TRANEXAMIC ACID
Evidence Summary for Use to Reduce Blood Loss and Transfusion Requirements in Orthopedic Surgery
(September 2014)
VHA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

INTRODUCTION
Significant perioperative blood loss and the subsequent need for transfusion of allogeneic blood can lead to complications including increased risk for post-operative infection, hemolysis, transfusion-induced coagulopathies, acute lung injury and less than favorable post-operative outcomes. There are a number of interventions that have been used to reduce surgical blood loss and the need for transfusion including autologous blood donation/transfusion, acute normovolemic hemodilution (NVHD) and various blood salvaging techniques.[1] Antifibrinolytic agents (e.g., aprotinin, epsilon aminocaproic acid and tranexamic acid) have been used for some time to minimize blood loss and transfusion requirements in patients undergoing surgeries associated with significant blood loss. Although these agents have been shown to reduce surgical blood loss and the need for transfusion, there has been concern regarding the potential for thromboembolic complications (e.g., deep vein thrombosis [DVT], pulmonary embolism [PE] or myocardial infarction [MI]) related to their mechanism of action.

In this document, the evidence for the use of anti-fibrinolytic agents (e.g., epsilon-aminocaproic acid and tranexamic acid) in reducing blood loss and transfusion requirements in patients undergoing orthopedic surgery will be reviewed. Evidence for aprotinin will not be included because it was removed from marketing in the US in 2007.

DESCRIPTION
Both epsilon aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic analogues of the amino acid lysine and act by inhibiting the activation of plasminogen to plasmin by competitively blocking the binding sites on plasminogen. Plasmin is responsible for degrading fibrin; an insoluble protein that consists of long fibrous strands which provides the framework for blood clotting. By preventing degradation of fibrin by plasmin (preventing fibrinolysis), the clot remains intact. Tranexamic acid is a more potent inhibitor of fibrinolysis *in vitro* than aminocaproic acid.[2]

Table 1. Characteristics of Aminocaproic Acid and Tranexamic Acid[3-4]

Characteristic	Aminocaproic Acid (EACA)	Tranexamic Acid (TXA)
FDA approved indication (injection)	Enhancing hemostasis when fibrinolysis contributes to bleeding.	In patients with hemophilia for short-term use (2-8 days) to reduce or prevent hemorrhage and reduce the need for replacement therapy during and following tooth extraction.
Dose	Not established in orthopedic surgery	Not established in orthopedic surgery
How supplied (injection)	250 mg/ml	100mg/ml
Plasma Conc. Producing 80% Anti-fibrinolytic activity	100 mcg/ml	10 mcg/ml
Half-life	1-3 hours	1-3 hours
Continued inhibition of fibrinolysis after IV dosing	3 hours	8-12 hours
Contraindications	• Do not use if there is evidence for an active intravascular clotting process (e.g., DIC) without concomitant use of heparin	• Patients with acquired defective color vision since this prohibits measuring one endpoint that should be followed as a measure of toxicity. • In patients with subarachnoid

		hemorrhage. Anecdotal experience indicates that cerebral edema and cerebral infarction may be caused by TXA in some patients. • In patients with active intravascular clotting. • In patients with hypersensitivity to TXA or its ingredients.
Warnings/precautions (selected)	• EACA should not be administered without a definite diagnosis and/or lab finding indicative of hyperfibrinolysis. • Rapid IV injection should be avoided since this may induce hypotension, bradycardia and/or arrhythmia. • Inhibition of fibrinolysis by EACA may theoretically result in clotting or thrombosis. • Should not be administered with Factor IX complex conc. Or Anti-inhibitor Coagulant conc. since the risk for thrombosis increases.	• Convulsions have been reported in association with TXA particularly with higher doses and during CV surgery and in patients accidentally given TXA into the neuraxial system. • Dose should be reduced in patients with renal insufficiency • Patients with history of thromboembolic disease may be at increased risk for venous or arterial thrombosis. • Should not be administered with Factor IX complex conc. Or Anti-inhibitor Coagulant conc. since the risk for thrombosis increases.

CV=cardiovascular, DIC=disseminated intravascular coagulation, EACA=epsilon aminocaproic acid, IV-intravenous, TXA=tranexamic acid

SUMMARY OF THE EVIDENCE *(Refer to Appendix 1 for detailed results)*
There have been a number of published systematic reviews and meta-analyses of anti-fibrinolytics in minimizing blood loss and transfusion requirements in patients undergoing orthopedic surgery. Since some of them are as recent as 2014, only those analyses published after 2010 have been included.[5-14] Additionally, no individual clinical trials, examining tranexamic acid or aminocaproic acid, were detailed in the evidence tables since many are included in the meta-analyses and most are limited by small sample size and are inadequately powered to determine the efficacy and safety of these agents with more widespread use. Most of the studies included in the meta-analyses excluded high risk patients including those patients undergoing joint revision procedures, patients with bleeding diatheses or receiving anticoagulation, history of thromboembolic events, cardiovascular disease or renal failure. Therefore, the efficacy and safety of antifibrinolytics in these subgroups of patients is unknown.

Most of the available evidence for use of antifibrinolytics in orthopedic surgery exists for tranexamic acid and only a few studies with epsilon aminocaproic acid. However, there is one study conducted in patients undergoing total knee replacement surgery in which patients were randomized to antifibrinolytics (TXA or EACA) or placebo. Total blood loss and the proportion of patients receiving transfusion with allogeneic blood were significantly less in the antifibrinolytic-combined group vs. placebo. The authors noted that there were no significant differences in outcomes between TXA and EACA but the numbers were small (n=35 TXA vs. n=33 EACA) and therefore, the study may have been underpowered to identify differences between the treatment groups. There is one meta-analysis published in 2006 that identified only four trials using EACA in orthopedic surgery, two in total hip arthroplasty (THA), one in spine surgery and one in cancer patients having orthopedic surgery. The authors of this meta-analysis did not report a benefit of EACA from these studies.[16] Another meta-analysis of antifibrinolytics that included studies involving aprotinin, EACA and/or TXA pooled the findings and reported an overall benefit of antifibrinolytics for reducing total blood loss and transfusion requirements with no resultant increase in the risk for thromboembolic events. However, because of the heterogeneity of the pooled estimates, small sample size of the included studies and the use of varied dosing regimens, the authors recommended a large, prospective, randomized clinical trial be conducted.

Evidence from the meta-analyses, detailed in Appendix 1, does consistently show a benefit of TXA versus control in reducing total blood loss by an average of approximately 500 ml in TKA and 300-400 ml in THA and reducing requirement for transfusion by 45% in TKA and 20-30% in THA. In total knee arthroplasty, the tourniquet used during surgery is believed to increase fibrinolysis after deflation with an increased risk of bleeding. In terms of an increased risk for thromboembolic events with the use of antifibrinolytic agents in orthopedic surgery, the available evidence does not support a higher risk (DVT or PE or MI) vs. control. However, most of the authors of the meta-analyses cited small trial size as an obvious limitation to concluding safety with routine use of these agents in orthopedic surgery and recommend larger, prospective, randomized trials be conducted to address the question of thromboembolic risk and mortality.[18-19] Evidence is insufficient to determine the safety and efficacy of EACA in orthopedic surgery or in comparison to TXA.

DOSE/DOSE FREQUENCY OR TIMING/ROUTE OF ADMINISTRATION
Evidence exists for the use of intravenous (IV), intra-articular (IA) or topical irrigation of joint with TXA for reducing total blood loss and transfusion requirements in orthopedic surgery. Most of the trials used intravenous bolus dosing (single or repeated) or continuous infusion of TXA as opposed to intra-articular or topical use. Topical irrigation doses of TXA range from 500 mg-3 grams in 50-100 ml saline. Intra-articular doses range from 250 mg-2 grams in 20-50 ml saline.[20] Evidence is insufficient to identify the optimal dose, route of administration and proper timing of dose. In several of the meta-analyses, a trend towards greater benefit was noted with higher doses of TXA. However, very high doses of TXA have rarely been associated with seizures.[4]

There are three trials comparing various routes of administration of TXA in orthopedic surgery. In the first trial, four different IV dosing regimens (*all doses were 10 mg/kg 1) intraoperative dose given before tourniquet deflation, 2) preoperative and intraoperative dose, 3) intraoperative and postoperative dose, 4) preoperative, intraoperative and postoperative dose*) and one local application were compared to placebo, with forty patients undergoing TKA in each group. The single intraoperative dose was not effective; the two-dose regimen (preoperative and intraoperative dose) was effective vs. control in reducing drain blood and total blood loss with TKA; but the intraoperative and postoperative dose was not. The preoperative, intraoperative and postoperative dosing regimen was most effective.[21] Intra-articular and IV dosing were compared to placebo in 150 patients having TKA. The timing of the intervention was during closure of the operative wound. Tranexamic acid 1.5 gm was mixed with 100 ml saline and given IV or IA. Total blood loss was 528 ml in the IV group, 426 ml in the IA group and 833 ml in the placebo group. Transfusion was required in 44% IV, 20% IA and 94% placebo. Transfusion amounts were 273 ml IV, 129 ml IA and 921 ml placebo.[22] In another trial, patients having THA were randomized to receive TXA (varied timing) or placebo. Groups included: 1) placebo, 2) 1 gm TXA 10 min before skin closure, 3) 1 gm TXA 10 min before closure and again 6 hr. later, 4) 1 gm TXA 10 min prior to surgery, and 5) 1 gm TXA 10 min prior to surgery and 6 hr. later. The authors reported that dosing 10 minutes prior to surgery and again 6 hr. later was the most effective regimen.[23]

Because most trials were small, used various doses of TXA, routes of administration and timing of dosing in various orthopedic surgery types, the optimal dosing regimen for TXA for reducing total blood loss and transfusion requirements in TKA or THA is unknown.

CONCLUSIONS
There is increasing interest in using antifibrinolytic agents for minimizing blood loss and transfusion requirements in patients undergoing orthopedic surgery, namely joint replacement surgery. There have been a number of mostly small trials, which have consistently shown at least a trend towards benefit of TXA in both TKA and THA without an increased risk for thromboembolic complications. Evidence is limited for using EACA in orthopedic surgery. Findings are consistent from a number of meta-analyses which have demonstrated reduced total blood loss by a mean of 500 ml in TKA and 300-400 ml in THA and a reduced need for transfusion of allogeneic blood by about 45% in TKA and nearly 30% in THA with TXA versus control. A majority of the authors of the meta-analyses have cited limitations including heterogeneity of study findings, small trial sample size, varied doses, timing and routes of administration of TXA, thereby precluding them from drawing conclusions regarding safety with more widespread use and from identifying the optimal dosing regimen. In addition, since many high-risk groups of patients (e.g.,

joint revision surgery, history of thromboembolic events, cardiovascular disease, bleeding diatheses or receiving anticoagulation, renal failure, etc.) were excluded from clinical trials, the safety and efficacy of tranexamic acid in these patients is unknown.

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APPENDIX 1
Table 2: Systematic Reviews/Meta-Analyses of Anti-Fibrinolytic Agents in Orthopedic Surgery

Citation (# of included studies, N, other details)	Population/ Intervention	Outcomes Results	Conclusions
TOTAL KNEE ARTHROPLASTY			
Alshryda 2011[5] (19 trials, n=1277) Trials were small, ranging from 24-136 participants. Different doses and methods of delivery were used. All but two studies used LMWH for DVT prevention.	**TKA**, TXA dose ranged from 700 mg to 10,500 mg. TXA vs. placebo or no control IV, oral or topical use was acceptable: • 18 studies used IV • 1 study also used oral in addition to IV • 1 study used topical Comparators: 18 used placebo and 1 used NVHD	**Proportion of patients transfused:** 14 trials (n=824) TXA led to reduction in proportion of pts requiring transfusion (RR 2.56, 95% CI 2.10-3.11, p<0.001). Trials did show consistent benefit but significant heterogeneity between study findings (I^2=75% suggesting high heterogeneity or high inconsistency) **Number of units transfused:** 13 trials (n=769) Crude pooled data show a four-fold increase in the number of units transfused in the group not receiving TXA **Total blood loss:** 9 trials (n=not stated) Mean difference of 591 ml between TXA and control (95% CI 536-647 ml, p<0.001). Significant heterogeneity was found I^2=78%) **Length of hospital stay:** 2 trials (n=60) NS **Complications (death, non-fatal MI, stroke, DVT or PE or any thrombosis, renal failure and re-operation due to bleeding:** **DVT:** 13 trials (n=801), p=0.98, I^2=0% heterogeneity **PE:** 19 trials (n=971). 5 reported PE, 1 in TXA and 4 controls. P=0.5 **Death:** 1 in each group p=0.98	Heterogeneity in findings was noted in 1) proportion of patients transfused and in 2) total blood loss. Subgroup analysis identified that a more homogenous treatment effect of TXA was noted with higher doses (>4000 mg) and a smaller, heterogeneous effect was noted for lower doses. Explanations for variability between studies are numerous including surgical technique, when the tourniquet was released, dose, timing and mode of administration differed, etc. Authors did acknowledge some evidence of publication bias where smaller trials with neutral findings could be missing. Limitations include the inability to analyze functional outcomes or quality of life due to the lack of that data being reported and studies were underpowered to assess the safety of TXA in TKA. Pooled safety data do not support an increased harm in these patients.
Yang 2012[6] (15 trials, n=837) Trials were small, ranging from 20-102 participants Only trials rated as high quality were included (Jadad ≥3).	**TKA,** 14 studies used low dose TXA 10-50mg/kg and 1 high dose, 150 mg/kg. Route of administration (IV or topical) not provided. Comparators: placebo and both group used pneumatic tourniquets	**Total blood loss:** 14 studies (n=817), Mean difference of 504.90 ml less in the TXA vs. placebo group (95% CI 620.89-388.92, p<0.00001). **Number of units transfused:** 6 trials (n=348). Number of transfusions in the TXA group was significantly less vs. control WMD: -1.43 units (95% CI -1.69 to -1.17, p<0.00001) **Odds Ratio for transfusion:** 14 trials (n=735) OR 0.16, 95% CI 0.10-0.25, p<0.00001 **Odds Ratio for developing DVT:** 14 trials (n=722) 10 DVT TXA vs. 13 placebo. (OR 0.75, 95% CI 0.34-1.67, p=0.48) **Odds Ratio for developing PE:**	Methods for determining quantity of blood lost differed. PT, APTT did not change during TXA treatment TXA reduced total blood loss, need for transfusion and the number of units transfused without an increase in ADEs.

		6 trials (n=349) 2 PE TXA, 4 placebo (OR 0.65, 95% CI 0.18-2.33, p=0.5)	
Tan 2013[7] (19 trials, n=1114) Trials were small, ranging from 20-102 participants Exclusion criteria in trials included prior cerebral apoplexy, thromboembolic diease, severe liver or kidney impairment and congenital or acquired coagulopathies	**TKA,** 19 trials, no summary of TXA doses used were listed. Timing of TXA administration varied as follows: 1) intraoperative=IV admin TXA prior to tourniquet deflation 2) pre-op and post-op=IV admin TXA before tourniquet inflation and at 3 hrs after 1st dose, and 3) intraoperative and post-op=IV admin. Prior to tourniquet deflation and 3 hrs later. Comparators: placebo and groups used pneumatic tourniquets	**Total blood loss:** 5 trials (n=374). Reduced blood loss by a mean of 570 ml (95% CI -663 to -478, p<0.00001). Significant heterogeneity was noted (I^2=77%) **Rate Ratio for transfusion:** 17 trials (n=1047) Transfusion rate was significantly lower in TXA vs. placebo (RR 0.39, 95% CI 0.25-0.61, p<0.00001) **Units of blood transfused per patient:** 15 trials (n=860). Number of units transfused per patient was lower with TXA vs. placebo (mean difference: -0.96 units, 95% CI -1.32 to -0.59, p<0.00001) **Safety:** 18 trials (n=1094). 12 of 534 pts TXA vs. 13 560 pts placebo. (RR 0.89, 95% CI 0.43-1.85, p=0.76)	Authors noted significant heterogeneity in outcomes. Subgroups were analyzed to determine cause including blood transfusion protocols or triggers, VTE prophylaxis and mode of administration. The heterogeneity in outcomes was not sufficiently explained by the subgroups. Some variation in the findings may be related to timing and frequency of TXA dosing. Limitations include small sample size, heterogeneity in many of the outcomes related to blood loss and transfusion needs and data are insufficient to analyze functional outcomes or quality of life. **Authors call for larger studies to confirm their findings.**
Panelli 2013[8] (7 trials, n=517) Trials were small. Trials included excluded the following pts: use of anticoagulants and presence of bleeding disorders	**TKA**, 7 trials all limited to topical application of TXA vs. placebo. Low dose was defined as 2 grams or less, high dose was > 2 grams of TXA. Comparators: placebo	**Total blood loss:** 4 trials (n=257). Topical TXA reduced total blood loss vs. controls (mean difference: -268.36 ml, 95% CI -491.55 ml to -45.18 ml, p=0.02) **Transfusion requirements:** 6 trials (n=512). Lower risk of transfusion in TXA vs. placebo (RR 0.47, 95% CI 0.26-0.84, p=0.01. No heterogeneity noted I^2=0% **Thromboembolic complications:** 6 trials (n=477) Five studies, no events. One study, 3 DVTs in 64 TXA, 1 DVT in 35 controls (RR 0.55, 95% CI 0.04-8.48, p=0.67)	Subgroup analysis showed trend towards greater benefit in reducing transfusion requirements with higher dose TXA (>2 grams) but differences were not statistically significant when studies were separated and pooled by how and high dose. In terms of included trial quality, only two were rated as high quality and three were lower quality. **Authors comment that although the differences in transfusion and total blood loss favored TXA, the clinical significance of the difference (e.g., mean 220 ml less blood loss) is uncertain.**
		**TOTAL HIP ARTHROPLASTY**	
Sukeik 2011[9] (11 trials, n=505) Trials were small, ranging from 36-100 participants.	**THA**, 11 trials limited to IV TXA only. Other routes were excluded. Doses and modes of administration differed:	**Total blood loss:** 6 trials (n=310). TXA significantly reduced total blood loss vs. placebo by 289.4 ml (95% CI -440.7 to -138.2 ml, p<0.001). Moderate heterogeneity was noted I^2=54%	Authors noted that multiple doses and the use of transfusion protocols produced a greater risk reduction in blood transfusion (mean 25%) as well as total blood loss.

Most studies rated as good quality All but three studies used LMWH for DVT prevention. Most trials excluded patients with history of CV disease, thromboembolic events, renal failure, those on warfarin or a therapeutic dose of LMWH.	TXA doses ranged from 10-30 mg/kg. In 5 studies, a single bolus was given, 3 used repeated bolus doses and 3 used prolonged infusion. Comparators: placebo (n=9 trials), another antifibrinolytic or no treatment (n=2 trials)	**Blood transfusion rate:** 7 trials (n=346). TXA reduced proportion of patients requiring blood transfusion by 20% (risk difference -20, 95% CI -0.29 to -0.11, p<0.001). Low heterogeneity was noted I^2=15% **Thromboembolic complications:** DVT: 10 trials (n=464). NS (p=0.46) PE: 3 reported PE in 11 trials, 2 in TXA and 1 control group. NS (p=0.76)	Two studies included in the meta-analysis did not find a benefit of TXA, one gave TXA at the end of the procedure and 3 hours later, the other gave a single pre-op dose and transfusion and total blood loss favored placebo in this study. **Because studies excluded high-risk patients or those undergoing revision surgeries therefore, conclusions regarding safety of TXA in these groups cannot be drawn. Larger studies are recommended.**
Zhou 2013[10] (19 trials, n=1030) Trials were small, ranging from 39-117 participants Most trials excluded patients with history of CV disease, thromboembolic events, renal failure, those on warfarin or with bleeding diathesis or a therapeutic dose of LMWH.	**THA,** 19 trials limited to IV only. Other routes (oral, injection into the articular cavity or IM) were excluded. Comparators: placebo or nothing	**Total blood loss:** 7 trials (n=382). TXA reduced total blood loss be a mean of 305.27 ml (95% CI -397.66 to -212.89 ml, p<0.001) *Other studies reported on intraoperative and post-op blood loss but only total blood loss is included here.* **Blood transfusion:** 18 trials (n=? 1000+). TXA reduced proportion of patients requiring transfusion by 28% (95% CI 0.19-0.42, p<0.001) **Units of blood transfused per patient:** 9 trials (n=?). TXA did not reduce the average number of transfusions per patient vs. placebo (WMD: 0.3 units, 95% CI -0.49 to 1.09 units, p=0.45) **Thromboembolic complications:** 19 trials DVT: TXA 15/539 vs. placebo 19/535 (OR 0.73, 95% CI 0.36-1.49, p=0.39) 3 trials PE: TXA 3/539 vs. 1/535 (OR 1.95, 95% CI 0.34-11.06, p=0.45)	Duration of hospitalization was reported in 2 studies and was not different between groups. Dose response trend was noted with higher doses associated with lower total blood loss but not with intra or post-op blood loss or transfusion rates. Because studies excluded high-risk patients or those undergoing revision surgeries therefore, conclusions regarding safety of TXA in these groups cannot be drawn. **Authors note that larger studies are recommended to define the optimal TXA regimen and to assess and confirm the safety and cost-effectiveness before recommending use in THA**
TOTAL KNEE AND TOTAL HIP ARTHROPLASTY			
Gandhi[11] (33 Published and unpublished trials 1995-2012, n=1957) 21 trials were of high quality	**TKA (n=19) and THA (n=14),** 33 trials (n=1957). Methods of admin: IV in 29 trials, intra-articularly in 3 studies, orally in 1 study and topical in 1. Comparators: placebo or nothing	**Total blood loss:** TKA: WMD -1.149 (95% CI -1.209 to -1, p<0.001). Significant heterogeneity was noted: I^2=85.7 THA: WMD -0.504 (95% CI -0.672 to -0.336. Moderate heterogeneity I^2=58 **Blood transfusion:** TKA: OR 0.145 (95% CI 0.094-0.223, p<0.001). No heterogeneity THA: OR 0.327 (95% CI 0.208-0.515, p<0.001) Moderate heterogeneity I^2=34 **Thromboembolic complications:**	Benefit of TXA found to be more pronounced in TKA vs. THA. **Authors conclude that incomplete reporting of complications prevented the pooling of safety data and state that larger trials are needed to confirm the safety and efficacy of routine use of TXA in primary TKA and**

		TKA-DVT: OR 1.030 (95% CI 0.439-2.42, p=0.6. No heterogeneity THA-DVT: 1.070 (95% CI 0.393-2.9, p=0.89. No heterogeneity Overall: TXA=30 DVT, 3 PE, 1 MI vs. control=20 DVT, 4 PE.	THA. *WMD for total blood loss: refers to ratio of differences between the mean of treatment and control divided by standard deviation. A negative WMD favors treatment and positive favors control.*
Poeran[12] **Retrospective analysis of 872,416 patients having TKA or TKA in 510 US hospitals 2006-2012	**TKA or THA**, IV administration only. Doses of TXA provided were grouped as follows: None, ≤1000 mg, 2000 mg and ≥ 3000 mg	Of 20,051 patients who received TXA, 5486 were matched to patients who did not receive TXA. **Blood transfusion (allogeneic or autologous):** OR 0.5, 95% CI 0.45-0.55 favoring TXA **Blood transfusion (allogeneic)** OR 0.47, 95% CI 0.42-0.53 favoring TXA **Complications:** Thromboembolic: OR 0.86, 95% CI 0.59-1.25 Renal Failure: OR 0.74, 95% CI 0.57-0.96 Combined complications: OR 0.75, 95% CI 0.61-0.92 ICU admit: OR 0.85, 95% CI 0.74-0.99	Retrospective, propensity matching showed a 69% reduced need for transfusion. TXA was not associated with an increased risk for perioperative complications include renal failure or thromboembolic events. Limitations- retrospective/observational and used administrative resources to pull data. Lack of clinical data to determine selective use of TXA in patients with arterial stents or history of TE disease. **Outcomes in certain populations of patients are unknown and are needed. Therefore thoughtful identification of those patients most likely to benefit (at increased of bleeding) from TXA is recommended. Also, studies focusing on optimal dosing regimens are needed.**
		MISCELLANEOUS ORTHOPEDIC SURGERY, INCLUDING TKA AND THA	
Yang[13] (9 trials, n=581)	**Spinal Surgery** (n=9 trials). IV TXA only. Other routes of admin were excluded. Doses ranged from 10-100 mg/kg. Single bolus in 2 trials, infusion in 2 trials and repeated bolus in 5 studies. Comparators: placebo or nothing	**Total blood loss:** 6 trials (n=397). TXA reduced TBL by mean 389.21 (95% CI 177.83-600.6, p-0.0003) vs. placebo. High heterogeneity noted: I^2=82% **Blood transfusion:** 7 trials (n=461). TXA reduced the rate of allogeneic transfusion by a relative 35% (RR 0.65, 95% CI 0.53-0.8, p<0.0001). No heterogeneity noted **Thromboembolic complications:** DVT: 7 trials (n=479). NS	Subgroup analysis: 1) Both high and low dose TXA reduced TBL. **Authors concluded that considering the significant heterogeneity of study findings as small sample sizes and number of studies included, larger studies are needed to confirm these findings and to identify the optimal TXA dose and timing of dose in those having spinal surgery.**
Huang[14] (46 trials, n=2925) Trials were excluded if patients on anticoagulants	**Orthopedic surgery** (n=46 trials): 11=THA, 4=THR, 2=hip fracture, 21=TKA, 8=spinal surgery	**Total blood loss:** 24 trials (n=1696). TXA reduced TBL a mean of 408.33 (95% CI -505.60 to -310.97, p<0.00001). Significant heterogeneity (I^2=89%)	Significant heterogeneity in outcomes. Subgroup analysis was not adequate to address heterogeneity and included type of surgery, TXA dose/regimen

| participated.

Trials were small, ranging from 20-147 participants. | 21 trials admin low dose TXA <15 mg/dL 18 used high dose ≥15 mg/kg

Single pre-op dose=20 trials, 26 used repeat bolus doses

Comparators: placebo or nothing | **Blood transfusion:**
42 trials (n=2649). TXA reduced the probability for a transfusion by 49% (RR 0.51, 95% CI 0.46-0.56, p<0.00001)
Blood/Units transfused:
Blood units: 11 trials (n=917). TXA reduced the mean number of transfusion/pt: WMD -0.78, 95% CI -0.19 to -0.37 units, p=0.0002
Blood volumes: 7 trials (n=397). TXA reduced transfused blood volumes/pt: WMD -205.33 ml, 95% CI -301.37 to -109.28, p<0.0001)
Thromboembolic complications:
44 trials (n=2689). TXA-30 DVT/1376 pts vs. 26 DVT/1313 pts control. (RR 1.11, 95% CI 0.69-1.79, p=0.66) | and DVT prevention used.

Authors concluded that because of the heterogeneity of findings between trials, small numbers of patients and included studies, larger prospective trials are needed to determine effectiveness and safety of TXA in major orthopedic surgery. |

ADEs=adverse events, APTT=activated partial thromboplastin time, DVT=deep vein thrombosis, LMWH=low molecular weight heparin, MI=myocardial infarction, NVHD=normovolemic hemodilution, OR=odds ratio, PE=pulmonary embolism, PT=prothrombin time, THA=total hip arthroplasty, TKA=total knee arthroplasty, TBL=total blood loss, TE=thromboembolic, THR-total hip replacement, TXA=tranexamic acid, WMD=weighted mean difference
I^2=denotes heterogeneity or inconsistency in study findings. Low=25%, moderate=50%, high=75%