SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT

Identification of novel biomarkers for venous thromboembolism recurrence
Subcommittee Predictive and diagnostic variables in thrombosis

Person responsible (Chair / Principal Investigator): Pierre-Emmanuel Morange

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease and a leading cause of death and disability worldwide. The economic impact of VTE is substantial, for example, annual total cost burden to the UK of management of VTE is estimated at approximatively £640 million. Recurrent VTE events are associated with 21% greater cost compared with the initial event.

About 50% of VTE are unprovoked, i.e., they occur without clear external factors like surgery, trauma, immobilization, hormone use or cancer. About 35% of these patients will face a recurrent event after the usual three to six-month course of anticoagulant treatment and current guidelines recommend the use of prolonged- most often life-long- treatment in these patients (1). Anticoagulant treatment is associated with a risk of major bleeding of about 3% per patient-year for the exposed patients and with high cost for the society. Current clinical rules designed to stratify patients according to their risk of recurrence, do not allow reducing the proportion of patients receiving prolonged anticoagulant treatment.

In plasma, the integrated effects of genetic, environmental and acquired factors that influence the risk of thrombosis are reflected in the circulating molecule profile. Currently, the only plasma biomarker routinely used for VTE is D-dimer, a split product from the cross-linked fibrin clot, which has low specificity. Several prediction models have been designed to assess the risk for recurrence in patients with a first episode of unprovoked VTE. For example, the ‘HERDOO2 risk score’ is based on clinical data and D-dimer measurement (2,3). The score identifies patients with a high risk of recurrence with a high sensitivity. However, it lacks specificity and only holds in women. The score identifies about 75% of patients as having a high risk of recurrence, whereas only 30% will eventually experience a recurrence. Consequently, current risk models result in the overuse of lifelong anticoagulant treatment that is associated with an increased risk of bleeding and unnecessary costs as the majority of patients will never experience a recurrent event. Thus, there is an urgent need to develop better predictive biomarkers with high sensitivity and specificity for accurate identification of patients who will develop a recurrence to avoid unacceptably high risk of debilitating iatrogenic complications in patients at low risk of recurrence.

A mandatory step before embarking into the search of novel biomarkers for VTE recurrence lies in establishing an exhaustive and accurate list of robust factors known to be associated with the risk of recurrence. Once this step is completed, it is then possible to search for additional predictive biomarkers using for example cutting-edge technologies that allow the profiling of molecular determinants in easily accessible body fluids (eg plasma, serum, whole blood).
SSC Subcommittee Project/Collaborative Project

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

To reach our goal, the project will include 2 steps:

Step 1: Conduct a meta-analysis/systematic review of published data to identify an unmet need for new biomarkers/prediction model.

A systematic review, aimed at providing a complete, exhaustive summary of current literature relevant to biomarkers associated with VTE recurrence will be performed.
- We will first perform a thorough search of the literature for relevant papers using PubMed, Web of Science...
- We will then perform a meta-analysis to combine results of eligible studies.

Step 2: Invite scientists with already existing bioresources to share their samples in order to test for the association of novel molecular determinants with VTE recurrence, and to participate in a new study with the aim to identify new biomarkers and develop new prediction models.

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

For step 2, we will invite scientists with already existing data/biosamples to participate in a new study with the aim to identify new biomarkers and develop new prediction models. For this second step we will invite all cohorts with information on recurrent VTE and for which biosamples are available for new measurements or have already been phenotyped but not yet published to join an international effort to share expertise and data. These cohorts include non exhaustively MARTHA (D Tregouet), INVENT (N.Smith), MEGA (F Rosendaal, A van Hylckama Vlieg), TROMSO (JB Hansen, S Braekkan), VIENNA (S Eichinger, P Kyrle)…

We will work with the SSC genomics (particularly with the co-chair DA Tregouet) to determine which of the identified candidates are likely causal biomarkers of the recurrence risk, through Mendelian Randomization (MR) techniques. We will approach consortia that would have performed GWAS on the identified phenotypic candidates (for example D-dimers level) and will ask for associated GWAS summary statistics to perform two stage MR. In case no large GWAS has been performed on given phenotypic candidates, such GWAS will be performed in the available cohorts contributing to the proposed SSC project that would have been genome wide genotyped and measured for the traits. Some of the allocated funds may be used to genotype/phenotype some cohorts/samples where necessary data are missing. This would enable us to perform single MR.
SSC Subcommittee Project/Collaborative Project

Expected timeline:

- Project stage/set up
  - Launch: Fall 2019
  - Duration: 3 years
  - Finalization/analysis: Fall 2022
  - Reporting: Spring 2023

Expected outcomes (ie. publications):

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

We plan to write at least 2 articles:

- The first on the meta-analysis/systematic review on existing data might be a SSC Communication type paper within the Journal of Thrombosis and Haemostasis
- The second paper will be an original article in a high impact journal.

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

The funding will be used to:

- organize a 3-day brainstorming meeting with the partners to decide upon which identified candidate biomarkers should be studied forward and metaanalyzed.
- measure relevant biomarkers in prospective cohorts in which these biomarkers are missing
- pay the cost of articles publishing (at least 2)

References