What are the contraindications, if any, for the use of tranexamic acid (TXA) during knee or hip arthroplasty?

Enayatollahi A, Anuon A, Azboy I, Çetin H, Demir B, Dietz M, Dragosloveanu S, Ehsani AA, Ghamgosar A, Heshmat R, Palmer, A, Scheau C, Shafiee G,

Recommendation: A history of hypersensitivity to TXA is an absolute contraindication.

Level of Evidence: Strong

Recommendation: In patients with a history of thromboembolic events, TXA can be safely administered.

Level of Evidence: Moderate

Recommendation: In patients with a history of seizure or visual disturbances we cannot recommend for or against the use of TXA.

Level of Evidence: Low

Recommendation: In patients with renal dysfunction, TXA is not contraindicated but dose adjustment according to serum creatinine level should be considered.

Level of Evidence: Strong

Rationale:

Basic science

In 1962, a chemical compound, trans 4 aminomethylcyclohexane-1-carboxylic acid, was developed by Utako and Shosuke Okamoto. This compound, which was renamed later as tranexamic acid (TXA), is a chemical relative of epsilon-amino-caproic-acid (EACA) which is 27x more powerful than EACA.[1] Tranexamic acid (TXA) is a synthetic lysine analog that attaches to the lysine -binding site on plasminogen and prevents its binding to fibrin apparatus, stabilizing fibrin's matrix structure and acts as a potent antifibrinolytic. TXA in concentrations of up to 10 mg/ml blood has no influence on coagulation factors (i.e., platelet count, coagulation time) in whole blood or citrated blood of healthy individuals. Its half-life in the serum is about 2 hours after intravenous administration and 95% of its dose is eliminated by kidneys as unchanged drug.[2]

Efficacy and safety

TXA is a potent antifibrinolytic with recognized efficacy in several clinical settings. Its utilization in joint replacement surgery has been endorsed by clinical practice guidelines.[3] Adoption of the use of TXA has reached nearly 95% in TJA patients globally as an essential component of blood management protocols.[4] In spite of this, the administration of TXA for

elective surgeries is considered off-label and has not been approved by many health authority organizations like the Food and Drug Administration (FDA). A significant and strong body of the literature has proved its efficacy in reducing bleeding in TJA populations. [5,6] In the era of modern patient blood management strategies, that include TXA utilization the need for postoperative blood transfusion in TJA settings is an infrequent event. TXA administration has been widely adopted, but safety concerns, particularly the risk of thromboembolic complications, persist. Many studies of TXA safety exclude patients with a history of venous thromboembolic event (VTE) or those at high risk for thrombotic events like myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), atrial fibrillation and/or vascular stent placement. The results of these reviews showed no increased risk of thromboembolic complications in patients receiving TXA during TJA compared with placebo, irrespective of dose, route or timing of administration. TXA is recommended for all TJA patients by the American Association of Hip and Knee Surgeons (AAHKS), the American Academy of Orthopaedic Surgeons (AAOS), the Hip Society, the Knee Society and the American Society of Regional Anesthesia and Pain Medicine (ASRA). [3,5–7] Despite these strong recommendations, concerns remain regarding the use of TXA in patient populations considered "high-risk" for thromboembolic complications. Due to the paucity of literature and lack of randomized trials in high-risk patients, we performed a systematic review and meta-analysis in high-risk patients undergoing hip and knee replacement to investigate the incidence of adverse effects of TXA utilization and compare those data with placebo or standard of care.

Use of TXA in high-risk patients

In our meta-analysis of data from 16 studies, the use of TXA in patients with a history of thromboembolism or any risk factors for thrombotic events (i.e., MI, CVA, TIA), which are considered high-risk patients, does not increase the risk of postoperative thromboembolic complications. Our results demonstrate that TXA administration in high-risk population undergoing TJA is safe. The findings show that TXA has protective effect against adverse events with a reduction in the risk of pulmonary embolism (PE) (RR = 0.80; 95% CI (0.68, 0.95); I^2=56%), MI (RR = 0.59; 95% CI (0.44, 0.79); I^2=87%), acute kidney injury (RR = 0.76; 95% CI (0.63, 0.92), I^2=98%), and all-cause mortality (RR = 0.45; 95% CI (0.30, 0.68). Furthermore, use of TXA did not increase the risk of deep vein thrombosis (DVT) (RR = 0.64; 95% CI (0.38, 1.08), I^2=96%) and CVA (RR = 0.86; 95% CI (0.64, 1.16). Our results are consistent with the work of Dang et al [24] who included 11 articles in their review. To the best of our knowledge, the study by Dang et al is the only published meta-analysis that focused on the safety of TXA administration in high-risk patients. We found moderate evidence that the administration of TXA is safe in patients at high risk of thromboembolic events. Clinicians should weigh the benefits of reducing blood loss and transfusion rate against any theoretical increased risk of VTE events.

Hypersensitivity to TXA

Tranexamic acid (TXA) is a widely used antifibrinolytic drug, but allergy to TXA has been rarely reported. Although screening measures to detect allergic individuals are yet to be defined, there are protocols for the investigation of suspicious allergic reactions to TXA.[25] Tranexamic acid is responsible for a wide and various spectrum of allergic reactions including anaphylactic reactions, characterized by different pathogenetic mechanisms (immunologic and non-immunologic). TXA is a synthetic analogue of lysine, the amino acid responsible for IgE binding in many allergens. Although allergic reactions to TXA are rare, it is important to be aware of a

potential hypersensitivity, especially in patients with multidrug hypersensitivity. [26] TXA is contraindicated in patients with a history of hypersensitivity to tranexamic acid

Seizure

TXA may cause seizures, including focal and generalized seizures. The most common setting for tranexamic acid-induced seizures has been during cardiovascular surgery (a setting in which TXA is not FDA-approved and which uses doses of up to 10-fold higher than the recommended human dose) and in patients inadvertently given tranexamic acid into the neuraxial system. Risk factors for TXA-associated seizure include higher dose of TXA, female gender, age over 70 years, comorbidity (APACHE II index (Acute Physiology and Chronic Health Evaluation II) > 20, and renal dysfunction.[27] In a national database analysis among 918,918 patients undergoing TJA, Kirksey MA, et al demonstrated that in 45.9% (421,890) of patients who received TXA, the odds of perioperative seizure was not elevated, even in patients with known history of seizure. [21,28][29]. However, the limited quality of the data available means we are unable to recommend for or against use of TXA in patients with a history of seizure who are candidates for TJA. Clinicians must weigh the risk versus benefit of the use of TXA in this subset of patients.

Renal dysfunction

Renal impairment is not a contraindication for the use of TXA but dose adjustment needs to be considered. (Table 2). The main route of elimination of TXA is by glomerular filtration and more than 95% of the administered TXA is excreted in urine as an unmetabolized drug.

Serum Creatinine (mg/dL)	TXA Intravenous Dosage
1.36 to 2.83	10 mg/kg twice daily
2.83 to 5.66	10 mg/kg daily
>5.66	10 mg/kg every 48 hours or 5 mg/kg every 24 hours

Table 2. Recommended dose adjustment of TXA in patients with renal dysfunction [29]

Visual Disturbances

Visual disturbances (i.e., color vision defects) have not been reported in humans but are observed in animals at doses 1.6 to 22 times the recommended doses in humans. No retinal changes have been observed in eye examinations of patients treated with tranexamic acid for up to 8 years. Manufacturers recommend ophthalmologic monitoring for patients using TXA for more than 3 months. [29]

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Method

In this meta-analysis, a systematic literature search was conducted on PubMed/Medline; Web of Science; Embase; Scopus; and ClinicalTrials.gov. Keywords were selected based on relevant systematic reviews, free words, and Medical Subject Headings (MeSH). Besides, all relevant publications and reference lists were manually searched to identify potential studies. In addition, the key terms were reviewed and finalized by a panel of subject experts who were experienced in orthopedics. Search strategies for all databases are presented in supplementary file 1. Duplicated citations were removed using EndNote X9 software, and a manual revision was performed for verification.

Inclusion and exclusion criteria

Our inclusion criteria required studies to be randomized clinical trials, cohort, or case-control studies evaluating the use of tranexamic acid (TXA) and its association with several postoperative complications in high-risk patients undergoing total joint arthroplasty (TJA) surgeries compared to controls. Studies of other types such as editorials, letters to editors, reports, notes, short communications, and patents were excluded.

Study selection

Two researchers independently screened titles and abstracts of studies. They then independently selected the full text of studies from the first screening phase and reported the reasons for the exclusion of studies. Discrepancies between authors at any stage were resolved via consensus between the two researchers, and when this was not sufficient, they discussed the matter with a third researcher whose decision was finalized.

Data extraction

The following information was extracted: basic characteristics of the included studies (first author, publication year, country, study design), concomitant high-risk diseases, surgical type, and outcomes. Clinical outcomes were also recorded: deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular accident (CVA), acute kidney injury (AKI), and mortality with a specific focus on the criteria for thrombotic risk events. All extracted data were carefully entered into a predefined standardized EXCEL file. Discrepancies between authors were resolved via consensus between the two researchers, and when this was not sufficient, they discussed the matter with a third researcher (MAE) whose decision was finalized.

Statistical analysis

The relative risks (RR) with their 95% CIs were calculated for binary outcomes in all included studies. The resulting estimates were considered as effect size and together with their corresponding standard errors were retrieved for meta-analysis. Heterogeneity was evaluated using Cochrane's Q test and I^2. $P < 0.1$ or $I2 > 50\%$ indicate significant heterogeneity among included

studies. To account for between-study variance, a random-effects meta-analysis model was then applied to combine calculated effect sizes and their standard errors. Forest plots were used to represent individual and overall risk ratios. Additionally, Egger's test was employed to investigate potential publication bias. Significance levels were set at the 5 % level and all statistical analyses were carried out using R version 4.0.2.

Results

Literature search

Through the initial literature search in electronic databases, a total of 5174 articles were identified. After removing duplicate reports, the titles and abstracts of the remaining studies were assessed. Following the application of screening criteria and the exclusion of obviously irrelevant studies, the decision was made to include articles who studied TXA utilization in high-risk populations only. 18 articles were made for full-text review. Among those, two were systematic reviews, one published and one in progress. Ultimately,16 relevant studies were included (Table 1).

Study	Country	Study design	Comorbidities	Surgical procedures	Outcome
Porter SB, et al, 2021[8]	USA	Retrospective	Had≥1 DVT, PE, MI, Stroke, prothrombotic state (factor V Leiden, protein C deficiency, protein S deficiency, or antiphospholipid antibody syndrome), AF, a coronary artery bypass graft, or a coronary artery stent	THA/ HHA	DVT, PE, MI, CVA, Death
Zak SG, et al, 2021[9]	USA	Retrospective	CAD	THA/ TKA	DVT, MI
Tang S, et al, 2022[10]	West China	Retrospective cohort	AF	TJA	
Yen SH, et al, 2021[11]	Taiwan	Prospective randomized parallel	Aged 50 years or older with a preoperative Hb level of ≥11 g/dL and a history of thromboembolic disease, CVD (MI or angina, stroke), or risk factors related to VTE, such as old age (≥70 years), obesity (BMI≥ 25), a history of cancer, or varicose veins of the leg.	TKA	DVT, PE, Death
Joo YB, et al, 2022[12]		Retrospective	VTE, MI, CVOD, cancer	TKA	DVT
Richardson MK, et al, 2024[13]	USA	Cohort	VTE (DVT, PE)	TJA	DVT, PE. MI, CVA, AKI, Death
Hsu LI, et al, 2023[14]	Taiwan	Population-based	DVT, PE, MI, CKD, Arterial thromboembolism, Ischemic stroke in patient records ≤ 3 years before surgery	TKA	DVT, PE, MI, CVA, AKI, Death
Qiu J, et al, 2019[15]	China	Prospective Randomized Study	Patients who receive continuous aspirin for prevention of cardiovascular or CVD	THA	DVT, PE, MI, CVA, Death

Heller S, et al, 2016[16]	USA	Retrospective	Patients received chemoprophylaxis for 4 weeks against Venous Thromboembolic Prophylaxis	TJA	DVT, PE
Goh GS, et al, 2021[17]	USA	Retrospective	Coagulopathy	THA/ TKA	DVT, PE, MI, Death
Whiting DR, et al, 2014[18]	USA	Retrospective	Had≥ risk factors for thromboembolic (DVT, PE, MI, CVA, CABG, Prothombotic condition (Factor V Leiden deficiency, protein C deficiency, antiphospholipid syndrome, etc)	THA/ TKA	DVT,
Poeran J, et al, 2014[19]	USA	Retrospective cohort		THA/ TKA	DVT, PE, MI, CVA, AKI, Death
Porter SB, et al, 2020[20]	USA	Retrospective Case-Control	Had≥ DVT, PE, MI, CVA, a prothrombotic state (Factor V Leiden, protein C deficiency, protein S deficiency, or antiphospholipid antibody syndrome), AF, atrial flutter, coronary artery bypass graft, or coronary artery stent	THA/ TKA	DVT, PE, MI, CVA, Death
Poeran J, et al, 2021[21]	USA	Retrospective cohort	VTE, MI, seizures, or ischemic stroke/transient ischemic attack	THA/ TKA	DVT, PE, MI, CVA, AKI, Death
Sabbag OD, et al, 2017[22]	USA	Retrospective		THA/ TKA	DVT
Duncan CM, et al, 2015[23]	USA	Retrospective cohort	VTE	THA/ TKA	DVT, Death
Poeran J, et al, 2021[21]	USA	Retrospective cohort	History of renal disease	THA/ TKA	DVT, PE, MI, AKI, Death
Poeran J, et al, 2021[21]	USA	Retrospective cohort	History of AF	THA/ TKA	DVT, PE, MI, AKI, Death

Table 1: characteristics of included studies

Postoperative complications

In total, 16 various studies meeting our inclusion criteria were found. Postoperative complications encompass a variety of events such as deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular accident (CVA), acute kidney injury (AKI), and mortality in patients undergoing either THA or TKA. Our findings revealed a reduced risk of the aforementioned complications in TXA group. In particular, the risk of DVT (RR = 0.64; 95% CI (0.38, 1.08)), PE (RR = 0.80; 95% CI (0.68, 0.95)), MI (RR = 0.59; 95% CI (0.44, 0.79)), AKI (RR = 0.76; 95% CI (0.63, 0.92)) and mortality (RR = 0.45; 95% CI (0.30, 0.68)) was significantly decreased in the TXA group. Although our results suggest a lower risk of CVA for the TXA group, the estimated pooled RR was not statistically significant (RR = 0.86; 95% CI (0.64, 1.16)). More

detailed results for outcomes of interest are shown in Figures 1-6. The results of Egger's test suggest that there is no significant publication bias for different outcomes with the exception of MI (P = 0.0174).

Deep venous thrombosis

16 studies reported on the presence of DVT. 2494 patients were reported to have DVT in the TXA group, whereas 7641 patients in the control group had DVT. TXA administration was associated with significantly less DVT than controls (RR = 0.64; 95% CI (0.38, 1.08), I^2=96%) (Fig. 1)

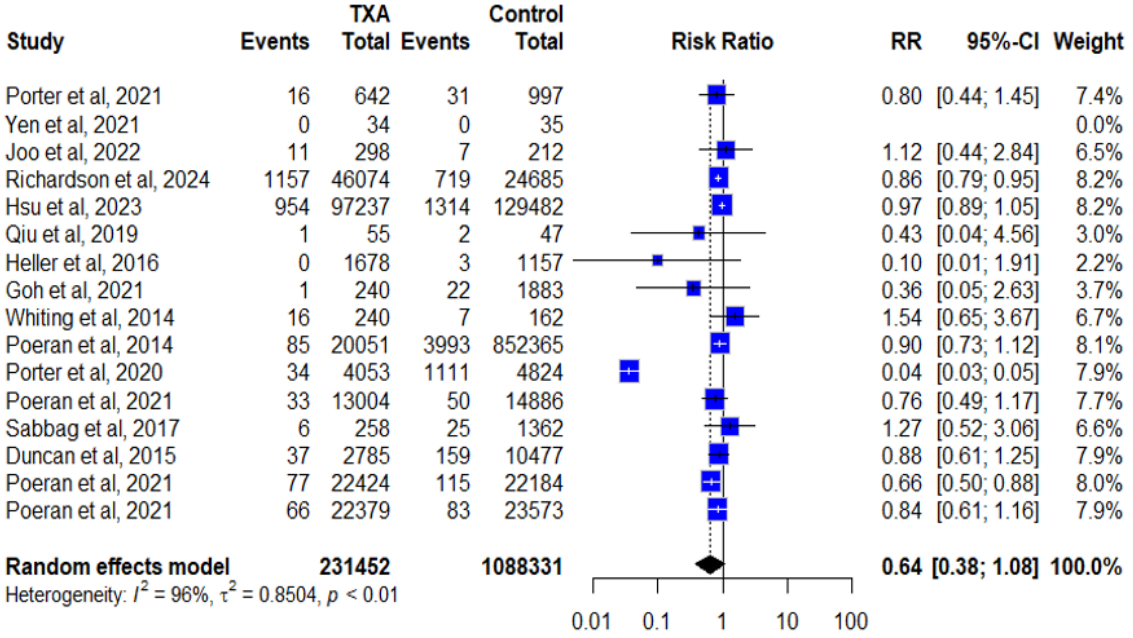

Fig.1 Association between TXA use and DVT

Pulmonary embolism

12 studies reported PE rates. In total, 1133 patients were reported to have an incidence of PE, whereas 4177 patients in the control group had an incidence of PE. There was a significant difference between TXA and placebo groups in the occurrence of PE (RR = 0.80; 95% CI (0.68, 0.95); I^2=56%); (Fig. 2).

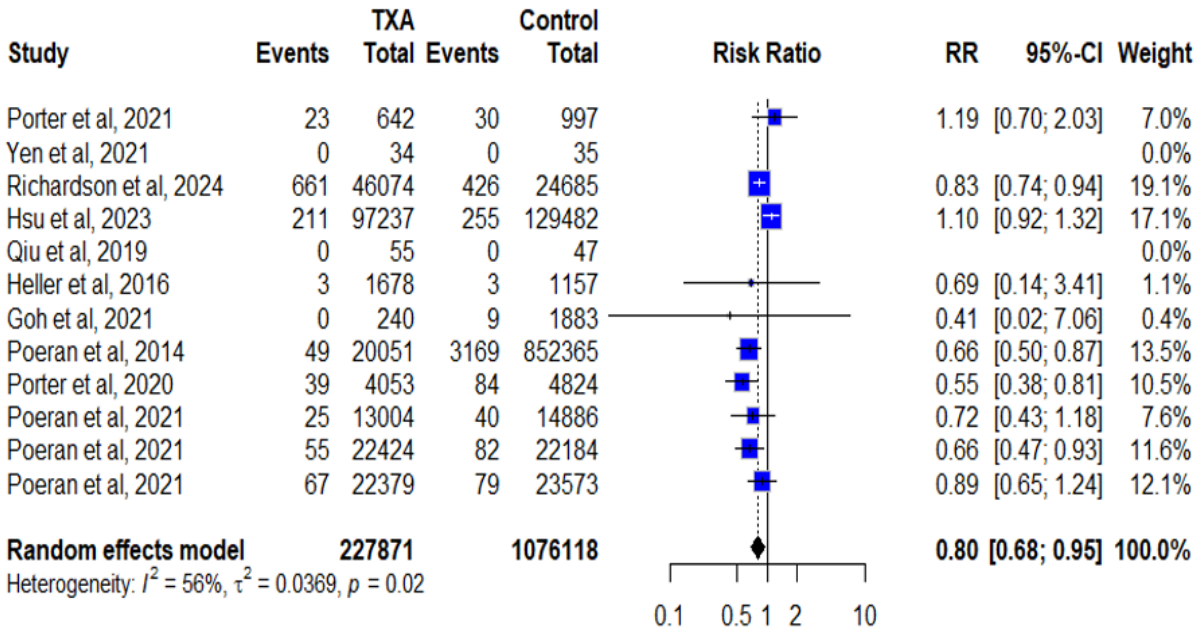

Fig.2 Association between TXA use and PE

Myocardial infarction

Ten studies reported the rate of MI. There were 621 MIs in the TXA group compared to 2987 in the control group. We found a significantly reduced risk of MI in the TXA users than in nonusers (RR = 0.59; 95% CI (0.44, 0.79); I^2=87%)(Fig.3)

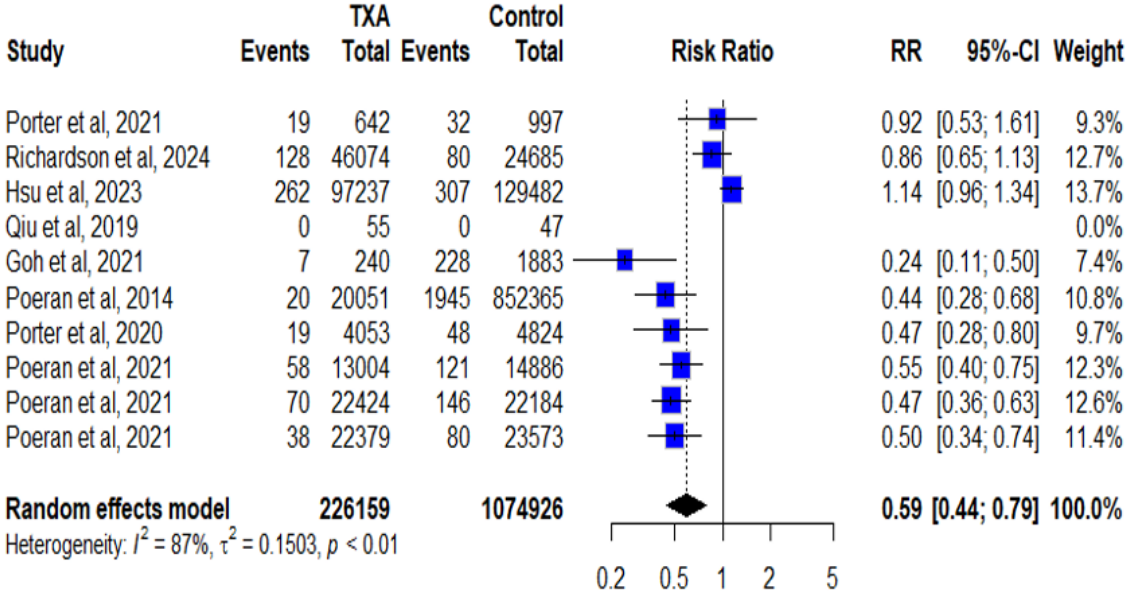

Fig. 3 Association between TXA use and MI

Cerebrovascular accident

CVD rate was mentioned in seven studies. In total, 1582 stroke events were in the TXA group compared to 2820 in the control group. We found no significant difference in the risk of CVD between two groups (RR = 0.86; 95% CI (0.64, 1.16) (Fig.4)

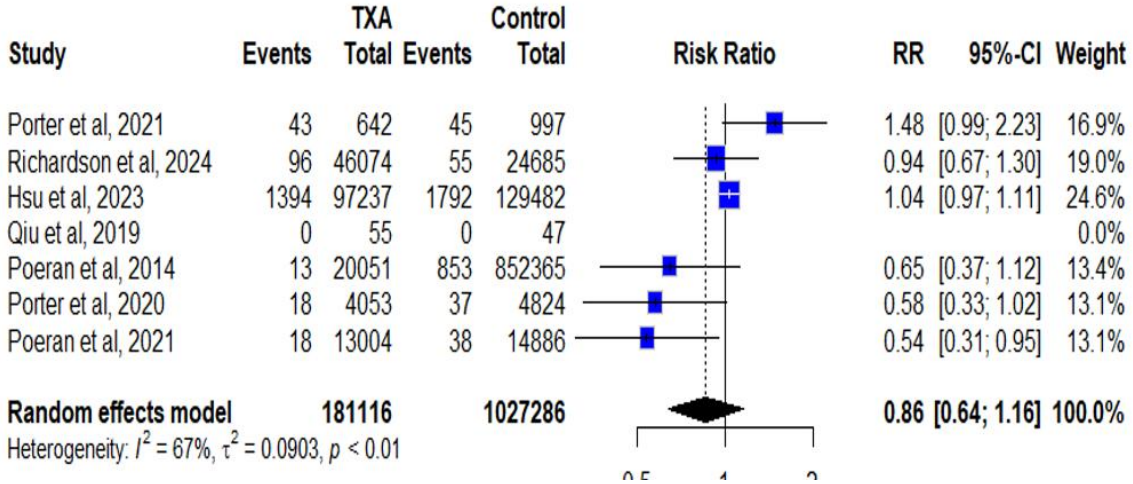

Fig. 4 Association between TXA use and CVA

Acute kidney injury

Six studies provided available data concerning AKI. The pooled analysis enlightened that the TXA group had a significantly lower AKI than the control group (RR = 0.76; 95% CI (0.63, 0.92), I^2=98%) (Fig.5).

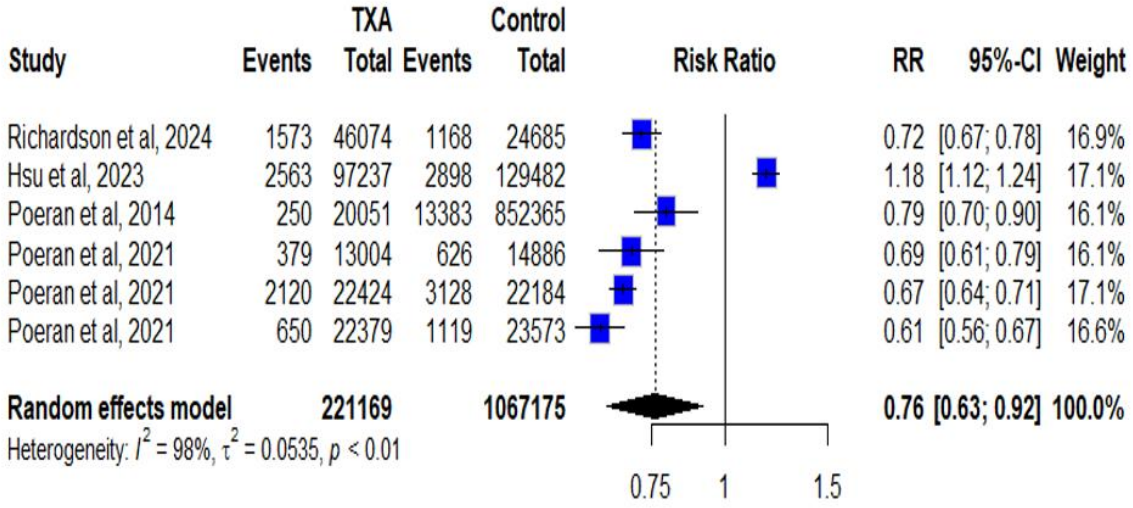

Fig. 5 Association between TXA use and AKI

Mortality

12 studies reported death events occurring postoperatively. There were 248 deaths in the TXA group compared to 1201 in the control group. The meta-analysis results showed a significant difference in the mortality risk between the two groups (RR = 0.45; 95% CI (0.30, 0.68)) (Fig. 6).

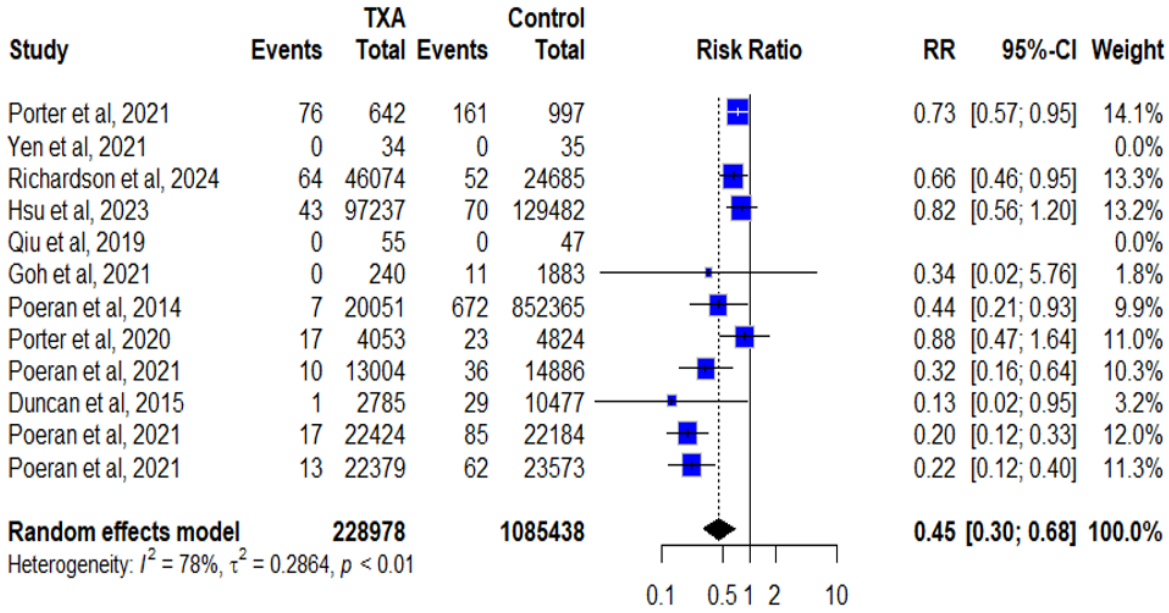

Fig. 6 Association between TXA use and mortality