



AAHKS[®]

AMERICAN ASSOCIATION OF
HIP AND KNEE SURGEONS
Clinical Practice Guideline

**Tranexamic Acid in Total Joint Arthroplasty
July 2018**

**Tranexamic Acid in Total Joint Arthroplasty: The Endorsed Clinical Practice
Guides of the American Association of Hip and Knee Surgeons, American Society of
Regional Anesthesia and Pain Medicine, American Academy of Orthopaedic
Surgeons, The Hip Society, and The Knee Society**

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Introduction

Hip and knee arthroplasties are routine orthopaedic procedures commonly associated with acute postoperative anemia, and in many cases requires an allogeneic or autologous blood transfusion. Several techniques have been used to limit postoperative blood loss and risk of transfusion. Tranexamic acid (TXA) is an antifibrinolytic agent that has fundamentally changed blood management in total joint arthroplasty (TJA) by making transfusion an infrequent event.

Although TXA is widely used in total hip arthroplasty (THA) and total knee arthroplasty (TKA), it has not yet become the standard of care. A significant body of literature has been compiled on the use of TXA in hip and knee arthroplasty but a comprehensive review and analysis of the existing evidence to provide clinical guidance is lacking. Therefore, The American Association of Hip and Knee Surgeons (AAHKS), The American Academy of Orthopaedic Surgeons (AAOS), The Hip Society (THS), The Knee Society (TKS) and The American Society of Regional Anesthesia and Pain Medicine (ASRA) have worked together to develop evidence-based guidelines on the use of TXA in primary TJA. The purpose of these guidelines is to improve the treatment of orthopaedic surgical patients and reduce practice variation by promoting a multidisciplinary evidence-based approach on the use of TXA.

The combined clinical practice guidelines are meant to address common and important questions related to the efficacy and safety of TXA in primary TJA. Utilizing the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*, the committee members completed a series of direct meta-analyses and network meta-analyses to support the clinical practice guidelines.¹ For each question, we have provided

a recommendation, assessed the strength of the recommendation, and elaborated on the rationale of the recommendation, which should be interpreted in accordance with the *AAOS Clinical Practice Guidelines and Systematic Review Methodology*.¹ The current clinical practice guidelines were based on the available evidence, so future updates may become necessary as additional literature becomes available with future research.

Guideline Question 1:

For patients undergoing primary TJA, what method of administration of TXA, compared to placebo, reduces the risk of transfusion and/or reduces blood loss?

Response/Recommendation:

Administration of intravenous (IV), topical, and oral TXA as well as combinations of individual formulations of TXA are all effective strategies when compared to placebo for reducing calculated blood loss and the need for transfusion during the perioperative episode of a primary TJA.

Strength of Recommendation: Strong

Rationale:

The direct meta-analysis of one moderate quality and 82 high quality studies provided significant evidence for the ability of TXA to reduce the risk of blood loss and need for transfusion during the perioperative episode of primary hip and knee arthroplasties.^{2,3} Subsequent network meta-analysis supported the blood-sparing properties of TXA.^{2,3}

Total Hip Arthroplasty

Intravenous and topical TXA have been shown with limited heterogeneity in direct meta-analysis to reduce blood loss.² Similarly, IV and topical TXA were found to reduce the risk of transfusion compared to placebo by 60% and 71%, respectively.² Network meta-analysis of low dose IV (< 20mg/kg or ≤ 1g), high dose IV (≥ 20mg/kg or > 1g), high dose topical (> 1.5g), oral, and combined IV/topical TXA reduced the risk for blood loss compared to placebo.² Correspondingly, network meta-analysis demonstrated low dose IV, high dose IV, high dose topical, low dose topical, and combined IV/topical TXA to significantly reduce the risk of transfusion.²

Due to a lack of studies directly comparing oral TXA with placebo, no conclusions could be derived in the direct meta-analysis.² Network meta-analysis was performed to provide an indirect comparison of oral TXA, which demonstrated significantly reduced blood loss compared to placebo.² Although oral TXA was shown to be equivalent regarding risk of transfusion to all other formulations of TXA in the network meta-analysis, oral TXA did not reduce the risk of transfusion compared to placebo. The inconsistency is the result of the network relying on indirect comparisons and a limited number of studies. Similar limitations were observed for lower doses ($\leq 1.5\text{g}$) of topical TXA in the network meta-analysis.² In the analysis, low dose topical TXA did not significantly reduce blood loss but did reduce the risk of transfusion compared to placebo.²

Total Knee Arthroplasty

Intravenous and topical TXA consistently demonstrated in direct meta-analysis the ability to reduce blood loss during the perioperative episode of a primary TKA.³ Topical and oral TXA reduced the risk of transfusion by 66% and 61% for each respective formulation of TXA when compared to placebo.³ Intravenous TXA administered as a single dose either before or after incision, reduced the risk of transfusion by either 81% or 55% compared to placebo.³ When multiple doses of IV TXA were administered, the observed reduction in transfusion was 75% compared to placebo.³ Subsequent network meta-analysis demonstrated low dose IV, high dose IV, low dose topical, high dose topical, and oral TXA as well as combinations of IV/topical and IV/oral TXA to reduce blood loss and risk of transfusion during the perioperative episode of a TKA.³

Guideline Question 2:

For patients undergoing primary TJA, what method of administration of TXA, compared to a different method of administration, reduces the risk of transfusion and/or reduces blood loss?

Response/Recommendation:

The analysis of studies did not identify a clearly superior method, or combinations of methods, for the administration of TXA. All methods of administration effectively demonstrate equivalent efficacy at reducing calculated blood loss and the risk of transfusion during the perioperative episode of a primary TJA.

Strength of Recommendation: Strong

Rationale:

The direct meta-analysis of 31 high quality studies provided no evidence to favor any specific method of TXA to reduce the risk of blood loss and need for transfusion during the perioperative episode of primary hip and knee arthroplasties.^{2, 3} Subsequent network meta-analysis included a more expansive comparison between the methods of TXA administration with no evidence to clearly support a superior method of administration.^{4, 5}

Total Hip Arthroplasty

Intravenous and topical TXA have been compared together in multiple randomized clinical trials, which through direct meta-analysis showed no difference in the risk of transfusion.² Network meta-analysis provided the opportunity to perform direct and indirect comparisons between low dose IV (< 20mg/kg or ≤ 1g), high dose IV (≥ 20mg/kg or > 1g), low dose topical (≤ 1.5g), high dose topical (> 1.5g), oral, and combined IV/topical TXA.² In terms of the ability to reduce blood loss, no method of

TXA administration was found to provide a significantly different outcome.² Similar results in the network meta-analysis were observed for risk of transfusion with the exception that a combination of IV and topical TXA was equivalent to oral TXA but superior to low dose IV, high dose IV, low dose topical, and high dose topical TXA.² However, the inconsistent result regarding combined IV/topical TXA likely represents bias from a limited number of studies and not superiority to other methods of TXA administration.

Total Knee Arthroplasty

Direct comparisons were performed between IV TXA and topical, oral, or combined IV/topical TXA, which found no difference in the risk of transfusion.³ Similar to the network meta-analysis of THA, direct and indirect comparisons were performed between low dose IV, high dose IV, low dose topical, high dose topical, and oral TXA as well as combinations of IV/topical and IV/oral TXA that resulted in no difference in their blood sparing properties.³ The significant differences between methods of TXA administration were observed in respect to the risk of transfusion being higher for low dose IV TXA compared to high dose IV or combined IV/topical TXA, which could represent a dose response or the limited number of studies.³

Guideline Question 3:

For patients undergoing primary TJA, does the dose amount of IV or topical TXA affect the risk of transfusion and/or reduction in blood loss?

Response/Recommendation:

Within the context of the TXA doses used in primary TJA, the dose amount of TXA was not found to significantly affect its reduction of calculated blood loss or the need for transfusion during the perioperative episode of a primary TJA.

Strength of Recommendation: Strong

Rationale:

Due to a limited number of studies, direct meta-analysis could not be performed on the six high quality publications that solely investigated the dose effect of either IV or topical TXA.^{2,3} Only two of the published studies observed a difference in favor of higher doses of IV or topical TXA.^{4,5} However, two different studies investigating the same comparative doses of topical TXA (1.5g and 3g) in primary TKA did not observe a difference in calculated blood loss or risk of transfusion with higher doses of topical TXA.^{6,7} Additionally, two publications of IV TXA in THA or TKA did not favor higher doses of IV TXA.^{8,9} When a network meta-analysis was performed regarding the dose effect of IV or topical TXA, it demonstrated limited evidence for a reduction in either transfusion risk or calculated blood loss with higher doses of TXA.^{2,3}

Although a dose response has only been observed in the analysis of TKA for IV TXA with the risk of transfusion, it does not preclude the presence of a dose response for IV or topical TXA. The anticipated dose response is likely not present at the levels of blood loss or the doses of TXA utilized for primary THA or TKA. In the network meta-

analysis of primary THA and TKA, the range of IV TXA doses were 10 mg/kg and three doses of 15 mg/kg while for topical TXA doses the range was between 0.5g and 3g.^{2,3}

Intravenous Tranexamic Acid

Network meta-analysis demonstrates no additional reduction in blood loss following a hip or knee arthroplasty with high dose IV ($\geq 20\text{mg/kg}$ or $> 1\text{g}$) TXA compared to low dose IV ($< 20\text{mg/kg}$ or $\leq 1\text{g}$) TXA.^{4,5} A dose response was observed in the network meta-analysis with a reduced risk of transfusion for higher doses of TXA in primary TKA, but similar results were not found for primary THA.^{2,3} Additional evidence shows no significant difference comparing single-dose and multiple doses of IV TXA, which further supports the notion that higher doses of IV TXA are not necessarily clinically needed to improve the blood-sparing effects in the setting of hip or knee arthroplasties.²⁻³

Topical Tranexamic Acid

Direct meta-analysis and network meta-analysis consistently reported no statistical difference between low dose ($\leq 1.5\text{g}$) and high dose ($> 1.5\text{g}$) topical TXA.²⁻³ A dose response was not observed for either blood loss or risk of transfusion regarding low dose or high dose topical TXA following hip or knee arthroplasty.^{2,3}

Guideline Question 4:

For patients undergoing primary TJA, do multiple doses of IV or oral TXA, compared to a single dose, reduce the risk of transfusion and/or reduce blood loss?

Response/Recommendation:

Administration of multiple doses of IV or oral TXA compared to a single dose of IV or oral TXA does not significantly alter the amount of calculated blood loss and need for transfusion during the perioperative episode of a primary TJA.

Strength of Recommendation: Strong

Rationale:

Direct meta-analysis was performed using six high quality studies to compare between a single dose and multiple doses of IV TXA during primary TKA, which demonstrated no additional benefit for multiple doses of IV TXA.³ Due to a limited number of studies, direct meta-analysis could not be performed for primary THA. However, the results of the available individual studies consistently demonstrate no additional benefit for multiple doses of IV TXA in primary THA.^{8, 10, 11}

An expanded comparison was performed through a network meta-analysis on primary hip and knee arthroplasties. Multiple doses of oral TXA have not been studied in primary THA, thus analysis was only available for IV TXA in primary THA. Network meta-analysis showed no additional benefit in terms of blood loss or risk of transfusion for multiple doses of IV TXA compared with a single dose.⁵ Similarly, the results for primary TKA supported no benefit for multiple doses of IV or oral TXA compared to a single dose of either IV or oral TXA.³

Guideline Question 5:

For patients undergoing primary TJA, does the timing of the administration of TXA in relation to the surgical incision affect the ability of TXA to reduce the risk of transfusion and/or blood loss?

Response/Recommendation:

In primary TJA, administration of IV TXA before the incision potentially reduces blood loss and the need for transfusion compared to its administration after incision.

Strength of Recommendation: Moderate

Rationale:

Direct meta-analysis investigating the affect on timing of TXA administration was available in five high quality studies.^{2,3} Due to a limited number of studies, direct meta-analysis was only performed for primary TKA.^{2,3} The result showed no significant difference between pre-incision and post-incision administration. However, trends towards significance were identified.³ Network meta-analysis for primary TKA demonstrated that a single dose of IV TXA before incision reduced the risk of transfusion compared to administration after incision; however, there was no significant difference regarding blood loss.³ In the setting of a primary THA, network meta-analysis failed to show any significant difference in blood loss or risk of transfusion between pre-incision and post-incision administration of TXA.²

Due to the inconsistency in the results of high quality studies, we are only able to provide “moderate” support to our recommendation. Despite the inconsistencies, we still recommend pre-incision TXA administration because the results demonstrate no potential

benefit for post-incision administration. In contrast, pre-incision administration does demonstrate benefit in some of the analyses.

Guideline Question 6:

For patients undergoing primary TJA without a history of a venous thromboembolic event (VTE), does the treatment with TXA affect the risk of VTE?

Response/Recommendation:

Administration of IV, topical, and oral TXA in patients without a known history of a VTE does not increase the risk of developing a VTE compared to placebo during the perioperative episode of a primary TJA.

Strength of Recommendation: Strong

Rationale:

Direct meta-analysis investigating the impact of TXA administration on the risk of VTE was performed utilizing 77 high and one moderate quality randomized clinical trial. Of those, 92% of the studies utilized history of a thromboembolic event as an exclusion criterium.¹² Individual results for hip and knee arthroplasty demonstrated no significant difference between all methods of TXA administration compared to placebo.¹² Since individual studies included were noted to be comprised of small sample sizes, the hip and knee arthroplasty populations were combined to analyze for differences between IV and topical application of TXA in order to comment on the incidence of rare complications like VTE.¹² This combined analysis further supports the group's conclusion that there is no evidence of increased risk of VTE with TXA administration (combined results had a relative risk closer to "no difference" than the subgroup analysis).¹² Given this overwhelming evidence, we provide "strong" support to our recommendation that TXA administration at doses typically utilized in hip and knee arthroplasty is not associated with an increased risk of VTE for patients without a known history of VTE.

Guideline Question 7:

For patients undergoing primary TJA with a history of a VTE, myocardial infarction (MI), cerebrovascular accident (CVA), transient ischemic attack (TIA), and/or vascular stent placement, does the treatment with TXA affect the risk of VTE?

Response/Recommendation:

There is a paucity of randomized clinical trials on the risk of adverse effects of IV, topical, and oral TXA in patients with known history of a VTE, MI, CVA, TIA, and/or vascular stent placement. The existing high quality literature regarding administration of TXA in patients of generally higher comorbidity burden does not suggest increased risk of adverse thromboembolic events during the perioperative episode of a primary TJA.

Strength of Recommendation: Moderate

Rationale:

Despite an established proposed mechanism of action for TXA as a fibrin clot stabilizer, clinician concerns remain over the use of any antifibrinolytic medication in patients considered at “high-risk” for thromboembolic events (e.g., previous history of VTE, MI with vascular stents, cerebral vascular occlusive disease) which continues to limit the widespread adoption of TXA use in hip and knee arthroplasty.¹³ Since no clinical trials have investigated specific risk factors, the American Society of Anesthesiologists (ASA) physical status classification system was used as a proxy to identify “high-risk” patients among the literature available. In a meta-regression analysis comparing a population of patients with greater than 50% ASA status ≥ 3 to another population with patients of greater than 50% ASA status 1 or 2, the results demonstrated no increase in the risk of VTE for patients undergoing a primary hip or knee arthroplasty.¹² Due to the absence of

experimental evidence, we also reviewed observational studies on the topic of TXA administration in patients with specific risk factors. Large database studies suggest TXA administration in patients with a history of VTE or ASA status of ≥ 3 does not experience an increased risk of VTE.¹⁴⁻¹⁷

In the “high-risk” patient population, we must consider the summation of the benefits and potential risks of administering TXA. Despite limited data on the safety of TXA, we wish to highlight a parallel lack of evidence for harm. Additionally, evidence has demonstrated that postoperative cardiovascular complications are associated with anemia and high blood transfusion rates.¹⁸⁻²⁰ Therefore we wish to highlight the overall positive summation of data on TXA efficacy in the context of limited evidence for added risk with the use of TXA. In sum, the calculation of the number needed to harm for VTE among the total joint population was 983 patients, but the number needed to be treated with IV TXA in THA and TKA to prevent a transfusion was only 4 and 3 patients, respectively.¹² Although the available data limits for stronger advocacy and more widespread use in those at “high-risk”, each patient with known risk factors should be considered individually and we advocate for a multidisciplinary approach when deciding whether to withhold or administer TXA.

Guideline Question 8:

For patients undergoing primary TJA, does the treatment with TXA affect the risk of arterial thromboembolic events (ATE)?

Response/Recommendation:

There is a paucity of randomized clinical trials on the risk of ATE due to the administration of TXA intravenously, topically, and orally. However, the existing evidence does not suggest that TXA increases the risk of developing an ATE compared to placebo during the perioperative episode of a primary TJA.

Strength of Recommendation: Moderate

Rationale:

Arterial thromboembolic events following primary hip or knee arthroplasty are exceptionally infrequent complications and are rarely reported in the randomized clinical trials as most patients who have known risk factors for these events are often excluded from these types of studies. In a direct meta-analysis investigating arterial and venous thromboembolic events, only 9 studies reported the incidence of ATE.¹² Due to the limited number of studies, the authors performed combined hip and knee arthroplasty direct meta-analysis only. The results demonstrated no statistical difference in the risk of ATE between IV or topical TXA and placebo.¹²

Although the direct meta-analysis was limited to high-quality studies, we are only able to provide “moderate” support to our recommendation. The combination of paucity of data, lack of studies specifically designed to investigate the complication of ATE, and exclusion of patients with known risk factors among those studies that were available,

diminished our ability to provide for a stronger recommendation and an individual risk-benefits assessment will be necessary.

Future Research:

As highlighted in the individual network meta-analyses for hip and knee arthroplasties, there exists a relatively small amount of literature on the use of oral TXA and low dose topical TXA. Therefore we believe there still exists an opportunity to meaningfully contribute to the current literature on TXA by investigating those formulations of TXA. However, if oral TXA is utilized, we suggest the use of 2 g of oral TXA approximately 2-hours before the desired affect of the medication to ensure appropriate pharmacokinetics are obtained.

The most substantial shortcoming of the current literature on TXA involves the lack of high-level evidence to support the use of TXA in patients with a history of a VTE, MI, CVA, TIA, and/or vascular stent placement. Although well-designed retrospective comparison studies have been published, we lack the ability to provide stronger support on the use of TXA in these patients considered to be high-risk. Therefore we would encourage future research to determine the safety of TXA in the high-risk patient.

Additionally, TJA is being performed more frequently in patients with a history of “chronic” cancers such as prostate cancer. Similar to other patient factors, we lack the ability to comment on the safety of TXA in this particular subset of patients, and we encourage further research on these patients.

Peer Review Process:

Following the committee's formulation of the Clinical Practice Guideline draft, it underwent a peer review by the board of directors from AAHKS, ASRA, and the Hip and Knee Societies. The AAOS Evidence-Based Quality and Value Committee reviewed the Clinical Practice Guideline draft for endorsement. Additionally, the three publications of the direct and network meta-analyses on the efficacy and safety of TXA in primary hip and knee arthroplasties that supported the formulation of the Clinical Practice Guideline have undergone peer review for publication.

Disclosure Requirement:

All authors or contributors to the Clinical Practice Guideline have provided a disclosure statement in accordance with the publicly available AAOS Orthopaedic Disclosure Program. All authors and contributors attest none of the disclosures present are relevant to the Clinical Practice Guidelines.

FDA Clearance Statement:

Tranexamic acid is a drug described in this Clinical Practice Guideline that has only been approved by the Food and Drug Administration (FDA) for dental bleeding prophylaxis in hemophilic patients and menorrhagia. According to the FDA, it is the prescribing physician's responsibility to ascertain the FDA clearance status for all medications prior to use in a clinical setting.

Acknowledgements:

We would like to thank AAHKS for providing the funding and administrative support.

We would like to thank Jayson Murray, Peter Shores, and Kyle Mullen from the AAOS Department of Research, Quality, and Scientific Affairs for their assistance with the analysis and guidance. Lastly, we thank the leadership of the AAHKS, AAOS, ASRA, and The Hip and The Knee Societies for help with organizational support.

References:

1. Surgeons AAoO. AAOS Clinical Practice Guideline and Systematic Review Methodology. In.:
2. Fillingham YA RD, Jevsevar DS, Yates AJ, Shores P, Mullen K, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ. The Efficacy of Tranexamic Acid in Total Hip Arthroplasty: A Network Meta-Analysis. *Journal of Arthroplasty*, 2018
3. Fillingham YA RD, Jevsevar DS, Yates AJ, Shores P, Mullen K, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ. The Efficacy of Tranexamic Acid in Total Knee Arthroplasty: A Network Meta-Analysis. *Journal of Arthroplasty*, 2018
4. Maniar R, Kumar G, Singhi T, Nayak R, Maniar P. Most effective regimen of tranexamic acid in knee arthroplasty: a prospective randomized controlled study in 240 patients. In: *Clinical orthopaedics and related research*. 2605. 2012
5. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, Syed KA, Muhammad Ovais Hasan S, De Silva Y, Chung F. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *Journal of Bone & Joint Surgery - American Volume* 92(15): 2503, 2010
6. Carvalho LH, Jr., Frois Temponi E, Machado Soares LF, Goncalves MB, Paiva Costa L, Tavares de Souza ML. Bleeding reduction after topical application of tranexamic acid together with Betadine solution in total knee arthroplasty. A randomised controlled study. *Orthopaedics & traumatology, surgery & research* 101(1): 83, 2015
7. Sarzaeem MM, Razi M, Kazemian G, Moghaddam ME, Rasi AM, Karimi M. Comparing efficacy of three methods of tranexamic acid administration in reducing hemoglobin drop following total knee arthroplasty. *Journal of Arthroplasty* 29(8): 1521, 2014
8. Barrachina B, Lopez-Picado A, Remon M, Fondarella A, Iriarte I, Bastida R, Rodríguez-Gascón A, Achaerandio M, Iturricastillo M, Aizpuru F, Valero C, Tobalina R, Hernanz R. Tranexamic Acid Compared with Placebo for Reducing Total Blood Loss in Hip Replacement Surgery: A Randomized Clinical Trial. In: *Anesthesia and analgesia*. 986. 2016
9. Lin P, Hsu C, Huang C, Chen W, Wang J. The blood-saving effect of tranexamic acid in minimally invasive total knee replacement: is an additional pre-operative injection effective? In: *The Journal of bone and joint surgery British volume*. 932. 2012
10. Hourlier H, Fennema P. Single tranexamic acid dose to reduce perioperative

morbidity in primary total hip replacement: a randomised clinical trial. In: *Hip international : the journal of clinical and experimental research on hip pathology and therapy*. 63. 2014

11. Imai N, Dohmae Y, Suda K, Miyasaka D, Ito T, Endo N. Tranexamic Acid for Reduction of Blood Loss During Total Hip Arthroplasty. In: *Journal of arthroplasty*. 1838. 2012

12. Fillingham YA RD, Jevsevar DS, Yates AJ, Shores P, Mullen K, Bini SA, Clarke HD, Schemitsch E, Johnson RL, Memtsoudis SG, Sayeed SA, Sah AP, Della Valle CJ. The Safety of Tranexamic Acid in Total Joint Arthroplasty: A Direct Meta-Analysis. *Journal of Arthroplasty*, 2018

13. Dai L, Bevan D, Rangarajan S, Sorensen B, Mitchell M. Stabilization of fibrin clots by activated prothrombin complex concentrate and tranexamic acid in FVIII inhibitor plasma. *Haemophilia* 17(5): e944, 2011

14. Duncan CM, Gillette BP, Jacob AK, Sierra RJ, Sanchez-Sotelo J, Smith HM. Venous thromboembolism and mortality associated with tranexamic acid use during total hip and knee arthroplasty. *The Journal of arthroplasty* 30(2): 272, 2015

15. Poeran J, Rasul R, Suzuki S, Danninger T, Mazumdar M, Opperer M, Boettner F, Memtsoudis SG. Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety. *BMJ* 349: g4829, 2014

16. Sabbag OD, Abdel MP, Amundson AW, Larson DR, Pagnano MW. Tranexamic Acid Was Safe in Arthroplasty Patients With a History of Venous Thromboembolism: A Matched Outcome Study. *The Journal of arthroplasty* 32(9S): S246, 2017

17. Whiting DR, Gillette BP, Duncan C, Smith H, Pagnano MW, Sierra RJ. Preliminary results suggest tranexamic acid is safe and effective in arthroplasty patients with severe comorbidities. *Clinical orthopaedics and related research* 472(1): 66, 2014

18. Hopewell S, Omar O, Hyde C, Yu LM, Doree C, Murphy MF. A systematic review of the effect of red blood cell transfusion on mortality: evidence from large-scale observational studies published between 2006 and 2010. *BMJ Open* 3(5), 2013

19. Koch CG, Khandwala F, Li L, Estafanous FG, Loop FD, Blackstone EH. Persistent effect of red cell transfusion on health-related quality of life after cardiac surgery. *Ann Thorac Surg* 82(1): 13, 2006

20. Mohnle P, Snyder-Ramos SA, Miao Y, Kulier A, Bottiger BW, Levin J, Mangano DT, Multicenter Study of Perioperative Ischemia Research G. Postoperative red blood cell transfusion and morbid outcome in uncomplicated cardiac surgery patients. *Intensive Care Med* 37(1): 97, 2011