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ERAS for Cardiac Surgery: Development of a Clinical Practice Guideline for Antifibrinolytic Administration in Cardiac Surgery

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ERAS for Cardiac Surgery: Development of a Clinical Practice Guideline for Antifibrinolytic Administration in Cardiac Surgery

by

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Executive Summary

Enhanced Recovery After Surgery (ERAS) guidelines are multimodal perioperative care pathways based on evidence-based practice to promote faster recovery after surgical procedures. For cardiac surgery ERAS, one intervention that is strongly recommended based on high levels of evidence is the use of antifibrinolytic medications, such as Tranexamic acid (TXA) and epsilon aminocaproic acid (EACA) which are synthetic antifibrinolytics and analogs of lysine, both known for exerting procoagulant effects by competitively inhibiting activation of plasminogen to plasmin. Antifibrinolytic medications have been shown to decrease blood loss as well as the need for blood transfusions and reoperation.

There is strong evidence from the literature for best practices and well-established international standard ERAS guidelines for cardiac surgery. Reports from key stakeholders in the pharmacy and anesthesia departments at the project site revealed that the routine use of antifibrinolytic administration is varied within the cardiac surgical setting. The project team conducted a chart audit that revealed over a three-month period, only 61% (n= 22/36) of cardiac surgery patients received an antifibrinolytic. Upon further investigation of the patients that did not receive an antifibrinolytic, 50% (7/14) of those patients required on pump cardiac surgery and should have received an antifibrinolytic. A review of the anesthesia records also revealed variations in dosing among the 22 patients that did receive an antifibrinolytic. 36% (8/22) of these patients received 10g of EACA, 59% (13/22) received 20g of EACA, and 4% (1/22) received 10mg of TXA. As a result of the chart audit findings, a clinical practice guideline was developed for TXA and EACA using the Clinical Guidance Recommendation template at the institution. The guideline was shared with the Surgery/Anesthesia CPIT Committee for possible future implementation.

Introduction

Enhanced Recovery After Surgery (ERAS) protocols are "evidence base practice, multimodal perioperative care pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery" (Melnyk et al., 2011, p. 342). The literature demonstrates the implementation of ERAS protocols leads to decreased lengths of stay, postoperative complications, costs, and increased patient satisfaction (Salenger et al., 2020). In May 2019, the ERAS Society published 22 recommendations highlighting strategies for preoperative, intraoperative, and postoperative care for cardiac surgery cases (Engelman et al., 2019). Due to the extensiveness of the ERAS recommendations, the scope of the Doctor of Nursing (DNP) Scholarly Project, and needs of the project site, it was determined that one intraoperative recommendation would be feasible. Therefore, this scholarly project focused on the administration of antifibrinolytics for patients undergoing on-pump cardiac surgery. The administration of antifibrinolytics, tranexamic acid (TXA) or epsilon aminocaproic acid (EACA), during on-pump cardiac surgical procedures is a class IA (strong) recommendation with a high level of evidence (Engelman et al., 2019). The 2011 American College of Cardiology Foundation/American Heart Association (AAF/AHA) Guideline for Coronary Artery Bypass Graft Surgery Executive Summary states "lysine analogues are useful intraoperatively and postoperatively in patients undergoing on-pump CABG to reduce perioperative blood loss and transfusion requirements" (Hollis et al., 2011, p. 2624). The 2015 Practice Guideline for Perioperative Blood Management by the American Society of Anesthesiologists (ASA) recommends the use of antifibrinolytics for patients undergoing cardiopulmonary bypass to reduce allogenic blood transfusion (American Society of Anesthesiologists Task Force on

Perioperative Blood Management, 2015). The 2017 European Association for Cardiothoracic Surgery (EACTS) guidelines on perioperative medication in adult cardiac surgery and patient blood management recommend the routine use of antifibrinolytic therapy intraoperatively and postoperatively to reduce bleeding, transfusions, and reoperations (Sousa-Uva et al., 2018). While bleeding and transfusion risks are still factors for adverse outcomes of off pump cardiac surgery, the current guidelines by the Society of Thoracic Surgery for blood conservation do not include recommendations for off pump cardiac surgery (Gerstein et al., 2017).

Clinical Problem

Despite strong evidence from the literature for best practices and well-established international standard ERAS guidelines, recent reports from key stakeholders from pharmacy and anesthesia departments at the project site, a medium sized level one trauma center, revealed that the use of antifibrinolytic administration was not currently being practiced within the cardiac surgical setting. Additionally, the anesthesia and pharmacy department stakeholders reported that a lack of an evidence-based practice guideline may be contributing to the lack of antifibrinolytics administration in some patients. However, the extent of any clinical data demonstrating the impacts of this potential clinical problem were unknown at the time. So, the project team conducted a chart audit to demonstrate a clinical problem and support the need for the proposed aims of this project. The independent chart audit that occurred between January 1, 2021 and March 31, 2021 demonstrated only 61% (n= 22/36) of cardiac surgery patients at the facility received an antifibrinolytic. Upon further investigation of the patients that did not receive an antifibrinolytic, 50% (7/14) of these patients required on pump cardiac surgery and should have received an antifibrinolytic. A review of the anesthesia records revealed variations in dosing among the 22 patients that did receive an antifibrinolytic. 36% (8/22) of these patients

received 10g of EACA, 59% (13/22) received 20g of EACA, and 4% (1/22) received 10mg of TXA.

Optimizing standardization is important to avoid clinical practice errors and complications to patient health through the perioperative period. Cardiac surgery patients who did not receive antifibrinolytics intra-operatively may be at an increased risk for bleeding, administration of blood transfusions, and reoperation for major hemorrhage or cardiac tamponade. A large, randomized control trial showed decrease in blood transfusion, major hemorrhage, cardiac tamponade, and reoperation in patients who received TXA (Engelman et al., 2019). There is high-level, class-IA evidence from the scientific and clinical literature that suggests the use of antifibrinolytics as best practice (Engelman et al., 2019). Consequently, the lack of a standardized guideline and variability of clinical practice validated by recent chart audits may indicate an increased risk to cardiac surgical patients. Therefore, an opportunity existed for this project team to provide the hospital leadership with EBP recommendations and a standardized ERAS-based guideline. This would help streamline process and improve the quality and consistency of ERAS guided practices involving antifibrinolytic medications in cardiac surgical patients.

Significance to Nurse Anesthesia

Anesthesia care of cardiac surgery patients throughout the perioperative period requires an up-to-date, evidence-based, dedicated team approach. The most life-threatening event associated with cardiac surgery is often bleeding complications (Leff et al., 2019). Cardiac surgery patients frequently require blood transfusions and use approximately 20% of the blood supply in the United States (Leff et al., 2019). A cardiac surgery patient that is adversely bleeding requires increased staffing resources in the intensive care unit as well as the operating

room. Antifibrinolytic medication administration, with tranexamic acid (TXA) and/or epsilon aminocaproic acid (EACA), decreased the amount of blood products transfused to the patient and decreased the incidence of reoperation for major hemorrhage and cardiac tamponade (Engelman et al., 2019). Lastly, recommendations on the administration of antifibrinolytics for on-pump cardiac surgery may assist, with ERAS guideline implementation, the project hospital site in optimizing intraoperative team workflow.

EBP Guideline Development

Informal multidisciplinary interviews with an on-site clinical pharmacist and anesthesiologists revealed that ERAS guidelines for cardiac surgery are not common practice. Due to the vast amount of ERAS recommendations for cardiac surgery patients, a comprehensive Cardiac Surgery ERAS guideline was not feasible to complete due to the project's academic/curricular limitations. Therefore, the project focused on one aspect of Engelman et al. (2019) based on project site needs. There was a lack of a standardized guidelines for administration of antifibrinolytic medication for elective, on pump cardiac surgery. A clinical practice gap existed between the current practice at the facility and the EBP recommendations of the ERAS Cardiac Surgery Society and the Society of Thoracic Surgery Blood Conservation. The project team worked with key stakeholders in the pharmacy and anesthesia departments at the project site to develop an EBP protocol that represents best practice guidance and meets the needs of the institution.

Project Scaffolding

The project site lacked a standardized guideline for antifibrinolytic medication administration for on pump cardiac surgery. After completing a chart review, a clinical practice gap was identified between current practice and evidence-based practice recommendations by

the ERAS Cardiac Surgery Society regarding antifibrinolytic administration for patients undergoing on pump cardiac surgery. Of the patients that did not receive an antifibrinolytic, 50% of those patients went on cardiopulmonary bypass and should have received an antifibrinolytic medication intraoperatively. Reports from stakeholders in the pharmacy and anesthesia departments at the facility indicated that the lack of an evidence-based practice guideline may have been a contributing factor to the lack of antifibrinolytics administration in some cardiac surgical patients. Consequently, the lack of standardized guidelines and variability of clinical practice validated by the chart audit indicated a possible increased risk to cardiac surgical patients for adverse outcomes.

Purpose

The purpose of this project was to develop, for hospital leadership, a standardized evidence-based practice guideline for administration of TXA and EACA using the project site's Clinical Guidance Council Recommendation Template. The following objectives and methods were framed using the Knowledge to Action Framework and have been established to achieve the project's overall aim: 1) review and synthesize the evidence from the literature around the use of ERAS guided antifibrinolytic medication practices in cardiac surgical patients, 2) develop a standardized, evidence-based, clinical practice guideline for administration of antifibrinolytics for on pump cardiac surgeries, and 3) submit the guidelines to the Clinical Process Improvement Team (CPIT) and present our recommendations to key stakeholders utilizing a SWOT format.

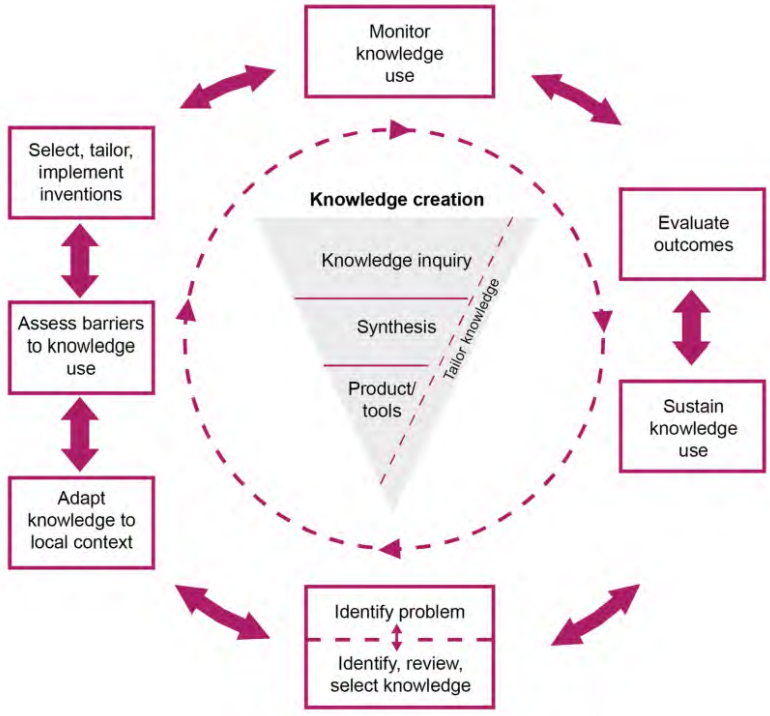
Evidence-Based Practice Framework

Knowledge to Action Framework

The conceptual framework that was used to guide this project was the Knowledge to Action (KTA) framework developed by Graham et al. (2006) and shown in Figure 1. The KTA

framework has been used to facilitate the development and application of research evidence into clinical practice. Williams et al. (2019) used this framework to synthesize ERAS data from other specialties, identify gaps within the cardiac surgery specialty, and apply the knowledge gained to cardiac surgery. The KTA process consists of the knowledge creation cycle and the action cycle.

Figure 1. ***Illustration of Graham et al. (2006) Knowledge to Action Framework***



Knowledge Creation Cycle. Regarding this project, the knowledge creation aspect (Figure 1) of KTA is demonstrated by the evidence synthesis table (see Appendix A), and this is described as knowledge inquiry, knowledge synthesis, and knowledge tools/products. Field et al. (2014) describes that KTA is "…used in practice with varying degrees of completeness" (Field et al. 2019; p. 6).

Action Cycle. This phase was conducted by reviewing and synthesizing the evidence from the literature around the use of ERAS guided antifibrinolytic medication practices in

cardiac surgical patients, developing a standardized evidence-based practice guideline for administration of antifibrinolytics for on pump cardiac surgeries, and submitting the guideline/recommendation to the Clinical Process Improvement Team (CPIT) and key stakeholders. Identify, review, and select knowledge was completed through an extensive literature search around the use of ERAS guided antifibrinolytic medication practices in cardiac surgical patients and also the comparative state of current practices which consisted of non-standardized intraoperative antifibrinolytic practices for cardiac surgical patients. Adapt knowledge to local context involved discussing literature findings and using provided data from retrospective chart audits with personnel from pharmacy, anesthesia, and the Clinical Practice Improvement Team (CPIT). Assessing barriers to knowledge use was completed through the process of developing the clinical practice guideline and meeting with pharmacy and anesthesia stakeholders. The project site's Clinical Guidance Council Recommendation template was utilized (Appendix B). Moreover, a presentation was created and presented along with the guideline draft to key stakeholders, pharmacy, anesthesia, and the Clinical Process Improvement Team (CPIT) utilizing a SWOT format.

The aspects of the KTA cycle (per Figure 1) were to identify a problem, identify, review, select knowledge; adapt knowledge to local context; and assess barriers to knowledge use. For the scope of this project, the team did not intend to execute the following KTA framework steps: the implementation of interventions, monitoring knowledge use, evaluation of outcomes, and sustainment of knowledge use.

Strengths, Weaknesses, Opportunities, and Threats Analysis

A SWOT analysis (See Appendix C) briefing format was used to present the best evidence from literature and make recommendations for future use of ERAS guided

antifibrinolytic therapy in cardiac surgical patients. A SWOT analysis is a process of identifying a company's Strengths, Weaknesses, Opportunities, and Threats (Moran et al., 2018). The strength component focused on current processes and patient outcomes which measures the quality of care being delivered. The weakness component looked at current processes and patient outcomes that might have indicated certain downfalls of the process. The opportunity component further explored the desired state of practice and patient outcomes related to ERAS guidelines and evidence from the literature. The threat component addressed barriers or individual reluctancy to future ERAS guideline implementation. The SWOT analysis helped stakeholders and clinical practice improvement leaders develop a full awareness of all the factors involved in ERAS guided practices using antifibrinolytics in cardiac surgical patients at the facility.

Ethics and Considerations/ Protection of Human Subjects

Following the project proposal's review and approval by the project site's Nursing Evidence-Based Practice Committee (NEBPRC), the approval letter (see Appendix D), proposal, and application were submitted to the Otterbein University Institutional Review Board (IRB). Once approval was obtained from the Otterbein University IRB, the official IRB determination document (see Appendix E) was submitted to the OH NRC for record-keeping. As previously mentioned, no names or unique patient/staff identifiers were requested, collected or stored. No personal health information (PHI) was collected. All collected information was fully de-identified prior to storage into a password-protected, secure spreadsheet. Only de-identified aggregate data was shared outside of the project site with Otterbein University Nursing Department faculty and students as part of dissemination of the DNP Final Scholarly Project Report presentation.

Literature Review and Synthesis

The PICO format provided a framework for examining and answering a specific question related to the previously described problem (Melnyk & Fineout-Overholt, 2005). The PICO format was used to develop the clinical question as well as provide strategic keys search terms to obtain the best evidence related to the problem. The four components include "population of interest [P], intervention of interest [I], comparison of interest [C], and outcome of interest [O]" (Melnyk & Fineout-Overholt, 2005, p. 29). The population and problem of interest for this project was centered on adult patients undergoing elective, on-pump cardiac surgery, and did not receive antifibrinolytics intra-operatively. The intervention of interest was focused on the use of standard ERAS guidelines in the intra-operative administration of antifibrinolytics for cardiac surgery patients. The comparative state focused on the current practice which consisted of non-standardized intraoperative antifibrinolytic practices for cardiac surgical patients. The outcomes of interest included the following: patient blood loss, blood transfusion requirement, re-operation following cardiac surgery, seizure activity, fibrinolytic lab, and costs associated with length of hospital stay. The PICO question was as follows: "(P) In patients who undergo elective, on-pump cardiac surgery, and do not receive antifibrinolytics intra-operatively, how does the use of (I) standard ERAS guidelines in the intra-operative administration of antifibrinolytics compared (C) to the current, non-standardized antifibrinolytic practices affect (O) patient blood loss, blood transfusion requirement, and re-operation following cardiac surgery?"

A search for relevant literature pertaining to intraoperative administration of antifibrinolytic medications during cardiac surgery was conducted. Database resources utilized through OneSearch included CINAHL, Cochrane Library, MEDLINE, and PubMed. Keywords

used included cardiac surgery, ERAS, enhanced recovery after surgery, antifibrinolytics, tranexamic acid, TXA, epsilon aminocaproic acid, EACA, bleeding, and blood transfusion. Articles were screened for relevance and 15 articles were selected based on inclusion of antifibrinolytics therapy, cardiac surgery patient population, on pump cardiac procedures, and strength of the studies. The 15 articles selected included seven systematic reviews and meta-analyses (Boer et al., 2020; Engelman et al., 2019; Guo et al., 2020; Habbab et al., 2020; Khair et al., 2019;Levy et al., 2020; Zufferey et al., 2021), five randomized control trails (Fergusson et al., 2008; Leff et al., 2019; Myles et al., 2017; Raghunathan et al., 2011; Zhou et al., 2021), two cohort studies (Blaine et al., 2016; Williams et al., 2019), and one observational study (Strauss et al., 2021). Further details regarding each article can be found in the Review of Evidence and Synthesis Table, which also includes an appraisal for each of the article's strengths, limitations, risks, and feasibility (see Appendix A).

Related Research

ERAS Beginnings and the Cardiac Surgery Field. Enhanced Recovery After Surgery (ERAS) programs challenge the status quo of the perioperative pathway and have gained significant support since the first ERAS Society supported US symposia on ERAS was held by Duke University in 2013 (ERAS Society, 2020). The ERAS Society started as an ERAS Study Group in 2001, comprised of leading surgeons, and officially registered as a non-profit medical society in 2010 based out of Stockholm, Sweden. The mission of ERAS programs is to modify the perioperative care process to improve patients' recovery through research, education, audit, and implementing evidence-based practice (ERAS Society, 2020).

ERAS guidelines have been published throughout the 2010s for colorectal surgery, bariatric surgery, breast reconstruction, head and neck cancer surgery, and gynecological

surgery. The cardiac surgery specialty was updated by Engelman et al. (2019), with the first expert-consensus review of evidence-based cardiac surgery ERAS practices. 197 studies were ultimately included in the meta-analysis and a formal ERAS Cardiac Society was created and aligned with the ERAS Society to develop the new guidelines. The ERAS Cardiac Society was comprised of 16 cardiac surgeons, anesthesiologists, and intensivists who were knowledgeable and experienced with ERAS. Twenty-two potential interventions were agreed upon and divided by phase of care. This scholarly project was ultimately motivated by Engelman and colleagues' (2019) guidelines as they were recognized to be critical to patients receiving elective cardiac surgery.

ERAS Recommendations for Antifibrinolytic Therapy. Engelman et al. (2019) recommended that TXA or EACA should be administered during on-pump cardiac surgical procedures, due to literature showing reduced total blood products transfused and reoperation for major hemorrhage or cardiac tamponade. Seizures have been dose-dependently implicated with administration of TXA, and the maximum total dose from Engelman et al. (2019) is 100 mg/kg. Additionally, Engelman and colleagues (2019) recommended the comprehensive, multi-societal, clinical practice guidelines published by Boer et al. (2018) regarding patient blood management. Boer et al. (2018) developed the 2017 guidelines by forming a task force composed of the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Cardiothoracic Anaesthesiology (EACTA). The 2017 EACTS/EACTA guidelines were recommended to be utilized by Engelman et al. (2019) due to reduced bleeding and transfusions of blood products, and decreased incidence of reoperation for bleeding.

Bleeding. A meta-analysis of randomized controlled trials by Guo et al. (2019), evaluating 49 studies and 10,591 adult patients, demonstrated a significant reduction in post-

operative blood loss in patients receiving intravenous tranexamic acid. Post-operative blood loss was evaluated in 44/49 studies and the average reduction in blood loss was approximately 247 mL per patient compared to control. The blood loss findings by Guo et al. (2019) are further supported by Myles et al. (2017). Myles and colleagues conducted a randomized controlled trial of adult patients undergoing coronary artery surgery at risk for perioperative complications. 4,631 patients had available outcome data, and patients either received intravenous TXA or placebo. Dosing ranged from 50 mg/kg to 100 mg/kg throughout the trial. The TXA group had a significantly reduced number of patients that had blood loss during surgery, though specific averages were not provided. A meta-analysis by Habbab et al. (2020), including seven randomized controlled trials and 692 total patients, evaluated the intrapericardial approach of administering TXA. The results of Habbab and associates further support the literature that TXA administration, albeit a different route in this meta-analysis, decreases blood loss for adult patients undergoing cardiac surgery. Overall, patients receiving topical TXA experienced a significant reduction in 24-hour blood loss on average of about 350 ml. Zufferey et al. (2021) conducted a model-based meta-analysis that included 64 randomized controlled trials total, and 56 reported post-operative blood loss. Zufferey and colleagues reported that TXA usage was associated with a maximum effect of reducing blood loss by forty percent.

The Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) study was a multi-center, randomized control trial conducted from 2002 until 2007 comparing aprotinin to the lysine analogs, TXA and EACA (Fergusson et al., 2008). A total of 2,331 high risk cardiac surgery patients were randomly assigned to one of the three groups to receive a specific antifibrinolytic: 781 received aprotinin, 770 received tranexamic acid, and 780 received aminocaproic acid (Fergusson et al., 2008). The original hypothesis was that aprotinin would be

superior to the lysine analogs in reducing massive postoperative bleeding. Fergusson et al. (2008) defined massive postoperative bleeding for the BART trial as output greater than 1.5L over eight hours. Of the 780 patients in the EACA group, 94 patients (12.1%) met the criteria for massive bleeding. In comparison, patients in the TXA group had similar results with 93 of 770 patients (12.1%) that met the massive bleeding criteria (Fergusson et al., 2008). While the rate of massive bleeding was similar in both groups, the EACA group had less patients die secondary to hemorrhage. Four patients died in the EACA group compared to eight patients in the TXA group (Fergusson et al., 2008). A small, single-center, double-blinded and randomized trial comparing TXA and EACA, included 114 patients undergoing on pump cardiac surgery to evaluate bleeding and transfusion postoperatively (Leff et al., 2019). Chest tube output was measured at four, six, twelve, and twenty-four hours postoperatively and again there was no statistically significant difference in the median output of the two groups.

Blood Transfusion Requirements. Blood transfusion requirements are reduced for adult patients undergoing cardiac surgery who receive TXA. Guo et al. (2019) examined transfusion rate related to on and off-pump cardiac surgery, types of surgery, type of administration, and amount of dose. Transfusion need was significantly reduced for off-pump cardiac surgery, on-pump cardiac surgery, patients undergoing CABG, and patients undergoing other surgeries. In patients receiving TXA intravenously, transfusion requirements were significantly reduced. Patients receiving TXA bolus or TXA bolus plus continuous infusion had a significant reduction in transfusion needs. Low-dose (≤10 mg/kg + 1 mg/kg/h), high-dose TXA bolus plus continuous infusion, low-dose bolus alone, and high-dose bolus alone significantly reduced transfusion needs. Myles et al. (2017) also showed decreased amount of the number of blood transfusions and a decreased number of patients who received a blood transfusion for patients receiving TXA

compared to control. Patients who received TXA were administered 46 percent fewer blood products, which could equate approximately to saving 57 units of blood products per every 100 patients treated. Habbab et al. (2020) were able to evaluate topical TXA administration and transfusion requirements in 6/7 trials of the meta-analysis. One study yielded a significant reduction in the incidence of packed RBC transfusion, while the other five studies did not show a significant reduction but showed a trend in favor of topical TXA. Though one study differs, the findings of five studies not showing a statistically significant difference in decreased blood transfusion rate by Habbab et al. (2020) parallel the findings of Guo et al. (2019) regarding topical TXA as this intervention did not reduce transfusion requirements in Guo's (2019) meta-analysis.

When comparing TXA to EACA in regard to transfusion outcomes and massive transfusion postoperatively, the BART study conducted by Fergusson et al. (2008) found no statistical differences. Over 60% of patients in both the TXA group and EACA group required at least one unit of packed red blood cells: 506 of 770 (65.7%) in the TXA group and 514 of 780 in the EACA group (65.9%). Fergusson et al. (2008) defined massive transfusion as the administration of greater than ten units of packed red blood cells. The TXA group had 17 of 770 patients (2.2%) compared to the EACA group with 22 of 780 patients (2.8%) require massive transfusion (Fergusson et al., 2008). In 2013, there was a shortage of EACA and institutions that typically used EACA had to switch to TXA (Blaine et al., 2016). The medication shortage provided an opportunity to do additional comparative studies with retrospective data. The single center study by Blaine et al. (2016) included 128 patients: 60 received TXA prior to the medication shortage and 68 received EACA after the medication shortage. Results from Blaine

et al. (2016) study was like Fergusson et al. (2008) and no statistical differences in bleeding or transfusion requirements were found through multivariate analysis.

Unlike the other studies, Leff et al. (2019) found that the TXA group was 2.4 times more likely to require a blood transfusion within the first 24 hours. The percentage of patients in the TXA group that required transfusion was 44.8%, while the EACA group was 25%. The types of blood products each group received were also evaluated. This evaluation revealed that 35.4% of the TXA group required transfusion of packed red blood cells and 17.2% required fresh frozen plasma. Comparatively, only 17.9% of the EACA group required packed red blood cells and 5.4% required fresh frozen plasma. Several limitations exist in this study because it was a single-center study with a small sample size. Their analysis also included trust scores that assessed patients' risks for requiring transfusions. The trust scores revealed a higher risk in the TXA group which could explain why more transfusions were necessary. Nonetheless, the study still supported the use of either EACA or TXA for on-pump cardiac surgery patients to reduce bleeding and blood transfusions (Leff et al., 2019).

Cost. Considering the similarities in clinical efficacy and safety of both EACA and TXA, the costs of each medication and local factors of the institution that influence costs should be considered when determining best practices for an institution. During the creation of practice protocols, the effects of medication shortages must also be considered. During a medication shortage, Blaine et al. (2016) found no difference between TXA and EACA in regard to bleeding and transfusion, however, the EACA group was more likely to receive rescue hemostatic medications such as recombinant factor VIIa and desmopressin. A single unit of packed red blood cells can cost $467 to $1,055 in the United States and the rescue medications can cost

several thousand (Blaine et al., 2016). In these scenarios, TXA could be more cost-efficient if rescue medications can be avoided (Blaine et al., 2016).

In 2011, Raghunathan et al. (2011) revaluated data from the BART trial to compare the "clinical value" of EACA and TXA. While clinical outcomes such as postoperative bleeding and mortality are of utmost importance, cost considerations can be vital when clinical outcomes are similar. Raghunathan et al. (2011) define clinical value as the "function of quality divided by costs and then multiplied by volume," with volume referring to number of uses (p. 18). Dosing for the BART study included a loading dose followed by a continuous infusion for both lysine analogs. The EACA regimen included a 10g loading dose, followed by 2g per hour infusion (Fergusson et al., 2008). The TXA regimen included a 30mg/kg loading dose, followed by 16/mg/kg/h continuous infusion. An additional 2mg/kg of TXA was also added to the bypass circuit (Fergusson et al., 2008). At the author's institution, TXA was 225 times more expensive than EACA for an 80kg patient undergoing a five-hour surgery (Raghunathan et al., 2011). TXA cost was $540 while the cost for EACA was only $2.40. After the clinical value equation was applied to this data, the author's institution changed the policy to administer EACA for all cases. The change in antifibrinolytics led to $100,000/year in cost savings, while anecdotally, bleeding rates and blood transfusions did not change (Raghunathan et al., 2011). Leff et al. (2019) also described the cost differentials between the two antifibrinolytic medications but mentioned different dosing costs. According to Leff et al. (2019), TXA is only 30 times more expensive at $30-100 per dose compared to EACA at $11-30 per dose. Leff et al. (2019) is a more current study and could represent more accurate costs for 2020. The cost of the medication, blood products, rescue medications, and reoperation are all essential factors to consider when evaluating costs.

Reoperation After Cardiac Surgery. Reoperation data for Guo and colleagues (2019) was available in 32 of 49 trials, totaling 8,937 patients. TXA administration significantly reduced risk of reoperation by 38 percent. Reoperation rates were 2.4 percent and 3.9 percent for TXA and control groups, respectively. Likewise, Myles et al. (2017) observed a significant reduction in reoperation for major hemorrhage or cardiac tamponade with intravenous TXA. Reoperation rates were 1.4 percent and 2.8 percent for TXA and placebo groups, respectively. The number needed to treat is the number of patients that need to receive a drug or intervention to see one-person benefit. In Myles et al. (2017), 71 patients were the number needed to treat to prevent one reoperation within 30 days. There was not enough data from Habbab et al. (2020) to determine if topical TXA administration reduced the need for reoperation after cardiac surgery.

When comparing reoperation data between TXA and EACA, outcomes were similar across several studies. The reoperation rates when TXA was compared to EACA in the BART study, were 8.1 percent for TXA and 8.2 percent for EACA (Fergusson et al., 2008). No differences in reoperation were also found by Leff et al. (2019). Reoperation within the first 24 hours after surgery occurred in 4 of 58 patients in the TXA group while reoperation occurred in 3 of 56 patients in the EACA group (Leff et al., 2019). In both groups during reoperation, one patient had an identifiable source of bleeding. The other patients in both groups had no identifiable source of bleeding and the cause of blood loss was determined to be related to coagulopathy (Leff et al., 2019).

Patient Outcomes and Complications. ERAS recommendations are provided to optimize a patient's perioperative experience, emphasizing reduced complications and length of stay. The concern around TXA administration is the potential for thromboembolic events such as myocardial infarction, stroke, pulmonary embolism, renal failure, and bowel infarction, as well

as seizures or death. (Engelman et al., 2019; Myles et al., 2017). Guo et al. (2020) observed no statistical difference between TXA administration and control in MI, stroke, pulmonary embolism, renal dysfunction, and mortality. Seizure was evaluated in 11 trials, totaling 6,784 patients. TXA was associated with a 3.21-fold increase in the risk of seizure. Seizure occurrence was 0.62 percent (21/3,378) for patients receiving TXA and 0.15 percent (5/3,406) for control groups. Importantly, none of the patients receiving low dose TXA intravenously experienced a seizure, whereas patients receiving high-dose TXA did experience seizure in Guo et al. (2019). Guo and colleagues' (2019) findings regarding seizure differences with dosing differs from Myles et al. (2017). Seizure occurrence was noted as a higher risk in the TXA group, but a dose reduction to 50 mg/kg (from 100 mg/kg) did not decrease seizure risk, though the sample size is underpowered. The number needed to harm, similar to number needed to treat but for causing one additional patient to experience a seizure, was 177 patients. Interestingly, the incidence of seizure in patients undergoing open-chamber heart surgery that received TXA was statistically significant compared to placebo, whereas no statistical significance was observed in seizure incidences for patients undergoing isolated coronary artery surgery that received TXA compared to placebo (Myles et al., 2017). Leff et al. (2019) was not powered to evaluate seizure risk related to the administration of TXA and EACA, however, it is noted that no seizures were observed in either group. Myles and associates (2017) demonstrated similar outcomes to Guo et al. (2020), with no significant difference between TXA and control in MI, stroke, pulmonary embolism, renal failure, bowel infarction, and mortality within 30 days of surgery. Comparing TXA and EACA, Fergusson et al. (2008) and Leff et al. (2019) had similar adverse event outcomes related to stroke, myocardial infarction, renal dysfunction, and rates of organ failure.

The EACA group had a decreased incidence of stroke and MI but had an increased incidence of cardiogenic shock compared with the TXA group (Fergusson et al., 2008).

Habbab et al. (2020) reported one trial with no difference in post-operative complications regarding topical TXA and control groups, including seizure. TXA dosage ranged from 1 to 2.5 g diluted in 100 to 250 mL of 0.9% NaCl or only 0.9% NaCl as a placebo. The TXA or placebo was poured before sternal closure into the pericardial cavity and over the mediastinal tissues. Topical TXA may not be absorbed systemically following administration due to the natural barrier that the pericardium acts as. Decreased systemic absorption could conceivably decrease seizure incidence compared to intravenous administration. TXA levels were not detected in a small patient group that received topical TXA. Mortality was not observed for either group in 3/7 trials or 3 other trials did not provide data for mortality.

Mechanical ventilation time was slightly decreased in the TXA group of Myles and colleagues (2017) but was not associated with an earlier discharge from the hospital. Habbab et al. (2020) reported a significant reduction in intensive care unit length of stay in 2/4 studies that provided data. Additionally, hospital length of stay data was provided for 3/7 studies and did not show significant differences. Length of stay data was not provided in Guo et al. (2020). Length of stay was evaluated in the BART study for the intensive care unit as well as total hospital stay. The median ICU length of stay was 1.5 days in the TXA group and 1.8 days in the EACA group (Fergusson et al., 2008). The total hospital length of stay median was 8.5 days in the TXA group and 8.0 days in the EACA group (Fergusson et al., 2008).

Optimal Dosing. The optimal dose of TXA for use in cardiac surgery is reviewed by Levy et al. (2018) and Zufferey et al. (2021). Generalized convulsive seizures were associated at high doses of TXA at 100 mg/kg. One TXA dosing strategy that achieved 100 percent

antifibrinolytic activity was a loading dose of 30 mg/kg followed infusion at 16 mg/kg/hr for six hours with 2 mg/kg added to the cardiopulmonary bypass pump prime, which is referenced by Zufferey et al. (2021) as high-dose TXA. Zufferey et al. (2021) and Zhou et al. (2021) distinguish that a platform effect occurs with TXA, meaning higher doses do not yield additional benefit, rather they pose additional harm to patients. An 80 percent effective concentration is stated to reduce postoperative blood loss and red blood cell transfusion (Zufferey et al., 2021). Low-dose TXA can achieve close to 80 percent effective concentrations by a pre-operative bolus of 20 mg/kg or 10 mg/kg followed by 1 mg/kg/h for 12 hours. The total TXA dose should be roughly 20 mg/kg (Zufferey et al., 2021). Zhou et al. (2021) suggest low-dose TXA to patients with a low bleeding risk undergoing valvular cardiac surgery with cardiopulmonary bypass, as low-dose TXA was equivalent to high-dose TXA in in-vivo fibrinolysis parameters. A large meta-analysis and systematic review regarding the exclusion criteria for TXA administration in cardiac surgery patients concluded that perioperative intravenous TXA in cardiac surgery patients did not increase the overall risk of adverse events compared with placebo, no intervention, or EACA. Patients with renal impairment may need alternate dosing due to longer elevation of systemic TXA levels, however, routine anticoagulant and anti-platelet medications are thought to negate this concern (Khair et al., 2019)

Dosing for the BART study included a loading dose followed by a continuous infusion for both lysine analogs. The EACA regimen included a 10g loading dose, followed by 2g per hour infusion (Fergusson et al., 2008). The first 200mg of the loading dose were given as a test dose, followed by 9800mg if no anaphylactic reaction was observed (Fergusson et al., 2008). The TXA dosing regimen described by Levy et al. (2018) is identical to the schedule used by Fergusson et al. (2008) in the BART study. TXA dosing included a 30mg/kg loading dose,

followed by 16mg/kg/h continuous infusion. The 30mg/kg loading dose was diluted into 250ml and given over 10 min after a 5 ml test dose was administered (Fergusson et al., 2008). An additional 2mg/kg of TXA was also added to the bypass circuit (Fergusson et al., 2008). The dosing schedule used in the BART study by Fergusson et al. (2008) was replicated by Leff et al. (2019).

A slightly different dosing regimen was used by Blaine et al. (2016). Prior to the shortage of EACA, patients undergoing cardiac surgery at the institution received EACA. An initial loading dose of 10-15 mg/kg was given over 10-15 min followed by an infusion for 6 hours at 1-2mg/kg/hour (Blaine et al., 2016). The same loading dose and infusion rate was used during the medication shortage for TXA administration. The loading doses for the bypass circuit differed slightly between the two medications. The EACA bolus for the bypass circuit was 2-3mg/kg while the TXA dose was 2-2.5mg/kg (Blaine et al., 2016).

While most of the studied dosing regimens for EACA include a bolus or loading dose, followed by an infusion, a recent study examined the efficacy of a two-bolus regimen of EACA. The goal for antifibrinolytic dosing during cardiac surgery is to maintain plasma levels of EACA greater than 130mg/L (Strauss et al., 2021). The regimen studied at by Strauss et al. (2021) included a 1g/hr infusion started after central line placemen continued for 5 hours. The infusion was then followed by a 5g bolus for the cardiopulmonary bypass circuit as well as 5g bolus prior to protamine administration (Strauss et al., 2021). The first bolus helps protect against fibrinolysis during cardiopulmonary bypass, while the second bolus protects fibrin formed after protamine administration. Out of 21 patients in the study, 16 patients-maintained concentrations greater than 130mg/L (Strauss et al., 2021). However, five of the 21 patients fell below the target plasma concentration prior to the second bolus given prior to protamine administration (Strauss

et al., 2021). This study contained a small sample size with limitations and therefore further pharmacokinetic and pharmacodynamic studies are needed to improve EACA dosing regimens.

Guideline Development

Summary of Relevant Literature

The use of TXA and EACA in adult patients undergoing on-pump cardiac surgery has shown considerable benefit to patients, classified as I-A by Engelman et al. (2019) as the benefit is much greater than the risk. Intravenous TXA and EACA as well as topical routes of TXA have both been used successfully to decrease the amount of blood loss after cardiac surgery, though optimal dosing is not currently established. Higher intravenous dosing of TXA, ≥ 100 mg/kg appears to be associated with incidences of seizure. More research is needed to determine further safety and efficacy of the impact of topical TXA on blood transfusion needs and post-operative outcomes. Intravenous TXA and EACA appears to show promise in decreasing blood transfusion needs in cardiac surgery patients and does not statistically differ from control groups in regard to post-operative outcomes. Decreasing the amount of blood transfusions to patients could create more opportunities for other patients to receive blood products, which could be very beneficial to an underserved, level-one trauma center that provides care frequently to at-risk patients with multiple comorbidities. Streamlining TXA and EACA administration could also provide cost-savings by decreasing incidences of reoperation following cardiac surgery.

The efficacy of antifibrinolytic use for on-pump cardiac surgery is well understood and the evidence supports the use of both lysine analogs to decrease postoperative bleeding and blood transfusions. There has not been a definitive recommendation for one over the other. The choice of lysine analogs can vary due to hospital formulary, regional practices, pharmacy

contracts, surgical case volume, and patient population. All local factors should be considered when determining best practice for an institution.

Project Outcomes and Evaluation

TXA SWOT Analysis and Guideline Recommendation

Strengths. Administration of TXA for on-pump cardiac surgical procedures was designated as a I-A recommendation by the Cardiac ERAS Society due to a reduction in total blood products transfused and a reduction in reoperation for major hemorrhage or tamponade. Utilizing a weight-based, low-dose strategy appears to be safe in regard to the possible adverse effect of seizure. In the event of a shortage of Amicar, this suggested guideline can help direct practitioners how to administer TXA.

Weaknesses. A consensus on the dosing regimen for TXA administration for on-pump cardiac surgical procedures does not exist, therefore, the guideline recommendation is based on thorough literature review. There was only one patient that received TXA from the data set and TXA is not commonly administered for cardiac surgical procedures, making it difficult to assess TXA administration practices.

Opportunities. A large, double-blinded, randomized controlled trial by Shi and colleagues that is designed to identify the TXA dose with maximal efficacy and minimal complications in cardiac surgery patients is scheduled to be completed by December 31st 2021. The results from Shi et al. could further help the project site determine TXA dosing for cardiac surgical procedures. Education to the peri-operative cardiac surgery team on the possible benefits of low-dose TXA administration strategies could help increase the team's comfort when utilizing TXA for future cardiac surgeries.

Threats. TXA has documented possible adverse effects of concern in the literature, importantly seizure and stroke. Though the adverse effects appear to be dose-dependent in the high-dosing strategy and TXA has documented benefits mentioned above, the risks may deter providers from administering TXA to cardiac surgical patients. Additionally, cardiac surgeons had the ability to dictate medications given by anesthesia which can limit changes in practice to reflect evidence base practice recommendations. One surgeon at the project site did not support the use of antifibrinolytics. The CPIT committee would need buy in from both the cardiac surgeons and anesthesiologists to create a change in practice that will be followed.

Guideline Recommendation. Based on the literature review and synthesis, the chart audit at the project site, as well as stakeholder input: the following EBP Guideline recommendations were formulated for the administration of TXA for on-pump cardiac surgery (See Appendix F). A low-dose strategy of approximately 20 mg/kg, either: 10 mg/kg bolus followed by 1mg/kg/hr over 12 hours or a single pre-operative bolus of 20 mg/kg. This contrasts from the current project site guideline of a 1g loading dose administered before sternotomy followed by a constant infusion at 400 mg/hr until sternal closure. This low-dose strategy may provide a safer profile for patients and be just as efficacious in reducing blood products transfused, post-operative bleeding, and re-operation rates. The same dose reduction is recommended for patients with renal impairment due to a lack of literature regarding dosing in this population.

EACA SWOT Analysis and Guideline Recommendation

Strengths. EACA is the main antifibrinolytic used at the project site for cardiac surgery patients. Recommendations from multiple professional organizations support the routine use of antifibrinolytic therapy for on pump cardiac surgery procedures. Current practice at the project

site included a 10g bolus of EACA after induction of anesthesia followed by a 10g bolus of EACA after cardiopulmonary bypass. One surgeon used EACA for all on pump cardiac surgery procedures.

Weaknesses. The chart audit revealed that of the 14 patients that did not receive an antifibrinolytic, seven of the patients should have received an antifibrinolytic because the procedure required cardiopulmonary bypass. A variation in dosing was also identified among the patients that did receive EACA intraoperatively. Review of the anesthesia record revealed that 36% (8/22) of the patients received 10g of EACA while 59% (13/22) received 20g of EACA. Omitting the second bolus dose of EACA could be putting patients at risk of falling below the therapeutic plasma level of EACA during a critical time of fibrin formation post cardiopulmonary bypass after the administration of protamine.

Opportunities. The findings of this project served as a starting point to improve the quality and consistency of EACA dosing for the cardiac surgery population. There is an opportunity to improve on the administration of EACA for all patients that require on pump cardiac surgery as well as improved consistency for dosing among providers.

Threats. Cardiac surgeons had the ability to dictate medications given by anesthesia which limited changes in practice to reflect evidence base practice recommendations. One surgeon at the project site does not support the use of antifibrinolytics. The CPIT committee will need buy in from both the cardiac surgeons and anesthesiologists to create a change in practice that will be followed.

Guideline Recommendation. Based on the literature review/synthesis, chart audit and stakeholder input, the following EBP Guideline recommendations were formulated for the administration of EACA for on pump cardiac surgery (See Appendix F). The dosing regimen

used at the project site should be changed from a two-bolus dose to a regimen that reflects dosing studied more consistently in the literature. The new dosing recommendation is a bolus of 10g followed by an infusion of 10-15mg/kg/hr. This dosing regimen reflects current pharmacy recommendations at the project site. A bolus followed by an infusion will help maintain consistency among providers, prevent missing administration of the second bolus, and provide weight-based dosing to limit side effects.

CPIT Committee Presentation

The Clinical Practice Guideline Recommendations were presented to the Surgery/Anesthesia CPIT committee via a virtual meeting on November 23, 2021. The project proposal and guideline recommendations were provided to the committee prior to the presentation for review. The project proposal and guideline recommendations were also forwarded on to the Cardiac CPIT committee for review and distribution to the cardiac team.

Feedback from the committee included clarification on current practices involving TXA and EACA. The clarification was made that EACA is the standard antifibrinolytic used at this institution, however, if there is a medication shortage TXA is an acceptable substitution. For this reason, it is important that the institution has guidelines in place for the use of both antifibrinolytic medications. There are no current plans for implementation of the guidelines but there may be consideration in the future.

Limitations

There were several limitations to this project. Data collection and analysis of outcomes such as blood loss, blood transfusions, and reoperation were outside the scope of this project. This limitation prohibited the assessment and determination of current practice efficacy. The literature provided no consensus on ideal dosing for TXA or EACA. The recommendations

provided were based on dosing previously studied in the literature as well as current pharmacy prescribing guidelines at the institution. Due to academic/curricular time limits for the scholarly project, the current project team was unable to complete implementation of the guideline at the project site.

Conclusion

Despite strong evidence from the literature for best practices and well-established international standard ERAS guidelines, reports from key stakeholders from pharmacy and anesthesia departments at the project site revealed that the use of antifibrinolytic administration is not consistently practiced within the cardiac surgical setting. Additionally, the anesthesia and pharmacy department stakeholders reported that a lack of an evidence-based practice guideline may be contributing to the lack of antifibrinolytics administration in some patients. However, the extent of any clinical data demonstrating any adverse outcomes were unknown. The project team conducted a chart audit to demonstrate a clinical problem and support the need for the proposed aims of this project. Review of the anesthesia records revealed a variation in dosing of EACA, limited use of TXA, and omission of antifibrinolytic administration in patients that met the standards for the use of TXA or EACA. Consequently, the lack of standardized guidelines aligned to the EBP recommendations by the ERAS Cardiac Surgery Society for antifibrinolytic medication administration for on pump cardiac surgery and subsequent variability of clinical practice validated by recent chart audit may be indicate an increased risk to cardiac surgical patients for adverse outcomes related to bleeding, blood transfusions, and the need for reoperation.

Therefore, the purpose of this project was to provide the hospital site leadership with recommendations to help streamline and improve the quality and consistency of ERAS guided

practices involving antifibrinolytic medications in cardiac surgical patients. The objectives outlined and described previously were met as indicated by the completion of this scholarly project. Ultimately, the findings of this scholarly project can serve as a beginning point for improved identification of current practice gaps as well addressing the needs of anesthesia providers and pharmacy caring for these cardiac surgical patients. The submission and future implementation of a standardized, evidence-based, clinical practice guideline may improve anesthesia practices and patient outcomes centered on using standardized ERAS protocols for administering antifibrinolytics to cardiac surgery patients.

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Appendix A

Review of Evidence and Synthesis Table

Citation (Author, Year, Title, etc.)	Conceptual Framework (Theoretical basis for study)	Design/ Method	Sample/Setting (Number, Characteristics, Exclusions, Criteria, Attrition, etc.)	Major Variables; definitions (Independent variables; Dependent variables)	Outcome Measurement (What scales used – reliability information – alphas)	Data Analysis (What stats used?)	Findings (Statistical findings or qualitative findings)	Level of Evidence Level =	Quality of Evidence Strength Limits Risks Feasibility
Article 1: Guidelines for Perioperative Care in Cardiac Surgery: Enhanced Recovery After Surgery Society Recommendations (10.1001/jamasurg.2019.1153)									
Engelman, D. T., Ben Ali, W., Williams, J. B., Perrault, L. P., Reddy, V., Arora, R. C., Roselli, E. E., Khoynezhad, A., Gerdisch, M., Levy, J. H., Lobdell, K., Fletcher, N., Kirsch, M., Nelson, G., Engelman, R. M., Gregory, A. J., & Boyle, E. M. (2019). Guidelines for perioperative care in cardiac surgery. *JAMA Surgery*, *154*(8), 755. https://doi.org/10.1001/jamasurg.2019.1153	Present consensus recommendations for the optimal perioperative management of patients undergoing cardiac surgery	Meta-analysis to determine recommendations by the ERAS Cardiac Society and endorsed by the Enhanced Recovery After Surgery Society	197 Studies included in the meta-analysis (4052 screened). 3089 removed on basis of title and abstract -963 Full-text articles assessed for eligibility -664 full-text articles excluded on study design or gaps on reporting -28 ineligible population -19 Overlapped studied -41 Case series studied removed -14 Commentaries removed Totaling 197 for meta-analysis	Independent: Receiving TXA, EACA, or placebo Dependent: Total blood products transfused, incidence of reoperation for major hemorrhage or tamponade, seizure incidence	Not provided	Society of Thoracic Surgeons/American Association for Thoracic Surgery 2017 updated document "Classification of Recommendations and Level of Evidence" American College of Cardiology/American Heart Association clinical practice guidelines to grade the consensus class (strength) of recommendation and level (quality) of evidence	Total blood products and incidences of re-operation for major hemorrhage or tamponade were reduced using TXA High doses of TXA associated with seizures Max total TXA dose recommended: 100 mg/kg TXA or EACA recommended during on-pump cardiac surgical procedures	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths**: Large meta-analysis. Recommendations from ERAS Cardiac Society and endorsed by ERAS Society **Limits:** Additional large RCTs would support routine use of anti-fibrinolytics **Risks:** Increased seizure risk with TXA use **Feasibility:** Anti-fibrinolytics accessible, cost effective, and easy to implement
Article 2: Tranexamic acid in patients undergoing coronary-artery surgery (10.1056/NEJMoa1606424)									
Myles, P. S., Smith, J. A., Forbes, A., Silbert, B., Jayarajah, M., Painter, T., Cooper, D., Marasco, S., McNeil, J., Bussieres, J. S., McGuinness, S., Byrne, K., Chan, M. T., Landoni, G., Wallace, S., & ATACAS Investigators of the ANZCA Clinical Trials Network. (2017). Tranexamic acid in patients undergoing coronary-artery surgery. The New England Journal of Medicine, 376(2), 136–148. Retrieved September 17, 2020, from https://doi.org/10.1056/NEJMoa1606424	Antifibrinolytic therapy reduces the risk of blood loss and transfusion among patients undergoing cardiac surgery, but it is unclear whether such therapy reduces the risk of reoperation for bleeding	Multicenter, double-blind RCT	N=4,631: Patients undergoing coronary artery surgery and were at risk for perioperative complications -2311 assigned to TXA -2320 assigned to placebo	Independent: Receiving TXA or placebo Dependent: Death; MI; CVA; renal failure; PE; bowel infarction; reoperation; transfusion of red cells during hospitalization; number of units of red cells that were transfused	Continuous secondary outcomes assessed with Student's t-test or Wilcoxon rank-sum test Wilcoxon-Breslow-Gehan test: For time-to-event outcomes. Data on LOS in hospital and ICU	Analysis of primary and dichotomous secondary outcomes were performed with: Chi-square tests from binomial regression with a logarithmic link; results expressed as risk ratios with 95% CI	TXA did not result in a higher risk of death of thrombotic complications than that with placebo among patients undergoing coronary artery surgery TXA group with lower risk of blood loss,	II: One or more randomized controlled trials	**Strengths:** Large, multicenter RCT **Limits:** Underpowered analysis regarding dose reduction of TXA to compare seizure risk; Few patients in study at the highest

			Eligible: Adults at increased risk for major complications related to age or co-existing conditions and who were about to undergo on-pump or off-pump coronary-artery surgery, with or without cardiac-valve replacement or other procedures	during hospitalization; duration of mechanical ventilation; length of stay in intensive care unit; length of stay in hospital; seizures; peptic ulceration; reintubation during hospitalization	censored at 30 days and in-hospital deaths assigned the highest length of stay		blood transfusion, and reoperation (57u PRBC saved per 100 patients treated) TXA group with higher risk of post-op seizures than placebo (0.7% vs. 0.1%, p=0.002) A 50 mg/kg dose of TXA did not reduce the risk of seizure compared to 100 mg/kg Slightly shorter duration of post-op mechanical ventilation in TXA vs. placebo (5 hours [95% CI, 8 to 14] vs. 6 hours [95% CI, 9 to 16], p<0.001)		risk of bleeding or thrombosis; attending anesthesiologists were sometimes aware of treatment group assignment; small proportion of off-pump surgery **Risks:** Post-op seizure risk with TXA **Feasibility:** TXA accessible, cost effective, and easy to implement
Article 3: Different dose regimes and administration methods of tranexamic acid in cardiac surgery: A meta-analysis of randomized trials (10.1186/s12871-019-0772-0)									
Guo, J., Gao, X., Ma, Y., Lv, H., Hu, W., Zhang, S., Ji, H., Wang, G., & Shi, J. (2019). Different dose regimes and administration methods of tranexamic acid in cardiac surgery: A meta-analysis of randomized trials. BMC Anesthesiology, 19(1), 1–16. Retrieved September 17, 2020, from https://doi.org/10.1186/s12871-019-0772-0	Provide information on the optimal dosage and delivery method of tranexamic acid that is effective with the least adverse outcomes	Meta-analysis of randomized controlled trials comparing TXA with placebo in adults who underwent elective heart surgery, including on- and off-pump operations	49 studies included in meta-analysis N=10,591 Inclusion: adults who underwent elective heart surgery Exclusion: urgent cases, patients < 18 years of age Characteristics: Mainly 2 types of intravenous administration methods. One was bolus infusion alone (14 trials) and the other was bolus injection followed by continuous infusion (22	Independent: Receiving TXA or placebo for adults undergoing elective cardiac surgery Dependent: blood transfusion rate; blood transfusion volume; post-op blood loss; re-operation rate; mortality during hospital stay; post-op complications (seizure, stroke, MI, PE, renal dysfunction)	Not provided	Dichotomous outcomes (transfusion rate, re-operation rate, incidence of adverse effects), calculated relative risk with 95% CI Continuous outcomes (post-op blood loss, transfusion volume), reported as mean and standard deviation, mean difference for pooled estimates with 95% CI Fixed-effect model used for analysis with no heterogeneity Outcomes with heterogeneity	TXA use significantly reduced the need for allogeneic blood transfusion by a relative rate of 29% (p < 0.00001) For trials that reported data on the volume of blood transfused in all patients, TXA use resulted in 0.6 units reduction of allogeneic blood per patient (p < 0.00001) For trials that reported data on the volume of blood transfused	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** Large meta-analysis of RCT. Investigates different dosing of TXA **Limits:** Some studies reported data on transfusion volume without data on transfusion rate. Underpowered results of high vs. low dose regimen TXA due to lack of network analysis **Risks:** High-dose TXA associate

			trials). Low dose for TXA bolus injection was < 50 mg/kg and ≤ 10 mg/kg + 1 mg/kg/h as low dose bolus plus continuous infusion			, subgroup analysis used to identify source Statistical analyses performed with RevMan and Stata	in those patients transfused, TXA use resulted in 1.02 units reduction of blood transfusion per patient ($p < 0.00001$) TXA treatment reduced post-op blood loss by around 247 mL per patient compared to control ($p < 0.00001$) Use of TXA significantly decreased the risk of reoperation by 38% ($p < 0.0001$) Use of TXA associated with 3.21-fold increase in risk of seizure ($p = 0.04$); Overall rate of seizure was 21/3378 (0.62%) for TXA and 5/3406 (0.15%) for control No significant difference between TXA and control group in mortality, stroke, MI, PE, renal dysfunction Risk of seizure only seen in high-dose TXA delivered intravenously High-dose TXA does not further decrease transfusion rate and has a strong tendency to cause more seizure attacks compared		d with increased risk of seizure vs. low risk for low-dose **Feasibility:** Accessible, cost-effective. Low dose implemented with bolus alone or bolus plus continuous infusion on IV pump

							to low-dose TXA Preferred low dose: (bolus of < 50 mg/kg, or 10 mg/kg + 1 mg/kg/h)		
Article 4: Antifibrinolytic therapy and perioperative considerations (10.1097/ALN.0000000000001997)									
Levy, J. H., Koster, A., Quinones, Q. J., Milling, T. J., & Key, N. S. (2018). Antifibrinolytic therapy and perioperative considerations. Anesthesiology, 128(3), 1–26. Retrieved September 25, 2020, from https://doi.org/10.1097/ALN.0000000000001997	Explore the role of fibrinolysis as a pathologic mechanism, review the different pharmacologic agents used to inhibit fibrinolysis, and focus on the role of tranexamic acid as a therapeutic agent to reduce bleeding in patients following surgery and trauma	Systematic review of perioperative considerations in antifibrinolytic therapy	Not provided	TXA, EACA, and Aprotinin reviewed in multiple surgery types	Not provided	Not provided	One prospective blinded dosing study à Patients receiving initial 10 mg/kg loading dose followed by infusion at 1/10th loading dose had significantly less chest tube draining than with lower doses, but did not alter transfusions, and higher doses did not provide additional reduction in bleeding A bolus dose of 10 mg/kg with an infusion of 1 mg/kg/h was provided a TXA plasma concentration that inhibited fibrinolytic activity in vitro A loading dose of 30 mg/kg followed by 16 mg/kg/h for 6 hours and 2 mg/kg added to the pump prime can achieve 100% inhibition of fibrinolytic activity Reports have shown generalized convulsive seizures in	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** Detailed review of anti-fibrinolytics across multiple surgery types. Benefit of TXA vastly outweighs side effect profile **Limits:** Optimal TXA dosing not established for cardiac surgery **Risks:** High dose TXA associated with seizures **Feasibility:** Accessible and cost-effective to utilize TXA. May lead to TXA strategy of bolus dosing followed by continuous infusion and pump prime

							the absence of new ischemic lesions on imaging at TXA doses of 100 mg/kg followed by 25-50 mg/kg/h with a total dose up to 259 mg/kg Recent meta-analysis of RCT and retrospective studies associated 4.1-fold increased risk in clinical seizures Patient numbers are too small to draw any definitive conclusions on TXA dosing and seizures in cardiac surgery patients; data suggest that other mechanisms contribute to seizures and persisting neurological damage		
Article 5: Topical use of tranexamic acid in cardiac surgery: A meta-analysis. (10.1055/s-0039-1691748)									
Habbab, L. M., Semelhago, L., & Lamy, A. (2019). Topical use of tranexamic acid in cardiac surgery: A meta-analysis. Thoracic and Cardiovascular Surgeon, 68(3), 212–218. Retrieved September 20, 2020, from https://doi.org/10.1055/s-0039-1691748	Investigate the evidence for the efficacy and safety of intrapericardial tranexamic acid in cardiac surgery	Meta-analysis	7 RCT: 6 on-pump and 1 off-pump comparing topical application of TXA to placebo… 6/7 double blinded Total: 372 patients received TXA and 320 control	Independent: Receiving topical TXA or receiving placebo for cardiac surgery Dependent: 24-hour blood loss, incidence of packed red blood cell infusion, detection of TXA in serum lab collection, graft patency, MI, cerebral infarction, atrial fibrillation, seizure, infection	Not provided	Data expressed as mean ± standard deviation Treatment effect as mean differences Statistical heterogeneity assessed using value of I^2 and the result of chi-squared test Statistical analysis using HDS meta-analysis calculator and Grapher statistical software	Intrapericardial TXA associated with considerable reduction in 24-hour blood loss in all 7 studies ($p = 0.005$) Incidence of packed RBC transfusion in TXA patients significantly lower in one study ($p = 0.01$); 5 other studies with trend in favor of TXA; 6/7 reported data on this outcome LOS in ICU	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** Meta-analysis of different TXA dosing route **Limits:** More research needed on topical TXA to determine safety and efficacy **Risks:** Possibility of pericardial adhesions after administration, making reoperation more difficult (more

							significantly lower in TXA patients in 2/4 studies reporting data (p = 0.002 and p = 0.002) Hospital LOS reported in 3 studies, mortality reported in 4 studies à Both not significantly different between two groups In one trial, TXA was not detected in any patient In one trial, post-op complications (graft patency, MI, cerebral infarction, atrial fibrillation, seizure, and infection) were similar		research needed) **Feasibility:** Surgeon able to administer. Follow-up needed to assess if possible, to do at project site
Article 6: 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery.									
Boer, C., Pagano, D., Meesters, M. I., Milojevic, M., Bendetto, U., Bolliger, D., Heymann, C., Jeppsson, A., Koster, A., Osnabrugge, R. L., Ranucci, M., Ravn, H., Vonk, A. B., & Wahba, A. (2018). 2017 EACTS/EACTA Guidelines on patient blood management for adult cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia, 32, 88–120. Retrieved September 16, 2020, from https://doi.org/10.1053/j.vca.2017.06.026	Creation of guidelines to provide practical recommendations for all clinicians working in the field of patient blood management in cardiac surgery, with emphasis on preoperative patient optimization and risk reduction, intraoperative maintenance of hemostasis and postoperative treatment for bleeding complications	Task force created by EACTS and EACTA Systematic review of published evidence in the field of blood conservation during adult-acquired cardiac surgery. Literature restricted from 2001-2017. Guideline focus on adult-acquired cardiac surgery, and did not include studies in transplantation, trauma, circulatory arrest, or long-term circulatory support.	7 trials reviewed and cited for administration of TXA and EACA	Independent: Receiving TXA, EACA, or placebo Dependent: Risk of reoperation due to major hemorrhage, need for transfusion of any blood products, seizure incidence	Classes of recommendations based on the Methodology for European Association for Cardio-Thoracic Surgery clinical guidelines Levels of evidence based on the Methodology Manual for European Association for Cardio-Thoracic Surgery clinical guidelines	Not provided	TXA and EACA recommended to reduce bleeding and transfusions of blood products (Class I, Level A) TXA recommended for reducing incidences of reoperation for bleeding (Class I, Level A) Risk of post-op seizure with TXA	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** Systematic approach to appraising the literature and guidelines formed from multiple expert organizations **Limits:** Additional large RCTs would aid in supporting use of anti-fibrinolytics routinely **Risks:** Increased seizure risk with use of TXA **Feasibility:** Feasible

									to administer TXA or EACA intraoperatively
Article 7: A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery.									
Jonathan Leff, Amanda Rhee, Singh Nair, Daniel Lazar, Sudheera Kokkada Sathyanarayana, & Linda Shore-Lesserson. (2019). A randomized, double-blinded trial comparing the effectiveness of tranexamic acid and epsilon-aminocaproic acid in reducing bleeding and transfusion in cardiac surgery. *Annals of Cardiac Anaesthesia*, *22*(3), 265–272. https://doi.org/10.4103/aca.ACA_137_18	Compare effectiveness of EACA to TA in reducing 24-hour chest tube drainage/blood loss and transfusion requirements in patients undergoing cardiac surgery on CPB.	Randomized, Double-Blinded Trial Single center study	Tertiary care university hospital N=114 Inclusion: age < 18yo, CABG, heart valve repair/replacement, or combo Exclusion: age < 18 yo, refusal of blood products for religion, allergy to antifibrinolytics, participation in another clinical trial, concurrent renal dysfunction (stage 4 or 5 CKD), history of stroke, dvt, or PE, known congenital bleeding disorders, weight <50kg or >150kg	Independent: antifibrinolytic group- EACA or TA Dependent: amount of 24-hour chest tube drainage, amount of blood products administered in 24 hours, 30-day mortality/morbidity, length of stay	Descriptive statistics for all baseline characteristics Continuous variables: independent sample student t-tests Categorical variables= chi square tests Transfusion Risk Understanding Scoring (TRUST) Tool	Chest tube drainage was analyzed using Mann-Whitney Wilcoxon test Blood products analyzed by chi-square analysis	No statistically significant difference between groups when analyzing chest tube drainage Percentage of patients receiving any form of blood product at any point of time during the first 24 h was 25% (n = 14) versus 44.8% (n = 26) in the EACA and TA group, respectively Patients receiving TA had 2.4 times higher odds of receiving any form of blood product at any point of time during the first 24 h (odds ratio [OR] = 2.4 95% confidence interval [CI], 1.1–5.4, P = 0.027)	II: One or more randomized controlled trials	**Strengths:** RCT No placebo group allowed them to evaluate effectiveness rather than efficacy **Limits:** small sample size, single center study- not generalizable, TA group had a higher risk population according to TRUST scores, **Risks:** limited risk, administration of a lysine analogues is standard of care Benefit of antifibrinolytic use is already established **Feasibility:** acceptabl

							The percentage of patients receiving PRBC alone during the first 24 h postoperatively was significantly higher in the TA group when compared to the EACA group, 34.5% (n = 20) versus 17.9% (n = 10) (OR = 2.4, 95% CI = 1.01–5.79, unadjusted P = 0.044). mean number of blood products transfused = 0.59 ± 1.3 in the EACA group, 1.20 ± 2.2 in the TA group (unadjusted P = 0.027) percentage of patients receiving FFP = 5.4% (3) in the EACA group versus 17.2% (10) in the TA group (OR = 3.6, 95% CI =0.95–14.16, unadjusted P = 0.046) Other blood products= no statistically significant difference no difference in the incidence of stroke, renal dysfunction, cardiac arrest, reoperation, death, and seizure in the two groups most common complicatio		e, low cost, includes both medications

							n in both groups was resp. failure		
Article 8: ε-Aminocaproic Acid and Clinical Value in Cardiac Anesthesia									
Raghunathan, K., Connelly, N. R., & Kanter, G. J. (2011). ε-Aminocaproic Acid and Clinical Value in Cardiac Anesthesia. *Journal of Cardiothoracic & Vascular Anesthesia*, *25*(1), 16–19.	Comparing the "clinical value" of TXA and EACA when used for blood conservation during high-risk cardiac surgery	Data from the BART (Blood Conservation Using Antifibrinolytics in a Randomized Trial) study was reanalyze using "clinical value" equation	Multicenter study N= 1,550 patients TXA (n=770) EACA (n= 780)	Independent = TXA or EACA TXA dose: 30mg/kg loading dose followed by a 15mg/kg/h infusion with an additional 2mg/kg for bypass circuit EACA dose: 10g loading dose followed by 2 g/h infusion Dependent= clinical outcomes, cost, satisfaction with care, functional status/well being	Clinical value analysis Clinical value= ([quality/costs] x volume)	Bonferri correction for multiple pair wise comparisons	Original BART study found no significant difference in EACA and TXA in safety and efficacy EACA is a cheaper option and has more clinical value than TXA 80kg patient, 5-hour surgery: EACA cost= $2.40, TXA= $540.00	II: One or more randomized controlled trials	**Strengths:** RCT Multicenter study **Limits:** BART data accessibility **Risks:** limited risk, administration of a lysine analogues is standard of care Benefit of antifibrinolytic use is already established **Feasibility:** acceptable, low cost, includes both medications
Article 9: A comparison of aprotinin and lysine analogues in high-risk cardiac surgery									
Fergusson, D. A., Hébert, P. C., Mazer, C., Fremes, S., MacAdams, C., Murkin, J. M., Teoh, K., Duke, P. C., Arellano, R., Blajchman, M. A., Bussières, J. S., Côté, D., Karski, J., Martineau, R., Robblee, J. A., Rodger, M., Wells, G., Clinch, J., & Pretorius, R. (2008). A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. *New England Journal of Medicine*, *358*(22), 2319–2331.	To determine if aprotinin was superior to the lysine analogues: aminocaproic acid or tranexamic acid	Multi-center, blinded randomized, controlled study comparing three antifibrinolytic agents commonly used in cardiac surgery.	Multicenter study 2331 high-risk cardiac surgical patients to one of three groups: 781 received aprotinin 770 received tranexamic acid 780 received aminocaproic acid August 2002 to October 2007 Inclusion: -patients who were at least 19 years of age -repeat cardiac surgery, isolated mitral-valve replacement, combined valve and	Independent variables: type of antifibrinolytic- aprotinin, aminocaproic acid, or tranexamic acid Dependent: Postoperative bleeding, death from any cause at 30 days	Primary outcome: massive postoperative bleeding Secondary outcome: Death from any cause at 30 days	Interim analyses of the primary clinical outcome and important safety outcomes when 33% and 66% of patients, respectively, were accrued three sequential analyses with the use of the O'Brien–Fleming spending function Primary Outcomes: pairwise comparisons, chi square tests, logistic regression models Secondary outcomes: pairwise chi-square	**Massive bleeding**: 261/2330= 11/.2% Aprotinin: 74/781 (9.5%) TXA: 93/770 (12.1%) EACA: 94/780 (12.1%) **Death and Adverse Outcomes:** **30-day death rate:** 108/2331 (4.6%) Aprotinin: 6% TXA: 3.9% EACA: 4.0% **Cardiac cause:** Aprotinin: 25 (3.2%) TXA: 10 (1.3%)	II: One or more randomized controlled trials	**Strengths:** RCT Multicenter study **Limits:** high risk cardiac surgery patients **Risks:** limited risk, administration of a lysine analogues is standard of care Benefit of antifibrinolytic use is already established **Feasibility:** unable to compare lysine analogs with aprotinin

			CABG surgery, multiple valve replacement or repair, and surgery of the ascending aorta or aortic arch - urgent or elective procedures Exclusion: - undergoing lower risk operations, such as isolated primary CABG with or without cardiopulmonary bypass, isolated mitral-valve repair or aortic-valve replacement, and infrequent procedures such as heart transplantation, implantation of a left ventricular assist device, and surgery to repair congenital heart defects			tests, Fisher's exact test, logistic-regression models	EACA: 13 (1.7%) **Transfusion : atleast one unit of PRBC** Aprontonin: 419/780 (53.7%) TXA: 506/770 (65.7%) EACA: 514/780 (65.9%)		
Article 10: Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage (10.1016/j.jclinane.2016.08.037)									
Blaine, K. P., Press, C., Lau, K., Sliwa, J., Rao, V. K., & Hill, C. (2016). Comparative effectiveness of epsilon-aminocaproic acid and tranexamic acid on postoperative bleeding following cardiac surgery during a national medication shortage. Journal of Clinical Anesthesia, 35, 516–523. https://doi.org/10.1016/j.jclinane.2016.08.037	Compare the effectiveness of epsilon-aminocaproic acid (εACA) and tranexamic acid (TXA) in contemporary clinical practice during a national medication shortage	Retrospective Cohort Study	All consecutive patients undergoing cardiac surgery with cardiopulmonary bypass between February 1 and June 3, 2013 n= 128 EACA= 68 TXA=60 εACA (loading dose 10-15 mg/kg over 10- 15 min, 2-3 mg/kg bolus into the bypass priming solution, then	Independent: EACA and TXA administrations Dependent: blood loss and transfusions	Quantitative Data total quantitative blood loss from all surgical drains, in mL, recorded during the first 8 hour after surgery.	Descriptive statistics Univariate regression analysis Multivariate linear regression Logarithmic transformation was used for non-Gaussian continuous variables All statistical analyses were performed in R Statistical Software v3.2.1 power analysis was performed using PASS Statistical Software	**Eight-hour output:** A multivariate linear regression line demonstrated a correlation coefficient of 0.32. no difference in TXA and EACA **Transfusion Requirement:** Multivariate linear regression for allogenic RBC transfusion returned a weak correlation coefficient of 0.14.	IV: Cohort or case series study	**Strengths:** RCT Multicenter study **Limits:** single center **Risks:** limited risk, administration of a lysine analogues is standard of care Benefit of antifibrinolytic use is already established **Feasibility:** acceptable. Ease of

			1-2 mg/kg per hour infusion for 6 hours). TXA (loading dose 10-15 mg/kg over 10-15 min, 2-2.5 mg/kg bolus in the bypass priming solution, then 1-2 mg/kg per hour for 6 hours)				no difference in TXA or EACA		implementation
Article 11: One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program									
Williams, J. B., McConnell, G., Allender, J. E., Woltz, P., Kane, K., Smith, P. K., Engelman, D. T., & Bradford, W. T. (2019). One-year results from the first US-based enhanced recovery after cardiac surgery (ERAS Cardiac) program. *Journal of Thoracic & Cardiovascular Surgery*, *157*(5), 1881.	Knowledge to action frameworkà knowledge creation and action cycle Knowledge creation: adapted to the local context with assessment of local barriers and enablers, including involvement of all stakeholders in the care of the cardiac surgery patient.	Synthesized enhanced recovery principles from other specialties to form an ERAS Cardiac protocol 18-month study: 9 pre and 9 post design	Pre-N=489 Post N=443 Baseline characteristics: Pre/POST -age= 65/65 -female=31/31 -nonwhite race=26/29 -bmi=29/29 -Peripheral arterial occlusive disease= 11/13 -Congestive heart failure or left ventricular ejection fraction 40%=31/31 -Prior stroke=23/21 -Diabetes mellitus= 57/58 -Hemoglobin A1C= 6.5/6.5 -Operative case type Isolated CABG= 62/61 Mitral/tricuspid= 15/14 Aortic= 16/18 Other= 7/7 Intra-aortic balloon pump= 16/17 Reoperation within first 48 h Postoperative= 1.5/1.5 Percutaneous interventions such as transcathete	Independent variables: (1) preoperative patient education, (2) carbohydrate loading 2 hours before general anesthesia, (3) multimodal opioid sparing analgesia, (4) goal directed perioperative insulin infusion, and (5) a rigorous bowel regimen Dependent variables: - opioid use -hospital LOS -ICU LOS -postoperative ventilator time -reintubation rate -ICU readmission rate -GI complications	Patient outcomes over 9 months post ERAS implementation	Fisher exact test. Student t Test Mann–Whitney U nonparametric test SAS software Post Hoc Analysis on two variables	Outcome: pre, post, p value Opioid use in mean milligrams of intravenous morphine equivalents: 29, 21 <.01 Hospital LOS, median (25th, 75th) days: 7 (5, 9), 6 (5,8), <.01 ICU LOS, median (25th, 75th), hours: 43 (25, 74), 28 (23, 52), <.01 Postoperative ventilator time, median (25th, 75th), hours: 5.2 (3.9, 7.3), 5.3 (3.9, 6.9), .53 Reintubation rate: 5.3, 4.1, .44 ICU readmission: 5.1, 3.6, .34 GI complications: 6.8, 3.6, .04	IV: Cohort or case series study	**Strengths:** Sample size, outcome measurements, pre and post population similar **Weaknesses:** -9-month lead time to implementation could have impacted data collect it the pre period **Limits:** nonrandomized, measured or unmeasured confounders could have influenced our findings. Did not include antifibrinolytics **Risks:** none **Feasibility:** theoretical framework applicable to project

			r heart valve implantation were not included						
Article 12: Exposure-response relationship of tranexamic acid in cardiac surgery: A model-based meta-analysis (10.1097/ALN.0000000000003633)									
Zufferey, P. J., Lanoiselée, J., Graouch, B., Vieille, B., Delavenne, X., & Ollier, E. (2021). Exposure-response relationship of tranexamic acid in cardiac surgery: A model-based meta-analysis. *Anesthesiology*, *134*, 165–178. https://doi.org/10.1097/ALN.0000000000003633	Characterizing the exposure-response relationship of tranexamic acid in cardiac surgery at high-dose and low-dose regimens	Systematic review and meta-analysis	82 clinical trials (49,817 patients) selected. 64 RCTs (12,378) for effectiveness analysis. 18 observational (37,439) for analysis of seizure. Searched for adults patients (>18 y.o), undergoing CPB for cardiac or thoracic aortic surgery)	For assessing exposure-response relationship: Restricted search to RCTs comparing IV dose of TXA to another IV TXA dose, or no treatment. Outcomes (dependent variables) were post-op blood loss, allogenic RBC transfusion, & rethoracotomy for any reason For assessing seizure: Expanded search to observational trials and RCTs (due to rare event). Independent variable was receiving TXA or another antifibrinolytic. Dependent variable was seizure occurrence	Quantitative data Post-op blood loss, RBC transfusion, re-thoracotomy, seizure occurrence	Descriptive statistics For each post-op blood loss, the timing of the measurement relative to the end of the surgery was collected. Proportions of patients requiring RBC transfusion and rethoracotomy, respectively, and proportion experiencing seizure were calculated TXA exposure in each treatment arm was evaluated by simulation. Mean TXA kinetic simulated on basis of dosing regimen, mean patient body weight and pharmacokinetic model by Grassin-Delyle et al. If information was missing on mean body weight, CPB duration, or surgery duration, a multivariate imputation was performed using multivariate imputation by chained equations, mice package in R software Mean TXA concentration from start of surgery to 12 hours was calculated	Reduction in post-op blood loss and RBC transfusion as exposure to TXA increased Once the concentration exceeds 80% effective concentration, further changes appear to have little impact on drug effect. Low-dose (10 mg/kg followed by 1 mg/kg/hr over 12h) was close to 80% effective concentration for post-op blood loss and above 80% for RBC transfusion TXA doses at 2g and 2-10g achieved similar reductions in RBC transfusion rate TXA should be initiated before CPB and should be designed to achieve effective concentrations approximately 4h after start of surgery (contributes the most to blood loss reduction at end of surgery) TXA administration increases the risk for post-op	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** Systematic review and meta-analysis. Included available data in literature for seizure occurrence **Limits:** Not compared to other antifibrinolytics. Simulations used. No ideal dose for TXA in cardiac surgery is recommended currently **Risks:** Increased seizure risk with TXA **Feasibility:** Acceptable. Ease of implementation

							seizure. High-dose (80-100 mg/kg) resulted in two-fold increase in post-op seizures. Low dose (~ 20 mg/kg) was associated with less than 1.2-fold increase in seizure rate. Open chamber surgery and duration of CPB were associated with higher rate of seizure independently of TXA exposure		
Article 13: Comparison of the in-vivo effect of two tranexamic acid doses on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass - a pilot investigation (10.1186/s12871-021-01234-8)									
Zhou, Z., Zhai, W., Yu, L., Sun, K., Sun, L., Xing, X., & Yan, M. (2021). Comparison of the in-vivo effect of two tranexamic acid doses on fibrinolysis parameters in adults undergoing valvular cardiac surgery with cardiopulmonary bypass - a pilot investigation. *BMC Anesthesiology*, *21*(33), 1–10. https://doi.org/10.1186/s12871-021-01234-8	To investigate if there is a dose dependent in-vivo effect of TXA on fibrinolysis parameters by measurement of fibrinolysis markers in adults undergoing cardiac surgery with CPB	Double blind, randomized, controlled prospective trial	30 patients randomly divided into placebo, low-dose TXA, and high-dose TXA by 1:1:1 Inclusion: Patients undergoing elective valvular CS with CPB & age > 18 Exclusion: Hx of cerebral infarction, the presence of arterial or venous thrombosis, a history of myocardial infarction in the previous 7 days, preoperative chronic kidney disease [CKD] (serum creatinine (Cr) by 1.6mg/dl for men and > 1.4mg/dl for women or needing for renal replacement therapy), preoperative chronic liver disease (grade B or C of the Child-	Independent: Receiving placebo, low dose TXA (10 mg/kg 15 min after intubation, followed by 1 mg/kg/hr infusion & 1 mg/kg added to venous reservoir during CPB), or high-dose TXA (30 mg/kg, followed by 16 mg/kg/hr & 2 mg/kg added to venous reservoir during CPB) Dependent: intra-op plasma levels of tissue plasminogen activator (tPA) was primary outcome. Plasminogen activator inhibitor-1 (PAI-1), thrombin activatable fibrinolysis inhibitor (TAFI),plasmin-antiplasmin complex (PAP), tissue plasminogen activator (tPA), and	Quantitative Data Fibrinolysis markers stated	Descriptive data Variables with normal distribution reported as means + SDs Continuous variables with non-normal distribution reported as medians ANOVA used to compare continuous variables with normal distribution between groups, and Welch's test used when variance existed between groups and the different time points Chi-squared or Fisher's exact test Mauchly's Test of spherecity for homogeneity Kruskal-Wallis H test	No significant difference in plasma concentrations with correcting for hemodiluti on of tPA between three groups, but was significant if hemodiluti on was not corrected In vivo effect of low dose TXA is equivalent to high dose TXA on fibrinolysis parameters in adults undergoing valvular cardiac surgery with CPB and low bleeding risk Standard coagulation test and TEG test did not reflect a difference in the effects of the two TXA doses on	II: One or more randomized controlled trials	**Strengths:** RCT. Compared low dose, high dose, and placebo **Limits:** Small sample size. Plasma TXA concentration not monitored at different sample points during study **Risks:** Increased seizure risk with TXA, though not observed in this study due to small sample size **Feasibility:** Price consideration of drawing fibrinolysis markers during surgery

			Pugh classification), a previous history of endocarditis, anemia(< 120 g/dl for men and < 110 g/dl for women), hyperlipidemia, acute heart failure, preoperative shock, treatment with preoperative coagulation medication within 5 days of surgery (warfarin, aspirin, antifibrinolytic or thrombolytic treatment), preoperative coagulopathy (international normalized ratio (INR) > 1.5, platelet count < 100 103/mm3, fibrinogen < 1 g/L), previous sternotomy, emergency procedures, endocarditis, combined procedures (combined with coronary artery bypass graft surgery, aortic surgery, carotid surgery, other nonvalvular surgery, experienced deep hypothermic circulatory arrest), allergy or contraindication to tranexamic acid, pregnancy, and participation in another study	thrombomodulin (TM) were secondary outcomes.			inhibiting fibrinolysis Increase in TM in high-dose TXA is a safety concern Hemodilution tends to obscure the underlying changes occurring in the hemostatic system during CPB D-Dimer levels significantly decreased in both TXA groups upon arrival to ICU and morning of POD1 No significant difference in fibrinogen levels between TXA groups		

Article 14: Exclusion criteria and adverse events in perioperative trials of tranexamic acid in cardiac surgery: A systematic review and meta-analysis (10.1007/s12630-019-01393-w)									
Khair, S., Perelman, I., Yates, J., Taylor, J., Lampron, J., Tinmouth, A., & Saidenberg, E. (2019). Exclusion criteria and adverse events in perioperative trials of tranexamic acid in cardiac surgery: A systematic review and meta-analysis. *Canadian Journal of Anesthesia*, *66*, 1240–1250. Retrieved August 23, 2021, from https://doi.org/10.1007/s12630-019-01393-w	To determine which patients are commonly excluded from TXA cardiac surgery clinical trials to determine if there are patient groups lacking safety data on TXA	Systematic review and meta-analysis	70 included studies Systematic review presents results of the cardiac surgery sub-study from a larger systematic review on exclusion criteria used in peri-op TXA trials in all surgical specialties Population of interest: patients undergoing elective or emergent CS To be eligible: studies had to report on at least one outcome of interest Included only RCTs that were full-text, peer-reviewed, and written in English and French Excluded duplicate publications, systematic reviews and meta-analyses, and non-randomized study designs. Studies without a comparator group were also excluded. Studies including pts other than CS were excluded.	Independent: Systemic TXA administered at any point peri-op, and at any dose, duration, and frequency. Compare groups were placebo, no intervention, or active comparator Dependent: Adverse events, exclusion criteria of each study	Quantitative data on adverse events and qualitative data on exclusion criteria Rate of adverse events based on receiving TXA, EACA, Aprotinin. Thrombotic and seizure events by sub-group meta-analysis Reasons for exclusion	Descriptive statistics to describe study characteristics and to identify exclusion criteria of peri-op TXA RCTs in cardiac surgery	Systemic TXA did not significantly increase the risk of VTE events, MI, stroke, or seizure post-op compared with placebo, no intervention, aprotinin, and EACA No significant difference in risk of adverse events between patients receiving systemic TXA and those administered placebo. Compared to Aprotinin, TXA was associated with significant 10% decrease in risk of adverse events Most frequent reason for excluding patients: presence of major cardiac, renal, hepatic comorbidities. Second most common was use of medication affecting coagulation. Another frequent exclusion was coagulopathy. Risk of adverse events not increased in available literature according to meta-analysis. Other populations	I: Systematic review and/or meta-analysis of randomized controlled trials	**Strengths:** One of the first systematic reviews to analyze the exclusion criteria of RCTs involving TXA in cardiac surgery. Large sample size **Limits:** Though there is data on commonly excluded populations, more needs to be done due to the small amount **Risks:** Possibility of increased seizure risk **Feasibility:** Acceptable. Ease of implementation

							excluded: TXA allergy, patients with abnormal coagulation profile, and patients with history of thromboembolism		
Article 15: A Pharmacokinetic and Pharmacodynamic Investigation of an ε-Aminocaproic Acid Regimen Designed for Cardiac Surgery With Cardiopulmonary Bypass.									
Strauss, E. R., Dahmane, E., Judd, M., Guo, D., Williams, B., Meyer, M., Gammie, J. S., Taylor, B., Mazzeffi, M. A., Gobburu, J., & Tanaka, K. A. (2021). A Pharmacokinetic and Pharmacodynamic Investigation of an ε-Aminocaproic Acid Regimen Designed for Cardiac Surgery With Cardiopulmonary Bypass. Journal of cardiothoracic and vascular anesthesia, 35(2), 406–417. https://doi.org/10.1053/j.jvca.2020.07.048	To investigate the pharmacokinetics and pharmacodynamics of an e-aminocaproic acid (EACA) regimen designed for cardiac surgery with cardiopulmonary bypass (CPB).	Prospective observational study requiring blood sampling to measure EACA concentrations and fibrinolysis markers (fibrinogen, Ddimer, a2-antiplasmin, and tissue plasminogen activator-plasminogen activator inhibitor [tPA-PAI-1] complex).	Single-center, tertiary medical center. Patients who underwent cardiac surgery with CPB between 2018 and 2019 for aortic or mitral valve replacement /repair or coronary artery bypass grafting. Previous sternotomy patients were included. N= 21 6 patients had creatinine clearance (CrCL) less than 60 mL/min, with expected decreases in the clearance of EACA and D-dimer Eligible patients were adults having elective coronary artery bypass grafting (CABG), mitral valve repair or replacement (MVR), aortic valve replacement (AVR), and/or ascending aorta replacement with	Independent: Adminstration of Amicar Dependent: Fibrinolysis measurements, perioperative bleeding, and tranfusion.	Levels of the following pharmacodynamic (PD) markers were assayed: fibrinogen, D-dimer, a2-antiplasmin (A2AP), and tissue plasminogen activator (tPA)-plasminogen activator inhibitor type 1 (PAI-1) complex. Blood samples for fibrinolysis markers analysis were drawn in 3.2% sodium citrate tubes at 5 time points: (1) at baseline (before initiation of EACA infusion), (2) 5 minutes after CPB initiation, (3) 30- to-45 minutes after CPB initiation, (4) 15 minutes after protamine, and (5) 1-to- 2 hours after the end of EACA infusion.	GraphPad Prism version 8.0 (GraphPad Software, La Jolla, CA) was used for statistical analysis. Data 408 E.R. Strauss et al. / Journal of Cardiothoracic and Vascular Anesthesia 35 (2021) 406417 were assessed for normality using histograms and the ShapiroWilk test. Median values were reported because data did not fit a normal distribution. Spearman correlation coefficients were calculated, and the Mann-Whitney U test was used for data comparisons. P values less than 0.05 were considered statistically significant for all tests	The pharmacokinetics of EACA, during CPB, were described by a 3-compartment disposition model. EACA concentrations were greater than 130 mg/L in all patients after CPB and in most patients during CPB. The D-dimer level trended up and reached a peak median level of 1.35 mg/L of fibrinogen equivalence units (FEU) at 15 minutes after protamine administration. The median change in Ddimer (DD-dimer) from baseline to 15 minutes after protamine was 0.34 (0.48 to 3.81) mg/L FEU. DD-dimer did not correlate with EACA concentration intraoperatively, urine output, body weight, glomerular filtration rate, cell salvage	Level VI: single study	**Strengths:** similar dosing regimine to project site **Limits:** small sample size **Risks:** limited **Feasibility:** increased blood sampling, Price consideration of drawing fibrinolysis markers during surgery.

			anticipated time on CPB of 120 minutes or less.				volume, and ultrafiltration volume. The median 24-hour chest tube output was 445 (180-1,011) mL.		

Appendix B

Clinical Guideline Recommendation Template

Specialty CGC

Approval Month + Year

Clinical Guidance Council Guideline

Guideline Title

GUIDELINE TITLE

OhioHealth is supportive of the following guideline from XXX:

+ Guideline
    + Additional points
    + For the most up-to-date version of the guideline, visit URL

WHY?

Reason behind the approval of the guideline. What problem was identified?

MEASURES OF SUCCESS

This guideline intends to improve the delivery of patient care. While adherence to the guideline and clinical outcomes may not be tracked regularly, an improvement should be noticed in the following metrics:

+ Measure
+ Measure
+ Measure

REFERENCES

List current references used

WHAT IS A GUIDELINE?

A guideline recommends how something should be done based upon evidence-based and/or best practice (e.g., Clinical Guidelines or Drug Use Guidelines) while permitting variation according to clinical judgment and the unique facts presented.

ACTION REQUIRED

Use this as a guide for your practice. Unique circumstances and need for individualization of care may require appropriate deviation from these guidelines.

APPROVAL

This guideline was approved by the following Clinical Guidance Councils:

+ Subcouncil name, date (XX/XXXX)
+ Main CGC, date (XX/XXXX)

CONTACT

For questions, contact:
SME name, credentials
SME title
SME e-mail

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Appendix C

TXA SWOT Analysis

Strengths: • 1-A strong recommendation from Cardiac ERAS Society • Reduced blood transfusions and reoperation for major hemorrhage or tamponade • Weight-based, low-dose strategy appears to be safer • Provides alternative to EACA if medication shortage occurs	**Weakness:** • No consensus on optimal dosing • Only one patient received TXA in the data collection • Not commonly used at project site for cardiac surgery
Opportunities: • Large, double-blinded, randomized controlled trial currently being completed to identify dosing with max efficacy and minimal complications • Education for staff on TXA benefits	**Threats:** • Dose dependent adverse effects of TXA administration: stroke and seizures • Support from cardiothoracic surgeons and anesthesia staff

EACA SWOT Analysis

Strengths: • Main antifibrinolytic used at project site • Support from multiple professional organizations for routine use	**Weakness:** • Omission in cases that meet standards for administration of an antifibrinolytic • Variation in dosing • Possible subtherapeutic dosing
Opportunities: • Improve the quality and consistency of EACA dosing	**Threats:** • Support from cardiothoracic surgeons • Buy in from anesthesia to use consistent dosing

Appendix D

OhioHealth Nursing Evidence-Based Practice Committee (NEBPRC) Approval

Chris Foltz BSN, SRNA
Katonya Lawson BSN, SRNA
Otterbein University

April 29, 2021

RE: ERAS for Cardiac Surgery: Development of a Clinical Practice Guideline for Antifibrinolytic Administration in Cardiac Surgery

Dear Ms. Lawson and Mr. Foltz:

The Nursing Evidence-Based Practice Review Committee (NEBPRC) has reviewed the proposal referenced above. Clear evidence was submitted to justify both the need for the practice change and that evidence supports the proposed plan. You have adequately addressed all concerns from the pre-review and the revisions are accepted.

The NEBPRC has determine that the project proposal you submitted does not meet the Federal definition of research as cited in CFR 45-46:102. According to the Federal Code, research is defined as:

> (l) *Research* means a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes.

You have permission to develop the evidenced-based guideline as written. Upon completion of the project and before dissemination (poster or manuscript), you must submit the results so that the OhioHealth can review the presentation to ensure Health

Appendix E

Otterbein University Institutional Review Board Approval

INSTITUTIONAL REVIEW BOARD

__X__ Original Review
_____ Continuing Review
_____ Amendment

Dear Dr. Garrett,

With regard to the employment of human subjects in the proposed research:

HS # 20/21-69
Garrett, Foltz, Lawson & Sribanditmongkol: ERAS for Cardiac Surgery: Development …

THE INSTITUTIONAL REVIEW BOARD HAS TAKEN THE FOLLOWING ACTION:

We have determined that the proposed activity is not characterized as human subjects research, in that the investigators are not:

1. Obtaining information or biospecimens through intervention or interaction with the individual, and using, studying, or analyzing the information or biospecimens; or
2. Obtaining, using, studying, analyzing, or generating identifiable private information or identifiable biospecimens.

Therefore, IRB review is not required.

Date: _____ Signed: Meredith C. Frey
Chairperson

(Revised January 2019)

Appendix F

Clinical Guidance Council Recommendation Guidelines

Cardiac Surgery Anesthesia CGC — Approval Month + Year

Clinical Guidance Council Guideline
Administration Tranexamic Acid (TXA) for On-Pump Cardiac Surgery

ADMINISTRATION OF TRANEXAMIC ACID (TXA) FOR ON-PUMP CARDIAC SURGERY

Tranexamic Acid (TXA)

+ Synthetic antifibrinolytic and analog of lysine
+ Antifibrinolytic medications have been shown to decrease blood loss as well as the need for blood transfusions and reoperation

Pharmacodynamics

+ Competitively inhibits the activation of plasminogen to plasmin
+ Plasmin is responsible for degradation of fibrin clots, fibrinogen, and other plasma proteins

Pharmacokinetics

+ 100% bioavailability with IV administration
+ 95% excreted unchanged in urine
+ Half-life (IV) of 2 hours; increased in renal impairment
+ Duration of 7-8 hours
+ Administer over a minimum of 10 minutes to avoid transient lowering of blood pressure

Indications

+ Acute fibrinolytic bleeding associated with on-pump cardiac surgery
+ No current recommendations for routine use in off-pump cardiac surgery

Current OhioHealth Prescribing Guideline

+ 1g loading dose administered before sternotomy followed by a constant intravenous infusion at 400 mg/hr until sternal closure
    + Addition of 500 mg to the cardiopulmonary bypass circuit
+ Infusion rates in cardiac surgery should be lowered in renal impairment
    + Reduce by 25% if SCr 1.6-3.3; reduce by 50% if SCr 3.3-6.6; reduce by 75% if SCr > 6.6

Optimal Dosing in the Literature

+ Guidelines regarding patient blood management recommend the routine use of tranexamic acid for adult cardiac surgery, however, no consensus exists on the dosing regimen to be administered
+ Low-dose TXA, total dose approximately < 20 mg/kg, appears sufficient to reduce post-operative blood loss and blood transfusion (Zufferey et al., 2021)
    + 10 mg/kg bolus followed by 1 mg/kg/hr over 12 h
    + Single pre-operative bolus of 20 mg/kg
+ Low-dose TXA, bolus injection < 50 mg/kg or 10 mg/kg + 1 mg/kg/hr (Guo et al., 2019)
+ High dosing at approximately 100 mg/kg has little effect in reducing transfusion requirement and tends to cause more seizure attacks, though “high-dose” varies greatly in the literature (Guo et al., 2019)

Practice Change Recommendation

+ Consider lowering dosing practices of TXA to reflect literature low-dose regimen
+ 10 mg/kg pre-operative bolus + 1 mg/kg/hr over 12 h or single pre-operative bolus of 20 mg/kg

WHAT IS A GUIDELINE?

A guideline recommends how something should be done based upon evidence-based and/or best practice (e.g., Clinical Guidelines or Drug Use Guidelines) while permitting variation according to clinical judgment and the unique facts presented.

ACTION REQUIRED

Use this as a guide for your practice. Unique circumstances and need for individualization of care may require appropriate deviation from these guidelines.

APPROVAL

This guideline was approved by the following Clinical Guidance Councils:

+ Subcouncil name, date (XX/XXXX)
+ Main CGC, date (XX/XXXX)

CONTACT

For questions, contact:
SME name, credentials
SME title
SME e-mail

OhioHealth
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Clinical Guidance Council Guideline
Administration Tranexamic Acid (TXA) for On-Pump Cardiac Surgery

CAUTION/CONTRAINDICATIONS

- TXA allergy
- Caution to patients with major renal, hepatic, and cardiac comorbidities, those using medications affecting hemostasis, those with know coagulopathy, those with an abnormal coagulation profile, those with recent coronary stenting, and those with a history of thromboembolism due to commonly being excluded from TXA cardiac surgery trials.
- Sufficient data is available to inform TXA administration to patients of these common exclusion categories (Khair et al., 2019)

WHY?

The American College of Cardiology Foundation/American Heart Association, American Society of Anesthesiologists, European Association for Cardiothoracic Surgery, the Society of Thoracic Surgeons/American Association for Thoracic Surgery, and the ERAS Cardiac Surgery Society have published recommendations and guidelines for the routine use of antifibrinolytics to reduce bleeding, blood transfusions, and reoperations for on-pump cardiac surgery.

MEASURES OF SUCCESS

This guideline intends to improve the delivery of patient care. While adherence to the guideline and clinical outcomes may not be tracked regularly, an improvement should be noticed in the following metrics:

+ Consistent dosing among anesthesia providers and surgeons
+ Estimated blood loss (ml)
+ Blood transfusion requirements
+ Re-operation dues to major hemorrhage or cardiac tamponade

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Cardiac Surgery Anesthesia CGC — Approval Month + Year

Clinical Guidance Council Guideline
Administration of Epsilon Aminocaproic Acid (EACA) for On-Pump Cardiac Surgery

ADMINISTRATION OF EPSILON AMINOCAPROIC ACID (EACA) FOR ON-PUMP CARDIAC SURGERY

Epsilon Aminocaproic Acid (EACA)
+ Synthetic antifibrinolytic and analog of lysine
+ Antifibrinolytic medications have been shown to decrease blood loss as well as the need for blood transfusions and reoperation.

Pharmacodynamics
+ Competitively inhibits the activation of plasminogen to plasmin.
+ Plasmin is responsible for degradation of fibrin clots, fibrinogen, and other plasma proteins

Pharmacokinetics
+ Eliminated unchanged by the kidneys
+ Half-life= unknown
+ Peak blood levels ~ 2 hours
+ Plasma levels greater than 130mg/L are necessary to inhibit fibrinolysis.

Indications
+ Acute fibrinolytic bleeding associated with on-pump cardiac surgery
+ No current recommendations for routine use in off-pump cardiac surgery

Precautions and Contraindications
+ Loading doses and boluses should be administered over 15-60 minutes

WHAT IS A GUIDELINE?
A guideline recommends how something should be done based upon evidence-based and/or best practice (e.g., Clinical Guidelines or Drug Use Guidelines) while permitting variation according to clinical judgment and the unique facts presented.

ACTION REQUIRED
Use this as a guide for your practice. Unique circumstances and need for individualization of care may require appropriate deviation from these guidelines.

APPROVAL
This guideline was approved by the following Clinical Guidance Councils:
+ Subcouncil name, date (XX/XXXX)
+ Main CGC, date (XX/XXXX)

CONTACT
For questions, contact:
SME name, credentials
SME title
SME e-mail

Clinical Guidance Council Guideline
Administration of Epsilon Aminocaproic Acid (EACA) for On-Pump Cardiac Surgery

OhioHealth Recommended Dosing

+ 5-10 g or 75-150 mg/kg loading dose followed by 1 g/hr or 10-15 mg/kg/hr IV
+ 10 g bolus, repeated up to 3x (10 g + 10 g +10 g)
+ Max daily dose is 30 g

Optimal Dosing in the Literature

+ 10g loading dose, followed by 2g/hr infusion
  (Fergusson et al., 2008 and Levy et al., 2018)
+ 10-15mg/kg loading dose, followed by 1-2mg/kg/hr for 6 hours
  + bolus dose for bypass circuit 2-3mg/kg (Blaine et al., 2016)

Current Practice at Grant Medical Center

+ 10g bolus dose, repeated up to 2x. Variation in repeated dosing.
  + First bolus prior to bypass and second dose post bypass.

Practice Change Recommendation

+ 10g bolus dose, followed by an infusion at 10-15mg/kg/hr
+ Maintains consistency among providers
+ Eliminates missing second bolus after bypass
+ Helps maintain steady state of drug concentration in blood

WHY?

The American College of Cardiology Foundation/American Heart Association, American Society of Anesthesiologists, European Association for Cardiothoracic Surgery, the Society of Thoracic Surgeons/American Association for Thoracic Surgery, and the ERAS Cardiac Surgery Society have published recommendations and guidelines for the routine use of antifibrinolytics to reduce bleeding, blood transfusions, and reoperations for on-pump cardiac surgery.

Clinical Guidance Council Guideline
Administration of Epsilon Aminocaproic Acid (EACA) for On-Pump Cardiac Surgery

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