The Journal of Arthroplasty 33 (2018) 3070–3082

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis

Yale A. Fillingham, MD [a, *], Dipak B. Ramkumar, MD [b], David S. Jevsevar, MD [b], Adolph J. Yates, MD [c], Peter Shores, MPH [d], Kyle Mullen, MPH [d], Stefano A. Bini, MD [e], Henry D. Clarke, MD [f], Emil Schemitsch, MD [g], Rebecca L. Johnson, MD [h], Stavros G. Memtsoudis, MD [i], Siraj A. Sayeed, MD [j], Alexander P. Sah, MD [k], Craig J. Della Valle, MD [a]

[a] Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, IL
[b] Department of Orthopaedic Surgery, Dartmouth Hitchcock Medical Center, Lebanon, NH
[c] Department of Orthopaedic Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA
[d] Department of Research, Quality, and Scientific Affairs, American Academy of Orthopaedic Surgeons, Rosemont, IL
[e] Department of Orthopaedic Surgery, University of California San Francisco, San Francisco, CA
[f] Department of Orthopaedic Surgery, Mayo Clinic, Phoenix, AZ
[g] Department of Orthopaedic Surgery, University of Toronto, Toronto, Ontario, Canada
[h] Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN
[i] Department of Anesthesiology, Hospital for Special Surgery, New York, NY
[j] South Texas Bone and Joint Institute, San Antonio, TX
[k] Institute for Joint Restoration, Fremont, CA

ARTICLE INFO

Article history:
Received 1 February 2018
Received in revised form
12 March 2018
Accepted 15 March 2018
Available online 22 March 2018

Keywords:
tranexamic acid
total knee arthroplasty
total hip arthroplasty
venous thromboembolic event
arterial thromboembolic event

ABSTRACT

Background: Tranexamic acid (TXA) is effective in reducing blood loss in total joint arthroplasty (TJA), but concerns still remain regarding the drug's safety. The purpose of this direct meta-analysis was to evaluate and establish a basis for the safety recommendations of the combined clinical practice guidelines on the use of TXA in primary TJA.

Methods: A search was completed for studies published before July 2017 on TXA in primary TJA. We performed qualitative and quantitative homogeneity testing and a direct comparison meta-analysis. We used the American Society of Anesthesiologists (ASA) score of 3 or greater as a proxy for patients at higher risk for complications in general and performed a meta-regression analysis to investigate the influence of comorbidity burden on the risk of arterial thromboembolic event and venous thromboembolic event (VTE).

Results: Topical, intravenous, and oral TXA were not associated with an increased risk of VTE after TJA. In addition, meta-regression demonstrated that TXA use in patients with an ASA status of 3 or greater was not associated with an increased risk of VTE after total knee arthroplasty.

Conclusion: Although most studies included in our analysis excluded patients with a history of prior thromboembolic events, our findings support the lack of evidence of harm from TXA administration in patients undergoing TJA. Moderate evidence supports the safety of TXA in patients undergoing total knee arthroplasty with an ASA score of 3 or greater. The benefits of using TXA appear to outweigh the potential risks of thromboembolic events even in patients with a higher comorbidity.

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to https://doi.org/10.1016/j.arth.2018.03.031.

* Reprint requests: Yale A. Fillingham, MD, Department of Orthopaedic Surgery, Rush University Medical Center, 1611 West Harrison Street Chicago, IL 60612.

https://doi.org/10.1016/j.arth.2018.03.031
0883-5403/

Over the past several years, antifibrinolytic drugs have been used extensively to reduce blood loss and the risk of transfusion after both total hip and total knee arthroplasties (THA and TKA), with numerous randomized trials supporting their efficacy [1–4]. One antifibrinolytic drug, aprotinin, was found to be more effective at reducing blood loss than both tranexamic acid (TXA) and ε-aminocaproic acid (EACA), but was removed from the market in 2008 because of an association with a significant increase in cardiovascular complications and death among cardiac surgery patients [5]. As TXA is significantly more potent than EACA and achieves higher synovial concentrations, its use has become more popular in orthopedic surgery [6].

TXA works by competitively inhibiting the activation of plasminogen to prevent fibrin degradation [7,8]. Given the clot-stabilizing properties of antifibrinolytic drugs, there is concern about the potential of these drugs to increase the risk of an arterial or venous thromboembolic event (ATE or VTE). Retrospective investigations of the safety regarding TXA administration in patients undergoing lower extremity total joint arthroplasty (TJA) has not demonstrated an increased risk of thromboembolic events with or without a prior history of a thromboembolic event [9–12]. However, the scientific literature lacks high-level evidence to allow evaluation of the safety of TXA with a sufficient population size to exclude an increased risk of thromboembolic events associated with the administration of TXA.

The American Association of Hip and Knee Surgeons (AAHKS), American Academy of Orthopaedic Surgeons (AAOS), Hip Society, Knee Society, and American Society of Regional Anesthesia and Pain Medicine (ASRA) have collaborated in the development of a clinical practice guideline on the use of TXA in TJA. We performed a systematic review and meta-analysis of randomized clinical trials to evaluate the safety of TXA administration in THA and TKA to support the clinical practice guideline. The aim of our study was to compare the risk of VTE and ATE for patients undergoing primary TJA treated with TXA, compared with those not treated with TXA.

Materials and Methods

The systematic review and meta-analysis was designed and performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [13].

Search Methodology

A research librarian was used to assist with the completion of the literature search of the Ovid MEDLINE, EMBASE, Cochrane Reviews, Scopus, and Web of Science databases. Initially, the search strategy established the primary search themes—"arthroplasty" and "tranexamic acid" followed by the use of Exploded Medical Subjection Headings terms and Boolean operators. We developed search strategies that were individualized for each database (Appendix B). Because of a limitation of access to all databases, searches for EMBASE and Web of Science included all published articles before October 2016, whereas Ovid MEDLINE, Cochrane Reviews, and Scopus included all published articles before July 2017. In addition, the bibliographies of relevant publications such as reviews and meta-analyses were evaluated for supplementary publications and to help validate the quality of our search methodology.

Study Selection Criteria

The inclusion and exclusion criteria were altered based on the thromboembolic outcome being investigated in the meta-analysis. Overlapping inclusion criteria for VTE and ATE were the following: (1) All study participants must have undergone either a primary TKA or THA and (2) At least one of the treatment arms of the study must have compared the use of TXA with a control group that received no antifibrinolytic agent. Publications that had multiple treatment arms with other antifibrinolytic agents like EACA were acceptable, but only the treatment arms with TXA or placebo would be included in the analysis. No exclusions were made regarding dosing route (ie, intra-articular/topical vs intravenous [IV]), administered dose (dosage amount and bolus vs continuous infusion), or timing of administration (preoperative, intraoperative, or postoperative) as none of these variables are considered to materially alter the risk of VTE.

The inclusion criteria specific to the investigation of VTE reported outcomes related to VTE including symptomatic deep venous thrombosis (proximal lower extremity deep venous thrombosis) or pulmonary embolism. As for the investigation of ATE, the study must have reported outcomes related to ATE including cerebrovascular accident (CVA) or myocardial infarction (MI). In addition, no limitations were imposed based on the form of postoperative VTE chemoprophylaxis used in the study.

The exclusion criteria for both VTE and ATE investigations were the following: (1) Patients undergoing a revision hip or knee arthroplasty or arthroplasties of any other joint; (2) Study subjects undergoing simultaneous or staged bilateral primary TKA or THA; (3) Secondary source articles including review articles, systematic reviews, meta-analyses, expert opinions; and (4) Published abstracts from the proceedings of a scientific meeting, unless an accompanying published manuscript was also available.

Data Collection

Two authors independently completed the title and abstract screening to eliminate duplicate publications and studies meeting any exclusion criteria. Any doubt regarding the inclusion or exclusion status of a study meant that it was included for full manuscript review. Two authors independently performed a full manuscript review to assess the inclusion or exclusion status of the remaining publications from the title and abstract screening.

The AAOS Department of Research, Quality, and Scientific Affairs completed the assessment of the quality and data extraction for all the publications from the full manuscript review following the process outlined in the *AAOS Clinical Practice Guidelines and Systematic Review Methodology* [14]. The quality assessment of the publications was performed based on an appraisal of the randomization, allocation concealment, blinding, completeness of outcome data, selective reporting, and conflict of interest. Because of the significant amount of published literature on the use of TXA in TJA, we further limited the pool of publications to only include randomized clinical trials of high quality and a single moderate quality study.

Study outcomes were monitored to investigate for consistency in the reporting of outcomes between the publications. VTE and ATE were all confirmed with various imaging modalities including ultrasound and computed tomography scan; however, no limitations were applied based on the method of screening for deep venous thrombosis in the randomized clinical trials of the meta-analyses.

Statistical Analysis

STATA 12.1 software (StataCorp, College Station, TX) was used to run direct meta-analysis when 4 or more authors provided data regarding VTE or ATE from a single treatment comparison. To minimize qualitative heterogeneity, articles examining equal treatment comparisons with consistent dosing and timing were included in the

Table 1
VTE Investigation Study Inclusions and Quality Assessment.

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias	Inclusion	Strength
Alipour, M., 2013	●	●	●	●	●	●	Include	High quality
Alshryda, S., 2013(a)	◑	●	●	○	●	○	Include	Moderate quality
Alshryda, S., 2013(b)	●	●	●	●	●	●	Include	High quality
Alvarez, J., 2008	◑	●	●	●	●	○	Include	High quality
Antinolfi, P., 2014	●	●	●	●	●	●	Include	High quality
Barrachina, B., 2016	●	●	●	●	●	●	Include	High quality
Benoni, G., 2001	●	●	●	●	●	◑	Include	High quality
Benoni, G., 2000	●	●	●	●	●	●	Include	High quality
Bidolegui, F., 2014	●	●	●	●	●	●	Include	High quality
Bradshaw, A., 2012	●	●	●	●	●	◑	Include	High quality
Carvalho, L. H., Jr., 2015	●	●	●	●	●	●	Include	High quality
Claeys, M., 2007	◑	●	●	●	●	●	Include	High quality
Digas, G., 2015	●	●	●	●	●	○	Include	High quality
Drosos, G., 2016	●	●	●	●	●	●	Include	High quality
Ekback, G., 2000	◑	●	●	●	●	●	Include	High quality
Emara, W. M., 2014	◑	●	●	●	●	●	Include	High quality
Engel, J., 2001	◑	●	●	●	●	●	Include	High quality
Fraval, A., 2016	●	●	●	●	●	●	Include	High quality
Garneti, N., 2004	●	●	●	●	◑	◑	Include	High quality
Gautam, V., 2013	◑	●	●	●	●	●	Include	High quality
Georgiadis, A. G., 2013	●	●	●	●	●	●	Include	High quality
Good, L., 2003	●	●	●	●	●	●	Include	High quality
Guzel, Y., 2016	◑	●	●	●	●	●	Include	High quality
Hiippala, S., 1995	●	●	●	●	●	●	Include	High quality
Hsu, C., 2015	●	●	●	●	●	●	Include	High quality
Husted, H., 2003	●	●	●	●	●	●	Include	High quality
Jaszczyk, M., 2015	●	●	●	●	●	●	Include	High quality
Johansson, T., 2005	●	●	●	●	●	●	Include	High quality
Kakar, P., 2009	◑	●	●	●	●	●	Include	High quality
Kazemi, S., 2010	◑	●	●	●	●	●	Include	High quality
Keyhani, S., 2016	◑	●	●	●	●	●	Include	High quality
Kim, T., 2014	●	●	●	●	●	●	Include	High quality
Kundu, R., 2015	●	●	●	●	●	●	Include	High quality
Lee, S., 2013	●	●	●	●	●	●	Include	High quality
Lee, Q. J., 2018	●	●	●	●	●	●	Include	High quality
Lee, Y., 2013	●	●	●	●	●	●	Include	High quality
Lemay, E., 2004	◑	●	●	●	●	●	Include	High quality
Levine, B. R., 2014	●	●	●	●	●	◑	Include	High quality
Lin, P.-C., 2011	◑	●	●	●	●	●	Include	High quality
Lin, P., 2012	●	●	●	●	●	●	Include	High quality
Lin, S.-Y., 2015	●	●	●	●	●	◑	Include	High quality
Liu, W., 2017	●	●	●	●	●	●	Include	High quality
Malhotra, R., 2011	●	●	●	●	●	●	Include	High quality
Maniar, R., 2012	●	●	●	●	◑	●	Include	High quality
Martin, J., 2014	●	●	●	●	●	◑	Include	High quality
Molloy, D., 2007	●	●	●	●	●	◑	Include	High quality
Motififard, M., 2015	●	●	●	●	●	●	Include	High quality
Orpen, N., 2006	●	●	●	●	●	●	Include	High quality
Ozta, S., 2015	◑	●	●	●	●	●	Include	High quality
Rajesparan, K., 2009	◑	●	●	●	●	●	Include	High quality
Roy, S. P., 2012	●	●	●	●	●	●	Include	High quality
Sa-Ngasoongsong, P., 2011	●	●	●	●	●	●	Include	High quality
Sa-Ngasoongsong, P., 2013	◑	●	●	●	●	○	Include	High quality
Sarzaeem, M. M., 2014	●	●	●	●	●	●	Include	High quality
Seo, J., 2013	●	●	●	●	●	◑	Include	High quality
Seviciu, A., 2016	●	●	●	●	●	●	Include	High quality
Shen, P., 2015	●	●	●	●	●	●	Include	High quality
Shinde, A., 2015	●	●	●	●	●	◑	Include	High quality
Song, E., 2016	●	●	●	●	●	●	Include	High quality
Sun, Q., 2016	●	●	●	●	●	●	Include	High quality
Sun, Q., 2017	●	●	●	●	●	●	Include	High quality
Tanaka, N., 2001	●	●	●	●	●	●	Include	High quality
Tzatzairis, T. K., 2016	●	●	●	●	●	●	Include	High quality
Ugurlu, M., 2016	●	●	●	●	●	●	Include	High quality
Veien, M., 2002	●	●	●	●	●	●	Include	High quality
Wang, C.-G., 2015	●	●	●	●	●	●	Include	High quality
Wang, C., 2016	●	●	●	●	●	●	Include	High quality
Wang, G., 2015	◑	●	●	●	●	●	Include	High quality
Wei, W., 2014	●	●	●	●	●	●	Include	High quality
Wong, J., 2010	●	●	●	●	●	○	Include	High quality
Xu, X., 2015	●	●	●	●	●	●	Include	High quality
Yamasaki, S., 2004	●	●	●	●	●	●	Include	High quality

(*continued on next page*)

Table 1 (*continued*)

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias	Inclusion	Strength
Yang, Y., 2015	●	●	●	●	●	●	Include	High quality
Yi, Z., 2016	●	●	●	●	●	●	Include	High quality
Yuan, X., 2017	●	●	●	●	●	●	Include	High quality
Yue, C., 2014	●	●	●	●	●	●	Include	High quality
Zhang, Y., 2016	●	●	●	●	●	●	Include	High quality
Zohar, E., 2004	●	●	●	●	●	●	Include	High quality

Filled circle represents free of flaws, empty circle represents significant flaws and partial filled circle represents moderate flaws.
VTE, venous thromboembolic event.

analysis. Quantitative heterogeneity coefficients for VTE and ATE outcomes were reported for all treatment comparisons. Many included data points did not have a risk ratio (RR) generated because of there being zero events for both treatment groups. However, these data were still used in the overall RR calculation.

Ninety-two percent of the studies in the meta-analysis comparing TXA administration with placebo excluded patients with a prior history of a thromboembolic event [15–92]. Because the results of the meta-analysis would not be applicable to patients with comorbidities associated with a higher risk of a thromboembolic event, metaregression analysis was used to assess the influence of comorbidity burden on the risk of thromboembolic events and the administration of TXA. Because individual comorbidities such as prior MI, CVA, peripheral vascular disease, VTE, or vascular stent placement were not commonly reported in publications, the American Society of Anesthesiologist (ASA) status was used as a proxy for the presence of comorbidities associated with an increased risk of a thromboembolic event. Consistent with prior publications, an ASA status of 3 or greater was considered to represent "high-risk" for a thromboembolic event [9–11]. Metaregression analysis was performed using the publications reporting ASA status among the study participants. We compared study populations of patients with more than 50% ASA status of 3 or greater with study populations of patients with more than 50% ASA status of 1 or 2. Because of the limited number of publications reporting both ASA status and the outcome of ATE, metaregression analysis was only performed for VTE. Metaregression analysis was run in STATA 12.1 software to investigate for any influence of the quality appraisal fields and ASA status of the patient populations on the risk of VTE. A P value >.05 was considered significant.

Using the data on the rates of VTE, the number needed to harm was calculated as the inverse of the attributable risk per patient. Because additional sister studies were performed on the efficacy of TXA, we used the data on the rates of transfusion to calculate the number needed to treat as the inverse of the absolute risk reduction per patient.

Results

The search strategy resulted in 2113 publications that underwent title and abstract screening. As a result of the initial screening, 1463 publications were a duplicate or met the exclusion criteria. Among the remaining 650 publications that underwent a full manuscript review, 361 publications met the exclusion criteria, whereas the remaining 289 publications underwent data extraction and quality assessment. After completion of the quality assessment, only randomized clinical trials representing the highest quality of evidence remained, leaving 79 publications with 7164 patients to be included for our meta-analysis of VTE or ATE.

Meta-Analysis of VTEs

After the quality assessment, 78 randomized clinical trials were available for the meta-analysis of VTE encompassing 7044 patients (Table 1) [15–92]. Published randomized clinical trials included comparisons between placebo and IV, topical, oral, combined IV/topical, or combined IV/oral TXA. Direct comparisons of VTE for meta-analysis were performed with THA or TKA publications when 4 or more publications investigated the same TXA intervention. The resulting THA comparisons were between placebo and IV or topical TXA. In the TKA publications, the analysis was performed for comparisons between placebo and IV, topical, or oral TXA. In addition, a combined analysis of all hip and knee arthroplasty studies was performed to provide a larger study population for IV and topical TXA compared with placebo.

Total Hip Arthroplasty

Among 22 randomized clinical trials comparing IV TXA with a placebo, the rates of VTE were 2.8% and 2.1%, respectively (RR 1.20; 95% confidence interval [CI], 0.62-2.33; $I^2 = 0\%$; Fig. 1A). Similarly, topical TXA demonstrated no difference in the rates of VTE compared with a placebo at 1.2% and 1.5%, respectively (RR 1.0; 95% CI, 0.21-4.89; $I^2 = 0\%$; Fig. 1B).

Total Knee Arthroplasty

Among the 35 randomized clinical trials comparing IV TXA with a placebo, the rates of VTE were 2.8% and 3.1%, respectively (RR 0.87; 95% CI, 0.58-1.32; $I^2 = 0\%$; Fig. 2A). Likewise, the meta-analysis of 25 studies on topical TXA had a similar rate of VTE compared with placebo at 2.6% and 2.9%, respectively (RR 0.89; 95% CI, 0.54-1.48; $I^2 = 0\%$; Fig. 2B). Only 5 studies were analyzed to compare VTE rates between oral TXA and placebo, but no difference was observed at 3.3% and 3.6%, respectively (RR 0.88; 95% CI, 0.38-2.04; $I^2 = 0\%$; Fig. 2C).

Combined THA and TKA

Among the 58 randomized clinical trials comparing IV TXA with a placebo, the number of patients in each group was 2131 and 2137, respectively. The rates of VTE were equivalent at 2.8% for both IV TXA and placebo (RR 0.98; 95% CI, 0.69-1.39; $I^2 = 0\%$; Fig. 3A). The 31 randomized studies comparing topical TXA and placebo had 1509 and 1502 patients per group, respectively. Like the results of IV TXA, topical TXA had a similar rate of VTE compared with placebo at 2.2% and 2.5%, respectively (RR 0.89; 95% CI, 0.56-1.41; $I^2 = 0\%$; Fig. 3B).

Meta-Analysis of ATEs

ATEs were rarely reported as a complication in the randomized clinical trials. After the quality assessment, 9 randomized clinical trials encompassing 817 patients were available for the meta-analysis (Table 2) [16,30,37,38,65,67,68,90,93]. Published randomized clinical trials included comparisons between placebo and IV, topical, oral, or combined IV/oral TXA. Direct comparisons of ATE for meta-analysis were not performed for THA or TKA studies because of a lack of 4 or more studies investigating the same TXA intervention. Therefore, direct meta-analysis was performed as a

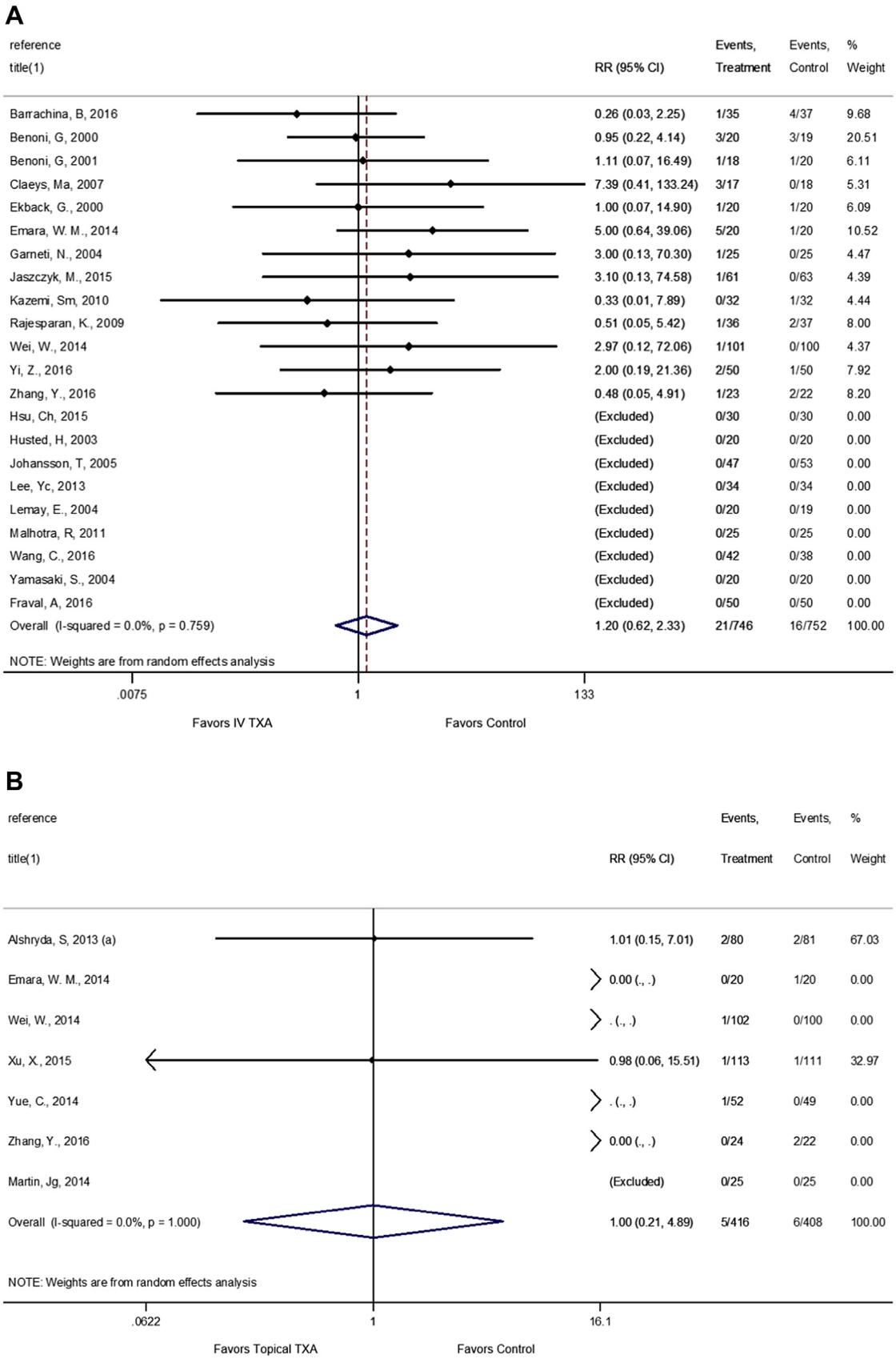
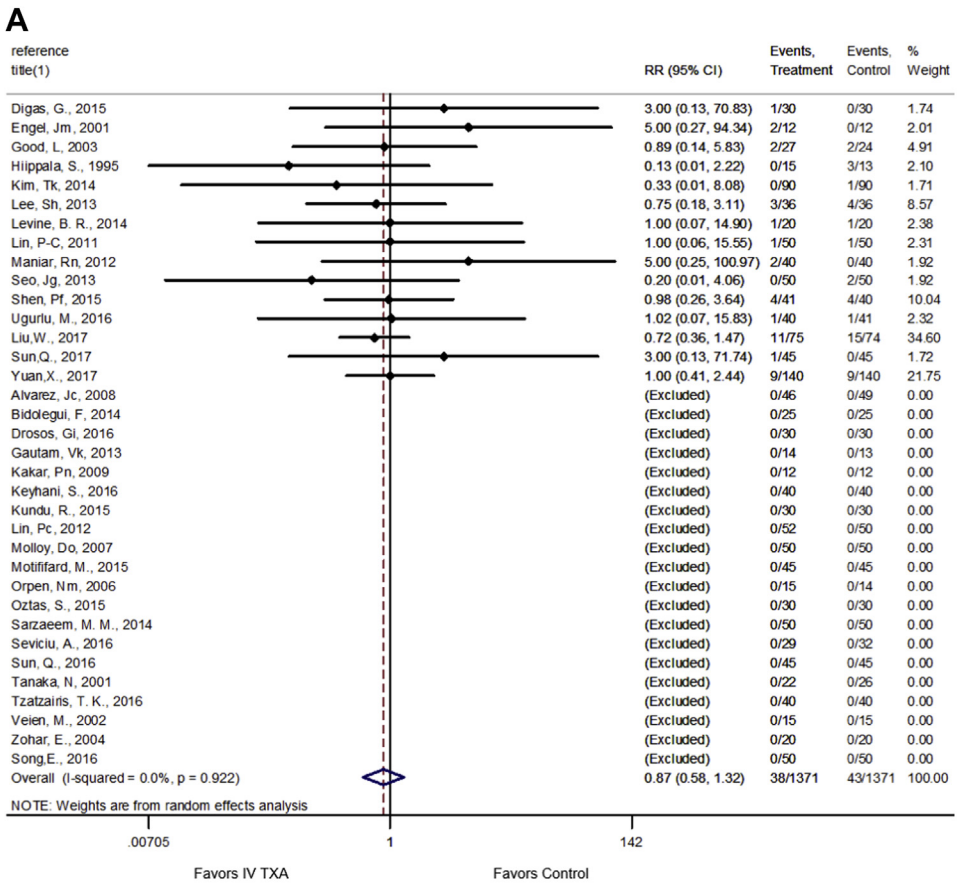


Fig. 1. (A) Forest plot of total hip arthroplasty (THA) venous thromboembolic event (VTE) for IV TXA vs control. (B) Forest plot of THA VTE for topical TXA vs control. CI, confidence interval; IV, intravenous; RR, risk ratio; TXA, tranexamic acid.



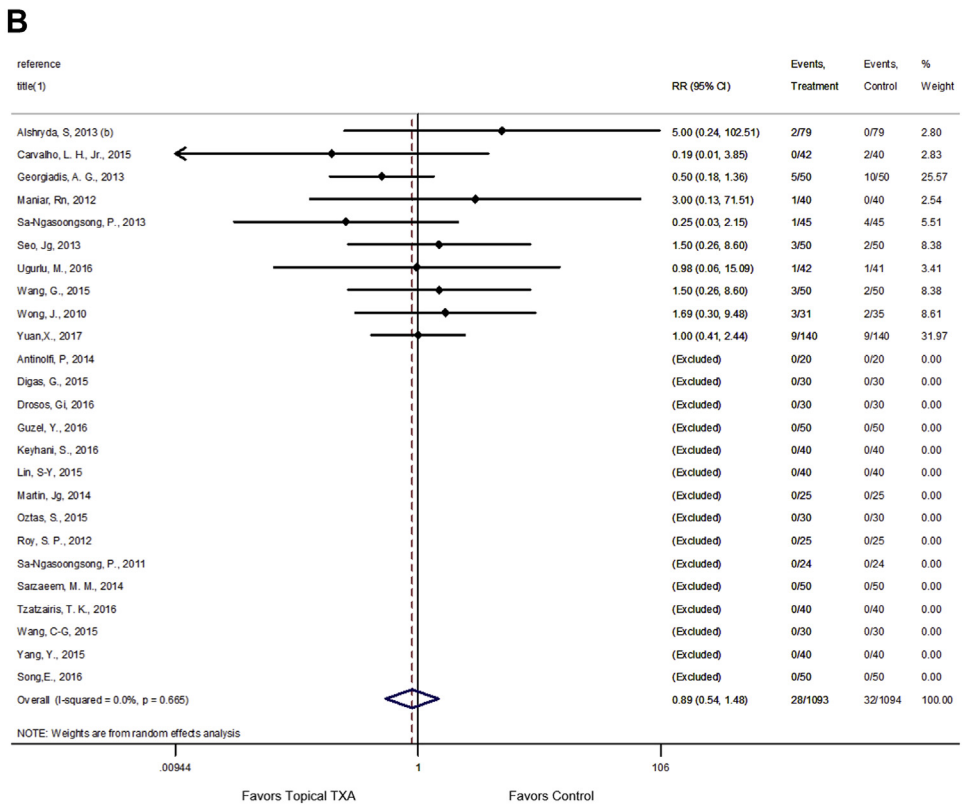


Fig. 2. (A) Forest plot of total knee arthroplasty (TKA) VTE for IV TXA vs control. (B) Forest plot of TKA VTE for topical TXA vs control. (C) Forest plot of TKA VTE for oral TXA vs control.

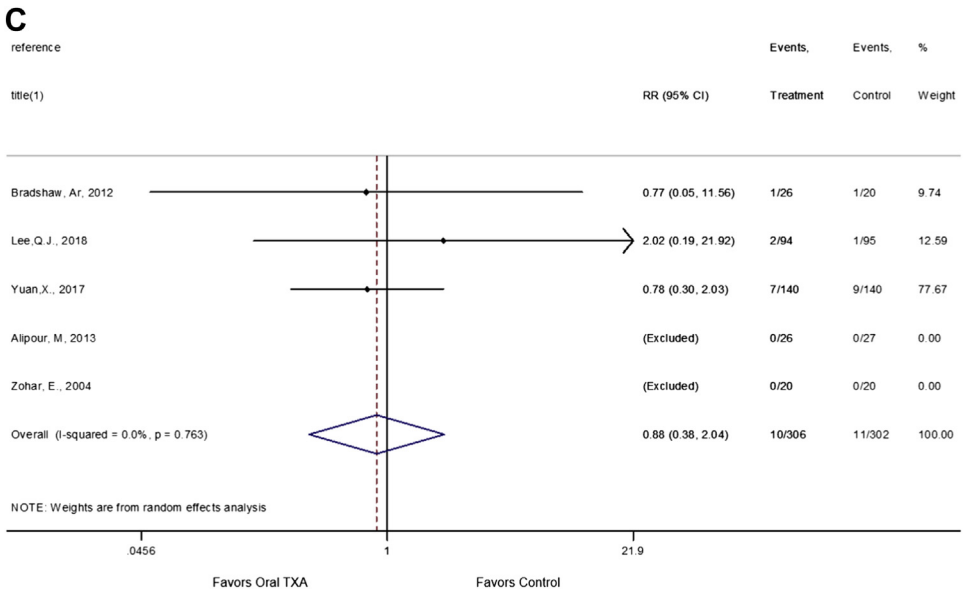


Fig. 2. (*continued*).

combined analysis of all hip and knee arthroplasty studies for IV and topical TXA.

TJA Results

Six randomized clinical trials compared IV TXA with a placebo, with equivalent rates of ATE reported of 0.9% and 0.5%, respectively (RR 1.40; 95% CI, 0.23-8.60; $I^2 = 0\%$; Fig. 4A). Similarly, the meta-analysis of 5 randomized clinical trials that studied topical TXA showed the rate of ATE was 0.8% for both groups (RR 1.0; 95% CI, 0.18-5.71; $I^2 = 0\%$; Fig. 4B).

Metaregression of VTE and ATE

The designation ASA status of 3 or higher among patients undergoing TKA had no significant impact on the risk of VTE; an analysis of the THA publications was not performed because of insufficient literature (Table 3). In addition, metaregression was performed for the subgroups of THA and TKA to assess for an influence on the VTE results based on the quality of the randomization, data reporting, and other biases of the included studies. None of these quality assessment appraisals had any significant impact on the target outcome of VTE, which helps provide validity to the quality of the studies included within the metaregression analysis (Table 3).

Discussion

TXA is frequently used during THA and TKA to reduce blood loss and the need for allogeneic transfusion [3]. Although the efficacy of TXA has been well documented with numerous randomized clinical trials and subsequent meta-analyses, many anesthesiologists and orthopedic surgeons continue to have concerns regarding the safety of TXA. We performed a direct meta-analysis and metaregression analysis of 79 randomized clinical trials to investigate the risk of VTE and ATE complications in TJA patients receiving TXA to establish a basis for the combined clinical practice guidelines of AAHKS, AAOS, Hip Society, Knee Society, and ASRA. We found evidence demonstrating a lack of increased risk of VTE among patients administered TXA, even in patients who would be considered higher risk.

Although the systematic review and meta-analysis was limited primarily to the inclusion of only high-quality, level-I evidence studies, our research nonetheless has several limitations. First, investigation of an infrequent outcome that results in a conclusion of no statistical difference raises concern regarding the statistical power. When two populations of patients, despite a large sample size, have similar complication rates, a post-hoc power analysis will always demonstrate a lack of statistical power. When an examiner assumes two populations to be identical, it is not possible to obtain a statistically powered sample size. Therefore, we must imply that the aggregate of a large number of level-I evidence studies consistently presenting the same result suggests a limited possibility of stating that there is no statistical difference when in reality a difference does exist (type II error). Second, we performed analysis using combined patient populations of hip and knee arthroplasties, which provides the opportunity to introduce additional heterogeneity. However, the combination of hip and knee arthroplasties does not appear to have influenced the observed heterogeneity, because all individual and combined analyses have no statistical evidence of heterogeneity on I-squared testing. Third, we had insufficient data to perform subgroup analysis based on the type of surgery and the risk of ATE. However, we were able to perform a combined analysis of hip and knee arthroplasties. Fourth, we did not account for the type of postoperative VTE chemoprophylaxis because of the variable not consistently reported in all randomized clinical trials. Because other large institutional database investigations have demonstrated no effect on the risk of VTE with TXA use regardless of the type of VTE chemoprophylaxis, we do not believe it presents bias to alter the conclusions [2,9]. Lastly, the interpretation of the results regarding the safety of TXA is limited by the inclusion and exclusion criteria used in the published literature. Because of concerns about the administration of TXA in high-risk patients, such as those with a history of thromboembolic and ischemic events as well as vascular stents, these patients were commonly excluded from randomized clinical trials. Because not all studies used the same inclusion and exclusion criteria, only a small number of the studies included in the current direct meta-analysis had higher-risk patients in their study population. Because we did not have the granularity to provide analysis of individual medical conditions, we attempted to perform a metaregression analysis to

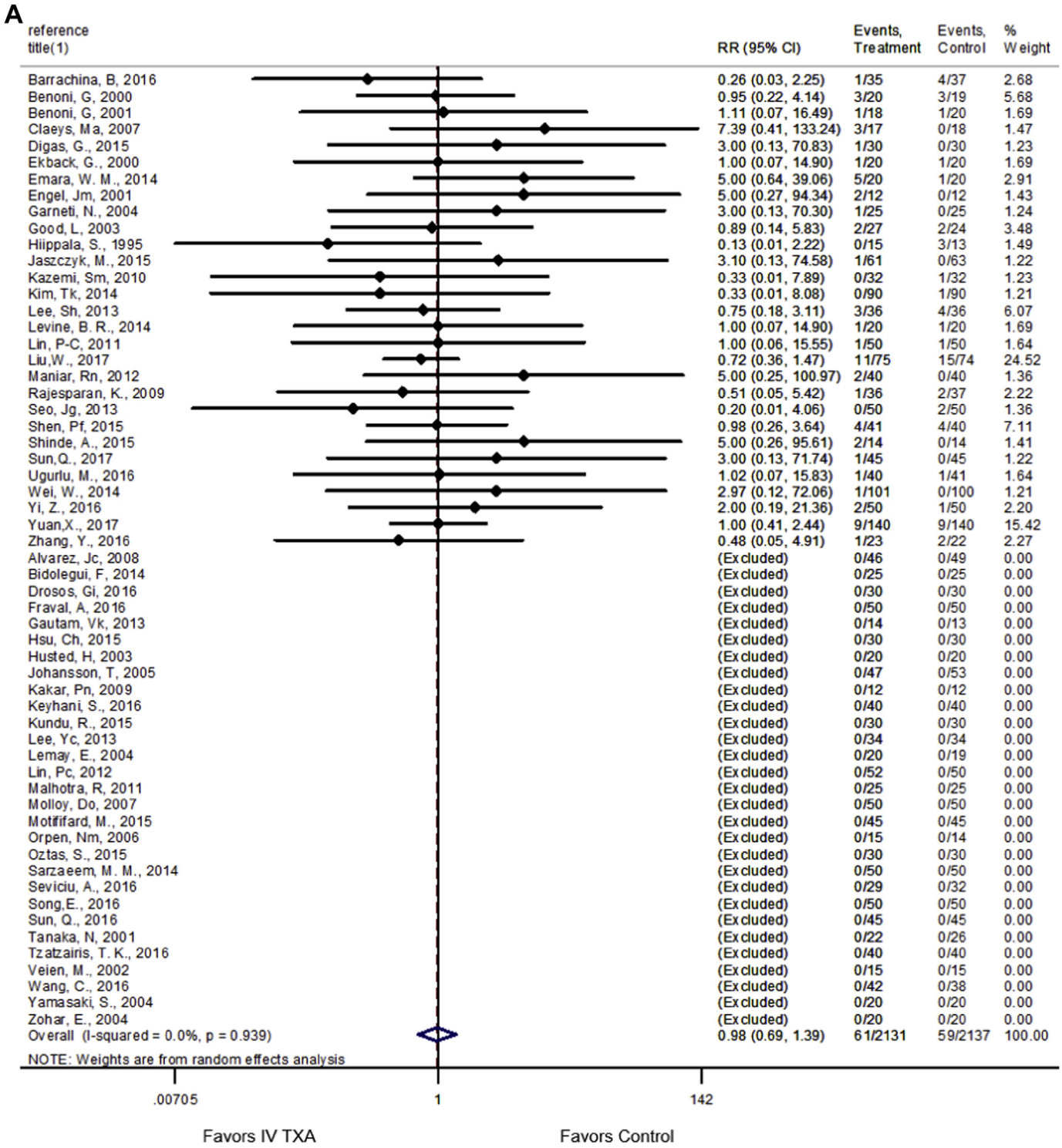


Fig. 3. (A) Forest plot of total joint arthroplasty (TJA) VTE for IV TXA vs control. (B) Forest plot of TJA VTE for topical TXA vs control.

help draw conclusions regarding the risk of VTE in high-risk patients using ASA status as a proxy for comorbidity burden that would potentially be associated with an increased risk of a thromboembolic event. However, the use of ASA status is still not a precise tool for isolating patients with risk factors for a thromboembolic event.

In patients undergoing a hip or knee arthroplasty, IV, topical, and oral TXA lack any observed influence on the risk of VTE. Concern has typically existed over the small sample sizes of individual randomized clinical trials and retrospective studies to accurately represent the lack of a difference between VTE rates of TXA administration and placebo. Prior investigation of the efficacy and safety of TXA, with a meta-analysis by Wei and Liu [94], provided no evidence for an increased risk of VTE with the use of IV TXA in a population of 2720 hip and knee arthroplasty cases. To provide a larger patient population, hip and knee arthroplasty

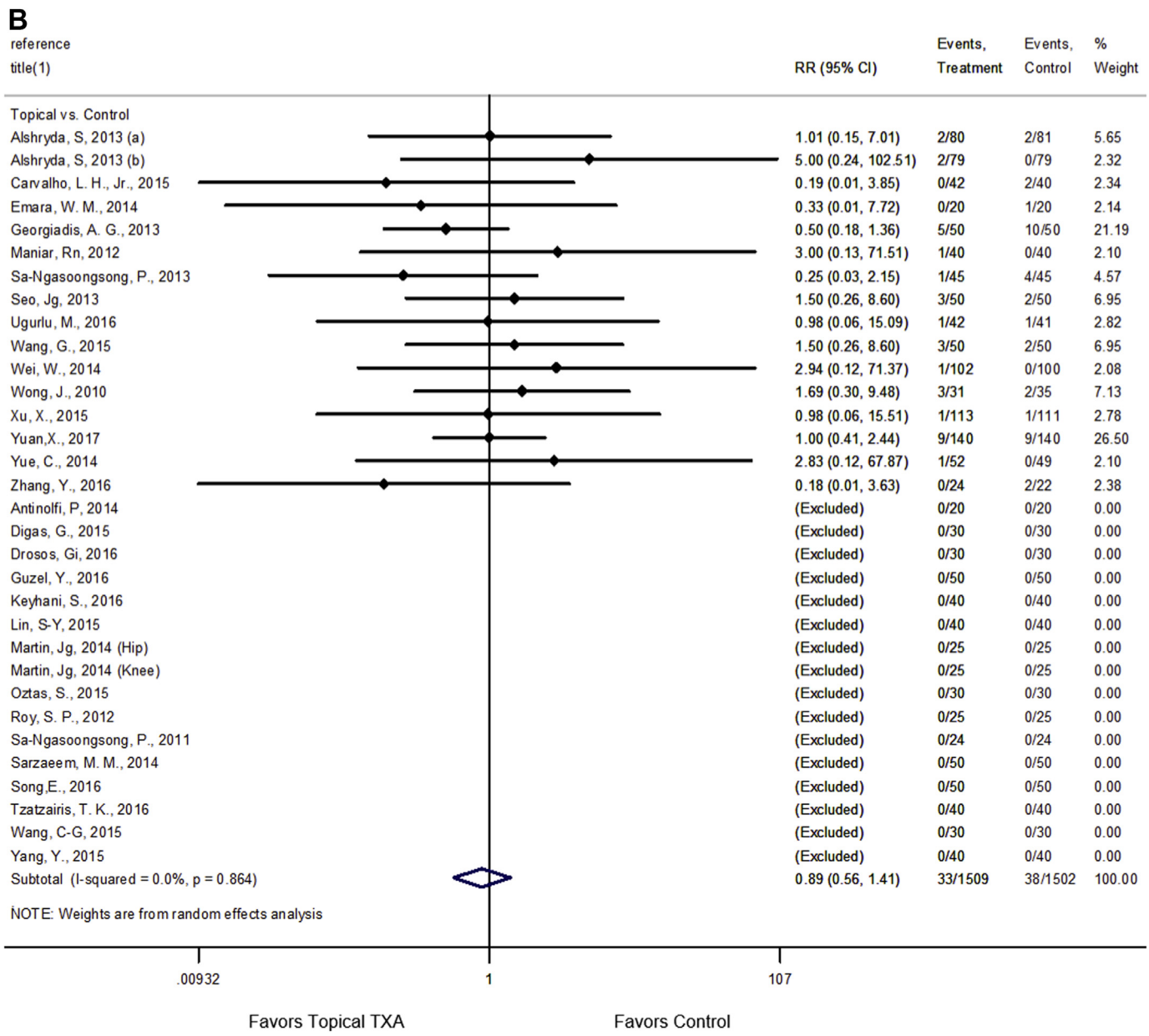
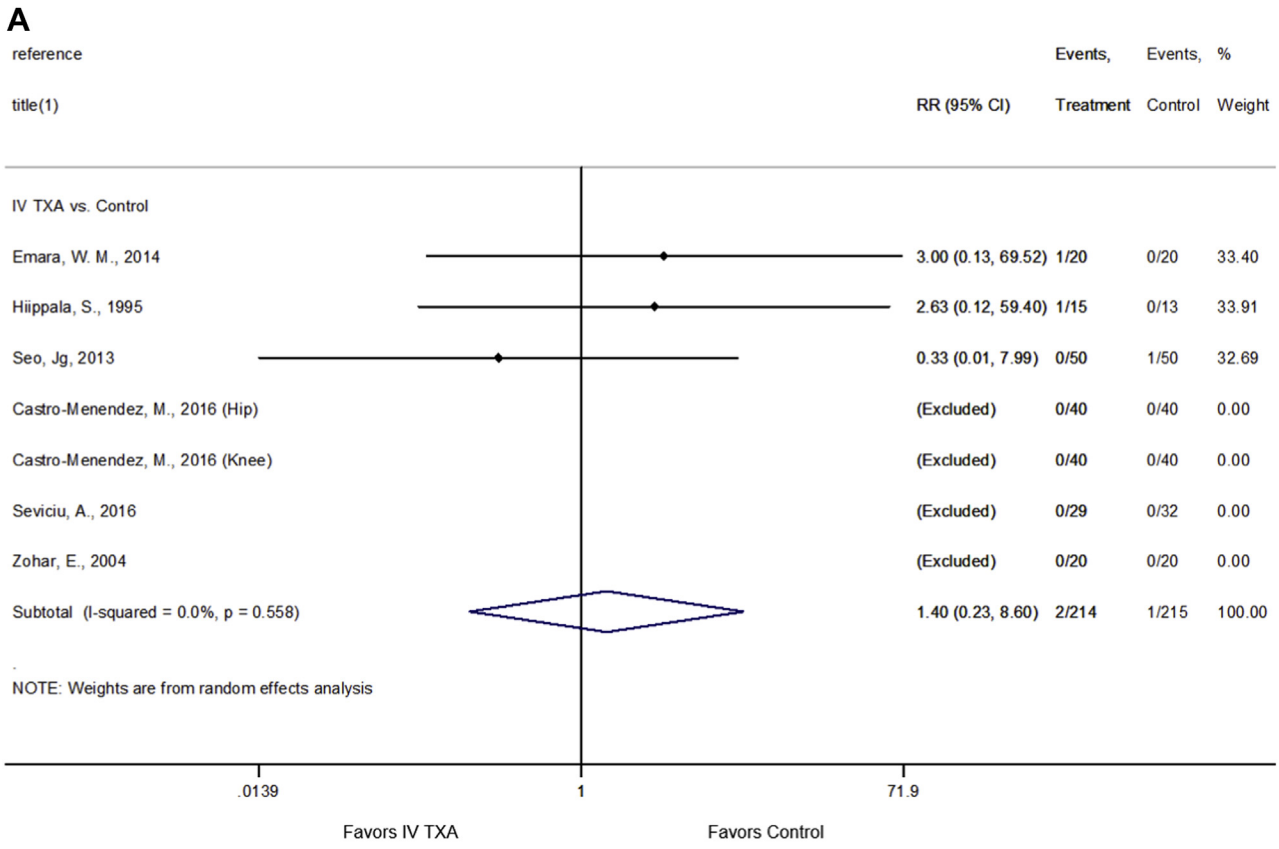


Fig. 3. (*continued*).

Table 2
ATE Investigation Study Inclusions and Quality Assessment.

Study	Random Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Reporting	Other Bias	Inclusion	Strength
Alshryda, S., 2013(b)	●	●	●	●	●	●	Include	High quality
Castro-Menendez, M., 2016	○	●	●	●	●	●	Include	High quality
Emara, W. M., 2014	◑	●	●	●	●	●	Include	High quality
Guzel, Y., 2016	◑	●	●	●	●	●	Include	High quality
Hiippala, S., 1995	●	●	●	●	●	●	Include	High quality
Sa-Ngasoongsong, P., 2013	●	●	●	●	●	●	Include	High quality
Seo, J, 2013	●	●	●	●	●	◑	Include	High quality
Seviciu, A., 2016	●	●	●	●	●	●	Include	High quality
Zohar, E., 2004	●	●	●	●	●	●	Include	High quality

Filled circle represents free of flaws, empty circle represents significant flaws and partial filled circle represents moderate flaws.
ATE, arterial thromboembolic event.



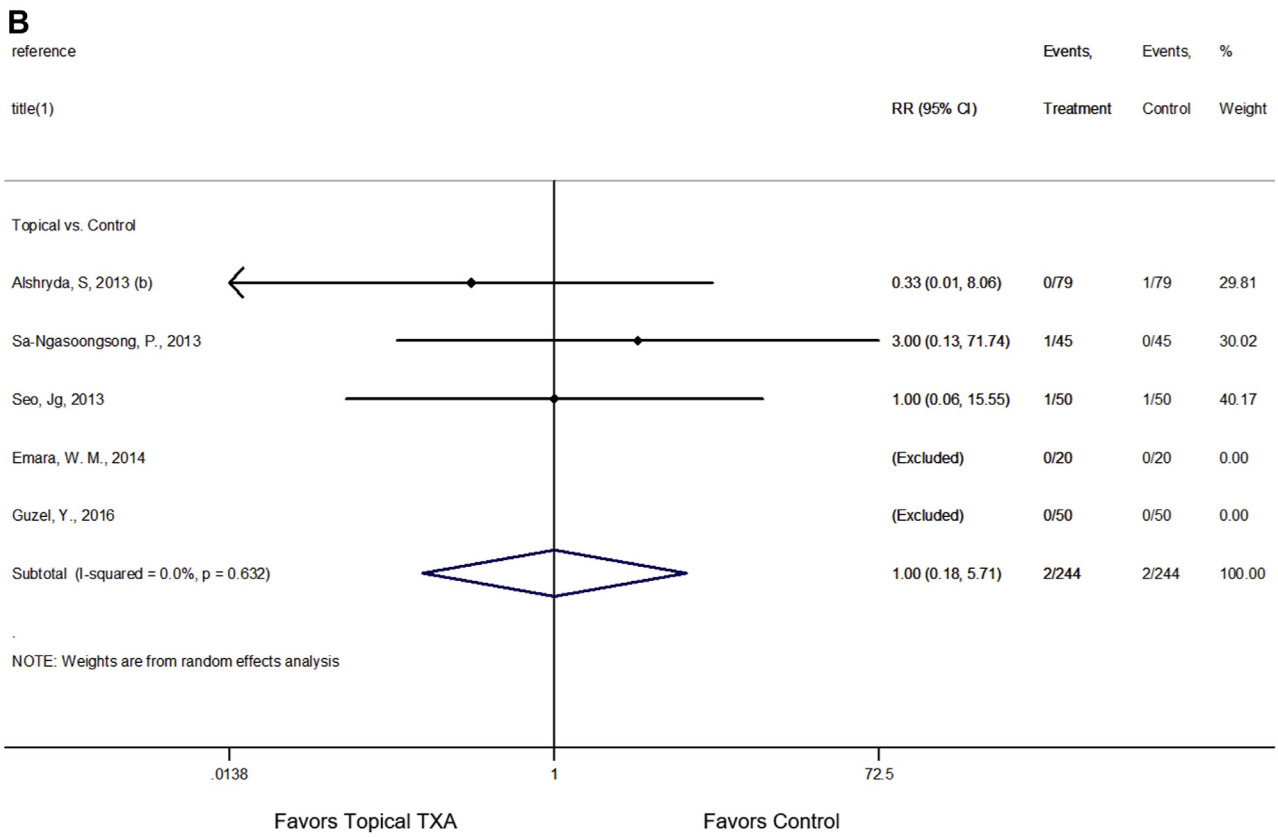


Fig. 4. (A) Forest plot of TJA arterial thromboembolic event (ATE) for IV TXA vs control. (B) Forest plot of TJA ATE for topical TXA vs control.

Table 3
THA and TKA Metaregression for VTE and ATE.

Outcome	Randomization[a]	Data Reporting[a]	Other Bias[a]	ASA Status >2[a]
THA				
VTE	.524	.812	.92	N/A[b]
ATE	N/A[b]	N/A[b]	N/A[b]	N/A[b]
TKA				
VTE	.826	N/A[c]	.956	.876
ATE	N/A[b]	N/A[b]	N/A[b]	N/A[b]

ASA, American Society of Anesthesiologist; ATE, arterial thromboembolic event; THA, total hip arthroplasty; TKA, total knee arthroplasty; VTE, venous thromboembolic event.

[a] Reported as *P* value, whereby a *P* value >.05 signifies no influence of the factor.

[b] Metaregression not performed because of insufficient literature/data.

[c] All studies are consistently unflawed thus create no need for metaregression analysis.

populations were combined in our study to give a population of 4268 cases for IV TXA and 3011 cases for topical TXA. When the populations of hip and knee arthroplasties are combined, the relative risk of VTE becomes closer to 1.0 than for the individual hip and knee arthroplasty meta-analyses. As a result, it provides strong evidence that the administration of TXA in patients without a history of thromboembolic events is not associated with an increased risk of VTE.

Currently, safety concerns regarding administration of TXA to patients thought to be at "high-risk" of a thromboembolic event (eg, prior history of VTE, MI, CVA, or placement of a vascular stent) have limited the broad adoption of TXA among this patient population. Because of the limitations presented by the inclusion and exclusion criteria applied to each individual randomized clinical trial, a metaregression analysis was performed using ASA status as a proxy for patients at higher risk of VTE and ATE. Because patients with medical conditions placing them at a higher risk for thromboembolic events would typically be considered an ASA status 3 or 4, the demarcation of ASA status 3 or greater was used to classify a "high-risk" patient. In this study, we could only perform a metaregression analysis on the effects of ASA status on VTE for TKA patients. Our results suggest that patients with a higher ASA status do not carry an increased risk of VTE with TXA administration. To put this in perspective, the number of patients needed to potentially attribute a single VTE event to the administration of TXA was 983 patients. Alternatively, using the same patient population, the number needed to treat with IV TXA to prevent an allogeneic transfusion after a THA or TKA was only 4 and 3 patients, respectively. As a result, we would advocate for a multidisciplinary approach that considers each patient's individual risk profile along with the potential benefits of administering TXA.

As part of a broader investigation regarding the risk of VTE and mortality associated with the administration of TXA in the setting of TJA, Duncan et al [10] used the same demarcation for ASA status. Their retrospective database study of more than 13,000 TJA patients demonstrated no increased risk of symptomatic VTE with the administration of TXA in patients with an ASA status of 3 to 5 [10]. More recently, the results of a smaller, yet more focused, retrospective matched cohort database study on the use of TXA in patients with a history of VTE did not demonstrate an increased risk of VTE compared with the control group [9]. Similar to the current metaregression analysis, Whiting et al [11] in an institutional database study, demonstrated that utilization of TXA in patients with severe comorbidities (ASA status 3 or 4) did not increase the risk of VTE. Whiting et al [11] also noted that patients with severe comorbidities and additional risk factors for thromboembolic events were more likely to experience a symptomatic VTE; however, they were unable to show that the concomitant administration of TXA was associated with the increased risk of VTE.

In the case of ATE, no meta-analysis could be performed in the THA or TKA subgroups because of a lack of the requisite number of 4 or more studies investigating the same comparison within each subgroup. However, it is worth noting that all individual studies did not demonstrate significant difference in ATE rates between the administration of TXA and placebo. Because we were unable to perform meta-analysis of the individual subgroups, a combined TJA patient population underwent meta-analysis. Similar to VTE, the combined meta-analysis of hip and knee arthroplasties, regardless of the route of administration, showed no difference in the rates of ATE.

Conclusion

Based on this meta-analysis of 78 high-level randomized clinical trials, we conclude that the administration of TXA does not increase the risk of VTE in TJA patients. In addition, we did not observe a difference in the results between TKA and THA. However, based on the limited number of high-quality trials and gaps in the inclusion of "high-risk" patients within the available literature, we can only moderately support the same conclusion for TJA patients with an ASA score of 3 or higher, which was used as a proxy for higher-risk patients with increased comorbidity burden. Although limited data exists on the administration of TXA in "high-risk" patients, it should be considered that patients with a higher comorbidity burden may benefit the most from the reduction in blood loss associated with the administration of TXA. In light of the lack of evidence for harm, it seems prudent to consider its use on a more regular basis after evaluation of each patient's characteristics.

Acknowledgments

The authors would like to thank AAHKS for providing funding for this study. The authors would like to thank Jayson Murray from the AAOS Department of Research, Quality, and Scientific Affairs for his assistance with oversight of the quality assessment, data extraction, and statistical analysis. The authors would like to thank Thomas Mead for his expertise as a research librarian to assist with development of the database searches. Lastly, they thank the leadership of the AAHKS, AAOS, ASRA, and the Hip and Knee societies for help with organizational support.

References

[1] Benoni G, Carlsson A, Petersson C, Fredin H. Does tranexamic acid reduce blood loss in knee arthroplasty? Am J Knee Surg 1995;8:88–92.
[2] Gillette BP, DeSimone LJ, Trousdale RT, Pagnano MW, Sierra RJ. Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty. Clin Orthop Relat Res 2013;471:150–4.
[3] Melvin JS, Stryker LS, Sierra RJ. Tranexamic acid in hip and knee arthroplasty. J Am Acad Orthop Surg 2015;23:732–40.
[4] Fillingham YA, Kayupov E, Plummer DR, Moric M, Gerlinger TL, Della Valle CJ. The James A. Rand Young Investigator's Award: a randomized controlled trial of oral and intravenous tranexamic acid in total knee arthroplasty: the same efficacy at lower cost? J Arthroplasty 2016;31(9 Suppl):26–30.
[5] Fergusson DA, Hebert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med 2008;358:2319–31.
[6] Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. Drugs 1999;57:1005–32.
[7] Okamoto S, Okamoto U. Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of fibrinolysis. Keio J Med 1962;11:105–15.
[8] Okamoto S, Sato S, Takada Y, Okamoto U. An active stereo-isomer (trans-form) of AMCHA and its antifibrinolytic (antiplasminic) action in vitro and in vivo. Keio J Med 1964;13:177–85.
[9] Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW. Tranexamic acid was safe in arthroplasty patients with a history of venous thromboembolism: a matched outcome study. J Arthroplasty 2017;32:S246–50.
[10] Duncan CM, Gillette BP, Jacob AK, Sierra RJ, Sanchez-Sotelo J, Smith HM. Venous thromboembolism and mortality associated with tranexamic acid use during total hip and knee arthroplasty. J Arthroplasty 2015;30:272–6.

[11] Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. Clin Orthop Relat Res 2014;472:66–72.
[12] Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, 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.
[13] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264–9, W64.
[14] American Academy of Orthopaedic Surgeons. AAOS Clinical Practice Guideline and Systematic Review Methodology. https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/Guideline%20and%20Systematic%20Review%20Processes_v4.0_Final.pdf.
[15] Alipour M, Tabari M, Keramati M, Zarmehri A, Makhmalbaf H. Effectiveness of oral tranexamic acid administration on blood loss after knee arthroplasty: a randomized clinical trial. Transfus Apher Sci 2013;49:574–7.
[16] Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX-H) (Provisional abstract). J Bone Joint Surg Am 2013;95:1969–74.
[17] Alshryda S, Mason J, Vaghela M, Sarda P, Nargol A, Maheswaran S, et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total knee replacement: a randomized controlled trial (TRANX-K). J Bone Joint Surg Am 2013;95:1961–8.
[18] Alvarez J, Santiveri F, Ramos I, Vela E, Puig L, Escolano F. Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied. Transfusion 2008;48:519–25.
[19] Antinolfi P, Innocenti B, Caraffa A, Peretti G, Cerulli G. Post-operative blood loss in total knee arthroplasty: knee flexion versus pharmacological techniques. Knee Surg Sports Traumatol Arthrosc 2014;22:2756–62.
[20] Barrachina B, Lopez-Picado A, Remon M, Fondarella A, Iriarte I, Bastida R, et al. Tranexamic acid compared with placebo for reducing total blood loss in hip replacement surgery: a randomized clinical trial. Anesth Analg 2016;122:986–95.
[21] Benoni G, Fredin H, Knebel R, Nilsson P. Blood conservation with tranexamic acid in total hip arthroplasty: a randomized, double-blind study in 40 primary operations. Acta Orthop Scand 2001;72:442–8.
[22] Benoni G, Lethagen S, Nilsson P, Fredin H. Tranexamic acid, given at the end of the operation, does not reduce postoperative blood loss in hip arthroplasty. Acta Orthop Scand 2000;71:250–4.
[23] Bidolegui F, Arce G, Lugones A, Pereira S, Vindver G. Tranexamic acid reduces blood loss and transfusion in patients undergoing total knee arthroplasty without tourniquet: a prospective randomized controlled trial. Open Orthop J 2014;8:250–4.
[24] Bradshaw A, Monoghan J, Campbell D. Oral tranexamic acid reduces blood loss in total knee replacement arthroplasty. Curr Orthop Pract 2012;23:209–12.
[25] Carvalho Jr LH, Frois Temponi E, Machado Soares LF, Goncalves MB, Paiva Costa L, Tavares de Souza ML. Bleeding reduction after topical application of tranexamic acid together with Betadine solution in total knee arthroplasty. A randomised controlled study. Orthop Traumatol Surg Res 2015;101:83–7.
[26] Claeys M, Vermeersch N, Haentjens P. Reduction of blood loss with tranexamic acid in primary total hip replacement surgery. Acta Chir Belg 2007;107:397–401.
[27] Digas G, Koutsogiannis I, Meletiadis G, Antonopoulou E, Karamoulas V, Bikos C. Intra-articular injection of tranexamic acid reduce blood loss in cemented total knee arthroplasty. Eur J Orthop Surg Traumatol 2015;25:1181–8.
[28] Drosos G, Ververidis A, Valkanis C, Tripsianis G, Stavroulakis E, Vogiatzaki T, et al. A randomized comparative study of topical versus intravenous tranexamic acid administration in enhanced recovery after surgery (ERAS) total knee replacement. J Orthop 2016;13:127–31.
[29] Ekback G, Axelsson K, Ryttberg L, Edlund B, Kjellberg J, Weckstrom J, et al. Tranexamic acid reduces blood loss in total hip replacement surgery. Anesth Analg 2000;91:1124–30.
[30] Emara WM, Moez KK, Elkhouly AH. Topical versus intravenous tranexamic acid as a blood conservation intervention for reduction of post-operative bleeding in hemiarthroplasty. Anesth Essays Res 2014;8:48–53.
[31] Engel J, Hohaus T, Ruwoldt R, Menges T, Jürgensen I, Hempelmann G. Regional hemostatic status and blood requirements after total knee arthroplasty with and without tranexamic acid or aprotinin. Anesth Analg 2001;92:775–80.
[32] Fraval A, Effeney P, Fiddelaers L, Smith B, Towell B, Tran P, et al. OBTAIN A: outcome benefits of tranexamic acid in hip arthroplasty. A randomized double-blinded controlled trial. J Arthroplasty 2017;32:1516–9.
[33] Garneti N, Field J. Bone bleeding during total hip arthroplasty after administration of tranexamic acid. J Arthroplasty 2004;19:488–92.
[34] Gautam V, Sambandam B, Singh S, Gupta P, Gupta R, Maini L. The role of tranexamic acid in reducing blood loss in total knee replacement. J Clin Orthop Trauma 2013;4:36–9.
[35] Georgiadis AG, Muh SJ, Silverton CD, Weir RM, Laker MW. A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty. J Arthroplasty 2013;28(8 Suppl):78–82.
[36] Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003;90:596–9.
[37] Guzel Y, Gurcan OT, Golge UH, Dulgeroglu TC, Metineren H. Topical tranexamic acid versus autotransfusion after total knee arthroplasty. J Orthop Surg (Hong Kong) 2016;24:179–82.
[38] Hiippala S, Strid L, Wennerstrand M, Arvela V, Mantyla S, Ylinen J, et al. Tranexamic acid (Cyklokapron) reduces perioperative blood loss associated with total knee arthroplasty. Br J Anaesth 1995;74:534–7.
[39] Hsu C, Lin P, Kuo F, Wang J. A regime of two intravenous injections of tranexamic acid reduces blood loss in minimally invasive total hip arthroplasty: a prospective randomised double-blind study. Bone Joint J 2015;97-B:905–10.
[40] Husted H, Blønd L, Sonne-Holm S, Holm G, Jacobsen T, Gebuhr P. Tranexamic acid reduces blood loss and blood transfusions in primary total hip arthroplasty: a prospective randomized double-blind study in 40 patients. Acta Orthop Scand 2003;74:665–9.
[41] Jaszczyk M, Kozerawski D, Kolodziej L, Kazimierczak A, Sarnecki P, Sieczka L. Effect of single preoperative dose of tranexamic acid on blood loss and transfusion in hip arthroplasty. Ortop Traumatol Rehabil 2015;17:265–73.
[42] Johansson T, Pettersson L, Lisander B. Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients. Acta Orthop 2005;76:314–9.
[43] Kakar P, Gupta N, Govil P, Shah V. Efficacy and safety of tranexamic acid in control of bleeding following TKR: a randomized clinical trial. Indian J Anaesth 2009;53:667–71.
[44] Kazemi S, Mosaffa F, Eajazi A, Kaffashi M, Besheli L, Bigdeli M, et al. Hip the effect of tranexamic acid on reducing blood loss in cementless total hip arthroplasty under epidural anesthesia. Orthopedics 2010;17.
[45] Keyhani S, Esmailiejah AA, Abbasian MR, Safdari F. Which route of tranexamic acid administration is more effective to reduce blood loss following total knee arthroplasty? Arch Bone Jt Surg 2016;4:65–9.
[46] Kim T, Chang C, Kang Y, Seo E, Lee J, Yun J, et al. Clinical value of tranexamic acid in unilateral and simultaneous bilateral TKAs under a contemporary blood-saving protocol: a randomized controlled trial. Knee Surg Sports Traumatol Arthrosc 2014;22:1870–8.
[47] Kundu R, Das A, Basunia SR, Bhattacharyya T, Chattopadhyay S, Mukherjee A. Does a single loading dose of tranexamic acid reduce perioperative blood loss and transfusion requirements after total knee replacement surgery? A randomized, controlled trial. J Nat Sci Biol Med 2015;6:94–9.
[48] Lee S, Cho K, Khurana S, Kim K. Less blood loss under concomitant administration of tranexamic acid and indirect factor Xa inhibitor following total knee arthroplasty: a prospective randomized controlled trial. Knee Surg Sports Traumatol Arthrosc 2013;21:2611–7.
[49] Lee Y, Park S, Kim J, Cho C. Effect of tranexamic acid on reducing postoperative blood loss in combined hypotensive epidural anesthesia and general anesthesia for total hip replacement. J Clin Anesth 2013;25:393–8.
[50] Lemay E, Guay J, Cote C, Roy A. Tranexamic acid reduces the need for allogenic red blood cell transfusions in patients undergoing total hip replacement. Can J Anaesth 2004;51:31–7.
[51] Levine BR, Haughom BD, Belkin MN, Goldstein ZH. Weighted versus uniform dose of tranexamic acid in patients undergoing primary, elective knee arthroplasty: a prospective randomized controlled trial. J Arthroplasty 2014;29(9 Suppl):186–8.
[52] Lin P, Hsu C, Huang C, Chen W, Wang J. The blood-saving effect of tranexamic acid in minimally invasive total knee replacement: is an additional preoperative injection effective? J Bone Joint Surg Br 2012;94:932–6.
[53] Lin P-C, Hsu C-H, Chen W-S, Wang J-W. Does tranexamic acid save blood in minimally invasive total knee arthroplasty? Clin Orthop Relat Res 2011;469:1995–2002.
[54] Lin S-Y, Chen C-H, Fu Y-C, Huang P-J, Chang J-K, Huang H-T. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. J Arthroplasty 2015;30:776–80.
[55] Malhotra R, Kumar V, Garg B. The use of tranexamic acid to reduce blood loss in primary cementless total hip arthroplasty. Eur J Orthop Surg Traumatol 2011;21:101–4.
[56] Maniar R, Kumar G, Singhi T, Nayak R, Maniar P. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. Clin Orthop Relat Res 2012;470:2605–12.
[57] Martin J, Cassatt K, Kincaid-Cinnamon K, Westendorf D, Garton A, Lemke J. Topical administration of tranexamic acid in primary total hip and total knee arthroplasty. J Arthroplasty 2014;29:889–94.
[58] Molloy D, Archbold H, Ogonda L, McConway J, Wilson R, Beverland D. Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement: a prospective, randomised controlled trial. J Bone Joint Surg Br 2007;89:306–9.
[59] Motififard M, Tahririan MA, Saneie M, Badiei S, Nemati A. Low dose perioperative intravenous tranexamic acid in patients undergoing total knee arthroplasty: a double-blind randomized placebo controlled clinical trial. J Blood Transfus 2015;2015:948304.
[60] Orpen N, Little C, Walker G, Crawfurd E. Tranexamic acid reduces early postoperative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients. Knee 2006;13:106–10.
[61] Özta S, Öztürk A, Akaln Y, Ahin N, Özkan Y, Otuzbir A, et al. The effect of local and systemic application of tranexamic acid on the amount of blood loss and allogeneic blood transfusion after total knee replacement. Acta Orthop Belg 2015;81:698–707.

[62] Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. J Bone Joint Surg Br 2009;91:776–83.
[63] Roy SP, Tanki UF, Dutta A, Jain SK, Nagi ON. Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2012;20:2494–501.
[64] Sa-Ngasoongsong P, Channoom T, Kawinwonggowit V, Woratanarat P, Chanplakorn P, Wibulpolprasert B, et al. Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial. Orthop Rev (Pavia) 2011;3:e12.
[65] Sa-Ngasoongsong P, Wongsak S, Chanplakorn P, Woratanarat P, Wechmongkolgorn S, Wibulpolprasert B, et al. Efficacy of low-dose intra-articular tranexamic acid in total knee replacement; A prospective triple-blinded randomized controlled trial. BMC Musculoskelet Disord 2013;14:340.
[66] Sarzaeem MM, Razi M, Kazemian G, Moghaddam ME, Rasi AM, Karimi M. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. J Arthroplasty 2014;29:1521–4.
[67] Seo J, Moon Y, Park S, Kim S, Ko K. The comparative efficacies of intra-articular and IV tranexamic acid for reducing blood loss during total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2013;21:1869–74.
[68] Seviciu A, Gross I, Fathima S, Walsh SM. Effects of tranexamic acid and bipolar sealer alone or in combination in primary total knee arthroplasty: a prospective, randomized, controlled trial. Arthroplasty Today 2016;2:77–82.
[69] Shen P, Hou W, Chen J, Wang B, Qu Y. Effectiveness and safety of tranexamic acid for total knee arthroplasty: a prospective randomized controlled trial. Med Sci Monit 2015;21:576–81.
[70] Shinde A, Sobti A, Maniar S, Mishra A, Gite R, Shetty V. Tranexamic acid reduces blood loss and need of blood transfusion in total knee arthroplasty: a prospective, randomized, double-blind study in Indian population. Asian J Transfus Sci 2015;9:168–72.
[71] Song EK, Seon JK, Prakash J, Seol YJ, Park YJ, Jin C. Combined administration of IV and topical tranexamic acid is not superior to either individually in primary navigated TKA. J Arthroplasty 2017;32:37–42.
[72] Sun Q, Yu X, Nie XY, Gong JP, Cai M. The efficacy comparison of tranexamic acid for reducing blood loss in total knee arthroplasty at different dosage time. J Arthroplasty 2017;32:33–6.
[73] Sun Q, Yu X, Wu J, Ge W, Cai M, Li S. Efficacy of a single dose and an additional dose of tranexamic acid in reduction of blood loss in total knee arthroplasty. J Arthroplasty 2017;32:2108–12.
[74] Tanaka N, Sakahashi H, Sato E, Hirose K, Ishima T, Ishii S. Timing of the administration of tranexamic acid for maximum reduction in blood loss in arthroplasty of the knee. J Bone Joint Surg Br 2001;83:702–5.
[75] Tzatzairis TK, Drosos GI, Kotsios SE, Ververidis AN, Vogiatzaki TD, Kazakos KI. Intravenous vs topical tranexamic acid in total knee arthroplasty without tourniquet application: a randomized controlled study. J Arthroplasty 2016;31:2465–70.
[76] Uğurlu M, Aksekili MAE, Çağlar C, Yüksel K, Şahin E, Akyol M. Effect of topical and intravenously applied tranexamic acid compared to control group on bleeding in primary unilateral total knee arthroplasty. J Knee Surg 2017;30:152–7.
[77] Veien M, Sørensen JV, Madsen F, Juelsgaard P. Tranexamic acid given intraoperatively reduces blood loss after total knee replacement: a randomized, controlled study. Acta Anaesthesiol Scand 2002;46:1206–11.
[78] Wang C, Kang P, Ma J, Yue C, Xie J, Pei F. Single-dose tranexamic acid for reducing bleeding and transfusions in total hip arthroplasty: a double-blind, randomized controlled trial of different doses. Thromb Res 2016;141:119–23.
[79] Wang C-G, Sun Z-H, Liu J, Cao J-G, Li Z-J. Safety and efficacy of intra-articular tranexamic acid injection without drainage on blood loss in total knee arthroplasty: a randomized clinical trial. Int J Surg 2015;20:1–7.
[80] Wang G, Wang D, Wang B, Lin Y, Sun S. Efficacy and safety evaluation of intra-articular injection of tranexamic acid in total knee arthroplasty operation with temporarily drainage close. Int J Clin Exp Med 2015;8:14328–34.
[81] Wei W, Wei B. Comparison of topical and intravenous tranexamic acid on blood loss and transfusion rates in total hip arthroplasty. J Arthroplasty 2014;29:2113–6.
[82] Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503–13.
[83] Xu X, Li X, Liu W, Wang Z. Longtime soaking of high concentration tranexamic acid in total hip arthroplasty: a prospective randomized controlled trial in 224 patients. Pak J Med Sci 2015;31:1306–11.
[84] Yamasaki S, Masuhara K, Fuji T. Tranexamic acid reduces blood loss after cementless total hip arthroplasty - prospective randomized study in 40 cases. Int Orthop 2004;28:69–73.
[85] Yang Y, Lv YM, Ding PJ, Li J, Ying-Ze Z. The reduction in blood loss with intra-articular injection of tranexamic acid in unilateral total knee arthroplasty without operative drains: a randomized controlled trial. Eur J Orthop Surg Traumatol 2015;25:135–9.
[86] Yi Z, Bin S, Jing Y, Zongke Z, Pengde K, Fuxing P. Tranexamic acid administration in primary total hip arthroplasty a randomized controlled trial of intravenous combined with topical versus single-dose intravenous administration. J Bone Joint Surg Am 2016;98:983–91.
[87] Yuan X, Li B, Wang Q, Zhang X. Comparison of 3 routes of administration of tranexamic acid on primary unilateral total knee arthroplasty: a prospective, randomized, controlled study. J Arthroplasty 2017;32:2738–43.
[88] Yue C, Kang P, Yang P, Xie J, Pei F. Topical application of tranexamic acid in primary total hip arthroplasty: a randomized double-blind controlled trial. J Arthroplasty 2014;29:2452–6.
[89] Zhang Y, Cheng T, Zhang X. Impact of tranexamic acid and autologous blood transfusion on postoperative complications after primary total knee arthroplasty: a retrospective comparative study. Int J Clin Exp Med 2016;9:3842–50.
[90] Zohar E, Ellis M, Ifrach N, Stern A, Sapir O, Fredman B. The postoperative blood-sparing efficacy of oral versus intravenous tranexamic acid after total knee replacement. Anesth Analg 2004;99:1679–83.
[91] Liu W, Yang C, Huang X, Liu R. Tranexamic acid reduces occult blood loss, blood transfusion, and improves recovery of knee function after total knee arthroplasty: a comparative study. J Knee Surg 2018;31:239–46.
[92] Lee QJ, Ching WY, Wong YC. Blood sparing efficacy of oral tranexamic acid in primary total knee arthroplasty: a randomized controlled trial. Knee Surg Relat Res 2017;29:57–62.
[93] Castro-Menendez M, Pena-Paz S, Rocha-Garcia F, Rodriguez-Casas N, Huici-Izco R, Montero-Vieites A. Efficacy of 2 grammes of intravenous tranexamic acid in the reduction of post-surgical bleeding after total hip and knee replacement. Rev Esp Cir Ortop Traumatol 2016;60:315–24.
[94] 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;25:151–62.

Appendix B. Formal Database Search Strategies

Database: Complete Ovid MEDLINE
Dates covered: 1946-2017
Date of search: July 5, 2017 (most recent search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	exp arthroplasty/
2	(arthroplast$ or "hip replacement$" or total knee or total hip).af.
3	1 or 2
4	exp tranexamic acid/
5	(tranexemic acid or tranexamic acid).af.
6	exp antifibrinolytic agents/
7	(antifibrinolytic agent$ or aminocaproic acid).af.
8	4 or 5 or 6 or 7
9	3 and 8

Database: EMBASE (Excerpta Medica dataBASE)
Dates covered: 1947-2016
Date of search: October 3, 2016 (most recent search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	exp arthroplasty/
2	(arthroplast$ or "hip replacement$" or total knee or total hip).af.
3	1 or 2
4	exp tranexamic acid/
5	(tranexemic acid or tranexamic acid).af.
6	exp antifibrinolytic agents/
7	(antifibrinolytic agent$ or aminocaproic acid).af.
8	4 or 5 or 6 or 7
9	3 and 8

Database: Web of Science (WOS)
Dates covered: 1964-2017
Date of search: October 5, 2017 (most recent search)
Librarian: Tom Mead, MLS
Filters: Exclude MEDLINE database

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	1 AND 2
4	Refined by: [excluding] Databases: (MEDLINE)

Database: Scopus
Dates covered: 1823-2017
Date of search: July 10, 2017 (most recent search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	1 AND 2

Database: Cochrane Library (DARE)
Dates covered: 1994-2017
Date of search: July 5, 2017 (most recent search)
Librarian: Tom Mead, MLS
Filters: None

Search Order	Search Parameters
1	(arthroplast* OR "HIP REPLACEMENT" OR "TOTALL KNEE" OR "TOTAL HIP")
2	("TRANEXAMIC ACID" OR "AMINOCAPROIC ACID" OR "ANTIFBRINOL*)
3	1 AND 2