

SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT: Identifying and Comparing Determinants of Adverse Outcomes in DOAC- and Warfarin-treated Patients who need an Urgent/Emergency Surgery

Subcommittee: Perioperative and Critical Care Thrombosis and Haemostasis

Person responsible (Chair / Principal Investigator): James Douketis, MD

Description Abstract

State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Suggested length is 2-3 paragraphs.

3.0 Study Design, Patient Population and Methodology

Study design and justification for this design?

- A prospectively-recruited patient registry of patients who are receiving a DOAC or VKA (warfarin) who require an urgent/emergency surgery.
- This design is suitable to gather data in an exploratory manner so as to investigate determinants of perioperative adverse events and to identify which of these (if any) are modifiable. The data gained from this study will generate hypotheses for subsequent prospective studies that would potentially assess different management strategies in this clinical setting (e.g., use of DOAC antidote- vs. PCC-based management).

Study outcomes

- Primary outcomes: 30-day perioperative incidence of arterial thromboembolism (stroke, systemic embolism, myocardial infarction), venous thromboembolism (deep vein thrombosis, pulmonary embolism), ISTH-defined major bleeding, and mortality.
- Secondary outcomes: to encompass utilization of: i) non-specific reversal agents (e.g., prothrombin complex concentrates, FEIBA, tranexamic acid, etc.); ii) specific reversal agents (e.g., idarucizumab, andexanet- α , vitamin K); and iii) other blood products (e.g., packed red blood cells, platelets, fresh frozen plasma, cryoprecipitate, fibrinogen, etc.).

Design and methodology (Data expected to collect, sample size and statistical analysis):

Describe concisely the research design and methods for achieving these goals. Suggested length 2-3 paragraphs

Study sample size and statistical analysis plan

- Given the exploratory, hypothesis-generating nature of the proposed study, the sample size is one of convenience, comprising **200** DOAC- and **200** warfarin-treated patients.
- Descriptive statistics (mean and standard deviation [SD] for normally distributed findings, median and inter-quartile [IQR] range for skewed findings, proportions and associated 95% confidence intervals [CIs]) will be used to describe the baseline patient characteristics, incidence of outcomes, and resources utilized.
- Multivariable, propensity-match, regression analysis will be used to identify independent determinants of: i) thromboembolic outcomes; ii) major bleeding; and iii) mortality.

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These will then be separated as to whether they are non-modifiable (e.g., age, sex) and modifiable (e.g., transfusion requirements) determinants.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Inclusion criteria: i) patient is receiving a DOAC (dabigatran, rivaroxaban, apixaban or edoxaban) or a VKA (warfarin) for stroke prevention atrial fibrillation/flutter, treatment or secondary prevention of venous thromboembolism or treatment of arterial vascular disease; ii) requires an urgent (within 24 hours) or emergency (within 8 hours) surgery; and iii) patient or delegate is willing and able to provide written informed consent and agree to telephone follow-up for 1 month after recruitment.

Exclusion criteria: i) patient receiving a non-warfarin VKA (to allow meaningful comparisons of outcomes and management between DOACs and VKAs).

Expected timeline:

- Project stage/set up: the Clinical Coordinating Center (at McMaster University, Hamilton, Canada) has been retained to carry out the study
- Launch: a planning meeting is scheduled for Jan 15, 2019 to launch the study and engage clinical sites (core list derived from PAUSE study clinical sites)
- Duration: we plan a 3-year period of study
- Finalization/analysis: planned analyses are listed in the protocol
- Reporting: any publications, comprising abstracts and peer-reviewed papers will be targeted towards ISTH Congresses and the Journal of Thrombosis and Haemostasi
- Expected outcomes (ie. publications): We aim to develop an “original research” paper submitted for peer-reviewed publication
- Publication type (SSC Communication, Guidance document or original article): original research

Description of project set/up and management, needed infrastructure and resources (summary):

- The study will be managed by the McMaster Centre for Transfusion Research (MCTR), which has considerable experience in cost-efficient coordination of multicenter trials.
- The infrastructure (i.e., support staff, web-based data collection system) is already in place as the MCTR is the coordinating center for the multi-center PAUSE study.
- Data will be gathered by MCTR with user-friendly (i.e., tick-boxes) electronic case report forms that will require minimal time for completion, to facilitate patient recruitment.

References:

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10. Kaatz S, Douketis JD, Zhou H, Gage BF, White RH. Risk of stroke after surgery in patients with and without chronic atrial fibrillation. *J Thromb Haemost*. 2010;8(5):884-90.
11. Pollack CV, Jr., Reilly PA, van Ryn J, Eikelboom JW, Glund S, Bernstein RA, et al. Idarucizumab for Dabigatran Reversal - Full Cohort Analysis. *N Engl J Med*. 2017.
12. Clark NP, Douketis JD, Delate T, et al. Risk factors for bleeding in the perioperative management of patients on warfarin: A sub-analysis of the BRIDGE trial. *Am J Cardiol* 2017 (in press).