Ulinastatin reduces postoperative bleeding and red blood cell transfusion in patients undergoing cardiac surgery

A PRISMA-compliant systematic review and meta-analysis

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Abstract

Background: Ulinastatin is a type of glycoprotein and a nonspecific wide-spectrum protease inhibitor like antifibrinolytic agent aprotinin. Whether Ulinastatin has similar beneficial effects on blood conservation in cardiac surgical patients as aprotinin remains undetermined. Therefore, a systematic review and meta-analysis were performed to evaluate the effects of Ulinastatin on perioperative bleeding and transfusion in patients who underwent cardiac surgery.

Methods: Electronic databases were searched to identify all clinical trials comparing Ulinastatin with placebo/blank on postoperative bleeding and transfusion in patients undergoing cardiac surgery. Primary outcomes included perioperative blood loss, blood transfusion, postoperative re-exploration for bleeding. Secondary outcomes include perioperative hemoglobin level, platelet counts and functions, coagulation tests, inflammatory cytokines level, and so on. For continuous variables, treatment effects were calculated as weighted mean difference (WMD) and 95% confidential interval (CI). For dichotomous data, treatment effects were calculated as odds ratio and 95% CI. Statistical significance was defined as P < .05.

Results: Our search yielded 21 studies including 1310 patients, and 617 patients were allocated into Ulinastatin group and 693 into Control (placebo/blank) group. There was no significant difference in intraoperative bleeding volume, postoperative re-exploration for bleeding incidence, intraoperative red blood cell transfusion units, postoperative fresh plasma transfusion volumes and platelet concentrates transfusion units between the 2 groups (all P > .05). Ulinastatin reduces postoperative bleeding (WMD = −0.73, 95% CI: −1.17 to −0.28, P = .001) and red blood cell (RBC) transfusion (WMD = −0.70, 95% CI: −1.26 to −0.14, P = .01), inhibits hyperfibrinolysis as manifested by lower level of postoperative D-dimer (WMD = −0.87, 95% CI: −1.34 to −0.39, P = .0003).

Conclusion: This meta-analysis has found some evidence showing that Ulinastatin reduces postoperative bleeding and RBC transfusion in patients undergoing cardiac surgery. However, these findings should be interpreted rigorously. Further well-conducted trials are required to assess the blood-saving effects and mechanisms of Ulinastatin.

Abbreviations: α2-AP = α2-antiplasmin, ACT = activated coagulation time, APTT = activated partial thromboplastin time, AT = antithrombin, AT-III:A = AT-III activity, CABG = coronary artery bypass grafting, CI = confidence interval, CPB = cardiopulmonary bypass, F1 + 2 = prothrombin fragment 1 + 2, FXI:C = factor XI pro-coagulant activity, IL = interleukin, MFI = mean fluorescence intensity, OR = odds ratio, PA = plasminogen activator, PAGM% = maximum platelet aggregation ratio, PMNE = polymorphonuclear elastase, TAT = thrombin-antithrombin complex, TEG = thromboelastography, TNF-α = tumor necrosis factor-α, TXB = thromboxane, WMD = weighted mean difference.

Keywords: bleeding, cardiac surgery, meta-analysis, transfusion, Ulinastatin
1. Introduction

The result of the blood conservation using antifibrinolytics in a randomized trial led to the suspension of aprotinin use in cardiac surgery by Food and Drug Administration in the USA in 2007 over concerns of increased mortality.[1] Subsequently, aprotinin was withdrawn from the Chinese market in December 2007.[2]

Ulinastatin or urinary trypsin inhibitor, is a type of glycoprotein and a nonspecific wide-spectrum protease inhibitor.[3,4] Currently, Ulinastatin is used in China, Korea, Japan, and India. A large body of convincing evidence has indicated that, Ulinastatin can not only reduce the release of pro-inflammatory cytokines, but also provide vital organ protection in patients undergoing cardiac surgery for coronary artery diseases, heart valve diseases, congenital heart diseases.[5–7] A previous study found that Ulinastatin normalized coagulation function and prevented changes in thromboelastography (TEG) during liver surgery.[8] Another study by Ji et al demonstrated that, Ulinastatin shortened activated partial thromboplastin time (APTT) and activated coagulation time (ACT) after systemic heparinization in patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB).[9] Whether Ulinastatin has similar beneficial effects on blood conservation in cardiac surgical patients as aprotinin remains undetermined.[10–12] Therefore, we performed this meta-analysis to evaluate the effects of Ulinastatin on bleeding and transfusion in patients undergoing cardiac surgery.

2. Methods

2.1. Ethical approval

This study was a meta-analysis of previously published literatures, ethical approval was not necessary under the ethical committee of Fujui Hospital.

2.2. Search strategy

We conducted a systemic review according to the preferred reporting items for systemic reviews and meta-analysis quality of reporting of meta-analysis Guidelines (Supplement Table 1, http://links.lww.com/MD/D776).[10] The protocol of current meta-analysis was published in PROSPERO with the registration number of CRD42018115698. Relevant trials were identified by computerized searches of MEDLINE, Cochrane Library and EMBASE till January 6th, 2019, using different combination of search words as follows: (cardiopulmonary bypass OR heart OR cardiac surgery OR coronary artery bypass surgery) AND (Ulinastatin OR urinary trypsin inhibitor OR Miraclid OR Ulinase OR Bikunin OR Urinastatin) AND (bleeding OR blood loss OR transfusion) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial) (Appendix, http://links.lww.com/MD/D771). No language restriction was used. We also searched the Chinese BioMedical Literature & Retrieval System (from 1978 to January 6th, 2019). Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

2.3. Inclusion and exclusion criteria

We included all clinical trials comparing Ulinastatin with placebo or blank with respect to bleeding and transfusion in patients undergoing cardiac surgery. In studies which also included other comparator drugs, only data of Ulinastatin and placebo/blank groups were abstracted. Primary outcomes of interest included intra- and postoperative blood loss, blood transfusion (red blood cells, plasma, platelet concentrates, cryoprecipitate), postoperative re-exploration for bleeding. Secondary outcomes of interest include perioperative hemoglobin level, platelet counts and functions, coagulation tests, inflammatory cytokines level, and so on.

Exclusion criteria included

1. studies published as review, case report or abstract;
2. animal or cell studies;
3. duplicate publications;
4. studies only comparing Ulinastatin with aprotinin, tranexamic acid;
5. studies lacking information about outcomes of interest.

The 2 authors (NXF and DHL) independently reviewed the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion was further determined by reading the full text.

2.4. Study quality assessment

Two authors (NXF and DHL) independently assessed the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions.[11] The Jadad score was used independently by 2 authors (NXF and DHL) to evaluate the methodological quality of each included trial.

The Jadad scoring system (ranging from 0 to 5) includes:

1. randomization process;
2. blindedness assessment; and
3. reporting of withdrawals/dropouts.

Higher scores indicate excellent methodologic qualities, and lower scores suggest poor qualities.[12]

2.5. Data abstraction

The following data were abstracted from the included studies to a data collection form by 2 authors (YTY and NXF) independently:

1. author, year of publication, and journal of included studies;
2. total number of patients, number of patients in Ulinastatin and control groups, gender, age;
3. type of surgical procedure, CPB time, and aortic cross-clamping time;
4. data regarding outcomes of interest in both groups.

Disagreements were resolved by discussion among all authors during the process of data abstraction. The authors of the included studies were contacted if necessary. For trials in which continuous outcomes were reported as median and range, median and standard deviation were estimated by utilizing the O’Rourke method.[13] When the results of the trial were reported as median and quartile, the Stela Pudar-Hozo method was used to estimate the mean and standard deviation.[14]

2.6. Statistical analysis

All data were analyzed by utilizing RevMan 5.3 (Cochrane Collaboration, Oxford, UK). Pooled odds ratio (OR) and 95%
confidence interval (CI) were estimated for dichotomous data, and weighted mean difference (WMD) and 95% CI for continuous data, respectively. Each outcome was tested for heterogeneity, and randomized-effects or fixed-effects model was used in the presence or absence of significant heterogeneity ($I^2 > 50\%$). Sensitivity analyses were done by examining the influence of statistical model on estimated treatment effects, and analyses which adopted the fixed-effects model were repeated again by using randomized-effects model and vice versa. In addition to that, sensitivity analysis was also performed to evaluate the influence of individual study on the overall effects. The possible effects of patient age, gender, country, surgery type, and CPB on postoperative bleeding and transfusion were evaluated by meta-regression. Publication bias was explored through visual inspection of funnel plots of the outcomes, and evaluated by Begg test with STATA 14.0 (Stata Corp, College station, TX). All P-values were 2-sided and statistical significance was defined as $P < .05$.

3. Results

3.1. Search results

As depicted in the flow chart (Fig. 1), database search identified 34 articles for complete evaluation. Finally, 21 eligible trials were included in the meta-analysis. Descriptive analyses of these articles were presented in Table 1. Of the 21 literatures, 9 were written in English, and the other 12 were in Chinese. Ulinastatin administration protocols (dosage, timing, and route) varied among included trials.

3.2. Included trials characteristics

As shown in Table 2, 5 studies included only CABG patients (3 studies for on-pump CABG and 2 for off-pump CABG), 6 studies included only valve surgical patients, 2 studies included only patients undergoing repair for congenital heart diseases, 1 study included only aortic surgical patients, the other 7 studies involving patients with mixed surgery procedures. The 21 eligible trials involved totally 1310 patients, and 617 patients were allocated into Ulinastatin group and 693 into Control (placebo/blank) group. Pre- and intraoperative data of these patients were presented in Table 2. The study by Shu et al measured 2 doses of Ulinastatin, it was; therefore, considered as 2 independent groups.

3.3. Study quality and risk bias

The risk of bias analysis was shown in Supplement Figures 1, http://links.lww.com/MD/D772 and 2, http://links.lww.com/MD/D773. Of the 21 included trials, 8 trials were
had Jadad scores ≥3 and were considered as high-quality randomized controlled trials (RCTs) (Supplement Table 2, http://links.lww.com/MD/D777).

3.4. Effects on intra- and postoperative bleeding

As shown in Figure 2 and Table 3, 3 trials [16,18,24] (118 patients) evaluated the effect of Ulinastatin on intraoperative bleeding, and 16 trials [9,16–22,24–29,33,34] (944 patients) reported blood loss in the first 24 hours postoperatively. Meta-regression suggested patient age, gender, country, surgery type, and CPB did not influence the result. Meta-analysis showed that, Ulinastatin administration did not significantly decrease intraoperative bleeding ([WMD = 0.13; 95% CI: −0.23 to 0.49; P = 0.49] without heterogeneity [I² = 39%, P = .19]), but significantly reduced postoperative bleeding volume ([WMD = −0.73; 95% CI: −1.17 to −0.28; P = .001] with heterogeneity [I² = 89%, P < .00001]).

As shown in Table 3, 4 trials [19,37,27,34] (302 patients) reported re-exploration for postoperative bleeding. Meta-analysis showed no difference in the rate of re-exploration for bleeding between Ulinastatin and Control groups (4/151[2.6%] vs 7/151 [4.6%], [OR = 0.59; 95% CI: 0.18–1.93; P = .38] without heterogeneity [I² = 0%, P = .60]).

3.5. Effects on intra- and postoperative blood transfusion

As depicted in Table 3 and Figure 3, 3 trials [18–20] (208 patients) reported data on intraoperative RBC transfusion volume, 10 trials [9,18,21,25–28,34] (640 patients) reported postoperative RBC

### Table 1

| First author | Year | Journal | Country | Language | Ulinastatin administration | Control |
|--------------|------|---------|---------|----------|-----------------------------|---------|
| Chen TT[16] | 2013 | Heart Surg Forum | China | English | 12,000 U/kg iv. after AI | Saline |
| Ji BY[9] | 2007 | J Cardiovasc Surg | China | English | 12,000 U/kg added to CPB prime | Saline |
| Ji HW[9] | 2009 | Zhonghua Yi Xue Za Zhi | China | Chinese | 300,000 U iv. before CPB | Saline |
| Jin XG[22] | 2005 | Chin Pharm J | China | Chinese | 300,000 U iv. after AI | Saline |
| Kim NY[16] | 2013 | Korean J Anesthesiol | Korea | English | 300,000 U iv. after Al | Saline |
| Le HB[30] | 2005 | Zhejiang Med | China | Chinese | 300,000 U added to CPB prime | Saline |
| Nakanishi K[16] | 2006 | Crit Care Med | Japan | English | 5,000 U/kg iv. before CPB | Saline |
| Pang XY[15] | 2016 | Am J Tier | China | English | 5,000 U/kg iv. after AI | Saline |
| Park JI[16] | 2013 | Korean J Thoracic Cardiovasc Surg | Korea | English | 5,000 U/kg iv. before ACC | Saline |
| Qiu Y[23] | 2015 | Chin Med J | China | English | 5,000–10,000 U/kg iv. before incision | No Uli |
| Shi J[44] | 2010 | PUMC Doctorate Thesis | China | Chinese | 1,000,000 U iv. after AI | Saline |
| Shi ZR[27] | 2008 | Jiangsu Med J | China | Chinese | 20,000 U/kg added to CPB prime | Saline |
| Shu YZ[26] | 2003 | Guangzhou Med J | China | Chinese | (130,000 U added to CPB prime | No Uli |
| Song JE[20] | 2011 | J Int Med Res | Korea | English | 5000 U/kg iv. before ACC | Saline |
| Tan RD[20] | 2011 | Mod Hosp | China | Chinese | 300,000 U iv. after AI | Saline |
| Wang Gy[24] | 2010 | Chin J ECC | China | Chinese | 6000 U/kg iv. after AI | Saline |
| Xu CE[17] | 2013 | J Cardiothorasc Vasc Anesth | China | English | 1000 U/kg iv. till end of surgery | Saline |
| Yang WH[36] | 2010 | Med Recap | China | Chinese | 12,000 U/kg iv. after AI | Saline |
| Yu JG[33] | 2003 | Chin J Anesthesiol | China | Chinese | 6000 U/kg iv. after AI | Saline |
| Zhang BJ[21] | 2007 | J Cardiovasc Dis | China | Chinese | 300,000 U iv. after AI | Saline |
| Zhai YJ[25] | 2004 | Chin J ECC | China | Chinese | 12,000 U/kg iv. after AI | Saline |

ACC = aortic cross-clamping, AI = anesthesia induction, CPB = cardiopulmonary bypass, Uli = Ulinastatin.
Table 2

| Sample size | Age, yr | Sex (M/F) | Surgery | CPB, min | ACC, min |
|-------------|---------|-----------|---------|----------|----------|
| Group Uli | Group C | Group Uli | Group C | Group Uli | Group C | Group Uli | Group C | Group Uli | Group C |
| Chen 2013 | 30 | 30 | 50±11 | 50±10 | 14/6 | 12/18 | SVR/VR | 103±21 | 100±23 | 75±21 | 69±20 |
| Ji 2007 | 15 | 15 | 57±7 | 57±6 | 11/4 | 11/4 | CPB-CABG | 108±29 | 117±34 | 60±22 | 67±23 |
| Ji 2009 | 18 | 18 | 60±8 | 59±9 | 15/5 | 16/2 | CPB-CABG | 120±19 | 105±16 | 74±16 | 66±11 |
| Jin 2005 | 15 | 12 | 37±14 | 37±14 | NR | NA | ASD/VSD/TOF/VR | 123±58 | 67±30 |
| Kim 2013 | 25 | 25 | 67±10 | 63±9 | 10/6 | 17/8 | OPCAB | NA | NA | NA |
| Le 2005 | 20 | 18 | 36±12 | 34±10 | 9/11 | 8/10 | ASD/VSD/VR | 111±58 | 107±53 | 66±42 | 66±40 |
| Nakanishi 2006 | 14 | 14 | 62±9 | 61±10 | 12/2 | 11/3 | CPB-CABG | 150±37 | 135±39 | 118±32 | 104±32 |
| Pang 2016 | 30 | 30 | 54±9 | 50±9 | 15/15 | 21/9 | CPB-CABG/VR | NR | NR | NR |
| Park 2013 | 41 | 69 | 59±14 | 48±14 | 10/31 | 27/42 | VP/VR | 126±38 | 117±32 | 78±28 | 71±27 |
| Qiu 2015 | 70 | 138 | 48±10 | 47±9 | 18/52 | 51/67 | VP/VR | 129±37 | 111±33 | 86±30 | 74±29 |
| Shi 2010 | 100 | 100 | 49±13 | 46±15 | 44/56 | 49/51 | CHD-RVCA/VR | 115±134 | 108±48 | 75±36 | 78±37 |
| Shi 2008 | 15 | 15 | 17±8 | 17±8 | 9/6 | 7/8 | ASD/VSD | 42±6 | 40±4 | 26±4 | 25±3 |
| Shu 2003 | UlI:12 | 12 | 38±7 | 41±10 | 9/3 | 8/4 | ASD/VSD/VR | 81±17 | 79±14 | 61±11 | 64±13 |
| UlI:2 | 12 | 30±9 | 7/5 | 88±19 | 58±11 |
| Song 2011 | 24 | 24 | 52±17 | 53±19 | 8/16 | 9/15 | AVR | 164±32 | 173±28 | 99±24 | 105±26 |
| Tan 2011 | 60 | 60 | 44±24 | 42±26 | 32/28 | 33/27 | ASD/VSD/VR | 93±16 | 91±17 | 56±14 | 56±14 |
| Wang 2010 | 20 | 20 | 58±8 | 60±8 | 15/5 | 16/4 | OPCAB | NA | NA | NA |
| Xu 2013 | 18 | 18 | 59±9 | 53±7 | 16/2 | 15/3 | Aortic surgery | 236±26 | 247±20 | 60±22 | 58±17 |
| Yang 2010 | 30 | 30 | 25±8 | 27±6 | 14/16 | 14/16 | SVR/VR | NR | NR | NR |
| Yu 2003 | 10 | 10 | 12±7 | 11±6 | 7/3 | 6/4 | ASD/VSD | 57±24 | 50±18 | 37±24 | 30±11 |
| Zhang 2004 | 18 | 15 | 36±12 | 35±10 | NR | NR | ASD/VSD/VR | 128±52 | 118±45 | 63±39 | 61±37 |
| Zhai 2004 | 20 | 20 | 25±56 | 31±62 | 8/12 | 10/10 | SVR/VR | NR | NR | NR |

ACC=atrial cross-clamping, ASD/VSD=atrial septum defect/ventricular septum defect, AVR=aortic valve replacement, CPB-cardiopulmonary bypass, CPB-CABG=coronary artery bypass grafting with cardiopulmonary bypass, Group C=Group Control, Group Uli=Group Ulinastatin, NA=non-applicable, NR=not-reported, OPCAB=off-pump coronary artery bypass grafting, SVR/VR=single valve replacement/VR= valve replacement, VP/VR=valvuloplasty/valve replacement.

Figure 2. Forest plot of bleeding.
Table 3
Meta-analysis of outcomes.

| Outcomes              | Trials (n) | Group Uli (n) | Group Ctrl (n) | Heterogeneity | Analysis model | WMD/OR | 95% CI | Overall effect |
|-----------------------|------------|---------------|----------------|---------------|---------------|---------|--------|----------------|
| **Bleeding**          |            |               |                |               |               |         |        |                |
| Pre-op (mL)           | 5          | 153           | 153            |               | Fixed         | 0.01    | -0.34  | 0.96           |
| Post-op (mL)          | 10         | 298           | 302            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Hemoglobin**        |            |               |                |               |               |         |        |                |
| Pre-op (g/dL)         | 5          | 153           | 153            |               | Fixed         | 0.01    | -0.34  | 0.96           |
| Post-op (g/dL)        | 10         | 298           | 302            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Platelet count**    |            |               |                |               |               |         |        |                |
| Pre-op (10^9/L)       | 14         | 383           | 474            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Post-heparinization** | Post-op (s) | 43            | 43             |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Heparin (mg)**      | 4          | 140           | 208            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Leukocyte count**   |            |               |                |               |               |         |        |                |
| Pre-op (10^9/L)       | 4          | 140           | 208            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **Neutrophil count**  |            |               |                |               |               |         |        |                |
| Pre-op (10^9/L)       | 4          | 95            | 163            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **TNF-a**             |            |               |                |               |               |         |        |                |
| Pre-op (pg/mL)        | 5          | 193           | 193            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| End-op (pg/mL)        | 10         | 312           | 328            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **PMAE**              |            |               |                |               |               |         |        |                |
| Pre-op (pg/mL)        | 5          | 193           | 193            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **L-6**               |            |               |                |               |               |         |        |                |
| Pre-op (pg/mL)        | 6          | 213           | 213            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **L-8**               |            |               |                |               |               |         |        |                |
| Pre-op (pg/mL)        | 4          | 163           | 163            |               | Fixed         | 0.91    | -2.35  | 1.69           |
| **L-10**              |            |               |                |               |               |         |        |                |
| Pre-op (pg/mL)        | 3          | 150           | 150            |               | Fixed         | 0.91    | -2.35  | 1.69           |

95% CI = 95% confidence interval, ACT = activated clotting time, APPT = activated partial thromboplastin time, Cryo = cryoprecipitate, Ctrl = control, End-op = end of operation, FFP = fresh frozen plasma, IL = interleukin, Intra-op = intraoperative, IV = inverse variance, MFI = mean fluorescence intensity, M-H = Mantel–Haenszel, OR = odds ratio, PAGM = platelet aggregation maximum, PC = platelet concentrates, PMAE = polymorphonuclear elastase, Pre-op = preoperative, Pre-op = preoperative, PT = prothrombin time, RBC = red blood cell, TNF = tumor necrosis factor, Uli = Ulinastatin, WMD = weighted mean difference.
transfusion volume, and 3 trials\cite{9,18,34} (280 patients) reported data on postoperative RBC transfusion incidence. Meta-analysis showed that, Ulinastatin did not reduce postoperative RBC transfusion incidence as compared to control (90/140 [64.3%] vs 95/140 [67.9%], [OR = 0.78; 95% CI: 0.42–1.45; P = .43]) without heterogeneity [I² = 0%, P = .47]), but significantly reduced postoperative RBC transfusion volume ([WMD = −0.70; 95% CI: −1.26 to −0.14; P = .01] with heterogeneity [I² = 95%, P < .00001]). Meta-regression suggested patient age, gender, country, surgery type, and CPB did not influence the result. In addition to that, 3 trials\cite{19,20,34} (358 patients) reported postoperative fresh frozen plasma transfusion, which were all comparable between Ulinastatin and Control groups ([WMD = −12.11; 95% CI: −56.19 to 31.97; P = .59] without heterogeneity [I² = 45%, P = .16]). In addition to that, 2 trials\cite{19,34} (310 patients) reported postoperative PC transfusion, and 1 trials\cite{20} (48 patients) reported postoperative cryoprecipitate transfusion.

3.6. Effects on hemoglobin levels

As shown in Table 3, 5 trials\cite{9,18,25,26,29} (306 patients), 3 trials\cite{18,26,29} (230 patients) and 5 trials\cite{9,18,25,26,29} (306 patients) reported respective hemoglobin level before operation, at the end of operation and 24 hours postoperatively. Meta-analysis showed that, Ulinastatin-treated patients and Control patients had similar hemoglobin levels at all the 3 time points (Pre-op: WMD = −1.70; 95% CI: −5.43 to 2.04; P = .37 without heterogeneity [I² = 0%, P = .83]; End-of-op: WMD = 11.80; 95%
3.7. Effects on heparin and protamine dosages, ACT values

As shown in Table 3, 4 trials\(^9,15,18,19\) (256 patients) reported intraoperative heparin dose and protamine dose for heparinization reversal, 2 trials\(^9,18\) (86 patients) reported ACT values at baseline, after heparinization and at the end of operation. There was no difference in intra-operative heparin ([WMD = 21.02; 95% CI: −6.46 to 48.49; \(P = .13\)]) with heterogeneity \(I^2 = 89\%\), \(P < .00001\)) and protamine doses ([WMD = 10.56; 95% CI: −11.17 to 32.28; \(P = .34\)]) with heterogeneity \(I^2 = 83\%\), \(P = .0006\)). However, Ji et al\(^9\) reported that post-heparinization ACT in Group Ulinastatin was significantly shorter than that in Group Control ([602 ± 126] s vs [824 ± 146] s, \(P < .05\)).

3.8. Effects on coagulation functions

As shown in Table 3, 4 trials\(^9,18-20\) (244 patients), 2 trials\(^9,18\) (86 patients) and 4 trials\(^9,16-20\) (244 patients), reported Prothrombin time (PT) and activated partial thromboplastin time (APTT) values at baseline, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups with respect to PT ([Pre-op: WMD = 0.01; 95% CI: −0.34 to 0.36; \(P = .95\)]) without heterogeneity \(I^2 = 40\%\), \(P = .20\)); End-of-op: WMD = 0.06; 95% CI: −0.58 to 0.46; \(P = .82\) with heterogeneity \(I^2 = 95\%\), \(P < .00001\)); 24 hours post-op: WMD = −0.01; 95% CI: −0.25 to 0.23; \(P = .94\) without heterogeneity \(I^2 = 0\%\), \(P = .77\)). APTT values peripheratively ([Pre-op: WMD = −0.92; 95% CI: −1.96 to 0.12; \(P = .08\)] with heterogeneity \(I^2 = 58\%\), \(P = .07\)); End-of-op: WMD = −3.79; 95% CI: −9.64 to 2.06; \(P = .20\)] without heterogeneity \(I^2 = 0\%\), \(P = .85\)); 24 hours post-op: WMD = −1.18; 95% CI: −3.47 to 1.12; \(P = .31\)] without heterogeneity \(I^2 = 0\%\), \(P = .40\)). Four trials\(^9,18,19,20\) (244 patients), 1 trial\(^9\) (36 patients) and 3 trials\(^9,19,20\) (194 patients), reported fibrinogen levels at baseline, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups, either ([Pre-op: WMD = 8.43; 95% CI: −12.45 to 29.31 without heterogeneity \(I^2 = 49\%\), \(P = .12\)]; \(P = .43\); 24 hours post-op: WMD = 2.48; 95% CI: −15.01 to 19.97; \(P = .78\) without heterogeneity \(I^2 = 0\%\), \(P = .48\)).

Antithrombin (AT) is a small protein molecule that inactivates several enzymes of the coagulation system.\(^28\) Shu and colleagues compared the influence of 2 doses of Ulinastatin and blank control on AT-III activity (AT-III:A) and Factor XI pro-coagulant activity (FXI:C) in patients undergoing cardiac surgery with CPB, and they found that there was no intergroup difference in AT-III:A, but patients receiving larger dose of Ulinastatin had highest FXI:C at the end of CPB and 6 hours later.\(^28\)

Thrombin-antithrombin complex (TAT) and prothrombin fragment 1+2 (F1+2), are 2 indices of in vivo thrombin generation.\(^44\) The trial by Kim et al\(^4\) investigated the influence of Ulinastatin versus saline on TAT and F1+2 in off-pump CABG patients, and suggested that Ulinastatin did not attenuate increased thrombin generation peri-operatively.

3.9. Effects on platelet count and functions

As shown in Table 3, 14 trials\(^9,18-21,23-27,29,30,32,33\) (857 patients) and 10 trials\(^9,19-21,23,26,27,29,32,33\) (689 patients) reported platelet count preoperatively and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups ([Pre-op: WMD = −0.75; 95% CI: −7.93 to 6.43; \(P = .84\)]; 24 hours post-op: WMD = 9.07; 95% CI: −4.44 to 22.58; \(P = .19\)] with heterogeneity \(I^2 = 81\%\), \(P < .00001\)).

As shown in Table 3, platelet aggregation function was evaluated by examining maximum platelet aggregation ratio (PAGM%) in 2 included trials\(^30,32\) which both indicated that Ulinastatin preserved postoperative platelet aggregation function better than control. CD62P, also known as P-selectin, is released from α-granules upon platelet activation and promotes platelet aggregation through platelet-fibrin and platelet-platelet binding.\(^49\) Three trials\(^9,30,32\) (103 patients) and 6 trials\(^9,21,24,27,32,33\) (183 patients) reported postoperative CD62P expression percentage (%) and mean fluorescence intensity (MFI), respectively. Meta-analysis showed that there was no intergroup difference in either CD62P expression percentage ([WMD = −7.04; 95% CI: −15.16 to 1.09; \(P = .09\)] with heterogeneity \(I^2 = 97\%\), \(P < .00001\)) or MFI ([WMD = −0.59; 95% CI: −3.29 to 2.11; \(P = .67\)] with heterogeneity \(I^2 = 66\%\), \(P = .01\))). Platelet factor-4 (PF-4), also a marker of platelet activation released from α-granules of platelets during aggregation.\(^13\) Yu et al demonstrated that Ulinastatin, as compared to saline, significantly lowered TXB\(_2\) levels in patients undergoing on-pump repair operation for congenital heart diseases.\(^33\)

3.10. Effects on fibrinolysis

As shown in Table 3, 4 trials\(^20,28,31,33\) (137 patients), 3 trials\(^28,31,33\) (89 patients) and 5 trials\(^20,22,28,31,33\) (197 patients), reported D-dimer levels at baseline, at the end of operation, and 24 hours postoperatively. Meta-analysis indicated that Ulinastatin-treated patients had lower D-dimer levels at the end of operation ([WMD = −1.07; 95% CI: −1.66 to −0.49; \(P = .0003\)] with heterogeneity \(I^2 = 94\%\), \(P < .00001\)), and 24 hours postoperatively when compared to those in Control patients ([WMD = −0.87; 95% CI: −1.34 to −0.39; \(P = .0003\)] with heterogeneity \(I^2 = 98\%\), \(P < .00001\)).

Additionally, Chen et al\(^22\) demonstrated that, Ulinastatin had no effect on concentrations of 2 fibrinolytic indexes, plasminogen activator (PA) and α2-antiplasmin (α2-AP), in patients undergoing heart valve replacement surgery.

3.11. Effects on TEG profiles

Park and colleagues\(^19\) failed to detect any significant differences between Ulinastatin and saline with respect to postoperative TEG profiles including R (clotting time), K (clot formation time), and MA (maximum clot firmness) values in cardiac surgical patients. That is contrary to previous study by Okida et al reporting that Ulinastatin normalized the coagulation function and prevented changes in TEG during liver resection surgery.\(^8\)

3.12. Effects on leukocyte and neutrophil counts

As shown in Table 3, 4 trials\(^15,18,21,23\) (348 patients) and 2 trials\(^18,23\) (258 patients) reported leukocyte count and neutrophil
count preoperatively, at the end of operation, and 24 hours postoperatively. No difference was found between Ulinastatin and Control groups in either leukocyte count (Pre-op: WMD = 0.07; 95% CI: −0.29 to 0.43; P = .71) without heterogeneity [I² = 0%; P = .93]; End-of-op: WMD = −0.27; 95% CI: −1.08 to 0.54; P = .52] without heterogeneity [I² = 39%; P = .18]; 24 hours post-op: WMD = −0.00; 95% CI: −0.79 to 0.78; P = .99] without heterogeneity [I² = 0%; P = .66)]. A neutrophil count (Pre-op: WMD = −0.01; 95% CI: −0.39 to 0.36; P = .95) without heterogeneity [I² = 9%; P = .88]; End-of-op: WMD = −0.04; 95% CI: −0.91 to 0.83; P = .92] without heterogeneity [I² = 0%; P = .89]; 24 hours post-op: WMD = 0.30; 95% CI: −0.60 to 1.20; P = .89] without heterogeneity [I² = 0%; P = .88]).

3.13. Effects on polymorphonuclear elastase (PMNE) and interleukins

As shown in Table 3, 5 trials [15,17,21,22,34] (386 patients) reported PMNE and tumor necrosis factor-α (TNF-α) preoperatively, at the end of operation, and 24 hours postoperatively. Six trials [9,15,17,22,24,34] (426 patients) reported interleukin-6 (IL-6) preoperatively, at the end of operation, and 24 hours postoperatively. Four trials [15,17,21,34] (326 patients) reported IL-8 preoperatively, at the end of operation, and 24 hours postoperatively. The present meta-analysis indicated that, Ulinastatin treatment could reduce postoperative bleeding and RBC transfusion requirements, preserve platelet function, inhibit hyperfibrinolysis, and attenuate systemic inflammation in cardiac surgical patients.

Systemic heparinization, hemodilution, and hypothermia applied during cardiac surgery with CPB significantly influence coagulation and fibrinolysis systems. The present meta-analysis showed that Ulinastatin administration could reduce postoperative bleeding and RBC transfusion requirement, preserve platelet function, inhibit hyperfibrinolysis, and attenuate systemic inflammation in cardiac surgical patients.

To our knowledge, this is the first meta-analysis dedicated to evaluate whether Ulinastatin could reduce blood loss and transfusion requirements. Some studies showed that Ulinastatin administration could reduce postoperative bleeding and RBC transfusion requirement, preserve platelet function, inhibit hyperfibrinolysis, and attenuate systemic inflammation in cardiac surgical patients.

3.14. Sensitivity analyses and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by the choice of statistical model (Supplement Table 3, http://links.lww.com/MD/D778). Sensitivity tests were also performed by exclusion of some studies to analyze the influence of the overall treatment effect on high heterogeneity outcomes (Supplement Table 4, http://links.lww.com/MD/D779) but no contradictory results were found. No significant publication bias was detected by funnel plots examination for postoperative bleeding (Fig. 4) and RBC transfusion (Fig. 5). The symmetry of funnel plots of both outcomes were further evaluated by Begg test (P = .436 and .266 for postoperative bleeding and RBC transfusion, respectively) (Supplement Figs. 3, http://links.lww.com/MD/D774 and 4, http://links.lww.com/MD/D775).

4. Discussion

To our knowledge, this is the first meta-analysis dedicated to evaluate whether Ulinastatin could reduce blood loss and transfusion requirements. The present meta-analysis suggested that, Ulinastatin administration could reduce postoperative bleeding and RBC transfusion requirement, preserve platelet function, inhibit hyperfibrinolysis, and attenuate systemic inflammation in cardiac surgical patients.
transfusion requirements. The inhibitory effect of Ulinastatin on inflammatory cytokines, especially polymorphonuclear neutrophils (PMNs). PMNs release inflammatory cytokines, elevate anti-inflammatory cytokines, and provide organ protection in patients undergoing cardiac surgery. The conclusion is further confirmed by our meta-analysis which indicated that Ulinastatin not only reduced postoperative bleeding and transfusion requirement, but also inhibited the release of inflammatory mediators such as TNF-α, PMNE, IL-6, and IL-8. Open heart surgery triggers systemic inflammatory response syndrome via the action of leukocytes, especially polymorphonuclear neutrophils (PMNs). PMNs degrade or inhibit the activity of fibrin, fibrinogen, platelets and coagulation factors, and lead to increased blood loss and transfusion requirements. The inhibitory effect of Ulinastatin on inflammatory cytokines may be related to the activity inhibition of the widely distributed serine proteases, inhibition of migration and activation of leukocytes, reduction in inflammatory cell infiltration and release of tissue toxic substances. It has also been proved that Ulinastatin is effective in lowering allogeneic blood transfusion induced PMNE and cytokines release. Interestingly, it has been indicated that Ulinastatin addition could attenuate in vitro storage lesion (eg, hemolysis, erythrophnosis) of human red blood cells. Notably, the administration strategy of Ulinastatin could significantly affect the outcomes of interests. The maximum recommended daily dosage of Ulinastatin in its product instructions is 30 × 10^4U (Guangdong Techpool Bio-pharma Co. Ltd., Guangdong, China). However, the doses required to treat severe acute diseases (eg, sepsis, acute pancreatitis) is much higher. In a recent randomized, double-blinded, placebo-controlled and single-dose escalation study, Chen et al demonstrated that, 2 hours of intravenous infusion of Ulinastatin ranging from 30 × 10^4U to 800 × 10^4U was well tolerated in healthy volunteers. The effects of Ulinastatin on blood loss reduction might be dose-dependent. In our meta-analysis, larger doses (eg, above 1.2 × 10^4U/kg or 300 × 10^4U) of Ulinastatin tended to reduce bleeding and blood transfusion requirement, while smaller doses (eg, 5000 U/kg) might not be sufficient to be effective. Ulinastatin administration only by intravenous bolus were unable to reduce bleeding in 5 trials, while 5 included trials demonstrated that adding Ulinastatin to CBP prime could significantly reduce blood loss. The half-life of Ulinastatin in healthy adults is only 40 minutes, which is shorter than the duration of cardiac surgery or CPB. It is also possible that CPB-induced hemodilution could reduce the effectiveness of Ulinastatin. Therefore, it is highly possible that, larger doses and longer period of Ulinastatin infusion may be necessary to be effective in reducing bleeding in cardiac surgical patients. It is also possible that, there are different effective Ulinastatin concentrations for different therapeutic purposes, such as anti-fibrinolysis, anti-inflammation, and so on. The optimal doses of Ulinastatin for different therapeutic purposes remain to be investigated. Notably, both Ulinastatin and aprotinin are trypsin inhibitors although derived from different sources. Whether ucinastatin have any effect on short- and long-term outcomes of cardiac surgical patients remains to be examined in adequately powered RCTs. This study has some limitations. Meta-analysis can increase the power of analysis by pooling many small low-quality studies, but varied Ulinastatin dosages and surgical operation types, different clinical practices, quality and heterogeneity issues of included studies may limit the certainty of the findings of meta-analysis. To clarify the hemostatic effectiveness of Ulinastatin in cardiac surgical patients, a prospective randomized, placebo-controlled, triple-blinded trial is ongoing in our center (ClinicalTrials.gov Identifier: NCT01060189).

To conclude, Ulinastatin reduces postoperative bleeding and transfusion requirement in cardiac surgical patients, possibly by inhibiting hyperfibrinolysis, preserving platelet function, and
alleviating inflammation. To confirm this, more well-designed and adequately-powered randomized trials are needed.

**Author contributions**

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