# Hemostatic Effect and Safety of TXA: An Umbrella Review

Short Title: Hemostatic Effect and Safety of TXA

Mingyang JIANG[1], Ke ZHANG[1], Chuanliang CHEN[1], Xiaochong ZOU[1], Kaicheng LIU[1], Yongheng DAI[1], Zhandong BO[1*]

[1]Department of Bone and Joint Surgery, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.

*** Address for Correspondence:**
Zhandong Bo, PhD
Department of Bone and Joint, the First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China.
Tel.: +86 13607817768.
Fax: +86 13607817768.
E-mail: drrbozhandong@126.com.

**Abstract**

**Aim:** To evaluate the hemostatic effect and safety of TXA.

**Methods:** Meta-analyses were retrieved from databases. Risk ratios (RR), odds ratios (OR), weighted mean difference (WMD), standard mean difference (SMD) and 95% confidence intervals (CI) were extracted to compare the effeteness of TXA in reducing TBL, transfusion rate, Hb drop, mortality, DVT, PE.

**Results:** In total, 136 trials (396 comparisons) including 17 kinds of surgeries were retrieved. The evidence for TXA using in total knee arthroplasty (TKA), total hip arthroplasty (THA), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, menstrual bleeding, plastic surgery, myomectomy, nasal surgery was assessed as possible for the association of reducing TBL. The evidence for TXA using in TKA, THA, postpartum bleeding, orthopaedic surgery, shoulder arthroplasty was assessed as probable for the association of reducing transfusion rate. The evidence for TXA using in liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery was considered to be possible for the association of reducing transfusion rate. The evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip fracture surgery was assessed as probable for the association of reducing Hb drop. The evidence for TXA using in TKA, THA, postpartum bleeding, shoulder arthroplasty was considered to be possible for the association of reducing Hb drop. The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as probable for the association of reducing mortality.

**Conclusion:** This umbrella review indicated that TXA was regarded as effective to reduce TBL, transfusion rate, Hb drop, mortality, and did not increase the incidence of DVT and PE. However, more convincing evidence should be provided to further clarify the level of efficacy and safety of TXA.

## Introduction

Antifibrinolytic drugs have been widely used in obstetrics and gynecology surgery, cardiac surgery, trauma, hip and knee replacement and other fields to reduce perioperative bleeding and blood transfusion. [1]

Among them, tranexamic acid (TXA) is the most common type used in surgery, and its main mechanism has been deeply studied.

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular permeability under physiological or pathological conditions, as well as the occurrence, development and cure of fibrinolysis-induced reactions, bleeding symptoms and allergic reactions.[2] TXA can inhibit the effect of fibrinolytic enzyme and show hemostatic, anti-allergic and anti-inflammatory effects. (1) Anti-fibrinolytic enzyme effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by the fibrinolytic enzyme was strongly inhibited. Also, in the presence of anti-fibrinolytic enzymes such as macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and the hemostatic effect was more significant.[3] (2) Hemostatic effect. Abnormal hyperactivity of the fibrinolytic enzyme will cause platelet agglutination inhibition and coagulation factor decomposition. Mild hyperactivity first leads to the decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can inhibit fibrin decomposition and play a hemostatic role.[4] (3) Anti-allergic and anti-inflammatory effects. TXA can inhibit the production of kinin and other active peptides (guinea pigs and rats) which cause vascular permeability enhancement, allergy and inflammatory lesions.[5]Nowadays, there are many meta-analyses to study the efficacy and safety of TXA in clinical events, such as trauma or surgical bleeding in the brain, uterus and other organs rich in plasminogen activator. However, it is still inconsistent whether TXA is effective and safe enough and whether it can be used in all clinical applications. With the increase in the number of systematic reviews available, a logical next step to provide decision-makers in healthcare with the evidence they require has been the conduct of reviews of existing systematic reviews. Syntheses of existing systematic reviews are referred to by many different names, one of which is an umbrella review. An umbrella review allows the findings of reviews relevant to a review question to be compared and contrasted. An umbrella review's most characteristic feature is that this type of evidence synthesis only considers for inclusion the highest level of evidence, namely other systematic reviews and meta-analyses.[6] Therefore, we summarized the results of existing meta-analyses and comprehensively evaluated their quality. The purpose of this review is to explore the efficacy and safety of TXA and to provide more options for the clinical application of hemostatic drugs.

## Methods

### *Search strategy*

This is an umbrella review (Systematic collection and evaluation of multiple systematic reviews and meta-analysis of specific research topics). Two researchers

systematically searched published systematic reviews and meta-analyses evaluating the hemostatic effect and safety of TXA from inception to Aug 17th, 2019. The language was restricted to English. The databases we searched included Medline, Embase, PubMed, The Cochrane Library and relative studies in referenceto retrieved articles. We used the following keywords: “TXA” and “meta-analysis”. Full text of potentially qualified articles was screened by another two researchers respectively.

***Inclusion and exclusion criteria***

Inclusion criteria: (1) meta-analyses of RCTs assessing hemostatic effect and safety of TXA; (2) meta-analyses of observational studies evaluating hemostatic effect and safety of TXA.

Exclusion criteria: (1) no meta-analysis; (2) studies on genetic polymorphisms related to TXA; (3) studies with incomplete or erroneous data; (4) meta-analyses in which endpoints of TXA was only a little part of the outcome; (5) the studies included in the meta-analysis were completely overlapping; (6) the endpoints of the meta-analysis were not of interest.

***Data extraction***

Two authors reviewed the contents of the retrieved meta-analyses independently. Total blood loss (TBL), Transfusion rate, Haemoglobin drop (Hb drop), deep venous thrombosis (DVT), pulmonary embolism (PE) and mortality were extracted and verified by a third author. The characteristics extracted were as follows: the first author, year of publication, number of studies, intervention measures in experimental group and control group, number of sample size, effect size (95%CI), meta-analyze metric, heterogeneity and p-value. If a quantitative synthesis was done, we also extracted the study-specific relative risk estimates (risk ratio, odds ratio, mean difference, Std mean difference) together with the corresponding CI and the number of cases and controls in each study for each risk factor. In the event of a dispute, a third author would coordinate the settlement. In this umbrella review, all data were extracted from previously published studies, thus no patient consent and ethical approval were required.

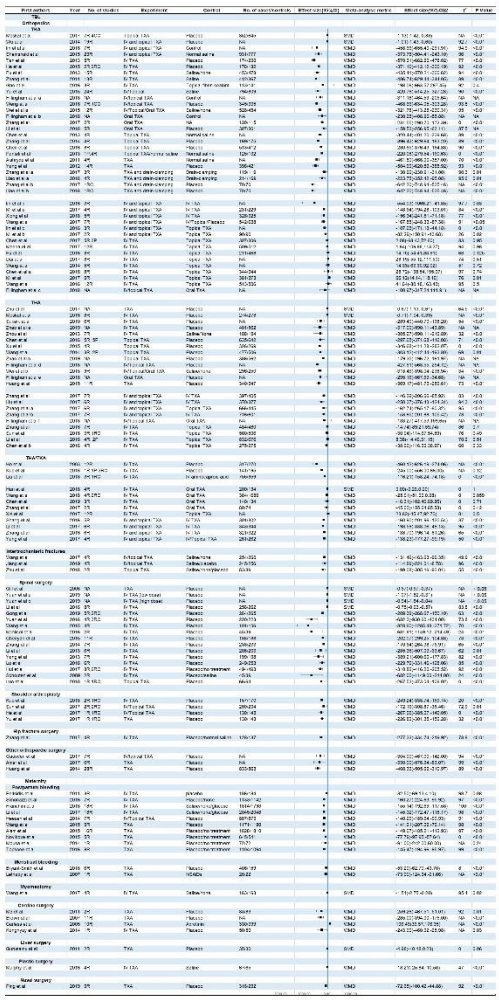
***Statistical analysis***

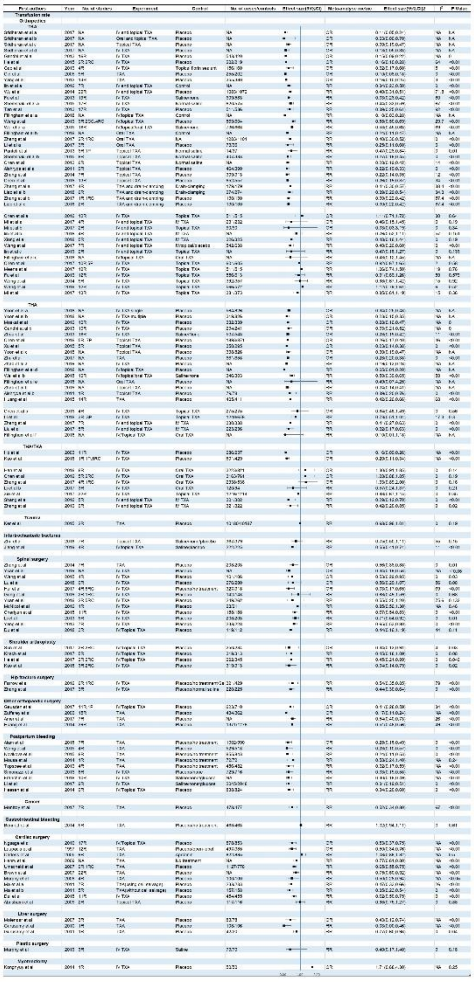
For each meta-analysis, we estimated the effect size and its 95% CI with both fixed-effects and random-effects models. To compare the hemostatic effect and safety of TXA more clearly, we unified the effect size as a forest plot. Between-study heterogeneity was assessed by the $I^2$ metric. $I^2$ ranges between 0% and 100% and are the ratio of between-study variance over the sum of the within-study and between-study variances. Values exceeding 50% or 75% are usually judged to represent large or very large heterogeneity, respectively. A p-value less than 0.05 was judged to be significant evidence. The criteria used for evidence categorization were showed in **Table 1**. Whenever more than one meta-analysis was conducted using the same endpoints, and the same study design and type of population, the most recent or most exhaustive study was considered. Stata (version 13.0) was used for statistical

137 analysis and calculation.
138
139 **Table 1**

| | |
|---|---|
| Convincing | Level 1a (high): concordance between meta-analyses of RCTs and meta-analyses of observational studies (any) |
| | Level 1b (low): meta-analyses of RCTs with results contrary to those from meta-analyses of observational studies (any) |
| Probable | Level 2a (high): meta-analyses of RCTs and prospective studies with no heterogeneity, no potential confounding factors identified, and agreement of results over time and among meta-analyses, including studies with different designs |
| | Level 2b (medium): meta-analyses of RCTs and prospective studies with no heterogeneity and no potential confounding factors identified |
| | Level 2c (low): meta-analyses of retrospective studies with no heterogeneity and no potential confounding factors identified |
| Possible | Level 3a (high): meta-analyses of RCTs and prospective studies lacking information on heterogeneity and potential confounding factors |
| | Level 3b (low): meta-analyses of retrospective studies or meta-analyses of any other study design with significant heterogeneity ($I2$ > 50%) and potential confounding factors |
| Limited/contrasting | Level 4: Limited studies included in meta-analyses ($n$ = 3) or evident contrasting results from meta-analyses with the same level of evidence |

140
141 **Result**
142 According to the retrieval strategy, 232 articles were initially obtained, of which 96
143 were excluded according to the type of articles by title evaluation. Through reviewing
144 the abstract and full text, 136 studies (396 comparisons) [7-142] were finally included to
145 compare the efficacy of TXA in the reduction of TBL, transfusion rate, Hb drop,
146 mortality, DVT and PE as shown in **Figure 1**. The effect sizes of each meta-analysis
147 and baseline characteristics for 136 meta-analyses of TXA related to TKA, THA,
148 postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery,
149 shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery, cardiac
150 surgery, nasal surgery, gastrointestinal bleeding, trauma, liver surgery, cancer and
151 myomectomy reported were shown in **Table 2**.
152
153 **Table 2**
154





| First authors | Year | No. of studies | Experiment | Control | No. of cases/controls | Effect size(95%CI) | Meta-analyse metric | Effect size(95%CI)2 | $I^2$ | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Hb drop** | | | | | | | | | | |
| **Orthopedics** | | | | | | | | | | |
| **TKA** | | | | | | | | | | |
| Wu et al | 2014 | 12R | IV and topical TXA | Placebo | NA | | SMD | -0.78(-1.07,-0.50) | 81.3 | <0.01 |
| Joseph et al | 2017 | 5R,4CC | Topical TXA | Placebo | 748/657 | | SMD | -0.78(-0.95,-0.60) | NA | <0.01 |
| Guo et al | 2018 | 3R | Oral TXA | Placebo | 260/255 | | SMD | -0.94(-1.12,-0.75) | 80.3 | <0.01 |
| Zhang et al | 2017 | 2R,1RC | Oral TXA | Control | 1169/981 | | WMD | -0.80(-0.88,-0.71) | 0 | <0.01 |
| Li et al | 2018 | 5R | Oral TXA | Placebo | 307/301 | | WMD | -0.49(-0.70,-0.29) | 55.9 | NA |
| Li et al a | 2017 | 2R | Oral TXA | Placebo | 73/66 | | WMD | -1.14(-1.89,-0.40) | 37.5 | <0.01 |
| Weng et al | 2016 | 4R,2RC | IV/topical TXA | Placebo | 328/354 | | WMD | -0.74(-1.19,-0.29) | 84.8 | <0.01 |
| Chen et al | 2013 | 4R | Topical TXA | Normal saline | NA | | WMD | -0.63(-0.96,-0.31) | 68.2 | 0.02 |
| Pantell et al | 2013 | 3R | Topical TXA | Normal saline | 99/99 | | WMD | -0.94(-1.24,-0.65) | 0 | <0.01 |
| Zhang et al | 2014 | 4R | Topical TXA | Placebo | 149/150 | | WMD | -0.71(-1.12,-0.30) | 71 | <0.01 |
| Chen et al | 2016 | 8R | Topical TXA | Placebo | 419/319 | | WMD | -0.66(-0.81,-0.52) | 41 | <0.01 |
| Tian et al | 2017 | 2RC | TXA | Placebo | 290/221 | | WMD | -0.52(-0.79,-0.25) | 62 | <0.01 |
| Zhang et al a | 2017 | 4R | TXA and drain-clamping | Drain-clamping | 179/179 | | WMD | -0.87(-1.04,-0.70) | 0 | <0.01 |
| Liao et al a | 2018 | 5R | TXA and drain-clamping | Drain-clamping | 274/229 | | WMD | -0.99(-1.29,-0.69) | 72.7 | <0.01 |
| Zhang et al b | 2017 | 1R,1RC | TXA and drain-clamping | Placebo | 60/60 | | WMD | -1.50(-1.79,-1.21) | NA | <0.01 |
| Liao et al b | 2018 | 1R | TXA and drain-clamping | Placebo | 60/60 | | WMD | -1.50(-1.79,-1.21) | NA | <0.01 |
| Xiong et al | 2018 | 4R | IV and topical TXA | IV TXA | 296/295 | | WMD | -0.56(-0.93,-0.19) | 90 | <0.01 |
| Wang et al | 2017 | 7R | IV and topical TXA | IV/topical/placebo | 542/638 | | WMD | -0.81(-1.91,-0.42) | 89.7 | <0.05 |
| Chen et al | 2017 | 4R,3P | IV TXA | Topical TXA | 291/295 | | WMD | -0.42(-0.89,0.05) | 94 | 0.08 |
| Meena et al | 2017 | 7R | IV TXA | Topical TXA | 301/305 | | WMD | -0.50(-0.96,-0.04) | 94 | 0.03 |
| Fu et al | 2016 | 7R | IV TXA | Topical TXA | 346/293 | | WMD | -0.35(-0.78,0.09) | 93.6 | 0.12 |
| Dai et al | 2017 | 9R | IV TXA | Topical TXA | NA | | WMD | -0.20(-0.54,0.14) | 90 | 0.24 |
| Wang et al | 2014 | 5R,1P | IV TXA | Topical TXA | NA | | WMD | -0.43(-1.11,0.25) | 95 | 0.22 |
| Chen et al a | 2016 | 12R | IV TXA | Topical TXA | 491/495 | | WMD | -0.18(-0.46,0.09) | 93 | 0.19 |
| Wang et al | 2016 | 15R | IV TXA | Topical TXA | 692/679 | | WMD | -0.15(-0.39,0.10) | 86 | 0.24 |
| **THA** | | | | | | | | | | |
| Chen et al | 2016 | 5R, 6P | Topical TXA | Placebo | 822/774 | | SMD | -0.66(-0.91,-0.41) | 81 | <0.01 |
| Wang et al | 2014 | 1R, 3P | Topical TXA | Placebo | 388/413 | | WMD | -0.86(-1.32,-0.39) | 89 | <0.01 |
| Zhu et al | 2017 | NA | TXA | Placebo | 224/175 | | WMD | -10.81(-14.03,-7.58) | 48 | <0.01 |
| Sun et al | 2016 | 2R,1RC | IV TXA | Topical TXA | 459/404 | | WMD | -0.29(-0.68,0.10) | 87 | 0.14 |
| Li et al | 2016 | 2R, 2P | IV TXA | Topical TXA | 697/540 | | WMD | -0.24(-0.34,-0.15) | 91.7 | <0.01 |
| Chen et al b | 2016 | 3R | IV TXA | Topical TXA | 241/241 | | WMD | -0.30(-0.68,0.08) | 0 | 0.12 |
| Zhang et al a | 2017 | 5R | IV and topical TXA | IV TXA | 662/547 | | WMD | -0.56(-0.78,-0.34) | 69 | <0.01 |
| Liu et al | 2017 | 3R | IV and topical TXA | IV TXA | 145/152 | | WMD | -0.11(-0.40,0.17) | 78.1 | 0.44 |
| Zhang et al | 2017 | 4R | IV and topical TXA | IV TXA | 202/210 | | WMD | -0.43(-0.75,-0.10) | 66 | 0.01 |
| Zhang et al b | 2017 | 4R | IV and topical TXA | Topical TXA | 612/391 | | WMD | -1.06(-1.30,-0.82) | 75 | <0.01 |
| **THA/TKA** | | | | | | | | | | |
| Liu et al | 2018 | 3R,1RC | IV TXA | IV aminocaproic acid | 755/959 | | WMD | -0.18(-0.29,-0.07) | 0 | <0.01 |
| Kuo et al | 2018 | 1P,3RC | IV TXA | Placebo | 434/307 | | WMD | -0.88(-1.31,-0.44) | NA | <0.01 |
| Han et al | 2018 | 5R | IV TXA | Oral TXA | 340/334 | | SMD | 0.03(-0.12,0.18) | 0 | 0.67 |
| Wang et al | 2018 | 4R,2RC | IV TXA | Oral TXA | 384/1650 | | WMD | -0.09(-0.20,0.02) | 0 | 0.12 |
| Li et al b | 2017 | 2R | IV TXA | Oral TXA | 80/74 | | WMD | -0.14(-0.47,0.19) | 0 | 0.41 |
| Chen et al | 2019 | 4R,2RC | IV TXA | Oral TXA | 3083/741 | | WMD | -0.06(-0.13,0.01) | 39 | <0.01 |
| Zhang et al | 2017 | 3R | IV TXA | Oral TXA | 220/214 | | WMD | 0.01(-0.09,0.10) | 0 | 0.88 |
| Xie et al | 2017 | 11R | IV TXA | Topical TXA | NA | | WMD | -0.33(-0.58,-0.07) | 92 | 0.01 |
| Shang et al | 2016 | 3R | IV and topical TXA | IV TXA | 221/222 | | WMD | -0.41(-0.73,-0.08) | 87 | 0.01 |
| Li et al | 2017 | 4R | IV and topical TXA | IV TXA | 243/244 | | WMD | -0.51(-0.83,-0.18) | 84 | <0.01 |
| Yang et al | 2017 | 3R | IV and topical TXA | IV/Topical TXA | 261/262 | | WMD | -0.44(-0.79,-0.09) | 88 | 0.01 |
| **Intertrochanteric fractures** | | | | | | | | | | |
| Wang et al | 2017 | 4R | IV/Topical TXA | Saline/none | 254/260 | | WMD | -0.31(-0.43,-0.18) | 0 | <0.01 |
| **Orthopaedic surgery** | | | | | | | | | | |
| Amer et al | 2017 | 5R | TXA | Placebo | NA | | WMD | -0.76(-1.02,-0.50) | 32 | <0.01 |
| **Shoulder arthroplasty** | | | | | | | | | | |
| Kuo et al | 2018 | 2R,3RC | IV TXA | Placebo | 316/310 | | WMD | -0.64(-0.81,-0.46) | 0 | <0.01 |
| Kirsch et al | 2017 | 5R | IV/Topical TXA | Placebo | 319/313 | | WMD | -0.64(-0.84,-0.44) | 0 | <0.01 |
| He et al | 2017 | 2R,2RC | IV/Topical TXA | Placebo | 292/345 | | WMD | -0.53(-0.83,-0.23) | 61.6 | <0.01 |
| Yu et al | 2017 | 1R,1RC | TXA | Placebo | 159/131 | | WMD | -0.43(-5.67,4.72) | 39 | 0.87 |
| **Hip fracture surgery** | | | | | | | | | | |
| Zhang et al | 2017 | 3R | IV TXA | Placebo/normal saline | 102/105 | | WMD | -1.36(-1.84,-0.88) | 0 | <0.01 |
| **Postpartum bleeding** | | | | | | | | | | |
| Wang et al | 2015 | 6R | TXA | Placebo | 707/720 | | WMD | -0.87(-1.30,-0.45) | 97 | <0.01 |
| Simonazzi et al | 2016 | 6R | IV TXA | Placebo/none | NA | | WMD | -0.61(-1.04,-0.18) | NA | <0.01 |

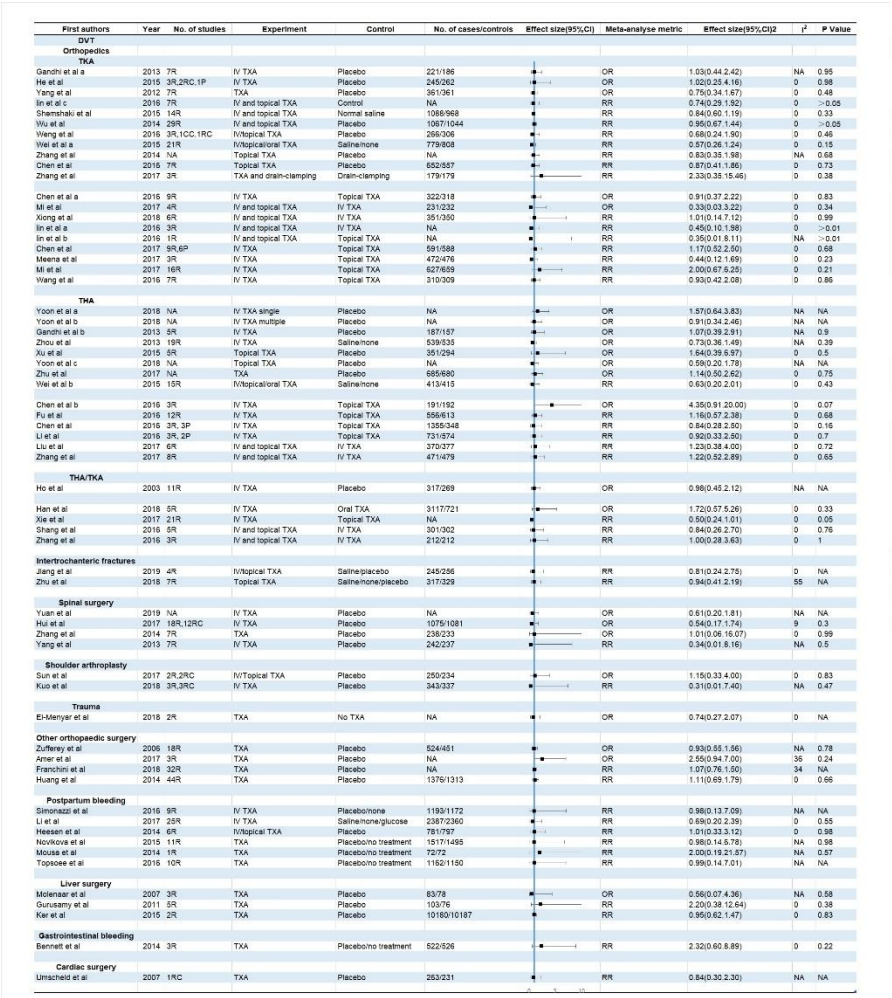
157

158

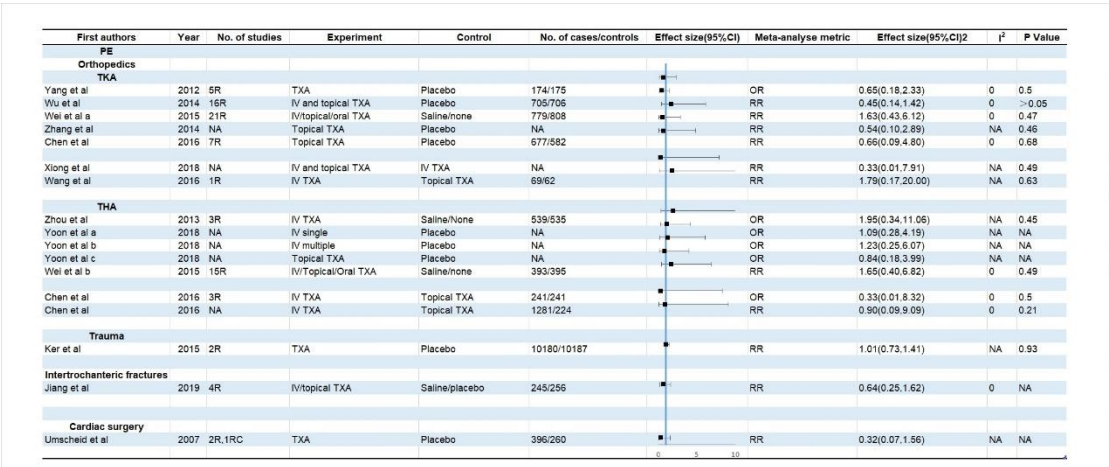
| First authors | Year | No. of studies | Experiment | Control | No. of cases/controls | Effect size(95%CI) | Meta-analyse metric | Effect size(95%CI)2 | $I^2$ | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mortality** | | | | | | | | | | |
| **Trauma** | | | | | | | | | | |
| El-Menyar et al | 2018 | 2R | TXA | No TXA | NA | | OR | 0.49(0.28,0.85) | 0 | NA |
| Ker et al | 2015 | 2R | TXA | Placebo | 10180/10187 | | RR | 0.90(0.85,0.97) | 0 | <0.01 |
| Weng et al | 2019 | 3R | IV TXA | Placebo | 327/330 | | RR | 0.64(0.41,1.00) | 0 | 0.05 |
| **Liver surgery** | | | | | | | | | | |
| Molenaar et al | 2007 | 3R | TXA | Placebo | 83/78 | | OR | 0.57(0.18,1.79) | NA | 0.33 |
| Gurusamy et al | 2011 | 3R | TXA | Placebo | 83/56 | | RR | 0.55(0.17,1.76) | 14 | 0.31 |
| **Gastrointestinal bleeding** | | | | | | | | | | |
| Bennett et al | 2014 | 8R | TXA | Placebo/no treatment | 851/850 | | RR | 0.60(0.42,0.87) | 0 | <0.01 |
| **Cardiac surgery** | | | | | | | | | | |
| Ngaage et al | 2010 | 8R,1RC | IV/Topical TXA | Placebo | 1473/2045 | | OR | 0.80(0.48,1.34) | NA | 0.4 |
| Hutton et al | 2012 | NA | TXA | Aprotinin | NA | | OR | 0.71(0.50,0.98) | NA | NA |
| Howell et al | 2012 | 23R | TXA | Placebo | 3048/4887 | | RR | 1.48(0.84,2.58) | NA | NA |
| Takagi et al | 2009 | 9R | TXA | Aprotinin | 1415/1419 | | RR | 0.68(0.47,0.99) | 0 | 0.05 |
| Henry et al | 2009 | 19R | TXA | Placebo | 922/880 | | RR | 0.55(0.24,1.25) | 0 | >0.05 |
| Umscheid et al | 2007 | 5R,1RC | TXA | Placebo | 747/550 | | RR | 0.55(0.26,1.18) | NA | 0.85 |
| Brown et al | 2007 | 18R | TXA | Placebo | NA | | RR | 0.67(0.33,1.37) | NA | 0.276 |

159

160



| First authors | Year | No. of studies | Experiment | Control | No. of cases/controls | Effect size(95%CI) | Meta-analyse metric | Effect size(95%CI)2 | $I^2$ | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| **DVT** | | | | | | | | | | |
| **Orthopedics** | | | | | | | | | | |
| **TKA** | | | | | | | | | | |
| Gandhi et al a | 2013 | 7R | IV TXA | Placebo | 221/186 | | OR | 1.03(0.44,2.42) | NA | 0.95 |
| He et al | 2015 | 3R,2RC,1P | IV TXA | Placebo | 245/262 | | OR | 1.02(0.25,4.16) | 0 | 0.98 |
| Yang et al | 2012 | 7R | TXA | Placebo | 361/361 | | OR | 0.75(0.34,1.67) | 0 | 0.48 |
| lin et al c | 2016 | 7R | IV and topical TXA | Control | NA | | RR | 0.74(0.29,1.92) | 0 | >0.05 |
| Shamshaki et al | 2015 | 14R | IV and topical TXA | Normal saline | 1088/968 | | RR | 0.84(0.60,1.19) | 0 | 0.33 |
| Wu et al | 2014 | 29R | IV and topical TXA | Placebo | 1067/1044 | | RR | 0.95(0.67,1.44) | 0 | >0.05 |
| Weng et al | 2016 | 3R,1CC,1RC | IV/topical TXA | Placebo | 266/306 | | RR | 0.68(0.24,1.90) | 0 | 0.46 |
| Wei et al a | 2015 | 21R | IV/topical/oral TXA | Saline/none | 779/808 | | RR | 0.57(0.26,1.24) | 0 | 0.15 |
| Zhang et al | 2014 | NA | Topical TXA | Placebo | NA | | RR | 0.83(0.35,1.98) | NA | 0.68 |
| Chen et al | 2016 | 7R | Topical TXA | Placebo | 652/557 | | RR | 0.87(0.41,1.86) | 0 | 0.73 |
| Zhang et al | 2017 | 3R | TXA and drain-clamping | Drain-clamping | 179/179 | | RR | 2.33(0.35,15.46) | 0 | 0.38 |
| Chen et al a | 2016 | 9R | IV TXA | Topical TXA | 322/318 | | OR | 0.91(0.37,2.22) | 0 | 0.83 |
| Mi et al | 2017 | 4R | IV and topical TXA | IV TXA | 231/232 | | OR | 0.33(0.03,3.22) | 0 | 0.34 |
| Xiong et al | 2018 | 6R | IV and topical TXA | IV TXA | 351/350 | | RR | 1.01(0.14,7.12) | 0 | 0.99 |
| lin et al a | 2016 | 3R | IV and topical TXA | IV TXA | NA | | RR | 0.45(0.10,1.98) | 0 | >0.01 |
| lin et al b | 2016 | 1R | IV and topical TXA | Topical TXA | NA | | RR | 0.35(0.01,8.11) | NA | >0.01 |
| Chen et al | 2017 | 9R,6P | IV TXA | Topical TXA | 591/588 | | RR | 1.17(0.52,2.50) | 0 | 0.68 |
| Meena et al | 2017 | 3R | IV TXA | Topical TXA | 472/476 | | RR | 0.44(0.12,1.69) | 0 | 0.23 |
| Mi et al | 2017 | 16R | IV TXA | Topical TXA | 627/659 | | RR | 2.00(0.67,6.25) | 0 | 0.21 |
| Wang et al | 2016 | 7R | IV TXA | Topical TXA | 310/309 | | RR | 0.93(0.42,2.08) | 0 | 0.86 |
| **THA** | | | | | | | | | | |
| Yoon et al a | 2018 | NA | IV TXA single | Placebo | NA | | OR | 1.57(0.64,3.83) | NA | NA |
| Yoon et al b | 2018 | NA | IV TXA multiple | Placebo | NA | | OR | 0.91(0.34,2.46) | NA | NA |
| Gandhi et al b | 2013 | 5R | IV TXA | Placebo | 187/157 | | OR | 1.07(0.39,2.91) | NA | 0.9 |
| Zhou et al | 2013 | 19R | IV TXA | Saline/none | 539/535 | | OR | 0.73(0.36,1.49) | NA | 0.39 |
| Xu et al | 2015 | 5R | Topical TXA | Placebo | 351/294 | | OR | 1.64(0.39,6.97) | 0 | 0.5 |
| Yoon et al c | 2018 | NA | Topical TXA | Placebo | NA | | OR | 0.59(0.20,1.78) | NA | NA |
| Zhu et al | 2017 | NA | TXA | Placebo | 685/680 | | OR | 1.14(0.50,2.62) | 0 | 0.75 |
| Wei et al b | 2015 | 15R | IV/topical/oral TXA | Saline/none | 413/415 | | RR | 0.63(0.20,2.01) | 0 | 0.43 |
| Chen et al b | 2016 | 3R | IV TXA | Topical TXA | 191/192 | | OR | 4.35(0.91,20.00) | 0 | 0.07 |
| Fu et al | 2016 | 12R | IV TXA | Topical TXA | 556/613 | | RR | 1.15(0.57,2.38) | 0 | 0.68 |
| Chen et al | 2016 | 3R, 3P | IV TXA | Topical TXA | 1355/348 | | RR | 0.84(0.28,2.50) | 0 | 0.16 |
| Li et al | 2016 | 3R, 2P | IV TXA | Topical TXA | 731/874 | | RR | 0.92(0.33,2.50) | 0 | 0.7 |
| Liu et al | 2017 | 6R | IV and topical TXA | IV TXA | 370/377 | | RR | 1.23(0.38,4.00) | 0 | 0.72 |
| Zhang et al | 2017 | 8R | IV and topical TXA | IV TXA | 471/479 | | RR | 1.22(0.52,2.89) | 0 | 0.65 |
| **THA/TKA** | | | | | | | | | | |
| Ho et al | 2003 | 11R | IV TXA | Placebo | 317/269 | | OR | 0.98(0.45,2.12) | NA | NA |
| Han et al | 2018 | 5R | IV TXA | Oral TXA | 3117/721 | | OR | 1.72(0.57,5.26) | 0 | 0.33 |
| Xie et al | 2017 | 21R | IV TXA | Topical TXA | NA | | RR | 0.50(0.24,1.01) | 0 | 0.05 |
| Shang et al | 2016 | 5R | IV and topical TXA | IV TXA | 301/302 | | RR | 0.84(0.26,2.70) | 0 | 0.76 |
| Zhang et al | 2016 | 3R | IV and topical TXA | IV TXA | 212/212 | | RR | 1.00(0.28,3.63) | 0 | 1 |
| **Intertrochanteric fractures** | | | | | | | | | | |
| Jiang et al | 2019 | 4R | IV/topical TXA | Saline/placebo | 245/256 | | RR | 0.81(0.24,2.75) | 0 | NA |
| Zhu et al | 2018 | 7R | Topical TXA | Saline/none/placebo | 317/329 | | RR | 0.94(0.41,2.19) | 55 | NA |
| **Spinal surgery** | | | | | | | | | | |
| Yuan et al | 2019 | NA | IV TXA | Placebo | NA | | OR | 0.61(0.20,1.81) | NA | NA |
| Hui et al | 2017 | 18R,12RC | IV TXA | Placebo | 1075/1081 | | OR | 0.54(0.17,1.74) | 9 | 0.3 |
| Zhang et al | 2014 | 7R | TXA | Placebo | 238/233 | | OR | 1.01(0.06,16.07) | 0 | 0.99 |
| Yang et al | 2013 | 7R | IV TXA | Placebo | 242/237 | | RR | 0.34(0.01,8.16) | NA | 0.5 |
| **Shoulder arthroplasty** | | | | | | | | | | |
| Sun et al | 2017 | 2R,2RC | IV/Topical TXA | Placebo | 250/234 | | OR | 1.15(0.33,4.00) | 0 | 0.83 |
| Kuo et al | 2018 | 3R,3RC | IV TXA | Placebo | 343/337 | | RR | 0.31(0.01,7.40) | NA | 0.47 |
| **Trauma** | | | | | | | | | | |
| El-Menyar et al | 2018 | 2R | TXA | No TXA | NA | | OR | 0.74(0.27,2.07) | 0 | NA |
| **Other orthopaedic surgery** | | | | | | | | | | |
| Zufferey et al | 2006 | 18R | TXA | Placebo | 524/451 | | OR | 0.93(0.55,1.56) | NA | 0.78 |
| Amer et al | 2017 | 3R | TXA | Placebo | NA | | OR | 2.55(0.94,7.00) | 36 | 0.24 |
| Franchini et al | 2018 | 32R | TXA | Placebo | NA | | RR | 1.07(0.76,1.50) | 34 | NA |
| Huang et al | 2014 | 44R | TXA | Placebo | 1376/1313 | | RR | 1.11(0.69,1.79) | 0 | 0.66 |
| **Postpartum bleeding** | | | | | | | | | | |
| Simonazzi et al | 2016 | 9R | IV TXA | Placebo/none | 1193/1172 | | RR | 0.98(0.13,7.09) | NA | NA |
| Li et al | 2017 | 25R | IV TXA | Saline/none/glucose | 2387/2360 | | RR | 0.69(0.20,2.39) | 0 | 0.55 |
| Heesen et al | 2014 | 6R | IV/topical TXA | Placebo | 781/787 | | RR | 1.01(0.33,3.12) | 0 | 0.98 |
| Novikova et al | 2015 | 11R | TXA | Placebo/no treatment | 1517/1495 | | RR | 0.98(0.14,6.78) | NA | 0.98 |
| Mousa et al | 2014 | 1R | TXA | Placebo/no treatment | 72/72 | | RR | 2.00(0.19,21.57) | NA | 0.57 |
| Topsoee et al | 2016 | 10R | TXA | Placebo/no treatment | 1162/1150 | | RR | 0.99(0.14,7.01) | NA | NA |
| **Liver surgery** | | | | | | | | | | |
| Molenaar et al | 2007 | 3R | TXA | Placebo | 83/78 | | OR | 0.56(0.07,4.36) | NA | 0.58 |
| Gurusamy et al | 2011 | 5R | TXA | Placebo | 103/76 | | RR | 2.20(0.38,12.64) | 0 | 0.38 |
| Ker et al | 2015 | 2R | TXA | Placebo | 10180/10187 | | RR | 0.95(0.62,1.47) | 0 | 0.83 |
| **Gastrointestinal bleeding** | | | | | | | | | | |
| Bennett et al | 2014 | 3R | TXA | Placebo/no treatment | 522/526 | | RR | 2.32(0.60,8.89) | 0 | 0.22 |
| **Cardiac surgery** | | | | | | | | | | |
| Umscheid et al | 2007 | 1RC | TXA | Placebo | 263/231 | | RR | 0.84(0.30,2.30) | NA | NA |

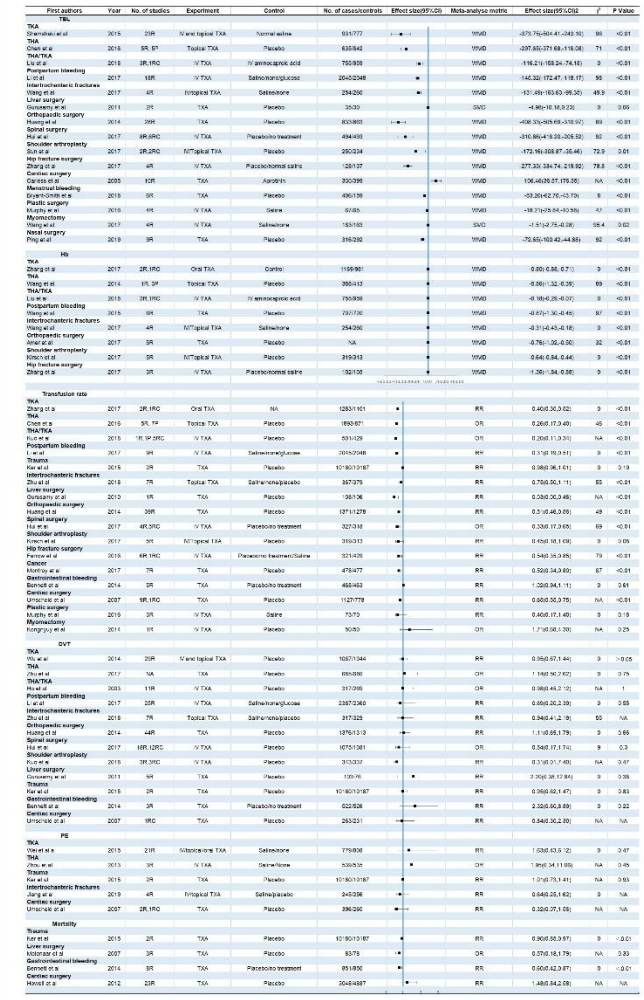


| First authors | Year | No. of studies | Experiment | Control | No. of cases/controls | Effect size(95%CI) | Meta-analyse metric | Effect size(95%CI)2 | $I^2$ | P Value |
|---|---|---|---|---|---|---|---|---|---|---|
| **PE** | | | | | | | | | | |
| **Orthopedics** | | | | | | | | | | |
| **TKA** | | | | | | | | | | |
| Yang et al | 2012 | 5R | TXA | Placebo | 174/175 | | OR | 0.65(0.18,2.33) | 0 | 0.5 |
| Wu et al | 2014 | 16R | IV and topical TXA | Placebo | 705/706 | | RR | 0.45(0.14,1.42) | 0 | >0.05 |
| Wei et al a | 2015 | 21R | IV/topical/oral TXA | Saline/none | 779/808 | | RR | 1.63(0.43,6.12) | 0 | 0.47 |
| Zhang et al | 2014 | NA | Topical TXA | Placebo | NA | | RR | 0.54(0.10,2.89) | NA | 0.46 |
| Chen et al | 2016 | 7R | Topical TXA | Placebo | 677/582 | | RR | 0.66(0.09,4.80) | 0 | 0.68 |
| Xiong et al | 2018 | NA | IV and topical TXA | IV TXA | NA | | RR | 0.33(0.01,7.91) | NA | 0.49 |
| Wang et al | 2016 | 1R | IV TXA | Topical TXA | 69/62 | | RR | 1.79(0.17,20.00) | NA | 0.63 |
| **THA** | | | | | | | | | | |
| Zhou et al | 2013 | 3R | IV TXA | Saline/None | 539/535 | | OR | 1.95(0.34,11.06) | NA | 0.45 |
| Yoon et al a | 2018 | NA | IV single | Placebo | NA | | OR | 1.09(0.28,4.19) | NA | NA |
| Yoon et al b | 2018 | NA | IV multiple | Placebo | NA | | OR | 1.23(0.25,6.07) | NA | NA |
| Yoon et al c | 2018 | NA | Topical TXA | Placebo | NA | | OR | 0.84(0.18,3.99) | NA | NA |
| Wei et al b | 2015 | 15R | IV/Topical/Oral TXA | Saline/none | 393/395 | | RR | 1.65(0.40,6.82) | 0 | 0.49 |
| Chen et al | 2016 | 3R | IV TXA | Topical TXA | 241/241 | | OR | 0.33(0.01,8.32) | 0 | 0.5 |
| Chen et al | 2016 | NA | IV TXA | Topical TXA | 1281/224 | | RR | 0.90(0.09,9.09) | 0 | 0.21 |
| **Trauma** | | | | | | | | | | |
| Ker et al | 2015 | 2R | TXA | Placebo | 10180/10187 | | RR | 1.01(0.73,1.41) | NA | 0.93 |
| **Intertrochanteric fractures** | | | | | | | | | | |
| Jiang et al | 2019 | 4R | IV/topical TXA | Saline/placebo | 245/256 | | RR | 0.64(0.25,1.62) | 0 | NA |
| **Cardiac surgery** | | | | | | | | | | |
| Umscheid et al | 2007 | 2R,1RC | TXA | Placebo | 396/260 | | RR | 0.32(0.07,1.56) | NA | NA |

According to the largest studies, the meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, menstrual bleeding, plastic surgery and nasal surgery reported significantly reduced TBL; the meta-analyses of TXA using for liver surgery and myomectomyreported reported that there was no significant difference in TBL; the meta-analyses of TXA using for cardiac surgery reported

significantly increased TBL. The meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, shoulder arthroplasty, hip fracture surgery reported significantly reduced Hb drop; the meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, liver surgery, orthopaedic surgery, spinal surgery, hip fracture surgery, cancer and cardiac surgery reported significantly reduced transfusion rate; the meta-analyses of TXA using for trauma, shoulder arthroplasty, gastrointestinal bleeding, plastic surgery and myomectomy reported there was no significant difference in transfusion rate. The meta-analyses of TXA using for TKA, THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding and cardiac surgery reported there was no significant difference in DVT. The meta-analyses of TXA using for TKA, THA, trauma, intertrochanteric fractures and cardiac surgery reported there was no significant difference in PE. The meta-analyses of TXA using for trauma and gastrointestinal bleeding reported significantly reduced mortality; the meta-analyses of TXA using for liver surgery and cardiac surgery reported there was no significant difference in mortality as shown in **Table 3**.

**Table 3**



However, considering all the effect sizes of the included studies, the results were controversial.

A summary of evidence from the retrieved meta-analyses of TXA is shown in **Table 4**. The evidence for TXA using in TKA (combine administration vs single administration; TXA vs placebo), THA (combine administration vs single administration; TXA vs placebo), TKA/THA (combine administration vs single administration; TXA vs placebo), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture surgery, cardiac surgery, menstrual bleeding, plastic surgery, myomectomy, nasal surgery was assessed as possible for the association of reducing TBL. There was probably no association between TXA and TBL in TKA (IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), TKA/THA (IV TXA vs topical/oral TXA) and liver surgery.

**Table 4**

| **Level of evidence** | **End points** | | | | | |
|---|---|---|---|---|---|---|
| | TBL | Transfusion rate | Hb drop | Mortality | DVT | PE |
| Convincing | - | - | - | - | - | - |
| Probable | - | Reducing transfusion rate of TKA (TXA vs placebo), THA (TXA vs placebo; combine administration vs single administration), TKA/THA( combine administration vs single administration), postpartum bleeding, orthopaedic surgery, shoulder arthroplasty | Reducing Hb drop of intertrochanteric fractures, orthopaedic surgery, hip fracture surgery | Reducing mortality of trauma, gastrointestinal bleeding | - | - |
| Possible | Reducing | Reducing | Reducing | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| | TBL of TKA (combine administration vs single administration; TXA vs placebo), THA (combine administration vs single administration; TXA vs placebo), TKA/THA (combine administration vs single administration; TXA vs placebo), postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, hip fracture | TBL of TKA/THA( TXA vs placebo), liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery | Hb drop of TKA(TXA vs placebo; combine administration vs single administration), THA(TXA vs placebo; combine administration vs single administration), TKA/THA(TXA vs placebo; combine administration vs single administration), postpartum bleeding, shoulder arthroplasty | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | surgery, cardiac surgery, menstrual bleeding, plastic surgery, myomectomy, nasal surgery | | | | | |
| No associations | No association with TKA(IV TXA vs topical/oral TXA), THA(IV TXA vs topical/oral TXA), TKA/THA(IV TXA vs topical/oral TXA), liver surgery | No association with TKA(combine administration vs single administration; IV TXA vs topical/oral TXA), THA(IV TXA vs topical/oral TXA), TKA/THA(IV TXA vs topical/oral TXA), trauma, intertrochanteric fractures, gastrointestinal bleeding, plastic surgery, myomectomy | No association with TKA(IV TXA vs topical TXA), THA(IV TXA vs topical TXA), TKA/THA(IV TXA vs topical TXA) | No association with liver surgery, cardiac surgery | No association with TKA, THA, TKA/THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding, cardiac surgery | No association with TKA, THA, trauma, intertrochanteric fractures, cardiac surgery |
| Limited/ | - | - | - | - | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Contrasting | | | | | | |

The evidence for TXA using in TKA (TXA vs placebo), THA (TXA vs placebo; combine administration vs single administration), TKA/THA (combine administration vs single administration), postpartum bleeding, orthopaedic surgery, shoulder arthroplasty was assessed as probable for the association of reducing transfusion rate. The evidence for TXA using in TKA/THA (TXA vs placebo), liver surgery, spinal surgery, hip fracture surgery, cancer, cardiac surgery was considered to be possible for the association of reducing transfusion rate. There was probably no association between TXA and transfusion rate in TKA (combine administration vs single administration; IV TXA vs topical/oral TXA), THA (IV TXA vs topical/oral TXA), TKA/THA (IV TXA vs topical/oral TXA), trauma, intertrochanteric fractures, gastrointestinal bleeding, plastic surgery, myomectomy.
The evidence for TXA using in intertrochanteric fractures, orthopaedic surgery, hip fracture surgery was assessed as probable for the association of reducing Hb drop. The evidence for TXA using in TKA (TXA vs placebo; combine administration vs single administration), THA (TXA vs placebo; combine administration vs single administration), TKA/THA (TXA vs placebo; combine administration vs single administration), postpartum bleeding, shoulder arthroplasty was considered to be possible for the association of reducing Hb drop. There was probably no association between TXA and Hb drop in TKA (IV TXA vs topical TXA), THA (IV TXA vs topical TXA), TKA/THA (IV TXA vs topical TXA).
The evidence for TXA using in trauma, gastrointestinal bleeding was assessed as probable for the association of reducing mortality. There was probably no association between TXA and mortality in liver surgery, cardiac surgery.
There was probably no association between TXA and DVT in TKA, THA, TKA/THA, postpartum bleeding, intertrochanteric fractures, orthopaedic surgery, spinal surgery, shoulder arthroplasty, liver surgery, trauma, gastrointestinal bleeding, cardiac surgery.
There was probably no association between TXA and PE in TKA, THA, trauma, intertrochanteric fractures, cardiac surgery.
Several other associations were found but were often affected by heterogeneity or potential confounding factors.

**Discussion**

Hemostatic drugs can accelerate blood coagulation or reduce capillary permeability and stop bleeding.[143] The normal hemostatic mechanism depends on the integrity of the structure and function of the vascular wall, platelet, coagulation system, anticoagulation system, fibrinolysis (fibrinolysis) system and hemorheology, as well as the physiological regulation and balance between them.[144] The hemostatic drugs used in the clinic can either reduce the arteries and capillaries, or enhance the platelet function, or accelerate or strengthen the blood coagulation process, or inhibit the clot dissolution process to achieve the purpose of hemostasis. [145]

The hemostatic drugs commonly used in the clinic are mainly divided into 4

categories: 1. Antifibrinolytic drugs: (1) aminocaproic acid acts by inhibiting the fibrinolytic system. It is mainly used for bleeding caused by the increase of fibrinolytic enzyme activity, such as obstetrics and gynecology, prostate, liver, pancreas, lung and so on. Early or preoperative use of drugs during operation can reduce blood leakage during operation and reduce the amount of blood transfusion. Overdose can lead to thrombosis with a tendency to thrombosis or a history of thrombotic vascular disease. Renal insufficiency should be used with caution. Due to the side effects of this drug, it has been less used at present.[146] (2) the mechanism of aminomethylbenzoic acid (hemostatic aromatic acid) is the same as that of aminocaproic acid, and its effect is 4-5 times stronger than that of aminohexanoic acid. Suitable for lung, liver, pancreas, prostate, thyroid, adrenal gland surgery abnormal bleeding, obstetrics and gynecology and postpartum hemorrhage and pulmonary tuberculosis hemoptysis, sputum with blood, hematuria, prostate hypertrophy bleeding, upper gastrointestinal bleeding and so on. It has a significant effect on chronic blood oozing.[147] (3) the mechanism of aminocycline (hemostatic cyclic acid, thrombotic acid) is the same as TXA, and its effect is slightly stronger than that of aminomethylbenzoic acid. The indication is similar to hemostatic aromatic acid. It is used for all kinds of hemorrhagic diseases, abnormal bleeding during the operation and so on. Side effects can be headache, dizziness, nausea, vomiting and other reactions.[148] 2. Drugs to reduce capillary permeability: (1) phenolsulfonethylamine (hemostatic) works by promoting the process of coagulation. It can increase platelet aggregation and adhesion in the blood, promote the release of clotting substances, accelerate blood coagulation.[149] Clinically, it is used to prevent and treat bleeding caused by surgical bleeding, thrombocytopenic purpura, or Henoch-Schonlein purpura and other causes. This product can be used in combination with other types of hemostatic drugs. Fewer side effects. (2) carbacarbital (Anluo blood) is a semicarbazide of adrenaline oxidation product adrenaline, which is often used as sodium salicylate (carbacarbital) or sodium sulfonate (sodium caroesulfonate). This product can promote capillary contraction. Reduce the permeability of capillaries, increase the retraction of the broken end of broken capillaries, and play a hemostatic role. Indications: This product is often used in idiopathic purpura, retinal hemorrhage, chronic pulmonary hemorrhage, gastrointestinal hemorrhage, epistaxis, hemoptysis, hematuria, hemorrhoid bleeding, uterine bleeding, cerebral hemorrhage and so on. Side effects: this product is low toxicity, but not suitable for mass use, can induce epilepsy and mental disorders. 3. Thrombin drugs: (1) the common name of batroxine is snake venom hemagglutinin for injection, which is a kind of batroxobin extracted from Brazilian spearhead. Clinically, it is used to treat bleeding caused by various causes, especially in patients with bleeding whose traditional hemostatic drugs are ineffective. Contraindication: bleeding caused by DIC and patients with a history of thrombosis or embolism are prohibited. In addition to emergency bleeding, the first 3 months of pregnancy should not be used. (2) Thrombin can directly act on the fibrinogen in the blood, promote the transformation into fibrin, accelerate the coagulation of the blood and stop the bleeding. Clinical use for trauma, surgery and oral hemostasis for gastrointestinal bleeding.[150] No injections. 4. Coagulation factors:

(1) Vitamin K1 is a natural vitamin used for injection. The effect was stronger than that of K3 and K4. (2) Sodium bisulfite mono-naphthoquinone (vitamin K3) is a synthetic vitamin, which is used in the treatment of vitamin K deficiency. (3) methylnaphthalene hydroquinone (vitamin K4, acetylnaphthoquinone) is a synthetic vitamin, which is used for oral administration.[151]

Fibrinolysis is related to the decomposition of fibrinolysis and the increase of vascular permeability under physiological or pathological conditions, as well as the occurrence, development and cure of fibrinolysis-induced reactions, bleeding symptoms and allergic reactions.[2] TXA can inhibit the effect of fibrinolytic enzyme and show hemostatic, anti-allergic and anti-inflammatory effects. (1) Anti-fibrinolytic enzyme effect. Aminocycline can strongly adsorb (LBS), which is the lysine binding site of fibrinolytic enzyme and plasminogen, and inhibit the binding of fibrinolytic enzyme and plasminogen to fibrin. Thus, the fibrinolysis induced by the fibrinolytic enzyme was strongly inhibited. Besides, in the presence of anti-fibrinolytic enzymes such as macroglobulin 2 in serum, the anti-fibrinolytic effect of TXA was more obvious, and the hemostatic effect was more significant.[3] (2) Hemostatic effect. Abnormal hyperactivity of the fibrinolytic enzyme will cause platelet agglutination inhibition and coagulation factor decomposition. Mild hyperactivity first leads to the decomposition of fibrin. Therefore, it is considered that in general bleeding, TXA can inhibit fibrin decomposition and play a hemostatic role.[4] (3) Anti-allergic and anti-inflammatory effects. TXA can inhibit the production of kinin and other active peptides (guinea pigs and rats) which cause vascular permeability enhancement, allergy and inflammatory lesions.[5]

In the current controversial situation, researchers are trying to use different methods to verify the safety of TXA. Because it is necessary to design a clinical trial with a large enough sample to illustrate the differences between these low probability events, the researchers turned to look for answers to questions from some population-based databases in recent years. To answer our questions about the use of TXA in different clinical situations. There are limitations, such as the fact that these studies are retrospective, or that there is only limited clinical data and the risk of confusion. Although these randomized trials do not comply with strict inclusion or exclusion criteria but are artificially defined, the benefits are considerable, such as the provision of large samples and the true clinical results of hundreds of hospital cases.

Poeran et al.[152] have recently found that the use of TXA in most joint operations can be benefit. Their study found that TXA is safe and effective in total hip or knee arthroplasty. In 872416 cases in 510 hospitals across the United States, the researchers found that the use of TXA reduced the rate of blood transfusions by 60 percent or more. The application of TXA could reduce the incidence of allogeneic or autologous blood transfusion (7.7% vs. 20.1%, $P < 0.001$), thrombus-related complications (0.6% vs.0.8%, $P < 0.0057$). The overall complications (1.9% v.s.2.6%, $P < 0.001$), the need for mechanical ventilation (0.1% vs.0.2%, $P < 0.0003$), and the need to enter ICU (3.1%

vs.7.5%, P < 0.001). Besides, the median hospitalization cost of patients treated with TXA was relatively low (P<0.001). Very importantly, while showing significant effectiveness, the use of TXA did not significantly increase the risk of complications, such as thrombus-related events (probability ratio 0.85: 1.02), acute renal failure (0.70: 1.11, This is a hidden danger to the use of antifibrinolytic drugs since protease inhibitors left the market), the overall complication (0.75: 0.98). The overall complications also include acute myocardial infarction, which is important because the pathogenesis of perioperative myocardial infarction is due to myocardial oxygen deficiency, coronary plaque rupture and platelet activation. If intraoperative bleeding is reduced as a result of the use of TXA, myocardial hypoxia caused by tachycardia and reduced hemoglobin in the blood can be effectively reduced. In this regard, preliminary data using the same data set may indicate no increased risk in cases with a history of coronary artery disease, but there is a clear need for more research in this area. In providing the data, the authors point out that although the use of TXA is becoming more and more popular, only 11.2 percent of patients were found to be using it in the 2012 year study. At the same time, they also stressed that although the use of TXA is safe in the population as a whole, the safety of using TXA in different subgroups needs to be further studied.

Another way to solve the safety problem of TXA is to reduce the amount of TXA in the whole body by local application of TXA in the surgical site. Gomez-Barrena et al.[153] recently published an article in JBJS comparing the efficacy of local TXA and intravenous TXA in patients with primary total knee arthroplasty. A phase III single-center double-blind randomized controlled trial was conducted to demonstrate that local administration of TXA (3 g TXA dissolved in 100 mL saline) was no worse than twice intravenous administration of TXA (15 mg/kg TXA dissolved in 100 mL saline, once before the tourniquet was loosened. It was used 3 hours after operation). The main indicators were defined as the need for postoperative blood transfusions. The secondary indicators included blood loss through drainage at 3 hours 24 hours, hemoglobin levels 24 hours, 48 hours and 5 days after the operation, and estimated total bleeding volume (calculated by the lowest hemoglobin level before and after the operation). Besides, complications and serious adverse reactions, days of hospitalization and active motion range of knee joint after operation were also within the scope of their evaluation. The sample size was calculated by a maximum expected transfusion rate of 5%, based on a 0 transfusion rate in previous studies of total knee arthroplasty. In the preliminary results, the significance was set to unilateral 0.025, the test efficiency was 99%, and the sample size of each group was 39 cases. There was no statistically significant difference in the main results (the transfusion rate was 0 in both groups), and there was no significant difference in the secondary results (blood loss in 3-24 h drainage and the calculated amount of blood loss 48 h and 5 d after the operation). The decline levels of hemoglobin at 24 h, 48 h and 5 d were similar between the two groups (local use of TXA group was 2.3 g/L, 2.1 g/L and 2.0 g/L). Intravenous use of TXA group was -2.5, -3.4, -2.6 g/dL).

On the other hand, the use of TXA in orthopedic patients is more economically efficient. Its performance in reducing the hospitalization cost of patients with total hip and total knee arthroplasty makes its application prospect more bright. TXA itself is cheap (about $6 per box on average), and studies by Poeran et al.[152] have shown that it can significantly reduce the average hospitalization costs of patients. Given that the number of joint replacements is likely to continue to rise across the United States and elsewhere over the next decade, an economical and effective treatment is indispensable.

Overall, the evidence so far has irrefutably confirmed the role of TXA in joint replacement: it can effectively reduce bleeding and transfusion rates. At present, the data on its safety in the perioperative period is considerable. However, for those at risk of thrombotic complications, the use of TXA still needs further research, as well as further research on the safe use of TXA and the minimum effective dose of TXA. Local use of TXA, is a better method than intravenous administration, especially in terms of reducing plasma concentrations. But strong enough evidence is still needed to prove its safety. At the same time, because of its economy and clinical effectiveness, the overall dosage of TXA is increasing. However, with the expansion of the use of TXA, there will be more new problems, so it is necessary to continue to assess the risks and benefits of TXA, especially for those cases where there is a risk of adverse events. To provide evidence-based evidence to ensure the reasonable clinical use of TXA, an umbrella review that systematically assessing the hemostatic effect and safety of TXA is crucial.

In our study, the results of 136 meta-analyses (396 comparisons) [7-142] including TXA to reduce TBL, transfusion rate, Hb drop, mortality, DVT and PE were reviewed; these meta-analyses included 15 kinds of surgeries. Most of the evidence comes from a meta-analysis of RCTs; only a few meta-analyses include observational studies. Based on these results, there may be evidence that TXA may help reduce TBL, transfusion rate, Hb drop and mortality in different kinds of surgeries. In terms of different ways of administration, intravenous combined topical application of TXA significantly reduced TBL in TKA and THA compared with intravenous or topical application of TXA alone; intravenous combined topical application of TXA significantly reduced transfusion rate in THA compared with intravenous or topical application of TXA alone; intravenous combined topical application of TXA significantly reduced Hb drop in TKA and THA compared with intravenous or topical application of TXA alone.

The potential clinical implications of this study are as follows: (1) This is the first umbrella review to assess the hemostatic effect and safety of TXA. The study summarized all meta-analyses of TXA used in different surgeries from the inception to now and classified the endpoints according to the level of evidence. (2) 136 meta-analyses with 396 comparisons were retrieved which included a large sample size of participants compared to other studies. This was of great significance in the field of evidence-based medicine. (3) With the increase of RCT and meta-analysis,

TXA is more and more widely used in reducing blood loss, but accompanied by great controversy. In this study, TXA used in surgeries reported by meta-analyses were systematically classified into three grade according to effect size, concordance of results, heterogeneity and potential confounding factors. Therefore, this study has better reference value for clinical drug use than other meta-analysis and general review.

The limitations of this study are as follows: (1) Baseline characteristics were not considered and this may lead to mixed bias. (2) We used the effect sizes reported in the retrieved studies. Therefore, it is difficult to assess the effect of these baseline characteristics on the results. (3) The experimental group and the control group were not unified. The comparison of different meta-analyses of the same surgery may be of limited significance. (4) There is no internationally uniform standard for the level of evidence. Therefore, we can only make a summary of the existing meta-analyses as a reference, but cannot give the exact quantitative conclusion. (5) Intervention measures and medication doses were not uniform in different meta-analyses of the same surgery. Since the results of all meta-analyses cannot be directly combined, there is no accurate criterion for the effectiveness of different meta-analyses of the same medication. (6) Some different meta-analyses may include the same RCT, so there may be some duplications among the participants included in this review. (7) There are few studies on the use of TXA in some surgeries (such as Myomectomy, Cardiac surgery), so the classification of these studies may not be accurate. (8) There may be no meta-analysis report on the use of TXA in some areas, but only sporadic RCT publication, we do not consider.

## Summary points

This umbrella review indicated that TXA was regarded as effective to reduce TBL, transfusion rate, Hb drops and mortality in different kinds of surgeries, and did not increase the incidence of DVT and PE.

## Future issues

(1) Future studies should include stratification by the dose of TXA to definitively exclude mixed bias. (2) In the future meta-analyses, authors should pay attention to unifying the intervention measures in the experimental group or the control group to avoid the heterogeneity, and reduce the difficulty of the combined effect size of umbrella review. (3) Multicenter large sample size RCTs should be implemented to promote more representative meta-analyses creation, to provide more convincing evidence for assessing hemostatic effect and safety of TXA. (4) The international criteria of the level of evidence for umbrella review should be identified as soon as possible, to provide a reference for the development of umbrella review in the future.

## Declarations


### Acknowledgments

None

### Funding

None.


### Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: Mingyang JIANG. Author, Ke ZHANG. Author; data collection: Chuanliang CHEN. Author; analysis and interpretation of results: Xiaochong ZOU. Author, Kaicheng LIU. Author. Yongheng DAI. Author; draft manuscript preparation: Zhandong BO. Author. Mingyang JIANG. Author. All authors reviewed the results and approved the final version of the manuscript.

### Availability of Data and Materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

### Ethnics Approval

None.

### Conflict of interest

All authors declared that there was no conflict of interest.

## References


1. Delaney M, Matthews DC, Gernsheimer TB. The use of antifibrinolytics in pediatric patients with hypoproliferative thrombocytopenia. *Pediatr Blood Cancer.* 2017;64:e26641.
2. He S, Bark N, Wang H, et al. Effects of acetylsalicylic acid on increase of fibrin network porosity and the consequent upregulation of fibrinolysis. *J Cardiovasc Pharmacol.* 2009;53:24-29.
3. Hong C, Takahashi S, Imamura M, et al. Earthworm fibrinolytic enzyme: anti-tumor activity on human hepatoma cells in vitro and in vivo. *Chin Med J.* 2007;120:898-904.
4. Xie J, Ma J, Huang Q, et al. Comparison of Enoxaparin and Rivaroxaban in Balance of Anti-Fibrinolysis and Anticoagulation Following Primary Total Knee Replacement: A Pilot Study. *Medical Science Monitor International Medical Journal of Experimental & Clinical Research.* 2017;23:704-711.
5. Sohn EH, Jang S, Joo H, et al. Anti-allergic and anti-inflammatory effects of butanol extract from Arctium Lappa L. *Clin Mol Allergy.* 2011;9:4.
6. Aromataris E, Fernandez R, Godfrey CM, Holly C, Tungpunkom P. Summarizing systematic reviews: Methodological development, conduct and reporting of an umbrella review approach. *International Journal of Evidence Based Healthcare*. 2015;13:132-140.
7. Carless PA, Moxey AJ, Stokes BJ, Henry DA. Are antifibrinolytic drugs equivalent in reducing blood loss and transfusion in cardiac surgery? A meta-analysis of randomized head-to-head trials. *BMC Cardiovasc Disord.* 2005;5:19.
8. Cid J, Lozano M. Tranexamic acid reduces allogeneic red cell transfusions in patients undergoing total knee arthroplasty: results of a meta-analysis of randomized controlled trials. *Transfusion.* 2005;45:1302-1307.
9. Murphy GJ, Mango E, Lucchetti V, et al. A randomized trial of tranexamic acid in combination with cell salvage plus a meta-analysis of randomized trials evaluating tranexamic acid in off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2006;132:475-480, 480 e471-478.
10. Brown JR, Birkmeyer NJ, O'Connor GT. Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery. *Circulation.* 2007;115:2801-2813.
11. Molenaar IQ, Warnaar N, Groen H, et al. Efficacy and safety of antifibrinolytic drugs in liver transplantation: a systematic review and meta-analysis. *Am J Transplant.* 2007;7:185-194.
12. Gill JB, Chin Y, Levin A, Feng D. The use of antifibrinolytic agents in spine surgery. A meta-analysis. *J Bone Joint Surg Am.* 2008;90:2399-2407.
13. Abrishami A, Chung F, Wong J. Topical application of antifibrinolytic drugs for on-pump cardiac surgery: a systematic review and meta-analysis. *Can J Anaesth.* 2009;56:202-212.
14. Gurusamy KS, Li J, Sharma D, Davidson BR. Pharmacological interventions to decrease blood loss and blood transfusion requirements for liver resection.

*Cochrane Database Syst Rev.* 2009;CD008085.
15. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *CMAJ.* 2009;180:183-193.
16. Schouten ES, van de Pol AC, Schouten AN, et al. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. *Pediatr Crit Care Med.* 2009;10:182-190.
17. Takagi H, Manabe H, Kawai N, et al. Aprotinin increases mortality as compared with tranexamic acid in cardiac surgery: a meta-analysis of randomized head-to-head trials. *Interact Cardiovasc Thorac Surg.* 2009;9:98-101.
18. Ngaage DL, Bland JM. Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies. *Eur J Cardiothorac Surg.* 2010;37:1375-1383.
19. Adler Ma SC, Brindle W, Burton G, et al. Tranexamic acid is associated with less blood transfusion in off-pump coronary artery bypass graft surgery: a systematic review and meta-analysis. *J Cardiothorac Vasc Anesth.* 2011;25:26-35.
20. Hutton B, Joseph L, Fergusson D, et al. Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies. *BMJ.* 2012;345:e5798.
21. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am.* 2012;94:1153-1159.
22. Zhang H, Chen J, Chen F, Que W. The effect of tranexamic acid on blood loss and use of blood products in total knee arthroplasty: a meta-analysis. *Knee Surg Sports Traumatol Arthrosc.* 2012;20:1742-1752.
23. Howell N, Senanayake E, Freemantle N, Pagano D. Putting the record straight on aprotinin as safe and effective: results from a mixed treatment meta-analysis of trials of aprotinin. *J Thorac Cardiovasc Surg.* 2013;145:234-240.
24. Li ZJ, Fu X, Xing D, et al. Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. *Eur Spine J.* 2013;22:1950-1957.
25. Panteli M, Papakostidis C, Dahabreh Z, Giannoudis PV. Topical tranexamic acid in total knee replacement: a systematic review and meta-analysis. *Knee.* 2013;20:300-309.
26. Tan J, Chen H, Liu Q, et al. A meta-analysis of the effectiveness and safety of using tranexamic acid in primary unilateral total knee arthroplasty. *J Surg Res.* 2013;184:880-887.
27. Yang B, Li H, Wang D, et al. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One.* 2013;8:e55436.
28. Zhou XD, Tao LJ, Li J, Wu LD. Do we really need tranexamic acid in total hip arthroplasty? A meta-analysis of nineteen randomized controlled trials. *Arch*

*Orthop Trauma Surg.* 2013;133:1017-1027.
29. Heesen M, Bohmer J, Klohr S, et al. Prophylactic tranexamic acid in parturients at low risk for post-partum hemorrhage: systematic review and meta-analysis. *Acta Anaesthesiol Scand.* 2014;58:1075-1085.
30. Huang F, Wu D, Ma G, et al. The use of tranexamic acid to reduce blood loss and transfusion in major orthopedic surgery: a meta-analysis. *J Surg Res.* 2014;186:318-327.
31. Mousa HA, Blum J, Abou El Senoun G, et al. Treatment for primary postpartum hemorrhage. *Cochrane Database Syst Rev.* 2014;CD003249.
32. Wang H, Shen B, Zeng Y. Comparison of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled and prospective cohort trials. *Knee.* 2014;21:987-993.
33. Zhang Y, Fu X, Liu WX, et al. Safety and efficacy of intra-articular injection of tranexamic acid in total knee arthroplasty. *Orthopedics.* 2014;37:e775-782.
34. Zhao-Yu C, Yan G, Wei C, et al. Reduced blood loss after intra-articular tranexamic acid injection during total knee arthroplasty: a meta-analysis of the literature. *Knee Surg Sports Traumatol Arthrosc.* 2014;22:3181-3190.
35. Alam A, Choi S. Prophylactic Use of Tranexamic Acid for Postpartum Bleeding Outcomes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Transfus Med Rev.* 2015;29:231-241.
36. Cheriyan T, Maier SP, 2nd, Bianco K, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. *Spine J.* 2015;15:752-761.
37. He P, Zhang Z, Li Y, et al. Efficacy and Safety of Tranexamic Acid in Bilateral Total Knee Replacement: A Meta-Analysis and Systematic Review. *Med Sci Monit.* 2015;21:3634-3642.
38. Huang F, Wu Y, Yin Z, et al. A systematic review and meta-analysis of the use of antifibrinolytic agents in total hip arthroplasty. *Hip Int.* 2015;25:502-509.
39. Ker K, Roberts I, Shakur H, Coats TJ. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev.* 2015;CD004896.
40. Novikova N, Hofmeyr GJ, Cluver C. Tranexamic acid for preventing postpartum hemorrhage. *Cochrane Database Syst Rev.* 2015;CD007872.
41. Shemshaki H, Nourian SM, Nourian N, et al. One step closer to sparing total blood loss and transfusion rate in total knee arthroplasty: a meta-analysis of different methods of tranexamic acid administration. *Arch Orthop Trauma Surg.* 2015;135:573-588.
42. Wang C, Xu GJ, Han Z, et al. Topical application of tranexamic acid in primary total hip arthroplasty: a systemic review and meta-analysis. *Int J Surg.* 2015;15:134-139.
43. Wang HY, Hong SK, Duan Y, Yin HM. Tranexamic acid and blood loss during and after cesarean section: a meta-analysis. *J Perinatol.* 2015;35:818-825.
44. Wang M, Zheng XF, Jiang LS. Efficacy and Safety of Antifibrinolytic Agents in Reducing Perioperative Blood Loss and Transfusion Requirements in Scoliosis Surgery: A Systematic Review and Meta-Analysis. *PLoS One.* 2015;10:e0137886.

45. Wei Z, Liu M. The effectiveness and safety of tranexamic acid in total hip or knee arthroplasty: a meta-analysis of 2720 cases. *Transfus Med.* 2015;25:151-162.
46. Wu Q, Zhang HA, Liu SL, et al. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol.* 2015;25:525-541.
47. Xu X, Xiong S, Wang Z, et al. Topical administration of tranexamic acid in total hip arthroplasty: A meta-analysis of Randomized Controlled Trials. *Drug Discov Ther.* 2015;9:173-177.
48. Yu X, Li W, Xu P, et al. Safety and Efficacy of Tranexamic Acid in Total Knee Arthroplasty. *Med Sci Monit.* 2015;21:3095-3103.
49. Yue C, Pei F, Yang P, et al. Effect of Topical Tranexamic Acid in Reducing Bleeding and Transfusions in TKA. *Orthopedics.* 2015;38:315-324.
50. Chen S, Wu K, Kong G, et al. The efficacy of topical tranexamic acid in total hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord.* 2016;17:81.
51. Chen Y, Chen Z, Cui S, et al. Topical versus systemic tranexamic acid after total knee and hip arthroplasty: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2016;95:e4656.
52. Farrow LS, Smith TO, Ashcroft GP, Myint PK. A systematic review of tranexamic acid in hip fracture surgery. *Br J Clin Pharmacol.* 2016;82:1458-1470.
53. Fu Y, Shi Z, Han B, et al. Comparing efficacy and safety of 2 methods of tranexamic acid administration in reducing blood loss following total knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2016;95:e5583.
54. Gao F, Ma J, Sun W, et al. Topical fibrin sealant versus intravenous tranexamic acid for reducing blood loss following total knee arthroplasty: A systematic review and meta-analysis. *Int J Surg.* 2016;32:31-37.
55. Li J, Zhang Z, Chen J. Comparison of efficacy and safety of topical versus intravenous tranexamic acid in total hip arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2016;95:e4689.
56. Lin C, Qi Y, Jie L, et al. Is combined topical with intravenous tranexamic acid superior than topical, intravenous tranexamic acid alone and control groups for blood loss controlling after total knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2016;95:e5344.
57. McNicol ED, Tzortzopoulou A, Schumann R, et al. Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. *Cochrane Database Syst Rev.* 2016;9:CD006883.
58. Moskal JT, Capps SG. Meta-analysis of Intravenous Tranexamic Acid in Primary Total Hip Arthroplasty. *Orthopedics.* 2016;39:e883-892.
59. Murphy GR, Glass GE, Jain A. The Efficacy and Safety of Tranexamic Acid in Cranio-Maxillofacial and Plastic Surgery. *J Craniofac Surg.* 2016;27:374-379.
60. Shang J, Wang H, Zheng B, et al. Combined intravenous and topical tranexamic acid versus intravenous use alone in primary total knee and hip arthroplasty: A meta-analysis of randomized controlled trials. *Int J Surg.* 2016;36:324-329.

61. Simonazzi G, Bisulli M, Saccone G, et al. Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials. *Acta Obstet Gynecol Scand.* 2016;95:28-37.
62. Sun X, Dong Q, Zhang YG. Intravenous versus topical tranexamic acid in primary total hip replacement: A systemic review and meta-analysis. *Int J Surg.* 2016;32:10-18.
63. Weng K, Zhang X, Bi Q, Zhao C. The effectiveness and safety of tranexamic acid in bilateral total knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2016;95:e4960.
64. Zhang P, Liang Y, Chen P, et al. Intravenous versus topical tranexamic acid in primary total hip replacement: A meta-analysis. *Medicine (Baltimore).* 2016;95:e5573.
65. Amer KM, Rehman S, Amer K, Haydel C. Efficacy and Safety of Tranexamic Acid in Orthopaedic Fracture Surgery: A Meta-Analysis and Systematic Literature Review. *J Orthop Trauma.* 2017;31:520-525.
66. Chen TP, Chen YM, Jiao JB, et al. Comparison of the effectiveness and safety of topical versus intravenous tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. *J Orthop Surg Res.* 2017;12:11.
67. Gausden EB, Qudsi R, Boone MD, et al. Tranexamic Acid in Orthopaedic Trauma Surgery: A Meta-Analysis. *J Orthop Trauma.* 2017;31:513-519.
68. He J, Wang XE, Yuan GH, Zhang LH. The efficacy of tranexamic acid in reducing blood loss in total shoulder arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2017;96:e7880.
69. Kirsch JM, Bedi A, Horner N, et al. Tranexamic Acid in Shoulder Arthroplasty: A Systematic Review and Meta-Analysis. *JBJS Rev.* 2017;5:e3.
70. Li C, Gong Y, Dong L, et al. Is prophylactic tranexamic acid administration effective and safe for postpartum hemorrhage prevention?: A systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96:e5653.
71. Li G, Sun TW, Luo G, Zhang C. Efficacy of antifibrinolytic agents on surgical bleeding and transfusion requirements in spine surgery: a meta-analysis. *Eur Spine J.* 2017;26:140-154.
72. Li GL, Li YM. Oral tranexamic acid can reduce blood loss after total knee and hip arthroplasty: A meta-analysis. *Int J Surg.* 2017;46:27-36.
73. Li JF, Li H, Zhao H, et al. Combined use of intravenous and topical versus intravenous tranexamic acid in primary total knee and hip arthroplasty: a meta-analysis of randomised controlled trials. *J Orthop Surg Res.* 2017;12:22.
74. Liu X, Liu J, Sun G. A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: A meta-analysis. *Int J Surg.* 2017;41:34-43.
75. Meena S, Benazzo F, Dwivedi S, Ghiara M. Topical versus intravenous tranexamic acid in total knee arthroplasty. *J Orthop Surg (Hong Kong).* 2017;25:2309499016684300.

76. Mi B, Liu G, Lv H, et al. Is combined use of intravenous and intraarticular tranexamic acid superior to intravenous or intraarticular tranexamic acid alone in total knee arthroplasty? A meta-analysis of randomized controlled trials. *J Orthop Surg Res.* 2017;12:61.
77. Mi B, Liu G, Zhou W, et al. Intra-articular versus intravenous tranexamic acid application in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg.* 2017;137:997-1009.
78. Montroy J, Fergusson NA, Hutton B, et al. The Safety and Efficacy of Lysine Analogues in Cancer Patients: A Systematic Review and Meta-Analysis. *Transfus Med Rev.* 2017;31:141-148.
79. Sun CX, Zhang L, Mi LD, et al. Efficiency and safety of tranexamic acid in reducing blood loss in total shoulder arthroplasty: A systematic review and meta-analysis. *Medicine (Baltimore).* 2017;96:e7015.
80. Tian P, Liu WB, Li ZJ, et al. The efficacy and safety of tranexamic acid in revision total knee arthroplasty: a meta-analysis. *BMC Musculoskelet Disord.* 2017;18:273.
81. Topsoee MF, Settnes A, Ottesen B, Bergholt T. A systematic review and meta-analysis of the effect of prophylactic tranexamic acid treatment in major benign uterine surgery. *Int J Gynaecol Obstet.* 2017;136:120-127.
82. Wang D, Wang L, Wang Y, Lin X. The efficiency and safety of tranexamic acid for reducing blood loss in open myomectomy: A meta-analysis of randomized controlled trials. *Medicine (Baltimore).* 2017;96:e7072.
83. Wang S, Gao X, An Y. Topical versus intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Int Orthop.* 2017;41:739-748.
84. Wang W, Yu J. Tranexamic acid reduces blood loss in intertrochanteric fractures: A meta-analysis from randomized controlled trials. *Medicine (Baltimore).* 2017;96:e9396.
85. Wang Z, Shen X. The efficacy of combined intra-articular and intravenous tranexamic acid for blood loss in primary total knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2017;96:e8123.
86. Xie J, Hu Q, Huang Q, et al. Comparison of intravenous versus topical tranexamic acid in primary total hip and knee arthroplasty: An updated meta-analysis. *Thromb Res.* 2017;153:28-36.
87. Yang L, Du S, Sun Y. Is combined topical and intravenous tranexamic acid superior to single use of tranexamic acid in total joint arthroplasty?: A meta-analysis from randomized controlled trials. *Medicine (Baltimore).* 2017;96:e7609.
88. Yu BF, Yang GJ, Li Q, Liu LL. Tranexamic acid decreases blood loss in shoulder arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2017;96:e7762.
89. Yuan QM, Zhao ZH, Xu BS. Efficacy and safety of tranexamic acid in reducing blood loss in scoliosis surgery: a systematic review and meta-analysis. *Eur Spine J.* 2017;26:131-139.
90. Zhang H, He G, Zhang C, et al. Is combined topical and intravenous tranexamic

acid superior to intravenous tranexamic acid alone for controlling blood loss after total hip arthroplasty?: A meta-analysis. *Medicine (Baltimore).* 2017;96:e6916.
91. Zhang LK, Ma JX, Kuang MJ, et al. The efficacy of tranexamic acid using oral administration in total knee arthroplasty: a systematic review and meta-analysis. *J Orthop Surg Res.* 2017;12:159.
92. Zhang LK, Ma JX, Kuang MJ, et al. Comparison of oral versus intravenous application of tranexamic acid in total knee and hip arthroplasty: A systematic review and meta-analysis. *Int J Surg.* 2017;45:77-84.
93. Zhang P, He J, Fang Y, et al. Efficacy and safety of intravenous tranexamic acid administration in patients undergoing hip fracture surgery for hemostasis: A meta-analysis. *Medicine (Baltimore).* 2017;96:e6940.
94. Zhang P, Liang Y, Chen P, et al. Combined application versus topical and intravenous application of tranexamic acid following primary total hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord.* 2017;18:90.
95. Zhang XQ, Ni J, Ge WH. Combined use of intravenous and topical versus intravenous tranexamic acid in primary total joint arthroplasty: A meta-analysis of randomized controlled trials. *Int J Surg.* 2017;38:15-20.
96. Zhang Y, Zhang JW, Wang BH. Efficacy of tranexamic acid plus drain-clamping to reduce blood loss in total knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2017;96:e7363.
97. Zhu J, Zhu Y, Lei P, et al. Efficacy and safety of tranexamic acid in total hip replacement: A PRISMA-compliant meta-analysis of 25 randomized controlled trials. *Medicine (Baltimore).* 2017;96:e9552.
98. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Antifibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2018;4:CD000249.
99. Dai WL, Zhou AG, Zhang H, Zhang J. Most Effective Regimen of Tranexamic Acid for Reducing Bleeding and Transfusions in Primary Total Knee Arthroplasty: A Meta-Analysis of Randomized Controlled Trials. *J Knee Surg.* 2018;31:654-663.
100. Dai Z, Chu H, Wang S, Liang Y. The effect of tranexamic acid to reduce blood loss and transfusion on off-pump coronary artery bypass surgery: A systematic review and cumulative meta-analysis. *J Clin Anesth.* 2018;44:23-31.
101. Du Y, Feng C. The Efficacy of Tranexamic Acid on Blood Loss from Lumbar Spinal Fusion Surgery: A Meta-Analysis of Randomized Controlled Trials. *World Neurosurg.* 2018;119:e228-e234.
102. El-Menyar A, Sathian B, Asim M, et al. Efficacy of prehospital administration of tranexamic acid in trauma patients: A meta-analysis of the randomized controlled trials. *Am J Emerg Med.* 2018;36:1079-1087.
103. Fillingham YA, Ramkumar DB, Jevsevar DS, et al. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-analysis. *J Arthroplasty.* 2018;33:3083-3089 e3084.
104. Franchini M, Mengoli C, Cruciani M, et al. Safety and efficacy of tranexamic acid for prevention of obstetric haemorrhage: an updated systematic review and

meta-analysis. *Blood Transfus.* 2018;16:329-337.
105. Franchini M, Mengoli C, Marietta M, et al. Safety of intravenous tranexamic acid in patients undergoing majororthopaedic surgery: a meta-analysis of randomised controlled trials. *Blood Transfus.* 2018;16:36-43.
106. Guo P, He Z, Wang Y, et al. Efficacy and safety of oral tranexamic acid in total knee arthroplasty: A systematic review and meta-analysis. *Medicine (Baltimore).* 2018;97:e0587.
107. Han X, Gong G, Han N, Liu M. Efficacy and safety of oral compared with intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: a meta-analysis. *BMC Musculoskelet Disord.* 2018;19:430.
108. Hui S, Xu D, Ren Z, et al. Can tranexamic acid conserve blood and save operative time in spinal surgeries? A meta-analysis. *Spine J.* 2018;18:1325-1337.
109. Kuo FC, Lin PY, Wang JW, et al. Intravenous tranexamic acid use in revision total joint arthroplasty: a meta-analysis. *Drug Des Devel Ther.* 2018;12:3163-3170.
110. Kuo LT, Hsu WH, Chi CC, Yoo JC. Tranexamic acid in total shoulder arthroplasty and reverse shoulder arthroplasty: a systematic review and meta-analysis. *BMC Musculoskelet Disord.* 2018;19:60.
111. Li H, Bai L, Li Y, Fang Z. Oral tranexamic acid reduces blood loss in total-knee arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2018;97:e12924.
112. Liao L, Chen Y, Tang Q, et al. Tranexamic acid plus drain-clamping can reduce blood loss in total knee arthroplasty: A systematic review and meta-analysis. *Int J Surg.* 2018;52:334-341.
113. Liu Q, Geng P, Shi L, et al. Tranexamic acid versus aminocaproic acid for blood management after total knee and total hip arthroplasty: A systematic review and meta-analysis. *Int J Surg.* 2018;54:105-112.
114. Lu VM, Ho YT, Nambiar M, et al. The Perioperative Efficacy and Safety of Antifibrinolytics in Adult Spinal Fusion Surgery: A Systematic Review and Meta-analysis. *Spine (Phila Pa 1976).* 2018;43:E949-E958.
115. Luo W, Sun RX, Jiang H, Ma XL. The efficacy and safety of topical administration of tranexamic acid in spine surgery: a meta-analysis. *J Orthop Surg Res.* 2018;13:96.
116. Moskal JT, Capps SG. Intra-articular Tranexamic Acid in Primary Total Knee Arthroplasty: Meta-analysis. *J Knee Surg.* 2018;31:56-67.
117. Sridharan K, Sivaramakrishnan G. Tranexamic Acid in Total Knee Arthroplasty: Mixed Treatment Comparisons and Recursive Cumulative Meta-Analysis of Randomized, Controlled Trials and Cohort Studies. *Basic Clin Pharmacol Toxicol.* 2018;122:111-119.
118. Wang F, Zhao KC, Zhao MM, Zhao DX. The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: A meta-analysis. *Medicine (Baltimore).* 2018;97:e12270.
119. Xiong H, Liu Y, Zeng Y, et al. The efficacy and safety of combined administration of intravenous and topical tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. *BMC*

*Musculoskelet Disord.* 2018;19:321.
120. Yoon BH, Kim TY, Ko YS, et al. Optimal use of tranexamic acid for total hip arthroplasty: A network meta-analysis. *PLoS One.* 2018;13:e0206480.
121. Zhu Q, Yu C, Chen X, et al. Efficacy and Safety of Tranexamic Acid for Blood Salvage in Intertrochanteric Fracture Surgery: A Meta-Analysis. *Clin Appl Thromb Hemost.* 2018;24:1189-1198.
122. Chen X, Zheng F, Zheng Z, et al. Oral vs intravenous tranexamic acid in total-knee arthroplasty and total hip arthroplasty: A systematic review and meta-analysis. *Medicine (Baltimore).* 2019;98:e15248.
123. Gong M, Liu G, Chen L, et al. The Efficacy and Safety of Intravenous Tranexamic Acid in Reducing Surgical Blood Loss in Posterior Lumbar Interbody Fusion for the Adult: A Systematic Review and a Meta-Analysis. *World Neurosurg.* 2019;122:559-568.
124. Jiang W, Shang L. Tranexamic acid can reduce blood loss in patients undergoing intertrochanteric fracture surgery: A meta-analysis. *Medicine (Baltimore).* 2019;98:e14564.
125. Ping WD, Zhao QM, Sun HF, et al. Role of tranexamic acid in nasal surgery: A systemic review and meta-analysis of randomized control trial. *Medicine (Baltimore).* 2019;98:e15202.
126. Weng S, Wang W, Wei Q, et al. Effect of Tranexamic Acid in Patients with Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *World Neurosurg.* 2019;123:128-135.
127. Yuan L, Zeng Y, Chen Z-Q, et al. Efficacy and safety of antifibrinolytic agents in spinal surgery. *Chin Med J.* 2019;132:577-588.
128. Zhao Z, Ma J, Ma X. Comparative efficacy and safety of different hemostatic methods in total hip arthroplasty: a network meta-analysis. *J Orthop Surg Res.* 2019;14:3.
129. Gandhi R, Evans HM, Mahomed SR, Mahomed NN. Tranexamic acid and the reduction of blood loss in total knee and hip arthroplasty: a meta-analysis. 6:184.
130. Umscheid CA, Kohl BA, Williams K. Antifibrinolytic use in adult cardiac surgery. *Curr Opin Hematol.* 14:455-467.
131. Laupacis A, Fergusson D. Drugs to Minimize Perioperative Blood Loss in Cardiac Surgery. 1997;85:1258.
132. Ho K, Ismail H. Use of intravenous tranexamic acid to reduce allogeneic blood transfusion in total hip and knee arthroplasty: a meta-analysis. *Anaesth Intensive Care.* 2003;31:529-537.
133. Zufferey P, Merquiol F, Laporte S, et al. Do antifibrinolytics reduce allogeneic blood transfusion in orthopedic surgery? *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 2006;105:1034-1046.
134. Gurusamy KS, Pissanou T, Pikhart H, et al. Methods to decrease blood loss and transfusion requirements for liver transplantation. *Cochrane Database Syst Rev.* 2011.
135. Kongnyuy EJ, Wiysonge CS. Interventions to reduce haemorrhage during myomectomy for fibroids. *Cochrane database of systematic reviews (Online).*

2011;CD005355.
136. Peitsidis P, Kadir RA. Antifibrinolytic therapy with tranexamic acid in pregnancy and postpartum. *Expert Opin Pharmacother.* 2011;12:503-516.
137. Sukeik M, Alshryda S, Haddad F, Mason J. Systematic review and meta-analysis of the use of tranexamic acid in total hip replacement. *The Journal of bone and joint surgery. British volume.* 2011;93:39-46.
138. De-jie F, Cheng C, Lin G, Liu Y. Use of intravenous tranexamic acid in total knee arthroplasty: a meta-analysis of randomized controlled trials. *Chinese Journal of Traumatology.* 2013;16:67-76.
139. Lethaby A, Duckitt K, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2013;1:CD000400.
140. Alshryda S, Sukeik M, Sarda P, et al. A systematic review and meta-analysis of the topical administration of tranexamic acid in total hip and knee replacement. *The bone & joint journal.* 2014;96:1005-1015.
141. Bennett C, Klingenberg SL, Langholz E, Gluud LL. Tranexamic acid for upper gastrointestinal bleeding. 2014;11:CD006640.
142. Zhang F, Wang K, Li F-N, et al. Effectiveness of tranexamic acid in reducing blood loss in spinal surgery: a meta-analysis. *BMC Musculoskelet Disord.* 2014;15:448.
143. Wang X, Lo EH. Triggers and mediators of hemorrhagic transformation in cerebral ischemia. *Mol Neurobiol.* 2003;28:229-244.
144. Wang Z, Yang JY, Song SJ, et al. Effect of dencichine on coagulation and the hemostatic mechanism. *Chinese Journal of New Drugs.* 2014;23:356-359.
145. Mannucci PM. Hemostatic drugs. *N Engl J Med.* 1998;339:245.
146. Henry D, Carless P, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a meta-analysis. *CMAJ.* 2009;180:183-193.
147. Juncosa JI, Takaya K, Le HV, et al. Design and Mechanism of (S)-3-Amino-4-(difluoromethylenyl)cyclopent-1-ene-1-carboxylic Acid, a Highly Potent γ-Aminobutyric Acid Aminotransferase Inactivator for the Treatment of Addiction. *J Am Chem Soc.* 2018;jacs.7b10965.
148. Mori J, Nagy Z, Di NG, et al. Maintenance of murine platelet homeostasis by the kinase Csk and the phosphatase CD148. *Blood.* 2018;131:blood-2017-2002-768077.
149. Wang Y, Kim K, Lee MS, Lee H. Hemostatic Ability of Chitosan-Phosphate Inspired by Coagulation Mechanisms of Platelet Polyphosphates. *Macromol Biosci.* 2018;18:1700378.
150. Potze W, Arshad F, Adelmeijer J, et al. Differential in vitro inhibition of thrombin generation by anticoagulant drugs in plasma from patients with cirrhosis. *PLoS One.* 2014;9:e88390.
151. Nelson KB, Dambrosia JM, Grether JK, Phillips TM. Neonatal cytokines and coagulation factors in children with cerebral palsy. *Ann Neurol.* 2010;44:665-675.
152. Poeran J, Rasul R, Suzuki S, et al. Tranexamic acid use and postoperative

outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ.* 2014;349:g4829.
153. Enrique GB, Miguel OA, Padilla-Eguiluz NG, et al. Topical intra-articular compared with intravenous tranexamic acid to reduce blood loss in primary total knee replacement: a double-blind, randomized, controlled, noninferiority clinical trial. *Journal of Bone & Joint Surgery-american Volume.* 2014;96:1937-1944.

**Figure Legends**

**Fig. 1** Flowchart

**Table 1** Criteria used to define the level of evidence for TXA
RCT= Randomized Controlled Trials

**Table 2** Results from 136 meta-analyses of association between TXA and TBL, transfusion rate, Hb drop, mortality, DVT and PE.
OR=Odds Ratio; RR=Risk Ratio; CI=Confidence Interval; RC=retrospective cohort; P=prospective cohort; R=randomized controlled trial

**Table 3** Results from the largest meta-analyses of TXA and TBL, transfusion rate, Hb drop, mortality, DVT and PE.
OR=Odds Ratio; RR=Risk Ratio; CI=Confidence Interval; RC=retrospective cohort; P=prospective cohort; R=randomized controlled trial

**Table 4** Evidence from meta-analyses of association between TXA and TBL, transfusion rate, Hb drop, mortality, DVT and PE.