74,1.33) | **tPA_acc+PAC** | | | | | | | |
| **0.34 (0.13,0.91)** | **0.67 (0.46,0.99)** | 0.60 (0.01,32.08) | 0.96 (0.63,1.48) | 0.97 (0.71,1.33) | **rPA+PAC** | | | | | | |
| 0.34 (0.07,1.65) | 0.67 (0.19,2.44) | 0.60 (0.01,38.68) | 0.96 (0.26,3.50) | 0.97 (0.28,3.42) | 1.00 (0.27,3.66) | **tPA+PAC+GP** | | | | | |
| **0.32 (0.11,0.93)** | 0.63 (0.37,1.09) | 0.56 (0.01,30.78) | 0.91 (0.51,1.61) | 0.91 (0.56,1.50) | 0.94 (0.64,1.38) | 0.94 (0.24,3.64) | **rPA+PAC+GP** | | | | |
| **0.31 (0.10,0.98)** | 0.62 (0.32,1.21) | 0.55 (0.01,30.77) | 0.89 (0.52,1.52) | 0.90 (0.49,1.65) | 0.92 (0.46,1.83) | 0.92 (0.23,3.73) | 0.98 (0.45,2.15) | **TNK+PAC+GP** | | | |
| **0.30 (0.12,0.77)** | 0.59 (0.30,1.16) | 0.53 (0.01,26.15) | 0.84 (0.39,1.84) | 0.85 (0.41,1.76) | 0.88 (0.41,1.89) | 0.88 (0.21,3.75) | 0.93 (0.40,2.20) | 0.95 (0.37,2.45) | **SK** | | |
| **0.27 (0.11,0.69)** | 0.54 (0.28,1.05) | 0.48 (0.01,25.15) | 0.77 (0.36,1.67) | 0.78 (0.38,1.59) | 0.80 (0.38,1.71) | 0.80 (0.19,3.41) | 0.85 (0.37,1.99) | 0.87 (0.34,2.22) | 0.92 (0.49,1.71) | **tPA** | |
| **0.21 (0.10,0.46)** | **0.42 (0.24,0.76)** | 0.38 (0.01,19.63) | 0.61 (0.30,1.23) | 0.61 (0.32,1.16) | 0.63 (0.32,1.25) | 0.63 (0.15,2.59) | 0.67 (0.30,1.47) | 0.68 (0.28,1.65) | 0.72 (0.40,1.30) | 0.78 (0.45,1.38) | **tPA+PAC** |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).
* Treatments are ordered by SUCRA rank. Comparisons between treatments should be read from column to row for each outcome (row treatment is reference).

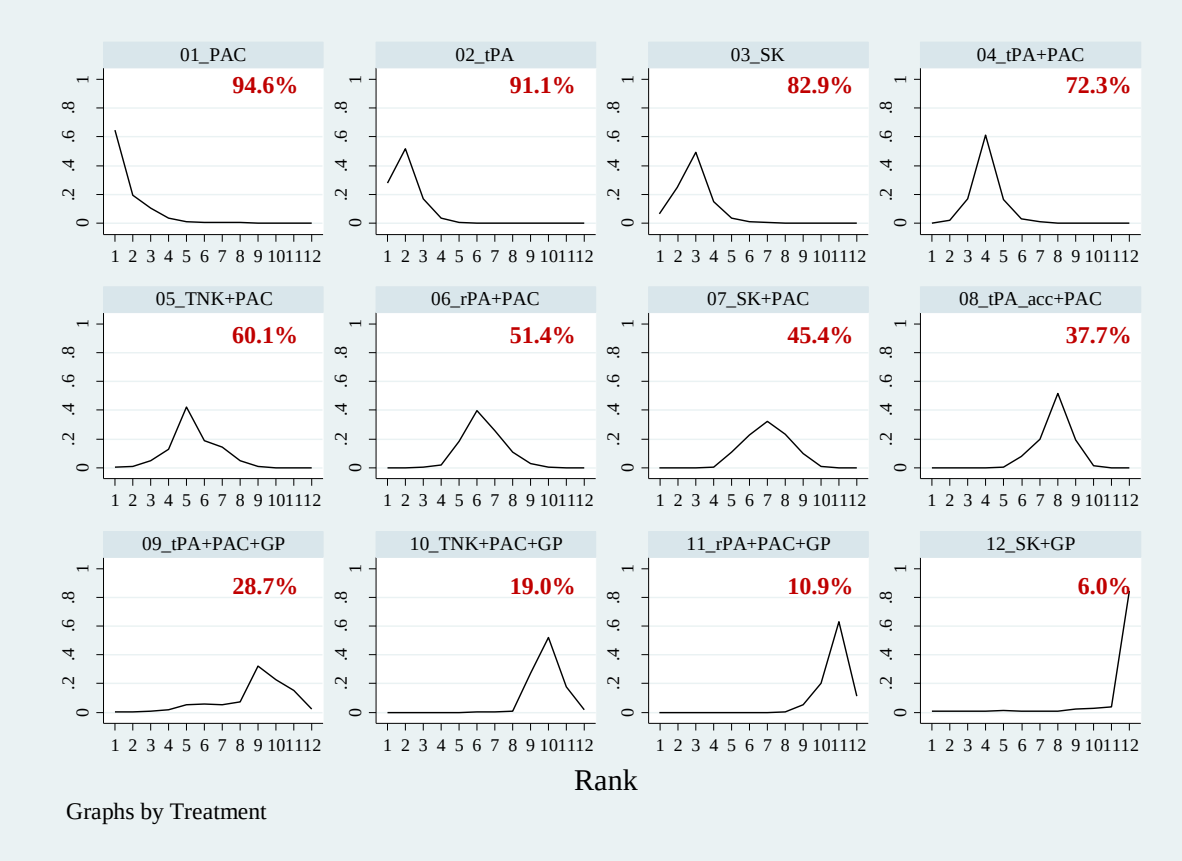
## Appendix 10 Treatment ranking and surface under the cumulative ranking curves (SUCRA) for each outcome

**eFigure 10.1 SUCRA ranking curve for all-cause mortality within 30-35 days.**



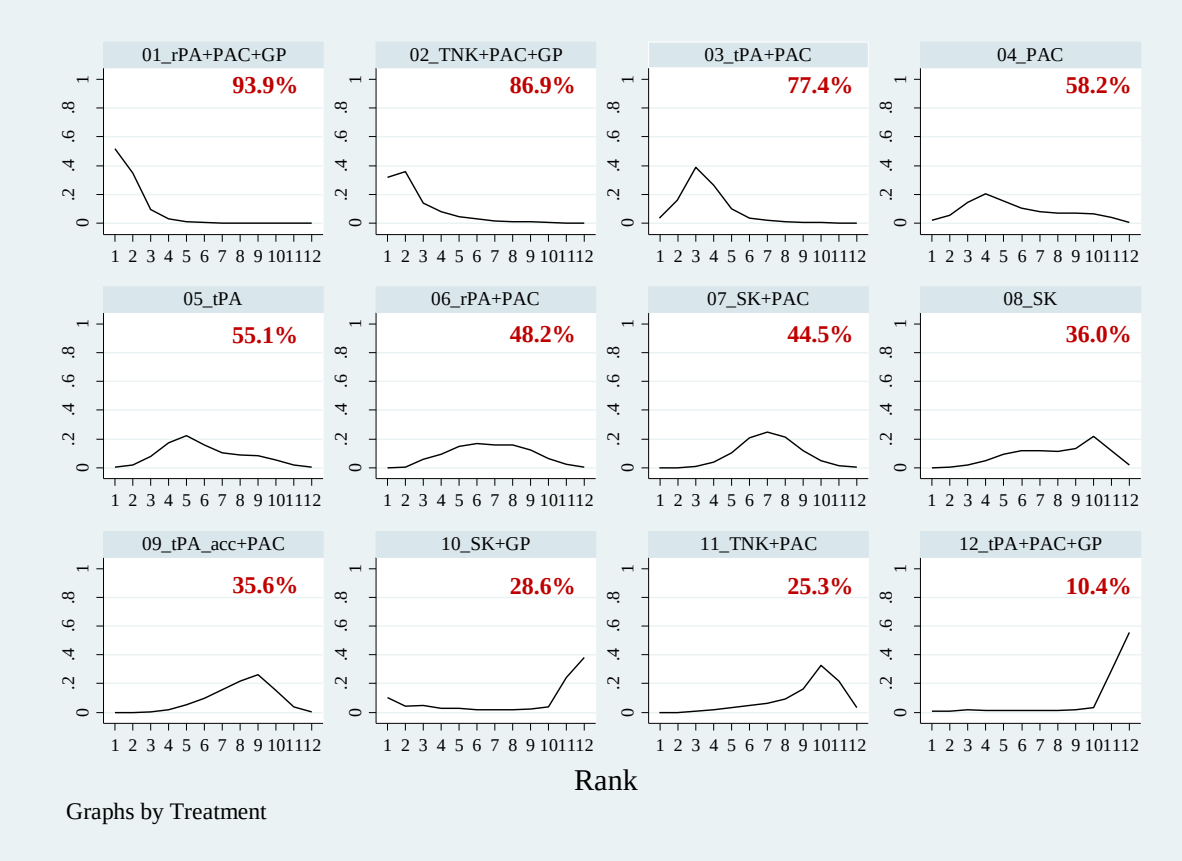

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eFigure 10.2 SUCRA ranking curve for major bleeding.**



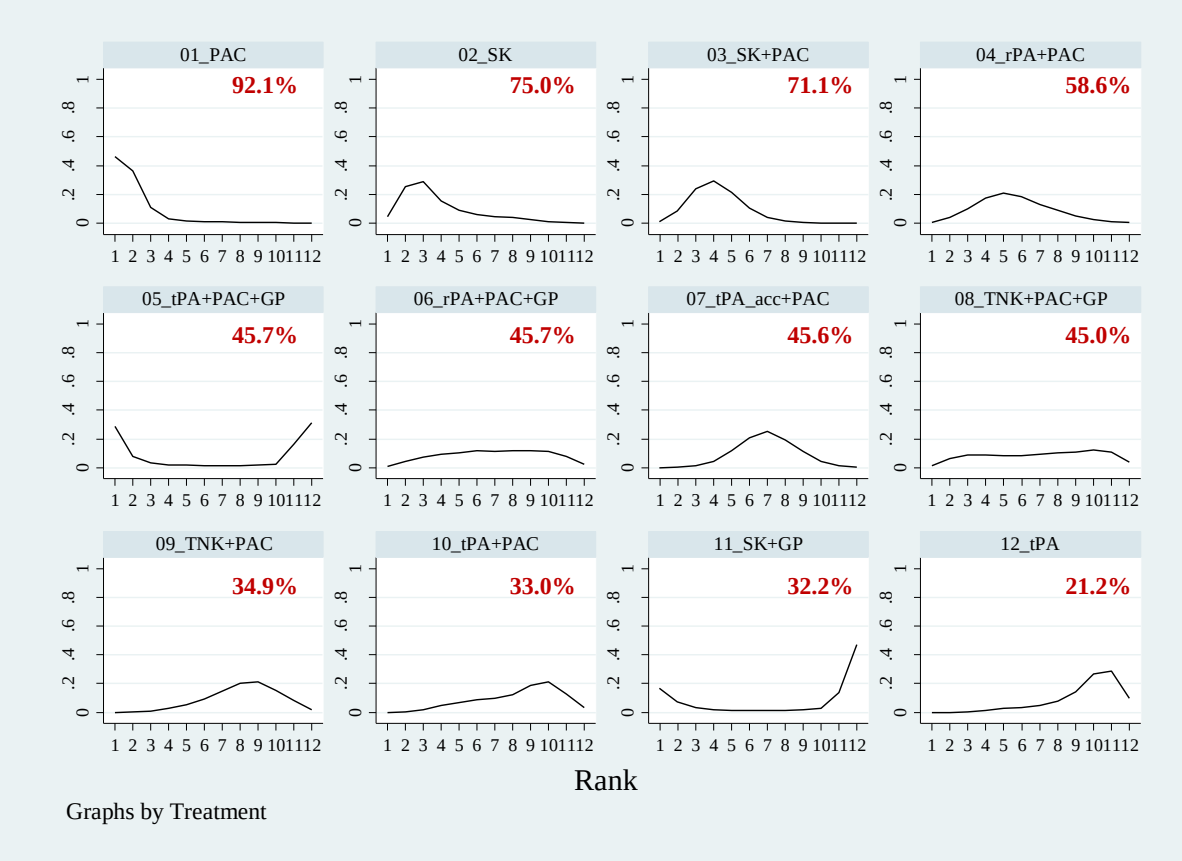

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eFigure 10.3 SUCRA ranking curve for recurrent infarction.**



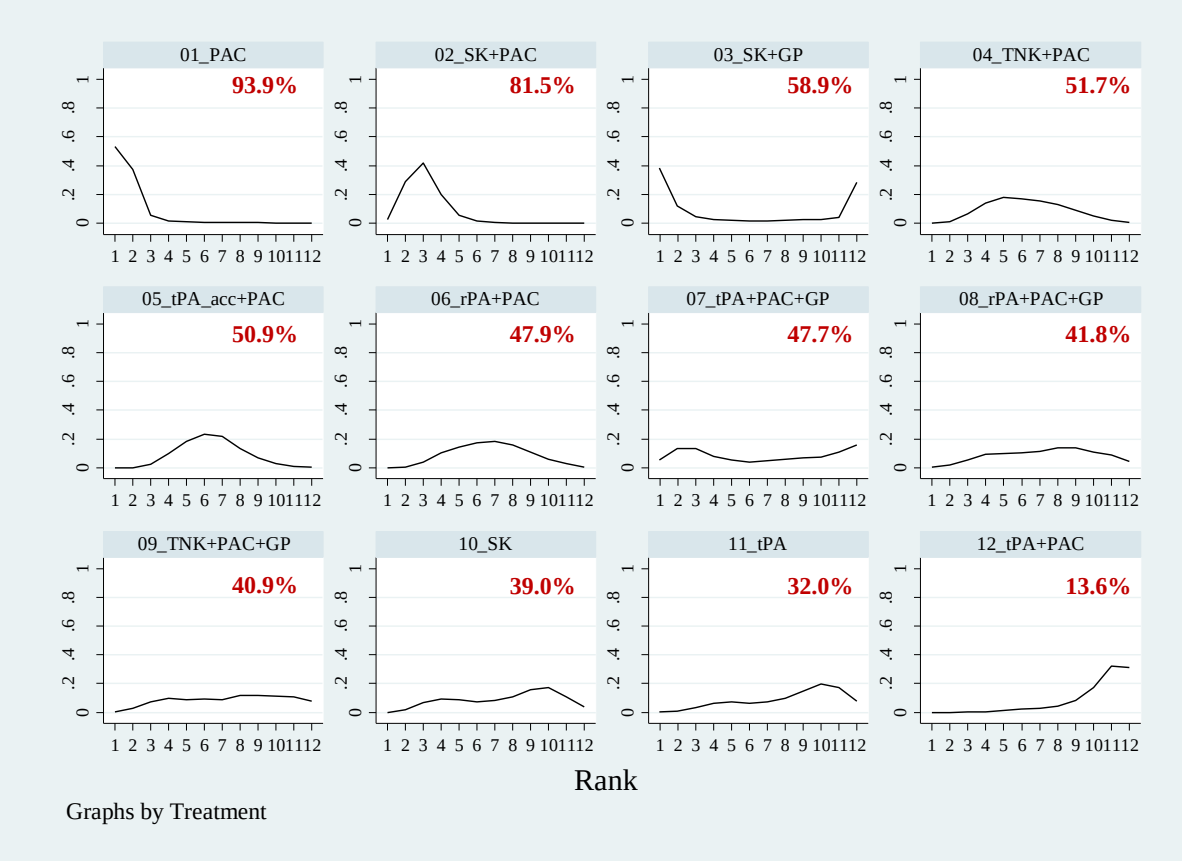

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eFigure 10.4 SUCRA ranking curve for all-type stroke.**



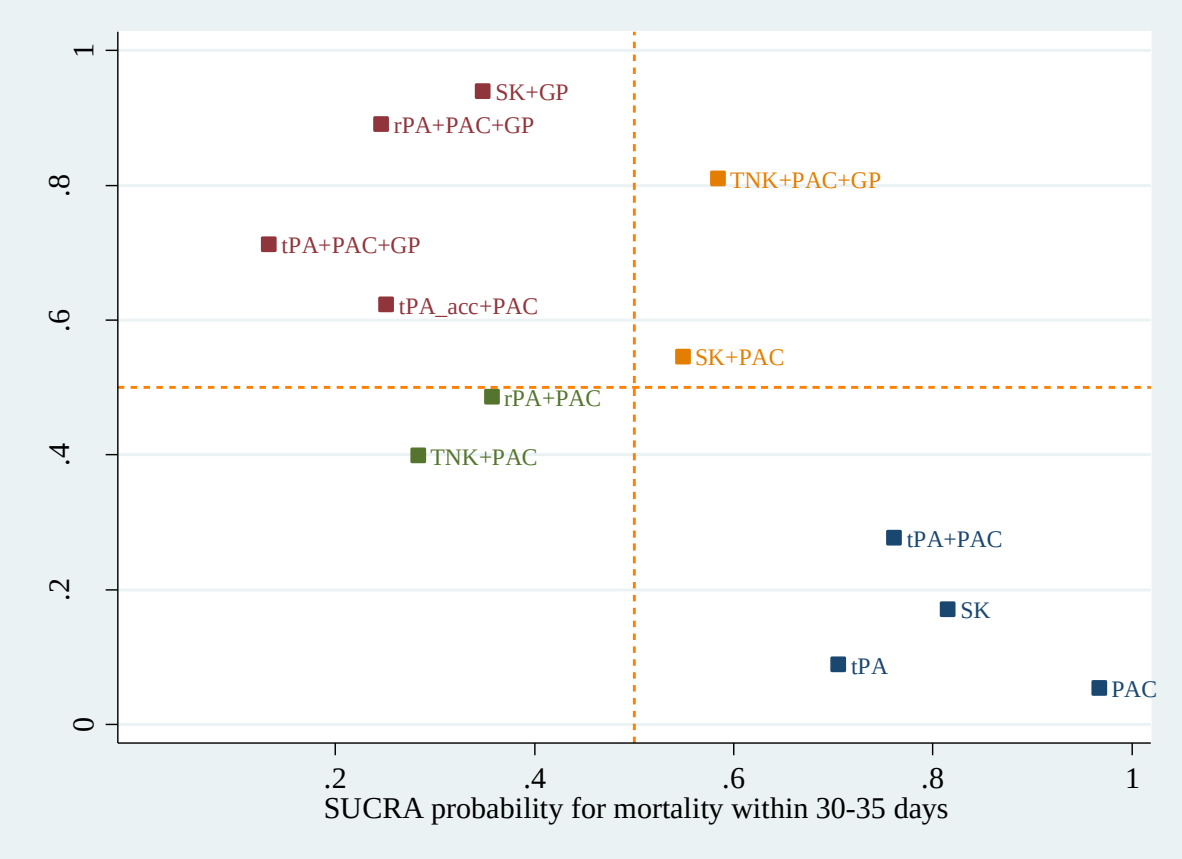

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eFigure 10.5 SUCRA ranking curve for hemorrhagic stroke.**




**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion)

**eFigure 10.6 Cluster rank plot of SUCRA probability for all-cause mortality within 30-35 days and major bleeding.**




**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

# Appendix 11 Net clinical benefit analysis

*Description of Net Clinical Benefit Analysis*

Net clinical benefit (NCB) analysis was performed to determine the value of using fibrinolytic therapy when balancing with its major side effect (bleeding). To provide more consistency, only the studies reporting for both number of mortality and major bleeding events were included into the analysis. Finally, 33 studies[11-13,18,19,21,29,33-37,42,43,54,58,60,62,66-71,75,78-81] (124,097 patients) were included in the analysis, which comprises 12 regimens. NCB can be calculated following the approach used in a previous meta-analysis[87] as stated below;

$$NCB = \Delta E_{R \rightarrow F} - wt \cdot (\Delta S_{F \rightarrow R})$$

Where $E_R$ = pooled risk estimates of all-cause mortality within 30-35 days for the reference, accelerated infusion alteplase with parenteral anticoagulants (tPA_acc+PAC)

$S_R$ = pooled risk estimates of major bleeding for the reference, tPA_acc+PAC

$E_R$ and $S_R$ were calculated by using meta-analyses of proportions in Stata with *metaprop* command from 13 of 33 included studies. The results of pooled risk estimates of tPA_acc+PAC for mortality ($E_R$) and major bleeding ($S_R$) were 0.060 (95%CI 0.051, 0.068) and 0.047 (95%CI 0.030, 0.064), respectively.

$E_F$ = pooled risk estimates of all-cause mortality within 30-35 days for each fibrinolytic agent as compared with PAC, getting from the results of network meta-analysis (eFigure 9.1)

$S_F$ = pooled risk estimates of major bleeding for each fibrinolytic agent as compared with PAC, getting from the results of network meta-analysis (eFigure 9.2)

$\Delta E_{R \rightarrow F}$ = $E_R$ - $E_F$ (difference in pooled risk estimates of all-cause mortality within 30-35 days between reference, $E_R$, and fibrinolytic agent, $E_F$).

$\Delta S_{F \rightarrow R}$ = $S_F$ - $S_R$ (difference in pooled risk estimates of major bleeding between, $S_F$, fibrinolytic agent and reference, $E_R$).

wt = weighting factor to indicate the relative effect of bleeding to death.[87] Based on the previous publications demonstrating the likelihood of death from major bleeding, about 16.1% of patient with major bleeding died within 30 days.[88] Hence, 0.15 seems to be a conservative estimation. For more information, please follow the section *"Description of derivation of weight factor"* as stated below.

Example of calculation

%NCB for tPA+PAC+GP = [0.060 - (0.715 x 0.060)] - 0.15 x [(1.275 x 0.047) - 0.047)] x 100
= (0.017 - 0.002) x 100
= 1.516

For interpretation, the more positive number of NCB indicates the more benefit gain for fibrinolytic regimen compared with the reference (tPA_acc+PAC).

*Description of derivation of weighting factor*

According to the NCB calculation method from Chatterjee et al[87], the weighting factor was derived from the previous publication[89], which is basically based on the likelihood of death and serious disability due to ICH.

- Quote "At hospital discharge, 76% of patients with intracranial hemorrhage had severe disability or died."

Similarly, weighting factor to indicate the relative effect of bleed to death associated with fibrinolytic therapy can be derived by two method as stated below;

- Method 1: Systematic review by pooling the number of patients who had experience with major bleeding and death from 33 studies that were included in NCB analysis.
    - After an attempt for additional extraction, none of the publication was reported on the number of death among the patients who had experienced with major bleeding.
- Method 2: Using previous publication
    - Mehta et al[92] reported the number of STEMI patients treated with fibrinolytic who had experienced with major bleeding, 14.8% of men and 17.1% of women (total 15.7%) died within 30 days.
        - This analysis used the data from 6 large RCTs (GUSTO-I[36] and GUSTO-III[37], ASSENT-2[13] and ASSENT-3[14], HERO-2[41], and GUSTO-IIb[12,13,35,36,40,90])

Based on the above evidence, the number of 0.15 seems to be a conservative estimation. The result of NCB is presented in eTable 11.1.

*Description of sensitivity analysis of NCB varying by weighting factor*

To assess the robustness, NCB were calculated with a different number of weighting factor from 0.15-0.6. This was based from the previous data to estimate for weighting factor as stated below.

- Amlani et al[93] reported the mortality after major bleeding was 20% in patients with STEMI who were treated with thrombolysis.
    - Major bleeding was defined as a hemoglobin drop ≥5 g/dl, intracranial hemorrhage, bleeding requiring surgery or blood transfusion of at least 2 units.
    - Data of the study were from the prospective registry conducted at the Hamilton General Hospital, Hamilton Health Sciences (HHS) and McMaster University, between May 1, 2003 and July 10, 2007.
- Another review article by Fitchett[91] stated that as the data from ASSENT-2[12], "the incidence of intracranial hemorrhage associated with thrombolysis was 0.64% to 0.94%, with an associated mortality of approximately 60%."

Therefore, the weighting factor ranged from ~0.15-0.6 were chosen to performed sensitivity analysis of NCB as presented in eFigure 11.1. The increase in weighting factor indicates the more severe type of bleeding event.

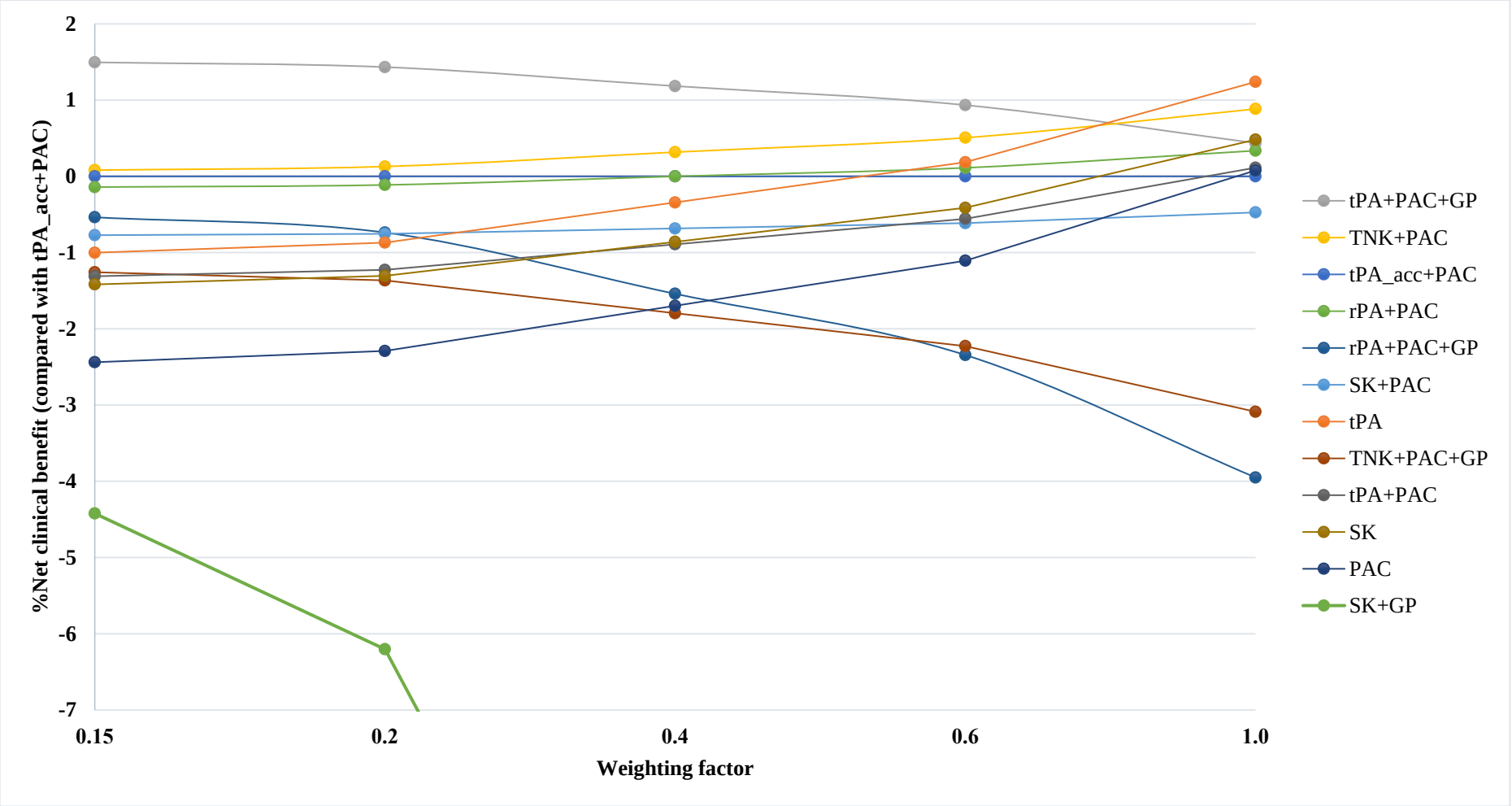
**eTable 11.1 Pooled risk estimates and net clinical benefit of treatment options compared with tPA_acc+PAC.**

| Treatment | No. of patients | No. studies | Pooled risk estimates (%) | | Net clinical benefit (%) |
|---|---|---|---|---|---|
| | | | Mortality | Major bleeding | |
| tPA+PAC+GP | 433 | 4 | 4.229 (2.130,8.397) | 5.800 (2.918,11.530) | 1.496 (-3.531,4.027) |
| TNK+PAC | 13,687 | 7 | 5.972 (5.328,6.693) | 3.610 (2.850,4.572) | 0.082 (-0.784,0.839) |
| rPA+PAC | 21,936 | 7 | 6.137 (5.552,6.783) | 3.992 (3.124,5.102) | -0.141 (-0.953,0.574) |
| rPA+PAC+GP | 8,640 | 3 | 5.846 (4.993,6.845) | 8.570 (5.631,13.041) | -0.537 (-2.206,0.757) |
| SK+PAC | 29,126 | 8 | 6.737 (6.213,7.305) | 4.203 (3.193,5.531) | -0.772 (-1.539,-0.097) |
| tPA | 5,272 | 2 | 7.309 (6.309,8.467) | 1.917 (1.148,3.204) | -1.001 (-2.353,0.114) |
| TNK+PAC+GP | 2377 | 3 | 6.846 (5.440,8.616) | 6.708 (4.991,9.014) | -1.257 (-3.373,0.406) |
| tPA+PAC | 8,847 | 10 | 7.474 (6.510,8.582) | 2.878 (1.983,4.176) | -1.311 (-2.613,-0.212) |
| SK | 5,510 | 3 | 7.665 (6.632,8.859) | 2.319 (1.425,3.776) | -1.418 (-2.830,-0.250) |
| PAC | 2,946 | 2 | 8.795 (7.329,10.554) | 1.594 (0.740,3.435) | -2.439 (-4.474,-0.844) |
| SK+GP | 119 | 1 | 4.992 (1.379,18.073) | 40.170 (2.346,687.841) | -4.422 (-114.654,4.864) |
| **tPA_acc+PAC (ref) †** | **24,930** | **12** | 5.912 (5.042,6.781) | 4.554 (2.775,6.334) | - |

† Pooled risk estimate of the treatment with tPA_acc+PAC (reference) was calculated by using meta-analyses of proportions.

**Abbreviations:** %NCB, Percentage of net clinical benefit; GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; ref, Reference; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion); wt, Weighting factor.

**eFigure 11.1 Sensitivity analyses of net clinical benefit by varying weighting factors from 0.15 to 0.6.**




* Plot of treatment with SK+GP for weighting factor 0.4-1.0 is omitted due to out of range.

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

# Appendix 12 Evaluation of the quality of evidence using GRADE framework for primary outcomes

**eTable 12.1 Estimates of effects and quality ratings for comparison of treatment options in all of the outcomes.**

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| **Mortality within 30-35 days** | | | | | | |
| SK vs. PAC | | | 0.87 (0.73,1.04) | ⊕⊕⊕◯‖ MODERATE | 0.87 (0.73,1.04) | ⊕⊕⊕◯ MODERATE |
| SK+GP vs. PAC | | | 0.57 (0.16,2.06) | ⊕◯◯◯†† VERY LOW | 0.57 (0.16,2.06) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. PAC | 0.73 (0.50,1.07) | ⊕⊕⊕◯* MODERATE | 0.87 (0.53,1.42) | ⊕⊕◯◯‖ LOW | 0.77 (0.65,0.90) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC vs. PAC | | | 0.68 (0.55,0.84) | ⊕◯◯◯†† VERY LOW | 0.68 (0.55,0.84) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. PAC | | | 0.78 (0.58,1.04) | ⊕◯◯◯†† VERY LOW | 0.78 (0.58,1.04) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. PAC | | | 0.70 (0.57,0.85) | ⊕⊕◯◯‖ LOW | 0.70 (0.57,0.85) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. PAC | | | 0.66 (0.53,0.84) | ⊕◯◯◯†† VERY LOW | 0.66 (0.53,0.84) | ⊕◯◯◯ VERY LOW |
| tPA vs. PAC | | | 0.83 (0.70,0.99) | ⊕⊕⊕◯‖ MODERATE | 0.83 (0.70,0.99) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. PAC | 0.84 (0.64,1.11) | ⊕⊕◯◯*,§ LOW | 0.70 (0.36,1.37) | ⊕⊕⊕◯¶ MODERATE | 0.85 (0.74,0.98) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. PAC | | | 0.48 (0.24,0.98) | ⊕◯◯◯†† VERY LOW | 0.48 (0.24,0.98) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. PAC | | | 0.67 (0.56,0.81) | ⊕⊕⊕◯¶ MODERATE | 0.67 (0.56,0.81) | ⊕⊕⊕◯ MODERATE |
| SK+GP vs. SK | 0.65 (0.18,2.34) | ⊕◯◯◯*,‡ VERY LOW | Not estimable | Not estimable | 0.65 (0.18,2.34) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. SK | 0.86 (0.76,0.97) | ⊕⊕⊕⊕ HIGH | 1.41 (0.80,2.48) | ⊕⊕⊕◯¶ MODERATE | 0.88 (0.78,0.99) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC vs. SK | | | 0.78 (0.65,0.94) | ⊕◯◯◯†† VERY LOW | 0.78 (0.65,0.94) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK | | | 0.89 (0.68,1.17) | ⊕◯◯◯†† VERY LOW | 0.89 (0.68,1.17) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK | | | 0.80 (0.68,0.94) | ⊕⊕⊕◯‖ MODERATE | 0.80 (0.68,0.94) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. SK | | | 0.76 (0.62,0.93) | ⊕◯◯◯†† VERY LOW | 0.76 (0.62,0.93) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK | 0.95 (0.84,1.07) | ⊕⊕⊕⊕ HIGH | 1.48 (0.58,3.78) | ⊕⊕⊕⊕ HIGH | 0.95 (0.84,1.08) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC vs. SK | 1.00 (0.89,1.13) | ⊕⊕⊕⊕ HIGH | 0.65 (0.40,1.05) | ⊕⊕⊕⊕ HIGH | 0.98 (0.87,1.10) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC+GP vs. SK | | | 0.55 (0.27,1.11) | ⊕◯◯◯†† VERY LOW | 0.55 (0.27,1.11) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK | | | 0.77 (0.67,0.89) | ⊕⊕⊕◯‖ MODERATE | 0.77 (0.67,0.89) | ⊕⊕⊕◯ MODERATE |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| SK+PAC vs. SK+GP | | | 1.35 (0.37,4.87) | ⊕⊕◯◯‖ LOW | 1.35 (0.37,4.87) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. SK+GP | | | 1.20 (0.33,4.35) | ⊕◯◯◯†† VERY LOW | 1.20 (0.33,4.35) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK+GP | | | 1.37 (0.37,5.07) | ⊕◯◯◯†† VERY LOW | 1.37 (0.37,5.07) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+GP | | | 1.23 (0.34,4.46) | ⊕◯◯◯†† VERY LOW | 1.23 (0.34,4.46) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK+GP | | | 1.17 (0.32,4.27) | ⊕◯◯◯†† VERY LOW | 1.17 (0.32,4.27) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK+GP | | | 1.46 (0.41,5.29) | ⊕⊕◯◯‖ LOW | 1.46 (0.41,5.29) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. SK+GP | | | 1.50 (0.41,5.41) | ⊕⊕◯◯‖ LOW | 1.50 (0.41,5.41) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK+GP | | | 0.85 (0.20,3.64) | ⊕◯◯◯†† VERY LOW | 0.85 (0.20,3.64) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK+GP | | | 1.18 (0.33,4.29) | ⊕◯◯◯†† VERY LOW | 1.18 (0.33,4.29) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+PAC | | | 0.89 (0.77,1.02) | ⊕⊕⊕◯¶ MODERATE | 0.89 (0.77,1.02) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC+GP vs. SK+PAC | | | 1.02 (0.80,1.30) | ⊕◯◯◯†† VERY LOW | 1.02 (0.80,1.30) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+PAC | 0.95 (0.72,1.25) | ⊕⊕⊕⊕ HIGH | 0.85 (0.60,1.22) | ⊕⊕⊕◯‖ MODERATE | 0.91 (0.82,1.02) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC+GP vs. SK+PAC | | | 0.87 (0.74,1.02) | ⊕⊕⊕⊕ HIGH | 0.87 (0.74,1.02) | ⊕⊕⊕⊕ HIGH |
| tPA vs. SK+PAC | 1.11 (0.97,1.26) | ⊕⊕⊕⊕ HIGH | 0.83 (0.51,1.34) | ⊕⊕⊕⊕ HIGH | 1.08 (0.96,1.23) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC vs. SK+PAC | 1.13 (1.00,1.27) | ⊕⊕⊕◯* MODERATE | 1.01 (0.76,1.36) | ⊕⊕⊕◯‖ MODERATE | 1.11 (0.99,1.24) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. SK+PAC | | | 0.63 (0.31,1.25) | ⊕⊕◯◯‖ LOW | 0.63 (0.31,1.25) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. SK+PAC | 0.86 (0.68,1.09) | ⊕⊕⊕⊕ HIGH | 1.02 (0.69,1.50) | ⊕⊕⊕◯‖ MODERATE | 0.88 (0.81,0.95) | ⊕⊕⊕⊕ HIGH |
| TNK+PAC+GP vs. TNK+PAC | 1.15 (0.94,1.40) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 1.15 (0.94,1.40) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC vs. TNK+PAC | | | 1.03 (0.88,1.20) | ⊕⊕◯◯‖ LOW | 1.03 (0.88,1.20) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. TNK+PAC | | | 0.98 (0.81,1.19) | ⊕◯◯◯†† VERY LOW | 0.98 (0.81,1.19) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC | | | 1.22 (1.02,1.47) | ⊕◯◯◯†† VERY LOW | 1.22 (1.02,1.47) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC | | | 1.25 (1.05,1.50) | ⊕⊕◯◯‖ LOW | 1.25 (1.05,1.50) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. TNK+PAC | | | 0.71 (0.35,1.42) | ⊕⊕◯◯‖ LOW | 0.71 (0.35,1.42) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. TNK+PAC | 0.99 (0.88,1.11) | ⊕⊕⊕◯* MODERATE | Not estimable | Not estimable | 0.99 (0.88,1.11) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC vs. TNK+PAC+GP | | | 0.90 (0.70,1.15) | ⊕◯◯◯†† VERY LOW | 0.90 (0.70,1.15) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| rPA+PAC+GP vs. TNK+PAC+GP | | | 0.85 (0.65,1.13) | ⊕◯◯◯[††] VERY LOW | 0.85 (0.65,1.13) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC+GP | | | 1.07 (0.81,1.40) | ⊕◯◯◯[††] VERY LOW | 1.07 (0.81,1.40) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC+GP | | | 1.09 (0.83,1.43) | ⊕◯◯◯[††] VERY LOW | 1.09 (0.83,1.43) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC+GP | | | 0.62 (0.30,1.27) | ⊕◯◯◯[††] VERY LOW | 0.62 (0.30,1.27) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC+GP | | | 0.86 (0.69,1.09) | ⊕⊕⊕◯[¶] MODERATE | 0.86 (0.69,1.09) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. rPA+PAC | 0.95 (0.84,1.08) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 0.95 (0.84,1.08) | ⊕⊕⊕⊕ HIGH |
| tPA vs. rPA+PAC | | | 1.19 (1.01,1.40) | ⊕⊕⊕⊕ HIGH | 1.19 (1.01,1.40) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC vs. rPA+PAC | 2.00 (0.51,7.85) | ⊕⊕◯◯[‡] LOW | 1.21 (1.03,1.42) | ⊕⊕⊕◯[¶] MODERATE | 1.22 (1.04,1.42) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. rPA+PAC | | | 0.69 (0.34,1.38) | ⊕◯◯◯[‖] VERY LOW | 0.69 (0.34,1.38) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC | 1.02 (0.77,1.35) | ⊕⊕◯◯[*,§] LOW | 0.97 (0.65,1.44) | ⊕⊕⊕⊕ HIGH | 0.96 (0.87,1.06) | ⊕⊕⊕⊕ HIGH |
| tPA vs. rPA+PAC+GP | | | 1.25 (1.02,1.53) | ⊕◯◯◯[††] VERY LOW | 1.25 (1.02,1.53) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. rPA+PAC+GP | | | 1.28 (1.05,1.56) | ⊕⊕⊕◯[‖] MODERATE | 1.28 (1.05,1.56) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. rPA+PAC+GP | | | 0.72 (0.36,1.46) | ⊕◯◯◯[††] VERY LOW | 0.72 (0.36,1.46) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC+GP | | | 1.01 (0.86,1.18) | ⊕⊕⊕◯[‖] MODERATE | 1.01 (0.86,1.18) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. tPA | 1.04 (0.93,1.18) | ⊕⊕⊕⊕ HIGH | 0.64 (0.36,1.13) | ⊕⊕⊕◯[¶] MODERATE | 1.02 (0.91,1.15) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC+GP vs. tPA | | | 0.58 (0.29,1.17) | ⊕◯◯◯[††] VERY LOW | 0.58 (0.29,1.17) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA | | | 0.81 (0.70,0.94) | ⊕⊕⊕⊕ HIGH | 0.81 (0.70,0.94) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC+GP vs. tPA+PAC | | | 0.57 (0.28,1.14) | ⊕◯◯◯[‖] VERY LOW | 0.57 (0.28,1.14) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA+PAC | 1.65 (0.67,4.08) | ⊕⊕◯◯[§] LOW | 0.78 (0.68,0.89) | ⊕⊕⊕◯[‖] MODERATE | 0.79 (0.69,0.91) | ⊕⊕⊕◯ MODERATE |
| tPA_acc+PAC vs. tPA+PAC+GP | | ⊕◯◯◯[†,‡] VERY LOW | Not estimable | Not estimable | 1.40 (0.70,2.78) | ⊕◯◯◯ VERY LOW |
| **Major bleeding** | | | | | | |
| SK vs. PAC | | | 1.46 (0.66,3.23) | ⊕⊕◯◯[‖] LOW | 1.46 (0.66,3.23) | ⊕⊕◯◯ LOW |
| SK+GP vs. PAC | | | 25.20 (1.37,462.41) | ⊕◯◯◯[††] VERY LOW | 25.20 (1.37,462.41) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. PAC | | | 2.64 (1.27,5.47) | ⊕⊕◯◯[‖] LOW | 2.64 (1.27,5.47) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. PAC | | | 2.26 (1.00,5.11) | ⊕◯◯◯[††] VERY LOW | 2.26 (1.00,5.11) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. PAC | | | 4.21 (1.85,9.59) | ⊕◯◯◯[††] VERY LOW | 4.21 (1.85,9.59) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| rPA+PAC vs. PAC | | | 2.50 (1.18,5.32) | ⊕◯◯◯ VERY LOW | 2.50 (1.18,5.32) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. PAC | | | 5.38 (2.35,12.29) | ⊕◯◯◯[††] VERY LOW | 5.38 (2.35,12.29) | ⊕◯◯◯ VERY LOW |
| tPA vs. PAC | | | 1.20 (0.54,2.68) | ⊕⊕◯◯[‖] LOW | 1.20 (0.54,2.68) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. PAC | 1.81 (0.92,3.54) | ⊕⊕◯◯[*,†] LOW | Not estimable | Not estimable | 1.81 (0.92,3.54) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. PAC | | | 3.64 (1.30,10.20) | ⊕◯◯◯[††] VERY LOW | 3.64 (1.30,10.20) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. PAC | | | 2.86 (1.33,6.16) | ⊕◯◯◯[‖] VERY LOW | 2.86 (1.33,6.16) | ⊕◯◯◯ VERY LOW |
| SK+GP vs. SK | 17.33 (1.05,284.53) | ⊕◯◯◯[*,†,‡] VERY LOW | Not estimable | Not estimable | 17.32 (1.05,284.33) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. SK | 1.91 (1.26,2.91) | ⊕⊕⊕◯[†] MODERATE | 1.08 (0.36,3.23) | ⊕⊕◯◯[‖] LOW | 1.81 (1.21,2.72) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC vs. SK | | | 1.56 (0.88,2.76) | ⊕◯◯◯[††] VERY LOW | 1.56 (0.88,2.76) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK | | | 2.89 (1.63,5.12) | ⊕◯◯◯[††] VERY LOW | 2.89 (1.63,5.12) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK | | | 1.72 (1.09,2.72) | ⊕⊕◯◯[‖] LOW | 1.72 (1.09,2.72) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. SK | | | 3.69 (2.09,6.53) | ⊕◯◯◯[††] VERY LOW | 3.69 (2.09,6.53) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK | 0.73 (0.43,1.24) | ⊕⊕⊕◯[†] MODERATE | 2.38 (0.47,12.05) | ⊕⊕⊕◯[¶] MODERATE | 0.83 (0.50,1.37) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK | 1.22 (0.75,2.00) | ⊕⊕⊕◯[†] MODERATE | 1.30 (0.50,3.36) | ⊕⊕⊕◯[‖] MODERATE | 1.24 (0.81,1.90) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. SK | | | 2.50 (1.08,5.82) | ⊕◯◯◯[††] VERY LOW | 2.50 (1.08,5.82) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK | | | 1.96 (1.21,3.20) | ⊕⊕◯◯[‖] LOW | 1.96 (1.21,3.20) | ⊕⊕◯◯ LOW |
| SK+PAC vs. SK+GP | | | 0.10 (0.01,1.77) | ⊕⊕◯◯[‖,**] LOW | 0.10 (0.01,1.77) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. SK+GP | | | 0.09 (0.01,1.56) | ⊕◯◯◯[††,**] VERY LOW | 0.09 (0.01,1.56) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK+GP | | | 0.17 (0.01,2.90) | ⊕◯◯◯[††,**] VERY LOW | 0.17 (0.01,2.90) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+GP | | | 0.10 (0.01,1.69) | ⊕◯◯◯[††,**] VERY LOW | 0.10 (0.01,1.69) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK+GP | | | 0.21 (0.01,3.71) | ⊕◯◯◯[††,**] VERY LOW | 0.21 (0.01,3.71) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK+GP | | | 0.05 (0.00,0.82) | ⊕⊕◯◯[‖,**] LOW | 0.05 (0.00,0.82) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. SK+GP | | | 0.07 (0.00,1.21) | ⊕⊕◯◯[‖,**] LOW | 0.07 (0.00,1.21) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK+GP | | | 0.14 (0.01,2.69) | ⊕◯◯◯[††,**] VERY LOW | 0.14 (0.01,2.69) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK+GP | | | 0.11 (0.01,1.94) | ⊕◯◯◯[††,**] VERY LOW | 0.11 (0.01,1.94) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| TNK+PAC vs. SK+PAC | | | 0.86 (0.58,1.27) | ⊕⊕⊕◯‖ MODERATE | 0.86 (0.58,1.27) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC+GP vs. SK+PAC | | | 1.60 (1.06,2.39) | ⊕◯◯◯†† VERY LOW | 1.60 (1.06,2.39) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+PAC | 0.98 (0.71,1.35) | ⊕⊕⊕◯† MODERATE | 0.87 (0.53,1.42) | ⊕⊕◯◯‖ LOW | 0.95 (0.76,1.18) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. SK+PAC | | | 2.04 (1.36,3.06) | ⊕⊕⊕◯¶ MODERATE | 2.04 (1.36,3.06) | ⊕⊕⊕◯ MODERATE |
| tPA vs. SK+PAC | 0.39 (0.25,0.62) | ⊕⊕⊕◯† MODERATE | 0.76 (0.34,1.72) | ⊕⊕⊕◯¶ MODERATE | 0.46 (0.30,0.70) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK+PAC | 0.71 (0.52,0.99) | ⊕⊕◯◯*,† LOW | 0.57 (0.29,1.14) | ⊕⊕⊕◯¶ MODERATE | 0.68 (0.52,0.91) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. SK+PAC | | | 1.38 (0.66,2.90) | ⊕⊕◯◯‖ LOW | 1.38 (0.66,2.90) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. SK+PAC | 1.00 (0.64,1.57) | ⊕⊕⊕⊕ HIGH | 1.14 (0.75,1.73) | ⊕⊕◯◯‖ LOW | 1.08 (0.82,1.43) | ⊕⊕⊕⊕ HIGH |
| TNK+PAC+GP vs. TNK+PAC | 1.86 (1.36,2.54) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 1.86 (1.36,2.54) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC vs. TNK+PAC | | | 1.11 (0.78,1.57) | ⊕⊕◯◯‖ LOW | 1.11 (0.78,1.57) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. TNK+PAC | | | 2.37 (1.45,3.89) | ⊕◯◯◯†† VERY LOW | 2.37 (1.45,3.89) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC | | | 0.53 (0.29,0.98) | ⊕◯◯◯†† VERY LOW | 0.53 (0.29,0.98) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC | | | 0.80 (0.50,1.27) | ⊕◯◯◯‖ VERY LOW | 0.80 (0.50,1.27) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC | | | 1.61 (0.78,3.31) | ⊕◯◯◯‖ VERY LOW | 1.61 (0.78,3.31) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC | 1.26 (1.00,1.60) | ⊕⊕◯◯*,† LOW | Not estimable | Not estimable | 1.26 (1.00,1.60) | ⊕⊕◯◯ LOW |
| rPA+PAC vs. TNK+PAC+GP | | | 0.60 (0.41,0.87) | ⊕◯◯◯†† VERY LOW | 0.60 (0.41,0.87) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. TNK+PAC+GP | | | 1.28 (0.76,2.14) | ⊕◯◯◯†† VERY LOW | 1.28 (0.76,2.14) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC+GP | | | 0.29 (0.16,0.52) | ⊕◯◯◯†† VERY LOW | 0.29 (0.16,0.52) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC+GP | | | 0.43 (0.27,0.69) | ⊕◯◯◯†† VERY LOW | 0.43 (0.27,0.69) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC+GP | | | 0.86 (0.41,1.83) | ⊕◯◯◯†† VERY LOW | 0.86 (0.41,1.83) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC+GP | | | 0.68 (0.51,0.91) | ⊕⊕⊕◯‖ MODERATE | 0.68 (0.51,0.91) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. rPA+PAC | 2.15 (1.53,3.02) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 2.15 (1.53,3.02) | ⊕⊕⊕⊕ HIGH |
| tPA vs. rPA+PAC | | | 0.48 (0.30,0.78) | ⊕⊕◯◯‖ LOW | 0.48 (0.30,0.78) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. rPA+PAC | 1.17 (0.40,3.41) | ⊕◯◯◯†,‡ VERY LOW | 0.68 (0.48,0.98) | ⊕⊕◯◯‖ LOW | 0.72 (0.51,1.01) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC | | | 1.45 (0.70,3.01) | ⊕◯◯◯‖ VERY LOW | 1.45 (0.70,3.01) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | **Risk ratio (95% confidence interval)** | **Quality of evidence** | **Risk ratio (95% confidence interval)** | **Quality of evidence** | **Risk ratio (95% confidence interval)** | **Quality of evidence** |
| tPA_acc+PAC vs. rPA+PAC | 1.12 (0.79,1.61) | ⊕⊕◯◯[*,†] LOW | 1.17 (0.66,2.06) | ⊕⊕◯◯[‖] LOW | 1.14 (0.89,1.46) | ⊕⊕◯◯ LOW |
| tPA vs. rPA+PAC+GP | | | 0.22 (0.12,0.40) | ⊕◯◯◯[††] VERY LOW | 0.22 (0.12,0.40) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. rPA+PAC+GP | | | 0.34 (0.21,0.54) | ⊕⊕⊕◯[‖] MODERATE | 0.34 (0.21,0.54) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. rPA+PAC+GP | | | 0.68 (0.30,1.52) | ⊕◯◯◯[††] VERY LOW | 0.68 (0.30,1.52) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC+GP | | | 0.53 (0.35,0.81) | ⊕⊕⊕◯[‖] MODERATE | 0.53 (0.35,0.81) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. tPA | 1.40 (0.89,2.20) | ⊕⊕⊕◯[†] MODERATE | 2.49 (0.84,7.34) | ⊕⊕⊕◯[¶] MODERATE | 1.50 (0.98,2.30) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. tPA | | | 3.02 (1.28,7.15) | ⊕◯◯◯[††] VERY LOW | 3.02 (1.28,7.15) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA | | | 2.37 (1.42,3.97) | ⊕⊕⊕◯[¶] MODERATE | 2.37 (1.42,3.97) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. tPA+PAC | | | 2.02 (0.92,4.41) | ⊕◯◯◯[‖] VERY LOW | 2.02 (0.92,4.41) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA+PAC | 2.25 (0.88,5.77) | ⊕◯◯◯[†,§] VERY LOW | 1.47 (0.95,2.28) | ⊕⊕◯◯[‖] LOW | 1.58 (1.09,2.30) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. tPA+PAC+GP | | ⊕◯◯◯[†,‡] VERY LOW | Not estimable | Not estimable | 0.79 (0.39,1.56) | ⊕◯◯◯ VERY LOW |
| **Recurrent infarction** | | | | | | |
| SK vs. PAC | | | 1.14 (0.79,1.65) | ⊕◯◯◯[‖] VERY LOW | 1.14 (0.79,1.65) | ⊕◯◯◯ VERY LOW |
| SK+GP vs. PAC | | | 1.58 (0.41,6.08) | ⊕◯◯◯[††] VERY LOW | 1.58 (0.41,6.08) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. PAC | 2.10 (1.06,4.18) | ⊕◯◯◯[*,†] VERY LOW | 0.93 (0.67,1.30) | ⊕◯◯◯[‖] VERY LOW | 1.09 (0.80,1.49) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. PAC | | | 1.21 (0.84,1.75) | ⊕◯◯◯[††] VERY LOW | 1.21 (0.84,1.75) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. PAC | | | 0.77 (0.47,1.25) | ⊕◯◯◯[††] VERY LOW | 0.77 (0.47,1.25) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. PAC | | | 1.08 (0.77,1.51) | ⊕◯◯◯[‖] VERY LOW | 1.08 (0.77,1.51) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. PAC | | | 0.71 (0.48,1.05) | ⊕◯◯◯[††] VERY LOW | 0.71 (0.48,1.05) | ⊕◯◯◯ VERY LOW |
| tPA vs. PAC | | | 1.03 (0.73,1.44) | ⊕◯◯◯[‖] VERY LOW | 1.03 (0.73,1.44) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. PAC | 0.82 (0.63,1.05) | ⊕◯◯◯[*,†] VERY LOW | 1.83 (0.89,3.76) | ⊕◯◯◯[‖] VERY LOW | 0.90 (0.69,1.18) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. PAC | | | 1.94 (0.79,4.75) | ⊕◯◯◯[††] VERY LOW | 1.94 (0.79,4.75) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. PAC | | | 1.14 (0.82,1.58) | ⊕◯◯◯[‖] VERY LOW | 1.14 (0.82,1.58) | ⊕◯◯◯ VERY LOW |
| SK+GP vs. SK | 1.39 (0.38,5.06) | ⊕◯◯◯[*,†,‡] VERY LOW | Not estimable | Not estimable | 1.39 (0.38,5.06) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. SK | 0.93 (0.67,1.28) | ⊕◯◯◯[†,§] VERY LOW | 1.12 (0.45,2.75) | ⊕⊕◯◯[‖] LOW | 0.96 (0.75,1.21) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. SK | | | 1.06 (0.74,1.52) | ⊕◯◯◯[††] VERY LOW | 1.06 (0.74,1.52) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| TNK+PAC+GP vs. SK | | | 0.67 (0.42,1.09) | ⊕◯◯◯[††] VERY LOW | 0.67 (0.42,1.09) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK | | | 0.94 (0.68,1.31) | ⊕◯◯◯[‖] VERY LOW | 0.94 (0.68,1.31) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK | | | 0.63 (0.43,0.91) | ⊕◯◯◯[††] VERY LOW | 0.63 (0.43,0.91) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK | 0.94 (0.75,1.19) | ⊕⊕◯◯[†] LOW | 0.34 (0.12,1.01) | ⊕⊕◯◯[‖,**] LOW | 0.90 (0.71,1.15) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. SK | 0.82 (0.62,1.09) | ⊕⊕◯◯[†] LOW | 0.57 (0.27,1.17) | ⊕⊕◯◯[‖] LOW | 0.79 (0.62,1.00) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK | | | 1.70 (0.70,4.13) | ⊕◯◯◯[††] VERY LOW | 1.70 (0.70,4.13) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK | | | 1.00 (0.74,1.35) | ⊕⊕◯◯[‖] LOW | 1.00 (0.74,1.35) | ⊕⊕◯◯ LOW |
| SK+PAC vs. SK+GP | | | 0.69 (0.18,2.56) | ⊕◯◯◯[‖,**] VERY LOW | 0.69 (0.18,2.56) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+GP | | | 0.77 (0.20,2.93) | ⊕◯◯◯[††,**] VERY LOW | 0.77 (0.20,2.93) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK+GP | | | 0.48 (0.12,1.93) | ⊕◯◯◯[††,**] VERY LOW | 0.48 (0.12,1.93) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+GP | | | 0.68 (0.18,2.58) | ⊕◯◯◯[††,**] VERY LOW | 0.68 (0.18,2.58) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK+GP | | | 0.45 (0.12,1.73) | ⊕◯◯◯[††,**] VERY LOW | 0.45 (0.12,1.73) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK+GP | | | 0.65 (0.17,2.42) | ⊕◯◯◯[‖,**] VERY LOW | 0.65 (0.17,2.42) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. SK+GP | | | 0.57 (0.15,2.12) | ⊕◯◯◯[‖,**] VERY LOW | 0.57 (0.15,2.12) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. SK+GP | | | 1.23 (0.26,5.88) | ⊕◯◯◯[††,**] VERY LOW | 1.23 (0.26,5.88) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK+GP | | | 0.72 (0.19,2.71) | ⊕◯◯◯[††,**] VERY LOW | 0.72 (0.19,2.71) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+PAC | | | 1.11 (0.88,1.40) | ⊕⊕⊕◯[‖] MODERATE | 1.11 (0.88,1.40) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC+GP vs. SK+PAC | | | 0.70 (0.47,1.05) | ⊕◯◯◯ VERY LOW | 0.70 (0.47,1.05) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+PAC | 0.93 (0.70,1.23) | ⊕⊕⊕◯[†] MODERATE | 1.03 (0.69,1.53) | ⊕⊕◯◯[‖] LOW | 0.99 (0.82,1.19) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. SK+PAC | | | 0.65 (0.50,0.85) | ⊕⊕⊕◯[¶] MODERATE | 0.65 (0.50,0.85) | ⊕⊕⊕◯ MODERATE |
| tPA vs. SK+PAC | 0.93 (0.73,1.19) | ⊕⊕⊕◯[†] MODERATE | 1.06 (0.56,2.03) | ⊕⊕◯◯[‖] LOW | 0.94 (0.75,1.18) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK+PAC | 0.83 (0.66,1.05) | ⊕⊕◯◯[*,†] LOW | 0.80 (0.47,1.37) | ⊕⊕◯◯[‖] LOW | 0.83 (0.67,1.01) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK+PAC | | | 1.78 (0.76,4.15) | ⊕⊕◯◯[‖] LOW | 1.78 (0.76,4.15) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. SK+PAC | 1.08 (0.90,1.30) | ⊕⊕⊕⊕ HIGH | 0.91 (0.65,1.27) | ⊕⊕◯◯[‖] LOW | 1.04 (0.90,1.21) | ⊕⊕⊕⊕ HIGH |
| TNK+PAC+GP vs. TNK+PAC | 0.63 (0.46,0.87) | ⊕⊕⊕◯[§] MODERATE | Not estimable | Not estimable | 0.63 (0.46,0.87) | ⊕⊕⊕◯ MODERATE |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| rPA+PAC vs. TNK+PAC | | | 0.89 (0.71,1.10) | ⊕⊕◯◯‖ LOW | 0.89 (0.71,1.10) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. TNK+PAC | | | 0.59 (0.44,0.79) | ⊕◯◯◯†† VERY LOW | 0.59 (0.44,0.79) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC | | | 0.85 (0.61,1.17) | ⊕◯◯◯†† VERY LOW | 0.85 (0.61,1.17) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC | | | 0.74 (0.54,1.02) | ⊕⊕◯◯‖ LOW | 0.74 (0.54,1.02) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. TNK+PAC | | | 1.60 (0.69,3.73) | ⊕◯◯◯‖ VERY LOW | 1.60 (0.69,3.73) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC | 0.94 (0.80,1.10) | ⊕⊕◯◯*,† LOW | Not estimable | Not estimable | 0.94 (0.80,1.10) | ⊕⊕◯◯ LOW |
| rPA+PAC vs. TNK+PAC+GP | | | 1.40 (0.95,2.07) | ⊕◯◯◯†† VERY LOW | 1.40 (0.95,2.07) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. TNK+PAC+GP | | | 0.93 (0.60,1.43) | ⊕◯◯◯†† VERY LOW | 0.93 (0.60,1.43) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC+GP | | | 1.34 (0.85,2.11) | ⊕◯◯◯†† VERY LOW | 1.34 (0.85,2.11) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC+GP | | | 1.17 (0.75,1.84) | ⊕◯◯◯†† VERY LOW | 1.17 (0.75,1.84) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC+GP | | | 2.53 (1.02,6.26) | ⊕◯◯◯†† VERY LOW | 2.53 (1.02,6.26) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC+GP | | | 1.48 (1.03,2.12) | ⊕⊕◯◯‖ LOW | 1.48 (1.03,2.12) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. rPA+PAC | 0.66 (0.54,0.80) | ⊕⊕⊕◯† MODERATE | Not estimable | Not estimable | 0.66 (0.54,0.80) | ⊕⊕⊕◯ MODERATE |
| tPA vs. rPA+PAC | | | 0.95 (0.71,1.28) | ⊕⊕◯◯‖ LOW | 0.95 (0.71,1.28) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. rPA+PAC | 1.75 (0.52,5.86) | ⊕◯◯◯†,‡ VERY LOW | 0.80 (0.62,1.05) | ⊕⊕◯◯‖ LOW | 0.84 (0.63,1.11) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC | | | 1.80 (0.77,4.20) | ⊕◯◯◯‖ VERY LOW | 1.80 (0.77,4.20) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC | 1.00 (0.80,1.25) | ⊕⊕◯◯*,† LOW | 1.21 (0.84,1.73) | ⊕⊕◯◯‖ LOW | 1.06 (0.91,1.23) | ⊕⊕◯◯ LOW |
| tPA vs. rPA+PAC+GP | | | 1.44 (1.01,2.05) | ⊕◯◯◯†† VERY LOW | 1.44 (1.01,2.05) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. rPA+PAC+GP | | | 1.26 (0.90,1.77) | ⊕⊕◯◯‖ LOW | 1.26 (0.90,1.77) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC+GP | | | 2.72 (1.14,6.48) | ⊕◯◯◯†† VERY LOW | 2.72 (1.14,6.48) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC+GP | | | 1.59 (1.25,2.04) | ⊕⊕◯◯‖ LOW | 1.59 (1.25,2.04) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. tPA | 0.89 (0.69,1.15) | ⊕⊕◯◯† LOW | 0.74 (0.30,1.85) | ⊕⊕◯◯‖ LOW | 0.88 (0.70,1.09) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. tPA | | | 1.89 (0.79,4.54) | ⊕◯◯◯†† VERY LOW | 1.89 (0.79,4.54) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA | | | 1.11 (0.84,1.45) | ⊕⊕◯◯‖ LOW | 1.11 (0.84,1.45) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. tPA+PAC | | | 2.16 (0.90,5.16) | ⊕◯◯◯†† VERY LOW | 2.16 (0.90,5.16) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| tPA_acc+PAC vs. tPA+PAC | 1.93 (0.18,21.08) | ⊕⊕◯◯[§] LOW | 1.26 (0.96,1.64) | ⊕⊕⊕◯[‖] MODERATE | 1.26 (0.98,1.64) | ⊕⊕⊕◯ MODERATE |
| tPA_acc+PAC vs. tPA+PAC+GP | | ⊕◯◯◯[†,‡] VERY LOW | Not estimable | Not estimable | 0.59 (0.25,1.35) | ⊕◯◯◯ VERY LOW |
| **All-type stroke** | | | | | | |
| SK vs. PAC | | | 1.39 (0.81,2.39) | ⊕⊕◯◯[‖] LOW | 1.39 (0.81,2.39) | ⊕⊕◯◯ LOW |
| SK+GP vs. PAC | | | 3.65 (0.17,78.58) | ⊕◯◯◯[††,**] VERY LOW | 3.65 (0.17,78.58) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. PAC | | | 1.52 (0.90,2.57) | ⊕⊕◯◯[‖] LOW | 1.52 (0.90,2.57) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. PAC | | | 1.93 (1.07,3.50) | ⊕◯◯◯[††] VERY LOW | 1.93 (1.07,3.50) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. PAC | | | 1.83 (0.88,3.82) | ⊕◯◯◯[††] VERY LOW | 1.83 (0.88,3.82) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. PAC | | | 1.66 (0.92,2.97) | ⊕◯◯◯[‖] VERY LOW | 1.66 (0.92,2.97) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. PAC | | | 1.80 (0.93,3.50) | ⊕◯◯◯[††] VERY LOW | 1.80 (0.93,3.50) | ⊕◯◯◯ VERY LOW |
| tPA vs. PAC | | | 2.24 (1.34,3.74) | ⊕⊕◯◯[‖] LOW | 2.24 (1.34,3.74) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. PAC | 2.02 (1.36,2.98) | ⊕⊕◯◯[*,†] LOW | Not estimable | Not estimable | 2.02 (1.36,2.98) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. PAC | | | 2.09 (0.09,50.82) | ⊕◯◯◯[††,**] VERY LOW | 2.09 (0.09,50.82) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. PAC | | | 1.80 (1.03,3.12) | ⊕◯◯◯[‖] VERY LOW | 1.80 (1.03,3.12) | ⊕◯◯◯ VERY LOW |
| SK+GP vs. SK | 2.63 (0.13,53.85) | ⊕◯◯◯[*,†,‡] VERY LOW | Not estimable | Not estimable | 2.62 (0.13,53.84) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. SK | 1.14 (0.77,1.68) | ⊕⊕◯◯[†,§] LOW | 0.18 (0.01,2.34) | ⊕⊕◯◯[‖,**] LOW | 1.09 (0.74,1.61) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. SK | | | 1.39 (0.86,2.25) | ⊕◯◯◯[††] VERY LOW | 1.39 (0.86,2.25) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK | | | 1.32 (0.69,2.51) | ⊕◯◯◯[††] VERY LOW | 1.32 (0.69,2.51) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK | | | 1.19 (0.75,1.90) | ⊕⊕◯◯[‖] LOW | 1.19 (0.75,1.90) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. SK | | | 1.30 (0.74,2.28) | ⊕◯◯◯[††] VERY LOW | 1.30 (0.74,2.28) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK | 1.65 (1.14,2.38) | ⊕⊕⊕◯[†] MODERATE | 0.02 (0.00,9.24) | ⊕⊕⊕◯[¶] MODERATE | 1.61 (1.12,2.33) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK | 1.42 (0.97,2.08) | ⊕⊕⊕◯[†] MODERATE | 3.41 (0.32,35.90) | ⊕⊕◯◯[‖,**] LOW | 1.45 (1.00,2.11) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK | | | 1.51 (0.06,35.85) | ⊕◯◯◯[††] VERY LOW | 1.51 (0.06,35.85) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK | | | 1.29 (0.84,1.98) | ⊕⊕◯◯[‖] LOW | 1.29 (0.84,1.98) | ⊕⊕◯◯ LOW |
| SK+PAC vs. SK+GP | | | 0.42 (0.02,8.77) | ⊕◯◯◯[‖,**] VERY LOW | 0.42 (0.02,8.77) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+GP | | | 0.53 (0.02,11.28) | ⊕◯◯◯[††] VERY LOW | 0.53 (0.02,11.28) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| TNK+PAC+GP vs. SK+GP | | | 0.50 (0.02,11.02) | ⊕◯◯◯[††] VERY LOW | 0.50 (0.02,11.02) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+GP | | | 0.45 (0.02,9.65) | ⊕◯◯◯[††] VERY LOW | 0.45 (0.02,9.65) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK+GP | | | 0.49 (0.02,10.67) | ⊕◯◯◯[††] VERY LOW | 0.49 (0.02,10.67) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK+GP | | | 0.61 (0.03,12.89) | ⊕◯◯◯[‖,**] VERY LOW | 0.61 (0.03,12.89) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. SK+GP | | | 0.55 (0.03,11.59) | ⊕◯◯◯[‖,**] VERY LOW | 0.55 (0.03,11.59) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. SK+GP | | | 0.57 (0.01,45.76) | ⊕◯◯◯[‖] VERY LOW | 0.57 (0.01,45.76) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK+GP | | | 0.49 (0.02,10.40) | ⊕◯◯◯[‖] VERY LOW | 0.49 (0.02,10.40) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+PAC | | | 1.27 (0.96,1.69) | ⊕⊕⊕◯[‖] MODERATE | 1.27 (0.96,1.69) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC+GP vs. SK+PAC | | | 1.20 (0.72,2.02) | ⊕◯◯◯[††] VERY LOW | 1.20 (0.72,2.02) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+PAC | 1.23 (0.76,1.99) | ⊕⊕⊕⊕ HIGH | 1.03 (0.75,1.42) | ⊕⊕◯◯[‖] LOW | 1.09 (0.84,1.42) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC+GP vs. SK+PAC | | | 1.18 (0.79,1.78) | ⊕⊕⊕◯[¶] MODERATE | 1.18 (0.79,1.78) | ⊕⊕⊕◯ MODERATE |
| tPA vs. SK+PAC | 1.39 (0.98,1.98) | ⊕⊕⊕◯[†] MODERATE | 13.58 (1.26,146.19) | ⊕⊕◯◯[‖,**] LOW | 1.47 (1.04,2.08) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK+PAC | 1.23 (0.86,1.75) | ⊕⊕◯◯[*,†] LOW | 7.77 (1.41,42.81) | ⊕⊕◯◯[‖,**] LOW | 1.32 (0.94,1.87) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. SK+PAC | | | 1.38 (0.06,32.00) | ⊕⊕◯◯[‖,**] LOW | 1.38 (0.06,32.00) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. SK+PAC | 1.18 (0.97,1.43) | ⊕⊕⊕⊕ HIGH | 1.20 (0.71,2.02) | ⊕⊕◯◯[‖] LOW | 1.18 (0.98,1.42) | ⊕⊕⊕⊕ HIGH |
| TNK+PAC+GP vs. TNK+PAC | 0.95 (0.62,1.46) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 0.95 (0.62,1.46) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC vs. TNK+PAC | | | 0.86 (0.63,1.17) | ⊕⊕◯◯[‖] LOW | 0.86 (0.63,1.17) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. TNK+PAC | | | 0.93 (0.60,1.45) | ⊕◯◯◯[††] VERY LOW | 0.93 (0.60,1.45) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC | | | 1.16 (0.74,1.81) | ⊕◯◯◯[††] VERY LOW | 1.16 (0.74,1.81) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC | | | 1.04 (0.67,1.63) | ⊕◯◯◯[‖] VERY LOW | 1.04 (0.67,1.63) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC | | | 1.08 (0.05,25.24) | ⊕◯◯◯[‖] VERY LOW | 1.08 (0.05,25.24) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC | 0.93 (0.75,1.16) | ⊕⊕◯◯[*,†] LOW | Not estimable | Not estimable | 0.93 (0.75,1.16) | ⊕⊕◯◯ LOW |
| rPA+PAC vs. TNK+PAC+GP | | | 0.90 (0.53,1.54) | ⊕◯◯◯[††] VERY LOW | 0.90 (0.53,1.54) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. TNK+PAC+GP | | | 0.98 (0.53,1.83) | ⊕◯◯◯[††] VERY LOW | 0.98 (0.53,1.83) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC+GP | | | 1.22 (0.66,2.28) | ⊕◯◯◯[††] VERY LOW | 1.22 (0.66,2.28) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| tPA+PAC vs. TNK+PAC+GP | | | 1.10 (0.59,2.05) | ⊕◯◯◯[††] VERY LOW | 1.10 (0.59,2.05) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC+GP | | | 1.14 (0.05,27.42) | ⊕◯◯◯[††] VERY LOW | 1.14 (0.05,27.42) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC+GP | | | 0.98 (0.60,1.59) | ⊕⊕⊕◯[‖] MODERATE | 0.98 (0.60,1.59) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. rPA+PAC | 1.09 (0.79,1.49) | ⊕⊕⊕◯[†] MODERATE | Not estimable | Not estimable | 1.09 (0.79,1.49) | ⊕⊕⊕◯ MODERATE |
| tPA vs. rPA+PAC | | | 1.35 (0.88,2.09) | ⊕⊕◯◯[‖] LOW | 1.35 (0.88,2.09) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. rPA+PAC | 13.00 (0.74,228.79) | ⊕◯◯◯[†,‡] VERY LOW | 1.15 (0.74,1.78) | ⊕⊕◯◯[‖] LOW | 1.22 (0.79,1.87) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC | | | 1.26 (0.05,29.46) | ⊕◯◯◯[‖,**] VERY LOW | 1.26 (0.05,29.46) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC | 1.10 (0.86,1.42) | ⊕⊕◯◯[*,†] LOW | 1.01 (0.61,1.69) | ⊕⊕◯◯[‖] LOW | 1.08 (0.86,1.36) | ⊕⊕◯◯ LOW |
| tPA vs. rPA+PAC+GP | | | 1.24 (0.73,2.12) | ⊕◯◯◯[††] VERY LOW | 1.24 (0.73,2.12) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. rPA+PAC+GP | | | 1.12 (0.66,1.91) | ⊕⊕◯◯[‖] LOW | 1.12 (0.66,1.91) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC+GP | | | 1.16 (0.05,27.51) | ⊕◯◯◯[††] VERY LOW | 1.16 (0.05,27.51) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC+GP | | | 1.00 (0.68,1.47) | ⊕⊕◯◯[‖] LOW | 1.00 (0.68,1.47) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. tPA | 0.87 (0.62,1.21) | ⊕⊕⊕◯[†] MODERATE | 5.63 (0.42,74.97) | ⊕⊕◯◯[‖,**] LOW | 0.90 (0.65,1.25) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. tPA | | | 0.93 (0.04,22.12) | ⊕◯◯◯[††] VERY LOW | 0.93 (0.04,22.12) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA | | | 0.80 (0.54,1.18) | ⊕⊕◯◯[‖] LOW | 0.80 (0.54,1.18) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. tPA+PAC | | | 1.04 (0.04,24.61) | ⊕◯◯◯[††] VERY LOW | 1.04 (0.04,24.61) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA+PAC | 0.32 (0.03,3.06) | ⊕◯◯◯[†,§] VERY LOW | 0.92 (0.62,1.37) | ⊕⊕◯◯[‖] LOW | 0.89 (0.60,1.31) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. tPA+PAC+GP | | ⊕◯◯◯[†,‡] VERY LOW | 0.86 (0.04,19.81) | Not estimable | 0.86 (0.04,19.81) | ⊕◯◯◯ VERY LOW |
| **Hemorrhagic stroke** | | | | | | |
| SK vs. PAC | | | 3.35 (1.30,8.63) | ⊕⊕◯◯[‖] LOW | 3.35 (1.30,8.63) | ⊕⊕◯◯ LOW |
| SK+GP vs. PAC | | | 1.76 (0.03,97.96) | ⊕◯◯◯[††] VERY LOW | 1.76 (0.03,97.96) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. PAC | 4.24 (0.41,43.99) | ⊕◯◯◯[*,†] VERY LOW | 1.72 (0.63,4.68) | ⊕⊕◯◯[‖] LOW | 1.98 (0.79,4.96) | ⊕⊕◯◯ LOW |
| TNK+PAC vs. PAC | | | 2.83 (1.04,7.67) | ⊕◯◯◯[††] VERY LOW | 2.83 (1.04,7.67) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. PAC | | | 3.18 (1.03,9.87) | ⊕◯◯◯[††] VERY LOW | 3.18 (1.03,9.87) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. PAC | | | 2.94 (1.09,7.89) | ⊕◯◯◯[‖] VERY LOW | 2.94 (1.09,7.89) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. PAC | | | 3.12 (1.08,9.00) | ⊕◯◯◯[††] VERY LOW | 3.12 (1.08,9.00) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| tPA vs. PAC | | | 3.66 (1.44,9.27) | ⊕⊕◯◯[‖] LOW | 3.66 (1.44,9.27) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. PAC | 4.26 (1.92,9.46) | ⊕◯◯◯[*,†,‡] VERY LOW | 10.49 (0.94,117.56) | ⊕◯◯◯[‖,**] VERY LOW | 4.66 (2.18,9.93) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. PAC | | | 2.94 (0.60,14.25) | ⊕◯◯◯[††] VERY LOW | 2.94 (0.60,14.25) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. PAC | | | 2.85 (1.10,7.41) | ⊕⊕◯◯[‖] LOW | 2.85 (1.10,7.41) | ⊕⊕◯◯ LOW |
| SK+GP vs. SK | 0.53 (0.01,26.15) | ⊕◯◯◯[*,†,‡] VERY LOW | Not estimable | Not estimable | 0.53 (0.01,26.15) | ⊕◯◯◯ VERY LOW |
| SK+PAC vs. SK | 0.64 (0.32,1.31) | ⊕⊕⊕◯[†] MODERATE | 0.24 (0.02,2.93) | ⊕⊕◯◯[¶,**] LOW | 0.59 (0.30,1.16) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC vs. SK | | | 0.84 (0.39,1.84) | ⊕◯◯◯[††] VERY LOW | 0.84 (0.39,1.84) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK | | | 0.95 (0.37,2.45) | ⊕◯◯◯[††] VERY LOW | 0.95 (0.37,2.45) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK | | | 0.88 (0.41,1.89) | ⊕⊕◯◯[‖] LOW | 0.88 (0.41,1.89) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. SK | | | 0.93 (0.40,2.20) | ⊕◯◯◯[††] VERY LOW | 0.93 (0.40,2.20) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK | 1.11 (0.59,2.10) | ⊕⊕⊕◯[†] MODERATE | 0.62 (0.02,24.42) | ⊕⊕⊕◯[¶] MODERATE | 1.09 (0.58,2.04) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. SK | 1.34 (0.73,2.46) | ⊕⊕⊕◯[†] MODERATE | 2.39 (0.29,19.51) | ⊕⊕⊕◯[¶] MODERATE | 1.39 (0.77,2.51) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. SK | | | 0.88 (0.21,3.75) | ⊕◯◯◯[††] VERY LOW | 0.88 (0.21,3.75) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK | | | 0.85 (0.41,1.76) | ⊕⊕⊕◯[¶] MODERATE | 0.85 (0.41,1.76) | ⊕⊕⊕◯ MODERATE |
| SK+PAC vs. SK+GP | | | 1.13 (0.02,59.40) | ⊕◯◯◯[‖,**] VERY LOW | 1.13 (0.02,59.40) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+GP | | | 1.61 (0.03,86.58) | ⊕◯◯◯[††] VERY LOW | 1.61 (0.03,86.58) | ⊕◯◯◯ VERY LOW |
| TNK+PAC+GP vs. SK+GP | | | 1.81 (0.03,100.99) | ⊕◯◯◯[††] VERY LOW | 1.81 (0.03,100.99) | ⊕◯◯◯ VERY LOW |
| rPA+PAC vs. SK+GP | | | 1.67 (0.03,89.75) | ⊕◯◯◯[††] VERY LOW | 1.67 (0.03,89.75) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. SK+GP | | | 1.78 (0.03,97.03) | ⊕◯◯◯[††] VERY LOW | 1.78 (0.03,97.03) | ⊕◯◯◯ VERY LOW |
| tPA vs. SK+GP | | | 2.08 (0.04,108.96) | ⊕◯◯◯[‖,**] VERY LOW | 2.08 (0.04,108.96) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. SK+GP | | | 2.65 (0.05,138.04) | ⊕◯◯◯[‖,**] VERY LOW | 2.65 (0.05,138.04) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. SK+GP | | | 1.67 (0.03,108.05) | ⊕◯◯◯[††] VERY LOW | 1.67 (0.03,108.05) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. SK+GP | | | 1.62 (0.03,86.40) | ⊕◯◯◯[††] VERY LOW | 1.62 (0.03,86.40) | ⊕◯◯◯ VERY LOW |
| TNK+PAC vs. SK+PAC | | | 1.43 (0.96,2.14) | ⊕⊕⊕◯[¶] MODERATE | 1.43 (0.96,2.14) | ⊕⊕⊕◯ MODERATE |
| TNK+PAC+GP vs. SK+PAC | | | 1.61 (0.82,3.14) | ⊕◯◯◯[††] VERY LOW | 1.61 (0.82,3.14) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence | Risk ratio (95% confidence interval) | Quality of evidence |
| rPA+PAC vs. SK+PAC | 2.09 (1.02,4.28) | ⊕⊕⊕⊕ HIGH | 1.30 (0.82,2.04) | ⊕⊕◯◯‖ LOW | 1.49 (1.01,2.18) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC+GP vs. SK+PAC | | | 1.58 (0.92,2.71) | ⊕⊕⊕◯¶ MODERATE | 1.58 (0.92,2.71) | ⊕⊕⊕◯ MODERATE |
| tPA vs. SK+PAC | 1.69 (0.83,3.44) | ⊕⊕⊕⊕ HIGH | 3.57 (0.48,26.66) | ⊕⊕⊕◯¶ MODERATE | 1.85 (0.95,3.58) | ⊕⊕⊕⊕ HIGH |
| tPA+PAC vs. SK+PAC | 2.15 (1.14,4.05) | ⊕⊕⊕◯* MODERATE | 3.90 (0.89,17.07) | ⊕⊕◯◯‖,** LOW | 2.35 (1.31,4.23) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. SK+PAC | | | 1.48 (0.41,5.38) | ⊕⊕◯◯‖ LOW | 1.48 (0.41,5.38) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. SK+PAC | 1.40 (1.04,1.88) | ⊕⊕⊕⊕ HIGH | 1.75 (0.82,3.73) | ⊕⊕⊕◯‖ MODERATE | 1.44 (1.09,1.90) | ⊕⊕⊕⊕ HIGH |
| TNK+PAC+GP vs. TNK+PAC | 1.13 (0.66,1.92) | ⊕⊕⊕⊕ HIGH | Not estimable | Not estimable | 1.13 (0.66,1.92) | ⊕⊕⊕⊕ HIGH |
| rPA+PAC vs. TNK+PAC | | | 1.04 (0.68,1.60) | ⊕⊕◯◯‖ LOW | 1.04 (0.68,1.60) | ⊕⊕◯◯ LOW |
| rPA+PAC+GP vs. TNK+PAC | | | 1.10 (0.62,1.96) | ⊕◯◯◯†† VERY LOW | 1.10 (0.62,1.96) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC | | | 1.29 (0.60,2.79) | ⊕◯◯◯†† VERY LOW | 1.29 (0.60,2.79) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC | | | 1.65 (0.82,3.33) | ⊕⊕◯◯‖ LOW | 1.65 (0.82,3.33) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. TNK+PAC | | | 1.04 (0.29,3.78) | ⊕⊕◯◯‖ LOW | 1.04 (0.29,3.78) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. TNK+PAC | 1.01 (0.75,1.35) | ⊕⊕⊕◯* MODERATE | Not estimable | Not estimable | 1.01 (0.75,1.35) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC vs. TNK+PAC+GP | | | 0.92 (0.46,1.83) | ⊕◯◯◯†† VERY LOW | 0.92 (0.46,1.83) | ⊕◯◯◯ VERY LOW |
| rPA+PAC+GP vs. TNK+PAC+GP | | | 0.98 (0.45,2.15) | ⊕◯◯◯†† VERY LOW | 0.98 (0.45,2.15) | ⊕◯◯◯ VERY LOW |
| tPA vs. TNK+PAC+GP | | | 1.15 (0.45,2.93) | ⊕◯◯◯†† VERY LOW | 1.15 (0.45,2.93) | ⊕◯◯◯ VERY LOW |
| tPA+PAC vs. TNK+PAC+GP | | | 1.46 (0.61,3.54) | ⊕◯◯◯†† VERY LOW | 1.46 (0.61,3.54) | ⊕◯◯◯ VERY LOW |
| tPA+PAC+GP vs. TNK+PAC+GP | | | 0.92 (0.23,3.73) | ⊕◯◯◯†† VERY LOW | 0.92 (0.23,3.73) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. TNK+PAC+GP | | | 0.90 (0.49,1.65) | ⊕⊕⊕◯¶ MODERATE | 0.90 (0.49,1.65) | ⊕⊕⊕◯ MODERATE |
| rPA+PAC+GP vs. rPA+PAC | 1.06 (0.72,1.56) | ⊕⊕⊕◯† MODERATE | Not estimable | Not estimable | 1.06 (0.72,1.56) | ⊕⊕⊕◯ MODERATE |
| tPA vs. rPA+PAC | | | 1.24 (0.58,2.65) | ⊕⊕⊕◯‖ MODERATE | 1.24 (0.58,2.65) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC vs. rPA+PAC | 9.00 (0.49,165.75) | ⊕◯◯◯†,‡ VERY LOW | 1.43 (0.71,2.90) | ⊕⊕◯◯‖ LOW | 1.59 (0.80,3.15) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC | | | 1.00 (0.27,3.66) | ⊕◯◯◯‖ VERY LOW | 1.00 (0.27,3.66) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC | 1.03 (0.72,1.45) | ⊕⊕◯◯*,† LOW | 0.74 (0.35,1.59) | ⊕⊕⊕⊕ HIGH | 0.97 (0.71,1.33) | ⊕⊕⊕⊕ HIGH |
| tPA vs. rPA+PAC+GP | | | 1.17 (0.50,2.74) | ⊕◯◯◯†† VERY LOW | 1.17 (0.50,2.74) | ⊕◯◯◯ VERY LOW |

| Comparison | Direct evidence | | Indirect evidence | | Network meta-analysis | |
|---|---|---|---|---|---|---|
| | **Risk ratio (95% confidence interval)** | **Quality of evidence** | **Risk ratio (95% confidence interval)** | **Quality of evidence** | **Risk ratio (95% confidence interval)** | **Quality of evidence** |
| tPA+PAC vs. rPA+PAC+GP | | | 1.49 (0.68,3.28) | ⊕⊕◯◯[‖] LOW | 1.49 (0.68,3.28) | ⊕⊕◯◯ LOW |
| tPA+PAC+GP vs. rPA+PAC+GP | | | 0.94 (0.24,3.64) | ⊕◯◯◯[††] VERY LOW | 0.94 (0.24,3.64) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. rPA+PAC+GP | | | 0.91 (0.56,1.50) | ⊕⊕◯◯[‖] LOW | 0.91 (0.56,1.50) | ⊕⊕◯◯ LOW |
| tPA+PAC vs. tPA | 1.22 (0.69,2.16) | ⊕⊕⊕◯[†] MODERATE | 3.34 (0.25,45.18) | ⊕⊕◯◯[¶,**] LOW | 1.27 (0.73,2.23) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. tPA | | | 0.80 (0.19,3.41) | ⊕◯◯◯[††] VERY LOW | 0.80 (0.19,3.41) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA | | | 0.78 (0.38,1.59) | ⊕⊕⊕◯[¶] MODERATE | 0.78 (0.38,1.59) | ⊕⊕⊕◯ MODERATE |
| tPA+PAC+GP vs. tPA+PAC | | | 0.63 (0.15,2.59) | ⊕◯◯◯[‖] VERY LOW | 0.63 (0.15,2.59) | ⊕◯◯◯ VERY LOW |
| tPA_acc+PAC vs. tPA+PAC | 0.19 (0.01,3.99) | ⊕⊕◯◯[§] LOW | 0.65 (0.34,1.24) | ⊕⊕◯◯[‖] LOW | 0.61 (0.32,1.16) | ⊕⊕◯◯ LOW |
| tPA_acc+PAC vs. tPA+PAC+GP | | ⊕◯◯◯[†,‡] VERY LOW | 0.97 (0.28,3.42) | Not estimable | 0.97 (0.28,3.42) | ⊕◯◯◯ VERY LOW |

[*] Inadequate concealment of allocation and unblinded unvalidated assessment by the physician; [†] Heterogeneity of outcome definition or outcome assessing between each trial; [‡] Wide confidence intervals and few events; [§] Large $I^2$; [¶] Contributing direct evidence of moderate quality; [‖] Contributing direct evidence of low or very low quality; [**] Imprecision; [††] Indirect estimate from order loops higher than first order.

# Appendix 13 Subgroup analyses

As the hypothesis that patients may not gain the full benefit in using of fibrinolytic agent because of bleeding side effect. According to the clinical practice guidelines and several publications of risk scores in prediction of major bleeding across the various types of patient with acute coronary syndromes; advanced age, female gender, renal impairment, and Asian participants were strongly recognized as a potent bleeding risk character.[1,2,5-8,92] Therefore, subgroup analysis was done based on those characters.

**eTable 13.1 Subgroup analyses for the risk of all-cause mortality within 30-35 days with treatment options in differing populations of patients with STEMI.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to accelerated infusion alteplase plus parenteral anticoagulants before (standard analysis) and after subgroup analyses.

| Treatment | Standard analysis | SUCRA rank | Advanced age (≥65-75 years) | SUCRA rank | Female | SUCRA rank | Renal impairment | SUCRA rank | Trials with Asian participants | SUCRA rank |
|---|---|---|---|---|---|---|---|---|---|---|
| tPA+PAC+GP | 0.72 (0.36,1.42) | 1 | N/A | | N/A | | N/A | | N/A | |
| rPA+PAC+GP | 0.99 (0.84,1.16) | 2 | N/A | | N/A | | N/A | | N/A | |
| tPA_acc+PAC (ref) | 1 | 3 | 1 | 1 | N/A | | N/A | | 1 | 1 |
| TNK+PAC | 1.01 (0.90,1.13) | 4 | 1.49 (0.53,4.16) | 4 | N/A | | N/A | | 1.25 (0.63,2.50) | 2 |
| SK+GP | 0.84 (0.23,3.06) | 5 | N/A | | N/A | | N/A | | N/A | |
| rPA+PAC | 1.04 (0.94,1.15) | 6 | 1.14 (0.90,1.43) | 3 | N/A | | N/A | | N/A | |
| SK+PAC | **1.14 (1.05,1.24)** | 7 | 1.07 (0.93,1.23) | 2 | N/A | | N/A | | N/A | |
| TNK+PAC+GP | 1.16 (0.92,1.46) | 8 | N/A | | N/A | | N/A | | 1.46 (0.56,3.80) | 3 |
| tPA | **1.24 (1.07,1.43)** | 9 | N/A | | N/A | | N/A | | N/A | |
| tPA+PAC | **1.26 (1.10,1.45)** | 10 | N/A | | N/A | | N/A | | N/A | |
| SK | **1.30 (1.12,1.50)** | 11 | N/A | | N/A | | N/A | | N/A | |
| PAC | **1.49 (1.24,1.79)** | 12 | N/A | | N/A | | N/A | | N/A | |
| Global inconsistency $chi^2$ (P value) | 10.92 (P=0.1422) | | 0.57 (P=0.4508) | | N/A | | N/A | | 0.40 (P=0.5272) | |
| Number of studies | 39 | | 4 | | 1 | | 0 | | 4 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 13.2 Subgroup analyses for the risk of major bleeding with treatment options in differing populations of patients with STEMI.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after subgroup analyses.

| Treatment | Standard analysis | SUCRA rank | Advanced age (≥65-75 years) | SUCRA rank | Female | SUCRA rank | Renal impairment | SUCRA rank | Trials with Asian participants | SUCRA rank |
|---|---|---|---|---|---|---|---|---|---|---|
| PAC | **0.35 (0.16,0.75)** | 1 | N/A | | N/A | | N/A | | N/A | |
| tPA | **0.42 (0.25,0.70)** | 2 | N/A | | N/A | | N/A | | N/A | |
| SK | **0.51 (0.31,0.83)** | 3 | N/A | | N/A | | N/A | | N/A | |
| tPA+PAC | **0.63 (0.44,0.92)** | 4 | N/A | | N/A | | N/A | | N/A | |
| TNK+PAC | **0.79 (0.63,1.00)** | 5 | N/A | | N/A | | N/A | | 0.89 (0.42, 1.88) | 1 |
| rPA+PAC | 0.88 (0.69,1.12) | 6 | N/A | | N/A | | N/A | | N/A | |
| SK+PAC | 0.92 (0.70,1.21) | 7 | N/A | | N/A | | N/A | | N/A | |
| tPA_acc+PAC (ref) | 1 | 8 | N/A | | N/A | | N/A | | 1 | 2 |
| tPA+PAC+GP | 1.27 (0.64,2.53) | 9 | N/A | | N/A | | N/A | | N/A | |
| TNK+PAC+GP | **1.47 (1.10,1.98)** | 10 | N/A | | N/A | | N/A | | 1.53 (0.60, 3.90) | 3 |
| rPA+PAC+GP | **1.88 (1.24,2.86)** | 11 | N/A | | N/A | | N/A | | N/A | |
| SK+GP | 8.82 (0.52,151.04) | 12 | N/A | | N/A | | N/A | | N/A | |
| Global inconsistency $chi^2$ (P value) | 3.89 (P=0.6919) | | N/A | | N/A | | N/A | | 0.10 (P=0.7546) | |
| Number of studies | 32 | | 0 | | 0 | | 0 | | 4 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

# Appendix 14 Sensitivity analyses

**eTable 14.1 Sensitivity analyses for the risk of all-cause mortality within 30-35 days with treatment options in differing populations of patients with STEMI.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after sensitivity analyses.

| Treatment | Standard analysis | SUCRA rank | Trial giving ASA in treatment protocol | SUCRA rank | Excluding trial conducted in China | SUCRA rank |
|---|---|---|---|---|---|---|
| tPA+PAC+GP | 0.72 (0.36,1.42) | 1 | 0.72 (0.36,1.42) | 1 | 0.72 (0.36,1.42) | 1 |
| rPA+PAC+GP | 0.99 (0.84,1.16) | 2 | 0.99 (0.84,1.16) | 2 | 0.99 (0.84,1.16) | 2 |
| tPA_acc+PAC (ref) | 1 | 3 | 1 | 3 | 1 | 3 |
| TNK+PAC | 1.01 (0.90,1.13) | 4 | 1.02 (0.90,1.13) | 4 | 1.01 (0.89,1.12) | 4 |
| SK+GP | 0.84 (0.23,3.06) | 5 | 0.84 (0.23,3.06) | 5 | 0.84 (0.23,3.06) | 5 |
| rPA+PAC | 1.04 (0.94,1.15) | 6 | 1.04 (0.94,1.15) | 6 | 1.04 (0.94,1.15) | 6 |
| SK+PAC | **1.14 (1.05,1.24)** | 7 | **1.14 (1.05,1.24)** | 7 | **1.14 (1.05,1.24)** | 7 |
| TNK+PAC+GP | 1.16 (0.92,1.46) | 8 | 1.16 (0.92,1.46) | 8 | 1.15 (0.91,1.44) | 8 |
| tPA | **1.24 (1.07,1.43)** | 9 | **1.24 (1.07,1.43)** | 9 | **1.24 (1.07,1.43)** | 9 |
| tPA+PAC | **1.26 (1.10,1.45)** | 10 | **1.26 (1.10,1.45)** | 10 | **1.26 (1.10,1.45)** | 10 |
| SK | **1.30 (1.12,1.50)** | 11 | **1.30 (1.12,1.50)** | 11 | **1.30 (1.12,1.50)** | 11 |
| PAC | **1.49 (1.24,1.79)** | 12 | **1.49 (1.24,1.80)** | 12 | **1.49 (1.24,1.79)** | 12 |
| Global inconsistency $chi^2$ (P value) | 10.92 (P=0.1422) | | 9.76 (P=0.2025) | | 10.92 (P=0.1422) | |
| Number of studies | 39 | | 35 | | 38 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 14.1 Table continued.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after sensitivity analyses.

| Treatment | Standard analysis | SUCRA rank | Trial reporting time to receive fibrinolytics ≤4 hrs | SUCRA rank | Trial reporting time to receive fibrinolytics ≤6 hrs | SUCRA rank | Excluding trial with small sample size (<25$^{th}$ percentiles) | SUCRA rank |
|---|---|---|---|---|---|---|---|---|
| tPA+PAC+GP | 0.72 (0.36,1.42) | 1 | 0.81 (0.37,1.81) | 1 | 0.82 (0.36,1.85) | 1 | 0.72 (0.31,1.65) | 1 |
| rPA+PAC+GP | 0.99 (0.84,1.16) | 2 | 0.96 (0.81,1.14) | 2 | 0.95 (0.67,1.35) | 2 | 0.99 (0.84,1.16) | 2 |
| tPA_acc+PAC (ref) | 1 | 3 | 1 | 4 | 1 | 4 | 1 | 3 |
| TNK+PAC | 1.01 (0.90,1.13) | 4 | 1.01 (0.90,1.13) | 5 | 1.03 (0.81,1.30) | 5 | 1.01 (0.90,1.13) | 4 |
| SK+GP | 0.84 (0.23,3.06) | 5 | N/A | | N/A | | 0.84 (0.23,3.06) | 5 |
| rPA+PAC | 1.04 (0.94,1.15) | 6 | 1.01 (0.90,1.14) | 6 | 1.00 (0.77,1.29) | 3 | 1.04 (0.94,1.15) | 6 |
| SK+PAC | **1.14 (1.05,1.24)** | 7 | **1.16 (1.06,1.27)** | 10 | 1.10 (0.88,1.37) | 7 | **1.14 (1.05,1.24)** | 7 |
| TNK+PAC+GP | 1.16 (0.92,1.46) | 8 | 1.17 (0.92,1.46) | 9 | 1.16 (0.81,1.67) | 9 | 1.16 (0.92,1.46) | 8 |
| tPA | **1.24 (1.07,1.43)** | 9 | 1.28 (0.58,2.82) | 8 | 1.15 (0.81,1.64) | 8 | **1.24 (1.07,1.43)** | 9 |
| tPA+PAC | **1.26 (1.10,1.45)** | 10 | 0.92 (0.61,1.41) | 3 | 1.09 (0.67,1.77) | 6 | **1.26 (1.10,1.45)** | 10 |
| SK | **1.30 (1.12,1.50)** | 11 | 1.21 (0.63,2.32) | 7 | 1.19 (0.82,1.73) | 10 | **1.30 (1.12,1.50)** | 11 |
| PAC | **1.49 (1.24,1.79)** | 12 | **1.69 (1.06,2.71)** | 11 | **1.48 (1.02,2.15)** | 11 | **1.48 (1.24,1.78)** | 12 |
| Global inconsistency $chi^2$ (P value) | 10.92 (P=0.1422) | | 5.17 (P=0.1599) | | 11.02 (P=0.1376) | | 10.91 (P=0.1424) | |
| Number of studies | 39 | | 31 | | 36 | | 36 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 14.1 Table continued.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after sensitivity analyses.

| Treatment | Standard analysis | SUCRA rank | Excluding trial with small sample size (<75$^{th}$ percentiles) | SUCRA rank | Excluding trial with adequate concealed allocation | SUCRA rank | Excluding trial with overall high risk of bias | SUCRA rank |
|---|---|---|---|---|---|---|---|---|
| tPA+PAC+GP | 0.72 (0.36,1.42) | 1 | N/A | | 0.66 (0.23,1.89) | 1 | 0.66 (0.31,1.41) | 1 |
| rPA+PAC+GP | 0.99 (0.84,1.16) | 2 | 1.00 (0.85,1.17) | 3 | 1.00 (0.85,1.17) | 4 | 1.00 (0.86,1.17) | 3 |
| tPA_acc+PAC (ref) | 1 | 3 | 1 | 1 | 1 | 3 | 1 | 2 |
| TNK+PAC | 1.01 (0.90,1.13) | 4 | 1.00 (0.89,1.12) | 2 | 1.00 (0.89,1.12) | 2 | 1.01 (0.90,1.13) | 4 |
| SK+GP | 0.84 (0.23,3.06) | 5 | N/A | | N/A | | 0.84 (0.23,3.06) | 5 |
| rPA+PAC | 1.04 (0.94,1.15) | 6 | 1.05 (0.95,1.16) | 4 | 1.05 (0.95,1.16) | 5 | 1.05 (0.95,1.16) | 6 |
| SK+PAC | **1.14 (1.05,1.24)** | 7 | **1.15 (1.06,1.25)** | 5 | **1.15 (1.06,1.25)** | 7 | **1.14 (1.05,1.24)** | 7 |
| TNK+PAC+GP | 1.16 (0.92,1.46) | 8 | 1.16 (0.91,1.47) | 6 | 1.14 (0.91,1.44) | 6 | 1.16 (0.92,1.46) | 8 |
| tPA | **1.24 (1.07,1.43)** | 9 | **1.26 (1.09,1.47)** | 7 | **1.28 (1.10,1.49)** | 8 | **1.23 (1.06,1.43)** | 9 |
| tPA+PAC | **1.26 (1.10,1.45)** | 10 | **1.32 (1.14,1.53)** | 8 | **1.34 (1.16,1.56)** | 9 | **1.27 (1.10,1.46)** | 10 |
| SK | **1.30 (1.12,1.50)** | 11 | **1.33 (1.15,1.55)** | 9 | **1.34 (1.16,1.56)** | 10 | **1.30 (1.12,1.50)** | 11 |
| PAC | **1.49 (1.24,1.79)** | 12 | **1.53 (1.26,1.85)** | 10 | **1.61 (1.30,1.98)** | 11 | **1.47 (1.22,1.77)** | 12 |
| Global inconsistency chi$^2$ (P value) | 10.92 (P=0.1422) | | 1.32 (P=0.8597) | | 2.18 (P=0.8242) | | 9.46 (P=0.2215) | |
| Number of studies | 39 | | 14 | | 21 | | 33 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 14.2 Sensitivity analyses for the risk of major bleeding with treatment options in differing populations of patients with STEMI.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after subgroup analyses.

| Treatment | Standard analysis | SUCRA rank | Trial giving ASA in treatment protocol | SUCRA rank | Excluding trial conducted in China | SUCRA rank | Trial with bleeding compatible with BARC type 3b or 3c | SUCRA rank |
|---|---|---|---|---|---|---|---|---|
| PAC | **0.35 (0.16,0.75)** | 1 | **0.36 (0.17,0.77)** | 1 | **0.35 (0.16,0.78)** | 1 | N/A | |
| tPA | **0.42 (0.25,0.70)** | 2 | **0.42 (0.25,0.71)** | 2 | **0.43 (0.25,0.73)** | 2 | 0.99 (0.29,3.36) | 5 |
| SK | **0.51 (0.31,0.83)** | 3 | **0.51 (0.31,0.84)** | 3 | **0.51 (0.31,0.86)** | 3 | 0.52 (0.09,3.15) | 2 |
| tPA+PAC | **0.63 (0.44,0.92)** | 4 | **0.64 (0.44,0.94)** | 4 | **0.64 (0.43,0.94)** | 4 | 0.83 (0.38,1.83) | 3 |
| TNK+PAC | **0.79 (0.63,1.00)** | 5 | **0.79 (0.63,1.00)** | 5 | 0.76 (0.55,1.04) | 5 | 0.72 (0.50,1.04) | 1 |
| rPA+PAC | 0.88 (0.69,1.12) | 6 | 0.88 (0.69,1.12) | 6 | 0.88 (0.67,1.15) | 6 | 0.90 (0.61,1.34) | 4 |
| SK+PAC | 0.92 (0.70,1.21) | 7 | 0.92 (0.70,1.21) | 7 | 0.93 (0.69,1.25) | 7 | 1.00 (0.59,1.69) | 7 |
| tPA_acc+PAC (ref) | 1 | 8 | 1 | 8 | 1 | 8 | 1 | 6 |
| tPA+PAC+GP | 1.27 (0.64,2.53) | 9 | 1.27 (0.64,2.53) | 9 | 1.27 (0.63,2.55) | 9 | 1.27 (0.61,2.66) | 8 |
| TNK+PAC+GP | **1.47 (1.10,1.98)** | 10 | **1.47 (1.10,1.98)** | 10 | **1.44 (1.00,2.08)** | 11 | 1.44 (0.87,2.37) | 9 |
| rPA+PAC+GP | **1.88 (1.24,2.86)** | 11 | **1.88 (1.24,2.86)** | 11 | **1.89 (1.20,2.97)** | 10 | **1.94 (1.08,3.49)** | 10 |
| SK+GP | 8.82 (0.52,151.04) | 12 | 8.88 (0.52,152.04) | 12 | 8.91 (0.52,154.13) | 12 | 9.00 (0.32,255.52) | 11 |
| Global inconsistency $chi^2$ (P value) | 3.89 (P=0.6919) | | 4.45 (P=0.6163) | | 3.69 (P=0.7188) | | 0.42 (P=0.5189) | |
| Number of studies | 32 | | 34 | | 31 | | 21 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 14.2 Table continued.**

The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after subgroup analyses.

| Treatment | Standard analysis | SUCRA rank | Trial reporting time to receive fibrinolytics ≤4 hrs | SUCRA rank | Trial reporting time to receive fibrinolytics ≤6 hrs | SUCRA rank | Excluding trial with small sample size (<25$^{th}$ percentiles) | SUCRA rank |
|---|---|---|---|---|---|---|---|---|
| PAC | **0.35 (0.16,0.75)** | 1 | 0.12 (0.01,2.75) | 1 | 0.13 (0.01,2.76) | 2 | **0.35 (0.16,0.76)** | 1 |
| tPA | **0.42 (0.25,0.70)** | 2 | 0.71 (0.23,2.18) | 5 | **0.42 (0.25,0.70)** | 1 | **0.43 (0.25,0.72)** | 2 |
| SK | **0.51 (0.31,0.83)** | 3 | 0.53 (0.09,3.14) | 3 | **0.51 (0.31,0.83)** | 3 | **0.51 (0.31,0.84)** | 3 |
| tPA+PAC | **0.63 (0.44,0.92)** | 4 | 0.59 (0.31,1.15) | 2 | **0.63 (0.44,0.92)** | 4 | **0.63 (0.43,0.92)** | 4 |
| TNK+PAC | **0.79 (0.63,1.00)** | 5 | 0.76 (0.57,1.02) | 4 | **0.79 (0.62,1.00)** | 5 | **0.79 (0.62,1.00)** | 5 |
| rPA+PAC | 0.88 (0.69,1.12) | 6 | 0.85 (0.60,1.19) | 6 | 0.88 (0.69,1.12) | 6 | 0.88 (0.68,1.12) | 6 |
| SK+PAC | 0.92 (0.70,1.21) | 7 | 1.02 (0.64,1.63) | 8 | 0.92 (0.70,1.22) | 7 | 0.92 (0.70,1.22) | 7 |
| tPA_acc+PAC (ref) | 1 | 8 | 1 | 7 | 1 | 8 | 1 | 8 |
| tPA+PAC+GP | 1.27 (0.64,2.53) | 9 | 1.28 (0.62,2.63) | 9 | 1.28 (0.64,2.58) | 9 | 1.29 (0.63,2.64) | 9 |
| TNK+PAC+GP | **1.47 (1.10,1.98)** | 10 | 1.49 (0.95,2.33) | 10 | **1.47 (1.09,1.99)** | 10 | **1.47 (1.09,2.00)** | 10 |
| rPA+PAC+GP | **1.88 (1.24,2.86)** | 11 | **1.82 (1.07,3.09)** | 11 | **1.88 (1.23,2.87)** | 11 | **1.88 (1.23,2.88)** | 11 |
| SK+GP | 8.82 (0.52,151.04) | 12 | N/A | | N/A | | 8.85 (0.52,151.68) | 12 |
| Global inconsistency chi$^2$ (P value) | 3.89 (P=0.6919) | | 1.31 (P=0.5207) | | 3.86 (P=0.6957) | | 4.33 (P=0.6322) | |
| Number of studies | 32 | | 25 | | 29 | | 29 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

**eTable 14.2 Table continued.**

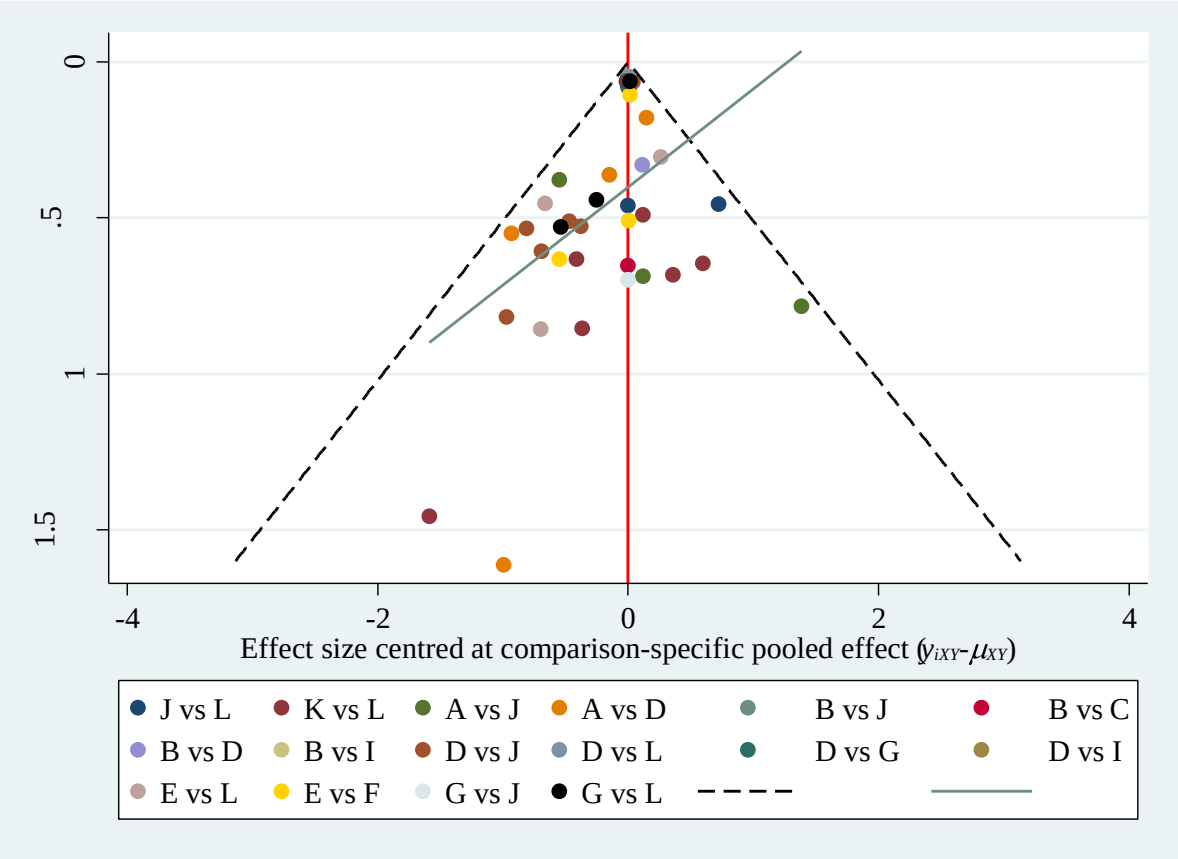
The following table shows the effect sizes (risk ratio) and the rank order (SUCRA ranks) compared to alteplase plus parenteral anticoagulants before (standard analysis) and after subgroup analyses.

| Treatment | Standard analysis | SUCRA rank | Excluding trial with small sample size (<75$^{th}$ percentiles) | SUCRA rank | Excluding trial with adequate concealed allocation | SUCRA rank | Excluding trial with overall high risk of bias | SUCRA rank |
|---|---|---|---|---|---|---|---|---|
| PAC | **0.35 (0.16,0.75)** | 1 | **0.38 (0.15,0.97)** | 2 | **0.33 (0.13,0.87)** | 1 | **0.35 (0.16,0.75)** | 2 |
| tPA | **0.42 (0.25,0.70)** | 2 | **0.37 (0.19,0.71)** | 1 | **0.43 (0.22,0.87)** | 2 | **0.35 (0.20,0.59)** | 1 |
| SK | **0.51 (0.31,0.83)** | 3 | **0.50 (0.27,0.95)** | 3 | **0.51 (0.26,1.00)** | 3 | **0.48 (0.29,0.78)** | 3 |
| tPA+PAC | **0.63 (0.44,0.92)** | 4 | 0.64 (0.36,1.16) | 4 | 0.60 (0.33,1.11) | 4 | **0.63 (0.43,0.92)** | 4 |
| TNK+PAC | **0.79 (0.63,1.00)** | 5 | 0.73 (0.50,1.07) | 5 | 0.72 (0.49,1.05) | 5 | 0.79 (0.62,1.01) | 5 |
| rPA+PAC | 0.88 (0.69,1.12) | 6 | 0.83 (0.59,1.19) | 6 | 0.83 (0.56,1.23) | 6 | 0.82 (0.63,1.08) | 6 |
| SK+PAC | 0.92 (0.70,1.21) | 7 | 0.93 (0.64,1.36) | 7 | 0.94 (0.62,1.43) | 8 | 0.88 (0.66,1.17) | 7 |
| tPA_acc+PAC (ref) | 1 | 8 | 1 | 8 | 1 | 9 | 1 | 8 |
| tPA+PAC+GP | 1.27 (0.64,2.53) | 9 | N/A | | 0.91 (0.28,3.01) | 7 | 1.50 (0.65,3.48) | 9 |
| TNK+PAC+GP | **1.47 (1.10,1.98)** | 10 | 1.27 (0.74,2.17) | 9 | 1.44 (0.86,2.41) | 10 | **1.47 (1.09,1.98)** | 10 |
| rPA+PAC+GP | **1.88 (1.24,2.86)** | 11 | 1.77 (0.99,3.20) | 10 | 1.76 (0.92,3.39) | 11 | **1.73 (1.10,2.72)** | 11 |
| SK+GP | 8.82 (0.52,151.04) | 12 | N/A | | N/A | | 8.28 (0.48,141.87) | 12 |
| Global inconsistency chi$^2$ (P value) | 3.89 (P=0.6919) | | 0.63 (P=0.7315) | | 2.47 (P=0.6495) | | 1.81 (P=0.9360) | |
| Number of studies | 32 | | 11 | | 18 | | 27 | |

**Abbreviations:** GP, Glycoprotein IIb/IIIa inhitibor; N/A, Not available; PAC, Parenteral anticoagulants; rPA, Reteplase; SK, Streptokinase; TNK, Tenecteplase; tPA, Alteplase (non-accelerated infusion); tPA_acc, Alteplase (accelerated infusion).

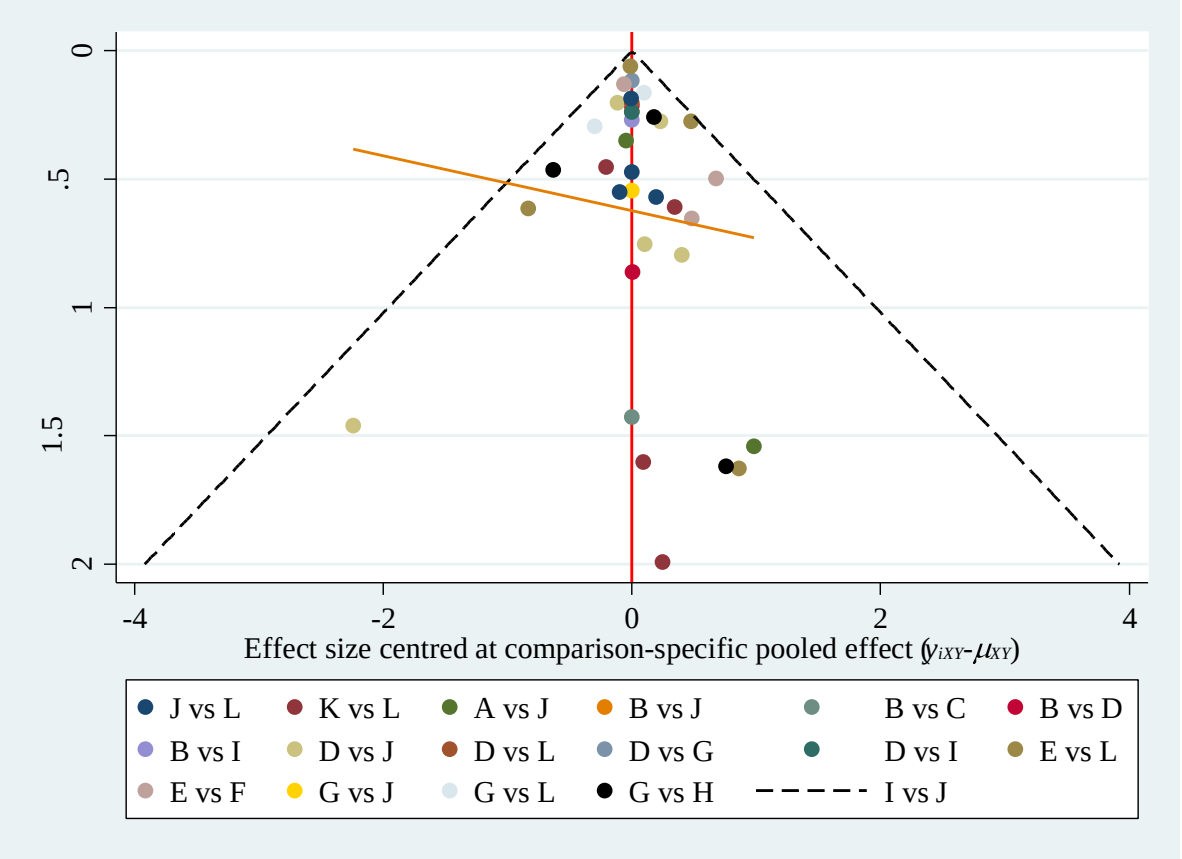
## Appendix 15 Comparison-adjusted funnel plot for each outcome from the network meta-analyses

**eFigure 15.1 Comparison-adjusted funnel plot for the network of all-cause mortality within 30-35 days in all comparisons.**



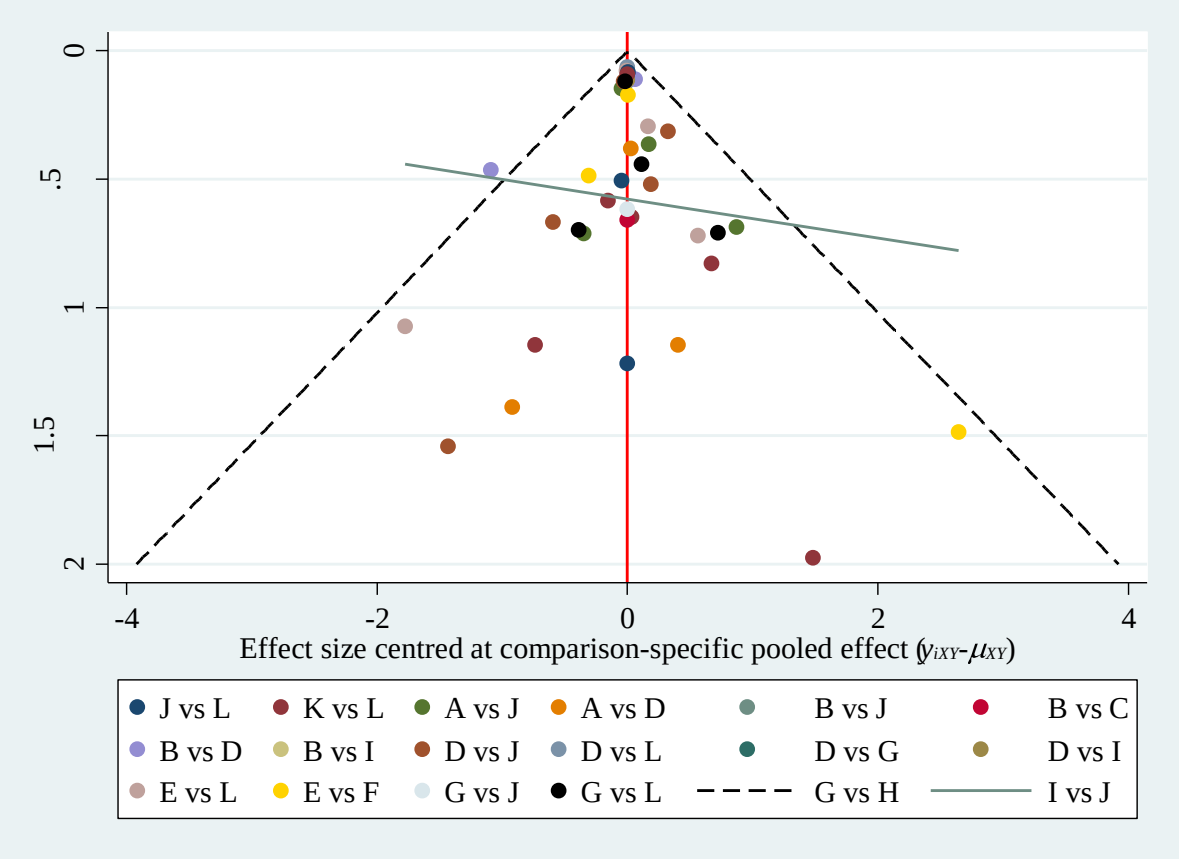

**Abbreviation:** A=PAC, B=SK, C=SK+GP, D=SK+PAC, E=TNK+PAC, F=TNK+PAC+GP, G=rPA+PAC, H=rPA+PAC+GP, I=tPA, J=tPA+PAC, K=tPA+PAC+GP, L=tPA_acc+PAC.

**eTable 15.2 Comparison-adjusted funnel plot for the network of major bleeding in all comparisons.**



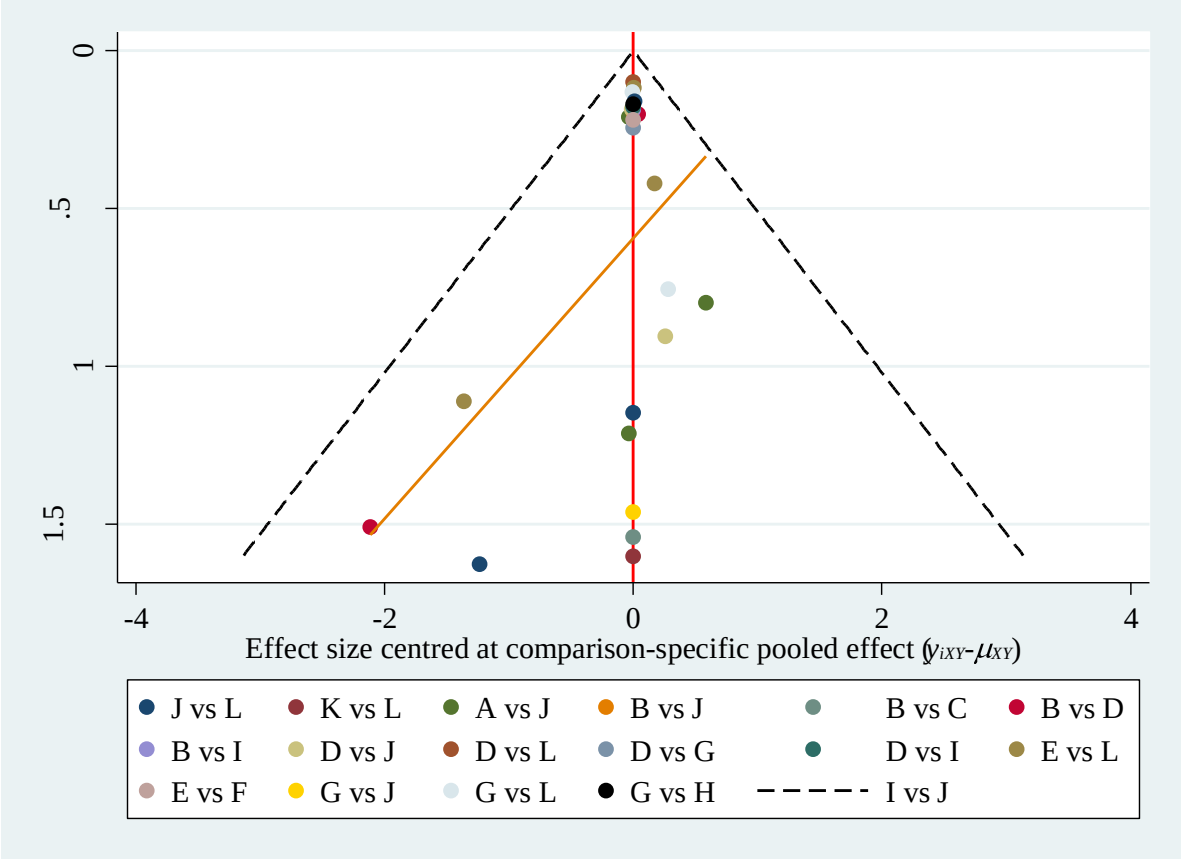

**Abbreviation:** A=PAC, B=SK, C=SK+GP, D=SK+PAC, E=TNK+PAC, F=TNK+PAC+GP, G=rPA+PAC, H=rPA+PAC+GP, I=tPA, J=tPA+PAC, K=tPA+PAC+GP, L=tPA_acc+PAC.

**eTable 15.3 Comparison-adjusted funnel plot for the network of recurrent infarction in all comparisons.**



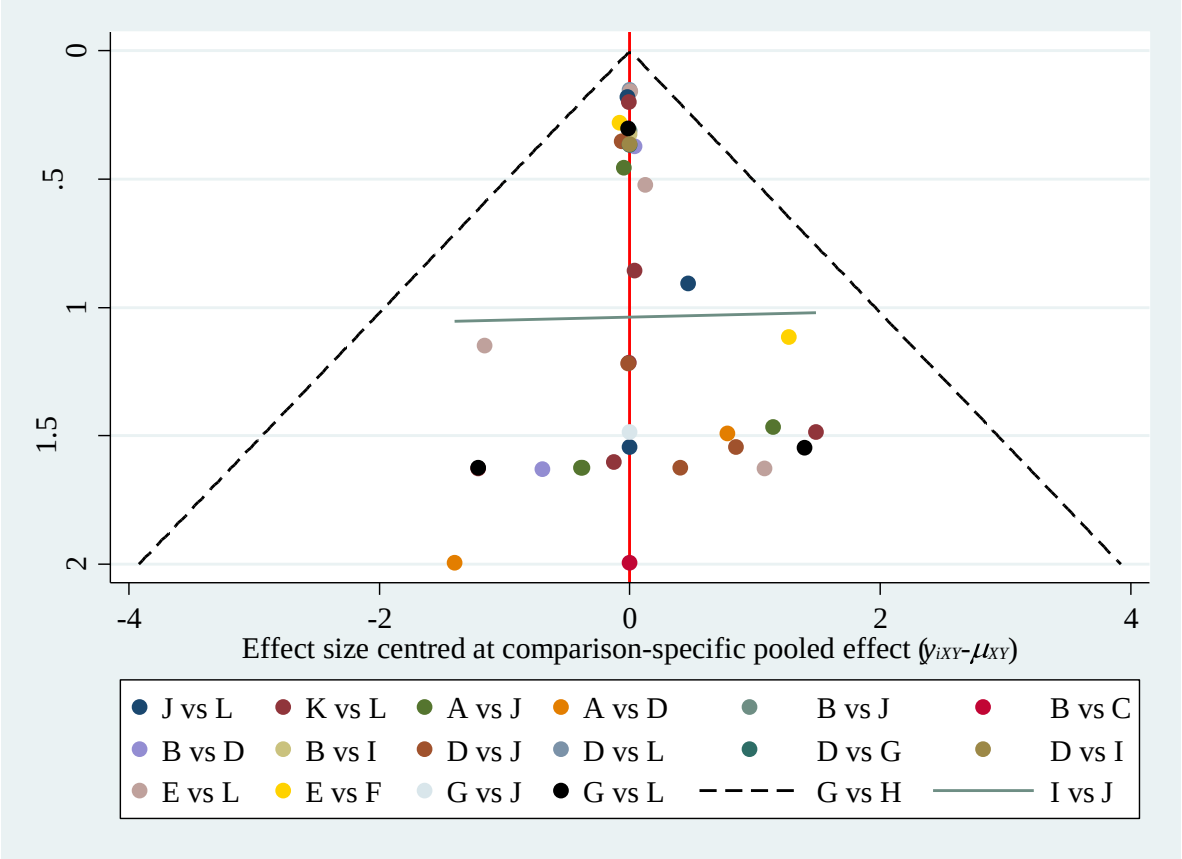

**Abbreviation:** A=PAC, B=SK, C=SK+GP, D=SK+PAC, E=TNK+PAC, F=TNK+PAC+GP, G=rPA+PAC, H=rPA+PAC+GP, I=tPA, J=tPA+PAC, K=tPA+PAC+GP, L=tPA_acc+PAC.

**eTable 15.4 Comparison-adjusted funnel plot for the network of all-type stroke in all comparisons.**




**Abbreviation:** A=PAC, B=SK, C=SK+GP, D=SK+PAC, E=TNK+PAC, F=TNK+PAC+GP, G=rPA+PAC, H=rPA+PAC+GP, I=tPA, J=tPA+PAC, K=tPA+PAC+GP, L=tPA_acc+PAC.

**eTable 15.5 Comparison-adjusted funnel plot for the network of hemorrhagic stroke in all comparisons.**




**Abbreviation:** A=PAC, B=SK, C=SK+GP, D=SK+PAC, E=TNK+PAC, F=TNK+PAC+GP, G=rPA+PAC, H=rPA+PAC+GP, I=tPA, J=tPA+PAC, K=tPA+PAC+GP, L=tPA_acc+PAC.

# Appendix 16 Assessment of small study effects by funnel plots and Egger's test in each outcome.

**eTable 16.1 Assessment of small study effects by Egger's test for each pairwise in each outcome.**

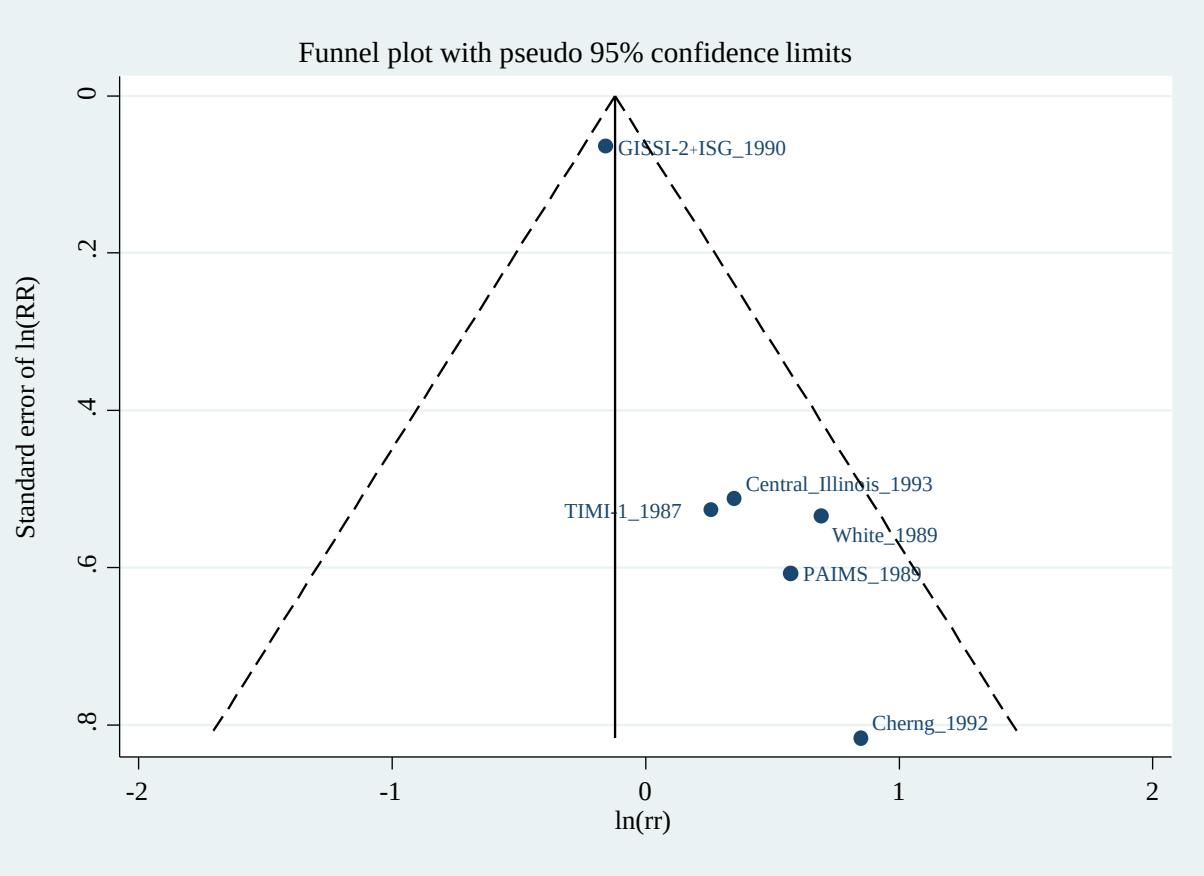
| Outcome | Comparison | | | Number of studies | P |
|---|---|---|---|---|---|
| Mortality within 30-35 days | SK+GP | vs. | SK | 1 | |
| | SK+PAC | vs. | PAC | 4 | 0.165 |
| | SK+PAC | vs. | SK | 2 | |
| | TNK+PAC+GP | vs. | TNK+PAC | 3 | 0.472 |
| | rPA+PAC | vs. | SK+PAC | 1 | |
| | rPA+PAC+GP | vs. | rPA+PAC | 3 | 0.890 |
| | tPA | vs. | SK | 1 | |
| | tPA | vs. | SK+PAC | 1 | |
| | tPA+PAC | vs. | PAC | 4 | 0.822 |
| | tPA+PAC | vs. | SK | 1 | |
| | tPA+PAC | vs. | SK+PAC | 6 | 0.001 |
| | tPA+PAC | vs. | rPA+PAC | 1 | |
| | tPA+PAC | vs. | tPA | 3 | 0.158 |
| | tPA_acc+PAC | vs. | SK+PAC | 1 | |
| | tPA_acc+PAC | vs. | TNK+PAC | 4 | 0.513 |
| | tPA_acc+PAC | vs. | rPA+PAC | 2 | |
| | tPA_acc+PAC | vs. | tPA+PAC | 1 | |
| | tPA_acc+PAC | vs. | tPA+PAC+GP | 4 | 0.155 |
| Major bleeding | SK+GP | vs. | SK | 1 | |
| | SK+PAC | vs. | SK | 2 | |
| | TNK+PAC+GP | vs. | TNK+PAC | 3 | 0.211 |
| | rPA+PAC | vs. | SK+PAC | 1 | |
| | rPA+PAC+GP | vs. | rPA+PAC | 3 | 0.786 |
| | tPA | vs. | SK | 1 | |
| | tPA | vs. | SK+PAC | 1 | |
| | tPA+PAC | vs. | PAC | 2 | |
| | tPA+PAC | vs. | SK | 1 | |
| | tPA+PAC | vs. | SK+PAC | 5 | 0.679 |
| | tPA+PAC | vs. | rPA+PAC | 1 | |
| | tPA+PAC | vs. | tPA | 3 | 0.904 |
| | tPA_acc+PAC | vs. | SK+PAC | 1 | |
| | tPA_acc+PAC | vs. | TNK+PAC | 4 | 0.817 |
| | tPA_acc+PAC | vs. | rPA+PAC | 2 | |
| | tPA_acc+PAC | vs. | tPA+PAC | 1 | |
| | tPA_acc+PAC | vs. | tPA+PAC+GP | 3 | 0.754 |
| Recurrent infarction | SK+GP | vs. | SK | 1 | |
| | SK+PAC | vs. | PAC | 3 | 0.764 |

| Outcome | Comparison | | | Number of studies | P |
|---|---|---|---|---|---|
| | SK+PAC | vs. | SK | 2 | |
| | TNK+PAC+GP | vs. | TNK+PAC | 3 | 0.605 |
| | rPA+PAC | vs. | SK+PAC | 1 | |
| | rPA+PAC+GP | vs. | rPA+PAC | 3 | 0.937 |
| | tPA | vs. | SK | 1 | |
| | tPA | vs. | SK+PAC | 1 | |
| | tPA+PAC | vs. | PAC | 4 | 0.485 |
| | tPA+PAC | vs. | SK | 1 | |
| | tPA+PAC | vs. | SK+PAC | 5 | 0.667 |
| | tPA+PAC | vs. | rPA+PAC | 1 | |
| | tPA+PAC | vs. | tPA | 4 | 0.636 |
| | tPA_acc+PAC | vs. | SK+PAC | 1 | |
| | tPA_acc+PAC | vs. | TNK+PAC | 4 | 0.844 |
| | tPA_acc+PAC | vs. | rPA+PAC | 2 | |
| | tPA_acc+PAC | vs. | tPA+PAC | 1 | |
| | tPA_acc+PAC | vs. | tPA+PAC+GP | 2 | |
| Total stroke | SK+GP | vs. | SK | 1 | |
| | SK+PAC | vs. | SK | 2 | |
| | TNK+PAC+GP | vs. | TNK+PAC | 1 | |
| | rPA+PAC | vs. | SK+PAC | 1 | |
| | rPA+PAC+GP | vs. | rPA+PAC | 2 | |
| | tPA | vs. | SK | 1 | |
| | tPA | vs. | SK+PAC | 1 | |
| | tPA+PAC | vs. | PAC | 3 | 0.556 |
| | tPA+PAC | vs. | SK | 1 | |
| | tPA+PAC | vs. | SK+PAC | 2 | |
| | tPA+PAC | vs. | rPA+PAC | 1 | |
| | tPA+PAC | vs. | tPA | 1 | |
| | tPA_acc+PAC | vs. | SK+PAC | 1 | |
| | tPA_acc+PAC | vs. | TNK+PAC | 3 | 0.620 |
| | tPA_acc+PAC | vs. | rPA+PAC | 2 | |
| | tPA_acc+PAC | vs. | tPA+PAC | 1 | |
| | tPA_acc+PAC | vs. | tPA+PAC+GP | 1 | |
| Hemorrhagic stroke | SK+PAC | vs. | PAC | 1 | |
| | SK+PAC | vs. | SK | 2 | |
| | TNK+PAC+GP | vs. | TNK+PAC | 2 | |
| | rPA+PAC | vs. | SK+PAC | 1 | |
| | rPA+PAC+GP | vs. | rPA+PAC | 3 | 0.911 |
| | tPA | vs. | SK | 1 | |
| | tPA | vs. | SK+PAC | 1 | |
| | tPA+PAC | vs. | PAC | 4 | 0.791 |
| | tPA+PAC | vs. | SK | 1 | |

| Outcome | Comparison | | | Number of studies | P |
|---|---|---|---|---|---|
| | tPA+PAC | vs. | SK+PAC | 4 | 0.193 |
| | tPA+PAC | vs. | rPA+PAC | 1 | |
| | tPA+PAC | vs. | tPA | 3 | 0.941 |
| | tPA_acc+PAC | vs. | SK+PAC | 1 | |
| | tPA_acc+PAC | vs. | TNK+PAC | 4 | 0.933 |
| | tPA_acc+PAC | vs. | rPA+PAC | 2 | |
| | tPA_acc+PAC | vs. | tPA+PAC | 1 | |
| | tPA_acc+PAC | vs. | tPA+PAC+GP | 3 | 0.159 |

**eFigure 16.1 Assessment of small study effects by contour-enhanced funnel plot of all-cause mortality within 30-35 days for treatment pairwise SK+PAC vs tPA+PAC.**

**eFigure 16.2 Assessment of small study effects by funnel plots of all-cause mortality within 30-35 days for treatment pairwise SK+PAC vs tPA+PAC**



# Appendix 17 Reference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