Safety and efficacy of intracoronary recombinant human prourokinase administration in patients with acute myocardial infarction and ST-segment elevation: A meta-analysis of randomized controlled trials

GANG FAN, XIANG-GE WU, WEN-PING JIAO, HONG-KAO ZHANG and DIAN-LONG GUO

Second Cardiology Department of Xianyang First People's Hospital, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi 712000, P.R. China

Received July 27, 2022; Accepted October 31, 2022

DOI: 10.3892/etm.2022.11739

Abstract. Slow blood flow or no reflow following percutaneous coronary intervention (PCI) in patients with acute ST-segment elevation myocardial infarction (STEMI) typically leads to an adverse prognosis. However, it is controversial whether to use prourokinase (Pro-UK) during PCI in patients with acute STEMI. The present meta-analysis compared the efficacy and safety of intracoronary Pro-UK administration in patients with acute STEMI. Published randomized controlled trials (RCTs) were analyzed to compare Pro-UK with non-Pro-UK treatment in patients with acute STEMI. PubMed, Cochrane Library and China National Knowledge Infrastructure were searched and meta-analysis was performed using Review Manager 5.3 software. A total of 13 RCTs were selected and 1,797 patients were considered in the meta-analysis, including 897 patients who received Pro-UK intervention and 900 patients who were in the control group. No significant heterogeneity was identified across these selected studies. Pro-UK therapy significantly decreased the incidence of major adverse cardiac events [risk ratio (RR), 0.68; 95% CI, 0.56-0.82, P<0.0001], left ventricular end-diastolic diameter [standardized mean difference (SMD), -0.26; 95% CI, -0.40 – -0.12; P=0.0003], corrected thrombolysis in myocardial infarction (TIMI) frame count [SMD, -0.45; 95% CI, -0.62 – -0.28; P<0.00001] and cardiac troponin I [SMD, -0.31; 95% CI, -0.46 – -0.17; P<0.0001]. In addition, Pro-UK administration increased TIMI grade 3 flow (RR, 1.16; 95% CI, 1.07-1.25; P=0.0003), TIMI myocardial perfusion grade 3 (RR: 1.39, 95% CI: 1.12-1.74, P=0.004), ST-segment resolution (RR, 1.23; 95% CI, 1.10-1.36; P=0.0002) and left ventricular ejection fraction (SMD, 0.38; 95% CI, 0.27-0.49; P<0.00001). No significant difference was identified in bleeding (RR, 1.12; 95% CI, 0.85-1.47; P=0.41). The present meta-analysis determined that intracoronary Pro-UK administration is efficacious and safe to decrease slow blood flow or no reflow phenomena following PCI and improve the prognosis of patients with acute STEMI.

Correspondence to: Dr Dian-Long Guo or Dr Gang Fan, Second Cardiology Department of Xianyang First People's Hospital, Shaanxi University of Chinese Medicine, 10 West BiYuan Road, Xianyang, Shaanxi 712000, P.R. China
E-mail: gdl_xydyrmyy@163.com
E-mail: nfgcardiology@126.com

Abbreviations: PCI, percutaneous coronary intervention; Pro-UK, prourokinase; RCTs, randomized controlled trials; STEMI, ST-segment elevation myocardial infarction; MACEs, major adverse cardiac events; STR, ST-segment resolution; TIMI, thrombolysis in myocardial infarction; CTFC, corrected TIMI frame count; TMPG, TIMI myocardial perfusion grade; LVEF, left ventricular ejection fraction

Key words: ST-segment elevation myocardial infarction, percutaneous coronary intervention, prourokinase, no reflow, slow blood flow, meta-analysis

Introduction

Coronary artery disease (CAD) is the most common cardiovascular disease and has a notable impact on global health (1). ST-segment elevation myocardial infarction (STEMI) is one of the most acute manifestations of CAD, which is typically characterized by acute onset and high mortality (2). The recanalization of infarct-associated arteries or culprit vessels and reestablishing myocardial perfusion is the primary treatment for STEMI (3). Percutaneous coronary intervention (PCI) is the most effective and widely used method for reopening occluded vessels (3). With the application of PCI, mortality of STEMI significantly decreased (4). However, a review revealed that certain patients may experience slow blood flow or no reflow following PCI, decreasing the benefits of PCI (5). It has been reported that the incidence of slow blood flow or no reflow after PCI in patients with STEMI is ~30%, which leads to an increase in infarct size, heart failure and mortality rate (6). Slow blood flow and no reflow following PCI in patients with STEMI are independent risk factors for short-time prognosis and long-time major adverse cardiovascular events (MACEs) (6).

High thrombus burden, prolonged reperfusion time, stent diameter and post-stent expansion are all potential factors verified to affect the incidence of slow blood flow and no reflow after PCI (7). Therefore, adequate anticoagulation before and during PCI is key for the prevention of slow blood flow and no reflow. However, anticoagulation may increase the risk of bleeding. How to properly balance decreased slow blood flow and no reflow and the potential increased risk of bleeding is an urgent cardiovascular problem for treatment of acute STEMI.

Recombinant human prourokinase (Pro-UK) is a fibrin-specific plasminogen activator that shares structural similarities with tissue plasminogen activator but functions via a different mechanism (8). Studies show that Pro-UK presents with fewer hemorrhagic complications and lower re-occlusion rate in patients with acute STEMI compared with conventional drugs (9,10). In addition, certain prospective study found that Pro-UK decreases MACEs whereas a retrospective study revealed that Pro-UK does not affect MACEs (11). To date, Pro-UK is not a frequent agent applied to patients for acute STEMI due to lack of evidence. To the best of our knowledge, there are limited studies investigating the efficacy and safety of Pro-UK in patients with acute STEMI (11,12). Therefore, further investigations are needed to assess intracoronary administration of Pro-UK and non-Pro-UK treatment in patients with acute STEMI.

Since Pro-UK is a coronary thrombolytic drug from China, most clinical trials on Pro-UK are led by Chinese scholars or conducted in China. In the present study, a meta-analysis of randomized controlled trials (RCTs) from China was performed to compare the safety and efficacy between Pro-UK and non-Pro-UK for treatment of acute STEMI. This analysis aimed to provide novel evidence-based medical information for the intracoronary application of Pro-UK in patients with acute STEMI.

Patients and methods

Search strategy. Studies published before June 2022 were retrieved from the following databases: PubMed (https://pubmed.ncbi.nlm.nih.gov/), Cochrane Library (https://www.cochranelibrary.com/) and China National Knowledge Infrastructure (CNKI) (https://www.cnki.net/). The terms 'STEMI' and 'PCI' or 'Percutaneous coronary intervention' and 'Prourokinase' or 'Pro-UK' were used as the key search words.

Selection criteria. Studies were included if the following criteria were met: i) RCT; ii) study subjects were patients with acute STEMI; iii) patients with acute STEMI received Pro-UK intracoronary therapy and iv) efficacy evaluation indicators included at least recanalization indicators, bleeding and MACEs. By contrast, studies were excluded if the following criteria were met: i) Non-RCT; ii) duplicate publication; iii) follow-up <30 days; iv) ongoing or unpublished study; v) the study did not contain the original data or statistical analysis could not be performed and vi) observational or cohort study.

Quality assessment. The included RCTs were assessed using the method of Jadad which is recommended by the Cochrane Library (13). The quality of RCTs was evaluated based on the following components: i) Randomized method; ii) allocation concealment; iii) blinding of participant personnel and outcome assessors; iv) complete outcome data; v) free of selective outcome reporting; and vi) clear causes for loss or quitting of the follow-up.

Data extraction. The data utilized in the present study were extracted by two independent authors (GF and DG) and not blinded. The information regarding first author, publication date, study design, baseline characteristics and endpoints was noted. The study method described in this article refers to previously published research by Fan *et al* (14). The endpoints included MACE, bleeding, ST-segment resolution (STR), corrected thrombolysis in myocardial infarction (TIMI) frame count (CTFC), TIMI grade 3 (TIMI-3), TIMI myocardial perfusion grade (TMPG), left ventricular ejection fraction LVEF, left ventricular end-diastolic diameter (LVEDd) and cardiac troponin I (cTnI). During extraction, a third reviewer was used to resolve any disagreement between the two authors.

Statistical analysis. The data were analyzed using Review Manager 5.3 software (Cochrane). Continuous effective outcomes are presented as standardized mean difference (SMD) while dichotomous effective outcomes were analyzed using risk ratio (RR). Continuous data were mean with SD in this study. The 95% CI was also calculated. The heterogeneity across studies was analyzed using Q-test. Values of $P>0.10$ and $I^2<50\%$ were considered to indicate no significant heterogeneity and the pooled outcomes were estimated using the Mantel-Haenszel fixed-effects model. $P\leq0.10$ and $I^2\geq50\%$ were considered to indicate significant heterogeneity and the pooled analyses were estimated using the Mantel-Haenszel random-effects model. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Included studies. Studies were screened from PubMed (n=21), Cochrane Library (n=14) and CNKI (n=164) databases. After scanning the publications, 106 of 199 studies were excluded because of irrelevant or duplicate records. After further reading, 15 of the remaining 93 studies were excluded based on the abstract. Among the remaining 78 papers, 11 were review articles, 47 were retrospective studies, five were ongoing studies and two studies were excluded owing to lack of data. Finally, a total of 13 studies comprising 1,797 patients were included in this meta-analysis, including 897 patients who received Pro-UK and 900 patients who were in the control group. The procedure for use in the study is presented in Fig. 1.

Quality assessment and baseline characteristics. The primary characteristics of the included studies are illustrated in Table I. Patient age ranged from 49.0 to 64.9 years. The bias condition of selected studies is illustrated in Fig. 2 and bias summary is indicated in Fig. 3. The quality and grading of the included articles is presented in Table II. The selected reports were RCTs from China. The Jadad scoring of the included studies ranged from 5 to 7, which indicated high quality.

Table I. Characteristics of included studies.

First author, year	Setting	Journal	N		Age, years (mean ± SD)		Endpoint		Control therapy	Follow-up days	(Refs.)
			Pro-UK	Control	Pro-UK	Control	Primary	Secondary			
Wu *et al*, 2020	Single-center	BMC Cardiovascular Disorders	25	25	59.5±14.4	61.0±12.6	Coronary physiological indexes	Angiographic/reperfusion assessment; infarct size; cardiac function	Saline	90	(15)
Jiang *et al*, 2020	Single-center	Coronary artery Disease	125	135	53.9±6.6	55.1±6.8	Infarct size; reperfusion assessment;	Cardiac function; MACEs; Hemorrhagic complications	Saline	180	(16)
Fu *et al*, 2019	Single-center	Catheter Cardiovascular Intervention	20	19	62.6±11.1	63.2±11.2	TIMI flow grade; CTFC	MACEs; Bleeding; Electrocardiogram features and myocardial necrosis markers	Thrombus aspiration	90	(17)
Huang *et al*, 2021	Multi-center	Frontiers in cardiovascular medicine	111	117	59.4±10.1	58.5±9.9	CTFC	TIMI flow grade; MACEs; Myocardial necrosis markers	Saline	30	(18)
Geng *et al*, 2018	Single-center	Journal of international Cardiology	118	112	53.5±11.4	55.2±10.4	Markers of infarct size and myocardial reperfusion	Indicators of cardiac functions; MACEs; bleeding	Saline	180	(19)
Xiao *et al*, 2019	Single-center	Coronary artery Disease	33	38	62.1±15.8	64.9±13	TMPG and IMR values	Cardiac functions; MACEs	Thrombus aspiration	90	(20)
Wang *et al*, 2020	Single-center	Coronary artery Disease	92	90	61.1±11.3	58.8±11	Incidence of restored myocardial reperfusion	TIMI flow grade; MACEs; CTFC	Saline	180	(21)
Lin *et al*, 2021	Single-center	Journal of Clinical Cardiology (China)	36	40	65.2±11.2	52.4±11.7	Incidence of restored myocardial reperfusion; CTFC	Cardiac functions; MACEs	Tirofiban	365	(22)
Wang *et al*, 2021	Single-center	Evolution and analysis of drug-use in hospitals of China	30	30	62.3±9.4	61.4±11.5	TIMI flow grade	Cardiac function; MACEs	Sodium nitroprusside	30	(23)
Zhao *et al*, 2021	Single-center	Medical Science Journal of central south China	50	50	49.6±3.5	49.9±3.9	TIMI flow grade	MACEs; Bleeding	Alteplase	180	(24)
Han *et al*, 2021	Single-center	Chinese journal crit care medicine	60	60	64.7±5.9	62.9±6.6	TIMI flow grade; CTFC; TMPG; Incidence of restored myocardial reperfusion	Cardiac functions; MACEs	Sodium nitroprusside	180	(25)
Han *et al*, 2013	Single-center	Cardiovascular Therapeutics	100	97	56.8.7±9.8	57.1±8.9	TIMI flow grade	MACEs; Bleeding	Anti-platelet	365	(26)
Zhao *et al*, 2021	Single-center	PJCCPVD	92	92	61.9±8.2	62.9±8.2	TIMI flow grade	Myocardial necrosis markers; MACEs	Tirofiban	60	(27)

Pro-UK, prourokinase; MACEs, major adverse cardiac events; CTFC, corrected TIMI frame count; TMPG, TIMI myocardial perfusion grade; PJCCPVD, Journal of Practical Cardiopulmonary Vascular Disease.

Table II. Quality of included studies.

First author, year	Randomized method	Allocation concealment	Blinding	Complete outcome data	Free of selective outcome reporting	Clear cause for loss or quitting of follow-up	Jadad score	(Refs.)
Wu *et al*, 2020	Yes	Yes	Single-blind	Yes	Yes	Yes	7	(15)
Jiang *et al*, 2020	Yes	Yes	Unclear	Yes	Yes	Yes	6	(16)
Fu *et al*, 2019	Yes	Unclear	Unclear	Yes	Yes	Yes	6	(17)
Dong *et al*, 2021	Yes	Yes	Single-blind	Yes	Yes	Yes	7	(18)
Wei *et al*, 2018	Unclear	Unclear	Single-blind	Yes	Yes	Yes	6	(19)
Xiao *et al*, 2019	Yes	Unclear	Single-blind	Yes	Yes	Yes	7	(20)
Wang *et al*, 2020	No	Yes	Single-blind	Yes	Yes	Yes	6	(21)
Lin *et al*, 2021	Yes	Unclear	Single-blind	Yes	Yes	Yes	6	(22)
Wang *et al*, 2021	Yes	Unclear	Unclear	Yes	Yes	Yes	6	(23)
Zhao *et al*, 2021	Unclear	Unclear	Unclear	Yes	Yes	Yes	5	(24)
Han *et al*, 2021	Yes	No	Unclear	Yes	Yes	Yes	6	(25)
Han *et al*, 2013	Yes	Yes	Single-blind	Yes	Yes	Yes	7	(26)
Zhao *et al*, 2021	Yes	Unclear	Unclear	Yes	Yes	Yes	6	(27)

Comparison of MACEs between groups. A total of 13 studies comprising 1,797 patients reported MACEs. There was no significant heterogeneity between studies (P=0.50; I^2=0%). The effect size of the pooled RRs was calculated using the Mantel-Haenszel fixed effects model. The results revealed that the Pro-UK group presented a significantly lower incidence of MACEs compared with that in the control group (RR, 0.68; 95% CI, 0.56-0.82; P<0.0001; Fig. 4).

Comparison of bleeding between two groups. A total of 13 studies reported bleeding, including 897 patients who received Pro-UK and 900 patients who in the control group. There was no significant heterogeneity between studies (P=0.83; I^2=0%). The results showed that there was no significant difference in bleeding incidence between the two groups (RR, 1.12; 95% CI, 0.85-1.47; P=0.41; Fig. 5).

Comparison of TIMI-3 between groups. A total of 10 studies comprising 1,301 patients reported TIMI-3, including 618 patients who received Pro-UK and 613 patients who were in the control group. There was no significant heterogeneity between studies (P=0.003; I^2=64%). The effect size of the pooled RRs was estimated using the random effects model. The Pro-UK group presented a significantly increased TIMI-3 rate compared with that in the control group (RR, 1.16; 95% CI, 1.07-1.25; P=0.0003; Fig. 6).

Comparison of TMPG-3 between groups. A total of five studies comprising 462 patients reported TMPG-3, including 235 patients who received Pro-UK and 227 patients who were in the control group. There was no significant heterogeneity between studies (P=0.02; I^2=67%). The effect size of the pooled RRs was calculated using the random effects model. The Pro-UK group presented a significantly increased TMPG-3 rate

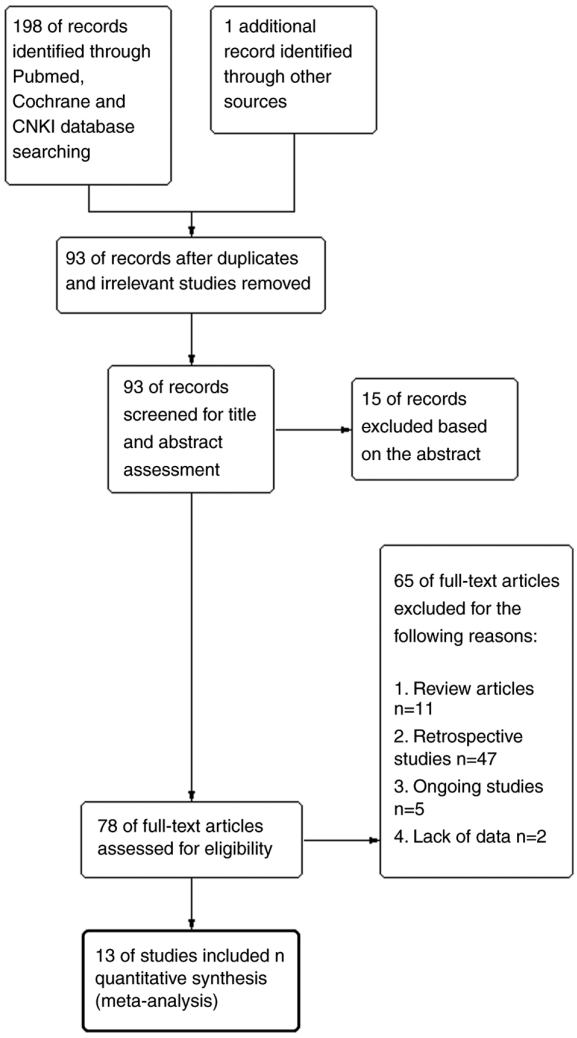

Figure 1. Flow diagram of study inclusion procedure. After screening the title/abstract, and assessing the full-text article, 13 studies were included in the final meta-analyses. CNKI, China National Knowledge Infrastructure.

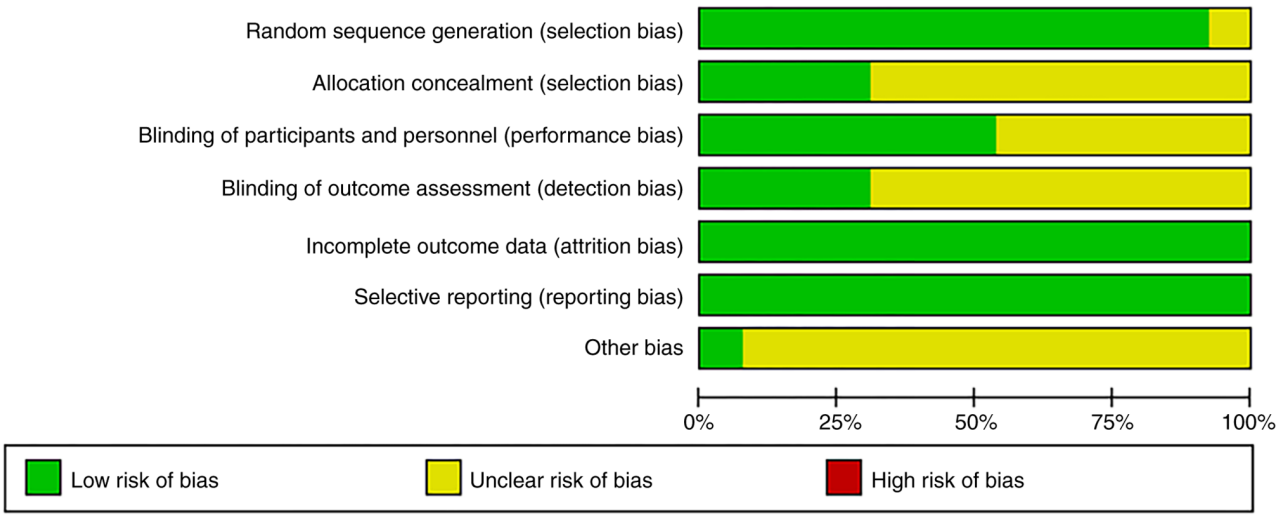

Figure 2. Risk bias of included studies.

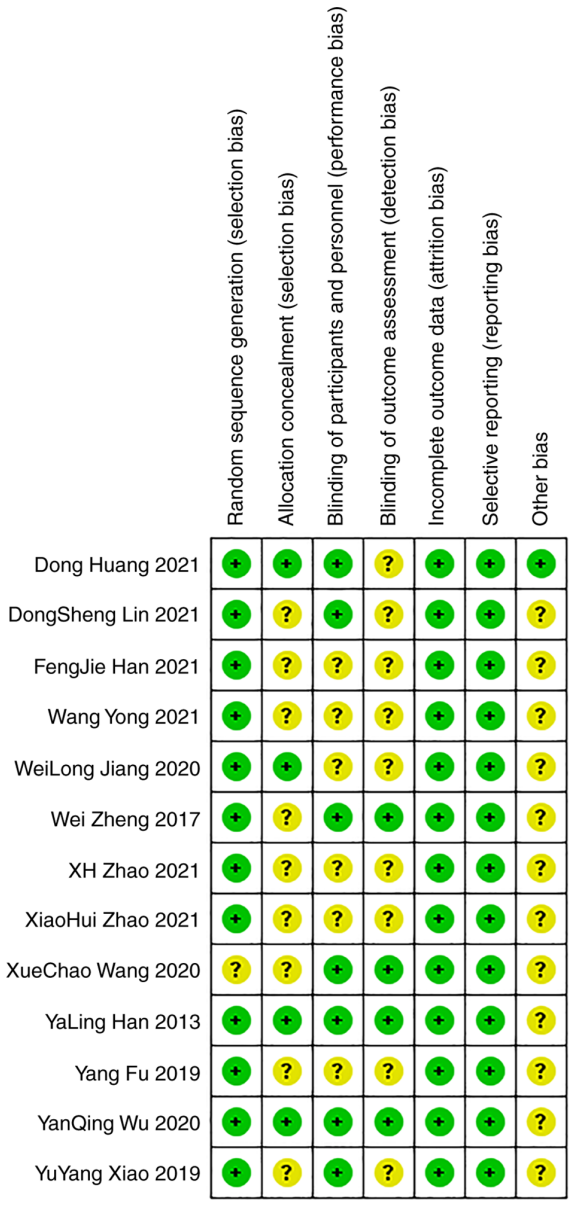

Figure 3. Risk summary of included studies. Red colors indicate high risk, Yellow colors indicate unclear risk, Green colors indicate low risk.

compared with that in the control group (RR, 1.39; 95% CI, 1.12-1.74; P=0.004; Fig. 7).

Comparison of STR between two groups. A total of nine studies comprising 1,256 patients reported STR, including 625 patients who received Pro-UK and 631 patients who were in the control group. There was no significant heterogeneity between studies (P=0.05; I^2=49%). The effect size of the pooled RRs was estimated using the Mantel-Haenszel random effects model. The Pro-UK group presented a significantly increased STR rate compared with that in the control group (RR, 1.23; 95% CI, 1.10-1.36; P=0.0002; Fig. 8).

Comparison of LVEF between groups. A total of 10 studies comprising 1,316 patients reported LVEF, including 655 patients who received Pro-UK and 661 patients who were in the control group. There was no significant heterogeneity between studies (P=0.08; I^2=42%). The effect size of the pooled SMD was estimated using the Mantel-Haenszel fixed effects model. The Pro-UK group presented a significantly higher LVEF compared with the control group (SMD: 0.38, 95% CI: 0.27-0.49, P<0.00001, Fig. 9).

Comparison of LVEDd between groups. A total of six studies comprising 796 patients reported LVEDd, including 304 patients who received Pro-UK and 402 patients who were in the control group. There was no significant heterogeneity between studies (P=0.36; I^2=9%). The effect size of pooled SMD was estimated using the fixed effects model. The Pro-UK group presented a significantly decreased LVEDd compared with that in the control group (SMD, -0.26; 95% CI, -0.40 – -0.12; P=0.0003; Fig. 10).

Comparison of CTFC between groups. A total of five studies comprising 570 patients reported CTFC, including 286 patients who received Pro-UK and 284 patients who were in the control group. There was no significant heterogeneity between studies (P=0.76; I^2=0%). The effect size of pooled SMD was estimated using Mantel-Haenszel fixed effects

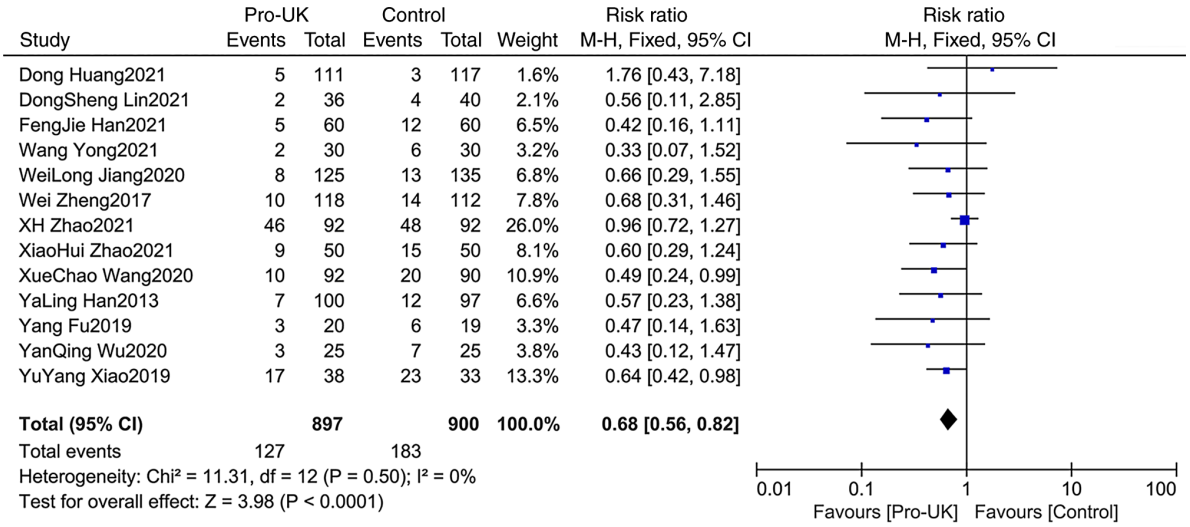

Figure 4. Meta-analysis of major adverse cardiac events. Pro-UK, prourokinase; M-H, Mantel-Haenszel.

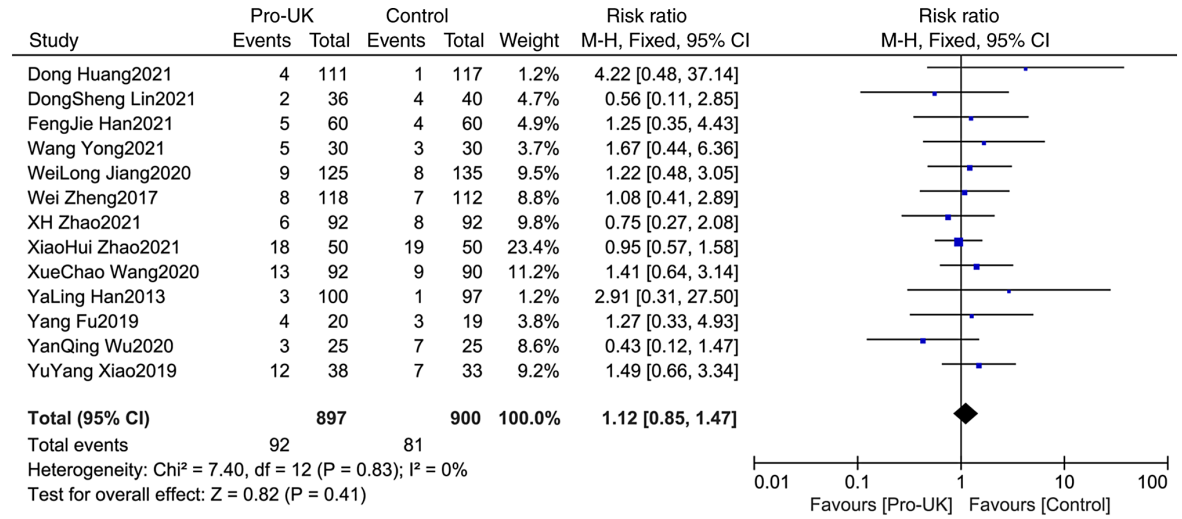

Figure 5. Meta-analysis of bleeding. Pro-UK, prourokinase; M-H, Mantel-Haenszel.

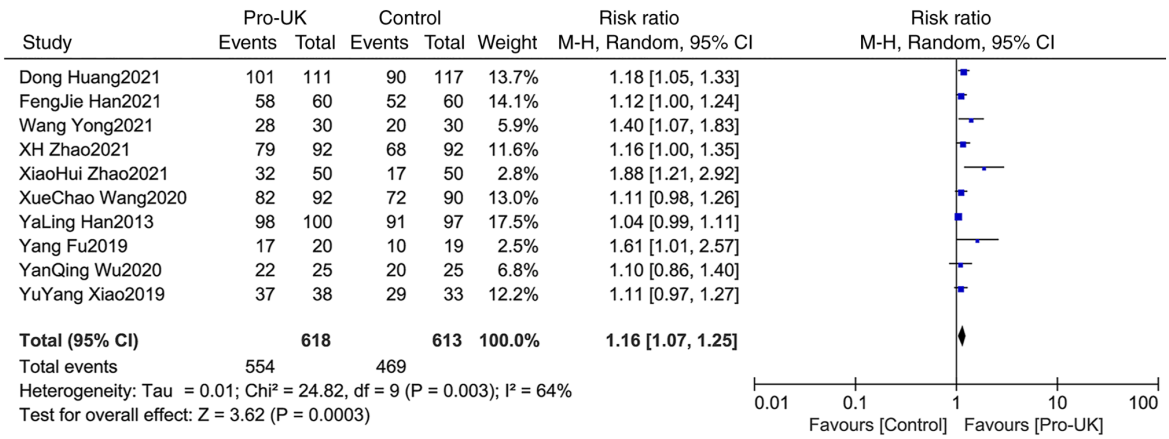

Figure 6. Meta-analysis of thrombolysis in myocardial infarction grade 3. Pro-UK, prourokinase; M-H, Mantel-Haenszel.

model. The Pro-UK group presented a significantly decreased CTFC compared with that in the Control group (SMD, -0.45; 95% CI, -0.62 – -0.28, P<0.00001; Fig. 11).

Comparison of cTnI between groups. A total of four studies comprising 722 patients reported cTnI, including 360 patients who received Pro-UK and 362 patients who were in the control

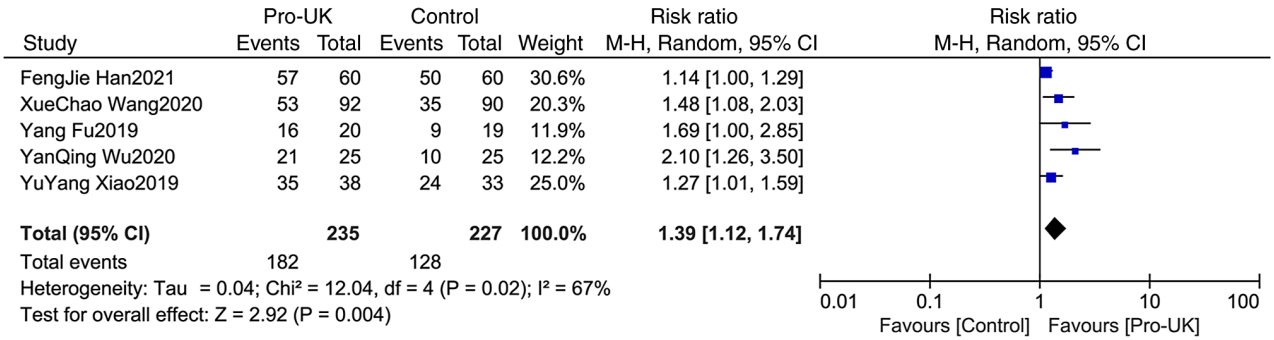

Figure 7. Meta-analysis of TIMI myocardial perfusion grade 3. Pro-UK, prourokinase; M-H, Mantel-Haenszel.

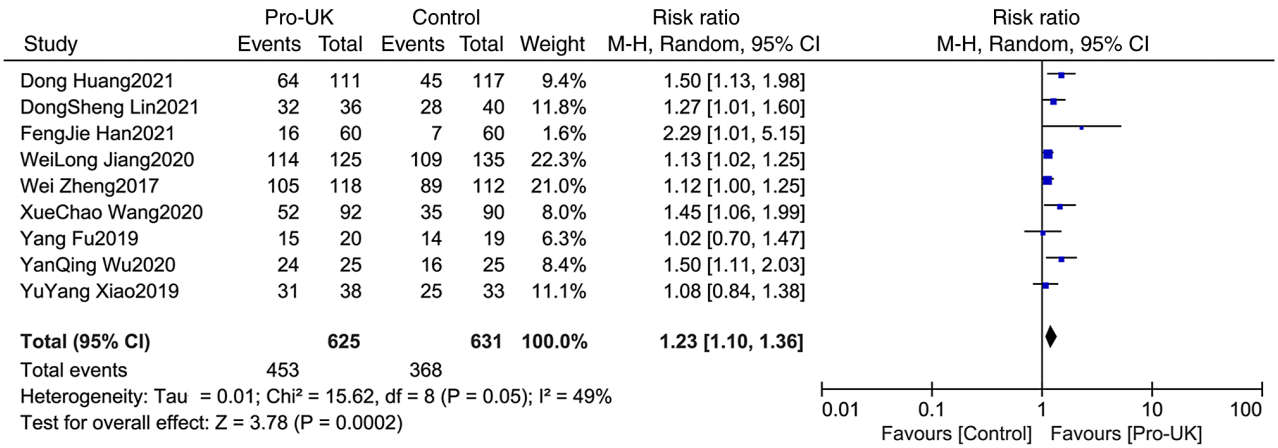

Figure 8. Meta-analysis of ST-segment resolution. Pro-UK, prourokinase; M-H, Mantel-Haenszel.

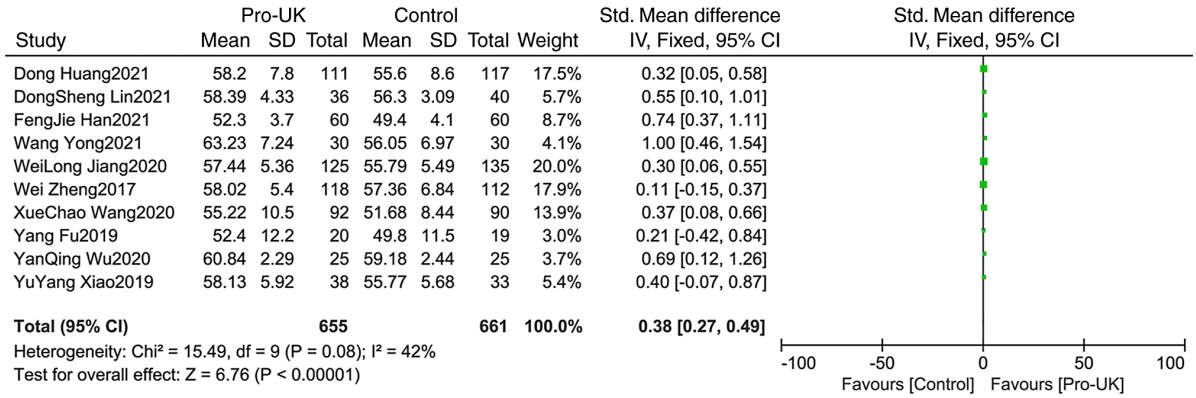

Figure 9. Meta-analysis of left ventricular ejection fraction.

group. There was no significant heterogeneity between studies (P=0.67; I^2=0%). The effect size of pooled SMD was estimated using the fixed effects model. The Pro-UK group presented a significantly decreased cTnI level compared with that in the control group (SMD, -0.31; 95% CI, -0.46 – -0.17; P<0.0001; Fig. 12).

Discussion

Altogether, 13 RCTs were included in the present meta-analysis. The pooled data estimations revealed that intracoronary Pro-UK administration was associated with decreased MACEs, LVEDd, CTFC and cTnI levels in patients with acute STEMI. Additionally, there were increased TIMI-3, TMPG-3, STR rate and LVEF levels in the Pro-UK group compared with those in the control group. No significant difference was identified regarding the safety indexes (bleeding) between groups.

The primary aim for the treatment of acute STEMI is to restore effective perfusion of the myocardium and minimize ischemic damage. PCI is the first option to reopen infarct-associated arteries and restore coronary blood flow (28). Stent implantation in patients with acute STEMI is beneficial. However, the incidence of slow blood flow or no reflow after PCI in patients with STEMI is ~30%, which

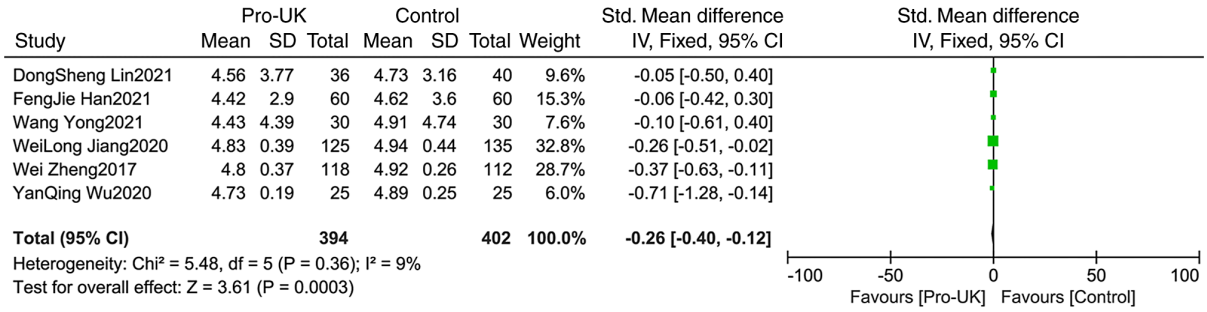

Figure 10. Meta-analysis of left ventricular end-diastolic diameter.

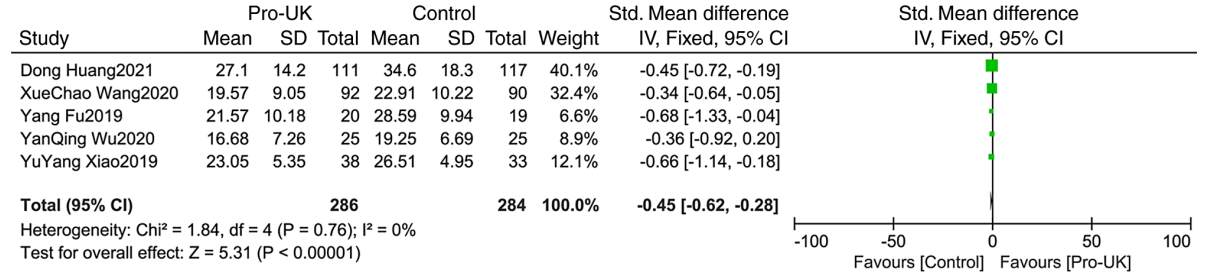

Figure 11. Meta-analysis of corrected TIMI frame count.

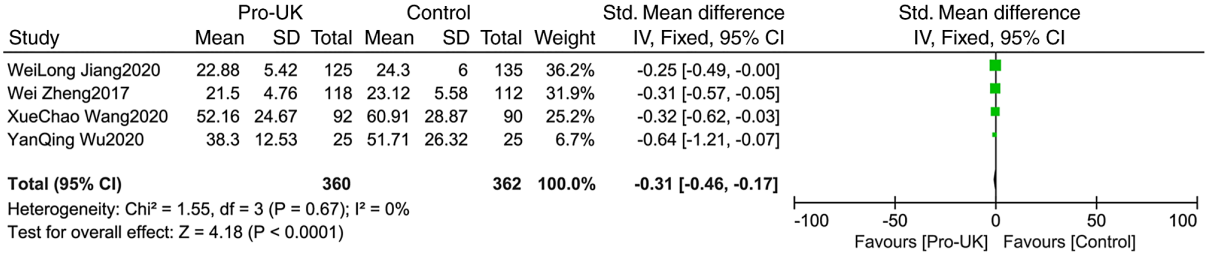

Figure 12. Meta-analysis of cardiac troponin I.

usually leads to worse prognosis (29). Patients with STEMI and slow blood flow or no reflow have higher MACE occurrence rate compared with those with optimal flow (30). Delayed reperfusion, high thrombosis burden, glucose levels and stent diameter are factors that contribute to slow blood flow or no reflow following PCI (31).

High-burden thrombosis is the most important risk factor for no reflow or slow blood flow phenomena following PCI (32). Thrombus aspiration (TA) is a common method used for treating intracoronary thrombus, but TA cannot completely remove the thrombus and no reflow rate is still high following emergency PCI (33). Moreover, TA may cause local micro-thrombosis, which leads to no reflow or slowed blood flow and affects myocardial perfusion, increasing the risk of recurrent myocardial infarction, cardiogenic shock and malignant arrhythmia (33). Evidence-based study have suggested that TA is not associated with a decrease in long-term mortality or clinical outcomes in patients with STEMI (34). Currently, drugs such as tirofiban, sodium nitroprusside, nicorandil and diltiazem are widely used to decrease coronary thrombus burden. However, the incidence of no reflow after PCI is still high, which affects the prognosis of acute STEMI (35,36).

Recombinant human Pro-UK is the precursor of urokinase. The activated plasminogen combines with the thrombus Y/E tablet segment. Pro-UK quickly reacts with kininase and selectively activates plasminogen in thrombus fibrin, but it does not activate free plasminogen. Therefore, Pro-UK may decrease or avoid cytotoxicity, coagulation system allergy and systemic hemorrhage and other adverse events (37).

In the current study, 13 relatively high-quality RCTs were included. The present results revealed that intracoronary administration of Pro-UK therapy was associated with a lower incidence of MACEs (RR 0.68; 95% CI, 0.56-0.82; P<0.0001), lower LVEDd (SMD, -0.26; 95% CI, -0.40 – -0.12; P=0.0003), CTFC (SMD, -0.45; 95% CI, -0.62 – -0.28; P<0.00001) and cTnI (SMD, -0.31; 95% CI, -0.46 – -0.17; P<0.0001) in treating patients with acute STEMI. Furthermore, Pro-UK treatment had higher TIMI-3 (RR, 1.16; 95% CI, 1.07-1.25; P=0.0003), TMPG-3 (RR, 1.39; 95% CI, 1.12-1.74; P=0.004), STR (RR, 1.23; 95% CI, 1.10-1.36; P=0.0002) and LVEF (SMD, 0.38; 95% CI, 0.27 – -0.49; P<0.00001). Bleeding incidence (RR, 1.12; 95% CI, 0.85-1.47; P=0.41) was comparable between groups. Based on the present meta-analysis, intracoronary administration of Pro-UK during PCI in treatment of patients

with acute STEMI should be recommended in clinical practice.

Certain limitations of the present meta-analysis should be mentioned. First, the meta-analysis was based on published RCTs and some large-scale ongoing trials were not included. Second, the analysis was performed on the trial level, not on the patient level. Third, there was only one multicenter trial in our meta-analysis that evaluated the Pro-UK effect. Additionally, the follow-up duration in studies was not uniform. Use of additional databases (such as Web of Science (https://www.webofscience.com/) and European Molecular Biology Organization (http://www.embo.org/) is required to validate the present results.

Intracoronary administration of Pro-UK not only decreases MACE, LVEDd, and cTnI levels, but also increases TIMI-3, TMPG-3, STR, and LVEF levels in patients with acute STEMI. Pro-UK is safe and effective to combine with PCI in treating patients with acute STEMI. However, more large-scale multicenter RCTs comparing Pro-UK and non-Pro-UK studies are needed to confirm this conclusion.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

All data generated and/or analyzed during this study are included in this published article.

Authors' contributions

GF and DG conceived and designed the study. GF, XW and WJ carried out literature search, study selection and quality assessment. WJ and HZ performed data extraction. GF and HZ confirm the authenticity of all the raw data. GF, XW, DG and WJ performed statistical analysis. GF wrote the manuscript. GF and DG interpreted the data and revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing of interests

The authors declare that they have no competing interests.

References

1. Ralapanawa U and Sivakanesan R: Epidemiology and the magnitude of coronary artery disease and acute coronary syndrome: A narrative review. J Epidemiol Glob Health 11: 169-177, 2021.
2. Poudel I, Tejpal C, Rashid H and Jahan N: Major adverse cardiovascular events: An inevitable outcome of ST-elevation myocardial infarction? A Literature Review. Cureus 11: e5280, 2019.
3. Vogel B, Mehta SR and Mehran R: Reperfusion strategies in acute myocardial infarction and multivessel disease. Nat Rev Cardiol 14: 665-678, 2017.
4. Ottani F, Limbruno U, Latini R, Misuraca L and Galvani M: Reperfusion in STEMI patients: Still a role for cardioprotection? Minerva Cardioangiol 66: 452-463, 2018.
5. Muller O, Trana C and Eeckhout E: Myocardial no-reflow treatment. Curr Vasc Pharmacol 11: 278-275, 2013.
6. Soeda T, Higuma T, Abe N, Yamada M, Yokoyama H, Shibutani S, Ong DS, Vergallo R, Minami Y, Lee H, *et al*: Morphological predictors for no Reflow phenomenon after primary percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction caused by plaque rupture. Eur Heart J Cardiovasc Imaging 18: 103-110, 2017.
7. Movahed MR and Butman SM: The pathogenesis and treatment of no-reflow occurring during percutaneous coronary intervention. Cardiovasc Revasc Med 9: 443, 2007.
8. Gurewich V: Fibrinolysis: A misunderstood natural defense whose therapeutic potential is unknown. Cardiovasc Drugs Ther 33: 749-753, 2019.
9. Liu Y, Yang Y, Li Y and Peng X: Comparison of efficacy and safety of recombinant human prourokinase and alteplase in the treatment of STEMI and analysis of influencing factors of efficacy. Evid Based Complement Alternat Med 2021: 6702965, 2021.
10. Chen T, Wang Q, Liu G, Jin Q, Liu C, Gao L, Chen Y and Guo J: Safety and efficacy of intracoronary thrombolytic therapy via a new infusion catheter in patients with ST-segment elevation myocardial infarction with large thrombus burden: A pilot study. Coron Artery Dis 32: 205-210, 2020.
11. Yao Z, Li W, Cheng L, Cao M, Pang Z and Li Y: Comparison of the effect of recombinant human pro-urokinase and tirofiban on myocardial blood flow perfusion in ST elevation myocardial infarction patients receiving primary percutaneous coronary intervention: A one-center retrospective observational study. Medicine (Baltimore) 98: e16143, 2019.
12. Gao J, Wang WJ, Liu YH and Luo DL: Efficacy analysis of half-dose recombinant human prourokinase thromboiysis compined with early PCI in 48 patients with ST-segment-elevation myocardial infarction (STEMI). Asian J Surg: Oct 6, 2022 (Epub ahead of print).
13. Beitland S, Sandven I, Kjærvik LK, Sandset PM, Sunde K and Eken T: Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: A systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 41: 1209-1219, 2015.
14. Fan G, Zhang YW, Lin L, Chen M, Wei J and Diao J: Optimal reperfusion strategy in patients with acute STEMI and multivessel disease-an updated meta-analysis. Herz 45: 272-279, 2020.
15. Wu Y, Fu X, Feng Q, Gu X, Hao G, Fan W and Jiang Y: Efficacy and safety of intracoronary prourokinase during percutaneous coronary intervention in treating ST-segment elevation myocardial infarction patients: A randomized, controlled study. BMC Cardiovasc Disord 20: 308, 2020.
16. Jiang W, Xiong X, Du X, Ma H, Li W and Cheng F: Safety and efficacy study of prourokinase injection during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction. Coron Artery Dis 32: 25-30, 2021.
17. Fu Y, Gu XS, Hao GZ, Jiang YF, Fan WZ, Fan YM, Wei QM, Fu XH and Li YJ: Comparison of myocardial microcirculatory perfusion after catheter-administered intracoronary thrombolysis with anisodamine versus standard thrombus aspiration in patients with ST-elevation myocardial infarction. Catheter Cardiovasc Interv 93: 839-845, 2019.
18. Huang D, Qian J, Liu Z, Xu Y, Zhao X, Qiao Z, Fang W, Jiang L, Hu W, Shen C, *et al*: Effects of Intracoronary Pro-urokinase or tirofiban on coronary flow during primary percutaneous coronary intervention for acute myocardial infarction: A Multi-center, placebo-controlled, single-blind, randomized clinical trial. Front Cardiovasc Med 8: 710994, 2021.
19. Geng W, Zhang Q, Liu J, Tian X, Zhen L, Song D, Yang Y, Meng H, Wang Y and Chen J: A randomized study of prourokinase during primary percutaneous coronary intervention in acute ST-segment elevation myocardial infarction. J Interv Cardiol 31: 136-143, 2018.

20. Xiao Y, Fu X, Wang Y, Fan Y, Wu Y, Wang W and Zhang Q: Effects of different strategies on high thrombus burden in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary catheterization. Coron Artery Dis 30: 555-563, 2019.
21. Wang X, Liu H, Wu H, Xiao Y, Bai S, Li X, Li X, Zhang L, Chen T, Li H, *et al*: Safety and efficacy of intracoronary prourokinase administration in patients with high thrombus burden. Coron Artery Dis 31: 493-499, 2020.
22. Lin D, Fu G, Chun HZ, Lixia M, Luohui and Zhaofei W: Effect of low-dose recombinant human prourokinase and tirofiban on myocardial perfusion in STEMI patients with primary PCI. J Clin Cardiol (China) 37: 215-219, 2021 (In Chinese).
23. Yong W, Gao J, Hu J, Wang Y, Qing H and Pei L: Improvement of combined application of sodium nitroprusside and recombinant human prourokinase in coronary artery on no-reflow in elderly patients with acute STEMI during emergency PCI. Evolution Analysis Drug-Use Hosp China 21: 19-22, 2021 (In Chinese).
24. Zhao X, Lu S, Jie C, Yang X and Huizhe W: The evaluation of recombinant human prourokinase versus alteplase in the treatment of acute STEMI. Med Sci J Central South China 49: 72-77, 2021 (In Chinese).
25. Han F, Haijun Z, Zhongming W, Cuiting Q, Hui Z, Hui J, Jing L, Qingqing Z and Yanxia Z: Effect of recombinant human prourokinase combined with sodium nitroprusside and tirofiban by intracoronary injection on the efficacy of PCI in STEMI patients with high thrombus load. Chin J Crit Care Med 41: 1028-1034, 2021 (In Chinese).
26. Han YL, Liu JN, Jing QM, Ma YY, Jiang TM, Pu K, Zhao RP, Zhao X, Liu HW, Xu K, *et al*: The efficacy and safety of pharmacoinvasive therapy with prourokinase for acute ST-segment elevation myocardial infarction patients with expected long percutaneous coronary intervention-related delay. Cardiovasc Ther 31: 285-290, 2013.
27. Zhao X, Shuangdong L, Jie C, Yang X and Huizhe W: Preventive effect of recombinant human prourokinase on no reflow phenomenon in patients with STEMI after PCI. J Prac Cardiovas Dis 29: 105-109, 2021 (In Chinese).
28. Keeley EC, Boura JA and Grines CL: Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review of 23 randomised trials. Lancet 361: 13-20, 2003.
29. Morishima I, Sone T, Okumura K, Tsuboi H, Kondo J, Mukawa H, Matsui H, Toki Y, Ito T and Hayakawa T: Angiographic no-reflow phenomenon as a predictor of adverse long-term outcome in patients treated with percutaneous transluminal coronary angioplasty for first acute myocardial infarction. J Am Coll Cardiol 36: 1202-1209, 2000.
30. Ito H, Okamura A, Iwakura K, Masuyama T, Hori M, Takiuchi S, Negoro S, Nakatsuchi Y, Taniyama Y, Higashino Y, *et al*: Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. Circulation 93: 1993-1999, 1996.
31. Dong-Bao L, Qi H, Zhi L, Shan W and Wei-Ying J: Predictors and long-term prognosis of angiographic slow/no-reflow phenomenon during emergency percutaneous coronary intervention for ST-elevated acute myocardial infarction. Clin Cardiol 33: E7-E12, 2010.
32. Kumar R, Khan KA, Shah JA, Ammar A, Kumar D, Khowaja S, Sial JA, Kazmi S, Murtaza M and Karim M: Quantification of thrombus burden as an independent predictor of intra-procedural No-reflow in patients with St-segment elevation myocardial infarction undergoing primary percutaneous coronary revascularization. J Ayub Med Coll Abbottabad 34: 288-294, 2022.
33. Scarpone M, Cenko E and Manfrini O: Coronary No-reflow phenomenon in clinical practice. Curr Pharm Des 24: 2927-2933, 2018.
34. Elgendy AY, Elgendy IY, Mahmoud AN and Bavry AA: Long-term outcomes with aspiration thrombectomy for patients undergoing primary percutaneous coronary intervention: A meta-analysis of randomized trials. Clin Cardiol 40: 534-541, 2017.
35. Zhang Z, Li W, Wu W, Xie Q, Li J, Zhang W and Zhang Y: Myocardial reperfusion with tirofiban injection via aspiration catheter: Efficacy and safety in STEMI patients with large thrombus burden. Herz 45: 280-287, 2020.
36. Zhang L, Qi X and Jia X: Effect of different methods of administration of diltiazem on clinical efficacy in patients with acute ST-segment elevation myocardial infarction. Med Sci Monit 24: 6544-6550, 2018.
37. Zhao L, Zhao Z, Chen X, Li J, Liu J and Li G; Group of Prourokinase Phase IV Clinical Trials Investigators: Safety and efficacy of prourokinase injection in patients with ST-elevation myocardial infarction: Phase IV clinical trials of the prourokinase phase study. Heart Vessels 33: 507-512, 2018.