Tranexamic acid for reduction of perioperative blood loss in major abdominal surgery

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Abstract

Blood loss and transfusion requirements during major abdominal operations are two of the key factors in determining perioperative outcomes. Tranexamic acid (TXA) has been known to reduce hemorrhage in many different surgical fields through its antifibrinolytic qualities.

Objectives

To assess the effectiveness and safety of TXA for reducing blood loss and transfusion requirements in major abdominal surgery.

Methods

An electronic database search of PubMed and Cochrane Library was conducted, to identify all studies published between database inception and July 2021.

All studies in major abdominal surgery, where TXA has been used to reduce blood loss or transfusion requirements were included, if they met predefined inclusion criteria.

Two independent reviewers screened trials for inclusion. Data collection was performed using a standardized data collection form. The primary outcomes assessed were perioperative blood loss and blood transfusion requirements. Secondary outcomes of interest were mortality, thromboembolic and other adverse events, operating time, hospital and ICU length of stay. Data was analyzed using the RevMan 5.4 software applying random-effects models. Quality of evidence was assessed using GRADE. Risk of bias (RoB) was assessed according to the RoB2-tool by Cochrane Collaboration.

Main results

Nineteen trials involving a total of 3.087 patients were included with an overall moderate RoB. Sample sizes varied from 18 to 734 patients. The number of patients requiring RBC transfusions *(MD 0.67; 95% CI 0.48 to 0.92)* as well as the required units of RBC *(MD -1.73; 95% CI -3.05 to -0.41)* and FFP *(MD -1.90; 95% CI -3.58 to -0.22)* were significantly lower in TXA versus control group. Differences in volume of perioperative blood loss, platelet or cryoprecipitate transfusions and all secondary outcomes were not significant.

Authors' conclusions

The present analyses support the administration of TXA in major abdominal surgery to reduce intraoperative blood loss and transfusion requirements. The results do not show an increase of thromboembolic events or other serious adverse events. However, given the moderate quality of evidence, these findings need to be further confirmed in adequately powered, well-designed randomized controlled trials.

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Referat

Blutverlust und Transfusionsbedürftigkeit beeinflussen maßgeblich die perioperativen Ergebnisse abdominalchirurgischer Interventionen. Tranexamsäure (TXA) wird bereits in vielen chirurgischen Disziplinen erfolgreich zur Reduktion hämorrhagischer Ereignisse eingesetzt. Diese Meta-Analyse dient der Untersuchung, inwieweit sie auch in der Abdominalchirurgie effektiv und sicher zu diesem Zweck eingesetzt werden kann.

Die elektronischen Datenbanken PubMed und Cochrane wurden nach bis Juli 2021 veröffentlichten Studien durchsucht und entsprechend vordefinierter Einschlusskriterien zur Inklusion ausgewählt. Anhand eines vorgefertigten Datenerfassungsformulars erfolgte die Sammlung der Ergebnisse. Die betrachteten Endpunkte waren primär: perioperativer Blutverlust und Transfusionsbedürftigkeit sowie sekundär: Mortalität, Thromboembolismus, andere unerwünschte Ereignisse, Operationszeit, Krankenhaus- und Intensiv-Liegedauer. Die Datenalyse erfolgte mit der RevMan 5.4 Software unter Anwendung des random-effects Modells. Zur Evidenzbewertung wurde GRADE, zur Bewertung des Risk of Bias (RoB) das RoB2-tool der Cochrane Collaboration verwendet.

Es konnten neunzehn Studien mit 3087 Patienten und einem moderaten RoB in die Meta-Analyse eingeschlossen werden. Die Stichprobengrößen variierten zwischen 18 und 734 Patienten. Unter Einsatz von TXA zeigte sich eine signifikante Reduktion der Erythrozytenkonzentrat (EK) bedürftigen Patienten *(MD 0.67; 95% CI 0.48 to 0.92)*, sowie der benötigten Mengen an EKs *(MD -1.73; 95% CI -3.05 to -0.41)* und FFPs *(MD -1.90; 95% CI -3.58 to -0.22)*. Weitere signifikante Unterschiede bezüglich der primären und sekundären Endpunkte konnten nicht nachgewiesen werden.
Somit unterstützen die Ergebnisse die Annahme, TXA könnte auch in der Abdominalchirurgie effektiv zur Reduktion von Blutverlust und Transfusionsbedürftigkeit angewendet werden, ohne dabei Hinweise auf eine Zunahme an thromboembolischen oder anderen unerwünschten Nebenwirkungen zu liefern.
Dennoch ist es in Anbetracht der moderaten Studienqualität notwendig, diese Ergebnisse durch weitere groß-angelegte klinische Studien zu verifzieren.

Schweitzer, Ann-Cathrin: Tranexamic acid for reduction of perioperative blood loss in major abdominal surgery, Halle (Saale), Univ., Med. Fak., Diss., 68 Seiten, 2025

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Declarations

List of Abbreviations

TXA = tranexamic acid

PRBC = packed red blood cells

RBC = red blood cells

FFP = fresh frozen plasma

TE = thromboembolic events

AE = adverse events

GCS = Glasgow Coma Scale

ESA = European

WHO = World Health Organisation

RoB = Risk of Bias

RoB2 = Risk of Bias Tool 2

tPA = tissue plasminogen activator

Dpt. = Department

RevMan 5.4. = Review Manager version 5.4.

OLT = orthotopic liver transplantation

ESLD = end stage liver disease

AP = aprotinin

EACA = epsilon-aminocapriotic-acid

CRLM = colorectal liver metastases

CRS = colorectal surgery

BCS = Budd-Chiari-Syndrome

ALF = acute liver failure

pFAP = primary familial amyloidotic polyneuropathy

CS = charbazocrome sodium sulfonate

PH = pulmonary hypertension

GIB = gastrointestinal bleeding

RCT = randomized controlled trial

Background

Description of the condition

In surgery, perioperative blood loss and consecutive transfusion requirements are a common source of short- and long-term complications, prolonged hospital stay and follow-up interventions. This also implies a high socioeconomic burden. Abdominal operations make up for a large proportion of all surgical procedures worldwide [Deutsches Statistisches Bundesamt]. Blood loss is a common problem in major abdominal surgery and it is of high importance to reduce it to a minimum.

Description of the intervention

Several options to reduce blood loss and transfusion requirements in surgery have been found effective over the last decades. In many different fields of surgery, TXA showed promising effects to achieve hemostasis and reduce perioperative blood loss. In surgery, the drug is usually applied intravenously, and application modes vary between single or repetitive boli and continuous infusion.

How the intervention might work

Mechanism of Action

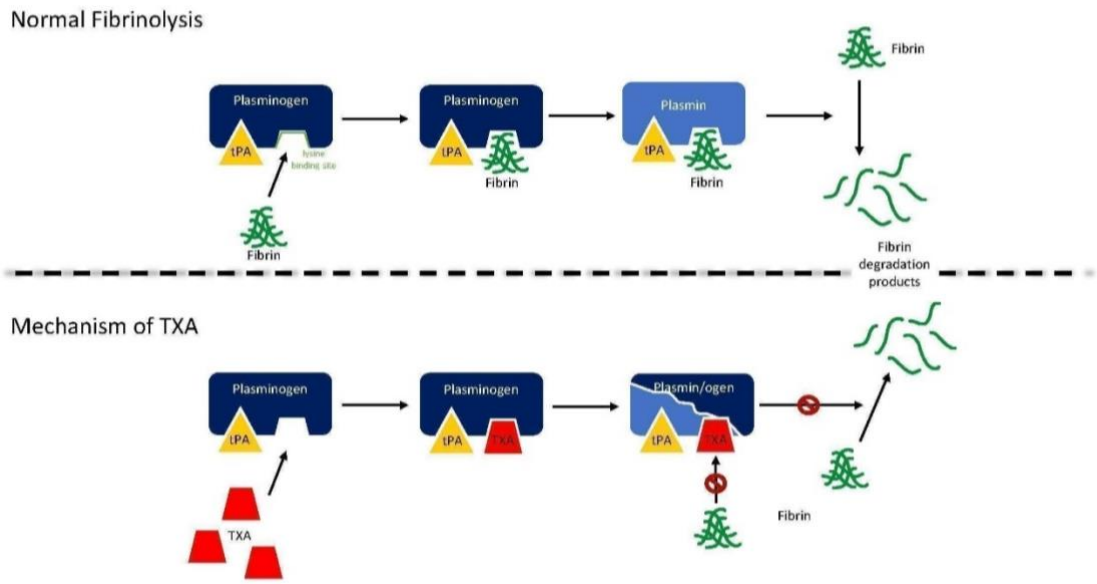
Tranexamic acid is a synthetic analogue to the amino acid lysine, which acts as an antifibrinolytic agent.

The fibrinolytic system is influenced by the interaction of various cofactors, activators, inhibitors and receptors. The initiation of fibrinolysis is commonly caused by damaged endothelial cells releasing tissue-Plasminogen Activator (tPA). In combination with tPA, plasminogen is able to bind fibrin at lysine binding sites forming a complex that leads to the activation of plasminogen to plasmin. After activation plasmin degrades fibrin and thereby leads to clot solution and bleeding.

TXA has a high affinity to the lysine binding sites on plasminogen. In its presence the binding sites for fibrin are blocked, preventing the activation of plasminogen to plasmin. If conversion into plasmin in the presence of a plasminogen activator like *tPA* is still possible, bound tranexamic acid makes interaction with and digestion of fibrin impossible. Therefore, it ultimately reduces fibrinolysis, stabilizes the fibrin-rich clot and reduces bleeding. [McCormack 2012]

An illustration of the mechanism of Action of tranexamic acid can be found in Figure 1.

Figure 1: Mechanism of Action



Why it is important to do this review

Why TXA in abdominal surgery?

Statistics of the “Paul-Ehrlich-Institut” show a decrease in transfused blood products of about 26% in Germany since 2011. Nevertheless, Germany still exceeds the international comparison. Data from 2013 showed that transfusion rates in Germany with 54.6 units per 1.000 have been higher than in any other developed country, taking the UK with 35.3 units as an example. [Carson 2017] Germany surpasses the other European countries also regarding the amount of transfusions during operations, as lately stated by the “BARMER Krankenhausreport 2019”. [Barmer Krankenhausreport 2019]

With the number of blood donations constantly decreasing over the last few years especially since the beginning of the global Covid-19 pandemic [Chiem 2021], it becomes more and more crucial to reduce the number of blood transfusions to the indispensable amount needed. This is even more the case since due to demographic transition the number of elderly in possible need of transfusion is constantly increasing, while the number of 18–65-year-old people suitable for donation is declining.

Not only are we facing a shortage of blood products if this progression continues, but also a high socioeconomic burden because of costs for the healthcare system. In Germany, the direct cost for the transfusion of one unit of packed red blood cells (PRBC) is estimated at 147.43 Euro. [Kleinerüschkamp 2016] Substantial additional indirect costs can be caused by negative effects following the transfusion - immediate effects such as hemolysis, allergic reaction, volume and potassium overload and long-term effects such as alloimmunization and immunomodulation.

Transfusion of red blood cells has been shown to cause nosocomial infection, mortality and be associated with prolonged length of stay (in ICU and hospital) regardless of the population observed being nonoperative or postoperative. [Taylor 2006]

Besides, transfusion-related acute lung injury is a severe complication. It is generally considered a rare event (incidence: 0.008 per 100 units of plasma transfused; 0.004 per 100 of all products transfused), known to be underreported. Nevertheless, TRALI remains the leading cause of transfusion-related mortality (up to 37%) [Meyer 2018]. With the therapeutic management being limited to supportive measures until the lung injury spontaneously resolves, reduction of RBC-transfusion whenever possible is the best way of prevention. [Bueter 2006]

In major abdominal surgery, intra- and postoperative bleeding constitute a noteworthy problem, often leading to acute anemia and the necessity of blood transfusions. According to "Deutsches Statistisches Bundesamt", in 2019, about 60.000 major abdominal operations (esophagectomies, gastrectomies, hepatectomies, colectomies, rectal and pancreatic resections) were carried out in Germany.

It is estimated that in around 30% of major abdominal surgeries, intra- and postoperative transfusions are required. [McCormack 2012] This means that annually about 18.000 patients in Germany could be facing negative short- and long-term outcomes associated with perioperative transfusion.

A study published in February 2018 found an independent association with worse short-term outcomes such as increased morbidity and mortality as well as a prolonged hospital stay in patients undergoing hepatectomy. [Hallet 2015] Furthermore, a study has shown negative effects on long-term outcomes after hepatectomy for colorectal liver metastases. Recurrence-free an overall survival were significantly decreased after transfusion.[Hallet, Tsang 2015] [Schiergens 2015] A systematic review and meta-analysis on patients undergoing common *curative-intent* pancreatic surgery associated receiving perioperative blood transfusion with a significantly lower 5-year survival rate. [Mavros 2015]

These observations emphasize the importance of reducing perioperative blood loss and need of PRBC-transfusion in abdominal surgery.

The cost of TXA is estimated at around 10-20 € per administration. While there is additional indirect cost such as laboratory and material expenses the overall savings could be socioeconomically highly beneficial. Blood loss and transfusion rates in abdominal surgery could be reduced and morbidity, length of hospital stay and cost positively influenced.

Efficacy in other major fields of surgery

The efficacy of TXA has already been studied in a wide variety of other major surgical disciplines associated with high blood loss. Plenty of evidence regarding orthopedic, cardiac, urological and gynecological surgery has been collected over the years.

TXA is a very important agent for the treatment of postpartum hemorrhage, as proven by the Woman Trial in 2017 [WOMAN-trial]. Furthermore, its administration reduces the risk of death in trauma-associated hemorrhage [CRASH-2] and increases the probability of successful treatment of traumatic brain injury, meaning a substantial reduction of mortality in mild and moderate head injuries [CRASH-3]

TXA also reduces the risk of transfusion and reoperation for hemorrhage in adult patients undergoing heart surgery without increased risk of death or thrombosis. [Relke 2021] It has become the standard antifibrinolytic in cardiovascular surgery, officially being recommended by the ESA guidelines. [ESA guidelines]

Administration of TXA is also recommended by the ESA for major orthopedic surgery, in specific total hip and knee endoprostheses and major spine surgery. Multiple studies in this area have proven the efficacy in reducing perioperative blood loss, allogenic blood transfusions and mortality without an increase in severe adverse effects like thrombosis in patients undergoing these types of surgery. [Pabinger 2017]

Since first being discovered in 1962 and being added to the WHO's list of essential medicines in 2011, TXA has long become a standard in many types of major surgery. Due to the high efficacy and favorable safety profile, routine use of TXA in patients undergoing major abdominal surgery could also be highly beneficial.

Why is it important to do this systematic review and meta-analysis?

Considering the aforementioned developments in surgery, blood loss and blood transfusion requirements, it is of major importance to reduce perioperative blood loss to a minimum by any means possible. TXA has already proven to be efficient in many different types of surgery. Whereas there are several potential risks attributed to its application like seizures, thromboembolic events, allergic reactions, gastrointestinal reactions (nausea, emesis, diarrhea) and visual impairments; many reviews have shown that the benefits of reduced risk of hemorrhage with reduction of blood loss, transfusion requirements and perioperative morbidity and mortality often outweigh the risks.

So far, none of the conducted systematic reviews and meta-analyses about TXA-administration in surgery address major abdominal surgery. With the importance of this discipline and the high possibility of blood loss and blood transfusions, the effects of TXA could prove highly beneficial. Therefore, it is of great importance to do this systematic review and meta-analysis as it could lead to improvements in patient blood management, operative outcomes as well as socioeconomic aspects of abdominal surgery.

Objectives

To determine the benefits and harms of the administration of TXA in patients undergoing major abdominal surgery.

Methods

Criteria for considering studies for this review

Types of studies

All studies with no limitations regarding study design, i.e., randomized controlled trials and non-randomized studies, were considered. Inclusion was taking place irrespective of blinding, publication status or sample size. Abstract and full text of the study had to be available in English or German.

Types of participants

Patients undergoing major abdominal surgery, defined as hepatectomy, esophagectomy, gastrectomy, colectomy, rectal or pancreatic resection. There were no restrictions regarding surgical access, surgery method, comorbidities, co-interventions or co-medication.

Types of interventions

All studies including at least one group of patients being treated with TXA were defined as eligible. Thus, one-armed studies with a single intervention group and trials comparing the intervention group to at least one group being treated with placebo, no intervention or another antifibrinolytic agent instead, were eligible.

Perioperative application of tranexamic acid had to be performed intravenously. There was no restriction regarding dosing or time of application. Single-bolus-infusion, repetitive intravenous boli as well as continuous intravenous infusion are possible.

Co-interventions, meaning the additional application of other drugs, were allowed if carried out equally throughout the trial groups. These included heparin for DVT-prophylaxis, ranitidine for prophylaxis of allergic reactions, as well as prednisolone and desmopressin; to name a few.

Types of outcome measures

Primary outcomes

1. perioperative blood loss
2. perioperative transfusion requirements
    a. whole blood/packed red blood cell transfusion
        i. number of patients
        ii. number of units/volume per patient
    b. FFP
    c. Platelets
    d. cryoprecipitate

Secondary outcomes

1. thromboembolic events
2. seizures
3. other adverse events
4. perioperative mortality
5. Operating time
6. Length of ICU & hospital stay

Search methods for identification of studies

Using their respective online search engines, the electronic databases PubMed and Cochrane Library were searched using a defined search strategy. The search was performed on all studies published between database inception and the cut-off date **July 22, 2021**.

Data collection and analysis

Selection of studies

The title and abstract of studies identified by the database search were screened by two independent reviewers to identify whether they meet the inclusion criteria. If a final assessment was not possible based on the abstract alone the full text of the publication was assessed. A study was included or excluded if both reviewers unanimously decided. When no agreement between the two independent reviewers could be reached, a third independent reviewer was involved as arbiter. The selection process is displayed in a PRISMA flow diagram (Figure 2).

Data extraction and management

The selected studies were transferred into the software RevMan 5.4.1. To document the extracted study characteristics and outcome data a standardized data collection form was used. The form was piloted on one study in the review. The following study characteristics and defined variables were independently collected by one review author.

- General information on the publication: title, authors, date of publication, status of publication, journal in which the article was published, language of publication, funding of the study.
- Study design and information regarding sample size, randomization, blinding and methodology
- Type of surgery performed.
- patient characteristics: sex, age, underlying disease for which surgery was performed
- dose regimen and timing of tranexamic acid administration
- length of follow-up

        - perioperative blood loss (as reported by the single studies) and blood transfusion requirement (yes/no, number and volume of transfused units)
        - thromboembolic events
        - seizures, other adverse events
        - mortality
        - operating time
        - length of ICU stay
        - length of hospital stay

Assessment of risk of bias in included studies

The risk of bias for each individual study was assessed according to the study design using the respective risk of bias tool developed by the Cochrane Collaboration.

The following domains of bias were considered:

- pre-intervention domains
    - bias due to confounding
    - bias in selection of participants into the study
        - sequence generation
        - allocation concealment
    - performance bias
        - blinding of participants, personnel and outcome assessors
- at-intervention domains
    - bias in classification of interventions
    - bias due to deviations from intended interventions
- post-intervention domains
    - bias due to missing data/incomplete outcome data
    - bias in measurement of the outcome
    - bias in selection of reported result/selective outcome reporting
- other bias
    - baseline imbalance
    - early stopping
    - academic bias (perceived bias, where beliefs influence the research)
    - source of funding bias

For randomized trials the risk of bias was calculated considering the following domains of bias:

- bias arising from the randomization process;
- bias due to deviations from intended interventions;
- bias due to missing outcome data;

- bias in measurement of the outcome;
- bias in selection of the reported result.

To assess the risk of bias for each domain the tool comprised a series of 'signaling questions' to be answered with "yes"| "probably yes"| "probably no"| "no"| "no information". Based on the responses a risk-of-bias judgement for each single-domain was made and one of the three levels "low", "some concerns" or "high" was assigned. An overall judgement for the risk of bias has been ascertained from the risk of bias of the single domains according to table 1:

Overall risk-of-bias judgement	**Criteria**
Low risk of bias	The trial is judged to be at *low risk of bias* for the domains selection, detection and performance bias for this result.
Some concerns	The trial is judged to raise *some concerns* in at least one of the aforementioned domains for this result, but not to be at high risk of bias for any domain.
High risk of bias	The trial is judged to be at *high risk of bias* in at least one of the aforementioned domains for this result. **or** The trial is judged to have *some concerns* for *multiple domains* in a way that substantially lowers confidence in the result.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as risk ratio (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data, we used the mean difference if outcome measurements were assessed on the same scale in all studies and standardized mean difference (SMD) if the same outcome was measured by different tools throughout the studies.

Dealing with missing data

We attempted to contact the study investigators in order to request further information in case of missing data.

For study protocols only providing median, range and sample size, we used the method introduced by Hozo to estimate the mean and standard deviation in order to pool data [Hozo 2005].

Assessment of heterogeneity

To measure heterogeneity among studies included in the analyses, the Chi²-test and the I² statistics were used. Heterogeneity was considered substantial if the p-value was <0.10 or if the Chi² statistic (relative to its degree of freedom) is large.

Heterogeneity according to I² values was classified using the subsequent intervals:

I²-value	**0-40%**	**30-60%**	**50-90%**	**70-100%**
Degree of heterogeneity	unimportant	*Moderate*	*Substantial*	*Considerable*

Data synthesis

The statistical analysis was carried out using the software RevMan 5.4.1

Subgroup analysis and investigation of heterogeneity

We performed a random-effects meta-analysis to address for unaccounted between-study heterogeneity.

Two groups of comparisons were carried out in this review. The main comparison was TXA versus inactive control group. These inactive control groups were divided into a placebo and a no intervention group. Additionally, TXA was compared to other antifibrinolytic agents, more specifically Aprotinin and EACA. The subgroup analyses were conducted only for the main comparison of TXA versus inactive control.

The following subgroup analyses were performed:

1. type of surgery (OLT vs. hepatectomy vs. other procedures)
2. intervention characteristics/dosing regimen:
    a. application interval b. low-dose vs. high-dose
3. low-risk of bias vs. high-risk of bias = sensitivity analysis

All primary and secondary outcomes have been included in the subgroup analyses, to detect any potential associations, especially regarding the incidence of TE.

The assessments have been carried out using the interaction tests available in RevMan both within subgroups of studies and across studies irrespective of the subgroups. The results have been reported by quoting the Chi² statistic and p-value, as well as the I² value following the aforementioned thresholds for significance.

Sensitivity analysis

To determine the effect of several aspects of the included studies that may have affected the results of the review a sensitivity analysis has been performed. These aspects included effects of random effects analyzes for outcomes with statistical heterogeneity and the risk of bias associated to single trials. Therefore, a comparison of high- versus low-risk of bias studies has been carried out for all primary and secondary outcomes of the main comparison (TXA vs. inactive control).

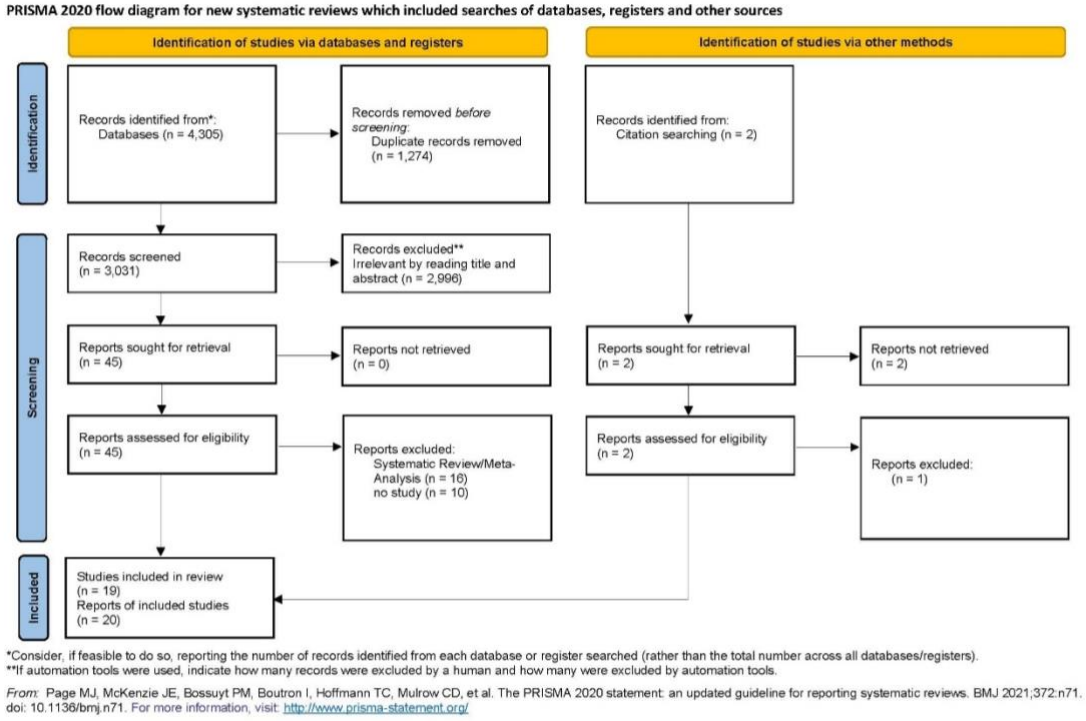
Results

Description of studies

Results of the search

Through the electronic searches of the databases PubMed and Cochrane library, we identified 4.305 references. After duplicate removal, 3.031 records remained to be screened. After reading title and abstract, 2.996 references were considered as clearly irrelevant and therefore excluded. 45 reports were sought for retrieval. After further assessing eligibility, 19 references remained to be included in the review. One additional reference was identified by scanning the reference list of the identified studies. The study identification process is shown in the PRISMA flow chart in Figure 2.

Figure 2: PRISMA flow diagram



Included studies

19 trials including 20 protocols were included. During the literature review, references to three ongoing studies were identified, that fit the eligibility criteria but could not yet be included because data collection and publication had not been finished. Twelve of the nineteen included studies were prospective randomized controlled trials while the remaining seven were non-randomized studies, either retrospective or prospective and often including historical controls.

Five of the trials had three arms and provided data for three comparisons, with one arm of each trial being a control group. Three of them included two eligible intervention groups, the other two included one eligible intervention group and one group treated with

other antifibrinolytics. One trial had four arms, with two eligible intervention groups, one treated with another antifibrinolytic and one control group. The remaining thirteen trials provided data for one comparison. Two of those compared an eligible intervention with another antifibrinolytic agent and one of them compared two groups of the same intervention with different patient characteristics and therefore could not be included in the primary analyses (Costa 2013).

A sensitivity analysis was carried out to separately address randomized and non-randomized trials. The characteristics of the included studies are shown in the 'Characteristics of included studies'-table. All trials included patients undergoing major abdominal surgery, mostly hepatobiliary (9 OLT, 1 hepatectomy), but also oncosurgical (3), colorectal (1), gastric (1) and major abdominal (3) procedures. The intervention of interest was TXA administered intravenously irrespectively of the dosage or application interval used. The doses used in the individual studies were highly variable, ranging from 10 mg/kg*h to 40 mg/kg*h continuously infused tranexamic acid and single or repetitive boli of 1g of TXA. Individual doses are shown in Table 1.

There were thirteen two-armed studies. The inactive controls varied between the trials: four used placebo (Boylan 1996; Kaspar 1997; Wu 2006; Wright 2020), three no intervention (Hamada 1995; Pfizer 2012; Chakravartty 2016) and two compared TXA with Aprotinin (Dalmau 2004; Massicotte 2011). In two studies, a historical control cohort (Grass 2019) was used, one of them using retrospective data in the intervention group as well (Jaffer 2021).

Six studies had three or more groups. Three trials included two negative controls comparing TXA either to the use of EACA and placebo (Dalmau 2000), Aprotinin and a historical cohort (Ickx 2006) or Aprotinin and no intervention (Devi 2008). One of them included a second intervention-group with TXA (Devi 2008). The remaining three studies each compared two different dosing regimens of TXA. One of them used normal saline as control (Prasad 2018) while the other two used no intervention as control (Karanicolas 2016; Badenoch 2017).

The proportion of females ranged from 27% to 80%. All but one study included only adult patients, the average age therefore ranging between 37 years and 65 years.

Excluded studies

Three studies identified in the primary search had to be excluded due to different reasons. For two of them the full text was not available (Ickx 1996; Yassen 1993), whereas the third study did not provide the observed data in a form compatible for inclusion in the analysis (Alhomoud 2016). Efforts to obtain the missing data were made but remained unsuccessful.

Risk of bias in included studies

The risk of bias is summarized in Figure 3 and Figure 4.

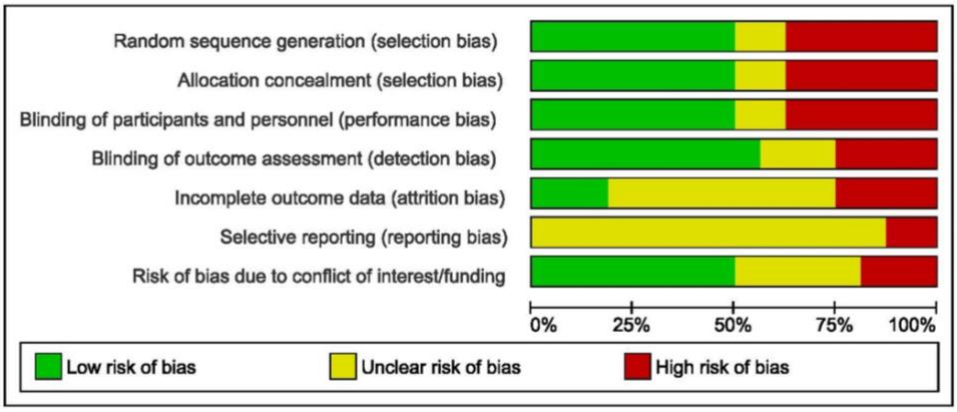


Figure 3: Risk of Bias graph

Tranexamic Acid versus Control

Fifteen trials were included under this comparison (Badenoch 2017; Boylan 1996; Chakravartty 2016; Dalmau 2000; Devi 2008; Grass 2019; Hamada 1995; Ickx 2006; Jaffer 2021; Karanicolas 2016; Kaspar 1997; Pfizer 2012; Prasad 2018; Wright 2020; Wu 2006).

Eight trials showed an overall low risk of bias (Boylan 1996; Dalmau 2000; Hamada 1995; Kaspar 1997; Pfizer 2012; Prasad 2018; Wright 2020; Wu 2006); seven trials were of high (Badenoch 2017; Chakravartty 2016; Devi 2008; Grass 2019; Ickx 2006; Jaffer 2021; Karanicolas 2016) risk of bias.

Tranexamic Acid versus Aprotinin

Four trials were included under this comparison (Dalmau 2004; Devi 2008; Ickx 2006; Massicotte 2011).

One trial was of low risk of bias (Dalmau 2004), three trials were of high risk of bias (Devi 2008; Ickx 2006; Massicotte 2011).

Tranexamic Acid versus EACA

One trial was included under this comparison (Dalmau 2000).

This trial showed an overall low risk of bias.

Allocation (selection bias)

See figure 3 and 4.

Blinding (performance and detection bias)

See figure 3 and 4.

Incomplete outcome data (attrition bias)

See figure 3 and 4.

Selective reporting (reporting bias)

See figure 3 and 4.

Other potential sources of bias

See figure 3 and 4.

To determine the risk of bias throughout the included studies several potential sources of bias have been individually addressed for each study. The risk of bias summary shows the results for each study individually, whereas the risk of bias graph gives an overview for all the studies included in the meta-analysis.

Overall, 50 % or more of the included studies showed a low risk of bias for selection, performance, detection and conflict of interest. Due to lack of information most studies had to be categorized as of unclear risk of bias for attrition and reporting bias.

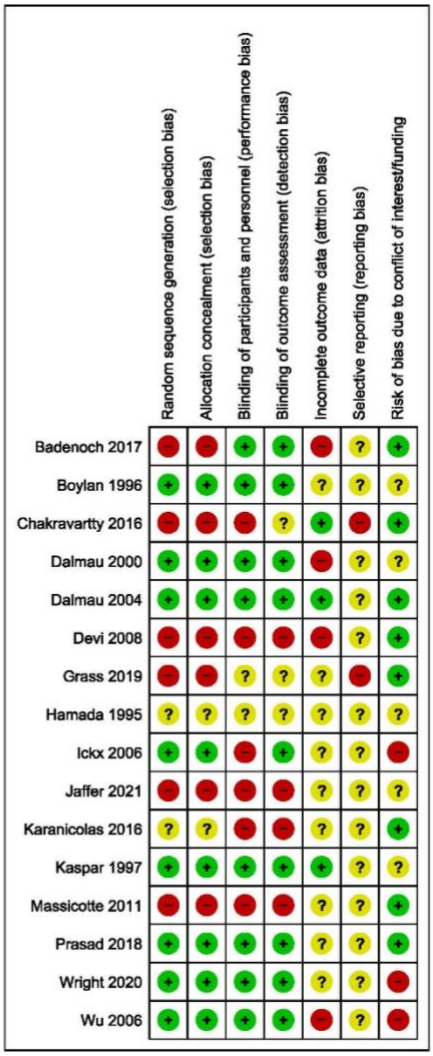


Figure 4: Risk of Bias graph

Effects of interventions

The main results are presented in the Summary of Findings Tables.

TXA versus inactive control (placebo or no intervention)

Fifteen studies were included in this comparison. Ten of them were randomized controlled trials (Hamada 1995; Boylan 1996; Kaspar 1997; Dalmau 2000; Ickx 2006; Wu 2006; Pfizer 2012; Chakravartty 2016; Prasad 2018; Wright 2020) while the remaining five were non randomized studies (Devi 2008; Karanicolas 2016; Badenoch 2017; Grass 2019; Jaffer 2021).

Nine of the included studies were of low risk and seven of high risk of bias. The trials were included for the outcomes they reported.

Subset analyses:

Fifteen studies were included in this comparison. Ten of them were randomized controlled trials (Hamada 1995; Boylan 1996; Kaspar 1997; Dalmau 2000; Ickx 2006; Wu 2006; Pfizer 2012; Chakravartty 2016; Prasad 2018; Wright 2020) while the remaining

five were non-randomized studies (Devi 2008; Karanicolas 2016; Badenoch 2017; Grass 2019; Jaffer 2021)

Nine studies were of low risk and seven of high risk of bias. Two of them provided information on different dosing regimen, therefore the results were included separately for each group (Karanicolas 2016; Prasad 2018).

TXA: different application intervals

We introduced four subgroups into the comparison: single bolus (Chakravartty 2016; Hamada 1995; Prasad 2018; Wright 2020) - single bolus with continuous infusion (Ickx 2006; Jaffer 2021; Karanicolas 2016; Prasad 2018) - repetitive boli (Devi 2008; Pfizer 2012; Wu 2006; Grass 2019) - continuous infusion (Badenoch 2017; Boylan 1996; Dalmau 2000; Kaspar 1997).

TXA: high dose versus low dose

Two trials were included in the high dose group (Boylan 1996; Ickx 2006) and thirteen were included in the low dose group (Badenoch 2017; Chakravartty 2016; Dalmau 2000; Devi 2008; Grass 2019; Hamada 1995; Jaffer 2021; Karanicolas 2016; Kaspar 1997; Pfizer 2012; Prasad 2018).

As no official cut-off between high- and low-dose application of TXA was to be found, the threshold has been defined by taking dosing regimen throughout varying studies on TXA administration in different surgical fields into consideration. The cut off was set at 20 mg/kg. Dosages in the low dose group were mostly ranging at ≤10 mg/kg, whereas the high-dose group included two trials with TXA-dosing of 40 mg/kg.

TXA: type of surgery

We defined four subgroups for the comparison: hepatectomy (Jaffer 2021; Karanicolas 2016; Wu 2006) - orthotopic liver transplantation (Badenoch 2017; Boylan 1996; Dalmau 2000; Devi 2008; Ickx 2006; Kaspar 1997) - gastric surgery (Chakravartty 2016) - other surgery (Grass 2019; Hamada 1995; Pfizer 2012; Prasad 2018; Wright 2020).

One Intervention versus another Intervention

TXA versus Aprotinin

Four studies were included in this comparison, two of which were randomized controlled trials (Dalmau 2004; Ickx 2006), while the other two were non-randomized studies (Devi 2008; Massicotte 2011).

Only one trial was of low risk of bias, three trials were of high risk of bias.

TXA versus EACA

One trial compared these two interventions (Dalmau 2000). As the data collection for several outcomes in the TXA-group has been continued after the primary endpoint of the

study, for each outcome the data including the highest number of participants was considered for this review.

The trial was of low risk of bias.

Primary outcomes

1. Volume of perioperative blood loss

TXA versus inactive control (placebo or no intervention)

There was no significant difference in the amount of blood loss between the TXA and the inactive control (placebo with normal saline or no intervention) groups (P = 0.57; MD -0.02 liters; 95% CI -0.08 to 0.05 liters) (

Figure 5).

Subset: application intervals

There was no significant difference for the effect of TXA administration on the amount of blood loss between the subgroups (P = 0.71) (
Figure 6).

Subset: dosage regimen

There was a significant difference between the subgroups for the effect of TXA administration regarding the amount of blood loss (P < 0.00001). Blood loss in the high dose subgroup was significantly lower in the TXA than in the control groups (P < 0.00001) with a mean difference of 3.69 litres [95% CI -4.93 to -2.45 litres]. In the low dose subgroup as well as in the overall population no significant difference was observed (Figure 7).

Subset: type of surgery

There was no significant difference for the effect of TXA administration on the amount of blood loss between the subgroups (P = 0.45) (Figure 7: dosage regimen blood loss
)

TXA versus Aprotinin

There was no significant difference in the volume of blood loss between the two comparisons, although there was a slight numerical difference in favor of the TXA group (P = 0.40; MD -0.34; 95% CI -1.13 to 0.45) (
Figure 9).

TXA versus EACA

The amount of blood loss was not reported in this trial.

2. Perioperative transfusion requirements

TXA versus inactive control (placebo or no intervention)

The proportion of patients in need of perioperative RBC transfusions (P = 0.009; RR 0.63; 95% CI 0.45 to 0.89) (Figure 10) as well as the number of RBC units transfused per patient (P = 0.01; MD -1.73 units; 95% CI -3.05 to -0.41) (Figure 10: TXA vs. control patients receiving RBC transfusion
) were significantly lower in the TXA group compared to the inactive control group. A total number of 1,026 RBC units was transfused, 565 in the TXA and 461 in the control groups. Overall, 321 of the 1.295 patients throughout the groups received RBC transfusion, 137 of them in the TXA and 184 in the control groups.

The number of transfused FFP units per patient was significantly lower in the TXA than in the control groups (P = 0.03; MD -1.90 units; 95% CI -3.58 to -0.22) (Figure 12). Regarding platelet (P = 0.27; MD -1.13 units; 95% CI -3.13 to 0.87) (Figure 12: TXA vs control FFP transfusion
) and cryoprecipitate (P = 0.22; MD -2.92 units; 95% CI -7.58 to 1.75) (Figure 13: TXA vs. control Platelet transfusion
) transfusions the differences between the groups showed no statistical significance.

Subset: application intervals

There was no significant difference for the effect of TXA administration in regard to the number of patients in need of RBC transfusions (
Figure 15), as well as the number of transfused units of RBC (
Figure 15: application interval patients in need of RBC transfusion), FFP (
Figure 16: application interval RBC transfusion (units)) and platelets (
Figure 18) between the subgroups. In the continuous infusion subgroups, a significantly lower proportion of patients was in need of RBC transfusion in the TXA compared to the control groups (P = 0.03), and the amount of RBCs transfused was also lower (P < 0.00001). In the subgroup single bolus with continuous infusion, the number of RBC (P = 0.01), FFP (P = 0.002) and platelet (P = 0.02) units transfused per patient was significantly lower in the TXA groups. This was also the case regarding platelet transfusions in the repetitive boli subgroup (P = 0.02).

For cryoprecipitate transfusions the subgroup analysis showed a significant difference between the groups (P < 0.00001). Only two subgroups - repetitive boli and continuous infusion - were included in this analysis. In both, there was a significant difference between the TXA and control groups. For the repetitive boli subgroup, the amount of cryoprecipitate transfusions was significantly higher in the TXA subgroups (P < 0.0001; MD 20.00, 95% CI 10.27 to 29.73), whereas it was significantly lower in the continuous infusion subgroup (P < 0.00001; MD -6.55, 95% CI -8.73 to -4.37) (Figure 19).

Subset: dosage regimen

No subgroup differences between high and low TXA dosage could be found regarding the proportion of patients in need of RBC transfusions (
Figure 20), as well as the amount of transfused units of RBC (
Figure 21), FFP (
Figure 22) and platelets (
Figure 23). For FFP transfusion the high dose subgroup showed significantly lower requirements in the TXA compared to the control groups (P = 0.04), whereas the result in the low dose group showed no differences (P = 0.31).

For cryoprecipitate transfusions the analysis showed a significant difference between the subgroups (P = 0.03). For the high dose subgroup, cryoprecipitate requirements were significantly lower in the TXA groups (P < 0.00001; MD -8.00, 95% CI -9.61 to -6.39), whereas no difference could be found in the low dose groups (Figure 24).

Subset: type of surgery

The analysis did not show significant differences between the subgroups for the proportion of patients in need of RBC transfusions (P = 0.88) (Figure 24: dosage regimen cryoprecipitate transfusion
) and was not applicable for the amount of transfused units of RBC (
Figure 26). The test for overall effect showed a significantly lower proportion of patients in need of red blood cell transfusions (P = 0.001) in the tranexamic acid group, but this difference was only significant in the OLT group (P = 0.004) (Figure 24: dosage regimen cryoprecipitate transfusion
).

For FFP (
Figure 27), platelet (
Figure 28) and cryoprecipitate transfusions (
Figure 29) the test for subgroup differences was not applicable, because all trials reporting on these outcomes belong to the OLT group. The overall effects did not show any significant differences between the intervention and control group.

TXA versus Aprotinin

There was no significant difference in the RBC transfusion requirements (P = 0.38; MD -0.13; 95% CI -0.41 to 0.16) (
Figure 30) or the amount of transfused fresh frozen plasma (P = 0.96; MD 0.01; 95% CI -0.24 to 0.25) (
Figure 31) or platelets (P = 0.89; MD 0.06; 95% CI -0.73 to 0.85) (
Figure 32). The analysis showed significant higher amounts of cryoprecipitate transfusions (P < 0.00001; MD 21.00; 95% CI 13.93 to 28.07) (
Figure 33) in the tranexamic acid group, only one of the four trials reported on this outcome.

TXA versus EACA

The trial showed significantly lower transfusion requirements in the TXA group than in the EACA group for RBC (P = 0.0007; MD -3.07, 95% CI -4.84 to -1.30) (
Figure 34), FFP (P = 0.003; MD -2.88; 95% CI -4.77 to -0.99) (
Figure 35) as well as cryoprecipitate (P = 0.003; MD -4.01; 95% CI -6.68 to -1.34) (

Figure 37). There was no statistically significant difference between the groups regarding the number of transfused units of platelets. (P = 0.82; MD -0.36, 95% CI -3.49 to 2.77) (

Figure 36).

Secondary outcomes

1. Thromboembolic events

TXA versus inactive control (placebo or no intervention)

There was a higher incidence of thromboembolic events in the intervention group, but the difference between the two groups did not reach statistical significance (P = 0.07; RR 1.84; 95% CI 0.96 to 3.50). A total of 41 events occurred, with 28 in the TXA and 13 in the control groups (
Figure 38).

Subset: application intervals

There were no significant differences for the effect of TXA administration on the incidence of thromboembolic events between the subgroups (P = 0.97). A total of 42 thromboembolic events, 29 in the TXA and 13 in the control groups occurred. In the single bolus and the single bolus & continuous infusion subgroups there was one event in each group. In the repetitive boli group two events took place in the TXA and one in the control groups, while in the continuous infusion subgroup 25 events occurred in the TXA and 10 in the control groups. (
Figure 39).

Subset: dosage regimen

The test for subgroup differences was not applicable for thromboembolic events because no such events were reported in the high dose subgroups (
Figure 40).

Subset: type of surgery

There were no significant differences in the occurrence of thromboembolic events between the subgroups (P = 0.95) (
Figure 41).

TXA versus Aprotinin

There was no significant difference in the incidence of thromboembolic events between the two interventions (P = 0.75) (
Figure 42).

TXA versus EACA

There was no significant difference in the proportions of patients developing thromboembolic events between the two groups (P = 0.97) (
Figure 43).

2. Seizures

TXA versus inactive control (placebo or no intervention)

Only three studies reported this outcome. Overall, only four seizure events occurred in these studies, three in the comparator and one in the TXA group. (
Figure 44).

Subset: application intervals

No significant difference for the effect of TXA administration between the subgroups in regards of seizure-like activity was observed (P = 0.91) (
Figure 45). In the single bolus and continuous infusion subgroup one seizure occurred in the control groups, in the repetitive boli subgroup there were three seizures in the control and one in the TXA groups. Other than that, there was no seizure-like activity.

Subset: dosage regimen

Only the low dose subgroup reported on this outcome. No difference between the TXA and control groups was found (

Figure 46).

Subset: type of surgery

No significant differences between the subgroups reporting on seizure-like activity were found (P = 0.91) (
Figure 47).

TXA versus Aprotinin

None of the included trials reported on this outcome.

TXA versus EACA

No data for this outcome was reported in this trial.

3. Other adverse events

TXA versus inactive control (placebo or no intervention)

No difference in the incidence of other adverse events between the TXA and the inactive control group could be found (RR 1.03; 95% CI 0.88 to 1.22). Overall, 411 events were reported, 200 in the intervention and 211 in the control groups (
Figure 48).

Subset: application intervals

The incidence of serious adverse events was not significantly different between the subgroups (P = 0.50) (
Figure 49).

Subset: dosage regimen

There was no significant difference between the subgroups regarding the incidence of adverse events (P = 0.44) (
Figure 50).

Subset: type of surgery

The presence of serious adverse events was not significantly different between the subgroups (P = 0.78) (
Figure 51).

TXA versus Aprotinin

The two groups showed no significant difference in the occurrence of adverse events (RR 1.38; 95% CI 0.46 to 4.11) (
Figure 52).

TXA versus EACA

There was no significant difference in the incidence of adverse events between the two comparisons (MD 0.75; 95% CI 0.18 to 3.15) (
Figure 53).

4. Perioperative mortality

No significant difference in perioperative mortality, as defined in the single studies, could be found between the TXA and the inactive control groups (RR 1.32; 95% CI 0.66 to 2.64). Throughout the studies 34 deaths occurred, 18 in the TXA and 16 in the control groups (
Figure 54).

Subset: application intervals

There was no significant difference for the effect of TXA administration on mortality between the subgroups (P = 0.65) (
Figure 55).

Subset: dosage regimen

The results regarding mortality were not significantly different between high and low dose subgroups (P = 0.36) (
Figure 56).

Subset: type of surgery

There was no significant difference in mortality between the groups (P = 0.64) (
Figure 57).

TXA versus Aprotinin

There was no significant difference in perioperative mortality between the two interventions (P = 0.55) (
Figure 58).

TXA versus EACA

There was no significant difference in the mortality at 5-month-follow-up between the TXA versus the EACA group (P = 0.69) (
Figure 59).

5. Operating time

TXA versus inactive control (placebo or no intervention)

There was no difference in operating time between the two groups (MD 4.29 minutes; 95% CI -10.40 to 18.97) (
Figure 60).

Subset: application intervals

The analysis showed a statistically significant difference in operating time between the subgroups (P = 0.0004). In the repetitive boli subgroup a significantly lower operating time was found in the intervention groups compared to the comparison groups (P < 0.0001). Analyses for the other subgroups failed to show any significance (Figure 61).

Subset: dosage regimen

Operating time was not reported in any of the high dose trials, therefore the test for subgroup differences was not applicable (
Figure 62).

Subset: type of surgery

The subgroup analysis did not show a significant difference between the groups regarding the operating time (P = 0.10) (
Figure 63). In the gastric surgery subgroup, the operating time was significantly lower in the tranexamic acid group compared to the control group (P = 0.010). The overall effect failed to show significant differences (P = 0.57).

TXA versus Aprotinin

Two of the included trials reported on the operating time. No significant difference between the tranexamic acid and the aprotinin group were found (
Figure 64).

TXA versus EACA

There was no significant difference between the two interventions regarding this outcome (
Figure 65).

6. Length of ICU & Hospital Stay

Neither the difference between the TXA and the inactive control groups in length of ICU stay (MD -0.43 days; 95% CI -1.31 to 0.45) (
Figure 66), nor in length of hospital stay (MD 2.49 days; 95% CI -0.33 to 5.32) (Figure 67) was statistically significant.

Subset: application intervals

There was no significant difference between the subgroups in length of hospital stay (P = 0.13). All subgroup results showed a shorter stay in the control group, and for the continuous infusion group the difference was statistically significant (P = 0.04) (
Figure 68).
The subgroup analysis for length of ICU stay showed significant differences between the groups (P = 0.02). Patients in the continuous infusion subgroups had a significantly lower length of ICU stay than in the TXA groups (P = 0.005), whereas in the other subgroups, no differences were found (
Figure 69).

Subset: dosage regimen

There was no significant difference between the subgroups regarding length of hospital stay (P = 0.47). While in the single study in the high dose subgroup, length of hospital stay was significantly shorter in the control group (P = 0.04), this was not the case for the low dose subgroup. (
Figure 70).

The analysis for length of ICU stay showed significant differences between the subgroups. While the overall test effect remained insignificant, the length of stay in the one study in the high dose group was significantly lower in the TXA compared to the control group (P = 0.005), whereas the results in the one study in the low showed no difference in length of stay (P = 1.00) (Figure 71).

Subset: type of surgery

There was no significant difference between the subgroups in length of hospital stay (P = 0.27) (
Figure 72). Regarding the duration of Intensive Care Unit stay significant subgroup differences were observed (P = 0.005). While the overall test effect was not statistically significant (P = 0.34), the OLT subgroup showed a significantly lower ICU length of stay in favor of the intervention group (P = 0.005). No significant difference was observed in the subgroup "other surgery" (P = 1.00) (
Figure 73).

TXA versus Aprotinin

Only one of the included trials reported on these outcomes. There was a numerical difference between the comparisons in favor of the tranexamic acid group for both outcomes (
Figure 74). Yet only for the length of hospital stay the difference was significant (p = 0.01) (Figure 75).

TXA versus EACA

The trial did not report these outcomes.

Discussion

Summary of main results

The aim of this systematic review was to evaluate the efficacy and safety of TXA for reducing blood loss and transfusion requirements in major abdominal surgery.

The meta-analyses identified several differences between the intervention groups, i.e. patients who received TXA, and the different comparators. Regarding the primary outcomes, the analyses found a lower number of patients in need of RBC transfusions as well as a lower amount of RBC units transfused per patient in the TXA group. While also FFP-, platelet- and cryoprecipitate-transfusions were less frequently required for patients treated with TXA, only for the transfusion of FFP the results showed statistical significance. Between group comparisons of perioperative blood loss also failed to identify significant differences.

In the primary analysis, none of the secondary outcomes of interest showed a significant difference between the TXA and control groups.

Sensitivity analyses:

The sensitivity analyses comparing high and low risk groups showed significant differences in the need for cryoprecipitate transfusions. (Figure 76) In the low risk subgroup, a significantly lower number of transfusions was needed in the TXA group, whereas it was significantly higher in the high risk subgroup. Nevertheless, there was no difference on an overall test effect level. There were no significant differences in the

sensitivity analyses regarding any of the other primary or secondary outcomes. (

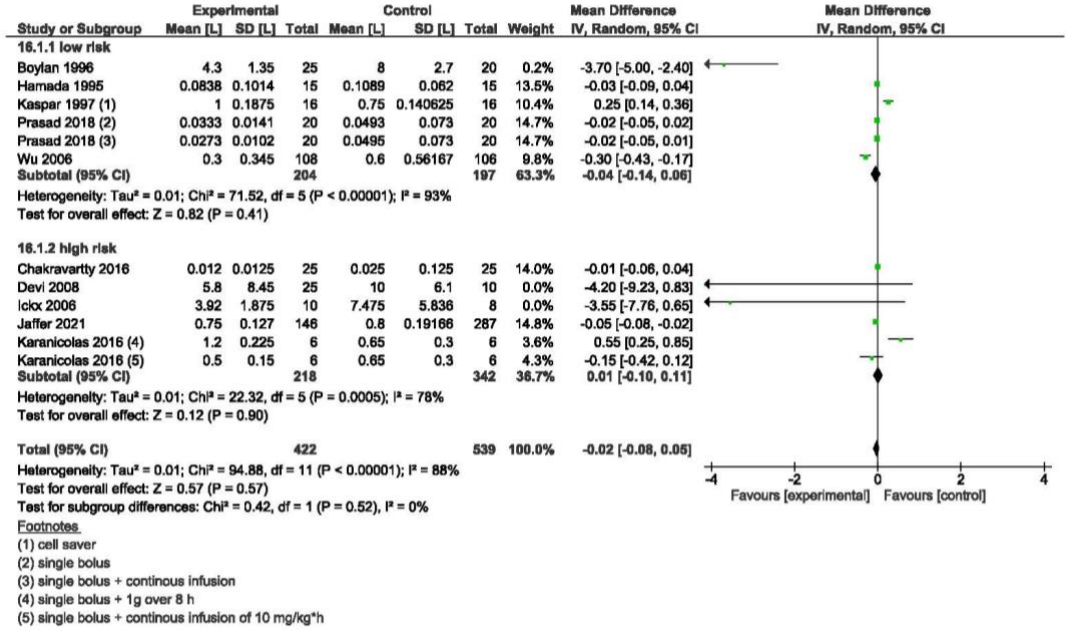


Figure 77,
Figure 78,
Figure 79,
Figure 80,
Figure 81)

Subset differences:

Application interval: single bolus vs. single bolus and continuous infusion vs. repetitive boli vs. continuous infusion

Significant differences between the subgroups were identified for cryoprecipitate transfusion requirements, operating time and length of ICU stay. The amount of cryoprecipitate transfusions in the TXA group was significantly higher in the “repetitive boli” subgroup, whereas it was significantly lower in the “continuous infusion” subgroup. The “repetitive boli” subgroup also showed a significantly shorter operating time in the TXA group, there were no significant differences in any of the other subgroups.

Length of hospital stay in the “continuous infusion” subgroup was significantly longer in the TXA group, whereas the length of ICU stay was significantly lower in this group.

No other significant differences in these subgroup analyses regarding any of the other primary or secondary outcomes were found.

Dosing regimen: high dose vs. low dose

In the high dose subgroups significant differences were found for volume of perioperative blood loss as well as the number of RBC, FFP and cryoprecipitate transfusions. All of these outcomes were found to be significantly lower in the TXA group.

In both the high and low dose subgroup, the length of ICU stay was significantly shorter in the intervention group. No other significant differences in primary or secondary outcomes were obtained.

Type of surgery: hepatectomy vs. OLT vs. gastric surgery vs. other surgery

In the “OLT” subgroup the proportion of patients in need of RBC transfusions and the length of ICU stay were significantly lower in the TXA group. In the “gastric surgery” subgroup, the operating time was significantly shorter in the intervention group. No significant differences between the subgroups were found for any of the other primary or secondary outcomes.

Overall completeness and applicability of evidence

Many of the trials included in this review lacked reporting on several important outcomes of interest, especially rare side effects like thromboembolism or seizures.

In terms of the settings of blood transfusion, a wide variation throughout the studies, especially regarding transfusion thresholds and usage of cell saving mechanisms, led to a reduction of comparability. Moreover, the exact volume of transfused units often could not be accurately discerned making a detailed assessment of the impact on need and volume of blood transfusions more difficult. While some of the studies provided data about both number of patients requiring and units of blood products transfused, others only provided some of the data.

Further, most of the included trials were conducted on patients with hepatobiliary operations pre-eminently hepatectomy or liver transplantations. This predominance might reduce generalizability on all major abdominal procedures, partly because some of the implemented techniques of reducing blood loss like portal vein clamping are specific to these procedures. Although studies on other abdominal operations were outnumbered, the subset analysis did not show any difference between the different types of surgery. Nevertheless, further trials on varying procedures should be conducted to achieve a greater generalizability and improve the validity of these results.

Up to this point studies have been focused on examining whether TXA administration could generally be beneficial to reducing blood loss and transfusion requirements. Therefore, evidence regarding different dosing regimen is limited, as conducted trials mostly did not implement high vs. low dose comparisons and no official cut-off has been defined yet. Subset analysis for dosage regimen suggested an advantage in high-dose application of TXA. More profound research implementing study protocols comparing different dosing regimen with pre-defined and standardized cut-offs is needed to confirm or falsify this suggestion. Likewise, application intervals need to be more thoroughly

addressed in upcoming studies to evaluate whether an impact on the outcomes can be observed.

Limitations

This Systematic Review with Meta-Analyses faces some limitations, mostly caused by the design of the included studies. First of all, many eligible trials were of a small sample size (≤ 60 patients), furthermore often being limited by a single-center and/or single-surgeon approach. While the latter can reduce bias due to individual preferences or abilities it may also reduce the applicability to the general population and introduce bias due to lack of external validation.

A large majority of the studies date back to over five years ago (n = 13), the oldest being conducted more than two decades ago in 1995, 1996, 1997 and 2000 (n = 4). Since then, many improvements in surgical technique, operation devices, patient blood management and new transfusion guidelines etc. have taken place. With this evolution crucially influencing outcomes, the heterogeneity throughout the studies makes it harder to unrestrictedly apply the results to current times.

Many limitations are also introduced by variations in study design, study protocols and quality of the studies. The lack of randomization and blinding can introduce major confounders leading to a higher risk of bias, that needs to be thoroughly addressed while interpreting the results. Comparability is being influenced by different dosing regimens, ranging from low- to medium-high-doses; as well as differing rates and timings of application (single or repetitive bolus, continuous infusion). We tried to address some of these issues by conducting subgroup analyses concerning these aspects. Another possible source of confounding are different antifibrinolytics, anticoagulants or other co-interventions that were carried out in some studies according to study protocol. Moreover, transfusion-thresholds were individual to each study, most of them initiated by a specific drop in Hct- or Hb-levels but none of them identical. These discrepancies across studies are likely to affect their results.

Current transfusion guidelines nationally [BÄK-guidelines] as well as internationally [AABB international guidelines] recommend similar transfusion thresholds. In hemodynamically stable adult patients' transfusion is recommended at Hb-concentrations of less than 7 g/dl. International guidelines recommend varying thresholds for patients undergoing cardiac (7.5 g/dl) or orthopedic surgery as well as those with preexisting cardiovascular disease (8 g/dl). In national guidelines transfusion is recommended at Hb-concentrations between 7-8 g/dl in patients with risk factors, limited compensation or signs of anemic hypoxia.

Profound differences in outcome assessment existed throughout the included trials. Estimation of blood loss (weighing of sponges etc.), the usage of intraoperative cell-salvage and systematic screening versus clinical evaluation for thromboembolic events being just some of them.

The review showed significant differences in transfusion requirements albeit not in blood loss although one is highly dependent on the other. As transfusion was triggered by specific thresholds, despite being distinct to each study, it was generally oriented at objectifiable laboratory parameters and international guidelines. Estimation of blood loss on the other hand can not to be assessed by using specific predefined thresholds. Therefore, it is heavily dependent on perioperative assessment techniques, which differed profoundly.

The deviating results of these two co-dependent outcomes suggest that underlying inaccuracies in assessment of blood loss, potentially inherent in the system, could limit the validity of these findings. More objectifiable criteria, generalizability and similarity between the trials to estimate perioperative blood loss would be needed to produce more reliable results.

Another limiting aspect is the diverse implementation of follow-up. No consistency in length existed across the trials, some did not state the duration of follow-up at all, failed to report on data assessed in the outpatient-department or simply limited the time of follow-up to the time until hospital-discharge. This may have resulted in underreporting of serious adverse events postoperatively, especially thromboembolism as its risk remains above-average in the first few weeks after the operation.

This limitation is relevant to secondary outcomes predominantly, as perioperative transfusion requirements have been assessed closely during hospitalization and can hardly be referred to the operation after discharge.

Secondary outcomes like serious adverse events, thromboembolism and perioperative mortality tend to have a higher latency and therefore are at a high-risk to be underreported in studies with short follow-up periods. Differences in screening for these outcomes throughout the studies increase the limitations furthermore.

A lack of information on population characteristics, especially ethnicity, complicates deduction on a universal patient population. While the results might be well applicable to a population of similar origins to the individual studies, dietary and genetic differences throughout different ethnicities reduce the generalizability. More in-depth information about differences in the individual patient population may reduce bias and eliminate a possible confounder. As most of the studies have been conducted in European or

Northern American countries with specific health care systems, results may best be applicable for their inherent populations.

Quality of the evidence

The overall quality of evidence throughout the included studies was heterogeneous. Most of the included randomized controlled trials were of low risk of bias and therefore of high quality of evidence. Some RCTs were of uncertain or intermediate to high risk of bias with some concerns regarding the quality of evidence.

As this systematic review also included case control and cohort studies inherently not adequately randomized and blinded, these studies are generally of a high risk of bias and reduce the overall quality of evidence. They would need propensity-score matching to reduce the influence of possible confounders and increase comparability. Many of the included trials used some kind of matching to improve the study quality, but information on the applied technique were not included in all of the study protocols to a satisfactory extent. The interpretation of thus obtained results should be limited to associations and generation of hypotheses. Thanks to the commonly large sample size the included retrospective studies are well suited to monitor less common events.

On the contrary most of the randomized trials and studies with small sample size were underpowered to detect rare but serious events. Especially due to the fact that several of the outcomes of interest like thromboembolism and mortality tend to be rare, thi further reduces the power to observe significant results.

The sensitivity analysis for risk of bias did not show significant differences for the primary outcomes blood loss, RBC-, FFP- and platelet transfusion requirements, as well as all the secondary outcomes. Solely for cryoprecipitate requirements a significant difference between the high and low risk trials was observed.

These findings show that the effects of TXA intervention on the monitored outcomes do not significantly vary based on the quality of the trials and therefore suggest a generally good applicability of the evidence.

The quality of evidence is shown in the "Summary of findings" tables.

Potential biases in the review process

During the review process several potential sources of bias occurred. First, a few of the included studies failed to report all the details and data of their observed outcomes. The effort to contact the authors and collect the missing data remained unsuccessful.

Furthermore, we used the method introduced by Hozo 2005 to estimate the sample standard deviation if only median and range were provided by the study protocols. This needs to be considered while interpreting the results of this review.

Another potential source of bias is attributed to the reviewers specifically applying to the study selection and data collection process. To minimize this bias the database search was performed by two independent reviewers according to predefined inclusion criteria, an unanimous decision was needed or if no agreement could be reached, a third independent reviewer was involved as arbiter. Data collection was performed using a standardized data collection form.

Agreements and disagreements with other studies or reviews

The use of TXA has been studied in many different medical fields over the past decades, mostly with the intention of preventing or treating bleeding of various causes. Especially in surgery plenty trials have been conducted and the evidence is growing constantly. Nevertheless, there are differences between the individual surgical disciplines according to the strength of the evidence.

In major orthopedic surgery TXA has been very well examined over the past. Many studies have shown a significant reduction of blood loss and transfusion requirements in various types of fracture surgery [Amer 2017; Haj-Younes 2020; Nikolaou 2021], total hip or knee arthroplasty [Cid 2005; Poeran 2014; Sukeik 2011] as well as in spine surgery [Cheriyan 2015]. Moreover, none of the studies, reviews or meta-analyses found an increased risk of thromboembolic (PE, DVT, MI) or other serious adverse events, although some of them remained inconclusive because of small sample sizes and low event rates. This strong body of evidence for the safety and effectiveness of TXA in orthopedic surgery caused the implementation in the ESA-recommendations for major spinal surgery, hip and knee replacement [ESA guidelines].

Similar results have been raised in cardiovascular surgery, where tranexamic acid evolved to being the standard antifibrinolytic [Koster 2013], also being recommended by the ESA guidelines. It has proven to minimize blood loss and transfusion requirements while simultaneously not elevating mortality, thromboembolic events or graft occlusion [Maddali 2007; Sigaut 2014]. Nevertheless, there is some evidence of a higher risk of postoperative seizures in coronary-artery surgery [Myles 2017].

As one of the first surgical disciplines integrating TXA in their standard repertoire for antifibrinolytic therapy the evidence on its use in obstetrics and gynecology has since grown rapidly. The results obtained throughout various different conditions like cesarean section [Gohel 2007; Gungorduk 2011; Wang 2015], postpartum hemorrhage [WOMAN-trial; Ducloy 2011; Heesen 2014], menorrhagia [La 1970], benign uterine surgery/myomectomy [Caglar 2008] and conization [Lundvall 1984] all confirmed the effectiveness of TXA in the reduction of blood loss. Most of the studies did not find any

differences in side effects or an increase in thromboembolism. Only one of the aforementioned trials found a slight increase of mild, transient adverse events that did not show statistical significance [Ducloy 2011]. Therefore, the evidence in this discipline also suggests safety and efficacy of TXA for blood loss reduction in many different population groups.

Several studies done in prostatic surgery showed the same effects of significantly reducing blood loss and transfusion requirements without differences in mortality, thromboembolic events or other side effects [Crescenti 2011; Hedlund 1969; Longo 2018].

In its use tranexamic acid is not limited to elective surgery but it has also proven to be a very important antifibrinolytic in trauma. As there are many different traumatic patterns where it may be of advantage, there is a wide variety in trials that have been or currently are still being conducted. The CRASH-2 trial in trauma patients with significant hemorrhage completed in 2010 showed TXA capable of significantly reducing all-cause mortality and risk of death due to bleeding. A study on primary intracerebral hemorrhage [TICH-2] in 2018 failed to show significant differences in functional status after 90 days but revealed a reduction in early deaths and serious adverse events in the TXA-group, needing to be confirmed by larger scale trials. Even more recent the CRASH-3 trial in patients with acute traumatic brain injury has been published. Tranexamic acid could be safely administered and early treatment within three hours of the injury reduced head injury-related death especially in mild-to-moderate injuries. The shorter the time to treatment, the better the results. No significant differences in risk of vascular occlusive events or seizures between the groups has been assessed. A recent review including patients with traumatic injury and TBI revealed a significant decrease in 1-month mortality after TXA-administration, whereas due to heterogeneity the meta-analyses for 24-hour and overall mortality as well as thromboembolic events could not be pooled [Karl 2022].

Up to date systematic reviews and meta-analyses in major abdominal surgery are mostly limited to liver surgery, more precisely OLT and liver resection. In liver transplantation reduced transfusion requirements without increased risk for hepatic artery thrombosis, venous thromboembolic events or perioperative mortality have been observed for TXA administration [Molenaar 2007]. Likewise, a Cochrane Review on Antifibrinolytics in liver resection showed a reduction of blood loss and allogeneic blood transfusion requirements without increased risk of thromboembolic events, mortality or other serious adverse effects. However, the results failed to show significance [Gurusamy 2009]. Recently the largest internationally registered, multicenter RCT on the effect of

tranexamic acid in liver resection (HeLiX Trial) has been conducted in several hospitals throughout Canada and the USA. Enrollment was completed in November 2022 and results of the primary analysis have been recently published (October 2024). TXA administration in patients undergoing liver surgery for cancer-related indication did not reduce bleeding or blood transfusion within 7 days of surgery, whereas there were significantly more complications albeit no significant difference in venous thromboembolism. Due to the five-year follow-up period final results of the study cannot be expected until 2027.

In treatment of upper gastrointestinal bleeding a Cochrane review "did not recommend tranexamic acid for routine clinical practice" although there seemed to be beneficial effects on mortality [Bennett 2014]. These findings were confirmed by HALT-IT, a large international randomized controlled trial carried out after the latest update of the review. No reduction of death from gastrointestinal bleeding was found, whereas thromboembolic and other adverse events were similar in both groups. A use of tranexamic acid in this context is therefore not endorsed outside of a RCT.

Just recently results of the POISE-3 Trial on TXA in patients undergoing noncardiac surgery have been published. With more than 9,500 patients from 114 hospitals across six continents included, power and applicability of this randomized placebo-controlled double-blinded trial are extraordinarily high. The primary analyses were able to show a significant reduction of the incidence of composite bleeding events in the tranexamic acid group but failed to establish noninferiority regarding cardiovascular outcomes.

The results of this systematic review go according to those of the aforementioned studies and reviews in multiple different medical fields. Efficacy of TXA in reducing transfusion requirements and possibly blood loss in abdominal surgery has been indicated.

Simultaneously the current evidence did not show any significant differences between TXA and control regarding serious adverse events, especially thromboembolism and mortality. Therefore, no major safety concerns on administrating TXA in abdominal surgery were detected. Nevertheless, as the limitations of the studies show, further investigation needs to be conducted with more precise monitoring of adverse events and implementation of standardized follow-up and screening protocols to produce more reliable results. Additionally non-inferiority trials might proof beneficial to ensure the safety of TXA administration particularly in regard to thromboembolic incidents, mortality and seizure-like activity.

Throughout the conducted studies there is a large heterogeneity in dosing regimens. Whereas in some disciplines a preferred dosage has already been established, in major

abdominal surgery as well as in many other fields a standard is yet to be set by further examination.

Authors' conclusions

Implications for practice

This systematic review with meta-analysis implicates that the use of tranexamic acid in major abdominal surgery could be beneficial to reducing transfusion requirements. For reduction of blood loss no significant results were observed, although the strong interdependence between blood loss and transfusion requirements suggests otherwise. As it is presumably the cause of insufficient assessment techniques further examination seems to be inevitable. Simultaneously, the current evidence does not suggest a higher incidence of thromboembolic events (DVT, PE, MI) or other serious adverse events after the administration of tranexamic acid. However, these findings need to be further investigated because the few trials included, the small sample sizes and the partially high risks of bias increase the risk of type I and type II errors.

Implications for research

While the evidence suggests that tranexamic acid may be safe and efficient in reducing blood loss and transfusion requirements in major abdominal surgery, more research is needed to confirm these findings. Trials with adequate power to determine rare events and including a large population need to be conducted. Furthermore, investigations need to be done on different fields of abdominal surgery to generate more reliable conclusions, considering that the current evidence is mostly based on studies regarding liver surgery. Moreover, future trials should further investigate adequate dosing regimens with the intent on standardizing mean dose, time, frequency and duration of administration as well as the most appropriate way of delivery for each individual type of abdominal surgery.

Characteristics of included studies

Boylan 1996

Methods	double-blind, randomized, placebo-controlled trial; single center
Participants	Origin/Country: Toronto, Canada Sample size: 45 (revised) Mean age: 49.2 years Performed surgery: primary isolated OLT Inclusion criteria: patients with necrotic liver disease undergoing primary isolated orthotopic liver transplantation; Toronto-Hospital CA
Interventions	Group 1: intervention (n = 25) tranexamic acid; continuous infusion; 40 ml/kg*h; from induction until portal vein unclamping Group 2: control (n = 20) normal saline; equal volume
Outcomes	perioperative blood loss in L; perioperative blood transfusion requirement (intra-/post-/perioperative) in units [total, PRBC, plasma, cryo, platelets]; thromboembolic events (30 d); 30 d-mortality; retransplantation

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomized into groups; study agents prepare by pharmacy using randomization schedule provided in sealed envelopes
Allocation concealment (selection bias)	Low risk	study agents prepared by pharmacy using randomization schedule provided in sealed envelopes; all other personnel blinded to randomization status → probably adequate, but details on sealed envelopes not provided (opaque/consecutively numbered)
Blinding of participants and personnel(performance bias)	Low risk	all personnel blinded to randomization status normal saline used as placebo
Blinding of outcome assessment (detection bias)	Low risk	personnel blinded to randomization status normal saline used as placebo

Incomplete outcome data (attrition bias)	Unclear risk	no information available
Selective reporting (reporting bias)	Unclear risk	important outcomes were not reported
Risk of bias due to conflict of interest/funding	Unclear risk	no information available

Kaspar 1997

Methods	prospective, placebo-controlled, double-blind study; single-center?
Participants	Origin/Country: Dallas, Texas, USA Sample size: 32 (revised) Sex: similar in both groups Mean age: similar in both groups Performed surgery: orthotopic liver transplantation Inclusion criteria: OLT, similar patient characteristics and comorbidities; Dpts. Of Anesthesiology + Pain Management, Baylor University Medical Center and University of Texas Southwestern Medical Center, Dallas
Interventions	Group 1: intervention (n = 16) tranexamic acid; continuous small-dose pump infusion; 2 mg/kg*h (1g in 500 ml saline); from induction until completion Group 2: control (n = 16) normal saline; equal volume
Outcomes	blood loss, blood transfusion requirements, TE, fibrinolysis; adverse events/complications

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	randomly assigned, study agents prepared by pharmacy using computer-generated randomization schedule
Allocation concealment (selection bias)	Low risk	study agents prepared by pharmacy using computer-generated randomization schedule
Blinding of participants and personnel(performance bias)	Low risk	all investigators blinded control with equal volume normal saline

Blinding of outcome assessment (detection bias)	Low risk	all investigators blinded control with equal volume normal saline
Incomplete outcome data (attrition bias)	Low risk	double-blind study performed on 32 consecutive patients undergoing OLT
Selective reporting (reporting bias)	Unclear risk	important outcomes were not reported
Risk of bias due to conflict of interest/funding	Unclear risk	no information provided

Dalmau 2000

Methods	double-blinded, prospective, randomized, placebo-controlled study; 2 LTX-centers
Participants	Support for judgement
Interventions	Group 1: intervention (n = 42; extended to n = 122) tranexamic acid; continuous infusion; 10 mg/kg*h; from induction until graft reperfusion Group 2: intervention (n = 42) EACA; continuous infusion; 16 mg/kg*h; from induction until graft reperfusion Group 3: control (n = 40) normal saline; equal volume?
Outcomes	blood transfusion requirement, TE, 5-months-mortality, reoperation; Hgb change; operation time

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	randomly assigned; infusions prepared by hospital pharmacy using computer-generated randomization schedule
Allocation concealment (selection bias)	Low risk	infusions prepared by hospital pharmacy using computer-generated randomization schedule provided in sealed envelopes → probably adequate, no details on sealed envelopes (opaque/consecutively nrd.)
Blinding of participants and personnel(performance bias	Low risk	all investigators blinded to composition for solutions

Blinding of outcome assessment (detection bias)	Low risk	all investigators blinded to composition for solutions
Incomplete outcome data (attrition bias)	High risk	post-randomization drop-outs: 3 exclusions because of incomplete data, 29 exclusions because of other reasons (153 → 124)
Selective reporting (reporting bias)	Unclear risk	important outcomes were not reported
Risk of bias due to conflict of interest/funding	Unclear risk	no information provided

Dalmau 2004

Methods	prospective, randomized, double-blind study; single adult LTX center
Participants	Origin/Country: Barcelona, Spain Sample size: 127 - 3 (revised) Sex: 38 women (30%), 89 men (70%) Mean age: 53.5 years Performed surgery: orthotopic liver transplantation Inclusion criteria: demographically similar, consecutive patients undergoing OLT; Dpt. Of Anesthesiology + Surgery, University Hospital of Bellvitge, Barcelona, Spain
Interventions	Group 1: intervention (n = 64) tranexamic acid; continuous infusion [10 mg/kg*h]; from induction until 2h after portal vein unclamping Group 2: intervention (n = 63) aprotinin; single bolus [$2*10^6$ KIU] & continuous infusion [500.000 KIU/h]; from induction until 2h after portal vein unclamping
Outcomes	blood transfusion requirements, TE, mortality, adverse effects

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	drug-preparation using randomization schedule in sealed envelopes
Allocation concealment (selection bias)	Low risk	drug-preparation using randomization schedule in sealed envelopes → probably adequate, but no details on sealed enve-lopes (opaque/consecutively numbered)

Blinding of participants and personnel(performance bias)	Low risk	anesthesiologist, nurse, surgeons unaware of randomization details; both drugs prepared in equal manner
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	there were no post-randomization drop-outs
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported
Risk of bias due to conflict of interest/funding	Low risk	no recipient of any grant or other financial support

Ickx 2006

Methods	prospective, double-blind, randomized trial with retrospective comparison with historical cohorts
Participants	Origin/Country: Brussels, Belgium Sample size: 51 (+ 8) (revised) Sex: 6 women (12%), 45 men (88%) Mean age: 51.5 years Performed surgery: primary OLT Inclusion criteria: demographically similar, cirrhotic patients, primary OLT; Hospital Erasme (Dpt. of Anesthesiology/Surgery/ICU/Laboratory of Hematology + Biology), Hospital Brugmann (Dpt. of Anesthesiology/ Surgery), Brussels, Belgium
Interventions	Group 1: intervention (n = 27) tranexamic acid; slow bolus over 30 min [40 mg/kg] & continuous infusion [40 mg/kg*h]; anhepatic phase 30 min before expected reperfusion until 2h after reperfusion Group 2: intervention (n = 24) aprotinin; slow bolus [280 mg] & continuous infusion [70 mg/h]; anhepatic phase 30 min before expected reperfusion until 2h after reperfusion Group 3: control (n = 8) historical cohort; no antifibrinolytic agent; matched
Outcomes	blood loss (intraop./POD1+2), blood transfusion requirement, Hgb change, TE, 30-day mortality,

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomly assigned, simple randomization; no further information
Allocation concealment (selection bias)	Low risk	surgeons not aware of treatment allocation
Blinding of participants and personnel (performance bias)	High risk	administration not blinded to investigators (technical reasons)
Blinding of outcome assessment (detection bias)	Low risk	blinded nurses assessing blood loss
Incomplete outcome data (attrition bias)	Unclear risk	information not available
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (AE)
Risk of bias due to conflict of interest/funding	High risk	Drugs were provided by Choay, Bournonville, France.

Wu 2006

Methods	prospective, double-blind, randomized trial
Participants	Origin/Country: Taichung & Taipei, Taiwan; Eastern Asian population Sample size: 214 (revised) Sex: 57 women (27%), 157 men (73%) Mean age: 59.5 years Performed surgery: (not major) liver resections for various liver tumors Inclusion criteria: demographically similar, Eastern Asian population (dietary/genetic differences to whites); Dpt. Of Surgery, Faculty of Med., National Yang-Ming Univ., Taipei; Dpt. Of Surgery/Anesthesiology/Pathology, Taichung Veterans Hospital; Dpt. Of Surgery, Cung-Shan Medical Univ., Taichung;
Interventions	Group 1: intervention (n = 108) tranexamic acid; loading-dose bolus [500 mg] & repetitive boli [250 mg] every 6h for 3 days; just before beginning of the operation until 3d after Group 2: control (n = 106) normal saline
Outcomes	blood loss, transfusion requirements, Hgb-change, TE, hospital mortality, operation time, AE/complications

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomization into one of two groups, double-blinded in sealed envelopes;
Allocation concealment (selection bias)	Low risk	randomization double-blinded in sealed envelopes; → probably adequate, but details on sealed envelopes not provided (opaque/consecutively numbered)
Blinding of participants and personnel(performance bias)	Low risk	anesthesiologist, nurse, surgeons unaware of randomization details control with equal volume of normal saline
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	High risk	sample sizes do not match
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (SD)
Risk of bias due to conflict of interest/funding	High risk	in part grant from National Science Council, Taiwan

Devi 2008

Methods	prospective, non-randomized trial with 3 cohorts, reporting to a single-center (randomly assigned according to individual preference)
Participants	Origin/Country: Hyderabad, India Sample size: 50; Drop-out(s): not stated - 1?; Revised sample size: 49 Sex: 10 women (20%), 40 men (80%) Mean age: 46 years [44 adults, 6 pediatric] Performed surgery: orthotopic liver transplantation with ESLD Inclusion criteria: consecutive patients undergoing OLT with ESLD; 44 adults, 6 pediatric; Dpts. Of Transfusion Medicine, Hepatology, Anesthesiology and Critical Care, Global Hospitals, Hyderabad, India
Interventions	Group 1: intervention (n = 10) tranexamic acid; repetitive boli [10 mg/kg] every 6-8 h; from induction until the end of surgery

	Group 2: intervention (n = 15) tranexamic acid; single bolus [10 mg/kg] & continuous infusion [5 mg/kg*h]; from induction until early reperfusion phase Group 3: intervention (n = 14) aprotinin; slow bolus [$2*10^6$ KIU] & continuous infusion [500.000 KIU/h] for adults; slow bolus [10.000 KIU/kg] & continuous infusion [5.000 KIU/h] for children; from induction until the end of surgery Group 4: control (n = 10) no intervention
Outcomes	blood loss, blood transfusion requirements, TE, mortality/survival, hospital/ICU length of stay, operation time

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	randomly assigned based on anesthesiologists' preference
Allocation concealment (selection bias)	High risk	no information provided
Blinding of participants and personnel (performance bias)	High risk	no information provided control with no intervention
Blinding of outcome assessment (detection bias)	High risk	no information provided control with no intervention
Incomplete outcome data (attrition bias)	High risk	one drop-out
Selective reporting (reporting bias)	Unclear risk	important outcomes were not reported (children/subgroups etc.)
Risk of bias due to conflict of interest/funding	Low risk	no funding, no conflicts of interest declared

Massicotte 2011

Methods	prospective survey (study with historical control)
Participants	Origin/Country: Montreal (Quebec), Canada; Madison (Wisconsin), USA Sample size: 400 (revised) Sex: women (33 %), men (67 %) Mean age: 52.5 years Performed surgery: OLT Inclusion criteria: demographically similar, consecutive patients; Dpt. Of Anesthesiology + Epidemiology Dpt. + Dpt. Of Hepatopancreatobiliary Surgery, Centre hospitalier de l'Université de Montréal, Hopital St-Luc, Montreal; Dpt. Of Anesthesiology, University of Wisconsin (Madison)
Interventions	Group 1: intervention (n = 300) tranexamic acid; single bolus [30 mg/kg] & continuous infusion [16 mg/kg*h]; from incision until portal vein anastomosis Group 2: control (n = 100) aprotinin; single bolus [$2*10^6$ U] & continuous infusion [500.000 U/h]; from incision until portal vein anastomosis
Outcomes	blood loss, blood transfusion requirement, Hgb-change, TE, mortality/survival (1y), operating time, adverse effects/complications

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	matched for sex, age, BMI + weight
Allocation concealment (selection bias)	High risk	no RCT; no information provided
Blinding of participants and personnel (performance bias)	High risk	no RCT; no information provided
Blinding of outcome assessment (detection bias)	High risk	no RCT; no information provided
Incomplete outcome data (attrition bias)	Unclear risk	no information provided
Selective reporting (reporting bias)	Unclear risk	most outcomes of interest reported

Risk of bias due to conflict of interest/funding	Low risk	no conflicts of interest declared

Karanicolas 2016

Methods	prospective, open label, phase II trials; cohort study, small sample numbe
Participants	Origin/Country: Waterloo & Toronto (Ontario), Canada Sample size: 18 (revised) Sex: 8 women (44%), 10 men (56%) Mean age: 65 years Performed surgery: open/laparoscopic major liver resection (> 2 segm.) Inclusion criteria: adults > 18 yrs Exclusion criteria: vasc./biliary reconstruction, platelets < 100.000*10^9/L, severe anemia (Hb<90 g/L), unable to receive BP, pregnant/lactating, severe renal insufficiency (< 30 mL/min), art./ven. thrombosis <3 months; known DIC, seizure disorder, TXA-hypersensitivity, chemo <4 weeks, anticoag./direct thrombin inh./thrombolytic therapy <1week; prev. enrolled
Interventions	Group 1: intervention (n = 6) tranexamic acid; single bolus [1 g] & continuous infusion [1 g] 15 min after initial bolus over a duration 8h Group 2: intervention (n = 6) tranexamic acid; single bolus [1 g] & continuous infusion [10 mg/kg*h] 15 min after initial bolus until the end of surgery Group 3: control (n = 6) no intervention
Outcomes	blood loss, blood transfusion requirements, TE, mortality, ICU/hospital stay, operating time, adverse events/complications; fibrinolysis

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	cohorts of 6 subjects enrolled sequentially to one of the 3 regimens: block randomization
Allocation concealment (selection bias)	Unclear risk	no information provided
Blinding of participants and personnel(performance bias	High risk	no information provided control with no intervention

Blinding of outcome assessment (detection bias)	High risk	no information provided control with no intervention
Incomplete outcome data (attrition bias)	Unclear risk	no drop-outs reported
Selective reporting (reporting bias)	Unclear risk	important outcomes were not reported
Risk of bias due to conflict of interest/funding	Low risk	Grant Miller Cancer Research Grant, Univ. of Toronto (no participation in study-design/ execution); no conflicts of interest declared

Badenoch 2017

Methods	retrospective, propensity matched case-control study, single-center
Participants	Origin/Country: Toronto (Ontario), Canada Sample size: 734 (revised) Sex: 228 women (31%), 506 men (69%) Mean age: 55 years Performed surgery: OLT Inclusion criteria: undergoing OLT meeting intervention/control criteria Dpts. Of Anesthesia + Pain Management/General Surgery, Toronto General Hospital; University Health Network, University of Toronto, Ontario, Canada; tertiary care teaching hospital
Interventions	Group 1 & 2: intervention (n = 367) tranexamic acid; > 10 mg/kg*h 1. repetitive boli [1 g] every hour 2. continuous infusion [10 mg/kg*h]: incision until 2h after reperfusion Group 3: control (n = 367) no intervention
Outcomes	blood transfusion requirements, TE, mortality, seizures, operating time, adverse events/complications

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	retrospective, propensity matched case-control study; not standardized/ randomized: relying on natural variation (bias due to incomplete matching)

Allocation concealment (selection bias)	High risk	no allocation
Blinding of participants and personnel(performance bias)	Low risk	data collection by blinded outcome adjudicators; control with no intervention
Blinding of outcome assessment (detection bias)	Low risk	data collection by blinded outcome adjudicators; control with no intervention
Incomplete outcome data (attrition bias)	High risk	missing values retrieved if possible, verify database accuracy by reabstracting 10%, compare outlying values to patient records
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (blood loss)
Risk of bias due to conflict of interest/funding	Low risk	no funding, no conflicts of interest declared

Jaffer 2021

Methods	retrospective comparative cohort study (from a prospective maintained institutional database)
Participants	Origin/Country: Toronto (Ontario), Canada Sample size: 433 (revised) Sex: ?, no difference between groups Mean age: ?, no difference between groups Performed surgery: hepatectomy for CRLM Inclusion criteria: adults, no missing data
Interventions	Group 1: intervention (n = 146) tranexamic acid; single bolus [1 g] prior to incision & continuous infusion [10 mg/kg], until completion **or** single bolus [1 g] during procedure Group 2: control (n = 287)
Outcomes	transfusion requirements, 90d-mortality, 30d-morbidity, length of stay

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	retrospective comparative cohort study
Allocation concealment (selection bias)	High risk	no information provided

Blinding of participants and personnel(performance bias)	High risk	surgeon-level bias: portal pedicle clamping in TXA group
Blinding of outcome assessment (detection bias)	High risk	retrospective
Incomplete outcome data (attrition bias)	Unclear risk	no information provided
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (blood loss, exact number of transfused units, AE)
Risk of bias due to conflict of interest/funding	Unclear risk	no information provided

Wright 2020

Methods	randomized, double-blind, placebo-controlled trial; single tertiary referral center
Participants	Origin/Country: Grand Rapids (Michigan), USA Sample size: 76 (revised) Sex: 17 women (22%), 59 men (78%) Mean age: 61 years Performed surgery: major oncological surgery Inclusion criteria: undergoing major oncological surgery (n=76); similar in demographics + surgical procedures
Interventions	Group 1: intervention (n = 39) tranexamic acid; single bolus [1 g]; before surgical incision Group 2: control (n = 37) plasma-lyte-A
Outcomes	blood loss, blood transfusion requirement, Hgb-change, TE, Clavien-Dindo, mortality; hospital/ICU-stay, operating time; adverse events/ complications
Notes	2nd interim analysis early due to slow accrual, likelihood to achieve sign. Result at 2.1 % → halted: pre-specified stopping rules

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	block randomization (1:1); randomization schema by honest broker (envelopes)

Allocation concealment (selection bias)	Low risk	randomization by honest broker (envelopes sequentially nrd. to determine allocation), study nr. assigned, provided to research pharmacy, formulation prepared + labeled ("TXA or P"), packaged in identical fashion
Blinding of participants and personnel (performance bias)	Low risk	all parties remained blinded
Blinding of outcome assessment (detection bias)	Low risk	outcome data abstracted by blinded house staff
Incomplete outcome data (attrition bias)	Unclear risk	4 TXA(10.3%), 3 P(8.1%) no compl. surgery → incl. for intention-to-treat-principles
Selective reporting (reporting bias)	Unclear risk	no information provided
Risk of bias due to conflict of interest/funding	High risk	Spectrum Health foundation

Chakravartty 2016

Methods	prospective trial
Participants	Origin/Country: Department of Surgery, King's College Hospital NHS Foundation Trust, Denmark Hill, London Sample size: 50 (revised) Sex: 40 women (80%), 10 men (20%) Mean age: 38.5 years Performed surgery: laparoscopic sleeve gastrectomy Inclusion criteria: national & international criteria for weight loss surgery Exclusion criteria: any anticoagulant or immunosuppressant medication
Interventions	Group 1: intervention (n = 25) tranexamic acid; single bolus [1 g]; at induction Group 2: control (n = 25) no intervention
Outcomes	TE, mortality, morbidity

Risk of bias table

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	prospective trial, patients matched → no randomization

Allocation concealment (selection bias)	High risk	no randomization - no allocation
Blinding of participants and personnel (performance bias)	High risk	no blinding of surgeons
Blinding of outcome assessment (detection bias)	Unclear risk	no information provided
Incomplete outcome data (attrition bias)	Low risk	no drop-outs
Selective reporting (reporting bias)	High risk	important outcomes not addressed (transfusion)
Risk of bias due to conflict of interest/funding	Low risk	no competing interests declared

Grass 2019

Methods	retrospective cohort study, non-randomized; single-center
Participants	Origin/Country: 200 caucasian (93.9%), 13 not caucasian (6.1%) Sample size: 213 (revised) Sex: 89 women (42%), 124 men (58%) Mean age: 54 years Performed surgery: elective CRS (partial or total colectomy, rectal resection, other) by single surgeon Inclusion criteria: adults Exclusion criteria: < 18y, preoperative use of anticoagulants, emergency operation, multidisciplinary procedure with additional organ resection
Interventions	Group 1: intervention (n = 81) tranexamic acid; repetitive (2x) bolus [1 g]; at induction & at closure Group 2: control (n = 132) historical cohort
Outcomes	blood loss, blood transfusion requirements, Hgb-change, TE, neurological events

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	non-randomized, retrospective with historical cohort; data prospectively

Allocation concealment (selection bias)	High risk	collected; single surgeon/single-center approach to limit selection bias
Blinding of participants and personnel (performance bias)	Unclear risk	no information provided
Blinding of outcome assessment (detection bias)	Unclear risk	no information provided
Incomplete outcome data (attrition bias)	Unclear risk	no information provided
Selective reporting (reporting bias)	High risk	important outcomes not reported (exact vol. of blood loss, type of AE)
Risk of bias due to conflict of interest/funding	Low risk	no specific grant, no conflict of interest declared

Prasad 2018

Methods	prospective, randomized, double-blind study
Participants	Origin/Country: Dpt. Of Anaesthesiology and Intensive Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India Sample size: 60 (revised) Sex: 18 women (30%), 42 men (70%) Mean age: 47.5 years Performed surgery: elective open abdominal tumor surgery Inclusion criteria: adults (m/f), ASA 1/2, elective surgery, informed consent Exclusion criteria: history of bleeding diathesis, PE, DVT, hepatic resection, liver surgery, laparoscopic tumor removal, known TXA allergy
Interventions	Group 1: intervention (n = 20) tranexamic acid; single bolus [10 mg/kg] & continuous infusion of normal saline; from before incision until 4h postop. Group 2: intervention (n = 20) tranexamic acid; single bolus [10 mg/kg] & continuous infusion [1 mg/kg*h]; from before incision until 4h postop. Group 3: control (n = 20) normal saline; equal administration
Outcomes	blood loss, blood transfusion requirements, Hgb-change, TE, seizures, adverse events/complications

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	randomly assigned by computer-generated randomization table
Allocation concealment (selection bias)	Low risk	drug infusions prepared by person with access to computer-generated table, not involved in data collection/patient management
Blinding of participants and personnel (performance bias)	Low risk	all blinded to intervention; total volume of infusion kept similar - control with equal volumes of normal saline
Blinding of outcome assessment (detection bias)	Low risk	data collection: person completely blinded; statistical analyze: not involved in randomization/data collection
Incomplete outcome data (attrition bias)	Unclear risk	no drop-outs reported
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (transfusion requirements, mortality)
Risk of bias due to conflict of interest/funding	Low risk	no support/sponsorship, only institutional/ clinical funds, no conflicts of interest declared

Hamada 1995

Methods	randomized, controlled study
Participants	Origin/Country: Onomichi & Hiroshima, Matsue; Japan Sample size: 30 (revised) Sex: not stated Mean age: 58.5 years Performed surgery: elective major abdominal surgery Inclusion criteria: adults, ASA 1/2 Exclusion criteria: preop. coagulopathy, anticoagulant/antiplatelet medication
Interventions	Group 1: intervention (n = 15) tranexamic acid; single bolus [1 g] with 50 mg CS; within 30 min Group 2: control (n = 15) no intervention
Outcomes	blood loss, operating time, thromboelastography

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no further information on randomization process provided
Allocation concealment (selection bias)	Unclear risk	no information provided
Blinding of participants and personnel (performance bias)	Unclear risk	control with no intervention
Blinding of outcome assessment (detection bias)	Unclear risk	control with no intervention
Incomplete outcome data (attrition bias)	Unclear risk	no drop-outs reported
Selective reporting (reporting bias)	Unclear risk	important outcomes not reported (transfusion requirements etc.)
Risk of bias due to conflict of interest/funding	Unclear risk	no information provided

Pfizer 2012

Methods	prospective randomized study
Participants	Sample size: 94; Post-randomization drop-out(s): 12 (6 each) Revised sample size: 82 Sex: 32 women (34%), 62 men (66 %) Mean age: not stated Performed surgery: major abdominal surgery (esophagectomy, biliary strictures, gastrectomy, pancreaticoduodenectomy, hemicolectomy, total proctocolectomy, other) Inclusion criteria: adults, major abdominal surgery, no healthy volunteers Exclusion criteria: platelets <100.000/mm³ or thrombocytopenia; known coagulopathy; anemia (Hb <8mg/dl); DVT/PE at screening/past 3 months; any associated major illness; anticoagulants (other than LMWH/prophylactic heparin), direct thrombin inhibitors, thrombolytic therapy within 1 week
Interventions	Group 1: intervention (n = 49) tranexamic acid; 3x slow bolus [15 mg/kg]; 15 min before surgery, 3 & 6 h after first bolus

	Group 2: control (n = 45) no intervention
Outcomes	postop./intraop./total blood loss, transfusion requirement, Hb-level, postop. DVT
Notes	Trial protocol, not published

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	no further information provided
Allocation concealment (selection bias)	Unclear risk	no further information provided
Blinding of participants and personnel (performance bias)	Unclear risk	no further information provided
Blinding of outcome assessment (detection bias)	Unclear risk	no further information provided
Incomplete outcome data (attrition bias)	Low risk	post-randomization drop-outs + reason reported, intention-to-treat analysis?
Selective reporting (reporting bias)	Low risk	all important outcomes reported
Risk of bias due to conflict of interest/funding	High risk	sponsored by Pfizer

Summary of findings tables

1 TXA compared to inactive control/other antifibrinolytics for reduction of perioperative blood loss

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: inactive control/other antifibrinolytics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with comparison	**Risk with TXA**			
Blood loss: TXA versus inactive control	29.1577 L (n = 539)	17.9264 L (n = 422)	MD **0.02 L lower** (0.08 lower to 0.05 higher)	961 (10 studies)	-[a]
Blood loss: TXA versus normal saline	9.4488 L (n = 182)	5.6606 L (n = 189)	MD **0.05 L lower** (0.18 lower to 0.07 higher)	371 (4 RCTs)	⊕⊕⊕◯ Moderate[b]
Blood loss: TXA versus no intervention	19.7089 L (n = 357)	12.2658 L (n = 233)	MD **0.01 L lower** (0.08 lower to 0.06 higher)	590 (6 observational studies)	⊕⊕◯◯ Low[a]
Blood loss: low risk of bias	9.5577 L (n = 197)	5.7444 L (n = 204)	MD **0.04 L lower** (0.14 lower to 0.06 higher)	401 (5 RCTs)	⊕⊕⊕⊕ High[b]
blood loss: high risk of bias	19.6 L (n = 342)	12.182 L (n = 218)	MD **0.01 L higher** (0.1 lower to 0.11 higher)	560 (5 observational studies)	⊕⊕◯◯ Low[c]
Blood loss: TXA vs. Aprotinin	11.46 L (n = 87)	11.86 L (n = 99)	MD **0.34 L lower** (1.13 lower to 0.45 higher)	186 (3 studies)	-[a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **MD:** mean difference

Explanations

a. studies of high and low risk of bias included in the analysis
b. large heterogeneity among the included trials
c. studies of high risk of bias, mostly due to study design (no RCT, historical control, retrospective study etc.)

2 TXA compared to inactive control for reduction of perioperative transfusion requirements

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with TXA**			
RBC transfusion: TXA vs. Control	24.805 U (n = 461)	31.93 U (n = 565)	MD **1.73 U lower** (3.05 lower to 0.41 lower)	1026 (6 studies)	-[a]
RBC transfusion: low risk of bias	21.37 U (n = 76)	14.93 U (n = 163)	MD **2.07 U lower** (5.21 lower to 1.08 higher)	239 (3 RCTs)	⊕⊕⊕⊕ High
RBC transfusion: high risk of bias	25 U (n = 385)	17 U (n = 402)	MD **1.45 U lower** (3.34 lower to 0.44 higher)	787 (3 observational studies)	⊕⊕◯◯ Low[b]
RBC transfusion: TXA vs. Control	**269 per 1.000**	**169 per 1.000** (121 to 239)	**RR 0.63** (0.45 to 0.89)	1251 (10 studies)	-[a]
RBC transfusion: low risk of bias	**341 per 1.000**	**201 per 1.000** (99 to 412)	**RR 0.59** (0.29 to 1.21)	537 (6 RCTs)	⊕⊕⊕⊕ High
RBC transfusion high risk of bias	**233 per 1.000**	**145 per 1.000** (103 to 203)	**RR 0.62** (0.44 to 0.87)	714 (4 observational studies)	⊕⊕◯◯ Low[b]
FFP transfusion: TXA vs. Control	59.55 U (n = 461)	43.57 U (n = 565)	MD **1.9 U lower** (3.58 lower to 0.22 lower)	1026 (6 studies)	-[a]
FFP transfusion: low risk of bias	20.55 U (n = 76)	14.57 U (n = 163)	MD **1.94 U lower** (4.58 lower to 0.71 higher)	239 (3 RCTs)	⊕⊕⊕⊕ High
FFP transfusion: high risk of bias	39 U (n = 385)	29 U (n = 402)	MD **3.02 U lower** (8.5 lower to 2.45 higher)	787 (3 observational studies)	⊕⊕⊕◯ Moderate[b]
Platelet transfusion: TXA vs. Control	27.42 U (n = 461)	20.93 U (n = 565)	MD **1.13 U lower** (3.13 lower to 0.87 higher)	1026 (6 studies)	-[a]
Platelet transfusion: low risk of bias	24.42 U (n = 76)	17.93 U (n = 163)	MD **1.52 U lower** (9.89 lower to 6.86 higher)	239 (3 RCTs)	⊕⊕⊕⊕ High

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with TXA**			
Platelet transfusion: high risk of bias	5 U (n = 385)	3 U (n = 402)	MD **0.58 U lower** (1.39 lower to 0.23 higher)	787 (3 observational studies)	⊕⊕◯◯ Low[b]
Cryoprecipitate transfusion: TXA vs. Control	32.3 U (n = 86)	33.2 U (n = 188)	MD **2.92 U lower** (7.58 lower to 1.75 higher)	274 (4 studies)	-[a,c]
Cryoprecipitate transfusion: low risk of bias	22.3 U (n = 76)	3.2 U (n = 163)	MD **6.55 U lower** (8.73 lower to 4.37 lower)	239 (3 RCTs)	⊕⊕⊕⊕ High
Cryopercipitate transfusion: high risk of bias	10 U (n = 10)	30 U (n = 25)	MD **20 U higher** (10.27 higher to 29.73 higher)	35 (1 observational study)	⊕⊕◯◯ Low[b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations
a. studies of high and low risk of bias were included in the analysis
b. included studies were of high or intermediate risk of bias
c. serious heterogeneity existed among the studies

3 TXA compared to inactive control in major abdominal surgery

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	Risk with TXA			
thromboembolic events	**12 per 1.000**	**22 per 1.000** (12 to 42)	**RR 1.84** (0.96 to 3.50)	2107 (13 studies)	-[a]
thromboembolic events - low risk	**13 per 1.000**	**15 per 1.000** (4 to 51)	**RR 1.16** (0.34 to 4.04)	589 (6 RCTs)	⊕⊕⊕⊕ High
thromboembolic events - high risk	**12 per 1.000**	**26 per 1.000** (12 to 55)	**RR 2.17** (1.02 to 4.63)	1518 (7 observational studies)	⊕⊕◯◯ Low[b]
seizures	**7 per 1.000**	**5 per 1.000** (1 to 35)	**RR 0.75** (0.11 to 5.09)	686 (3 studies)	-[a]
seizures - low risk	**0 per 1.000**	**0 per 1.000** (0 to 0)	not estimable	40 (1 RCT)	⊕⊕⊕⊕ High
seizures - high risk	**7 per 1.000**	**5 per 1.000** (1 to 36)	**RR 0.75** (0.11 to 5.09)	646 (2 observational studies)	⊕⊕◯◯ Low[b]
adverse events	**228 per 1.000**	**235 per 1.000** (201 to 279)	**RR 1.03** (0.88 to 1.22)	1744 (10 studies)	-[a]
adverse events - low risk	**166 per 1.000**	**129 per 1.000** (85 to 197)	**RR 0.78** (0.51 to 1.19)	477 (6 RCTs)	⊕⊕⊕⊕ High
adverse events - high risk	**254 per 1.000**	**274 per 1.000** (231 to 328)	**RR 1.08** (0.91 to 1.29)	1235 (4 observational studies)	⊕⊕◯◯ Low[b]
mortality	**18 per 1.000**	**24 per 1.000** (12 to 48)	**RR 1.32** (0.66 to 2.64)	1669 (9 studies)	-[a]
mortality - low risk	**32 per 1.000**	**28 per 1.000** (7 to 109)	**RR 0.89** (0.23 to 3.40)	449 (5 RCTs)	⊕⊕⊕⊕ High
mortality - high risk	**13 per 1.000**	**24 per 1.000** (10 to 58)	**RR 1.76** (0.72 to 4.30)	1220 (4 observational studies)	⊕⊕◯◯ Low[b]
operating time	2613.2 min (n = 859)	2598.2 min (n = 737)	MD **4.29 min higher** (10.4 lower to 18.97 higher)	1596 (8 studies)	-[a]
operating time - low risk	673.2 min (n = 158)	644.2 min (n = 162)	MD **11.67 min lower** (63.28 lower to 39.95 higher)	320 (3 RCTs)	⊕⊕⊕⊕ High
operating time - high risk	1940 min (n = 701)	1954 min (n = 575	MD **10.49 min higher** (4.5 lower to 25.48 higher)	1276 (5 observational studies)	⊕⊕◯◯ Low[b]

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with control	**Risk with TXA**			
hospital stay	66 d (n = 79)	78 d (n = 101)	MD **2.49 d higher** (0.33 lower to 5.32 higher)	613 (5 studies)	-[a]
hospital stay - low risk	31 d (n = 57)	35.5 d (n = 64	MD **1.75 d higher** (1.54 lower to 5.04 higher)	121 (2 RCTs)	⊕⊕⊕⊕ High
hospital stay - high risk	35 d (n = 309)	42.5 d (n= 183)	MD **2.77 d higher** (1.76 lower to 7.3 higher)	492 (3 observational studies)	⊕⊕◯◯ Low[b]
ICU stay	10 d (n = 67)	8.5 d (n = 89)	MD **0.43 d lower** (1.31 lower to 0.45 higher)	156 (3 studies)	-[a]
ICU stay - low risk	4 d (n = 57)	3 d (n = 64)	MD **0.44 d lower** (1.41 lower to 0.53 higher)	121 (2 RCTs)	⊕⊕⊕⊕ High
ICU stay - high risk	6 d (n = 10)	5.5 d (n = 25)	MD **0.5 d lower** (4.84 lower to 3.84 higher)	35 (1 observational study)	⊕⊕◯◯ Low[b]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. studies of high and low risk of bias were included in this analysis

b. studies included were of high or intermediate risk of bias

4 TXA compared to Aprotinin for reduction of perioperative transfusion requirements

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: Aprotinin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with Aprotinin	**Risk with TXA**			
RBC transfusion: TXA vs. Aprotinin	15.94 U (n = 187)	16.54 U (n = 399)	MD **0.13 U lower** (0.41 lower to 0.16 higher)	586 (4 observational studies)	⊕◯◯◯ Very low[a]
FFP transfusion: TXA vs. Aprotinin	26.79 U (n = 187)	24.4 U (n = 399)	MD **0.01 U higher** (0.24 lower to 0.25 higher)	586 (4 observational studies)	⊕◯◯◯ Very low[a]
Platelet transfusion: TXA vs. Aprotinin	7.64 U (n = 187)	7.12 U (n = 399)	MD **0.06 U higher** (0.73 lower to 0.85 higher)	586 (4 observational studies)	⊕◯◯◯ Very low[a]
Cryoprecipitate transfusion: TXA vs. Aprotinin	9 U (n = 14)	30 U (n = 25)	MD **21 U higher** (13.93 higher to 28.07 higher)	39 (1 observational study)	⊕◯◯◯ Very low[b]
Thromboembolic events: TXA vs. Aprotinin	**30 per 1.000**	**35 per 1.000** (14 to 88)	**RR 1.16** (0.46 to 2.95)	617 (4 observational studies)	⊕◯◯◯ Very low[a]
Adverse events: TXA vs. Aprotinin	**79 per 1.000**	**110 per 1.000** (37 to 326)	**RR 1.38** (0.46 to 4.11)	127 (1 RCT)	⊕⊕⊕⊕ High
Mortality: TXA vs. Aprotinin	**86 per 1.000**	**121 per 1.000** (39 to 370)	**RR 1.41** (0.46 to 4.32)	578 (3 observational studies)	⊕◯◯◯ Very low[a]
Operating time: TXA vs. Aprotinin	256.83 min (n = 114)	245 min (n = 325)	MD **3.27 min lower** (14.01 lower to 7.47 higher)	439 (2 observational studies)	⊕◯◯◯ Very low[b]
ICU stay: TXA vs. Aprotinin	700 per 1.000	**357 per 1.000** (161 to 805)	**RR 0.51** (0.23 to 1.15)	24 (1 observational study)	⊕◯◯◯ Very low[b]
Hospital stay: TXA vs. Aprotinin	24 d (n = 14)	19.5 d (n = 25)	MD **4.5 d lower** (8.12 lower to 0.88 lower)	39 (1 observational study)	⊕◯◯◯ Very low[b]

Explanations
a. included studies with high and low risk of bias
b. non-randomized study with a high risk of bias

5 TXA compared to EACA for reduction of perioperative transfusion requirements

Patient or population: patients undergoing major abdominal surgery
Intervention: TXA
Comparison: EACA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with EACA	**Risk with TXA**			
RBC transfusion: TXA vs. EACA	6 U (n = 42)	2.93 U (n = 122)	MD **3.07 U lower** (4.84 lower to 1.3 lower)	164 (1 RCT)	⊕⊕⊕⊕ High
FFP transfusion: TXA vs. EACA	4.45 U (n = 42)	1.57 U (n = 122)	MD **2.88 U lower** (4.77 lower to 0.99 lower)	164 (1 RCT)	⊕⊕⊕⊕ High
Platelet transfusion: TXA vs. EACA	8.29 U (n = 42)	7.93 U (n = 122)	MD **0.36 U lower** (3.49 lower to 2.77 higher)	164 (1 RCT)	⊕⊕⊕⊕ High
Cryoprecipitate transfusion: TXA vs. EACA	4.21 U (n = 42)	0.2 U (n = 122)	MD **4.01 U lower** (6.68 lower to 1.34 lower)	164 (1 RCT)	⊕⊕⊕⊕ High
Thromboembolic events: TXA vs. EACA	**48 per 1.000**	**49 per 1.000** (10 to 234)	**RR 1.03** (0.22 to 4.92)	164 (1 RCT)	⊕⊕⊕⊕ High
Adverse events: T TXA vs. EACA	**95 per 1.000**	**71 per 1.000** (17 to 300)	**RR 0.75** (0.18 to 3.15)	84 (1 RCT)	⊕⊕⊕⊕ High
Mortality: TXA vs. EACA	**95 per 1.000**	**71 per 1.000** (17 to 300)	**RR 0.75** (0.18 to 3.15)	84 (1 RCT)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Additional table: Doses used in the trials

Study	Bolus	time of admin.	continuous infusion	start time	end time	
Hamada 1995	1 x 1g		-	≤ 30 min after induction		
Boylan 1996	-		40 mg/kg*h	after induction	portal vein unclamping	≤ 20 mg
Kaspar 1997	-		2 mg/kg*h	after induction	upon completion	~0.83g (566-1667 mg)
Dalmau 2000	-		10 mg/kg*h	at induction	portal vein unclamping	
Dalmau 2004	-		10 mg/kg*h	at induction	portal vein unclamping	
Ickx 2006	1x 40 mg/kg	slow over 30 min	40 mg/kg*h	anhepatic phase, 30 min before reperfusion	2h after reperfusion	
Wu 2006	1x 500 mg, ?x 250 mg	loading dose, every 6h	-	just before operation	3 days postop.	
Devi 2008	10 mg/kg	every 6-8h	-	at induction	end of surgery	
		once	5 mg/kg*h		early reper-fusion phase	
Massicotte 2008	1x 30 mg/kg		16 mg/kg*h	Incision	portal vein anastomosis	
Pfizer 2012	3x 15 mg/kg	After 0, 3 6h	-	15 min before surgery	6h after first bolus	
Chakravartty 2015	1x 1g		-	at induction		
Karanicolas 2016	1x 1g		1g over 8h		after 8h	
	1x 1g		10 mg/kg*h		end of surgery	
Badenoch 2017	? x 1g	every 1h	-	?	?	
	-		10 mg/kg*h	incision	2h after reperfusion	
Prasad 2019	1x 10 mg/kg		-	10 min prior to incision	4h postop.	
			1 mg/kg*h			
Grass 2019	2x 1g	induction closure	-	induction	closure	
Jaffer 2020	1x 1g	prior to incision	10 mg/kg	incision	closure	~1.61g (1-3g)
		once	-	during surgery		
Wright 2020	1x 1g	over 15 min	-	before incision		

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Theses

1. Implications for TXA being beneficial to reducing blood loss and transfusion requirements in major abdominal surgery have been made. Significant differences regarding RBC (number of patients + amount of units) and FFP transfusion in favor of TXA were shown.
2. No significant increase of AE and TE under TXA administration has been conducted.
3. Subset differences showed a significant decrease of blood loss and transfusion requirements within the high-dose subgroup.
4. Overall completeness and applicability needs to be increased with most of the included studies dating back more than five years ago, interventions being predominantly hepatobiliary surgery esp. OLT and variating highly in dosing regimen as well as application interval.
5. Further research through adequately powered RCTs is necessary to investigate possible efficacy of TXA on reducing blood loss and transfusion requirement in major abdominal surgery.
6. Implementation of standardized dosing regimen, application intervals and way of delivery are needed to increase comparability.

Appendices

Search Strategy

Search strategy for PubMed platform NCBI (inception to July 22, 2021)

1 "General Surgery"[MeSH Terms] (39763)

2 "surgical procedures, operative"[MeSH Terms] (3287418)

3 "opera*"[Text Word] OR "surg*"[Text Word] OR "resect*"[Text Word] (4032363)

4 OR/1-3 (5364446)

5 "Tranexamic Acid"[MeSH Terms] (4051)

6 "tranexam*"[Text Word] (5997)

7 OR/5-6 (5997)

8 "Blood Transfusion"[MeSH Terms] (88410)

9 "Blood"[MeSH Terms] (1134812)

10 "blood*"[Text Word] (3935387)

11 OR/9-10

12 "transfusion*"[Text Word] (158303)

13 AND/11-12

14 "Blood Loss, Surgical"[Mesh] (18882)

15 "blood loss*"[Text Word] (64665)

16 OR/14-15 (64665)

17 "Hemorrhage"[MeSH Terms] (34653)

18 "hemorrhag*"[Text Word] OR "bleed*"[Text Word] (506303)

19 OR/17-18 (596971)

20 13 OR 16 OR 19 (736249)

21 4 AND 7 AND 20 (3036)

22 clinical trials as topic [mesh: noexp] (360833)

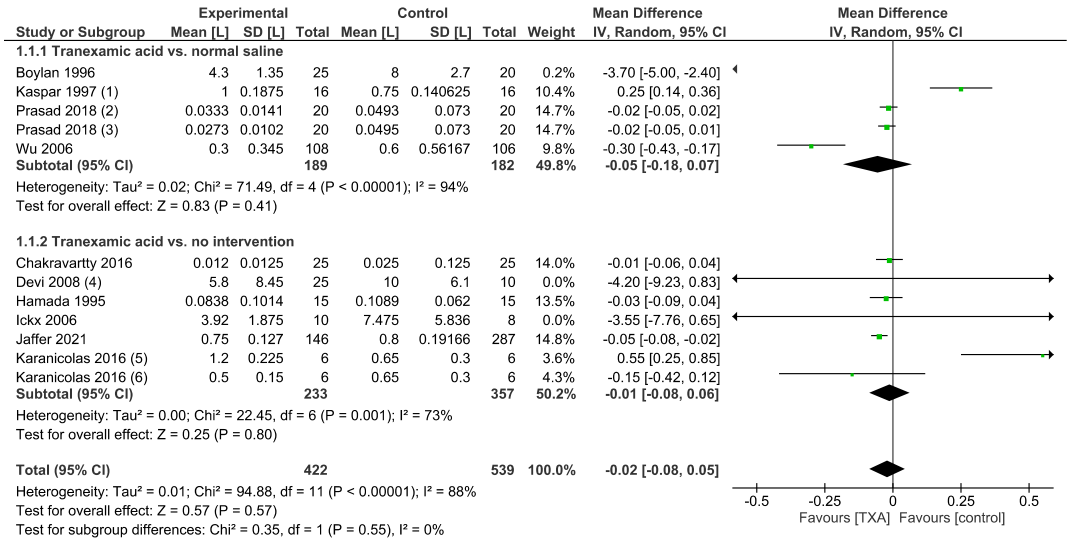
23 "RCT"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "randomly"[Title/Abstract] OR "trial"[Title] (1253215)

24 OR/22-23 (1471297)

25 21 AND 24 (1268)

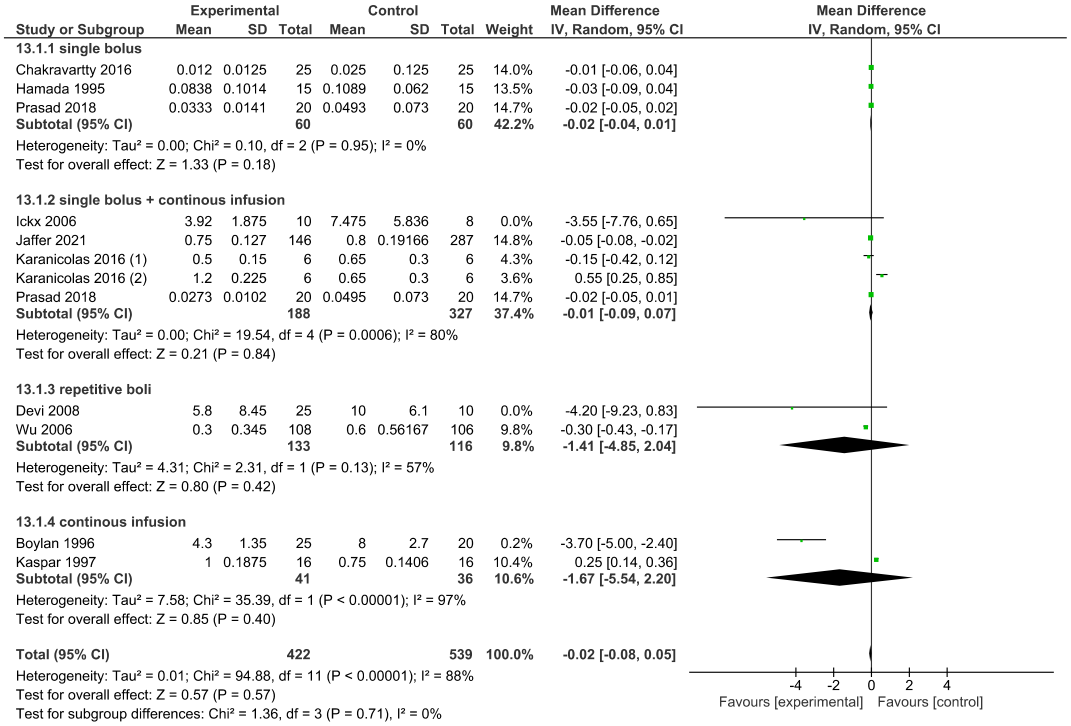
Figures

Analysis:
Blood loss



Footnotes
(1) cell saver
(2) single bolus
(3) single bolus + continous infusion
(4) non-randomized
(5) single bolus + 1g over 8 h
(6) single bolus + continous infusion of 10 mg/kg*h

Figure 5: TXA vs. placebo - blood loss



Footnotes
(1) single bolus + continous infusion of 10 mg/kg*h
(2) single bolus + 1g over 8 h

Figure 6: subset application interval - blood loss

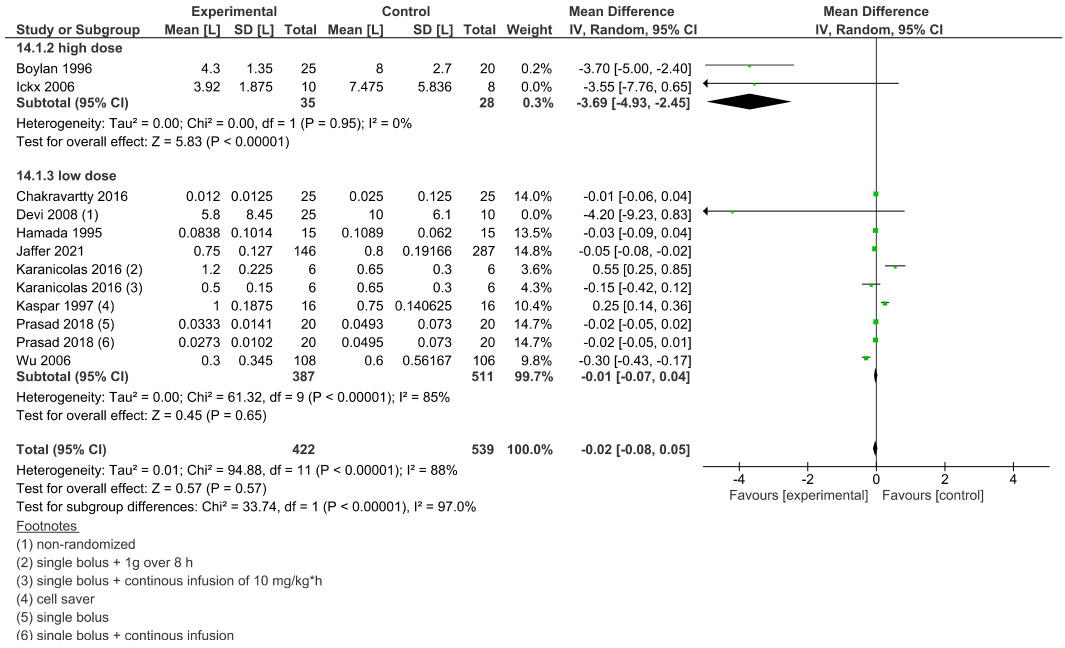


Figure 7: dosage regimen blood loss

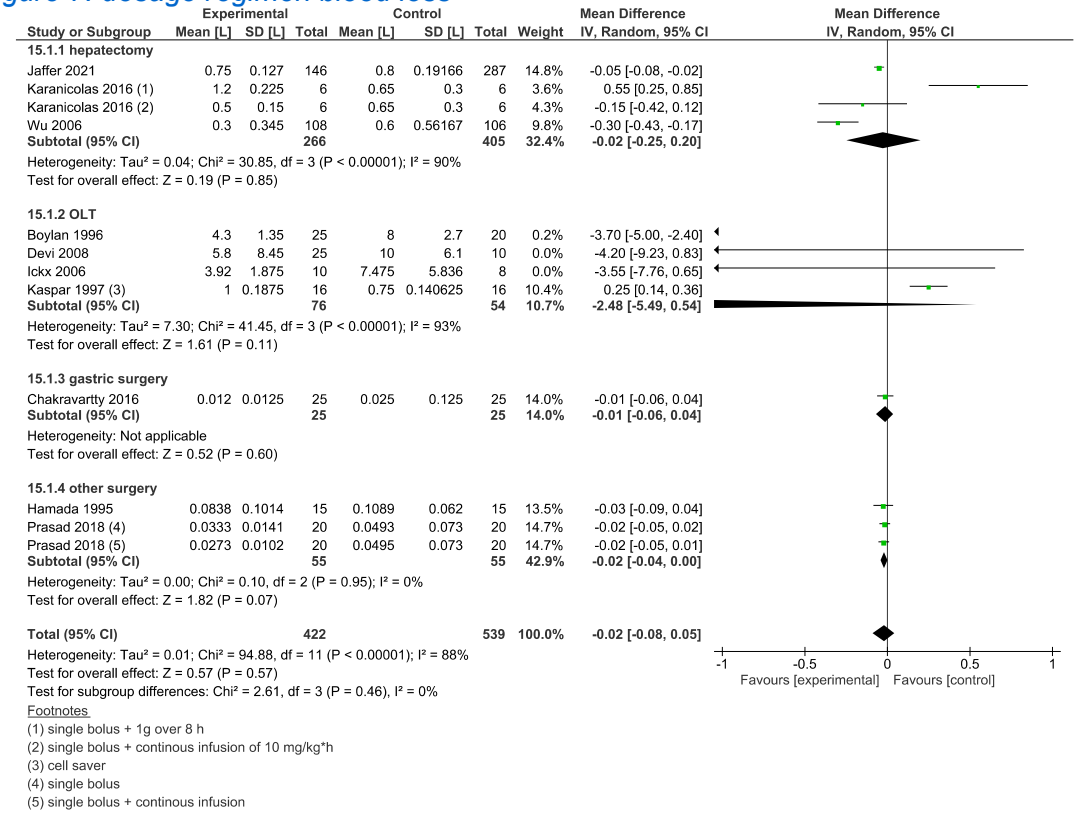


Figure 8: type of surgery blood loss

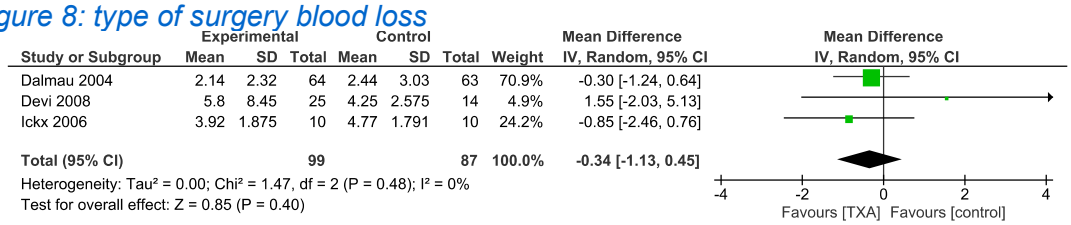


Figure 9: TXA vs. Aprotinin blood loss

Transfusion requirements

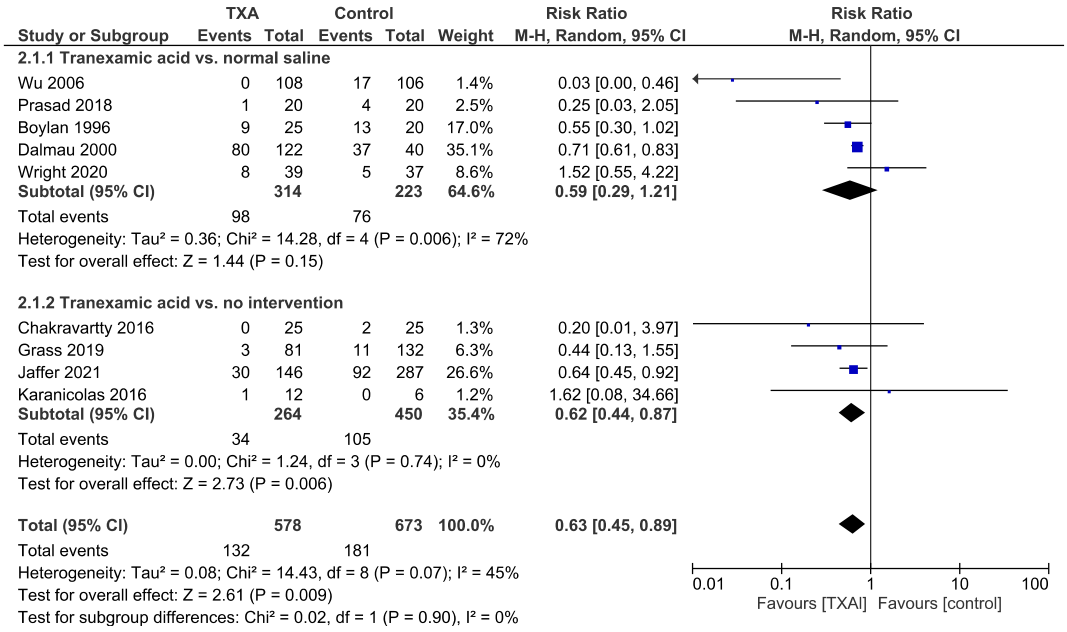


Figure 10: TXA vs. control patients receiving RBC transfusion

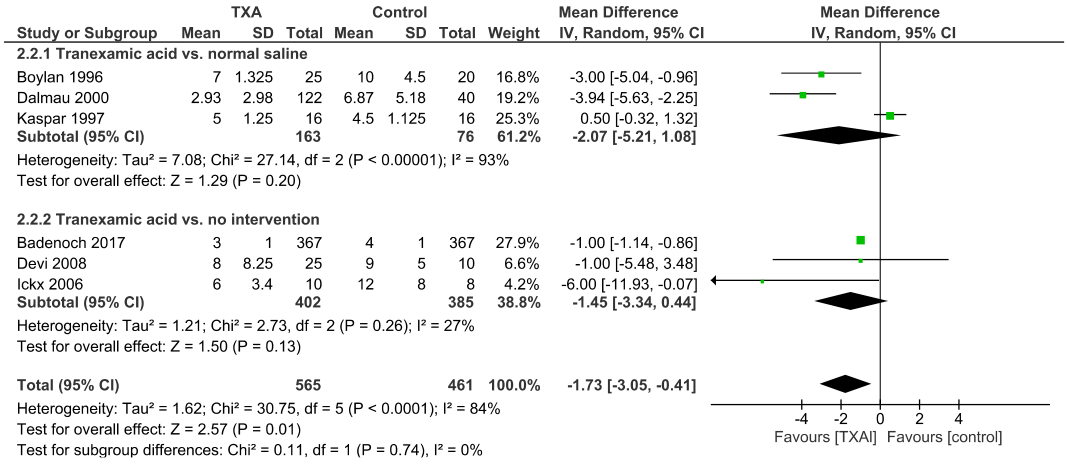


Figure 11: TXA vs. control RBC transfusion (units)

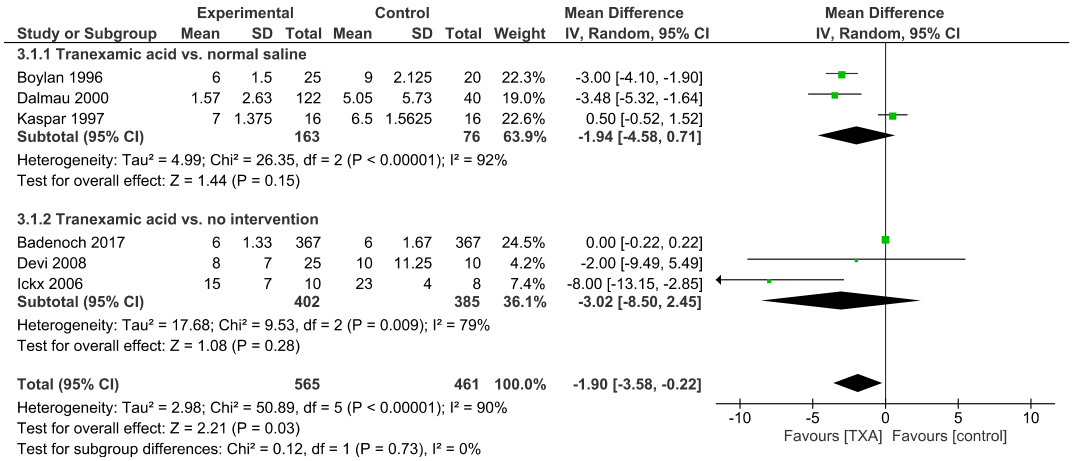


Figure 12: TXA vs control FFP transfusion

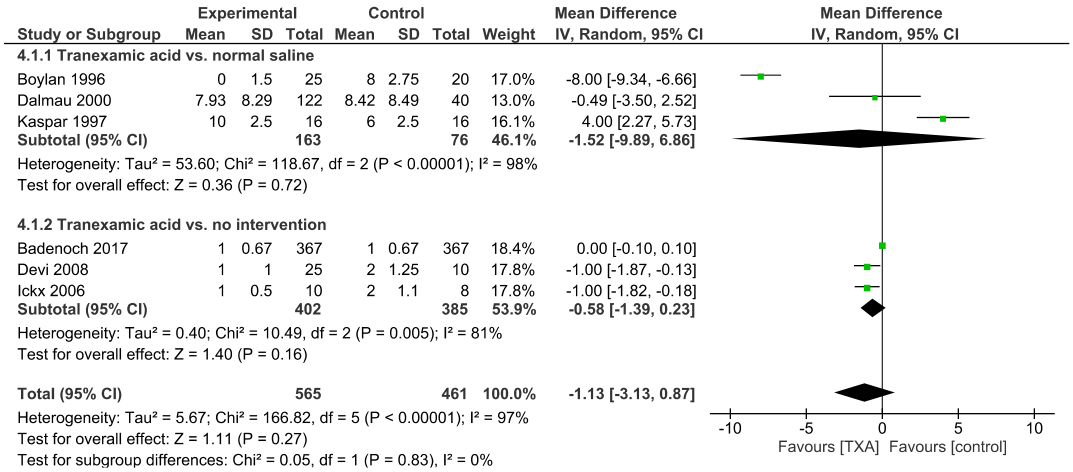


Figure 13: TXA vs. control Platelet transfusion

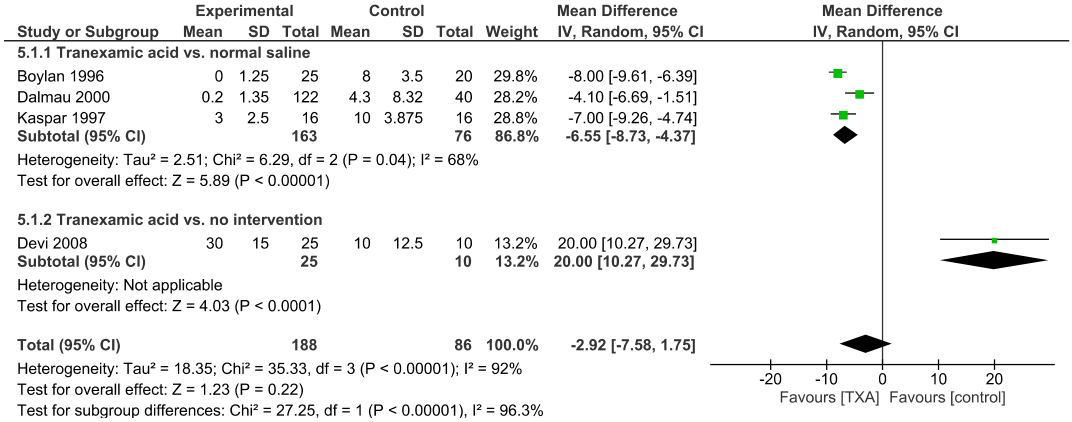


Figure 14: TXA vs. control cryoprecipitate transfusion

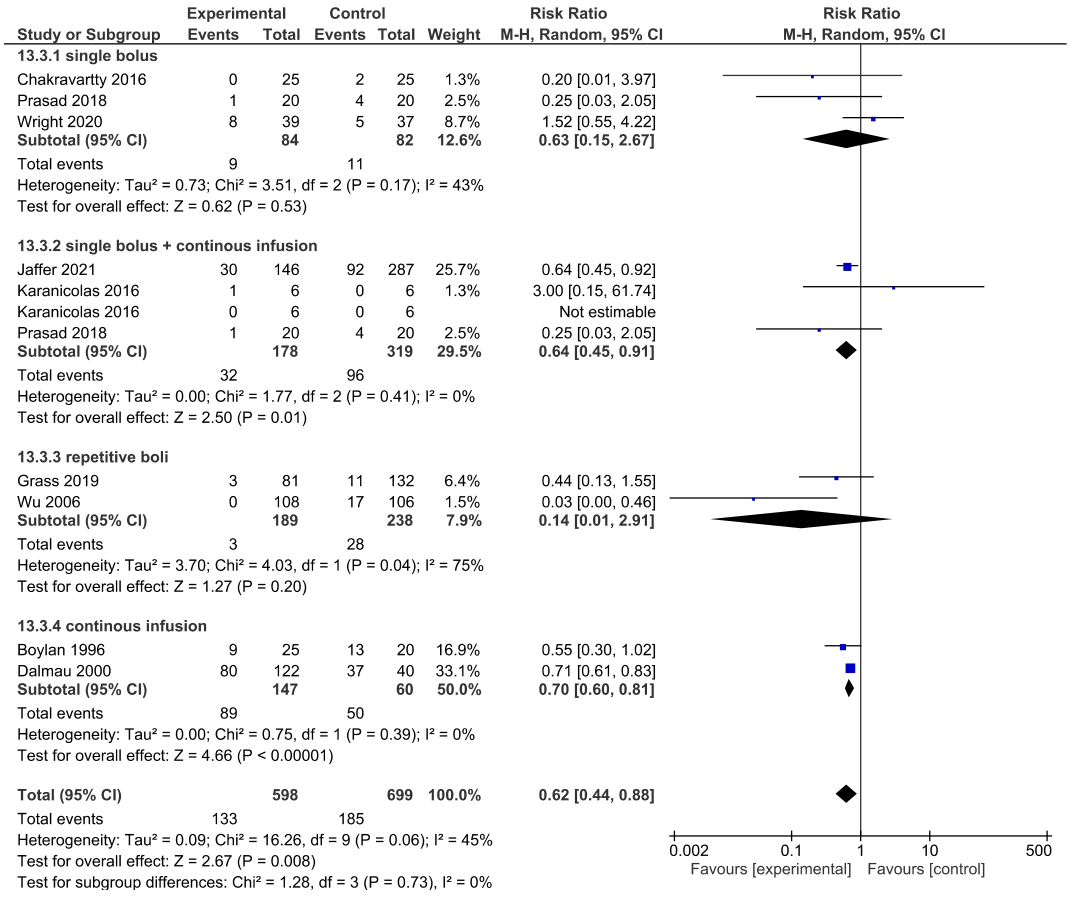


Figure 15: application interval patients in need of RBC transfusion

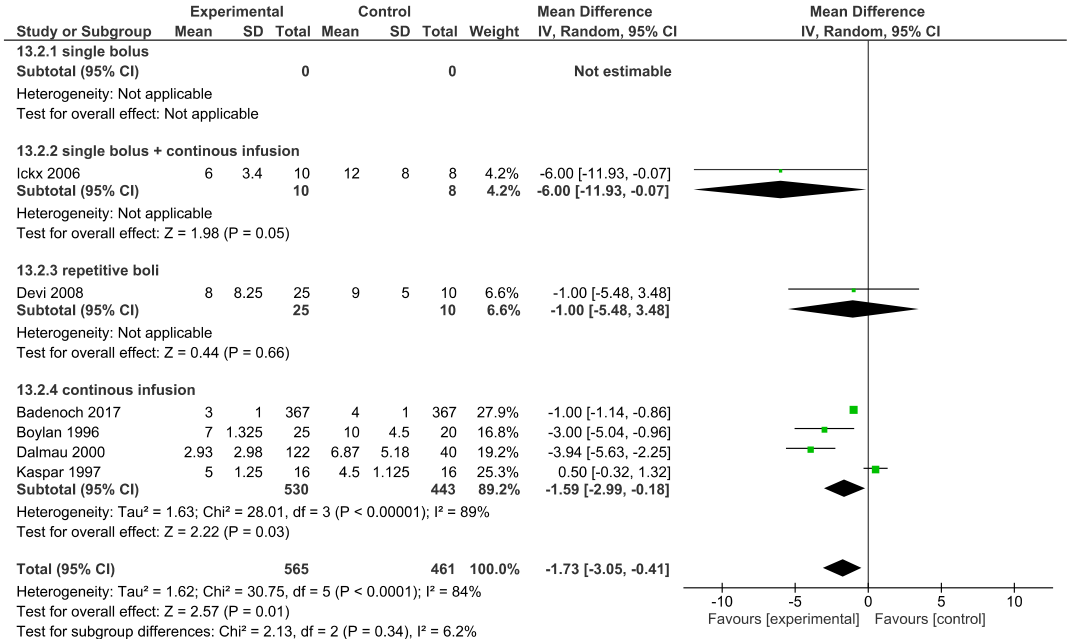


Figure 16: application interval RBC transfusion (units)

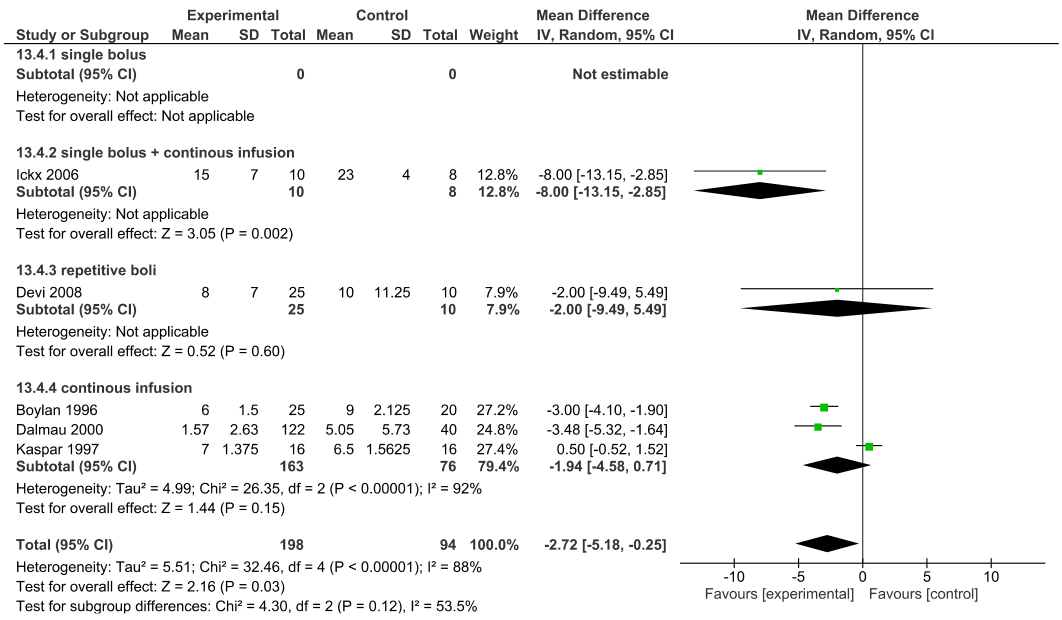


Figure 17: application interval FFP transfusion

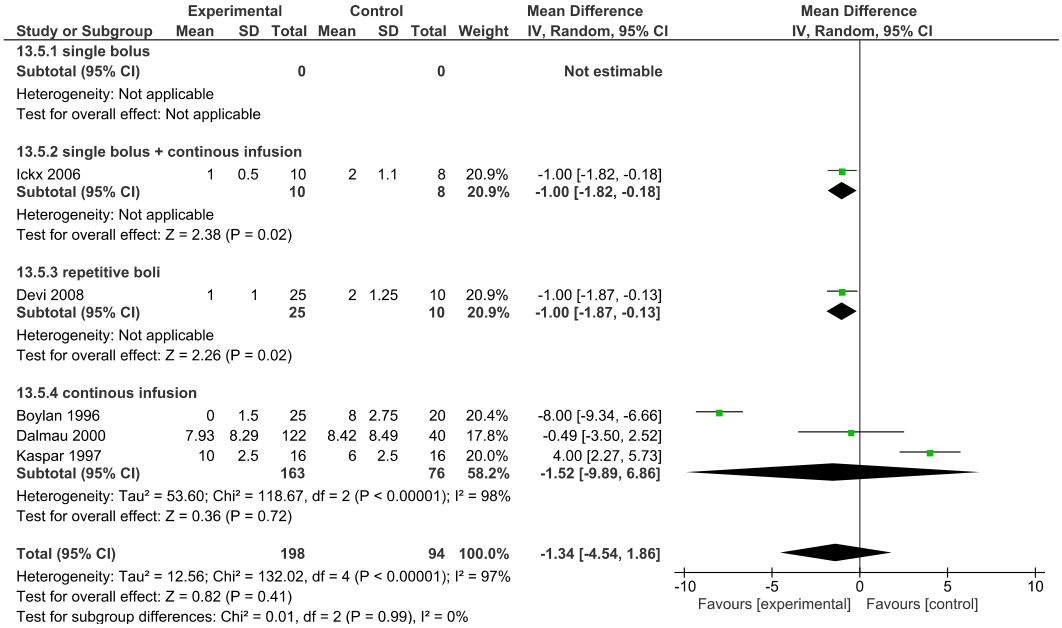


Figure 18: application interval platelet transfusion

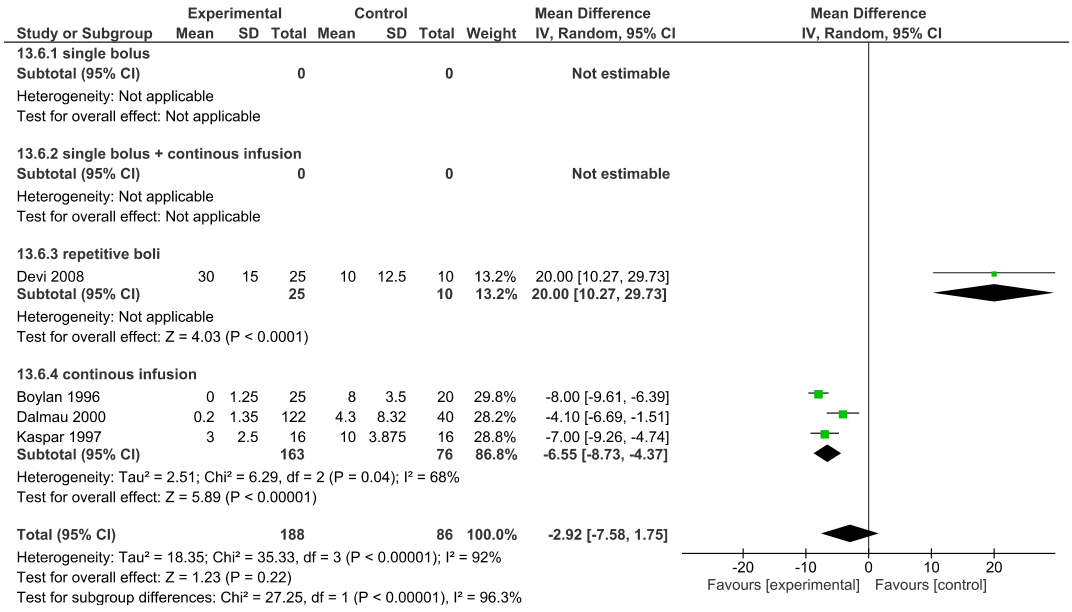


Figure 19: application interval cryoprecipitate transfusion

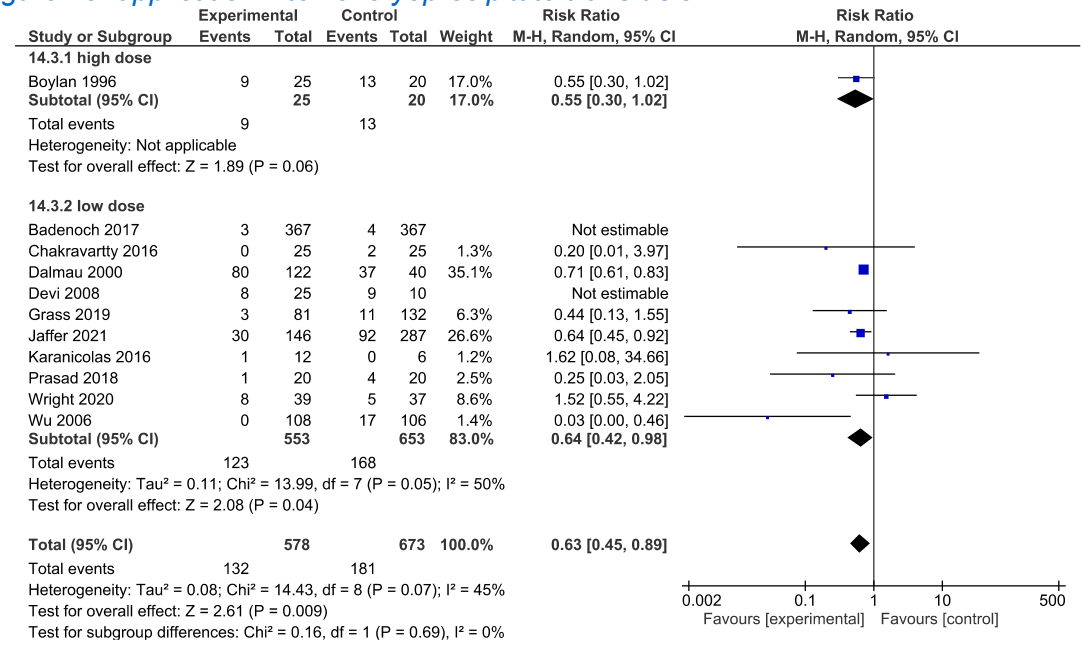


Figure 20: dosage regimen patients in need of RBC transfusion

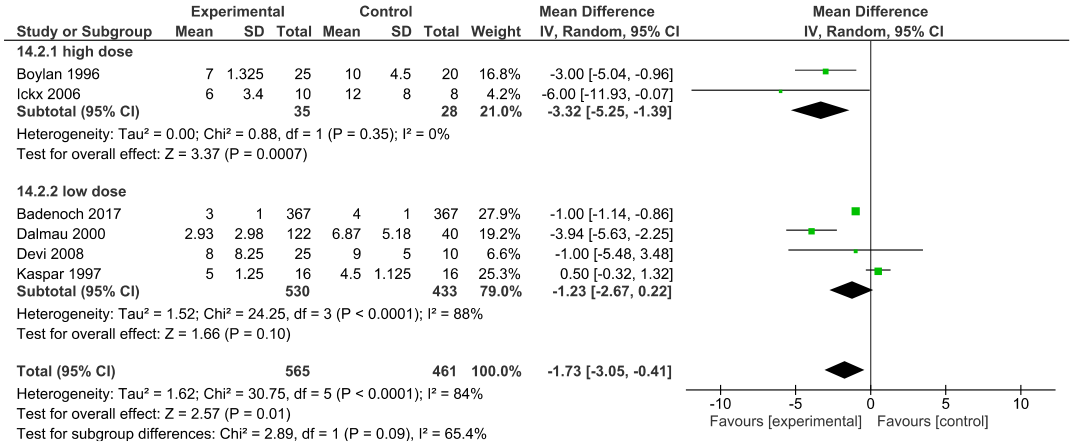


Figure 21: dosage regimen RBC transfusion (units)

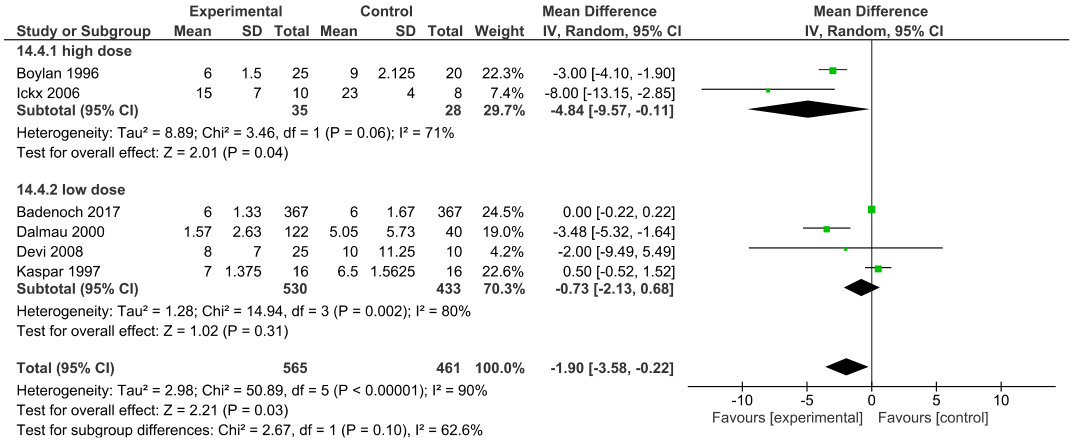


Figure 22: dosage regimen FFP transfusion

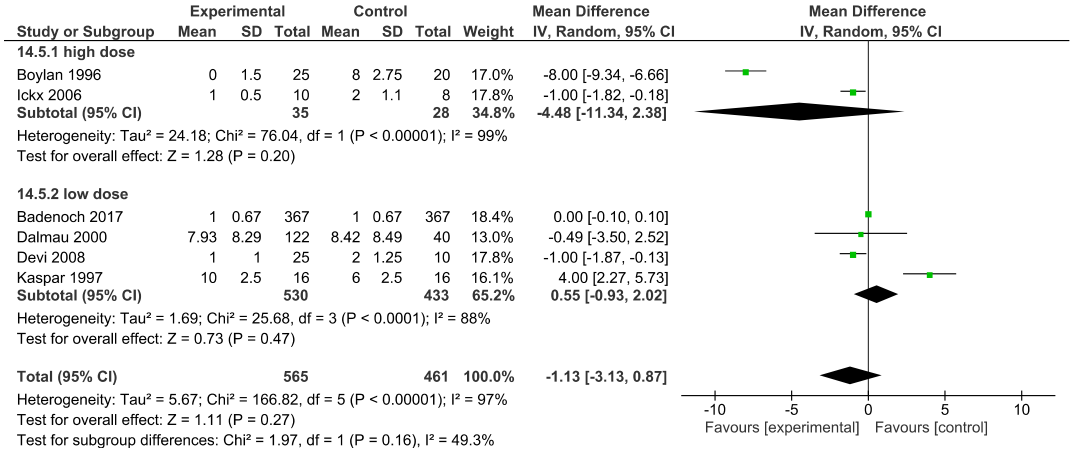


Figure 23: dosage regimen platelet transfusion

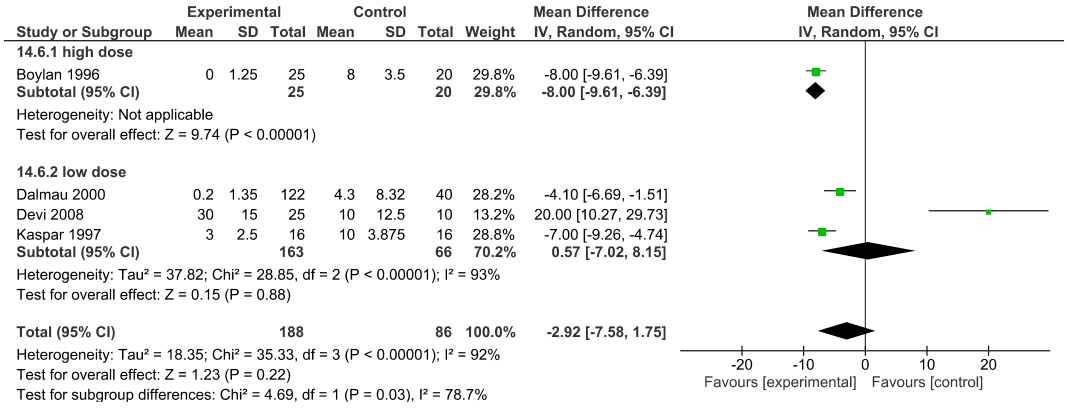


Figure 24: dosage regimen cryoprecipitate transfusion

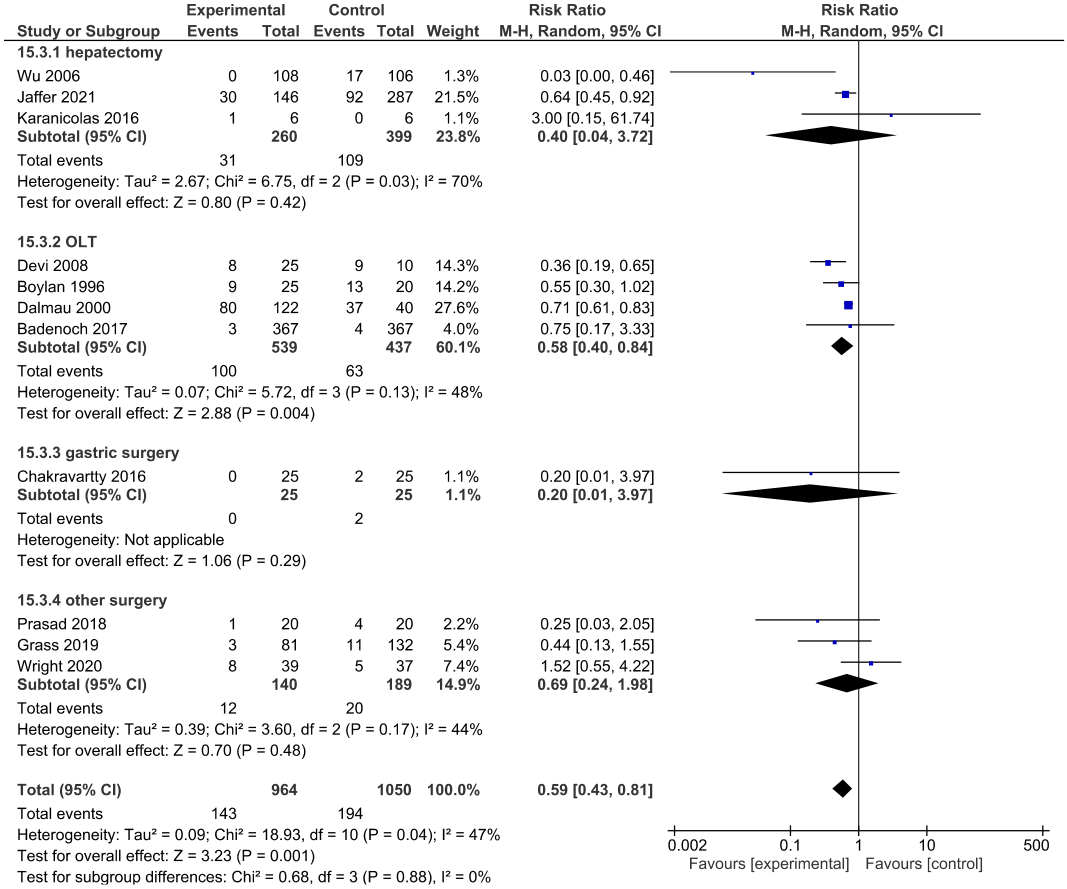


Figure 25: type of surgery patients in need of RBC transfusion

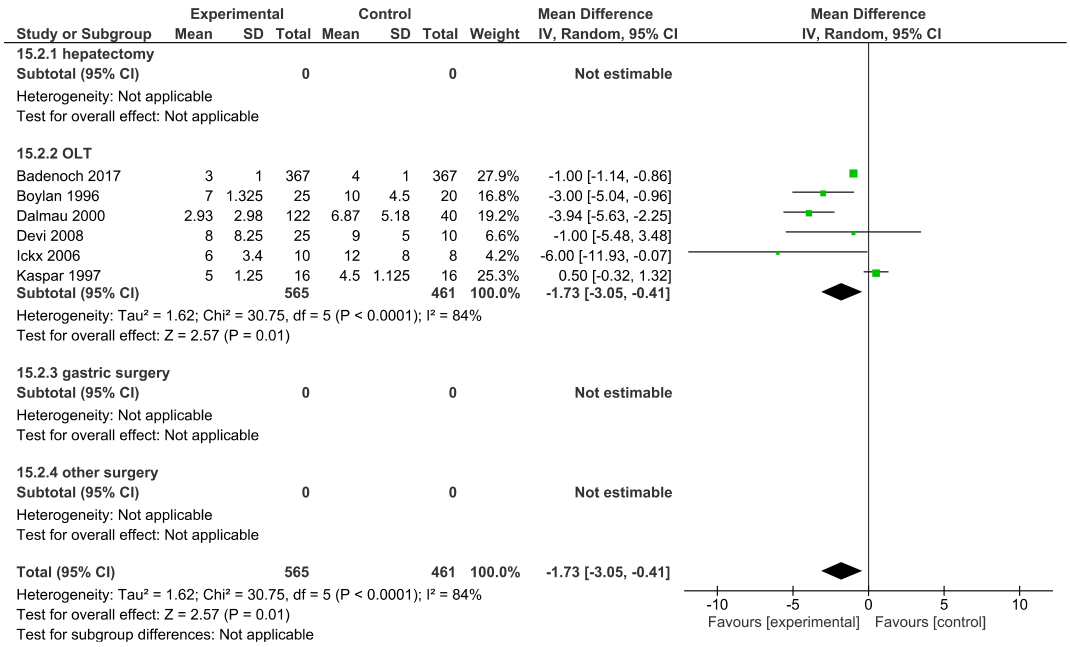


Figure 26: type of surgery RBC transfusion (units)

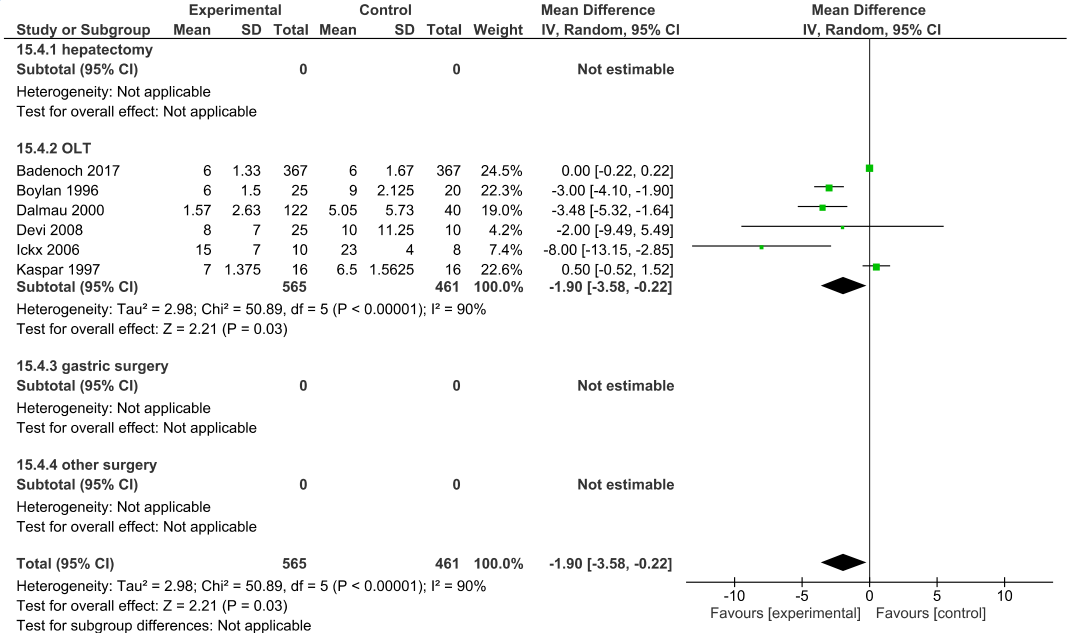


Figure 27: type of surgery FFP transfusion

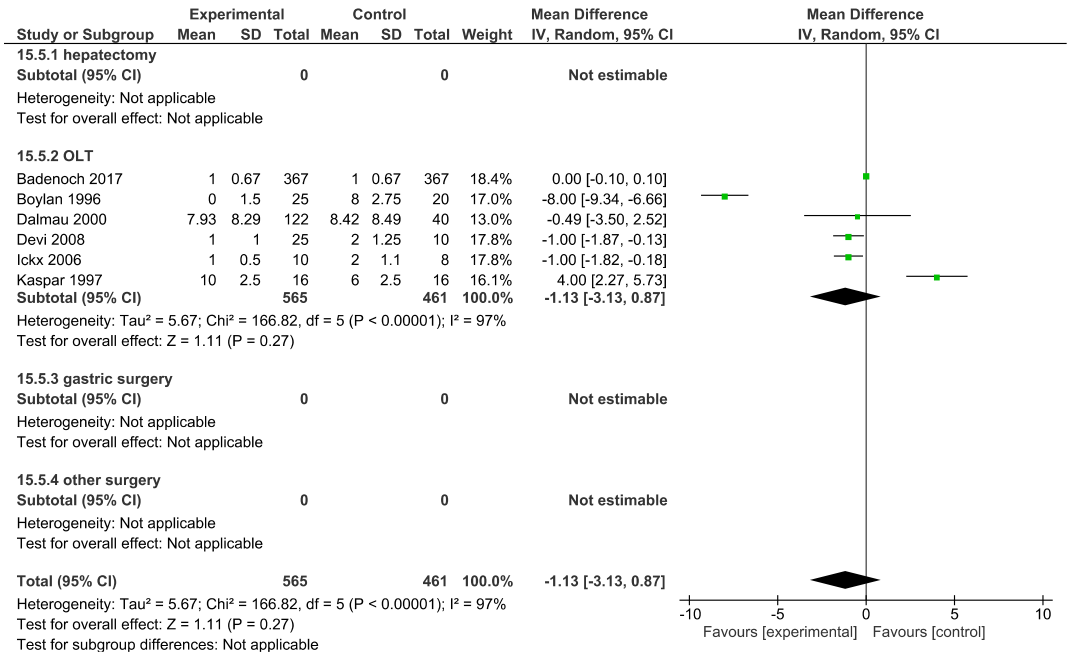


Figure 28: type of surgery platelet transfusion

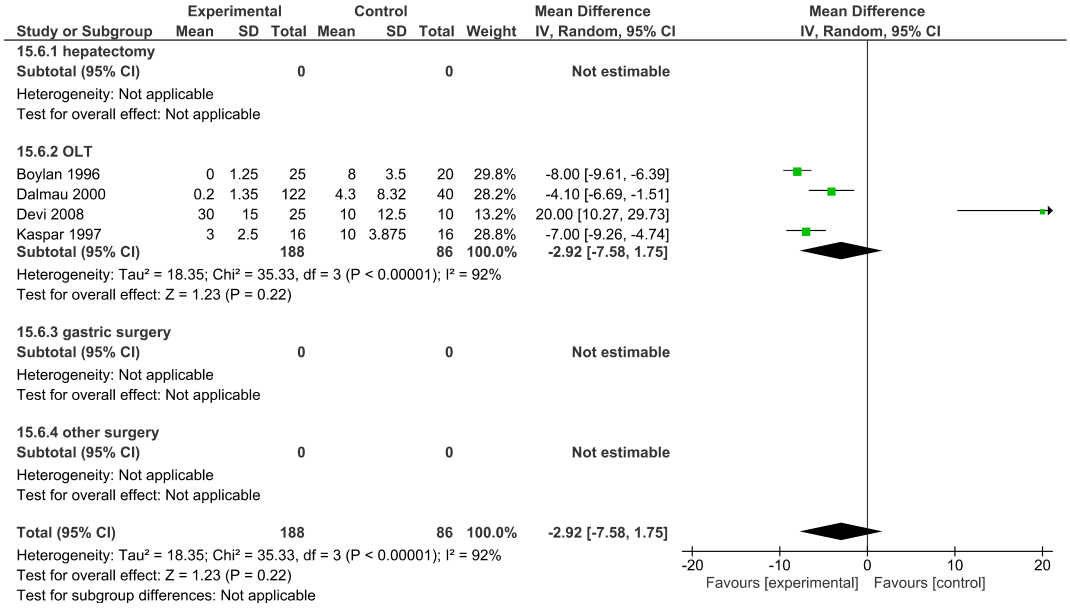


Figure 29: type of surgery cryoprecipitate transfusion

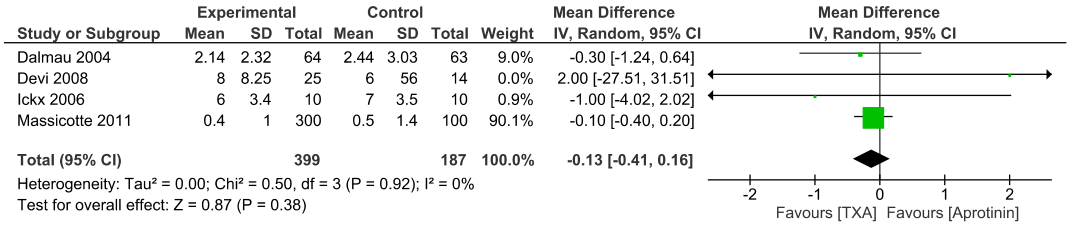


Figure 30: TXA vs Aprotinin RBC transfusion

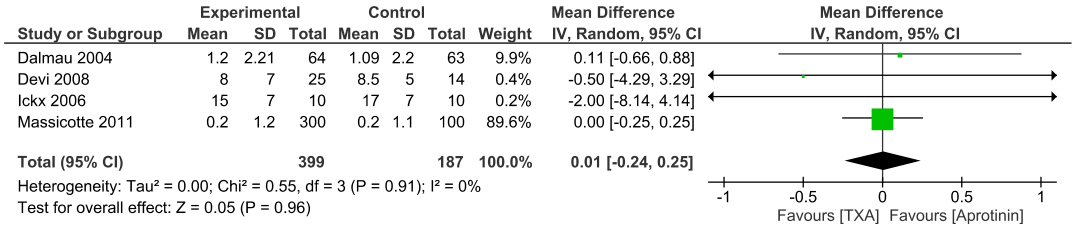


Figure 31:TXA vs. Aprotinin FFP transfusion

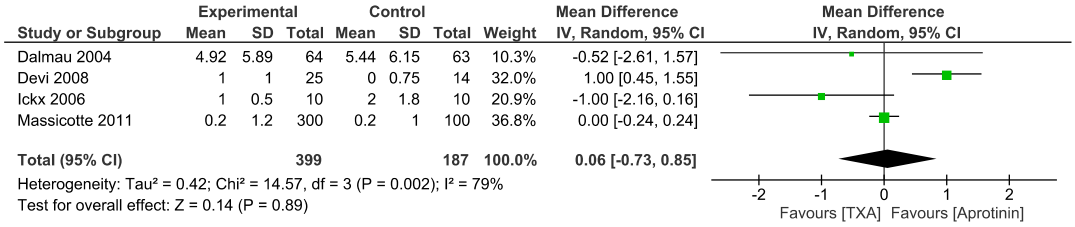


Figure 32: TXA vs. Aprotinin Platelet transfusion

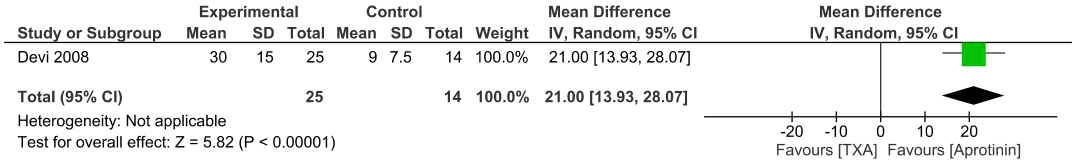


Figure 33: TXA vs. Aprotinin cryoprecipitate transfusion

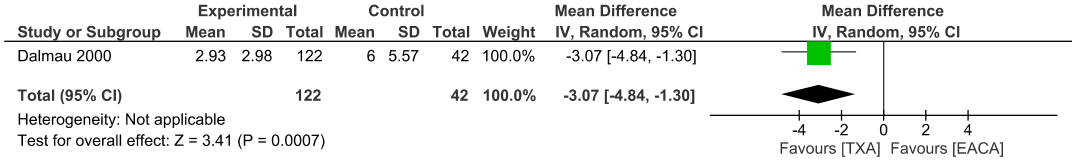


Figure 34: TXA vs EACA RBC transfusion

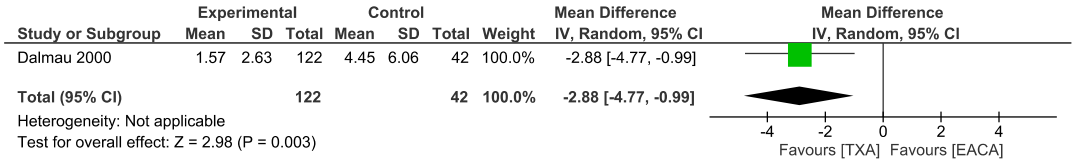


Figure 35: TXA vs EACA FFP transfusion

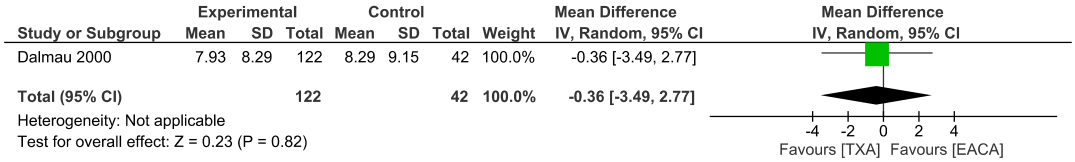


Figure 36: TXA vs. EACA platelet transfusion

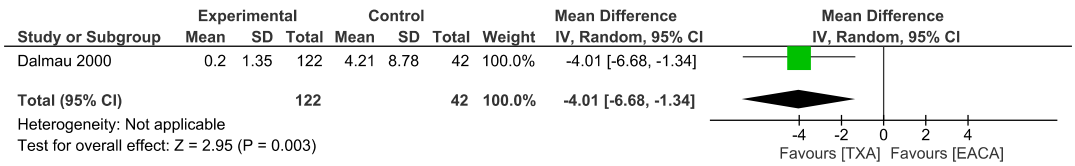


Figure 37: TXA vs. EACA cryoprecipitate transfusion

Secondary outcomes

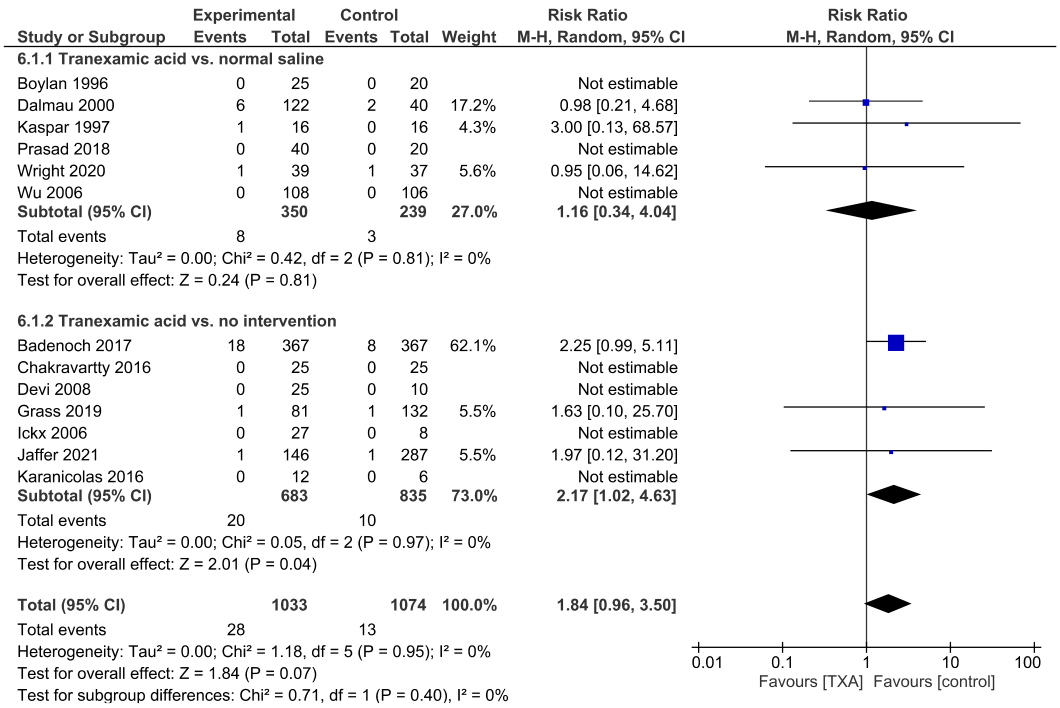


Figure 38: TXA vs. control - TE

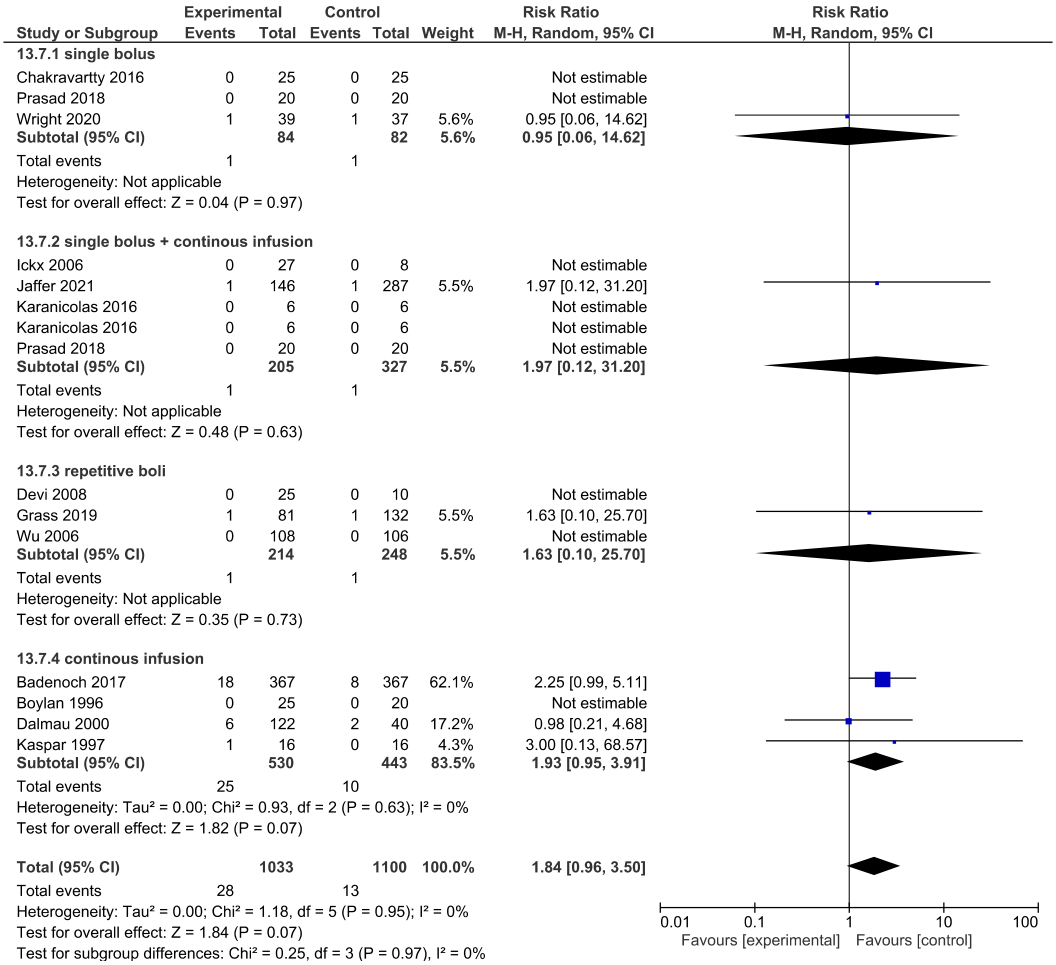


Figure 39: application interval - TE

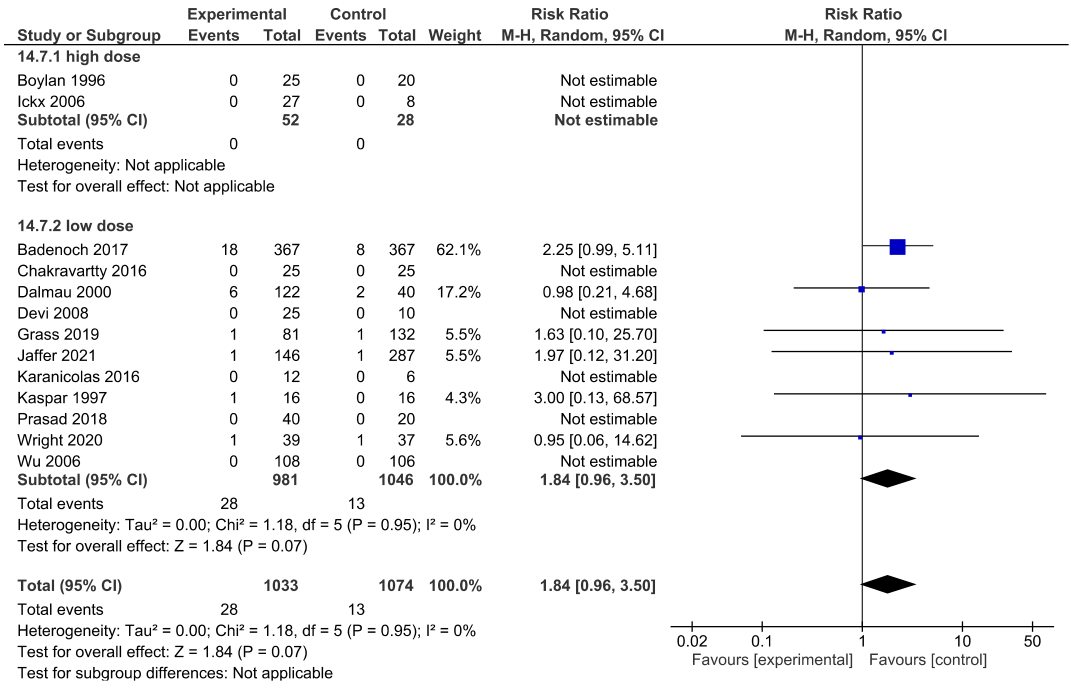


Figure 40: dosage regimen - TE

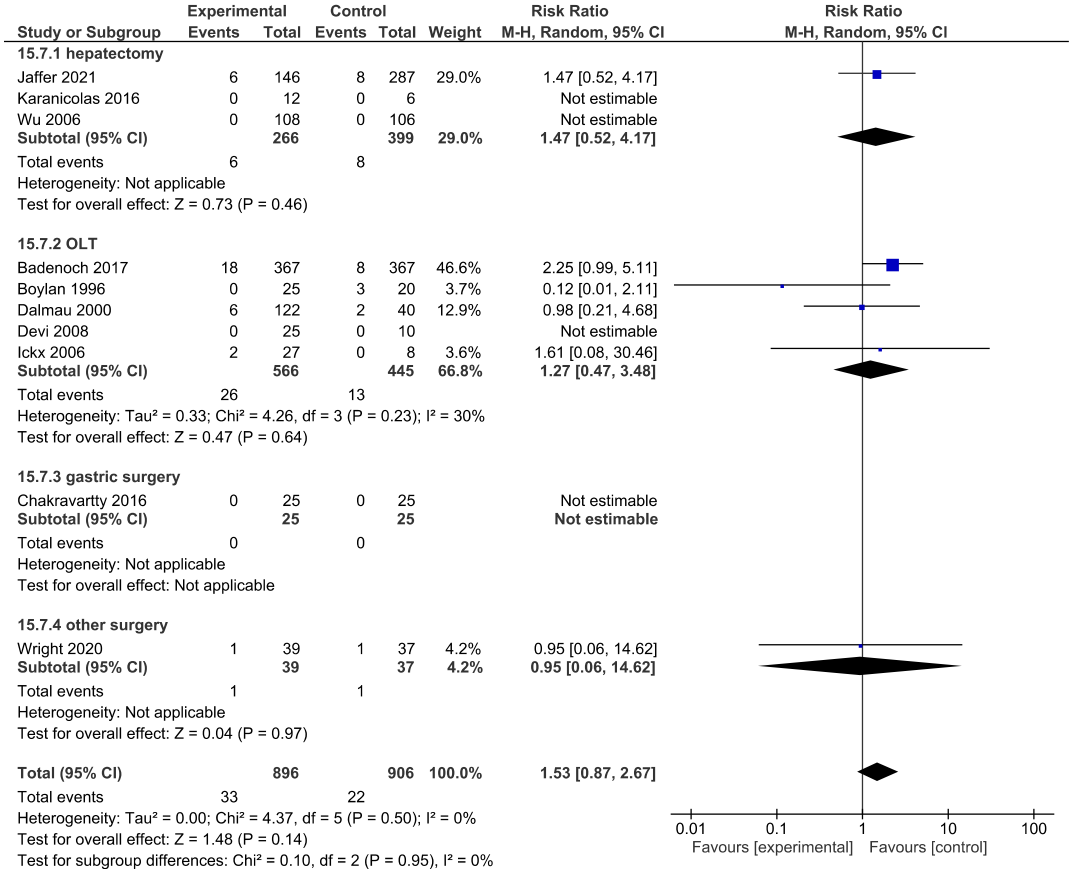


Figure 41: type of surgery - TE

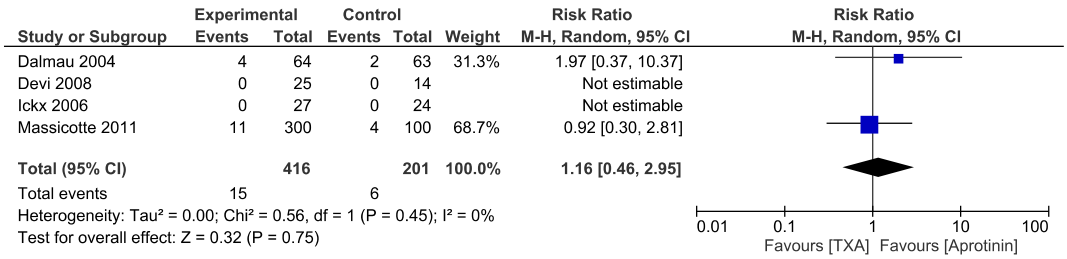


Figure 42: TXA vs. Aprotinin- TE

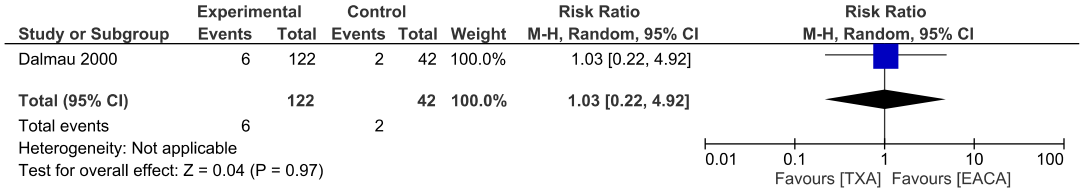


Figure 43: TXA vs. EACA - TE

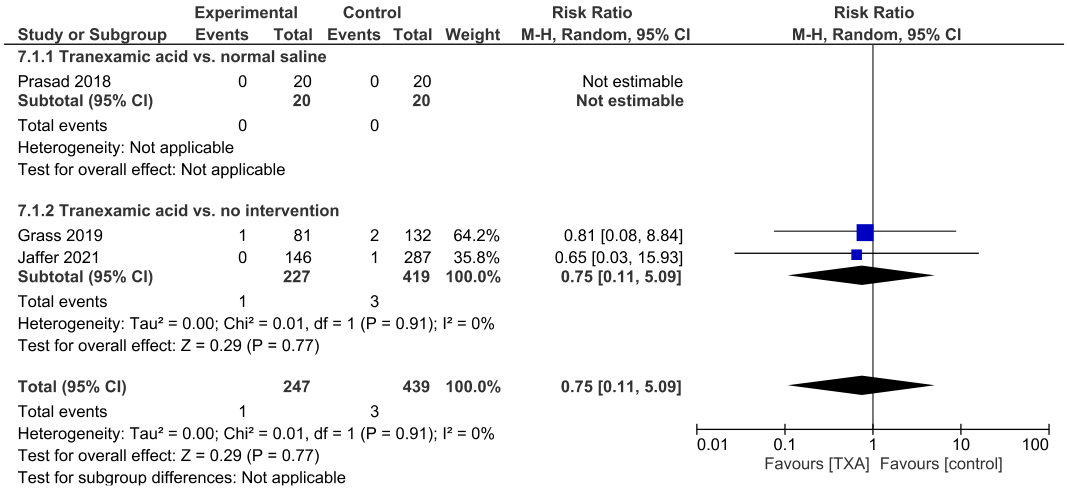


Figure 44: TXA vs. control - seizures

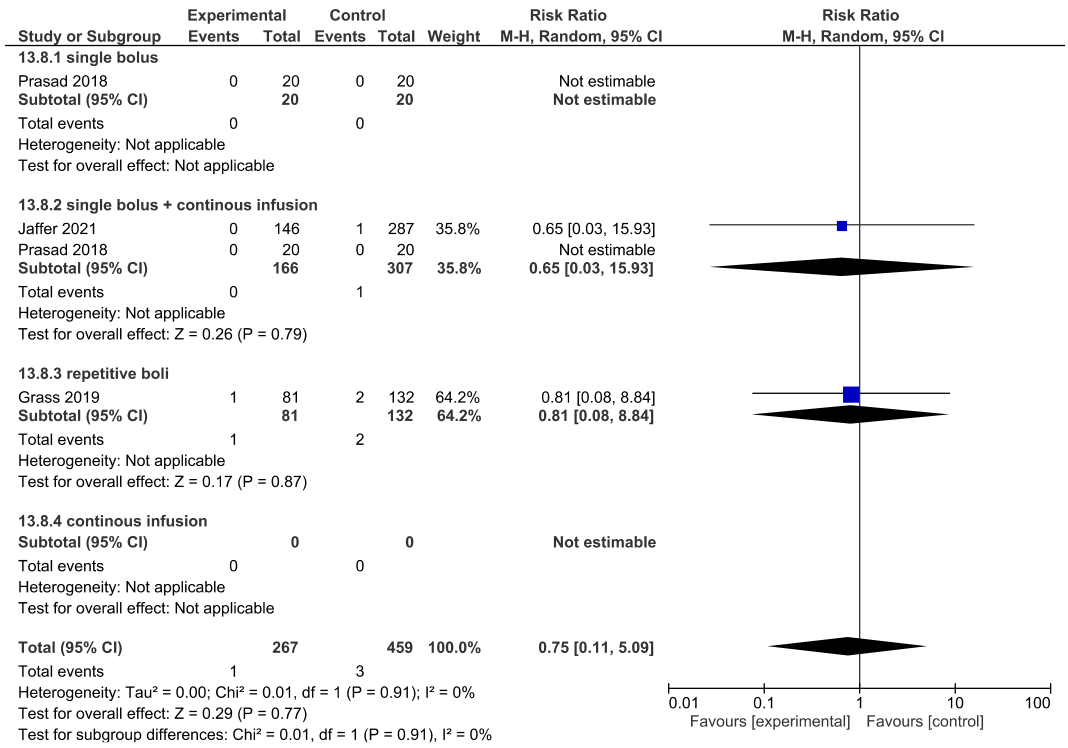


Figure 45: application interval - seizures

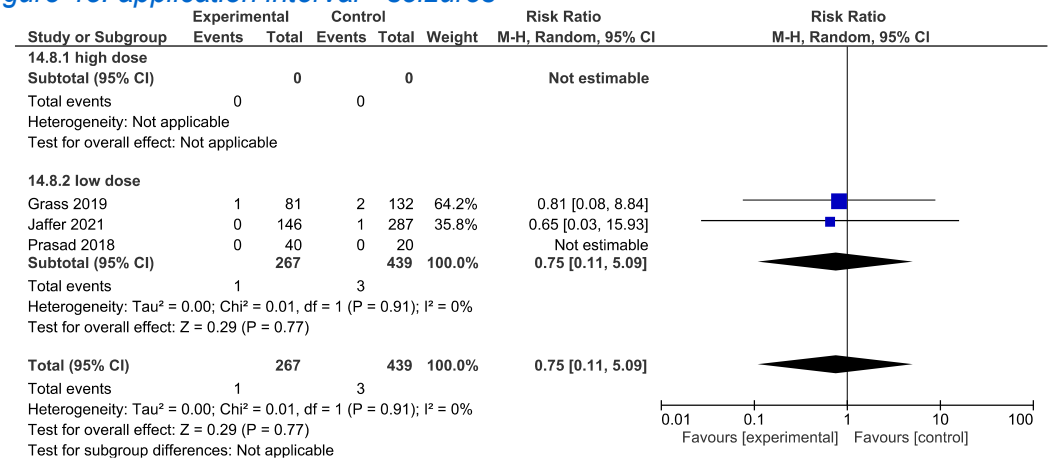


Figure 46: dosage regimen - seizures

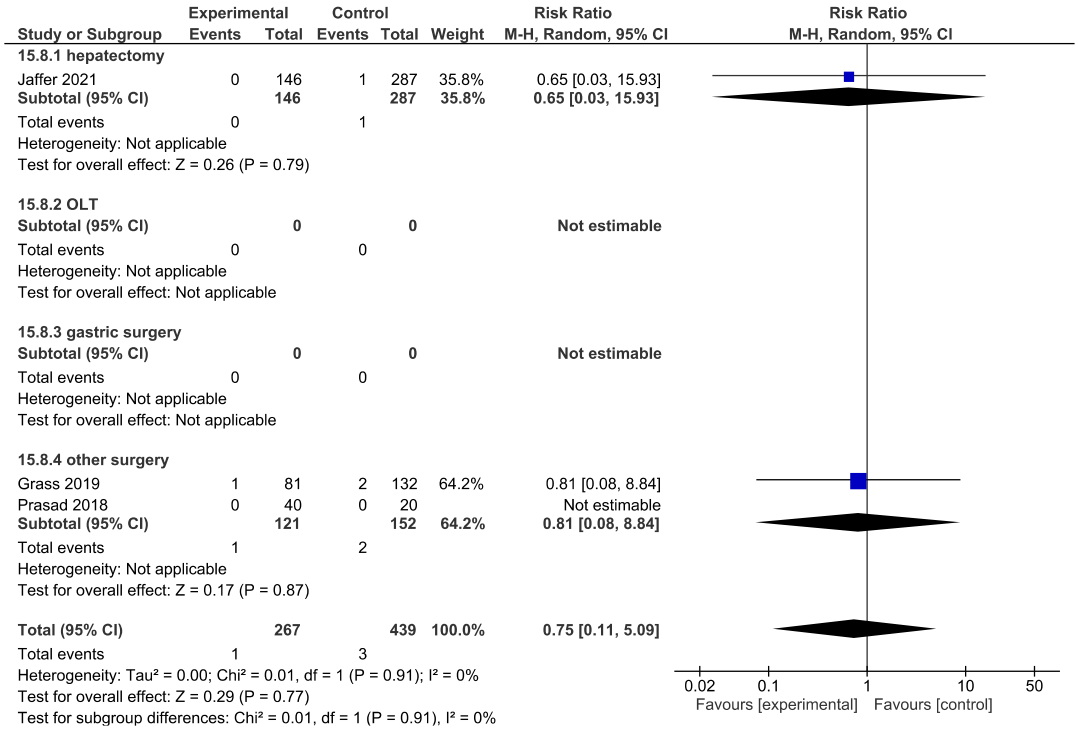


Figure 47: type of surgery - seizures

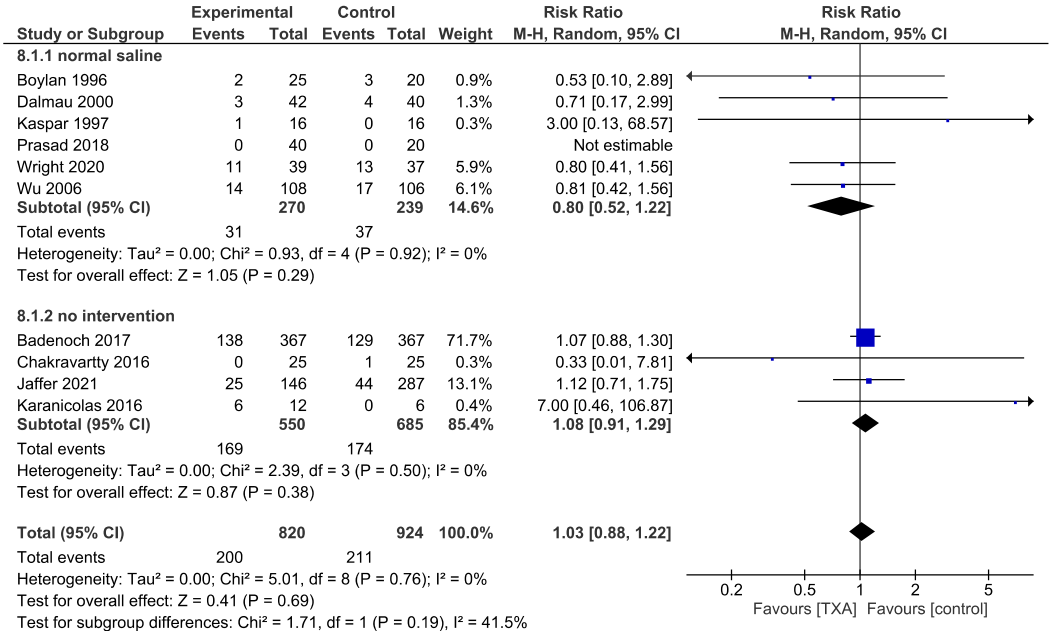


Figure 48: TXA vs. control - AE

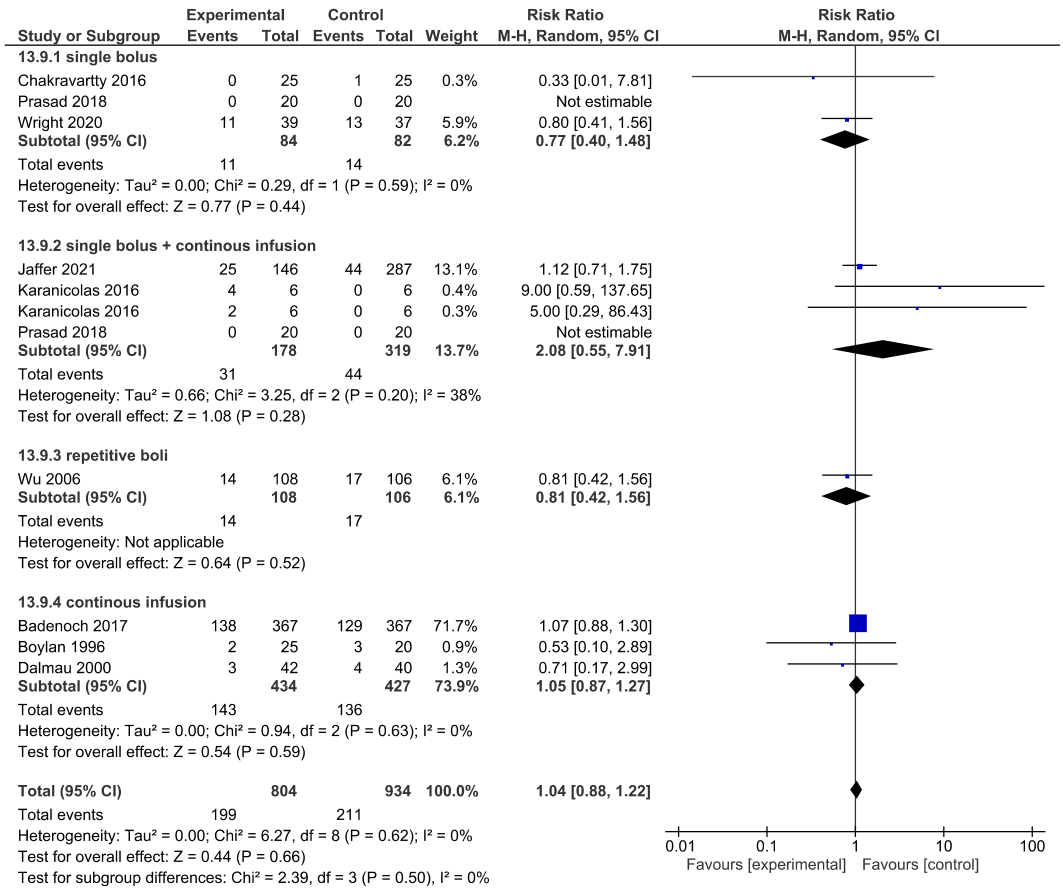


Figure 49: application interval - AE

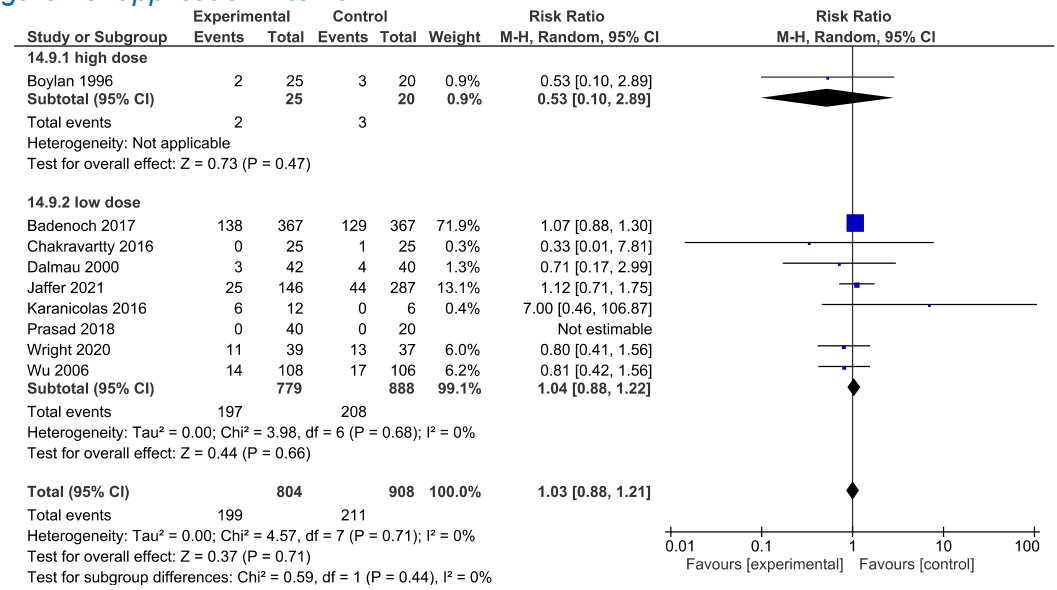


Figure 50: dosage regimen - AE

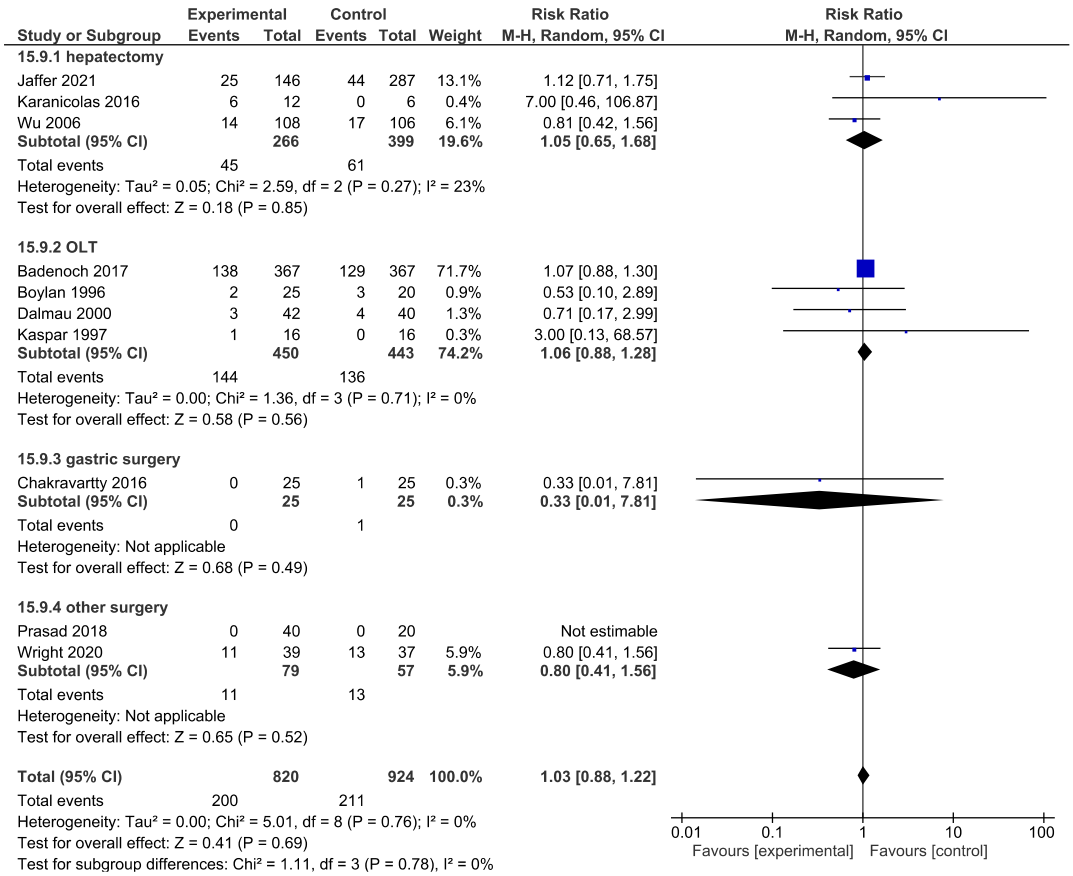


Figure 51: type of surgery - AE

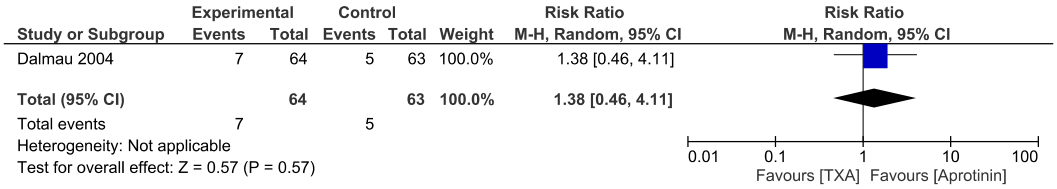


Figure 52: TXA vs. Aprotinin - AE

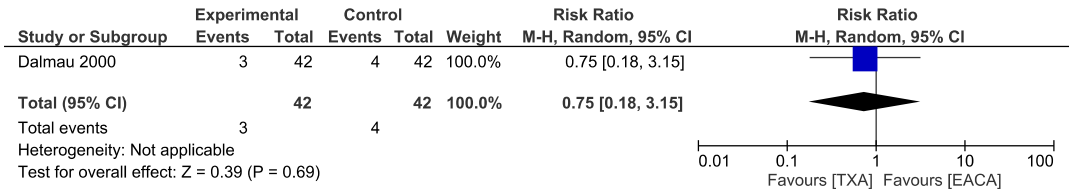


Figure 53: TXA vs. EACA - AE

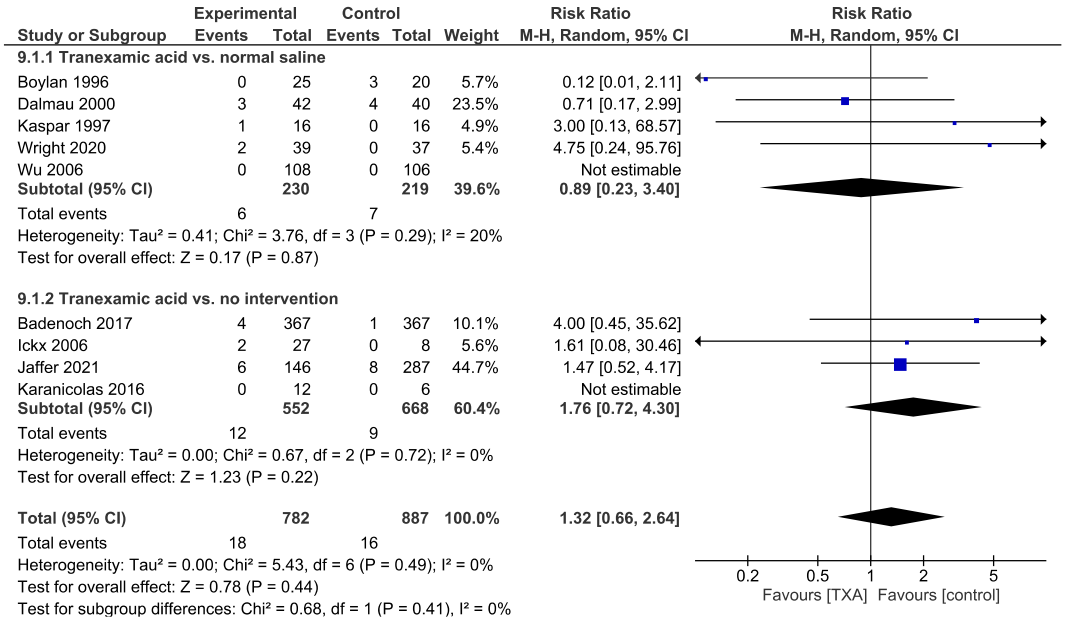


Figure 54: TXA vs. control - mortality

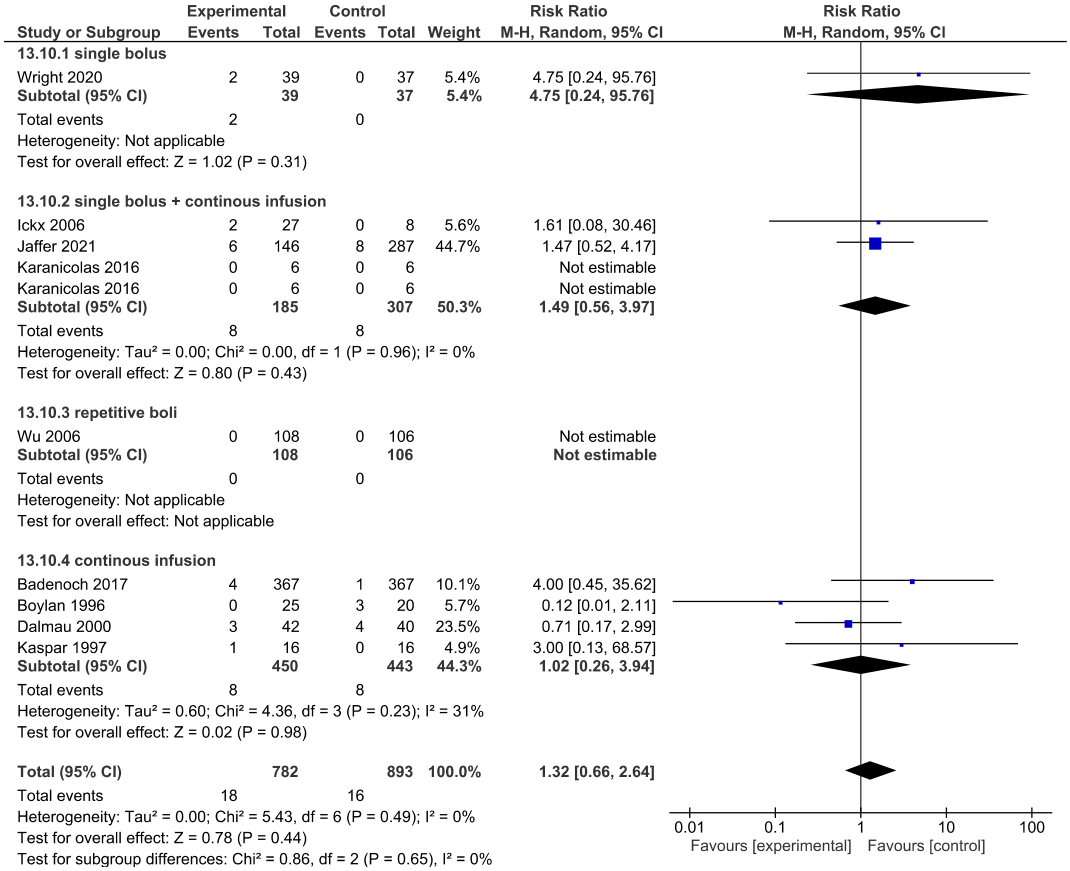


Figure 55: application interval - mortality

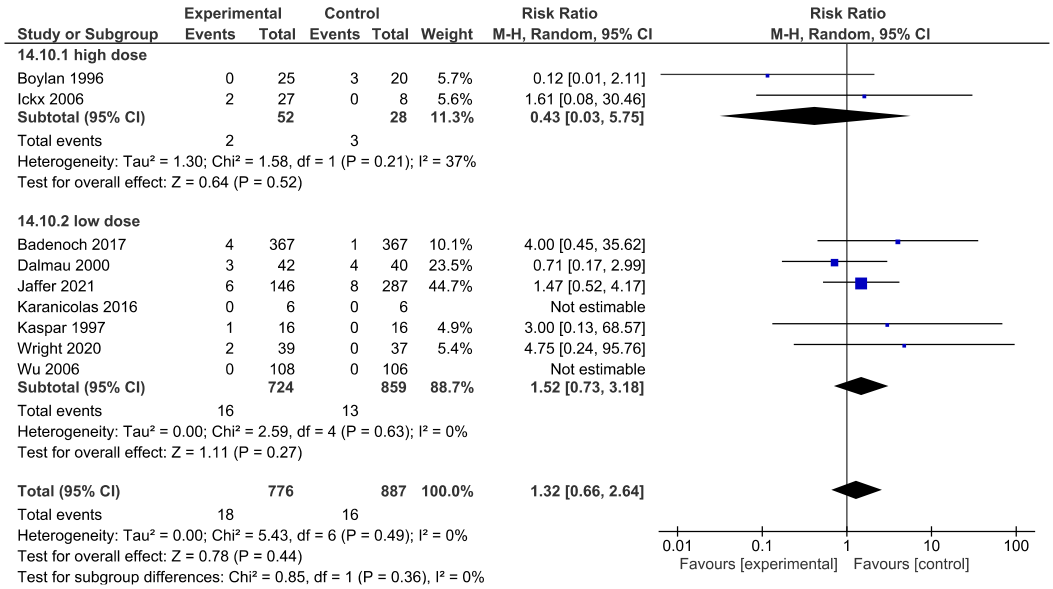


Figure 56: dosage regimen - mortality

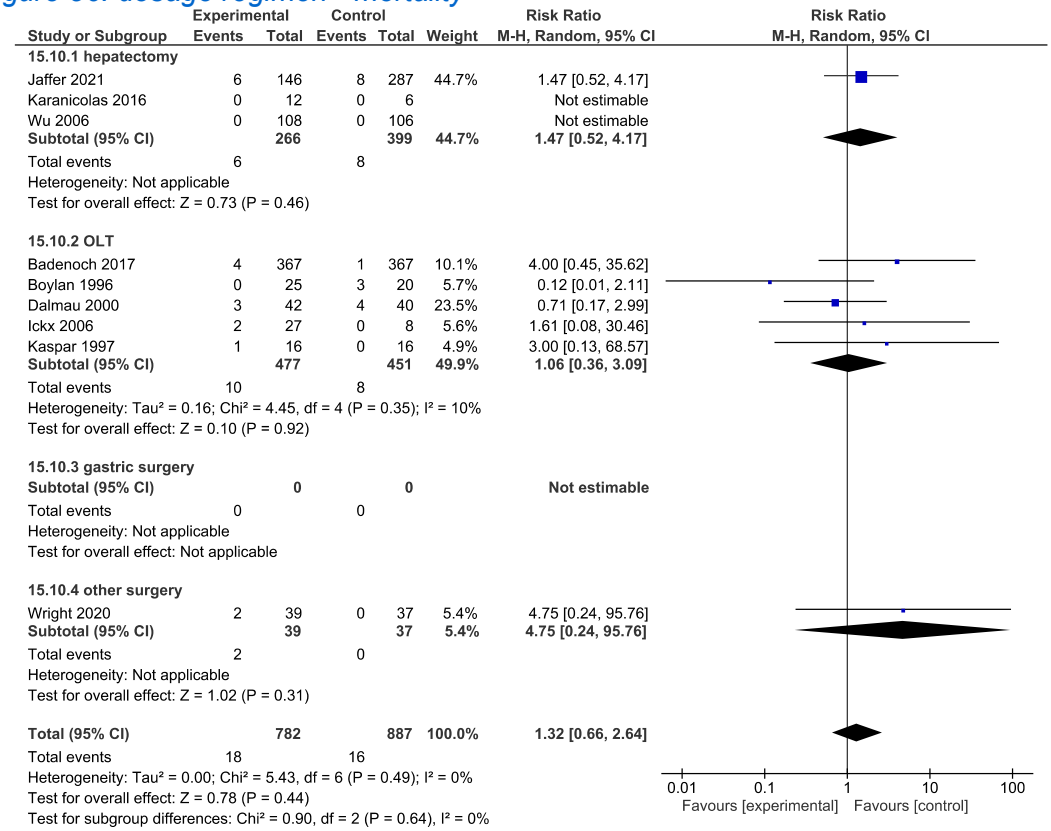


Figure 57: type of surgery - mortality

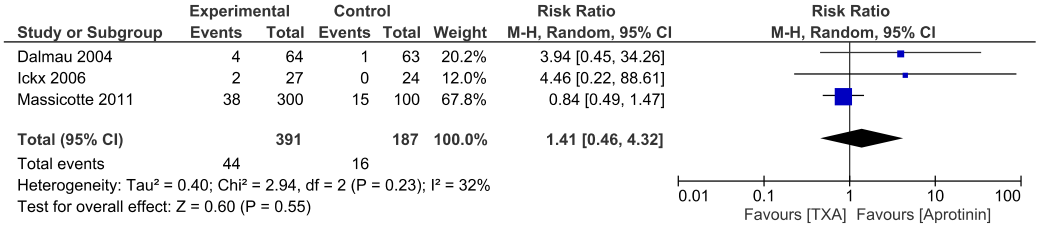


Figure 58: TXA vs. Aprotinin - mortality

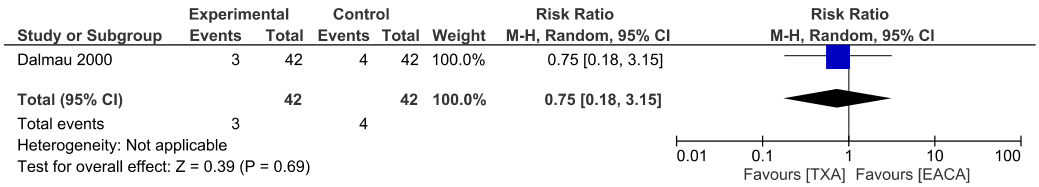
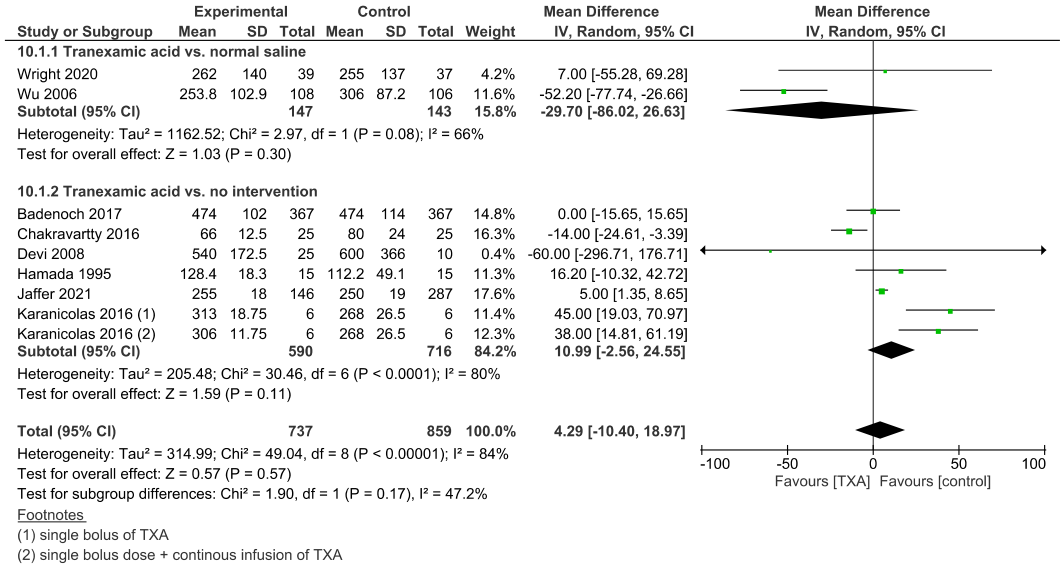


Figure 59: TXA vs. EACA - mortality



Footnotes

(1) single bolus of TXA

(2) single bolus dose + continous infusion of TXA

Figure 60: TXA vs. control - operating time

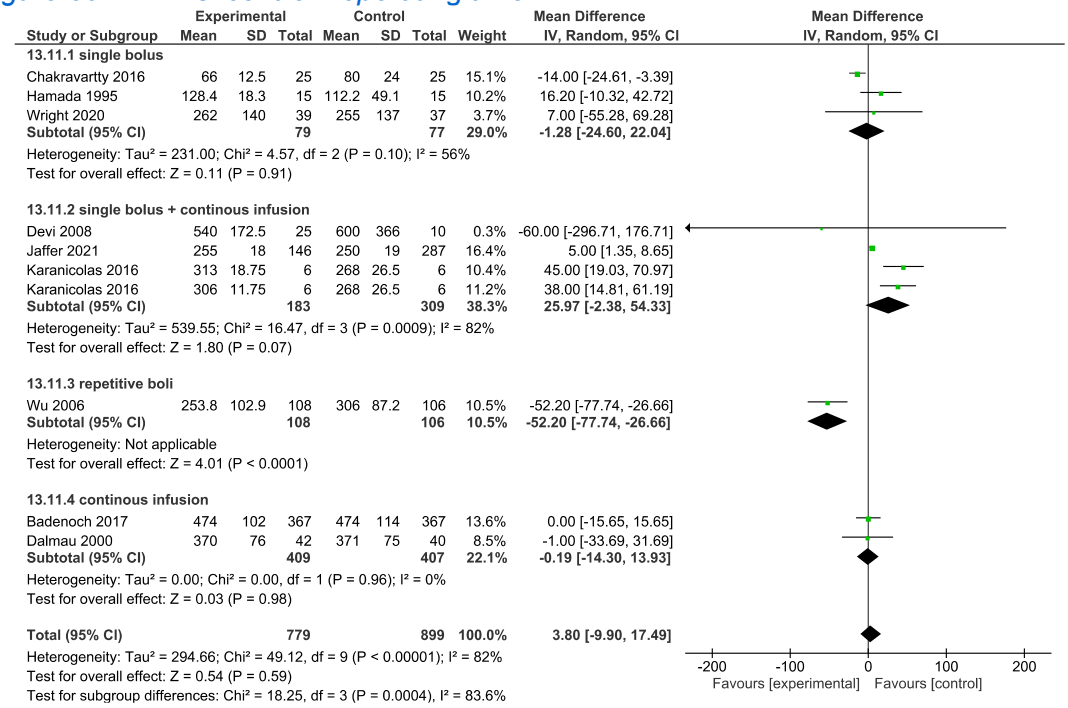


Figure 61: application interval - operating time

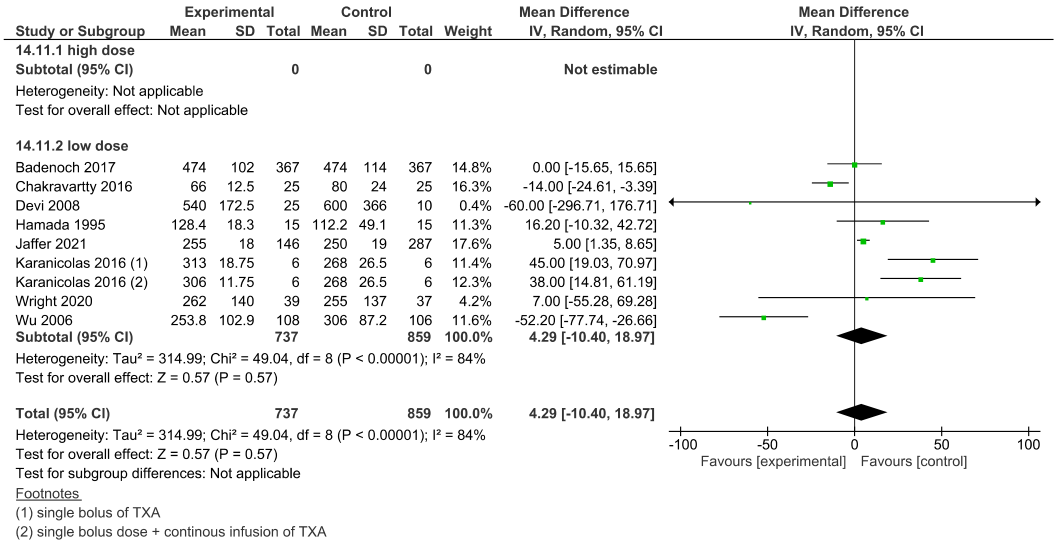


Figure 62: dosage regimen - operating time

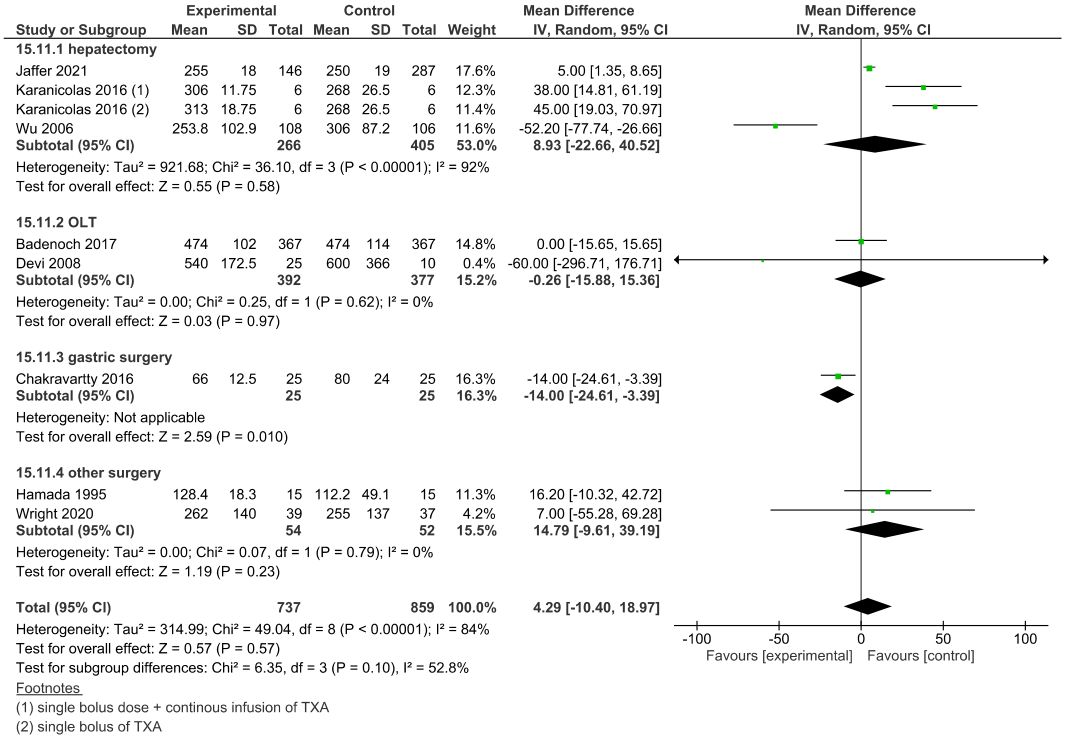


Figure 63: type of surgery - operating time

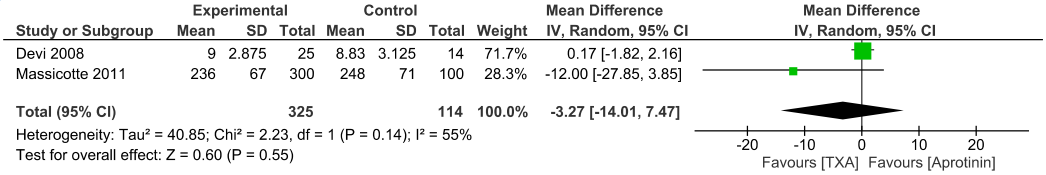


Figure 64: TXA vs. Aprotinin - operating time

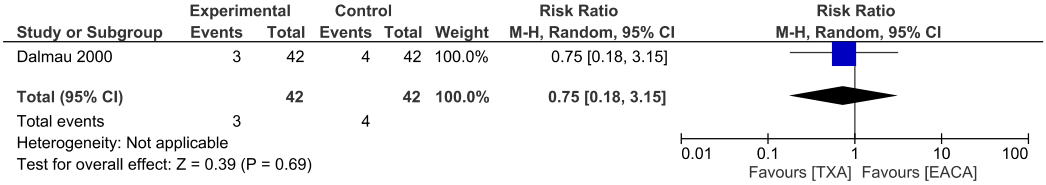


Figure 65: TXA vs. EACA - operating time

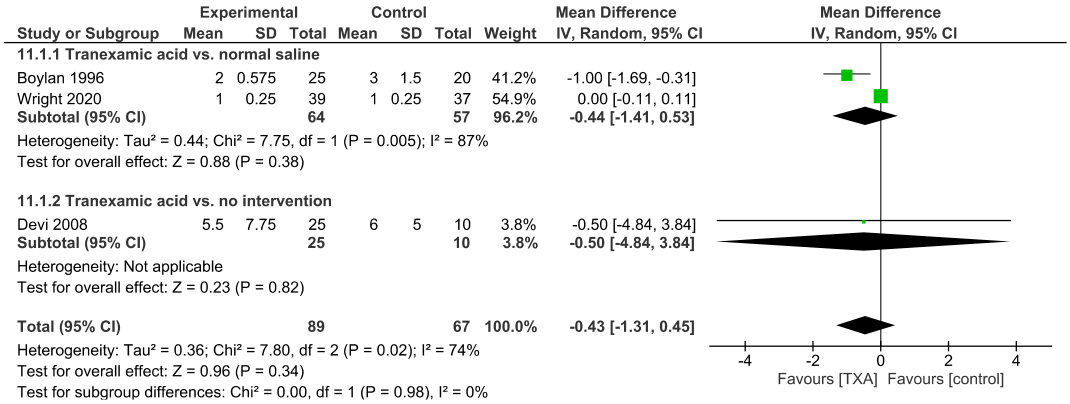
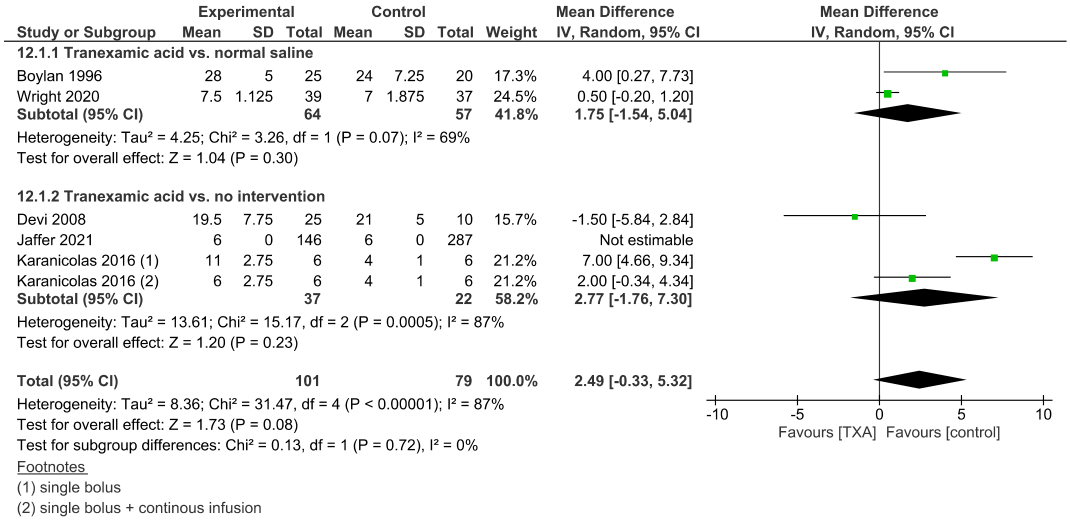


Figure 66: TXA vs. Control - ICU stay



Footnotes

(1) single bolus

(2) single bolus + continous infusion

Figure 67: TXA vs. control - hospital stay

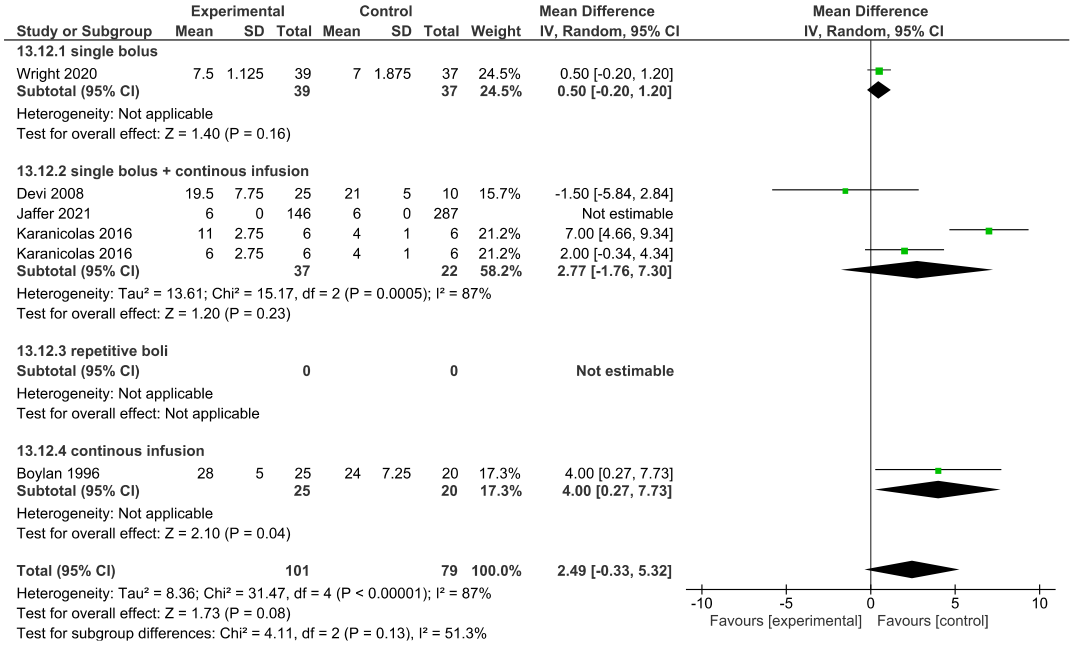


Figure 68: application interval - hospital stay

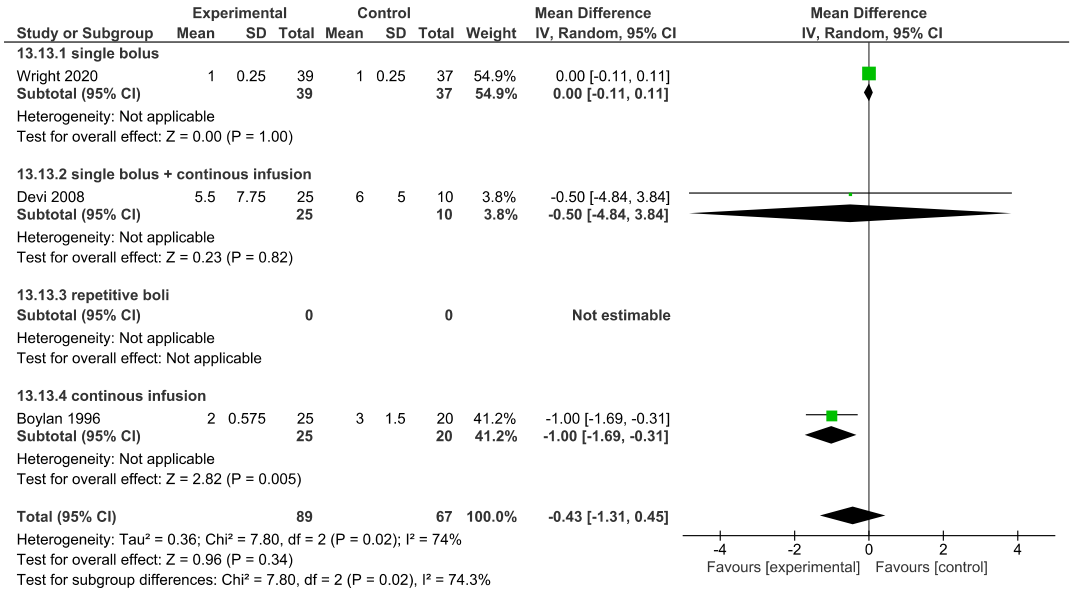
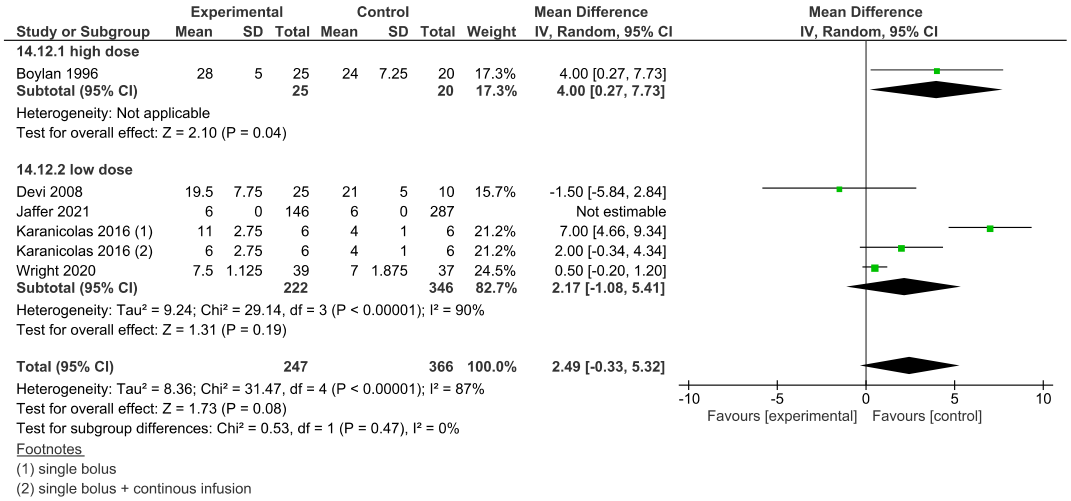


Figure 69: application interval - ICU stay



Footnotes
(1) single bolus
(2) single bolus + continous infusion

Figure 70: dosage regimen - hospital stay

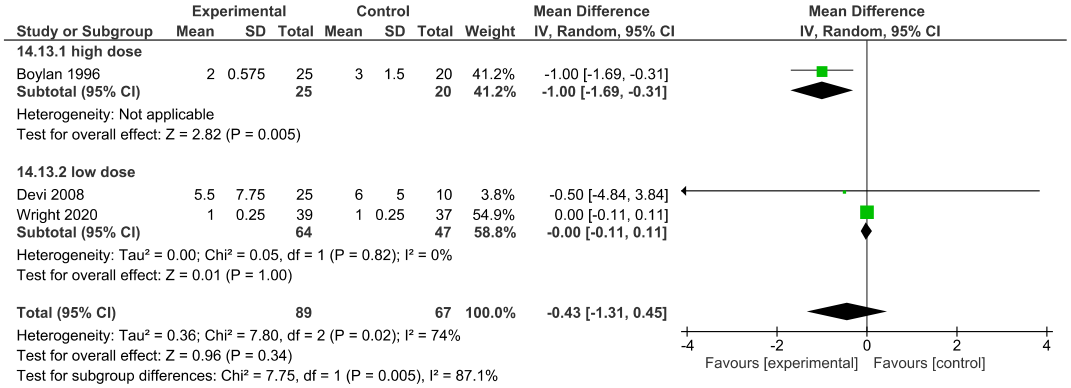


Figure 71: dosage regimen - ICU stay

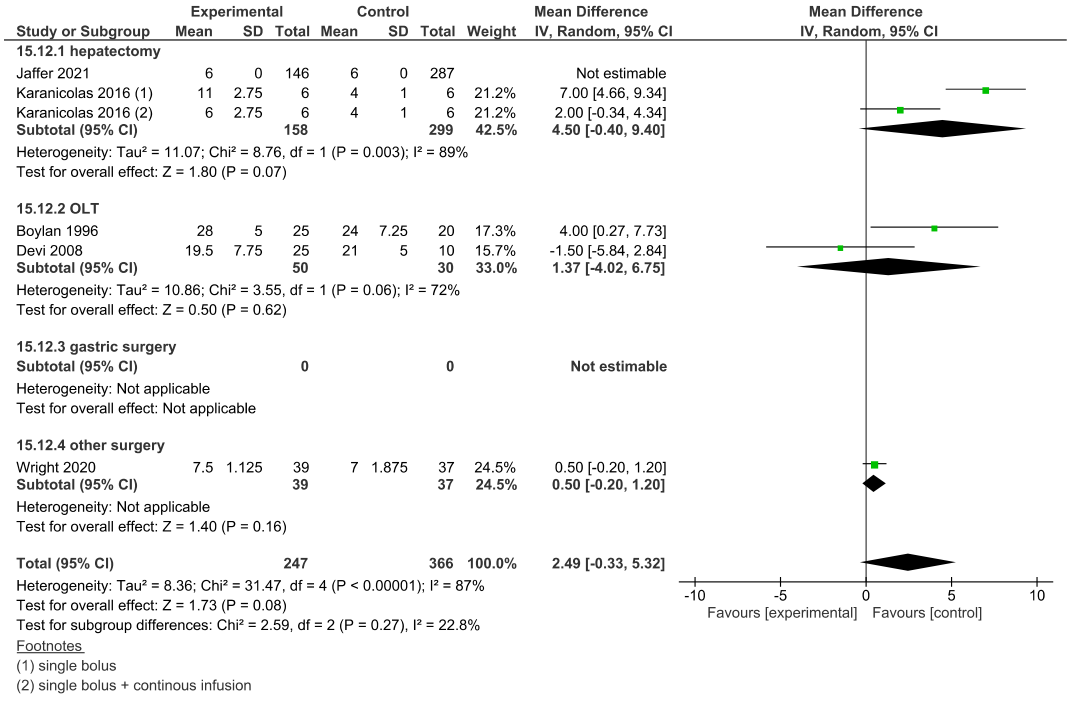


Figure 72: type of surgery - hospital stay

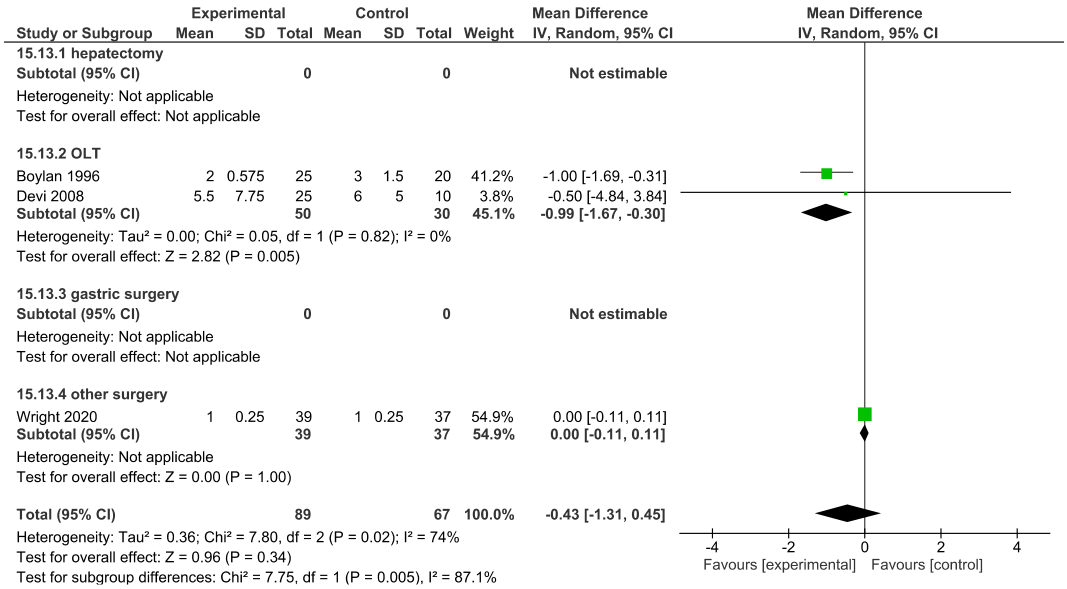


Figure 73: type of surgery - ICU stay

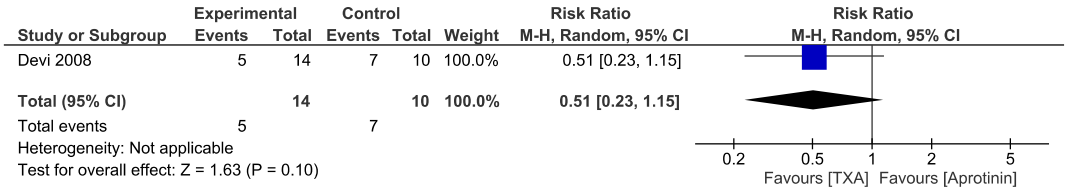


Figure 74: TXA vs. Aprotinin - ICU stay

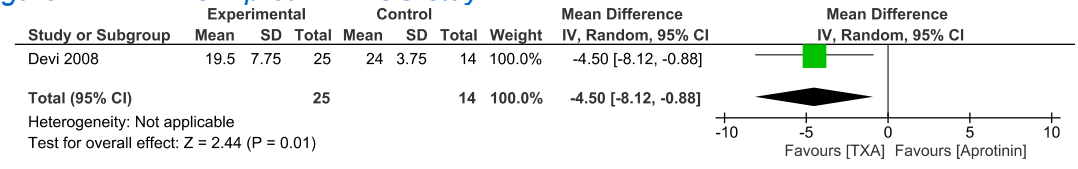


Figure 75: TXA vs. Aprotinin - hospital stay

Sensitivity analysis

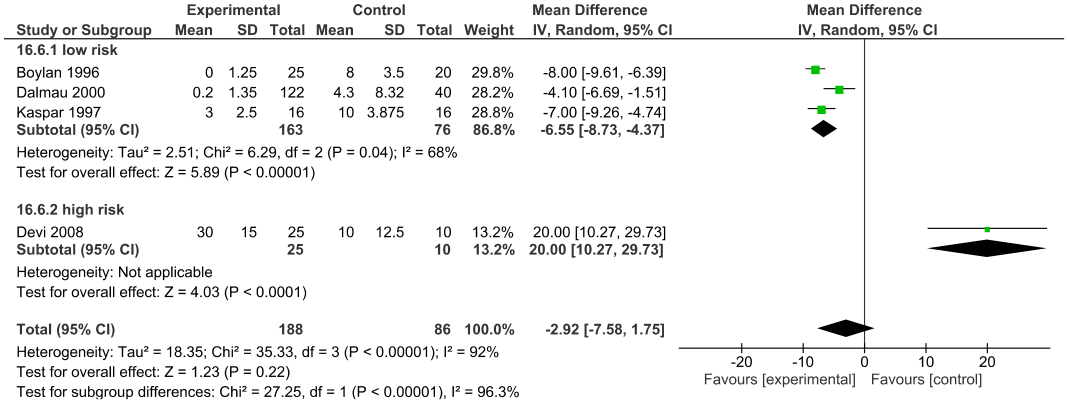
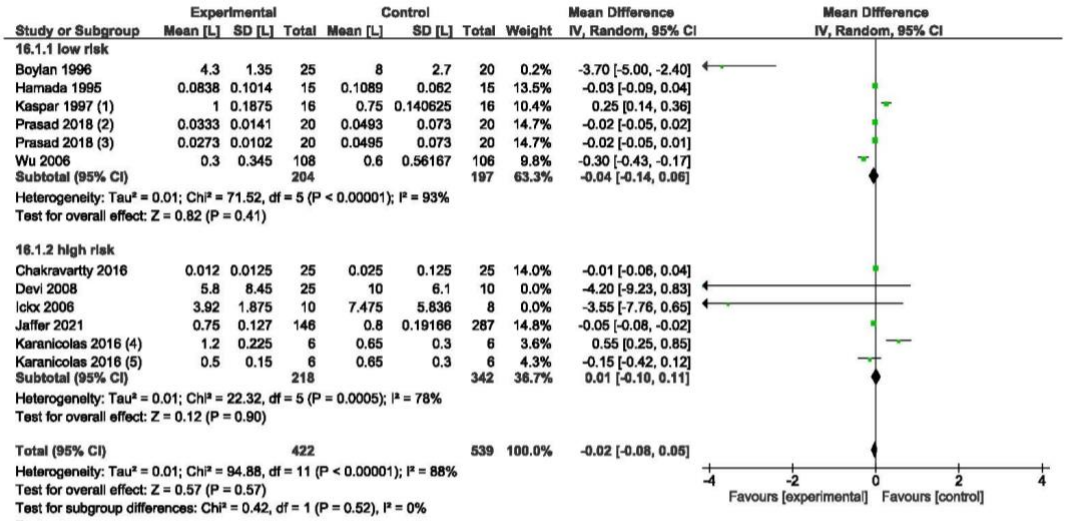


Figure 76: sensitivity analysis – cryoprecipitate transfusion



Footnotes
(1) cell saver
(2) single bolus
(3) single bolus + continous infusion
(4) single bolus + 1g over 8 h
(5) single bolus + continous infusion of 10 mg/kg*h

Figure 77: sensitivity analysis - blood transfusion

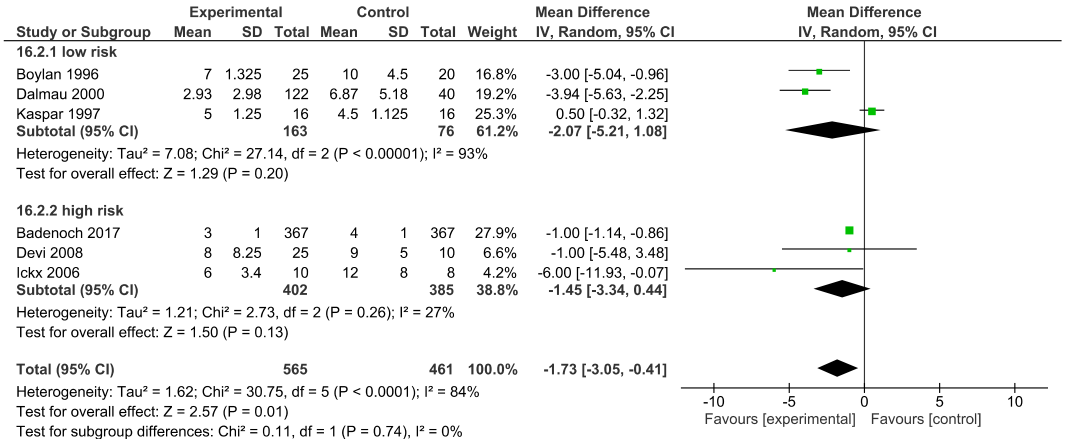


Figure 78: sensitivity analysis - RBC transfusion (units)

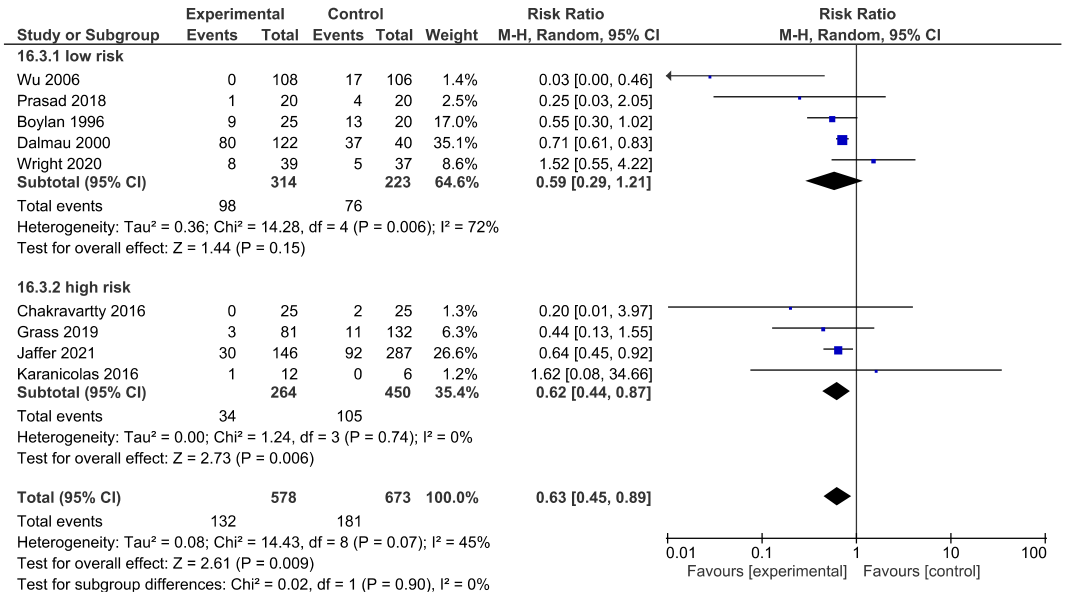


Figure 79: sensitivity analysis – patients receiving RBC transfusion

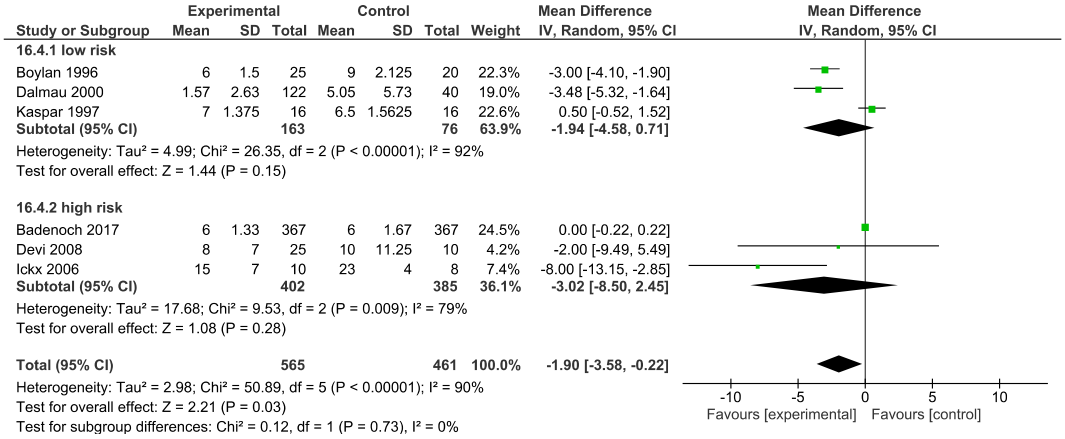
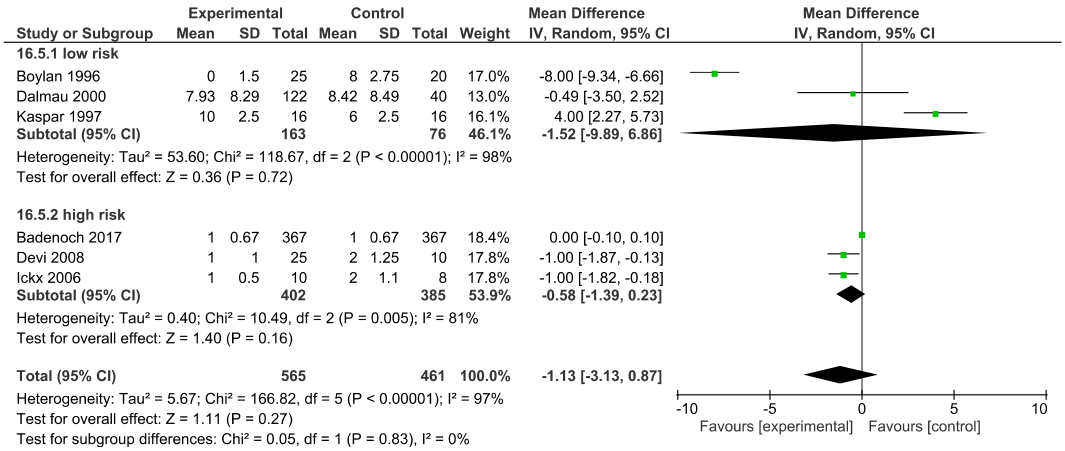


Figure 80: sensitivity analysis – FFP transfusion



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Declarations

Declarations of interest

(1) I declare that I have not completed a doctoral procedure or begun a doctorate at any other university.
(2) I declare that the information provided is truthful and that I have not submitted the academic work to any other academic institution to obtain an academic degree.
(3) I declare under oath that I have written the work independently and without outside help. All rules of good academic practice have been observed; no sources or resources other than those specified by me have been used and passages taken from the works used, either verbatim or in content, have been identified as such.