Title: Bleeding and thrombotic events after resumption of oral anticoagulants following gastrointestinal bleeding

Subcommittee on Control of Anticoagulation

Person responsible (Chair / Principal Investigator): Marcello Di Nisio

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.

Objectives: To evaluate 1) the clinical and endoscopic characteristics of patients who experience gastrointestinal bleeding while receiving oral anticoagulant treatment with direct oral anticoagulants or vitamin K antagonists, 2) the type and dose of anticoagulant treatment resumed after bleeding, 3) the incidence of recurrent gastrointestinal bleeding and thromboembolism.

Design: Multicenter, international, retrospective study.

Study population: Patients who develop upper or lower gastrointestinal bleeding while on oral anticoagulants for the treatment or secondary prevention of VTE, prevention of stroke or peripheral embolism in AF or mechanical heart valves.

Study outcomes: The primary outcomes of interest are ischemic stroke, systemic embolism, VTE, and recurrent gastrointestinal bleeding. Secondary outcomes include major bleeding other than gastrointestinal, re-hospitalization, and death from any cause. Information on thromboembolic events and recurrent bleeding occurring after the index gastrointestinal bleeding will be retrieved from patients charts review and contact with treating physicians to the longest possible follow-up.

Study sample, feasibility, and analysis plan: We plan to enroll a minimum of 500 patients in approximately 5 centers. Kaplan-Meier curves will be constructed separately for bleeding and thromboembolism from the moment of the first gastrointestinal bleeding as well as from the moment of anticoagulation resumption and used to calculate cumulative incidences. Cox proportional hazards models for time to recurrent gastrointestinal bleeding, thrombosis, and death will be constructed with resumption of DOACs or VKAs as a time-varying variable adjusting for potential confounders.
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

Design: Multicenter, international, retrospective study.

We will collect information on patient characteristics (e.g. age, sex), bleeding site and source, management of bleeding (e.g. endoscopy, plasma or blood transfusion, administration of PCC or antidotes), intensive care unit admission, length of hospital stay, concomitant target medications (e.g. aspirin and non-steroidal anti-inflammatory drug), low-molecular-weight heparin or other parenteral anticoagulants use after the index gastrointestinal bleeding, duration of anticoagulant therapy interruption, type and dose of anticoagulant resumed after gastrointestinal bleeding.

A web-based database will be available to all participating centers for data collection.

Study outcomes

The primary outcomes of interest are ischemic stroke, systemic embolism, VTE, and recurrent gastrointestinal bleeding. Secondary outcomes include major bleeding other than gastrointestinal, re-hospitalization, and death from any cause.

Validation of study outcomes requires objective evidence of either clinically overt gastrointestinal tract bleeding (e.g., visualization of blood in stool, vomit, or gastric aspirate; evidence from endoscopy or colonoscopy) or thrombosis (e.g., positive computed tomographic scan, ventilation-perfusion scan, or ultrasonography). Date and cause of death will be ascertained from death certificates and medical record review. All study outcomes will be centrally adjudicated.

Study sample, feasibility, and analysis plan: Continuous variables will be presented either as means with standard deviations or as medians and interquartile ranges (IQR), as appropriate. They will be analyzed with two-sample t-tests for normally distributed variables and Mann-Whitney test for skewed distributions. Binomial data will be presented as proportions, and compared using Chi-square or Fisher’s exact test, as appropriate. A p-value less than 0.05 will be considered statistically significant in a two-sided test. Kaplan-Meier curves will be constructed separately for bleeding and thromboembolism from the moment of the first gastrointestinal bleeding as well as from the moment of anticoagulation resumption, and used to calculate cumulative incidences. Cox proportional hazards models for time to recurrent gastrointestinal bleeding, thrombosis, and death will be constructed with resumption of DOACs or VKAs as a time-varying variable adjusting for potential confounders. When a patient resumes DOACs or VKAs at a certain time point, the period before resumption will contribute to the time at risk of the group who does not resume anticoagulation after the index gastrointestinal
bleeding. In other words, the period of time for all patients not on anticoagulation (irrespective of the timing of DOAC or VKA resumption) will be analyzed together as the “unexposed period”, and the period of time for all patients on anticoagulation (after resumption of DOACs or VKAs) will be analyzed together as the “exposed period”. Patients will be censored in the analysis at the end of the study period, or at the time of having thromboembolism, recurrent gastrointestinal bleeding, or death. If patients are lost to follow-up, they will be included in survival analysis up to the point that medical records are no longer available.

In the absence of adequate information from prospective studies, a formal sample size calculation is not feasible. The current study aims to enroll an initial cohort of about 500 patients with upper or lower gastrointestinal bleeding during anticoagulant treatment.

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

Suggested length 2-3 paragraphs

Study population

Patients who develop upper or lower gastrointestinal bleeding while on oral anticoagulants for the treatment or secondary prevention of VTE, prevention of stroke or peripheral embolism in AF or mechanical heart valves. Patients resuming DOAC will be compared with those who resumed VKAs or did not resume any anticoagulant treatment. All patients with a gastrointestinal bleeding which occurred in the period between January 2014 to August 2017 are eligible.

Participating Centers

Italy

University G. D’Annunzio, Chieti, Italy: Di Nisio M, Ferrante N, D'Addezio A, Porreca E
SSC Subcommittee Project/Collaborative Project

University of Insubria, Varese, Italy: Ageno W

The Netherlands

Academic Medical Center, Amsterdam, The Netherlands: Coppens M, Bavalia R, van Es N

Canada

University of Ottawa, Ottawa: Carrier M

McMaster University, Hamilton, Canada: Schulman S

Expected timeline:

- Ethical committee submission: June 2018
- Launch: July 2018
- Duration: 6 to 12 months
- Finalization/analysis: March 2019
- Reporting: May 2019

Publication type (SSC Communication, Guidance document or original article):

Original article


