Efficacy and safety of intracoronary pro-urokinase injection during percutaneous coronary intervention in treating ST elevation myocardial infarction patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract. – OBJECTIVE: Intracoronary injection of pro-urokinase (Pro-UK) during percutaneous coronary intervention (PCI) seems to be a promising treatment in improving myocardial perfusion. In this systematic review and meta-analysis, we aimed at investigating the efficacy and safety of intracoronary Pro-UK injection during PCI in ST elevation myocardial infarction (STEMI) patients.

MATERIALS AND METHODS: A comprehensive literature searched on PubMed, Embase, Cochrane, Ovid-MEDLINE, Ovid-Embase, Ovid-Cochrane Databases and ClinicalTrials.gov from inception until June 1, 2022, in English only. The primary outcome was myocardial perfusion, including thrombolysis in myocardial infarction (TIMI) grades, corrected TIMI frame count (CTFC), TIMI myocardial perfusion grades (TMPG). The secondary outcomes were ST-segment resolution (STR), major adverse cardiovascular events (MACE), myocardial marker, cardiac function and hemorrhagic complications.

RESULTS: We identified 5 studies (all RCTs) involving 761 participants. Under PCI procedure, compared with placebo, intracoronary Pro-UK injection may improve myocardial perfusion, including increasing the TIMI grades [odd ratio (OR) 0.46; 95% confidence interval (CI) 0.28-0.75; p = 0.002; I^2 = 0%], CTFC (OR -3.47; 95% CI [-5.60, -1.33]; p = 0.001; I^2 = 0%) and TMPG (OR 0.17; 95% CI [0.06-0.44]; p = 0.0003; I^2 = 0%), increase the rate of STR (OR 2.25; 95% CI [1.56-3.26]; p < 0.0001; I^2 = 0%), reduce the incidence of MACE (OR 0.51; 95% CI [0.33-0.81]; p = 0.004; I^2 = 0%) and reduce myocardial infarct size (CK, standardized mean difference [SMD] -0.45; 95% [CI] [-0.62, -0.28]; p < 0.00001; I^2 = 10%. CK-MB, [SMD] -0.43; 95% CI [-0.68, -0.18]; p = 0.0007; I^2 = 60%. cTnI, [SMD] -0.31; 95% CI [-0.46, -0.17]; p < 0.0001; I^2 = 0%). Moreover, the treatment may improve the cardiac functions (LVFE, pooled mean difference [MD] 1.23; 95% CI [0.66-1.79]; p < 0.0001; I^2 = 24%. LVEDd, pooled MD -0.13; 95% CI [-0.17, -0.09]; p < 0.00001; I^2 = 0%). But there is no statistically significant difference between the Pro-UK group and placebo in the occurrence of hemorrhagic complications (OR 1.19; 95% CI [0.75-1.87]; p = 0.46; I^2 = 0%).

CONCLUSIONS: Intracoronary Pro-UK injection during PCI in STEMI patients is an effective and safe treatment to perform. The treatment may improve myocardial perfusion and rate of STR, as well as decreasing the incidence of MACE and myocardial infarct size. Importantly, the treatment may improve the cardiac functions and life quality. In the future, more multi-centered and massive sample studies are required.

Key Words:
  Pro-urokinase, Percutaneous coronary intervention, ST elevation myocardial infarction, Intracoronary, Myocardial perfusion.

Abbreviations

TIMI: thrombolysis in myocardial infarction; CTFC: corrected TIMI frame count; TMPG: TIMI myocardial perfusion grades; STR: ST-segment resolution; MACE: major adverse cardiovascular events; CK: creatine kinase; CK-MB: creatine kinase isoenzyme-MB; cTnI: cardiac troponin I; HC: hemorrhagic complications; LVEF: left ventricular ejection fraction; LVEDd: left ventricular end-diastolic diameters; OR: odd ratio; CI: confidence interval; SMD: standard mean difference; MD: mean difference.

Introduction

ST elevation myocardial infarction (STEMI) is a common cause of morbidity and mortality worldwide[1]. More than 37.7 thousands of adults have fatal heart arrests annually in the United States, many of which are caused by STEMI[2].

STEMI is usually caused by occlusive thrombosis following coronary plaque rupture. From so far, percutaneous coronary intervention (PCI) is still the best re-perfusion therapy that successfully improves the survival and reduces combined clinical endpoints in STEMI patients. However, in addition to all the benefits that PCI brings to STEMI patients, there are also bleeding complications and cardiovascular events, and over 30-day and 1-year mortality in patients with a good prognosis after PCI is still seen[3]. Therefore, more efforts must be made in the context of PCI treatment of STEMI patients.

Pro-urokinase (Pro-UK), known as a single-chain plasminogen activator, reduced hemorrhagic complications and re-occlusion rate in patients compared with the traditional fibrinolytic agentsis[4,5]. It is a naturally occurring protein that can be produced using recombinant DNA technology. Although newly and very promising, Pro-UK is still not frequently used for PCI in STEMI patients because of insufficient evidence. In detail, there are very limited studies investigating efficacy and safety of Pro-UK in STEMI. A large randomized clinical trial[6] showed that 20 mg of Pro-UK intravenously injected, followed by 30 mg of Pro-UK intravenous infusion within 30 min, is effective and tolerable in patients with STEMI. But the efficiency and safety of intracoronary Pro-UK injection during PCI in treating patients with STEMI is still not clear.

Several randomized controlled trials[7-11] (RCTs) evaluating the efficacy and safety of Pro-UK in STEMI patients with PCI have been performed in recent years. However, no systematic reviews and meta-analysis have been reported concerning the intracoronary injection of Pro-UK during PCI. Herein, we performed the first meta-analysis on the available RCTs to determine the following: (1) the effectiveness and safety of intracoronary Pro-UK injection, compared against placebo in adults with STEMI during PCI; (2) the influence on myocardial perfusion, myocardial infarct size, ST-segment resolution (STR), cardiac functions, hemorrhagic complications and major adverse cardiovascular events (MACE) during the follow-up.

Materials and Methods

Search Strategy and Study Selection Criteria

This systematic review and meta-analysis was performed based on the Cochrane Handbook for Systematic Reviews of Interventions[12] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines[13]. The PRISMA 2020 checklist is available in the **Supplementary Table I**.

We considered studies to be eligible if they met the following criteria: (i) Types of studies: RCT published in peer-reviewed medical journals; (ii) Types of participants: age > 18 years; symptom onset within 6 hours before randomization, and intention to undergo PCI. (iii) Types of interventions: Pro-UK at any dose *vs.* placebo. (iv) Types of outcome measure: myocardial perfusion (TIMI grades, CTFC, TMPG); myocardial markers (CK, CK-MB, cTnI); STR; cardiac functions (LVEF and LVEDd); hemorrhagic complications and MACE during the follow-up.

We performed a comprehensive literature search on PubMed, Embase, Cochrane, Ovid-MEDLINE, Ovid-Embase, Ovid-Cochrane Databases AND Clinicaltrials.gov from inception until June 1, 2022, in English only. RCTs were included, which investigated the effects of intracoronary Pro-UK injection in STEMI patients with PCI. Controlled vocabulary (i.e., MeSH and Emtree) and keywords were used. Search terms included "percutaneous coronary intervention", "ST elevation myocardial infarction", "pro-urokinase" and their variants. The complete search strategy is available in the **Supplementary Figure 1**.

After records were imported into the Endnote X_9 reference management software (www.endnote.com), duplicate records were removed automatically by software and manually by reviewers (X.-S. Yin, Y.-W. Huang). Two reviewers independently screened the titles and abstracts for relevance. If records were seemed to be potentially relevant by either reviewer, the full-text articles were retrieved to assess its eligibility. Disagreements were resolved by discussion or a third-party adjudication, if required.

Data Extraction and Quality Assessment

Two reviewers independently extracted data using the same standardized table. We extracted the following information from included studies: (i) Basic characteristics: first author name, year of publication, country, study design, and number of participants; (ii) participant characteristics: rate of male, class of cardiac function, infarction related artery, follow-up endpoints and time, (iii) intervention characteristics: intracoronary Pro-UK dose, and (iv) data on outcomes of interest, etc.

Two reviewers assessed the risk of bias of each study independently and using the same Co-

chrane Collaboration's tool[12]. The following items for risk of bias were examined: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete data outcome (attrition bias), selective reporting (reporting bias), and other biases (such as stopping early and funding source). The risk of bias was determined as "high risk," "unclear risk," or "low risk." Disagreements were resolved by discussion or third-party judgement, if necessary.

Two reviewers assessed the quality of studies using the Jaded scale. The items assessed included random sequence production (0-2 points); allocation concealment (0-2 points); blinding method (0-2 points); withdrawal (0-1 points). Total scores were 4-7 for high quality studies and 1-3 for low quality studies. Disagreements were resolved by discussion or third-party judgement, if necessary. The total scores of each trial are available in the **Supplementary Table II.**

Statistical Analysis

Based on different data variables, we calculated odds ratios (ORs) or standardized mean difference (SMD) or mean difference (MD) and their corresponding 95% CIs to measure the effect size while comparing Pro-UK and Placebo among STEMI patients accepting PCI. Meta-analyses were performed using random effects model accounting for clinical heterogeneity[14]. $p < 0.05$ was considered statistically significant. The heterogeneity between trials was assessed using the Cochran Q test ($p < 0.1$ or $I^2 > 50\%$ were considered to represent significant heterogeneity)[15]. Publication bias across individual study was graphically evaluated using a funnel plot and also with the Egger's test at a significance level of $p < 0.05$[16]. Specific data of the intervention and control groups were extracted from publications. All statistical analyses were conducted with Review Manager software (version 5.3, RevMan, Copenhagen, DK) and Stata Software (version 16, IBM Corp. Chicago, IL, USA).

Results

Result of Literature Search

The initial search yielded 60 records. We excluded 39 duplicates and a further 14 records after title and abstract screening. Then, 14 potentially eligible articles were retained for full-text evaluation. Finally, five studies[7-11] representing 5 RCTs were included, according to the inclusion criteria. Figure 1 illustrates the process of literature search.

Characteristics of Eligible Studies

Baseline characteristics of the included studies are summarized in Table I. The five studies[7-11] were published between 2018 and 2021, with sample sizes ranging from 39 to 260 participants, and a total of 761 subjects. One study was multi-center[8], while other four studies were conducted at a single center[7, 9-11]. The subjects were mainly men (75%). The dosage of Pro-UK was consistent across included studies with 10 mg or 20 mg diluted in 10 ml of saline within 3 min directly through the balloon catheter to the distal end of the culprit lesion. In the control group 10 ml of saline within 3 min were administered in the same way. Overall, five studies were categorized as being at low risk of bias and high quality. Details of the risk of bias are presented in Figure 2 and **Supplementary Table III**.

Association Between Intracoronary Pro-UK Injection and Outcomes

Table II summarizes the overview of the association between intracoronary Pro-UK injection and various clinical outcomes.

Primary and Interested Outcome Measurement

We identified 5 studies (all RCTs) involving 761 participants undergoing PCI. Compared with placebo, intracoronary Pro-UK injection may increase the TIMI grades (OR 0.46; 95% CI [0.28-0.75]; $p = 0.002$; $I^2 = 0\%$, Figure 3A), CTFC (OR -3.47; 95% CI [-5.60, -1.33]; $p = 0.001$; $I^2 = 0\%$, Figure 3B), TMPG (OR 0.17; 95% CI [0.06-0.44]; $p = 0.0003$; $I^2 = 0\%$, Figure 3C). That means that intracoronary Pro-UK injection could improve the myocardial perfusion. The rate of STR analyzed by 12-lead ECG (OR 2.25; 95% CI [1.56-3.26]; $p < 0.0001$; $I^2 = 0\%$, Figure 4A) and the incidence of MACE (OR 0.51; 95% CI [0.33-0.81]; $p = 0.004$; $I^2 = 0\%$, Figure 4B) was significantly improved. The myocardial infarct size analyzed by myocardial marker (CK, [SMD] -0.45; 95% CI [-0.62, -0.28]; $p < 0.00001$; $I^2 = 10\%$. CK-MB, [SMD] -0.43; 95% CI [-0.68, -0.18]; $p = 0.0007$; $I^2 = 60\%$. cTnI, [SMD] -0.31; 95% CI [-0.46, -0.17]; $p < 0.0001$; $I^2 = 0\%$, Figure 5A, 5B, 5C) was significantly reduced. Moreover, there was no statistically significant difference between the Pro-UK group and placebo in the occurrence
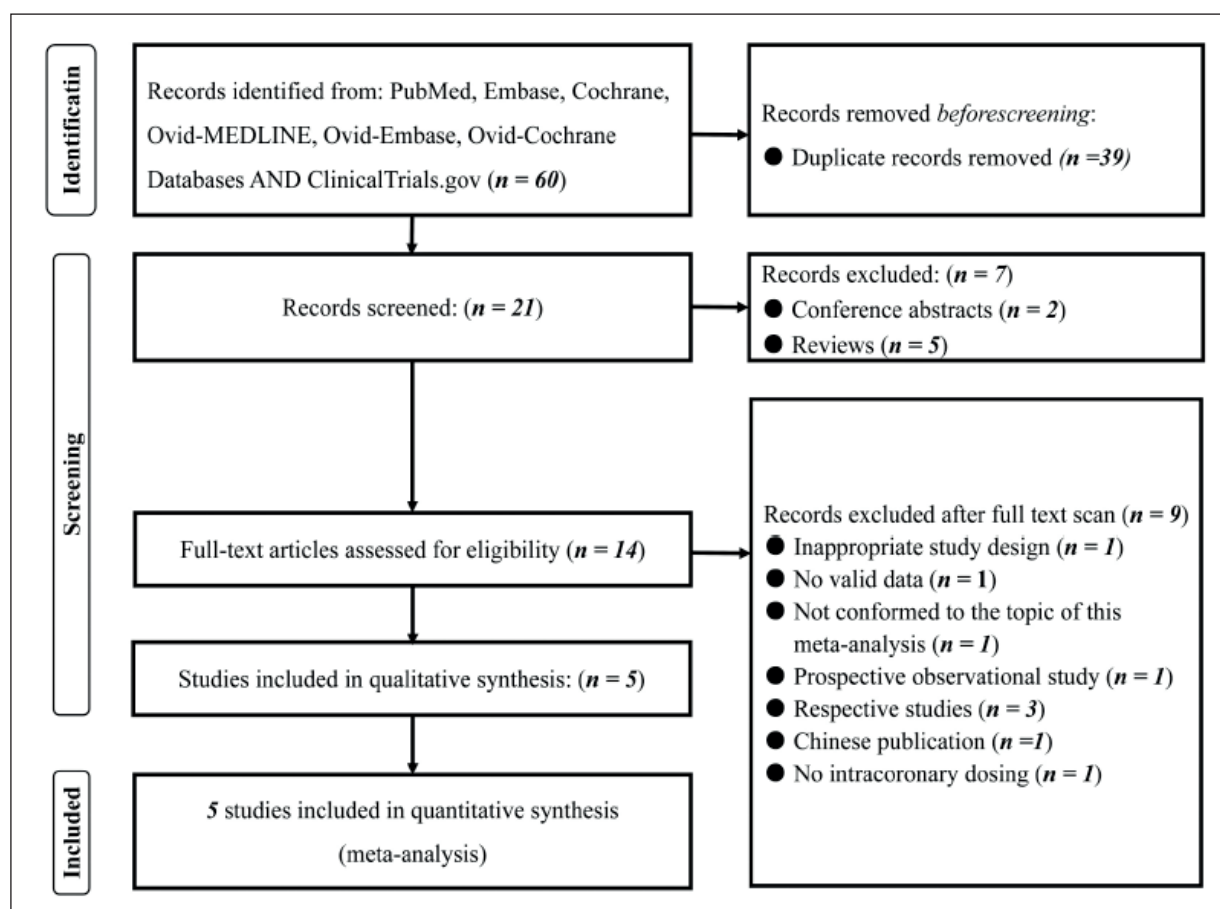
Figure 1. Process of literature search based on PRISMA flowchart.

of hemorrhagic complications (OR 1.19; 95% CI [0.75-1.87]; $p = 0.46$; $I^2 = 0\%$, Figure 6). Although our pooling results did not observe the increase of bleeding complications, the potential risk of bleeding must be considered.

To confirm the robustness of our findings, we performed the sensitivity analysis using data from studies categorized as low risk of bias for different clinical endpoints. Sensitivity analysis of each endpoint showed that the overall effect of Pro-UK treatment was consistent with the overall estimates for all studies (**Supplementary Appendix I**).

Subgroup Analysis of Cardiac Functions

After PCI, the cardiac functions were measured by echocardiography at 1 day, 7 days, 30 days, and 180 days. Importantly, the treatment may improve the cardiac functions (LVFE, pooled MD 1.23; 95% CI [0.66-1.79]; $p < 0.0001$; $I^2 = 24\%$. LVEDd, pooled MD -0.13; 95% CI [-0.17, -0.09]; $p < 0.00001$; $I^2 = 0\%$, Figure 7, 8 and **Supplementary Appendix II**).

Publication Bias

For the safety and efficacy analyses on different endpoints, funnel plot and the Egger's test revealed no evidence of asymmetry. The results are available in **Supplementary Figure 2**. However, the results from such analyses should be treated with considerable caution based on a limited number of studies.

Discussion

Principal Findings

PCI can effectively dredge the infarcted coronary arteries and has become the first-line treatment strategy for the clinical management of STEMI[17]. However, the efficacy of PCI is counteracted by some serious side effects. Slow flow/no flow is one of the prognostic risk factors in STEMI patients. To improve the treatment outcomes of PCI, some drugs, such as Pro-UK, are being used to improve coronary blood flow after

Table I. Baseline characteristics of included studies.

Author	Year of Publication	Country	Study Design	Participants	Male-%	Class of cardiac function	Infarction related artery	Intracoronary Pro-UK dose	Endpoints	Cardiac function examinations	Clinical follow-up, days
Geng et al[7]	2018	China	Single-Center RCT	230	63.9	Killip	LAD, RCA, LCX, LM	10 mg Pro-UK 10 ml saline	TIMI grades, STR, MACE, HC, CK, CK-MB, cTnI	ECG (LVEF, LVEDd)	30, 180
Fu et al[8]	2019	China	Multi-Center RCT	39	79.5	Killip	—	10-20 mg	TIMI grades, CTFC, TPMG, STR, MACE, HC	ECG (LVEF, LVEDd)	90
Wang et al[9]	2020	China	Single-Center RCT	182	81.9	Killip	LAD, RCA, LCX	20 mg	TIMI grades, CTFC, STR, MACE, HC, CK-MB, cTnI	ECG (LVEF, LVEDd)	30, 180
Wu et al[10]	2020	China	Single-Center RCT	50	86.0	Killip	LAD, RCA, LCX	10 mg	TIMI grades, CTFC, TPMG, STR, MACE, HC, CK, CK-MB, cTnI	ECG (LVEF, LVEDd)	90
Jiang et al[11]	2021	China	Single-Center RCT	260	63.5	Killip	LAD, RCA, LCX, LM	10 mg Pro-UK 10 ml saline	TIMI grades, STR, MACE, HC, CK, CK-MB, cTnI	ECG (LVEF, LVEDd)	180

Abbreviations: RCT, randomized controlled trial; LAD, left anterior descending artery; LM, left main stem; LCX, left circumflex artery; RCA, right coronary artery; TIMI grades, thrombolysis in myocardial infarction grades; CTFC, corrected TIMI frame count, TMPG, TIMI myocardial perfusion grades; STR, ST-segment resolution; MACE, major adverse cardiovascular events; CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; cTnI, cardiac troponin I; HC, hemorrhagic complications. LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic. diameters.

Table II. Overview of the safety and efficacy analyses on different endpoints.

Items	Outcome	Trials, n	Result OR (95% CI)	p-value	Heterogeneity (I^2, p for Cochran Q)	Certainty	Importance
Myocardial Perfusion	TIMI grades	5	0.46 (0.28, 0.75)	p =0.002	I^2 = 0%, p = 0.97	High ⊕⊕⊕⊕⊕	Critical
	CTFC	3	-3.47 (-5.60, -1.33)	p = 0.001	I^2 = 0%, p = 0.46		
	TMPG	2	0.17 (0.06-0.44)	p = 0.0003	I^2 = 0%, p = 0.56		
STR		5	2.25 (1.56, 3.26)	p < 0.0001	I^2 = 0%, p = 0.42	High ⊕⊕⊕⊕⊕	Critical
MACE		5	0.51 (0.33, 0.81)	p = 0.004	I^2 = 0%, p = 0.90	High ⊕⊕⊕⊕⊕	Critical
HC		5	1.19 (0.75, 1.87)	p = 0.46	I^2 = 0%, p = 0.73	High ⊕⊕⊕⊕⊕	Critical
			SMD (95% CI)	**p-value**	**Heterogeneity (I^2, p for Cochran Q)**		
Myocardial Marker	CK	3	-0.45 (-0.62, -0.28)	p < 0.00001	I^2 = 10%, p = 0.33	High ⊕⊕⊕⊕⊕	Critical
	CK-MB	4	-0.43 (-0.68, -0.18)	p = 0.0007	I^2 = 60%, p = 0.06		
	cTnI	4	-0.31 (-0.46, -0.17)	p < 0.0001	I^2 = 0%, p = 0.71		
			MD (95% CI)	**p-value**	**Heterogeneity (I^2, p for Cochran Q)**		
Cardiac Function	LVEF 1 d	2	-0.43 (-2.04, 1.18)	p = 0.60	I^2 = 0%, p = 0.65	-	-
	7 d	3	1.51 (0.52, 2.50)	p = 0.003	I^2 = 0%, p = 0.91	-	-
	30 d	3	1.12 (0.15, 2.10)	p = 0.02	I^2 = 61%, p = 0.08	-	-
	180 d	2	1.89 (0.69, 3.09)	p = 0.002	I^2 = 0%, p = 0.39	-	-
	Pooled	10	1.23 (0.67, 1.79)	p < 0.0001	I^2 = 24%, p = 0.22	High ⊕⊕⊕⊕⊕	Critical
	LVEDd 1 d	2	-0.09 (-0.18, -0.01)	p = 0.02	I^2 = 20%, p = 0.26	-	-
	7 d	2	-0.15 (-0.21, -0.09)	p < 0.00001	I^2 = 0%, p = 0.42	-	-
	30 d	3	-0.14 (-0.20, -0.07)	p < 0.0001	I^2 = 0%, p = 0.46	-	-
	Pooled	6	-0.13 (-0.17, -0.09)	p < 0.00001	I^2 = 0%, p = 0.61	High ⊕⊕⊕⊕⊕	Critical

Abbreviations: OR, odd ratio; CI = confidence interval; SMD, standard mean difference; MD, mean difference. TIMI grades, thrombolysis in myocardial infarction grades; CTFC, corrected TIMI frame count, TMPG, TIMI myocardial perfusion grades; STR, ST-segment resolution; MACE, major adverse cardiovascular events; CK, creatine kinase; CK-MB, creatine kinase isoenzyme-MB; cTnI, cardiac troponin I; HC, hemorrhagic complications. LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic diameters.
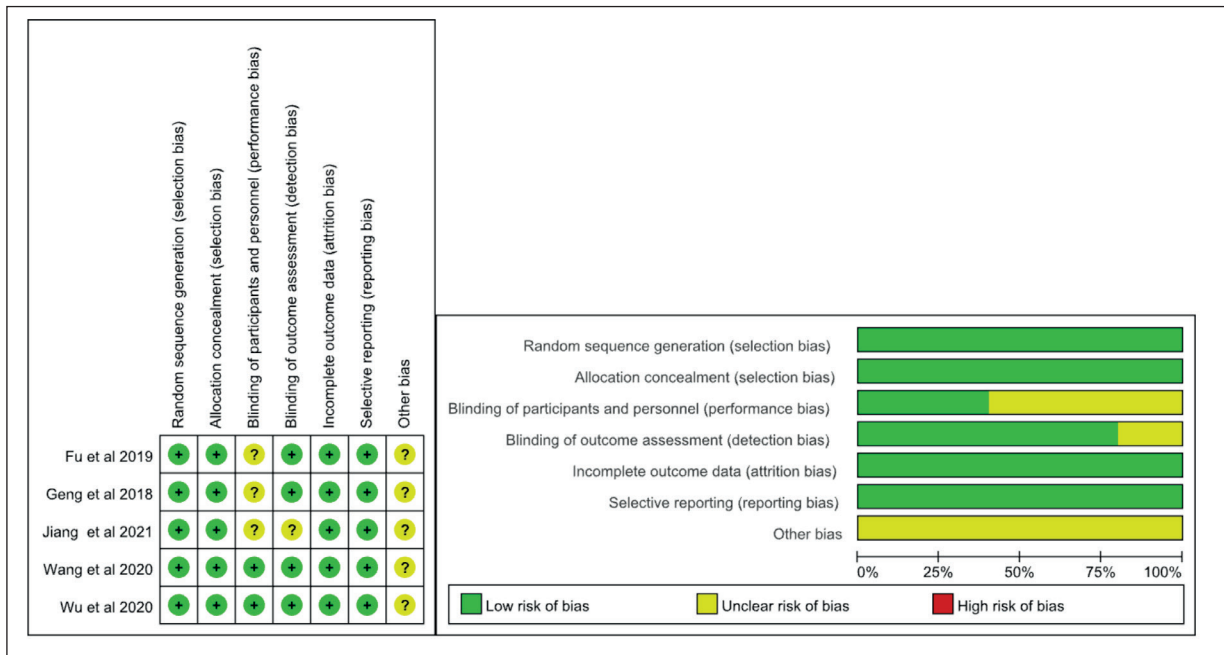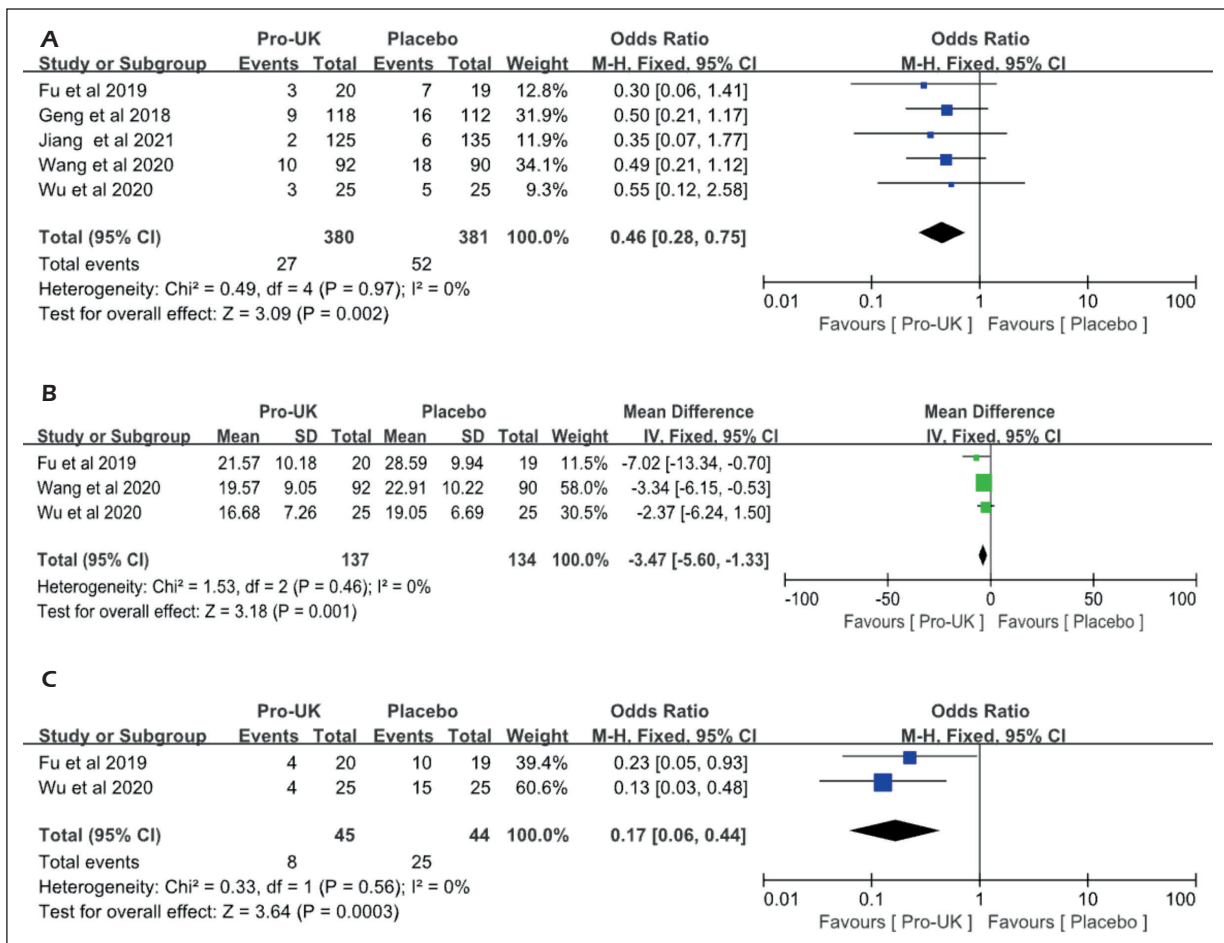
Figure 2. Risk of bias assessment.

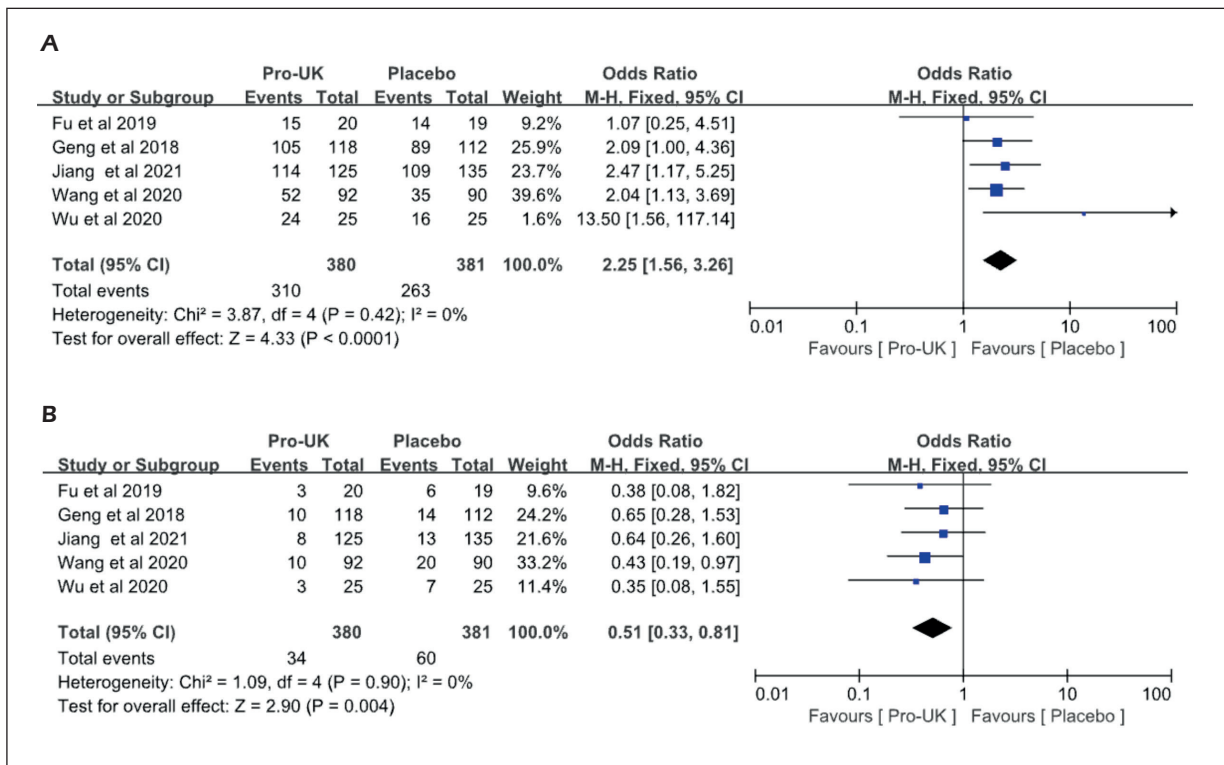**Figure 3.** The myocardial perfusion **(A)** TIMI grades, CTFC **(B)**, TMPG between the pro-UK and placebo groups **(C)**.

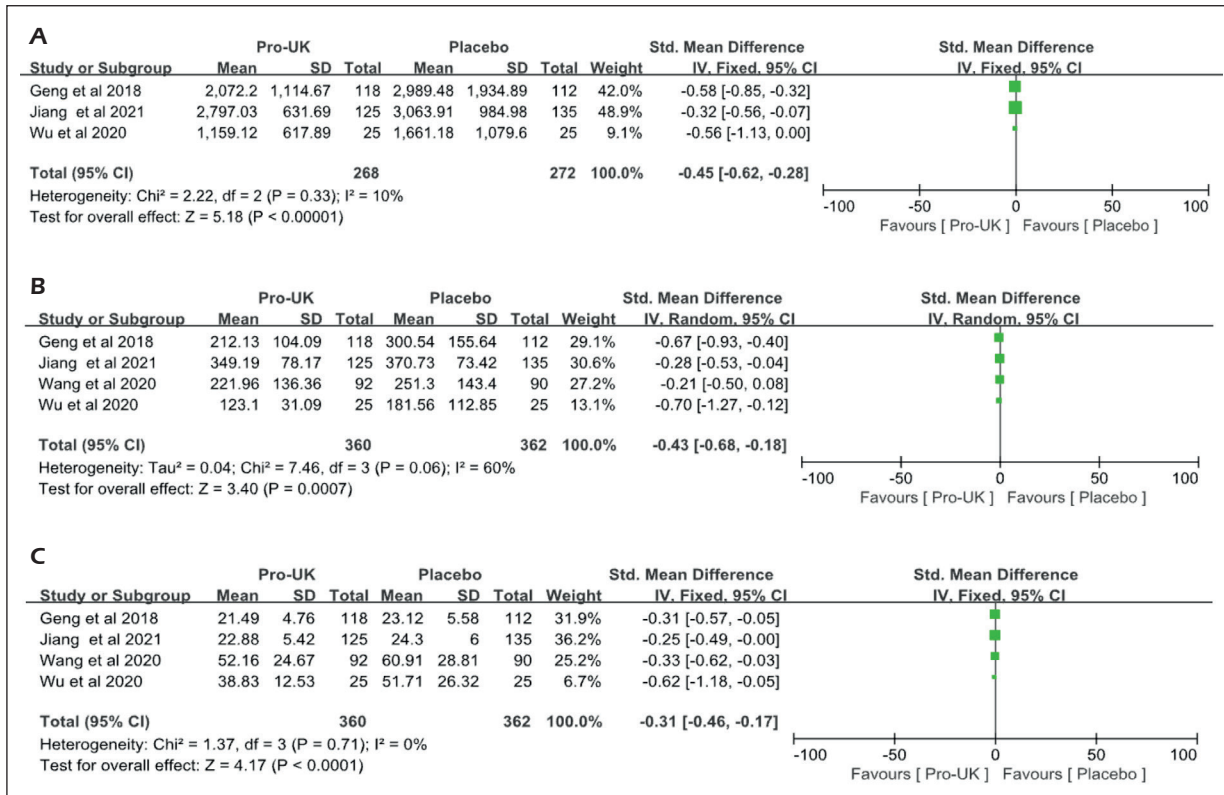**Figure 4.** The STR **(A)** and MACE **(B)** between the pro-UK and placebo groups.

Figure 5. The myocardial marker: CK peak value **(A)**, CK-MB peak value **(B)**, nTnI peak value between the pro-UK and placebo groups **(C)**.
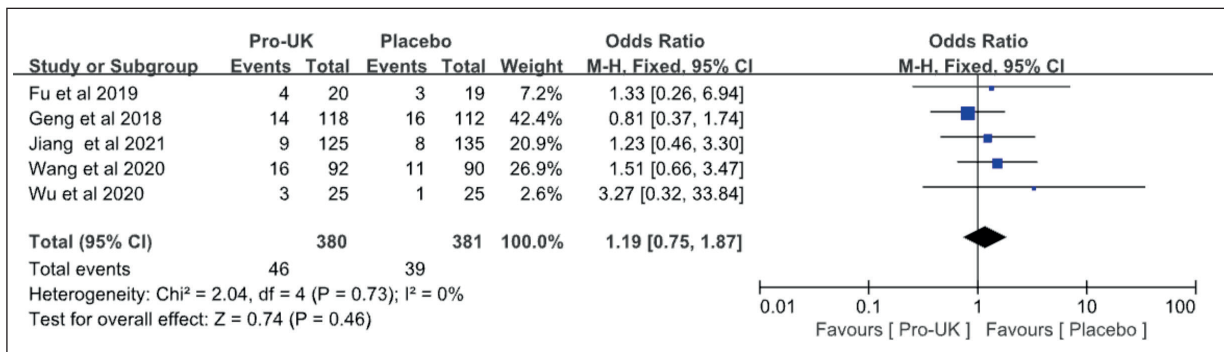
Figure 6. The hemorrhagic complications between the pro-UK and placebo groups.

PCI[18]. In the investigation of Guo et al[19], the authors showed that intracoronary Pro-UK injection could lower the incidence of slow flow comparing with patients solely treated with PCI. That meant that Pro-UK had the potential to ameliorate blood flow condition after PCI. Another previous study[20] showed that the recovery of myocardial ischemia injuries was positively related to the restoration of STR. In our paper, we further identified the findings of Guo et al[19] and van't Hof et al[20]. Our meta-analysis had comprehensively and systematically reviewed the current available literature that compared intracoronary Pro-UK injection during PCI with placebo for treating STEMI, and we obtained three major findings. Firstly, in patients with STEMI, intracoronary Pro-UK injection may improve myocardial perfusion and reduce re-occlusion rate. Besides, this
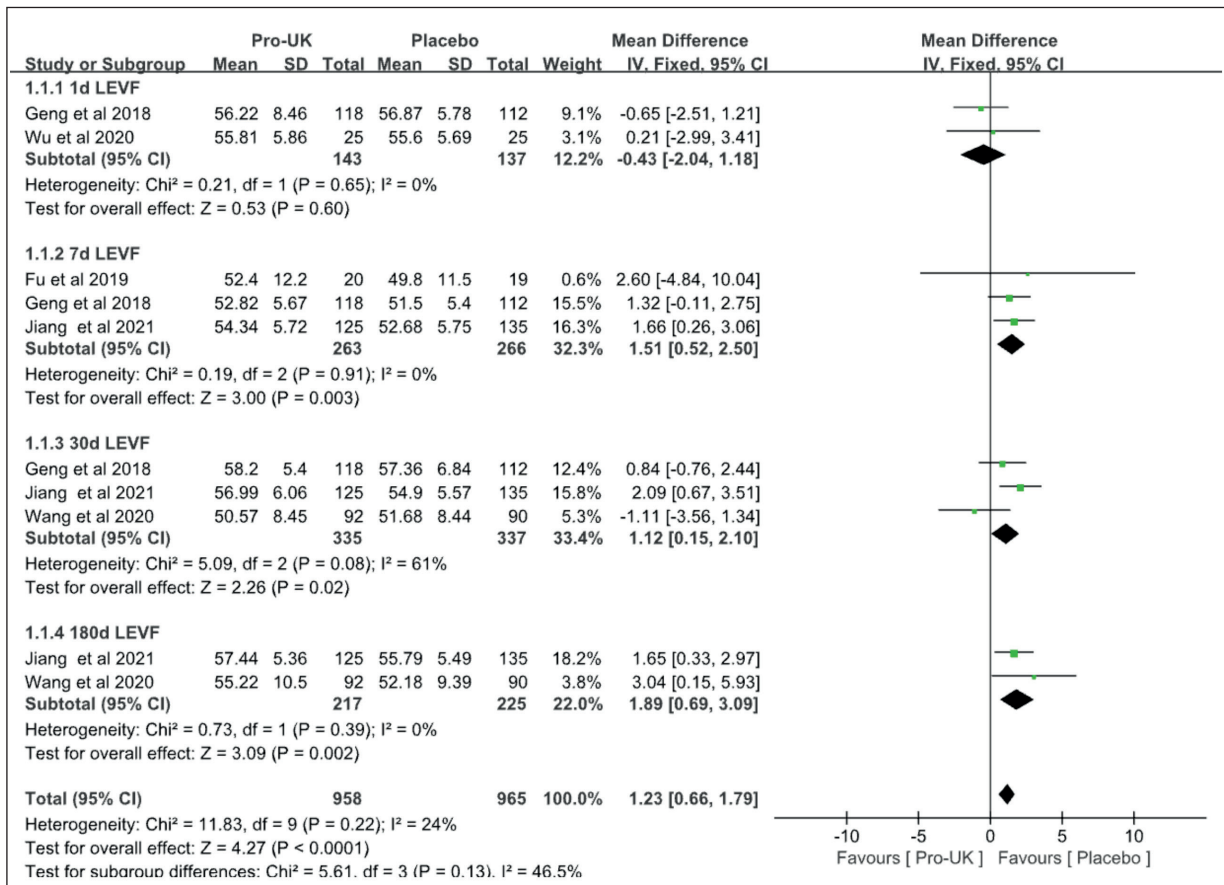

Figure 7. The 1 d, 7 d, 30 d,180 d cardiac function: LVFE between the pro-UK and placebo groups.
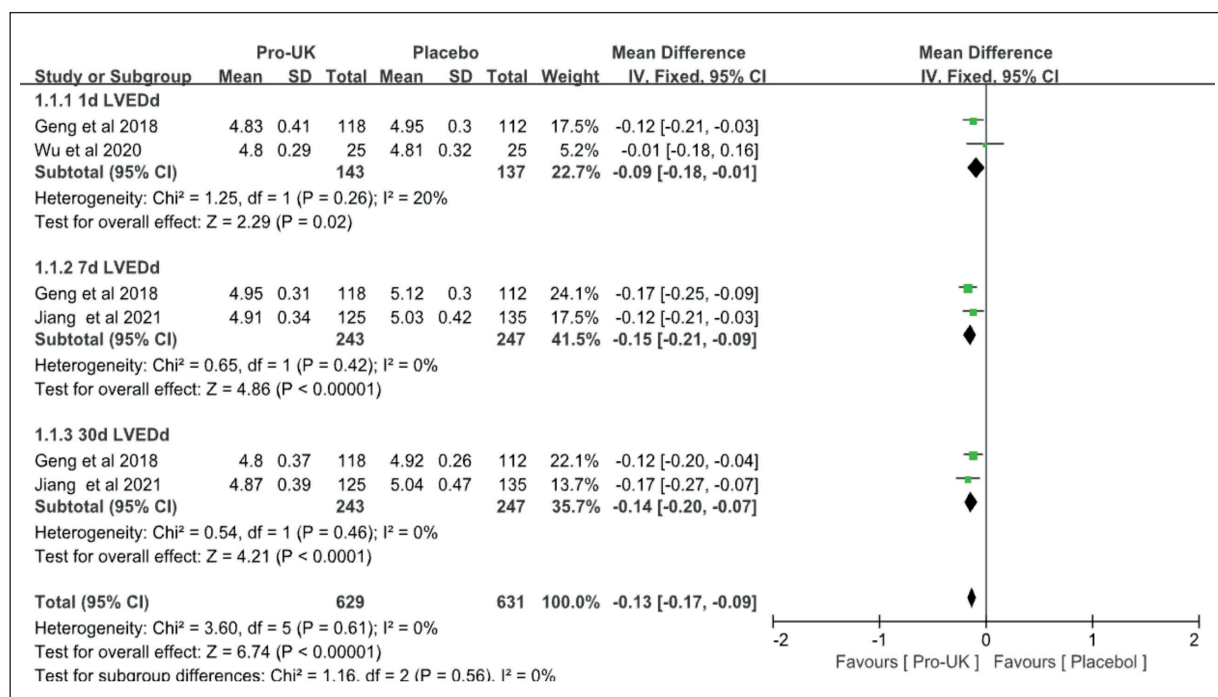
Figure 8. The 1 d, 7 d, 30 d cardiac function: LVEDd between the pro-UK and placebo groups.

treatment had positive effect on STR and MACE. This was similar to previous studies[4,5]. Although our pooling results did not observe the increase of bleeding complication, but because of other anti-thrombotic and anticoagulant regimens (aspirin, ticagrelor, tirofiban, and heparin) utilization in the clinical practice, the potential bleeding risk of Pro-UK must be considered. Secondly, cardiac functions (1-day LVEF) after PCI did not recover immediately. From the 7th day onwards, the LVEF was gradually improved. This indicated that the recovery of cardiac functions was a long and comparatively slow process. So, more attention should be paid during clinical treatment. Thirdly, LVEDd got improved immediately after PCI.

Via pooling the finding of previous studies, our investigation is the first to identify and further reinforce earlier results that 10 mg of Pro-UK within 3 min directly through the balloon catheter to the distal end of the culprit lesion are safe and effective. Second, we pooled RCTs data onto a fixed-effects model accounting for clinical heterogeneity to ensure a more conservative estimation of the efficacy and safety of intracoronary Pro-UK administration for the treatment of STIMI. Third, we evaluated the certainty of evidence using GRADE (**Supplementary Table IV**) approaches to facilitate clinical decision-making.

Strengths and Limitations of the Review

This systematic review and meta-analysis have several strengths, as for example the theme, a comprehensive literature search, a duplicate and independent screening and data extraction. However, certain limitations of this meta-analysis need to be acknowledged. Firstly, all the included studies were confined to China; the articles written in languages other than English were not included. For more generalizable findings, data from the other races or countries and articles in languages other than English are required. Secondly, whether different dosage and administration route of the drug may influence the efficacy and safety or not, it remains unclear. So, relevant urgent studies are necessary. Future studies are needed to explore the most ideal dosage and route of Pro-UK administration.

Conclusions

Intracoronary Pro-UK injection during PCI in STEMI patients is an effective and safe treatment to perform. The treatment may improve myocardial perfusion and rate of STR, as well as decreasing the incidence of MACE and myocardial infarct size. Importantly, the treatment may im-

prove the cardiac functions and life quality. In the future, more multi-centered and massive sample studies are required.

Authors' Contributions

X.-S. Yin, Y.-W. Huang, Z.-P. Li, and J. Yang developed the literature research. X.-S. Yin, Y.-W. Huang, J.-L. Dong, J.-M. Zou, L. Tian performed the study selection. X.-S. Yin, Y.-W. Huang, Z.-P. Li analyzed the data. X.-S. Yin, Y.-W. Huang interpreted the results and wrote the manuscript. All authors reviewed and approved the manuscript.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declared that they have no conflict of interests.

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