NAME OF PROJECT: Biomarkers for and prediction of venous thromboembolism after stroke
Subcommittee: Predictive and Diagnostic Variables in Thrombotic Disease
Person responsible (Chair / Principal Investigator): Vania M. Morelli

Description Abstract

Patients with acute ischemic stroke (AIS) are at risk of developing venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) [1]. Although clinically overt PE may occur in only 1% of patients after AIS [1,2], PE is associated with considerable morbidity and mortality in stroke patients [2]. The risk of VTE is highest in the initial 3 months following AIS and declines rapidly thereafter [3].

Decisions on pharmacological prophylaxis of VTE and its duration after AIS could be a dilemma in the clinics, as the benefits of anticoagulation in reducing the VTE risk may be offset by bleeding complications [4]. Identification of patients at high risk of VTE after AIS would form the basis for targeted, individualized thromboprophylaxis. However, current data on VTE prediction in stroke patients are scarce, and prediction models based on clinical factors alone discriminate poorly between stroke patients at high and low risk of VTE [5].

Therefore, the overall aim of this project is to identify and combine the best predictors for VTE after AIS in order to improve patient stratification and aid clinical decisions on therapeutic intervention, which may contribute to reduce the incidence of VTE in stroke patients. This project will be developed in phases. As a first step, a systematic review of existing literature on clinical factors and biomarkers for VTE after AIS will be carried out to inform the main gaps in knowledge related to the topic. The systematic review will help to direct further research efforts aimed at identifying clinical factors and biomarkers that can be used to develop a risk prediction model for VTE after AIS in an adult population.

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

Step 1

• To launch the first step, a protocol intended to provide the rationale and pre-planned methodological and analytic approach of the systematic review will be drafted according to PRISMA 2015 for protocols guidelines [6].

• The systematic review will focus on cohort studies comprising an adult population with AIS, with an objectively confirmed DVT of the lower limbs (asymptomatic and symptomatic events) or PE as the main outcome. Pre-specified candidate predictors for VTE occurrence after AIS will be sought (e.g. stroke severity scores, stroke-related complications, and markers of coagulation and inflammation). If appropriate, statistical techniques to combine and summarize the results of multiple studies will be carried out.

• Findings of the systematic review will be particularly relevant to highlight those potential predictors requiring investigation in further steps of the project.

Step 2

• Data from population-based cohort studies will be used. In a nested case-control study derived from one or more cohorts, we will identify individual predictors for VTE after AIS that will be used to build a prediction model. The final model will be externally validated in a nested case-
SSC Subcommittee Project/Collaborative Project

control study derived from other cohort studies. In this step, we initially plan to use data from the Tromsø Study and the Nord-Trøndelag Health Study (HUNT).

- Nested case-control design: all subjects with VTE within 6 months after AIS will be included as cases (i.e. the Tromsø study, 50 cases; HUNT study, 100 cases). For each case, we will randomly sample 4 stroke patients without VTE matched on age, sex and stroke-year (incidence density sampling).
- Data on stroke type and stroke-related clinical factors will be collected using the stroke registries, and by systematic review of medical records. Plasma and DNA samples collected at baseline will be used to assess protein and genetic biomarkers.
- Models will be built using logistic regression, and their performance will be assessed by discrimination and calibration measures.
- Population-based cohorts with validated information on stroke, VTE, and biological material (i.e. DNA and plasma) are invited to join.

Step 3

- As a future perspective, we plan a study design involving a cohort of hospitalized patients with AIS, with blood samples collected shortly after acute stroke. Such design may offer a unique opportunity to perform an extensive investigation of biomarkers potentially modifiable by the stroke event that have the ability to predict VTE. DVT of the lower limbs will be expected to occur in 11%-14% of patients within 10 days after acute stroke when screening with radiological procedures is applied, with the vast majority of the events being asymptomatic [7].

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):
The study population is described in the section above.

Expected timeline:
- Project stage/set up: Planning stage
- Launch: August 2019
- Duration: 4 years (step 1: 2020-21; step 2: 2020-22; step 3: 2020-23)
- Finalization/analysis: 2023
- Reporting: Scientific publications

Expected outcomes (ie. publications): 3-4 scientific papers are expected to be published
- Publication type (SSC Communication, Guidance document or original article):
  SSC Communication and original article

Description of project set/up and management, needed infrastructure and resources (summary):
- The project will be led by Vania M. Morelli with partners from the Faculty of Health Science, UiT-The Arctic University of Norway.
- We would like to establish international collaboration, and invite researchers with interest and expertise in the field of our project to become partners in any of the proposed steps/phases.

References: