Study Title: Anticoagulation in Emergency General Surgery: Who bleeds more? The ACES TRIAL

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Background and significance:

Emergency general surgery (EGS) represents illnesses of diverse pathology with urgent/emergent treatment needs being the common denominator.¹ A characteristic feature of EGS is its limitation in patient preparation. It is difficult and often impossible to eliminate certain patient dependent factors to reduce the operative risk. It has been reported that the annual case rate in the EGS population is (1,290 per 100,000) higher than the sum of all cancer diagnoses.¹ The EGS burden is substantial and continues to increase. The elderly patient population represents 48% of the overall EGS population. With the increase in the prevalence of atherosclerotic disease in the elderly there has been an increase in the use of antiplatelets and anticoagulants.^{2,3}

Warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation, and historically has been the drug of choice for treatment of atrial fibrillation, deep venous thrombosis and pulmonary embolism. Nonetheless, the narrow therapeutic window and frequent lab monitoring have limited the use of Warfarin in recent years.

Direct oral anticoagulants (DOACs), are relatively novel and have increased in popularity. DOACs offer clinical advantages over warfarin, such as increased risk reduction in stroke, rapid onset/offset of action, fewer drug interactions, and predictable pharmacokinetics without the need for routine monitoring of coagulation status.⁴ On the other hand, with the exception of dabigatran whose antidote idarucizumab was approved in 2015, the lack of access to other reversal agents, due to cost constraints and availability, increase bleeding risk in the acute setting.

In clinical trials evaluating efficacy and major hemorrhage risk in patients treated with DOACs vs. warfarin for atrial fibrillation, the incidence of clinically relevant bleeding with DOACs was shown to be comparable to, or lower than warfarin (depending on dose). ⁵⁻⁸Kobayashi et el. evaluated the bleeding risk of Warfarin and antiplatelets vs. DOACs in the trauma population and concluded that patients taking DOACs were not at higher risk for intracranial hemorrhage, intracranial hemorrhage progression or death when compared to patients on traditional oral anticoagulants and antiplatelets.⁹On the other hand a recent study by Zeeshan showed that the use of DOACs generally carried a higher risk of bleeding and need for operative intervention in patients with intracranial hemorrhage when compared to those taking warfarin.¹⁰

While DOACs are increasing in use in the EGS patient population, the risk of bleeding and the reversal of these agents to reduce hemorrhage is still evolving. Given the paucity of data regarding the impact of DOACs in this patient population, it becomes empiric to identify bleeding patterns and outcomes in the EGS population taking DOACs. We hypothesize that patients taking a DOAC will have a higher bleeding incidence and need for an unplanned intervention secondary to hemorrhage in EGS patients undergoing an urgent or emergent operation when compared to patients taking warfarin and antiplatelets.

Specific Aims of MCT:

Primary Aim:

To determine the bleeding risk and need for unplanned intervention (operative, interventional radiology, ultrasound aspiration) secondary to hemorrhage or hematoma of EGS patients taking a DOAC undergoing an urgent or emergent operation compared to those taking a traditional anticoagulant and antiplatelet therapy based on blood loss and transfusion requirements.

Secondary Aims:

1. To evaluate the mortality rate between those taking a DOAC vs warfarin and antiplatelets

2. To evaluate the rate of post thrombotic complications over the course of hospitalization **Experimental Design/Methods:**

Design

Prospective Observational

Inclusion criteria:

All patients who are confirmed to be taking dabigatran,rivaroxaban, apixaban, warfarin and antiplatelet therapy (aspirin, clopidogril, ticagrelor) undergoing an urgent or emergent surgical intervention by the emergency general surgery service within 24 hours of arrival to the hospital will be enrolled.

Exclusion criteria

Exclusion criteria will include those who are prisoners, pregnant, ward of the state, less than 18 years of age and those who received an index operation at an outside facility and were transferred will be excluded.

Therapeutic intervention:

This is a prospective observational study. The decision and time to operation will be the sole responsibility of the attending acute care surgeon. There will be no guidelines or protocols used in order not to influence surgeon decision making.

Outcome measures:

Primary outcome

To determine the bleeding risk and need for unplanned intervention (operative, interventional radiology, ultrasound aspiration) secondary to hemorrhage or hematoma of EGS patients taking a DOAC undergoing an urgent or emergent operation compared to those taking a traditional anticoagulant or antiplatelet therapy based on blood loss and transfusion requirements.

Secondary outcome

The secondary outcomes will examine indication for operation, time to operative theater, intraoperative time, surgical site infections (superficial, deep, organ space), incidence of open abdomen, post-operative transfusion requirement, post-operative thrombotic complications, intensive care unit and hospital length of stay, discharge disposition, and mortality.

Variables:

- Demographics:
- Age
- Sex
- Race
- History:
- Diabetes Mellitus
- Liver disease
- Cancer
- Chemotherapy
- AIDS
- Chronic kidney disease

- Congestive heart failure
- Myocardial infarction
- COPD
- PVD
- Stroke
- Dementia
- Hemiplegia
- Rheumatic or Connective tissue disease
- Peptic ulcer disease
- Pre-op:
- Indication for operation and AAST grade
- DOAC/AC/Antiplatelet (dabigatran, rivaroxaban, apixaban, warfarin, aspirin or clopidogrel, ticagrelor)
- Time to OR
- Last documented DOAC/AC/Antiplatelet
- Reversal products given before OR
- Time to targeted reversal agent
- WBC
- Hgb
- Hct
- Plat
- pH
- Base Excess
- PT
- PTT
- INR
- Lactate
- Fibrinogen
- Creatinine
- Bilirubin
- TEG
- Heart rate
- Blood pressure
- Pulse
- Temp
- GCS
- Intubated
- Continuous vasopressor use
- Intra-op:
- Operative time
- Intra-operative colloids
- Intra-operative crystalloids
- Intra-operative reversal agent given
- Intra-operative vasopressors needed
- Recorded intra-op temp <36
- Estimated blood loss
- WHO 5 point bleeding scale
- Use of intraoperative hemostatic agents
- Open abdomen
- Open abdomen information:
- Indication for open abdomen
- Number of re-explorations until closure
- Primary fascial closure achieved
- Skin closed after fascial closure
- Post-operative:
- Post-op PRBC
- Post-op FFP
- Post-op platelets
- Post-op reversal agents
- Documented transfusion reaction

- Surgical site infection
- Post-op hematoma (superficial, deep, organ space)
- Post-op hemorrhage
- Unplanned reoperation/intervention (IR, US aspiration, OR)
- DVT PPX started (Post-op day)
- Therapeutic AC started (post-op day)
- Antiplatelet started (post-op day)
- Enteric fistula
- AKI
- ARDS
- DVT
- PEStroke
- Strol
 MI
- IVII
 ICU LOS
- Hospital LOS
- Disposition (home, acute, snf, AMA, hospice, morgue)
- If death, document the cause of death as indicated on the death certificate

Data collection and statistical analysis:

Data collection tool: Each institution will prospectively collect data points (demographics, management variables, outcomes) on a standardized form. Investigators at each institution will enter the collected data into the Research Electronic Data Capture (REDCap) portal. REDCap is a data collection tool that relies on a thorough study-specific data dictionary designed by the PI of the study. REDCap was developed specifically around HIPAA-Security guidelines and is implemented and maintained according to University of Maryland guidelines. Accordingly, REDCap servers are securely housed in an on-site limited access data center. All web-based information transmission is encrypted. The data is all stored on a private, firewall-protected network. All users are given an individual user ID and password and their access is restricted on a role-specific basis.

Statistical analysis: The goal of this prospective observational study is to determine the bleeding risk and need for unplanned interventions due to bleeding in EGS patients taking DOACs vs. warfarin and antiplatelets which will be determined on bivariate analysis. Descriptive variables to be analyzed will include demographic and clinicopathologic variables. Continuous data will be compared using the Student's t test for normally distributed variables and the Wilcoxon rank-sum test for non-normal data; categorical variables will be compared using Pearson's chi-square, and Fisher's exact test. Variables that are statistically significant and clinically important will be entered into a logistic regression model to determine independent risk factors that influence bleeding and the need for unplanned interventions. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) will be presented. P-values below 0.05 will be considered statistically significant (corresponding to a 95% CI for the OR that does not include 1.00)

Given the lack of data regarding bleeding progression and complications in the EGS patient population taking Warfarin and DOACs, our sample size and power estimates are based on the medical and trauma literature reports of bleeding and complication rates in patients taking warfarin and DOACs. We have performed a power analysis with the assumption that 2 times as many patients will be taking antiplatelets and Warfarin compared to the DOAC group with difference in bleeding and complications ranging from 7-15%. We anticipate needing up to

190 patients in the DOAC group and 380 patients in the antiplatelet/warfarin group to achieve a power of 80% and an alpha value of 0.05.

Total number of patients = 570. With recruitment of 12 institutions over an 18-month period, the aim would be for approximately 48 patients from each institution (3 per month).

The Principal Investigators at the University of Maryland Medical Center will procure and analyze the data, which will then be distributed for review by all co-authors. Statistical analyses will be performed in conjunction with a statistician at the R Adams Cowley Shock Trauma Center.

Consent for Procedures:

A waiver of informed consent will be requested as patients will be managed according to institutional patient management protocols. No alterations of patient care will occur due to this study.

Risk/Benefit Analysis

This is a prospective observational study designed to record data on patients managed according to institutional patient management protocols. There is no intervention conducted in this trial therefore the greatest risk involved in participating is a breach of confidentiality. This risk will be minimized by de-identification of all patient information and storing all study data on a secure password protected server that is only accessible by authorized study personnel. Given the lack of data related to the subject, the primary benefit is delineation of the bleeding risk and outcomes in the EGS patient population taking DOACs

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