Clinical Biochemistry 71 (2019) 1–13

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Reducing red blood cell transfusion in orthopedic and cardiac surgeries with Antifibrinolytics: A laboratory medicine best practice systematic review and meta-analysis

James H. Derzon[a,*], Nicole Clarke[b,g], Aaron Alford[c], Irwin Gross[d], Aryeh Shander[e], Robert Thurer[f]

[a] RTI International, Research Triangle Park, NC, United States of America
[b] Pharmerit International, Bethesda, MD, United States of America
[c] National Network of Public Health Institutes, Washington, DC, United States of America
[d] Acumen Inc., San Diego, CA, United States of America
[e] Englewood Hospital and Medical Center, New Jersey, United States of America
[f] Gauss Surgical, Los Altos, CA, United States of America
[g] Vector Oncology, Memphis, TN, United States of America

ARTICLE INFO

Keywords:
Antifibrinolytics
Tranexamic acid
ε-Aminocaproic acid
Red blood cell transfusion
Systematic review
Meta- analysis

ABSTRACT

Objectives: To evaluate the effectiveness of antifibrinolytics tranexamic acid (TA), ε-aminocaproic acid (EACA), and aprotinin to decrease overuse of red blood cell transfusions in adult surgical and non-surgical patients.
Methods: This review followed the Centers for Disease Control and Prevention (CDC) Laboratory Medicine Best Practice (LMBP™) Systematic Review (A-6) method. Eligible studies were assessed for evidence of effectiveness of TA or EACA in reducing the number of patients transfused or the number of whole blood transfusions.
Results: Seventy-two articles met LMBP™ inclusion criteria. Fifty-six studies assessed Topical, Intra-articular Injection, or Intravenous TA, 4 studied EACA, and 12 studied the effectiveness of aprotinin. The overall strength of the body of evidence of effectiveness for each of these practices was rated as high.
Conclusion: LMBP™ recommends the use of topical, intra-articular injection, or intravenous tranexamic acid and the use of ε-aminocaproic acid for reducing overuse of red blood cell transfusion.

1. Introduction

Blood loss is a major concern in many surgical and non-surgical medical conditions [1]. Total surgical blood loss may range from 1.5 to 2 l in some orthopedic procedures, with up to 40% of patients requiring postoperative transfusions [2]. Perioperative transfusions are associated with major morbidity and mortality [3] including risks for infection and prolonged length of hospital stay [4,5]. Preoperative planning is foundational to reducing or avoiding perioperative allogeneic transfusion. A complete patient history may discover clinically important disorders in hemostasis – e.g., excessive bleeding during prior surgical and dental procedures, epistaxis, menorrhagia, disproportionate bleeding with major trauma, and easy bruising or joint muscle swelling after minor trauma [6]. In addition to an appropriate patient history, a general multimodal approach to blood conservation, involving surgical, and pharmacological considerations includes the use of antifibrinolytics to reduce perioperative transfusion and perioperative morbidity [7].

Three antifibrinolytics are important therapeutic modalities for reducing blood loss and transfusions in surgical and nonsurgical settings [6]. They are the serine protease aprotinin (AP), the synthetic lysine analogues tranexamic acid (TXA), and epsilon aminocaproic acid (EACA).

Aprotinin was introduced in clinical practice in the 1950's for treatment of fibrinolysis associated with pancreatitis carcinoma. In the early 1990's, it was often used in complex cardiac surgery because it was shown to substantially reduce blood loss in 22 patients undergoing open-heart surgery [8]. However, aprotinin use ended with the publication of the BART (Blood Conservation using Antifibrinolytics in a Randomized Trial) trial which associated it with increased risk of death of patients. Aprotinin was withdrawn from the market in May 2008 [9]. However, the BART trial data was later called into question and Health

Abbreviations: LMBP, Laboratory Medicine Best Practice; RBC, red blood cell; TA, tranexamic acid; EACA, ε-aminocaproic acid

* Corresponding author at: Sr. Research Public Health Analyst, RTI International, Social, Statistical, and Environmental Sciences, Center for Advanced Research Methods, 701 13th St. #750, Washington, DC 20005, United States of America.
E-mail addresses: jderzon@rti.org (J.H. Derzon), aalford@nnphi.org (A. Alford), igross@accumen.com (I. Gross).

https://doi.org/10.1016/j.clinbiochem.2019.06.015
Received 13 March 2019; Received in revised form 2 June 2019; Accepted 28 June 2019
Available online 03 July 2019

Canada published a safety review of aprotinin in September 2011 which concluded that in non-complex cardiac surgery aprotinin's benefits may outweigh their risks [10]. Aprotinin is currently available in Canada for restricted use in isolated coronary bypass graft surgery [11]. After a review of the risks and benefits of antifibrinolytic drugs the European Medicines Agency (EMA) also recommended, in February 2012, lifting the suspension of aprotinin [12]. The FDA has not restored the use of aprotinin for reduction of blood loss in surgical procedures in the US.

The removal of AP in the US lead to EACA and TXA being the most commonly used antifibrinolytics for reducing blood loss for cardiac and non-cardiac surgery [7]. When given orally both EACA and TXA are readily absorbed from the gastrointestinal tract and rapidly excreted in urine. TXA and ECAC are used commonly in the reduction of perioperative bleeding in both cardiac and non-cardiac surgery [13,14].

As a part of the patient blood management program, hospital laboratories have a critical role in red blood cell transfusion reduction. The blood bank laboratory can achieve this goal by working in partnership with surgeons, anesthesiologists, nurses and pharmacists to monitor and document blood use based on the antifibrinolytic type, and administration mode in surgical and non-surgical procedures.

In this review, we assess the effectiveness of TXA and EACA in different routes of administration (intravenous, intra-articular and topical) for reducing the number of red blood cell transfusions and the number of units transfused using the Laboratory Medicine Best Practice (LMBP) Systematic Review A-6 Method [15]. Since aprotinin is currently prohibited in the United States, we include findings for aprotinin in the supplemental materials (see Supplement E), but do not make a recommendation for or against its use in reducing RBC transfusion overuse.

2. Methods

The LMBP A6 method was designed to assess and summarize evidence from to identify evidence-based practices which improve patient safety and laboratory medicine quality [15]. Following a strategy consistent with GRADE standards [16], the LMBP method assesses the quality, quantity, and consistency of evidence across studies and can include evidence generated through multiple study formats. An experienced review coordinator manages the review while trained staff abstract and summarize study findings and procedures using a standardized summary form. For each LMBP review, an expert panel is convened. Members are selected based on their diverse perspectives and expertise in clinical medicine, laboratory management, and evidence review methods (Supplement A). This panel provides individual and collective input on the systematic review conduct, results interpretation, and drafts preliminary recommendations for the LMBP workgroup. The multidisciplinary LMBP workgroup (which consists of medical professionals with expertise in laboratory medicine, clinical practice, health services research, and health policy evidence; Supplement B) conducts an independent review of the draft recommendations and provides the final language for the recommendation.

2.1. ASK (A1): What practices are effective in reducing RBC transfusion in surgical and nonsurgical adult patients?

The LMBP systematic review process began with the review team conducting an initial assessment of the literature on LMBP workgroup-proposed topics and drafting initial population, intervention, comparator and outcome (PICO) statement(s) that the literature might answer. The workgroup reviews the topics and PICO statement and provided feedback. Based on this feedback, the PICO statement was refined (see Fig. 1) and the CDC Division of Laboratory Sciences selected RBC transfusion overuse as a priority quality gap that could be addressed through systematic review and formal practice recommendations. Three general categories of interventions to reduce transfusion overuse were identified by the expert panel and are presented in separate papers: the use of antifibrinolytics (this report), anemia management practices [17], and restrictive transfusion policies (in press) [131].

Population[1]**: Orthopedic and Cardiac** Surgical adult patients.

Intervention: Aprotinin, TA, and EACA in different administration modes (intravenous, intra- articular and topical).

Comparator: No perioperative antifibrinolytics used.

Outcomes: Number of patients transfused and/or number of RBC units transfused.

2.2. ACQUIRE (A-2): Literature search and request for unpublished quality assurance studies

This LMBP™ systematic review sought to identify and retrieve all English-language research articles assessing the effectiveness of aprotinin and the lysine analogue antifibrinolytics in reducing overuse of RBC transfusion. Using PubMed, EMBASE and CINAHL we searched articles published in English between 1990 and 2016. The initial search found 2073 citations and abstracts which were screened against eligibility criteria by two reviewers. All articles likely to contribute to the review were retrieved for full text review. Bibliographies from the retrieved articles were screened for additional evidence, and we conducted outreach to identify the grey literature and obtain unpublished quality assurance studies. In addition to searching the open web for grey literature, author searches were conducted on Open Grey, the New York Academy of Science Grey Literature Producers List, the National Library of Medicine, and the HHS Dictionary of Health Organizations. In addition, a call for unpublished studies was promoted through the CDC's LMBP's website. The search strategies for both the published and grey literatures is available in **Supplement C**.

Based on LMBP systematic review criteria [15], a total of 72 published articles on the impact of antifibrinolytics on the percent of patients transfused or the number of units transfused were identified and included in the review. Thirteen articles presented findings on the effectiveness of aprotinin, 57 on the effectiveness of tranexamic acid, and 4 on the effectiveness of EACA. The literature flow diagram is shown in Fig. 2.

To avoid confusion, we distinguish between “articles” and “studies.” An “article” describes a single report or publication. An article can contain one or several “studies,” defined as a unique intervention applied to a unique study-sample. In meta-analysis, evidence is constructed at the study level, with each study contributing one representative finding to the synthesis. While LMBP recommendations are developed based on the entire body of evidence contributing to the review, whenever possible standardized measures of impact, “effect sizes,” were generated to document the magnitude and direction of intervention impact.

2.3. APPRAISE (A-3): Screening and evaluation of individual studies

Two independent reviewers conducted all literature screening, abstraction, and evaluation. Results were compared and differences were resolved through discussion and consensus. These processes reduced subjectivity and potential for bias. Article titles and abstracts were screened for their potential to contribute to the review and were retrieved if they appeared to report on the effectiveness of a practice to reduce the proportion of patients receiving blood transfusions and/or the number of units of allogeneic blood transfused. All articles which provided quantifiable estimates of an intervention's impact on the outcomes of interest were eligible, even if their results could not be standardized and included in the meta-analysis [15]. References for all included studies are provided in the Bibliography.

All eligible studies were abstracted using a standardized data

[1] Excluded populations are pediatrics, pregnancy, gynecologic bleeds, trauma bleeds, and patients with genetic diseases.

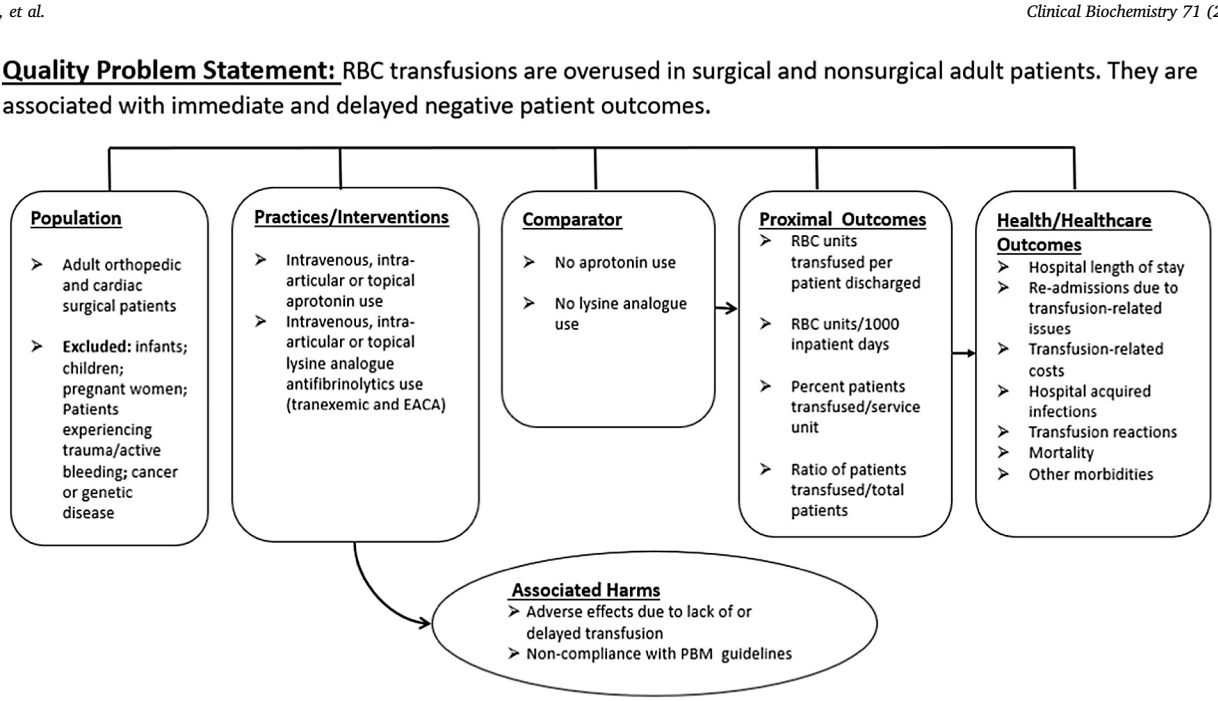

Fig. 1. Quality problem and PICO statement.

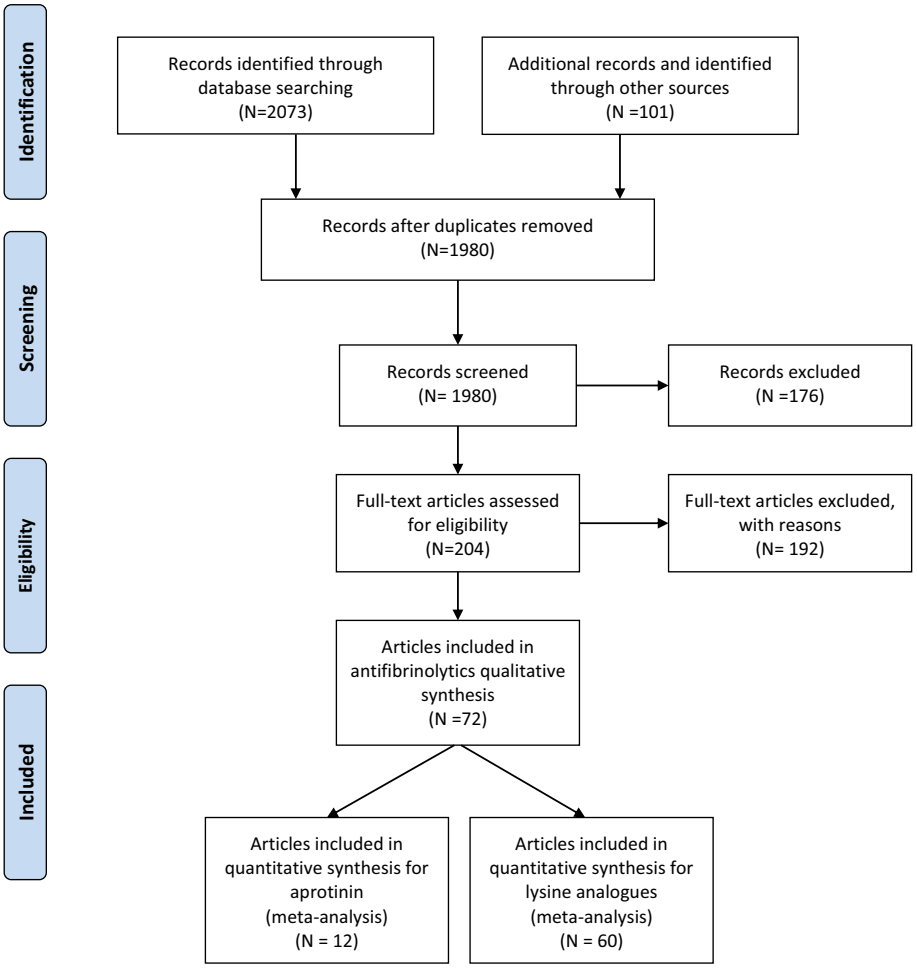

Fig. 2. Antifibrinolytics literature flow diagram.

Table 1
Body of evidence: antifibrinolytics and ε-aminocaproic acid.

Study	Quality/effect size	Sample	Setting	Time period
Intravenous tranexamic acid				
[18] Aguilera 2012	Good/Substantial	*N* = 68	Hosp de la Santa Creu, Barcelona, Spain	2006–2010
[19] Álvarez 2008	Good/Substantial	*N* = 95	Hospital del Mar, Barcelona, Spain	3/2005–12/2005
[20] Aslam 2015	Good/Substantial	*N* = 254	Quaid –e-Azam Int Hospital, Islamabad	1/2012–12/2014
[21] Bagsby 2012	Good/Substantial	*N* = 103	University of Louisville, KY	Not described
[22] Baker 2015	Good/Substantial	*N* = 844	St Michael Hosp, Toronto Canada	5/2013–4/2014
[23] Camarasa 2006	Good/Moderate	*N* = 127	Hosp de Mataro Barcelona, Spain	3/2004–3/2005
[24] Charoencholvanich 2011	Good/Substantial	*N* = 50	Siriraj Hospital, BangKok, Thailand	3/2008–5/2008
[25] Claeys 2007	Fair/Substantial	*N* = 40	Not Provided	Not Provided
[26] Craik 2014	Good/Substantial	*N* = 248	Epsom General Hospital, Surry, UK	2009–2012
[27] Diprose 2005	Good/Substantial	*N* = 180	Southampton University Hospitals NHS Trust, Southampton, UK	1/2002–2/2003
[28] Endres 2011	Good/Min-None	*N* = 97	Not provided	1/2009–12/2010
[29] Gautam 2013	Fair/Substantial	*N* = 27	Lok Nayak Hospital, New Delhi, India	Not provided
[30] Greiff 2012	Good/Substantial	*N* = 64	St. Olav University Hospital, Trondheim, Norway	
[31] Hogan 2016	Good/Substantial	*N* = 173	Univ Colorado Hosp, Aurora, CO	11/2012–10/31/2013
[32] Huang 2016	Good/Substantial	*N* = 108	West China Med Cntr, Chengdu, China	3/2012–12/2014
[33] Johansson 2005	Good/ Moderate	*N* = 100	Linoping University & Kamar Hospital, Sweden	9/2002–12/2003
[34] Karski 2005	Good Moderate	*N* = 312	Toronto Gen Hospital, Ontario, Canada	Not provided
[35] Karam 2013	Good/Substantial	*N* = 87	Riddle Mem Hospital, Media, PA	12 months–not specified
[36] Kazemi 2010	Good/Substantial	N = 64	Not specified	2006–2008
[37] Kim 2014	Good/Substantial	*N* = 326	Not specified	9/2009–5/2011
[38] Kopanidis 2016	Good/Substantial	*N* = 200	Austin Hosp, Victoria, AU	2011–2013
[39] Kumar 2013	Good/Substantial	*N* = 200	Inst Med Edu & Res, Chandigarh, India	2011–2012
[40] Later 2009	Good/Moderate	*N* = 298	LUMC University Hospital,, Leiden, The Netherlands	6/2004–10/2006
[41] Liu 2017	Good/Substantial & Min-None	*N* = 10,321	159 hospitals in Taiwan	2007–2012
[42] Lozano 2008	Good/Substantial	*N* = 414	Hosp ClinicProvincial, Barcelona, Spain	1–3/2005; 5–9/2005
[43] MacGillivray 2011	Fair/Moderate	*N* = 60	American Hosp, Dubai, UAE	Not specified
[44] Maniar 2012	Fair/Moderate	*N* = 200	Not specified	8/2010–4/2011
[45] McGoldrick 2015	Good/Substantial	*N* = 200	Tallaght Hospital, Dublin, Ireland	Not described
[46] Mohib 2015	Good/Substantial	*N* = 100	Aga Khan Hospital, Karachi, Pakistan	5/2014–10/2014
[47] Molloy 2007	Good/Substantial	*N* = 150	Musgrave Park Hospital Belfast, Northern Ireland	12/2004–10/2005
[48] Mutsuzaki 2012	Good/Substantial	*N* = 140	Ichihara Hospital, Ibaraki, Japan	57 months
[49] Niskanen 2005	Fair/Moderate	*N* = 39	Paijat- Hame Hosp, Heinola, Finland	2003
[50] Orpen 2006	Good/Moderate	N = 29	North Hampton, General Hospital UK	Not specified
[51] Ortega-Andreu 2011	Good/Substantial	*N* = 132	La Paz Hospital at Cantoblanco, Madrid, Spain	4/2008–5/2009
[52] Pongcharoen 2016	Fair/Min-None	*N* = 109	Thammasat University, Thailand	2011–2013
[53] Rajesparan 2009	Good/Moderate	*N* = 73	Royal Infirmary – Edinburgh, Scotland	Not specified
[54] Ralley 2010	Good/Substantial	*N* = 493	London Hlth Sci Cntr, Ontario CN	04–06/2007; 04–06/2008
[55] Raviraj 2012	Fair/Substantial	*N* = 175	Fortis Hospitals, Bangalore, India	Not specified
[56] Santos 2006	Good/Moderate	*N* = 60	Not specified	03–06/2001
[57] Sepah 2011	Good/Substantial	*N* = 99	Aga Khan University, Karachi, Pakistan	11/2005–11/2008
[58] Shi 2013	Good/Substantial	*N* = 552	7 Medical Cntrs in China	1/2010–6/2011
[59] Taghaddomi 2009	Good/Substantial	*N* = 100	Chaem Hospital- Mashad, Iran	10/2006–9/2007
[60] Volquind 2016	Good/Substantial	*N* = 62	Hospital Pompeia de Cazias Do Sul, Brazil	6/2012–5/2013
[61] Wang 2016	Good/Substantial	*N* = 124	West China Hospital, Sichuan University	9/2014–11/2014
Intra-articular injection tranexamic acid				
[62] Alshryda 2013	Good/Substantial	*N* = 161	North Tees, Stockton, UK	2009–2010
[63] Chen 2016	Fair/Substantial	*N* = 100	Singapore Gen Hosp	Not provided
[64] Goyal 2016	Good/Substantial	*N* = 1981	Setting unclear	2009–2014
[65] Onodera 2012	Good/Substantial	*N* = 100	Hokkaido, Japan	2006–2009
[66] Oztas 2015	Good/Substantial	*N* = 90	Bursa High Specialty, Turkey	2012–2013
[67] Sa-ngasoongson 2011	Good/Substantial	*N* = 48	Ramathibodi Hosp, Thailand	9/2008–10/2009
[68] Tahmasebi 2014	Good/Substantial	*N* = 100	Teharan Univ Hosp, Iran	4/2013–4/2014
[69] Xu 2015	Good/Substantial	*N* = 224	1stAffiliatHosp, Nanchang, CN	3/2013–2014
Topical Tranexamic Acid				
[70] Georgiadis 2013	Good/Substantial	N-101	Henry Ford Hospital, Detroit MI	6/2011–9/2012
[71] Konig 2013	Good/Substantial	*N* = 290	Univ of Pittsburg Med Cntr, PA	9/2010–3/2012
[72] Martin 2014	Good/Substantial	N = 100	Genesis Med CNTR, West Central Park, IA	1/2012–6/2012
[73] Wind 2013	Good/Substantial	*N* = 2069	Not specified	1/2009–5/2012
Epsilon amino-caproic acid				
[74] Berenholtz 2009	Good/Substantial	*N* = 182	Johns Hopkins, Baltimore, MD	2001–2006
[75] Kikura 2006	Good/Moderate	*N* = 100	Emory Hospital, Atlanta, GA	Not provided
[23] Camarasa 2006	Good/Substantial	*N* = 127	Hosp de Mataro, Barcelona, Spain	3/2004–3/2005
[76] Kreisler 2005	Good/Moderate	*N* = 67	Univ Kansas Hosp, Kansas	Not provided

abstraction form, and abstraction forms for the included studies are provided in **Supplement D**. Abstracted studies are then evaluated for research quality in accordance with LMBP methods which assess the likely generalizability of the findings and their potential for bias [15]. When study quality is rated Good or Fair, the study findings are considered when developing the recommendation. Poor quality studies do not contribute to the recommendation. Because not all study results are amenable to quantitative synthesis, the measured impact of each study on the outcome is given a qualitative rating of Substantial, Moderate, or Minimal/None [15]. These summary judgments are then summarized in a body of evidence table (Table 1). Both the qualitative and quantitative findings are used to determine the consistency and pattern(s) of results

across studies and to assess the overall strength of the body of evidence for establishing practice effectiveness (High, Moderate, Suggestive, and Insufficient).

As mentioned, all studies of good or fair quality contribute to the review, and findings from contributing studies were converted to a common metric, the effect size, whenever possible. When studies reported on the proportion of patients transfused these findings were transformed, when necessary, to odds ratios (OR). The OR documents the relative odds of the outcome (i.e., the odds of receiving an allogeneic transfusion given the practice relative to the odds of receiving an allogeneic transfusion absent the practice). An OR < 1 indicates that the tested practice is more effective than the comparator while an OR > 1 indicates the comparator is more effective than the tested practice in reducing the proportion of patients transfused. The difference in RBC units transfused, being a continuous measure, was transformed into the d-statistic, the standardized difference in means. The d-score is centered on zero and has a standard deviation of 1. The d-score is calculated using the following formula:

$$d = \frac{\overline{X}_{G1} - \overline{X}_{G2}}{S_p}$$

where $\overline{X}_{G1}$ is the mean of the treatment group, $\overline{X}_{G2}$ is the mean of the comparison group, and S_p is the two groups pooled standard deviation. When the d-score is negative, fewer RBC units are transfused in the treatment group relative to the comparison group; a positive d-score indicates the treatment group received more RBC units transfused relative to the comparison group. As a rule of thumb, d-scores of 0.2 (or −0.2 depending on the direction of coding) are considered small effects, 0.5 are considered moderate, while 0.8 or larger are considered large [77]. However, these standards should be interpreted in the context of the phenomena being measured. A small effect may be meaningful if the intervention is inexpensive and an undesired outcome prevented.

Random effects meta-analysis is used to combine evidence from individual studies to calculate an estimate of the overall impact of the practice (the grand mean) and calculate a 95% confidence interval for each intervention and outcome [78]. Random effects assume that each study is sufficiently unique as to estimate a unique population value and the results from random effects modeling are considered generalizable to unmeasured populations [79]. Forest plots are used to display each study's results and the overall average impact of the practice provided at the bottom of each plot.

Sampling theory tells us to expect variation in study results due to sampling error. If study results vary more than expected from sampling error, then the distribution is said to be heterogeneous, suggesting real differences in impact which may be attributable to differences in study sample, the internal or external context of the study, or other factors influencing implementation or intervention execution. When heterogeneity is observed, the total variability of a results distribution can be split into that expected from within-study differences and between-study differences. The percent of total variability associated with between-study differences is estimated using I^2 [80]. I^2 is calculated as follows:

$$I^2 = 100\% * \left(\frac{Q - (k-1)}{Q}\right)$$

where Q = the homogeneity test statistic, and k = the number of independent studies. I^2 between 0.1% and 25% is considered small heterogeneity, 50–74% is considered medium heterogeneity, and an I^2 of 75% and above is considered large heterogeneity [80,81].

3. Results

Seventy articles provided lysine analogue data on the effectiveness of TXA and EACA in reducing RBC transfusion preoperatively in orthopedic and cardiac surgeries. Thirteen articles assessed the effectiveness of aprotinin in reducing red blood cell transfusion. A range of dosages and methods of administration assessed the effectiveness of TXA in reducing patient transfusion and the number of units transfused. In the following analyses, we summarize the overall effectiveness of these antifibrinolytics by mode of administration. Treatment doses are noted in study descriptions in the forest plot.

Most of the intravenous TXA studies were performed outside of the USA and had small to moderate numbers of participants in the studies, however, a significant number of studies were randomized control trials [19,23–25,27,30,33,34,36,37,40,43,46,47,49,52,53,55,56,59,61]. The largest single center study of 844 participants within 1 year was from one Canadian institution [22]. Seven medical centers in China reported the next largest number of study participants in 1 year [58] while Taiwan reported over ten thousand participants over a 5 year period from 159 hospitals [41]. Only three studies were conducted in the US [21,31,35] and the time period for the actual practice periods was uncertain in two of three studies [21,35].

The four studies performed on topical application of TXA were from the USA [70–73]. Studies on EACA in this review tended to be older, based on surgical procedures performed between 2001 and 2006. Two of the four EACA studies were randomized controlled trials [23,75] and three were performed in the USA [74–76]. Of the eight intra-articular TXA studies, four were randomized controlled trials [62,66,67,69].

3.1. Intravenous (IV) TA

Of the 44 articles assessing the effectiveness of IV-TXA in reducing RBC transfusion in patients, 34 were related to orthopedic surgical procedures (knee and/or hip) [18–25,29,31–33,35–38,41–55,57,61,66,73], 5 were related to cardiovascular procedures [34,40,56,58,59], one study was on patients undergoing percutaneous nephrolithotomy [39]; and one was on patients experiencing degenerative spinal stenosis and instability [28]. Intravenous TXA dosages used were primarily 10 mg/kg [19,21,23,24,31,37,42–44,55,56,61]; 15 mg/kg [25,32,33,36,38,39,43,46,61], or 20 mg/kg [22,35,54].

Thirty-seven of the articles [18–24,26–28,30–37,39–42,45–48,50,51,53,54,56–61] received a study quality rating of “Good,” while seven were rated “Fair” [25,29,43,44,49,52,55]. Qualitative ratings of the impact of intravenous TXA found 31 studies showing substantial reductions in RBC transfusion overuse [18–22,24–27,29–32,35–39,42,45–48,51,54,55,57–61], 10 returned moderate reductions [23,33,34,40,43,44,49,50,53,56], and 3 returned minimal to no reduction in RBC transfusion overuse [28,41,52]. Based on the body of evidence summary in Table 1, there is High overall strength of evidence for the intravenous TXA practice [15].

The 44 IV-TXA reports produced 52 independent effect sizes on the impact of IV-TXA on the percentage of patients transfused. While there is significant heterogeneity in the distribution of effects (I^2 = 69.70%), the majority of studies returned significant positive results in support of using of intravenous TXA to reduce the percentage of patients transfused (Fig. 3). Overall, based on random effects modeling, IV-TXA reduces significantly and substantially the proportion of patients receiving RBC transfusions (mean OR = 0.264; 95% CI: 0.215–0.324; $p < .001$). Eighteen reports provided 25 independent effect sizes for the reduction in units transfused using IV-TXA (Fig. 4). Results from these studies are highly heterogeneous (I^2 = 89.31%) and the random effects overall impact in reducing overuse of red blood cell units of transfused among surgical and nonsurgical adult patients is substantial and significant (mean d = −0.553; 95% CI: −0.706 to −0.400; $p < .001$).

3.2. Intra-articular injection TA

Eight articles assessed the effectiveness of intra-articular injection TXA in reducing overuse of RBC transfusion [62–69]. All articles

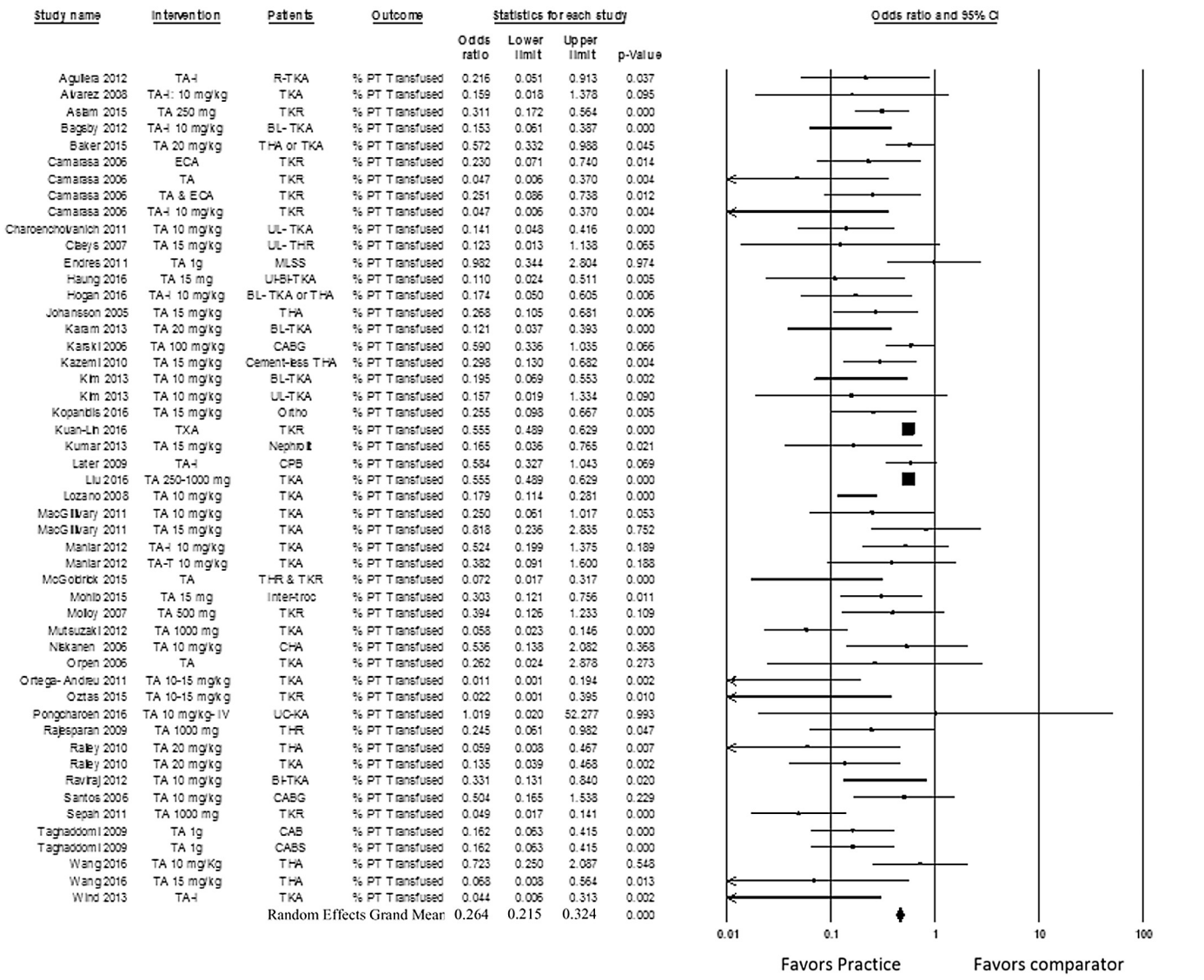

Fig. 3. Intravenous tranexamic acid: patients transfused.

returned substantial effects favoring the use of intra-articular injection TXA and all but one [63] were judged to be of "Good" quality. There is High overall strength of evidence for the use of intra-articular injection TXA based on the body of evidence summary in Table 1. The 8 articles produced 9 independent effect sizes on intra-articular injection TA's impact on reducing percentage of patients transfused (mean OR = 0.284; 95% CI: 0.218–0.370; $p < .001$) and the distribution of results is homogeneous ($I^2 = 0.00\%$; Fig. 5) suggesting that results do not vary more than would be expected from sampling error. Only two of the intra-articular injection TXA articles provided meta-analyzable evidence on the reduction in units transfused [63,69]. The results are again homogeneous ($I^2 = 0.00\%$) showing a significant overall impact in reducing the number of RBC units of transfused (mean d = −1.053; 95% CI: −1.308 to −0.798; $p < .001$; Fig. 6).

3.3. Topical TA

Topical use of TXA to reduce RBC transfusion overuse was assessed in 4 articles [70–73]. All studies were determined to be of Good quality and returned substantial effects favoring the use of topical TA. Based on the body of evidence summary in Table 1, there is High overall strength of evidence for the use of intra-articular injection TA. Five independent effect sizes were abstracted from 4 of the articles [70–73] on topical TA's impact on reducing percentage of patients transfused. The distribution of results was heterogeneous ($I^2 = 68.38\%$) with an overall random effects mean favoring the use of topical TXA to reduce the percentage of patients transfused (mean OR = 0.089; 95% CI: 0.015–0.511; $p = .01$; See Fig. 7). Only one study provided meta-analyzable evidence on the reduction in units transfused through use of topical TXA [71]. For both total hip and knee arthroscopy, topical TXA significantly and homogeneously reduced the number of RBC units transfused (mean d = −0.643; 95% CI: −0.922 to −0.365; $p < .001$; See Fig. 8).

3.4. Epsilon Amino-Caproic Acid (EACA)

Four good studies assessed EACA's impact on reducing overuse of RBC transfusion. Two studies were judged to substantially reduce RBC transfusion [23,74] and two had moderate effects [75,76]. Three studies [23,75,76] provided nearly homogeneous estimates ($I^2 = 2.81\%$) of the significant impact of EACA on the number of patients transfused (mean OR = 0.430; 95% CI: 0.221–0.836; $p = .01$; Fig. 9). The three studies on EACA's impact on reducing the number of RBC units transfused [23,74,75] returned homogeneous result ($I^2 = 0.00\%$) favoring

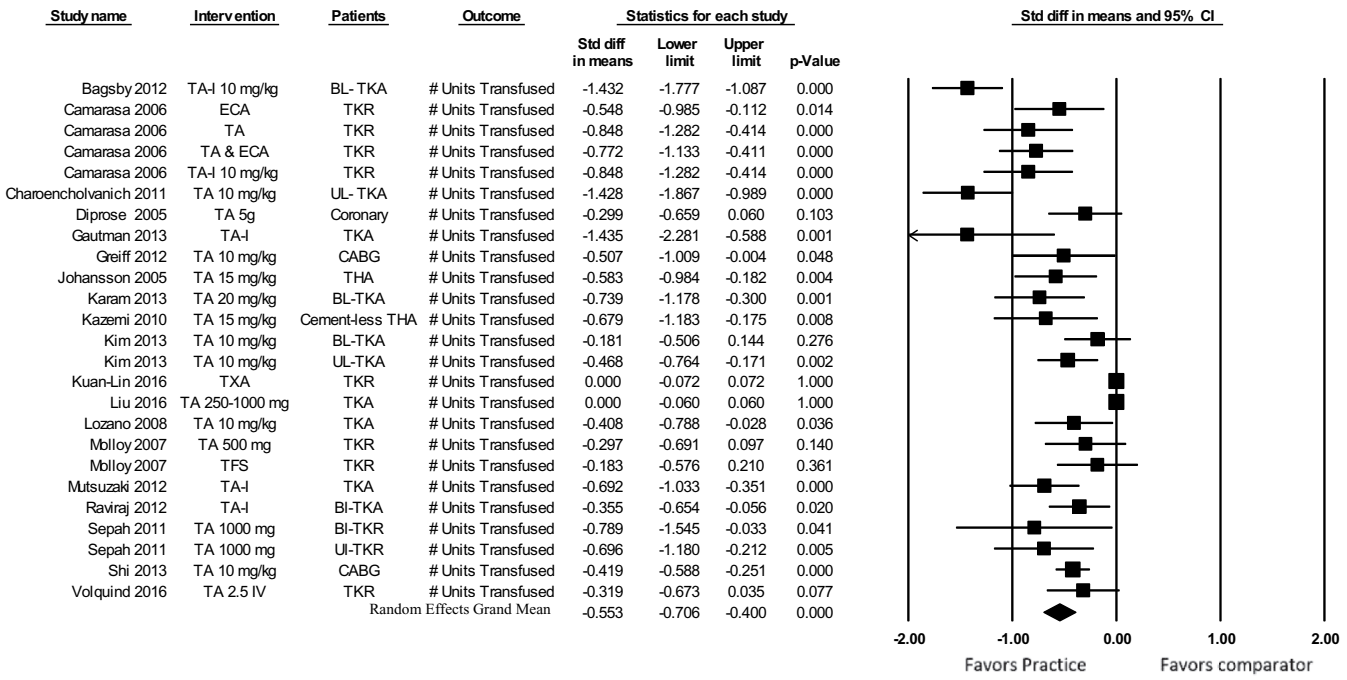

Fig. 4. Intravenous tranexamic acid: units transfused.

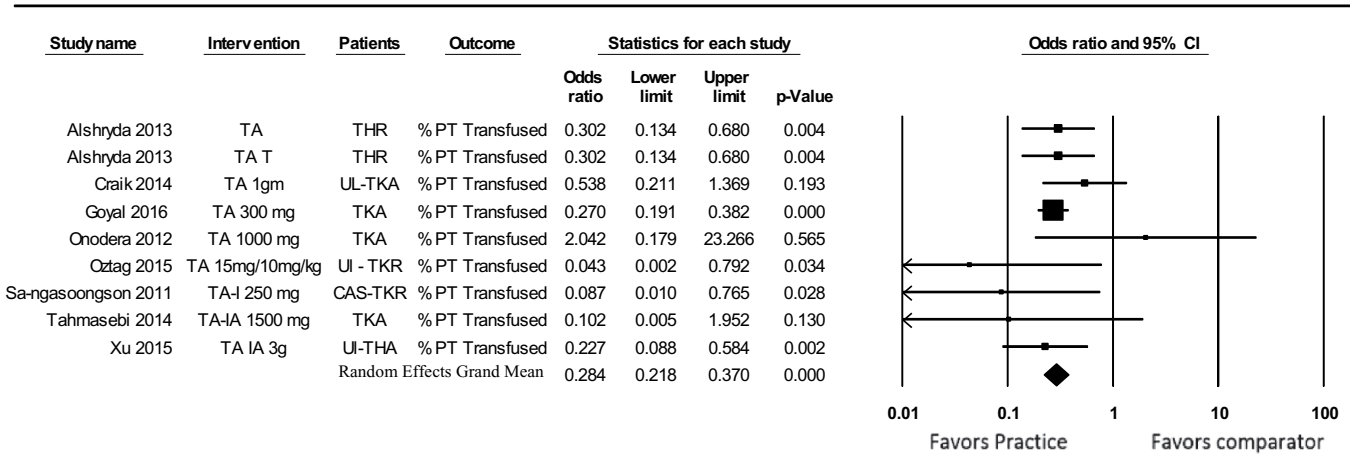

Fig. 5. Intra-articular injection tranexamic: patients transfused.

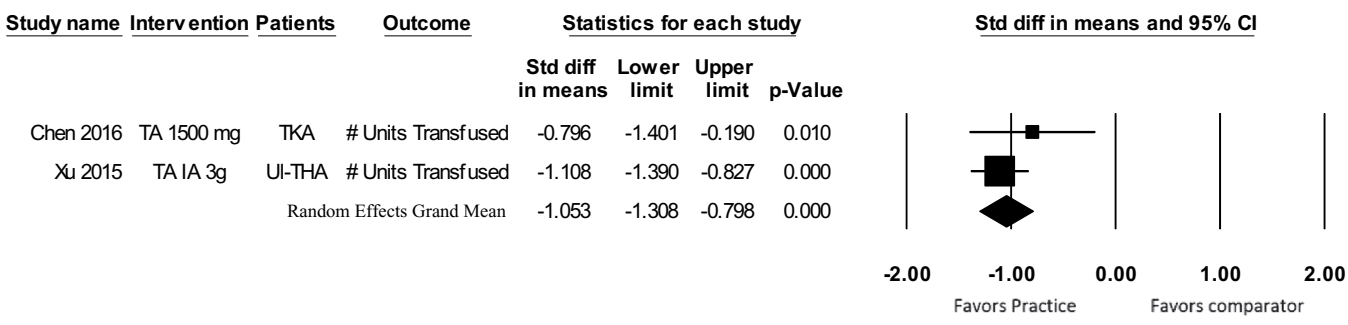

Fig. 6. Intra-articular injection tranexamic: units transfused.

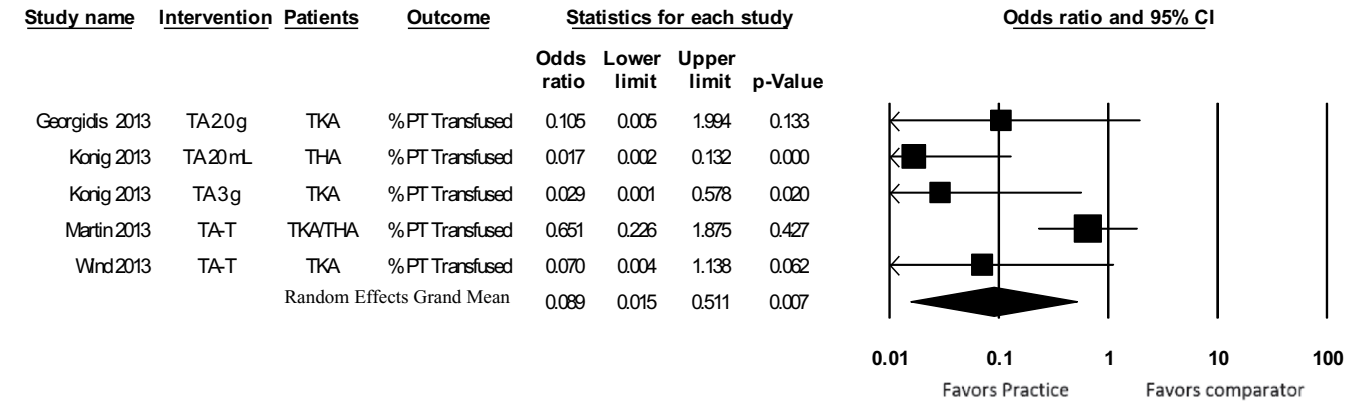

Fig. 7. Topical tranexamic acid: patients transfused.

the use of EACA to reduce the number RBC units transfused (mean d = −0.339; 95% CI: −0.546 to −0.132; $p < .001$; Fig. 10).

4. Discussion

Patient blood management is focused on holistic patient management which includes minimizing patient transfusion requirements and decreasing the risk of adverse transfusion-related events [82]. The studies summarized in this review overwhelmingly show that fewer patients experience transfusion and limited blood supplies are conserved when antifibrinolytics are administered. The use of antifibrinolytics, administration mode and dose for reducing blood loss is determined by the patient's clinical history, hospital and treatment protocols, and physician's judgment tailored to the anatomical area for treatment. Laboratories may also play a role. Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) have been recommended to help detect, manage and monitor hemostasis during and after cardiac surgery [83] and may help guide transfusion decisions for trauma patients [84,85]. Similarities, differences, and the interpretation of these tests for trauma-related transfusion is discussed elsewhere [85]. To reduce the risk of perioperative blood transfusion, preoperative interventions to ensure anemia management prior to surgery is very important [17]. Perioperative blood conservation interventions are particularly important among high-risk subpopulations. These include those with advanced age, small body size, with multiple comorbidities and those on antithrombotic drugs. In each of these situations, blood conservation strategies will likely include antifibrinolytic therapy [86].

Most often, TXA is administered intravenously and off-label (without approval by the U.S. Food and Drug Administration; FDA). TXA is used for a variety of conditions and to prevent or reduce blood loss during hip, knee, cardiac, facial, and spinal surgery as well as cesarean section and trauma. [87]. TXA has a high therapeutic index and is included in the list of essential medicines that has been compiled by the World Health Organization [88]. Most of the studies in this review assess administration modes of TXA therapy in orthopedic surgery rather than cardiac surgery. Assuming therapeutic equivalence in reducing perioperative bleeding in cardiac surgery, US institutions reverted to the lysine analogs since the withdrawal of aprotinin. Used often interchangeably, these agents have not been re-evaluated in contemporary practice [89].

As documented in this review and others, antifibrotics are effective in reducing blood loss for many clinical applications [90–97]. However, many questions on other clinical effects of TXA remain to be answered. These include the anti-inflammatory response to cardiopulmonary bypass, the association of dosage levels with thromboembolic events and with adverse neurological effects such as seizures, and TA's morbidity and mortality. Clinical trials are necessary on the safety and use of TXA in various clinical settings [98,99].

In vitro studies demonstrate that TXA has a 6 to 10 times greater affinity for plasminogen/plasmin than EACA [100–102], and this difference is reflected in their clinical dosing. Typical “low dose” TXA is 10 to 20 mg/kg compared to EACA dosages which range from 75 to 150 mg/kg [103]. At this time, TXA is FDA-approved to decrease hemorrhage associated with tooth extraction in hemophiliacs, and the indications discussed in this review are off-label [104]. The FDA label for EACA is more general, stating the medication is approved to enhance “hemostasis when fibrinolysis contributes to bleeding” [105; p. 4].”

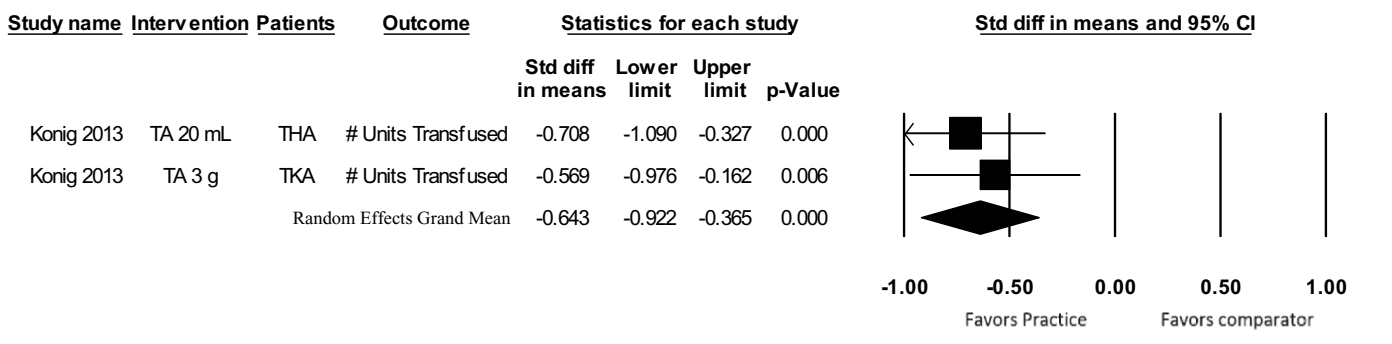

Fig. 8. Topical tranexamic acid: units transfused.

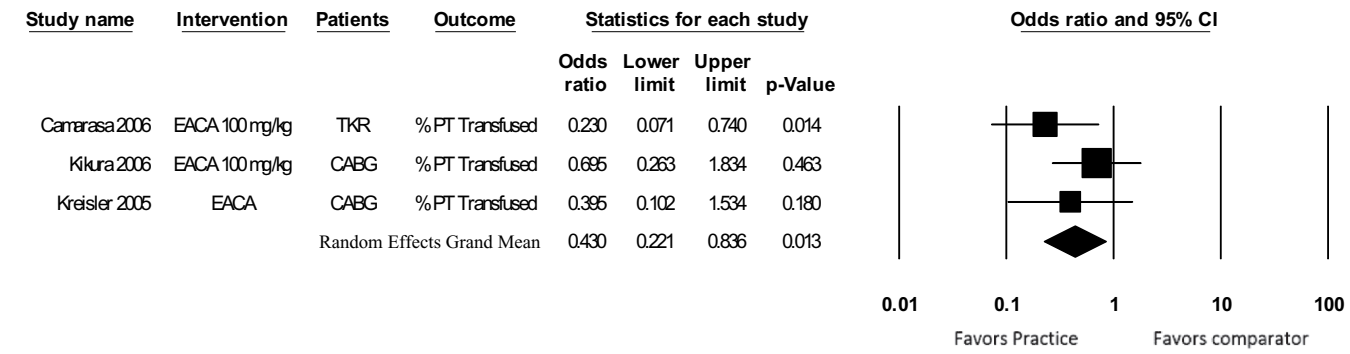

Fig. 9. Epsilon-aminocaproic acid: patients transfused.

4.1. Economic evaluation

An economic evaluation on studies in this review was not performed but several other studies have documented that TXA is a cost-effective addition to blood conservation programs [33,57,106–108]. The lysine analogue antifibrinolytics have a well-elucidated mechanism of action and a large therapeutic index. They are inexpensive, safe, and decrease postoperative transfusion requirements.

Several studies in this review mentioned cost savings associated with antifibrinolytic use. In one study, thromboembolic events were not increased by the application of EACA and surgery costs were reduced through lower transfusion rates. In this THA study, EACA was found to be safe, cost-efficient, and effective in reducing blood loss [109]. In a second study, when topically applied before tourniquet release, EACA reduced blood loss after TKA and was found to be as safe and less expensive than TXA [110].

A single-center, retrospective, observational cohort study of 120 patients undergoing cardiovascular surgery with or without cardiopulmonary bypass concluded TXA and EACA were equally effective and safe for managing cardiovascular surgical bleeding. The authors conclude that due to their substantial cost difference and their comparable efficacy and safety, EACA may have better value over TXA for reducing cardiovascular surgical bleeding [13].

Routine TXA use was associated with lower mean direct hospital total costs after primary total hip and knee arthroplasty of 580 of 1018 patients at Mayo Clinic as the increase in pharmacy costs was more than offset by cost savings in other categories [111]. The cost of TXA in the United States is reported to be roughly $60 per gram, and only about $6 per gram in Canada and Europe [107].

Multiple studies in this review show TXA reducing blood loss and transfusion overuse in patients undergoing total knee arthroplasty (TKA). Consequently, TXA has become a routine blood conservation agent for TKA. A two-year multicenter retrospective study of five hospitals within a single healthcare system compared the efficacy of EACA to TXA in reducing postoperative blood transfusion and compared the agent cost per surgery [14]. Of 2922 primary unilateral TKA cases, 820 patients received EACA (28.1%), 610 patients received TA (20.9%), and 1492 patients received no antifibrinolytic (51.1%). Between the EACA and TXA groups the differences in mean RBC units transfused per patient were insignificant ($p = .822$), the difference in percent of patients transfused was insignificant ($p = .236$), and the discharge Hb levels were insignificant ($p = .322$). However, EACA medication acquisition cost averaged $2.23 per surgery compared with an average of $39.58 per surgery for TXA. EACA and TXA both significantly decreased postoperative transfusion rates compared with no antifibrinolytic therapy. At a substantially lower cost, EACA proved comparable to TXA for unilateral TKA [14].

4.2. HARMS

Topical TXA administration to animal central nervous systems has caused seizures in a dose-related fashion [28,98]. This corresponds with reports of human seizures induced by accidental TXA intrathecal injections [112,113]. Recently, among patients undergoing cardiac surgery, the dose-response relationship of TXA has been proposed as a modifiable risk factor for seizures [98,114].

A Cochrane review examining the topical use of TXA found reliable evidence that while topical TXA reduced bleeding and blood transfusion in surgical patients, many studies are underpowered and report the risk of thromboembolism [90]. Of the 15 studies reporting on risk of thromboembolism in this systematic review, only one small study found an increased risk for deep venous thrombosis associated with intravenous TXA [25]. Of the 39 intravenous TXA studies, 10 reported no additional risk of thromboembolism [20,24,26,29,31,41,42,45,53,60].

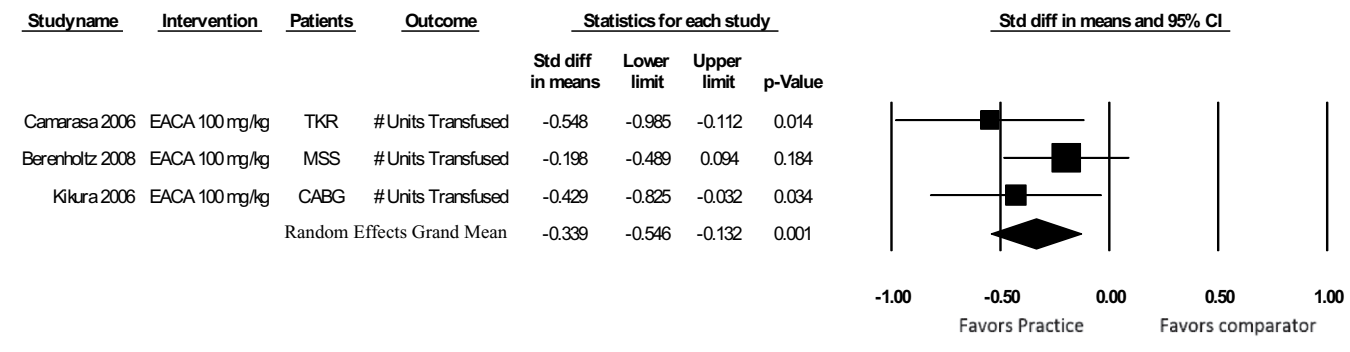

Fig. 10. Epsilon-aminocaproic acid: units transfused.

Of the 8 intra-articular, TXA studies 3 reported no additional risk of thrombotic complications [64,65,69], 1 of the 4 topical TXA studies reported no significant change in the rate of symptomatic deep venous thrombosis or pulmonary embolism [73], and 1 of the 4 EACA articles found no increased risk of deep vein thrombosis [74]. Thrombosis risk was not mentioned in the remainder of the studies summarized in this review. A very large randomized trial of the effect of TXA in traumatic brain injury found significant reductions of in the odds of fatal and non-fatal thrombotic events following use of TXA [115]. A study published after our data collection period ended found TXA reduced units transfused as well as the occurrence of thrombotic complications, but was associated with a higher risk of postoperative seizures [116]. A recent meta-analysis found no significant relations between TXA and thromboembolic events [117].

Clinically relevant adverse effects of TXA include gastrointestinal disturbances (nausea, vomiting, diarrhea); blood pressure drop and dizziness from too fast intravenous administration; incidental allergic skin reactions; and infrequent temporal vision impairment and convulsions [101,118]. The relative risk of harm from different antifibrinolytics and no treatment in cardiac surgery have been summarized elsewhere [119]. Patient and surgery type may also affect the incidence of harms associated with TXA [120,121]. In addition, TXA is not recommended when the following are present: renal failure; epilepsy; benign gynecological interventions (e. g. myomectomy); in combination with activated factor concentrate; factor VIII inhibitor bypass activity (FEIBA); 1 ml = 25 E* factor VIII inhibitor bypass activity; or fibrinolysis due to disseminated intravascular coagulation without any significant bleeding [101,118].

4.3. Study limitations

While not excluded from this review, most of the reviewed studies excluded patients with a history of venous thromboembolism and coagulopathies. Therefore, recommendations may not generalize to patients with these conditions.

As a result of the withdrawal of aprotinin, US institutions reverted to the lysine analogs, using them interchangeably with the assumption of therapeutic equivalence and non-inferiority to aprotinin in reducing perioperative bleeding in cardiac surgery. There have been few studies evaluating these agents in contemporary practice [89,119,122]. Aprotinin has been shown to have a better risk-benefit profile than TXA in high-risk than among low- to moderate-risk, patients. This suggests greater support for its use with high-risk cases [123]. Several reports compare the benefits and risk of aprotinin and TXA in various surgical procedures [124]. Given the potential for complications of TXA in cardiac patients, additional studies on the neurological risk, appropriate indications, and dosing of TXA are needed in the USA [124,125].

Most of the studies in this review assess administration modes of TXA therapy in orthopedic surgery rather than cardiac surgery. Most IV TXA studies were orthopedic with a few on cardiac procedures. All of the studies on topical use of TXA were on orthopedics. A range of dosages of TXA were use in both IV TXA and Intra-articular TXA which indicates the need for further study to confirm an optimal dose appropriate for reduction of blood transfusion and the route of administration. Additional studies are needed to assess the modes of administration of TXA in several other surgical and non-surgical applications in different patient settings.

Findings for the effectiveness of intravenous TXA and topical TXA in reducing the number of patients transfused showed medium heterogeneity and there was large heterogeneity in results for the effectiveness of intravenous TXA in reducing the number of whole blood units transfused. This suggests that practice or patient characteristics may influence the reduction in overuse which can be expected from adopting these practices. However, a clear majority of the studies reported significant reductions in each outcome, and no studies reported a significant increase in outcomes attributable to the use of these practices.

4.4. Future research needs

While there is strong support for the use of TXA as an antifibrinolytic treatment applied in a perioperative setting, definitive trials on morbidity and mortality are necessary to understand in what other situations the use of TXA is desirable. Several large randomized multisite trials are currently underway which assess the use of TXA in several of these situations [126–128].

Absent from many of the studies included in this review is documentation that the use of antifibrinolytics does not result in patient harm. Similarly, there are patient risks associated with transfusion and our confidence in the use of antifibrinolytics to reduce transfusion rates would be bolstered through concurrent evidence that patients benefited from reduced exposure to transfusion.

The concentration and doses of antifibrinolytics ranged between 10 and 15 mg/kg in most cases but further studies are needed to finalize more stringent information on the specific dosages associated with the modes of administrations [129]. In the vast majority of patients, this standardized dosing regimen falls within the recommended 10 mg to 20 mg/kg per dose. Multiple dose regimens such as this have been shown to be more effective than a single bolus dose [130]. Research and specific guidelines on TXA dose regimens need to be developed to minimize the risk of seizure and to assess thromboembolic risk.

5. Conclusions

This Laboratory Medicine Best Practice systematic review recommends four practices based on the overall availability and quality of evidence from the studies in this review. They are: (1) Intravenous, (2) Intra-articular injection, (3) and Topical tranexamic acid are recommended for reducing the proportion of patients transfused and units of red blood cell transfused in orthopedic and cardiac surgical adult patients. (4) Epsilon-aminocaproic acid is recommended for reducing the proportion of patients transfused and units of red blood cell transfused in orthopedic and cardiac surgical adult patients.

Funding

Funded in part by CDC (W911NF-07-D-001/DO 0191/TCN 07235) with Battelle Memorial Institute.

Disclaimer

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry (CDC/ATSDR).

Declaration of Competing Interest

Dr. Thurer is a consultant to Gauss Surgical Inc. (Los Altos, CA). In the early phases of this study, he was an employee of the Haemonetics Corporation (Braintree, MA).

Acknowledgements

The authors are deeply indebted to Dr. Bereneice Madison of the Centers for Disease Control and Prevention, Center for Surveillance, Epidemiology and Laboratory Sciences for her grace, leadership, and unflagging support for this work. Without her advocacy, effort, and diligence this work would not have been possible. We also wish to thank the Society for the Advancement of Blood Management for use of their library resources.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinbiochem.2019.06.015.

References

[1] D.M. Lerman, T.B. Rapp, Minimizing blood loss in orthopaedic surgery: the role of antifibrinolytics, Bull. Hosp. Jt Dis. 73 (2) (2015) 83–89.
[2] M.S. Carling, A. Jeppsson, B.I. Eriksson, H. Brisby, Transfusions and blood loss in total hip and knee arthroplasty: a prospective observational study, J. Orthop. Surg. Res. 10 (1) (2015).
[3] Task Force on Perioperative Blood Management, Practice guidelines for perioperative blood management: An updated report by the American Society of Anesthesiologists Anesthesiology 122 (2) (2015) 241–275.
[4] A. Shander, I. Gross, S. Hill, M. Javidroozi, S. Sledge, A new perspective on best transfusion practices, Blood Transfus. 11 (2) (2013) 193–202.
[5] V.J. Drew, L. Barro, J. Seghatchian, T. Burnouf, Towards pathogen inactivation of red blood cells and whole blood targeting viral DNA/RNA: design, technologies, and future prospects for developing countries, Blood Transfus. 15 (6) (2017) 512.
[6] D.R. Spahn, L.T. Goodnough, Alternatives to blood transfusion, Lancet 381 (9880) (2013) 1855–1865.
[7] D. Cardone, A.A. Klein, Perioperative blood conservation, Eur. J. Anaesthesiol. 26 (9) (2009) 722–729.
[8] D. Royston, The current place of aprotinin in the management of bleeding, Anaesthesia 70 (2014) 46–e17.
[9] D.A. Fergusson, P.C. Hébert, C.D. Mazer, S. Fremes, C. MacAdams, J.M. Murkin, K. Teoh, P.C. Duke, R. Arellano, M.A. Blajchman, A comparison of aprotinin and lysine analogues in high-risk cardiac surgery, N. Engl. J. Med. 358 (22) (2008) 2319–2331.
[10] P.C. Hébert, D.A. Fergusson, B. Hutton, C.D. Mazer, S. Fremes, M. Blajchman, C. MacAdams, G. Wells, J. Robblee, J. Bussieres, K. Teoh, Regulatory decisions pertaining to aprotinin may be putting patients at risk, Can. Med. Assoc. J. 186 (18) (2014) 1379–1386.
[11] E. Ortmann, M. Besser, A. Klein, Antifibrinolytic agents in current anaesthetic practice, Br. J. Anaesth. 111 (4) (2013) 549–563.
[12] EMA, European Medicines Agency Recommends Lifting Suspension of Aprotinin 2012, https://goo.gl/uV7m7N Accessed 12/17/2018.
[13] O. Falana, G. Patel, Efficacy and safety of tranexamic acid versus ϵ-aminocaproic acid in cardiovascular surgery, Ann. Pharmacother. 48 (12) (2014) 1563–1569.
[14] J. Churchill, K. Puca, E. Meyer, M. Carleton, M. Anderson, Comparing ε-aminocaproic acid and tranexamic acid in reducing postoperative transfusions in total knee arthroplasty, J. Knee Surg. 30 (05) (2016) 460–466.
[15] R.H. Christenson, S.R. Snyder, C.S. Shaw, J.H. Derzon, R.S. Black, D. Mass, P. Epner, A.M. Favoretto, E.B. Liebow, Laboratory medicine best practices: systematic evidence review and evaluation methods for quality improvement, Clin. Chem. 57 (6) (2011) 816–825.
[16] G.H. Guyatt, A.D. Oxman, G.E. Vist, R. Kunz, Y. Falck-Ytter, P. Alonso-Coello, H.J. Schunemann, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 336 (7650) (2008) 924–926.
[17] J. Derzon, A. Alford, N. Clarke, I. Gross, A. Shander, R. Thurer, Anemia management and audit feedback practices for reducing overuse of RBC transfusion: a laboratory medicine best practice systematic review and meta-analysis, Am. J. Clin. Pathol. 151 (1) (2019) 18–28.
[18] X. Aguilera, S. Videla, M. Aimenara, J.A. Fernandez, I. Gich, F. Cieaya, Effectiveness of tranexamic acid in revision total knee arthroplasty, Acta Orthop. Belg. 78 (1) (2012) 68.
[19] J.C. Álvarez, F.X. Santiveri, I. Ramos, E. Vela, L. Puig, F. Escolano, Tranexamic acid reduces blood transfusion in total knee arthroplasty even when a blood conservation program is applied, Transfusion (Paris) 48 (3) (2008) 519–525.
[20] K.S. Aslam, A.K. Niazi, O. Nabi, Efficacy of tranexamic acid in reducing blood loss in total knee replacements, J. Pak. Med. Assoc. 65 (11 Suppl 3) (2015) S210–S214.
[21] D.T. Bagsby, C.A. Samujh, J.L. Vissing, J.A. Empson, D.L. Pomeroy, A.L. Malkani, Tranexamic acid decreases incidence of blood transfusion in simultaneous bilateral total knee arthroplasty, J. Arthroplast. 30 (12) (2015) 2106–2109.
[22] J.E. Baker, K. Pavenski, R.A. Pirani, A. White, M. Kataoka, J.P. Waddell, A. Ho, E.H. Schemitsch, N. Lo, E.R. Bogoch, A. Pronovost, K. Luke, A. Howell, A. Nassis, A.K.Y. Tsui, R.M. Tanzini, R. Pulendrarajah, C.D. Mazer, J. Freedman, G.M.T. Hare, Universal tranexamic acid therapy to minimize transfusion for major joint arthroplasty: a retrospective analysis of protocol implementation, Can. J. Anaesth. 62 (11) (2015) 1179–1187.
[23] M.A. Camarasa, G. Ollé, M. Serra-Prat, A. Martín, M. Sánchez, P. Ricós, A. Pérez, L. Opisso, Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: a randomized clinical trial, Br. J. Anaesth. 96 (5) (2006) 576–582.
[24] K. Charoencholvanich, P. Siriwattanasakul, Tranexamic acid reduces blood loss and blood transfusion after TKA: a prospective randomized controlled trial, Clin. Orthop. Relat. Res. 469 (10) (2011) 2874–2880.
[25] M.A. Claeys, N. Vermeersch, P. Haentjens, Reduction of blood loss with tranexamic acid in primary total hip replacement surgery, Acta Chir. Belg. 107 (4) (2007) 397–401.
[26] J.D. Craik, S.A. Ei Shafie, A.G. Kidd, R.S. Twyman, Can local administration of tranexamic acid during total knee arthroplasty reduce blood loss and transfusion requirements in the absence of surgical drains? Eur. J. Orthop. Surg. Traumatol. 24 (3) (2013) 379–384.
[27] P. Diprose, M.J. Herbertson, D. O'Shaughnessy, C.D. Deakin, R.S. Gill, Reducing allogeneic transfusion in cardiac surgery: a randomized double-blind placebo-controlled trial of antifibrinolytic therapies used in addition to intra-operative cell salvage, Br. J. Anaesth. 94 (3) (2005) 271–278.
[28] S. Endres, M. Heinz, A. Wilke, Efficacy of tranexamic acid in reducing blood loss in posterior lumbar spine surgery for degenerative spinal stenosis with instability: A retrospective case control study, BMC Surg. 11 (1) (2011).
[29] V.K. Gautam, B. Sambandam, S. Singh, P. Gupta, R. Gupta, L. Maini, The role of tranexamic acid in reducing blood loss in total knee replacement, J. Clin. Orthop. Trauma 4 (1) (2013) 36–39.
[30] G. Greiff, R. Stenseth, A. Wahba, V. Videm, S. Lydersen, W. Irgens, L. Bjella, H. Pleym, Tranexamic acid reduces blood transfusions in elderly patients undergoing combined aortic valve and coronary artery bypass graft surgery: a randomized controlled trial, J. Cardiothorac. Vasc. Anesth. 26 (2) (2012) 232–238.
[31] C.A. Hogan, L.K. Golightly, S. Phong, M.R. Dayton, C. Lyda, G.R. Barber, Perioperative blood loss in total hip and knee arthroplasty: outcomes associated with intravenous tranexamic acid use in an academic medical center, SAGE Open Med. 4 (2016) 205031211663702.
[32] G.-P. Huang, X.-F. Jia, Z. Xiang, Y. Ji, G.-Y. Wu, Y. Tang, J. Li, J. Zhang, Tranexamic acid reduces hidden blood loss in patients undergoing total knee arthroplasty: a comparative study and meta-analysis, Med. Sci. Monit. 22 (2016) 797–802.
[33] T. Johansson, L. Pettersson, B. Lisander, Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients, Acta Orthop. 76 (3) (2005) 314–319.
[34] J. Karski, G. Djaiani, J. Carroll, M. Iwanochko, P. Seneviratne, P. Liu, W. Kucharczyk, L. Fedorko, T. David, D. Cheng, Tranexamic acid and early saphenous vein graft patency in conventional coronary artery bypass graft surgery: a prospective randomized controlled clinical trial, J. Thorac. Cardiovasc. Surg. 130 (2) (2005) 309–314.
[35] J.A. Karam, M.R. Bloomfield, T.M. DiIorio, A.M. Irizarry, P.F. Sharkey, Evaluation of the efficacy and safety of tranexamic acid for reducing blood loss in bilateral total knee arthroplasty, J. Arthroplast. 29 (3) (2014) 501–503.
[36] S.M. Kazemi, F. Mosaffa, A. Eajazi, M. Kaffashi, L.D. Besheli, M.R. Bigdeli, R.F. Zanganeh, The effect of tranexamic acid on reducing blood loss in cementless total hip arthroplasty under epidural anesthesia, Orthopedics 33 (1) (2010) 17–22.
[37] T.K. Kim, C.B. Chang, Y.G. Kang, E.S. Seo, J.H. Lee, J.H. Yun, S.H. Lee, Clinical value of tranexamic acid in unilateral and simultaneous bilateral TKAs under a contemporary blood-saving protocol: a randomized controlled trial, Knee Surg. Sports Traumatol. Arthrosc. 22 (8) (2014) 1870–1878.
[38] P. Kopanidis, A. Hardidge, L. McNicol, S. Tay, P. McCall, L. Weinberg, Perioperative blood management programme reduces the use of allogenic blood transfusion in patients undergoing total hip and knee arthroplasty, J. Orthop. Surg. Res. 11 (1) (2016).
[39] S. Kumar, M.S. Randhawa, R. Ganesamoni, S.K. Singh, Tranexamic acid reduces blood loss during percutaneous nephrolithotomy: a prospective randomized controlled study, J. Urol. 189 (5) (2013) 1757–1761.
[40] A.F.L. Later, J.J. Maas, F.H.M. Engbers, M.I.M. Versteegh, E.F. Bruggemans, R.A.E. Dion, R.J.M. Klautz, Tranexamic acid and aprotinin in low- and intermediate-risk cardiac surgery: a non-sponsored, double-blind, randomised, placebo-controlled trial☆, Eur. J. Cardiothorac. Surg. 36 (2) (2009) 322–329.
[41] K.-L. Liu, I.-H. Chen, S.-H. Wen, Low dose tranexamic acid reduces blood transfusion rate after total knee arthroplasty: a population-based study in Taiwan, J. Formos. Med. Assoc. 116 (1) (2017) 24–31.
[42] M. Lozano, M. Basora, L. Peidro, I. Merino, J.M. Segur, A. Pereira, F. Salazar, J. Cid, L. Lozano, R. Mazzara, F. Macule, Effectiveness and safety of tranexamic acid administration during total knee arthroplasty, Vox Sang. 95 (1) (2008) 39–44.
[43] R.G. MacGillivray, S.B. Tarabichi, M.F. Hawari, N.T. Raoof, Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty, J. Arthroplast. 26 (1) (2011) 24–28.
[44] R.N. Maniar, G. Kumar, T. Singhi, R.M. Nayak, P.R. Maniar, Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients, Clin. Orthop. Relat. Res. 470 (9) (2012) 2605–2612.
[45] N.P. McGoldrick, Cost benefit analysis of the use of tranexamic acid in primary lower limb arthroplasty: a retrospective cohort study, World J. Orthop. 6 (11) (2015) 977.
[46] Y. Mohib, R.H. Rashid, M. Ali, A.J. Zubairi, Does tranexamic acid reduce blood transfusion following surgery for inter-trochanteric fracture? A randomized control trial, J. Pak. Med. Assoc. 65 (11) (2015) S17.
[47] D.O. Molloy, H.A.P. Archbold, L. Ogonda, J. McConway, R.K. Wilson, D.E. Beverland, Comparison of topical fibrin spray and tranexamic acid on blood loss after total knee replacement, J. Bone Joint Surg. (Br.) 89-B (3) (2007) 306–309.
[48] H. Mutsuzaki, K. Ikeda, Intra-articular injection of tranexamic acid via a drain plus drain-clamping to reduce blood loss in cementless total knee arthroplasty, J. Orthop. Surg. Res. 7 (1) (2012) 32.
[49] R.O. Niskanen, O.L. Korkala, Tranexamic acid reduces blood loss in cemented hip arthroplasty: a randomized, double-blind study of 39 patients with osteoarthritis, Acta Orthop. 76 (6) (2005) 829–832.
[50] N.M. Orpen, C. Little, G. Walker, E.J.P. Crawfurd, Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients, Knee 13 (2) (2006) 106–110.
[51] M. Ortega-Andreu, G. Talavera, N.G. Padilla-Eguiluz, H. Perez-Chrzanowska, R. Figueredo-Galve, C.E. Rodriguez-Merchán, E. Gómez-Barrena, Tranexamic acid in a multimodal blood loss prevention protocol to decrease blood loss in revision

total knee arthroplasty: a cohort study, Open Orthop. J. 10 (1) (2016) 439–447.
[52] B. Pongcharoen, C. Ruetiwarangkoon, Does tranexamic acid reduce blood loss and transfusion rates in unicompartmental knee arthroplasty? J. Orthop. Sci. 21 (2) (2016) 211–215.
[53] K. Rajesparan, L.C. Biant, M. Ahmad, R.E. Field, The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement, J. Bone Joint Surg. (Br.) 91-B (6) (2009) 776–783.
[54] F.E. Ralley, D. Berta, V. Binns, J. Howard, D.D.R. Naudie, One intraoperative dose of tranexamic acid for patients having primary hip or knee arthroplasty, Clin. Orthop. Relat. Res. 468 (7) (2010) 1905–1911.
[55] A. Raviraj, A. Anand, M. Chakravarthy, S. Kumarswamy, A. Prabhu, S. Pai, Tranexamic acid reduces blood loss in simultaneous bilateral total knee arthroplasty: a randomized control trial, Eur. J. Orthop. Surg. Traumatol. 22 (5) (2011) 381–386.
[56] A.T.L. Santos, R.A.K. Kalil, C. Bauemann, J.B. Pereira, I.A. Nesralla, A randomized, double-blind, and placebo-controlled study with tranexamic acid of bleeding and fibrinolytic activity after primary coronary artery bypass grafting, Braz. J. Med. Biol. Res. 39 (1) (2006) 63–69.
[57] Y.J. Sepah, M. Umer, T. Ahmad, F. Nasim, M. Umer Chaudhry, M. Umar, Use of tranexamic acid is a cost effective method in preventing blood loss during and after total knee replacement, J. Orthop. Surg. Res. 6 (1) (2011) 22.
[58] J. Shi, H. Ji, F. Ren, G. Wang, M. Xu, Y. Xue, M. Chen, J. Qi, L. Li, Protective effects of tranexamic acid on clopidogrel before coronary artery bypass grafting, JAMA Surg. 148 (6) (2013) 538.
[59] R.J. Taghaddomi, A. Mirzaee, A.S. Attar, A. Shirdel, Tranexamic acid reduces blood loss in off-pump coronary artery bypass surgery, J. Cardiothorac. Vasc. Anesth. 23 (3) (2009) 312–315.
[60] D. Volquind, R.A. Zardo, B.C. Winkler, B.B. Londero, N. Zanelatto, G.P. Leichtweis, Use of tranexamic acid in primary total knee replacement: effects on perioperative blood loss, Braz. J. Anesthesiol. 66 (3) (2016) 254–258.
[61] C. Wang, P. Kang, J. Ma, C. Yue, J. Xie, F. Pei, Single-dose tranexamic acid for reducing bleeding and transfusions in total hip arthroplasty: a double-blind, randomized controlled trial of different doses, Thromb. Res. 141 (2016) 119–123.
[62] S. Alshryda, J. Mason, P. Sarda, A. Nargol, N. Cooke, H. Ahmad, S. Tang, R. Logishetty, M. Vaghela, L. McPartlin, A.P.S. Hungin, Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement, J. Bone Joint Surg. Am. 95 (21) (2013) 1969–1974.
[63] J.Y. Chen, P.L. Chin, H. Moo, H.N. Pang, D.K.J. Tay, S.-L. Chia, N.N. Lo, S.J. Yeo, Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: a double-blinded randomised controlled noninferiority trial, Knee 23 (1) (2016) 152–156.
[64] N. Goyal, D.B. Chen, I.A. Harris, N. Rowden, G. Kirsh, S.J. MacDessi, Clinical and financial benefits of intra-articular tranexamic acid in total knee arthroplasty, J. Orthop. Surg. (Hong Kong) 24 (1) (2016) 3–6.
[65] T. Onodera, T. Majima, N. Sawaguchi, Y. Kasahara, T. Ishigaki, A. Minami, Risk of deep venous thrombosis in drain clamping with tranexamic acid and carbazochrome sodium sulfonate hydrate in total knee arthroplasty, J. Arthroplast. 27 (1) (2012) 105–108.
[66] S. Oztas, A. Ozturk, Y. Akalin, N. Sahin, Y. Ozkan, A. Otuzbir, B. Avcu, The effect of local and systemic application of tranexamic acid on the amount of blood loss and allogeneic blood transfusion after total knee replacement, Acta Orthop. Belg. 81 (4) (2015) 698–707.
[67] P. Sa-ngasoongsong, T. Channoom, V. Kawinwonggowit, P. Woratanarat, P. Chanplakorn, B. Wibulpolprasert, S. Wongsak, U. Udomsubpayakul, S. Wechmongkolgorn, N. Lekpittaya, Postoperative blood loss reduction in computer-assisted surgery total knee replacement by low dose intra-articular tranexamic acid injection together with 2-hour clamp drain: a prospective triple-blinded randomized controlled trial, Orthop. Rev. (Pavia) 3 (2) (2011) 12.
[68] M.N. Tahmasebi, K. Bashti, G. Ghorbani, M.R. Sobhan, Intraarticular administration of tranexamic acid following total knee arthroplasty: a case-control study, Arch. Bone Jt. Surg. 2 (3) (2014) 141.
[69] X. Xu, X. Li, W. Liu, Z. Wang, Longtime soaking of high concentration tranexamic acid in total hip arthroplasty: a prospective randomized controlled trial in 224 patients, Pak. J. Med. Sci. 31 (6) (2015) 1306–1311.
[70] A.G. Georgiadis, S.J. Muh, C.D. Silverton, R.M. Weir, M.W. Laker, A prospective double-blind placebo controlled trial of topical tranexamic acid in total knee arthroplasty, J. Arthroplast. 28 (8) (2013) 78–82.
[71] G. Konig, B.R. Hamlin, J.H. Waters, Topical tranexamic acid reduces blood loss and transfusion rates in total hip and total knee arthroplasty, J. Arthroplast. 28 (9) (2013) 1473–1476.
[72] J.G. Martin, K.B. Cassatt, K.A. Kincaid-Cinnamon, D.S. Westendorf, A.S. Garton, J.H. Lemke, Topical administration of tranexamic acid in primary total hip and total knee arthroplasty, J. Arthroplast. 29 (5) (2014) 889–894.
[73] T.C. Wind, W.R. Barfield, J.T. Moskal, The effect of tranexamic acid on blood loss and transfusion rate in primary total knee arthroplasty, J. Arthroplast. 28 (7) (2013) 1080–1083.
[74] S.M. Berenholtz, J.C. Pham, E. Garrett-Mayer, C.W. Atchison, J.P. Kostuik, D.B. Cohen, S. Nundy, T. Dorman, P.M. Ness, M.J. Klag, P.J. Pronovost, K.M. Kebaish, Effect of epsilon aminocaproic acid on red-cell transfusion requirements in major spinal surgery, Spine (Phila Pa 1976) 34 (19) (2009) 2096–2103.
[75] M. Kikura, J.H. Levy, K.A. Tanaka, J.G. Ramsay, A double-blind, placebo-controlled trial of epsilon-aminocaproic acid for reducing blood loss in coronary artery bypass grafting surgery, J. Am. Coll. Surg. 202 (2) (2006) 216–222.
[76] K.R. Kreisler, R.A. Vance, J. Cruzzavala, J.D. Mahnken, Heparin-bonded cardiopulmonary bypass circuits reduce the rate of red blood cell transfusion during elective coronary artery bypass surgery, J. Cardiothorac. Vasc. Anesth. 19 (5) (2005) 608–611.
[77] J. Cohen, Statistical Power Analysis for the Behavioral Sciences, Hillsdale, NJ, Earlbaum, 1988.
[78] S.W. Raudenbush, Random effects models, in: H. Cooper, L.V. Hedges (Eds.), The Handbook of Research Synthesis, Russell Sage, New York, NY, 1994, pp. 301–321.
[79] J.E. Hunter, F.L. Schmidt, Fixed effects vs. random effects meta-analysis models: implications for cumulative research knowledge, Int. J. Select Assess. 8 (4) (2000) 275–292.
[80] J.P.T. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (11) (2002) 1539–1558.
[81] J.P.T. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7414) (2003) 557–560.
[82] S. Engelbrecht, E.M. Wood, M.F. Cole-Sinclair, Clinical transfusion practice update: Haemovigilance, complications, patient blood management and national standards, Med. J. Aust. 199 (6) (2013) 397–401.
[83] National Institute for Health and Care Excellence (NICE), Detecting, Managing and Monitoring Haemostasis: Viscoelastometric Point-of-Care Testing (ROTEM, TEG, and Sonoclot systems), https://bit.ly/2K00ULw, (2014) Accessed 01/23/2019.
[84] H. Hunt, S. Stanworth, N. Curry, T. Woolley, C. Cooper, O. Ukoumunne, Z. Zhelev, C. Hyde, Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) for trauma-induced coagulopathy in adult trauma patients with bleeding, Cochrane Database Syst. Rev. (2) (2015).
[85] A. Sankarankutty, B. Nascimento, L.T. da Luz, S. Rizoli, TEG® and ROTEM® in trauma: similar test but different results? World J. Emerg. Surg., BioMed. Central (2012) S3.
[86] The Society of Thoracic Surgeons Blood Conservation Guideline Task Force, V.A. Ferraris, S.P. Ferraris, S.P. Saha, E.A. Hessel II, C.K. Haan, B.D. Royston, C.R. Bridges, R.S. Higgins, G. Despotis, J.R. Brown, Perioperative blood transfusion and blood conservation in cardiac surgery: the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists clinical practice guideline, Ann. Thorac. Surg. 83 (5) (2007) S27–S86.
[87] M. McEvoy, Tranexamic Acid (TXA): Drug Whys: A Comprehensive Examination of TXA, the Support for Its Prehospital Use, and Off-Label Administration of TXA by EMS for Trauma Patients with Major Hemorrhage, 2018. https://goo.gl/LGXaSQ. (Accessed 12/13/2018).
[88] X. Muschart, P. Vincent, What's new for tranexamic acid? J. Emerg. Med. 51 (3) (2016) 332–333.
[89] K.P. Blaine, C. Press, K. Lau, J. Sliwa, V.K. Rao, C. Hill, Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage, J. Clin. Anesth. 35 (2016) 516–523.
[90] D.A. Henry, P.A. Carless, A.J. Moxey, D. O'Connell, B.J. Stokes, D.A. Fergusson, K. Ker, Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion, Cochrane Database Syst. Rev. 3 (2011) CD001886.
[91] J.R. Brown, N. Birkmeyer, G.T. O'Connor, Meta-analysis comparing the effectiveness and adverse outcomes of antifibrinolytic agents in cardiac surgery, Circulation 115 (22) (2007) 2801–2813.
[92] M. Levi, M.E. Cromheecke, E. de Jonge, M.H. Prins, B.J. de Mol, E. Briët, H.R. Büller, Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints, Lancet 354 (9194) (1999) 1940–1947.
[93] A. Laupacis, D. Fergusson, Drugs to minimize perioperative blood loss in cardiac surgery: meta-analyses using perioperative blood transfusion as the outcome, Anesth. Analg. 85 (6) (1997) 1258–1267.
[94] T. Cheriyan, S.P. Maier II, K. Bianco, K. Slobodyanyuk, R.N. Rattenni, V. Lafage, F.J. Schwab, B.S. Lonner, T.J. Errico, Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis, Spine J. 15 (4) (2015) 752–761.
[95] G. Song, P. Yang, J. Hu, S. Zhu, Y. Li, Q. Wang, The effect of tranexamic acid on blood loss in orthognathic surgery: a meta-analysis of randomized controlled trials, Oral Surg. Oral Med. Oral Pathol. Oral Radiol. 115 (5) (2013) 595–600.
[96] C. Wang, G.-j. Xu, Z. Han, J.-x. Ma, X.-l. Ma, X. Jiang, Y. Wang, Topical application of tranexamic acid in primary total hip arthroplasty: a systemic review and meta-analysis, Int. J. Surg. 15 (2015) 134–139.
[97] S. Alshryda, P. Sarda, M. Sukeik, A. Nargol, J. Blenkinsopp, J. Mason, Tranexamic acid in total knee replacement: a systematic review and meta-analysis, J. Bone Joint Surg. 93 (12) (2011) 1577–1585 British volume.
[98] W.C.K. Ng, A. Jerath, M. Wasowicz, Tranexamic acid: a clinical review, Anaesthesiol. Intensive Ther. 47 (4) (2015) 339–350.
[99] P. Perel, K. Ker, C.H. Morales Uribe, I. Roberts, Tranexamic acid for reducing mortality in emergency and urgent surgery, Cochrane Database Syst. Rev. 1 (1) (2013) CD010245.
[100] A. Dhir, Antifibrinolytics in cardiac surgery, Ann. Card. Anaesth. 16 (2) (2013) 117.
[101] I. Pabinger, D. Fries, H. Schöchl, W. Streif, W. Toller, Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis, Wien. Klin. Wochenschr. 129 (9–10) (2017) 303–316.
[102] R. Rossaint, B. Bouillon, V. Cerny, T.J. Coats, J. Duranteau, E. Fernández-Mondéjar, B.J. Hunt, R. Komadina, G. Nardi, E. Neugebauer, Management of bleeding following major trauma: an updated European guideline, Crit. Care 14 (2) (2010) R52.
[103] L.T. Goodnough, A. Shander, Current status of pharmacologic therapies in patient blood management, Anesth. Analg. 116 (1) (2013) 15–34.
[104] Food and Drug Administration, Highlights of Prescribing Information: Lysteda (Tranexamic Acid) Tablets, https://goo.gl/ZEuRB9, (2018) Accessed 08/18/2018.
[105] Food and Drug Administration, Drugs@FDA: FDA Approved Drug Products:

Amicar NDA 15–197/S-036, 037, 038, 039, https://goo.gl/EbcyDG, (2018) Accessed 12/13/2018.
[106] C. Guerriero, J. Cairns, P. Perel, H. Shakur, I. Roberts, C.T. Collaborators, Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial, PLoS One 6 (5) (2011) e18987.
[107] Z.X. Lin, S.K. Woolf, Safety, efficacy, and cost-effectiveness of tranexamic acid in orthopedic surgery, Orthopedics 39 (2) (2016) 119–130.
[108] J.R. Tuttle, S.A. Ritterman, D.B. Cassidy, W.A. Anazonwu, J.A. Froehlich, L.E. Rubin, Cost benefit analysis of topical tranexamic acid in primary total hip and knee arthroplasty, J. Arthroplast. 29 (8) (2014) 1512–1515.
[109] M.G. Sucher, M. Giordani, A. Figoni, A.J. Nedopil, Peri-operative blood-loss after total hip arthroplasty can be significantly reduced with topical application of epsilon-aminocaproic acid, Int. Orthop. 40 (10) (2016) 2019–2023.
[110] R.A. Harper, M.G. Sucher, M. Giordani, A.J. Nedopil, Topically applied epsilon-aminocaproic acid reduces blood loss and length of hospital stay after total knee arthroplasty, Orthopedics 40 (6) (2017) e1044–e1049.
[111] B.P. Gillette, H. Maradit Kremers, C.M. Duncan, H.M. Smith, R.T. Trousdale, M.W. Pagnano, R.J. Sierra, Economic impact of tranexamic acid in healthy patients undergoing primary total hip and knee athroplasty, J. Arthroplast. 28 (8) (2013) 137–139.
[112] P.S. Garcha, C.V. Mohan, R.M. Sharma, Death after an inadvertent intrathecal injection of tranexamic acid, Anesth. Analg. 104 (1) (2007) 241–242.
[113] H.-M. Yeh, H.-P. Lau, P.-L. Lin, W.-Z. Sun, M.S. Mok, Convulsions and refractory ventricular fibrillation after intrathecal injection of a massive dose of tranexamic acid, Anesthesiology 98 (1) (2003) 270–272.
[114] Z. Lin, Z. Xiaoyi, Tranexamic acid-associated seizures: a meta-analysis, Seizure 36 (2016) 70–73.
[115] I. Roberts, P. Perel, D. Prieto-Merino, H. Shakur, T. Coats, B.J. Hunt, F. Lecky, K. Brohi, K. Willett, Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial, BMJ 345 (2012) e5839.
[116] P.S. Myles, J.A. Smith, A. Forbes, B. Silbert, M. Jayarajah, T. Painter, D.J. Cooper, S. Marasco, J. McNeil, J.S. Bussières, Tranexamic acid in patients undergoing coronary-artery surgery, N. Engl. J. Med. 376 (2) (2017) 136–148.
[117] K. Ker, P. Edwards, P. Perel, H. Shakur, I. Roberts, Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis, BMJ 344 (2012) e3054.
[118] L. Tengborn, M. Blombäck, E. Berntorp, Tranexamic acid – an old drug still going strong and making a revival, Thromb. Res. 135 (2) (2015) 231–242.
[119] B. Hutton, L. Joseph, D. Fergusson, C.D. Mazer, S. Shapiro, A. Tinmouth, Risks of harms using antifibrinolytics in cardiac surgery: systematic review and network meta-analysis of randomised and observational studies, BMJ 345 (2012) e5798.
[120] K. Martin, G. Wiesner, T. Breuer, R. Lange, P. Tassani, The risks of aprotinin and tranexamic acid in cardiac surgery: a one-year follow-up of 1188 consecutive patients, Anesth. Analg. 107 (6) (2008) 1783–1790.
[121] P. Meybohm, E. Herrmann, J. Nierhoff, K. Zacharowski, Aprotinin may increase mortality in low and intermediate risk but not in high risk cardiac surgical patients compared to tranexamic acid and ε-aminocaproic acid–a meta-analysis of randomised and observational trials of over 30.000 patients, PLoS One 8 (3) (2013) e58009.
[122] K. Martin, J. Knorr, T. Breuer, R. Gertler, M. MacGuill, R. Lange, P. Tassani, G. Wiesner, Seizures after open heart surgery: comparison of ε-aminocaproic acid and tranexamic acid, J. Cardiothorac. Vasc. Anesth. 25 (1) (2011) 20–25.
[123] K. Karkouti, D.N. Wijeysundera, T.M. Yau, S.A. McCluskey, G. Tait, W.S. Beattie, The risk-benefit profile of aprotinin versus tranexamic acid in cardiac surgery, Anesth. Analg. 110 (1) (2010) 21–29.
[124] D.L. Ngaage, J.M. Bland, Lessons from aprotinin: is the routine use and inconsistent dosing of tranexamic acid prudent? Meta-analysis of randomised and large matched observational studies, Eur. J. Cardiothorac. Surg. 37 (6) (2010) 1375–1383.
[125] S.M. McHugh, L. Kolarczyk, R.S. Lang, L.M. Wei, M. Jose, K. Subramaniam, A comparison of high-dose and low-dose tranexamic acid antifibrinolytic protocols for primary coronary artery bypass surgery, Indian J. Anaesth. 60 (2) (2016) 94–101.
[126] H. Shakur, D. Elbourne, M. Gülmezoglu, Z. Alfirevic, C. Ronsmans, E. Allen, I. Roberts, The WOMAN Trial (World Maternal Antifibrinolytic Trial): tranexamic acid for the treatment of postpartum haemorrhage: an international randomised, double blind placebo controlled trial, Trials 11 (1) (2010) 40.
[127] P.S. Myles, J. Smith, J. Knight, D.J. Cooper, B. Silbert, J. McNeil, D.S. Esmore, B. Buxton, H. Krum, A. Forbes, Aspirin and tranexamic acid for coronary artery surgery (ATACAS) trial: rationale and design, Am. Heart J. 155 (2) (2008) 224–230.
[128] J. Williams-Johnson, A. McDonald, G.G. Strachan, E. Williams, Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial, West Indian Med. J. 59 (6) (2010) 612–624.
[129] S. Grassin-Delyle, O. Theusinger, R. Albrecht, S. Mueller, D. Spahn, S. Urien, P. Stein, Optimisation of the dosage of tranexamic acid in trauma patients with population pharmacokinetic analysis, Anaesthesia 73 (6) (2018) 719–729.
[130] C. Watts, M. Pagnano, Minimising blood loss and transfusion in contemporary hip and knee arthroplasty, J. Bone Joint Surg. Br. 94 (11_Supple_A) (2012) 8–10.
[131] Derzon, J. H., Clarke, N., Alford, A., Gross, I., Shander, A., & Thurer, R. (In press). Restrictive Transfusion Strategy, Computerized Physician Order Entry, and Clinical Decision Support Practices for Reducing Overuse of Red Blood Cell Transfusion: A Laboratory Medicine Best Practice Systematic Review and Meta-Analysis. American Journal of Clinical Pathology.