SECRETO Newsletter

March 2019

Welcoming new SECRETO Sites

We are happy to welcome Tartu and Vilnius to the SECRETO team, with congratulations for starting participant recruitment! The study is now enrolling participants at 17 sites, with more sites to be opened during this spring.

Tartu University Hospital
Department of Neurology

From left to right: Dr. Janika Kõrv, MD, PhD, Associate Professor, neurologist; Ester Vatsk, head nurse and study coordinator; Dr Riina Vibo, MD, PhD, research fellow and neurologist; Dr Liisa Kõrv, MD, resident of neurology.

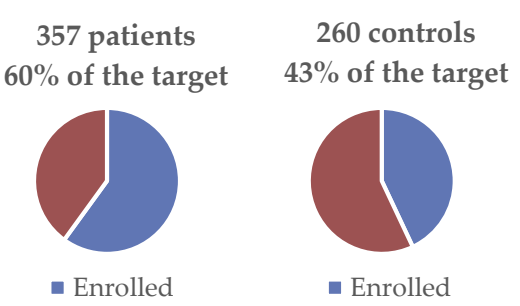
Vilnius University Hospital Santaros klinikos
Department of Neurology

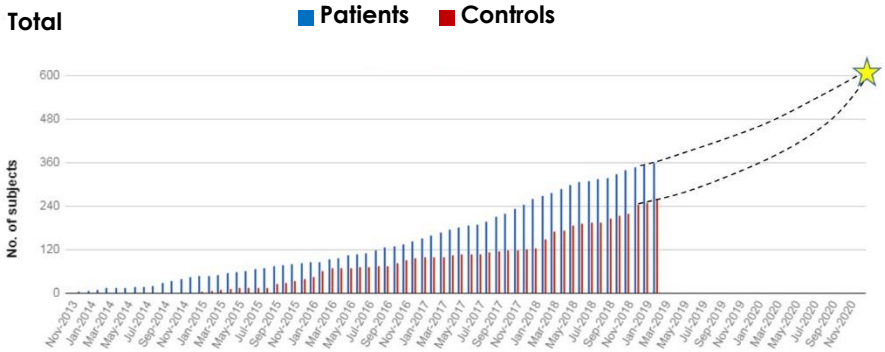
Front line (sitting), from left to right: Jurgita Valaikiene; Aleksandra Gavrilova.

Standing, from left to right: Rytis Masiliunas, Kristina Ryliskiene (Principal Investigator), Dalius Jatuzis.

Recruitment

Recently, the recruitment pace of control subjects has been very good. Please keep up the good work and actively continue to screen for patients as well as enroll controls so that we can achieve our goal of 600 patients and 600 controls by the end of 2020. By looking at the recruitment trajectories, this is a feasible goal, but achieving it is dependent on your active contribution!





SECRETO at ESOC in Milan

We are planning of having a short SECRETO investigator meeting during the ESOC to discuss study progress, analysis plans, and interim results (ongoing hypercoagulation analysis). The time and place will be announced shortly.

Two e-posters by the SECRETO Consortium have been approved to be presented at the ESOC:

Title: *Association between early-onset cryptogenic ischemic stroke and migraine subtypes in the SECRETO study*
Poster Reference: *AS22-010*
Presenter: *Nicolas Martinez-Majander*

Title: *Abdominal obesity increases the risk of cryptogenic ischemic stroke in young adults: The SECRETO study*
Poster Reference: *AS23-010*
Presenter: *Nina Jaakonmäki*

Recruitment of patients with other findings of uncertain causality

There are a number of findings that may arise during diagnostic work-up, of which causality is uncertain and systematic data of these would be desirable. Examples of such conditions are summarized below.

Recruitment of patients with PFO

Patients with PFO are included in SECRETO. Please find attached a recent position paper by a multidisciplinary panel of PFO experts published in the European Heart Journal. The panel suggests that when a PFO is thought likely to be implicated in a cryptogenic stroke, the event should be classified as a PFO-related stroke rather than a cryptogenic stroke. However, the panel emphasized the limited evidence on the pathogenic mechanisms on thromboembolism related to PFO and the need to identify new high-risk PFO phenotypes as well as search additional risk factors that would help in prediction of events (Pristipino et al. Eur Heart J 2018, DOI: 10.1093/eurheartj/ehy649).

Therefore, we are going in the right direction in SECRETO and should continue including all patients with PFO, irrespective of associated features and possibly scheduled PFO closure. Only by doing so, we are able to gather a large amount of data that will help elucitating the ultimate mechanisms of PFO-related stroke and assessing its prognosis.

Conditions and findings when a patient could be included

Large-artery findings of uncertain or unknown causality

- Atherosclerotic carotid or vertebral artery plaque or low-grade stenosis (<50%) in a relevant artery without an attached luminal thrombus.
- Atherosclerotic stenosis (any degree) in intracranial or extracranial artery contralateral to the brain infarction or in the opposite circulation territory (either posterior or anterior circulation), i.e. in irrelevant artery.

Aortic arch plaques ≤4 mm in thickness without a mobile component.

- Intracranial or extracranial artery stenosis or occlusion of unknown etiology.
- Carotid web.

Echocardiography findings of uncertain causality or unknown etiology

- Patent foramen ovale (PFO), irrespective of the ROPE score.
- Atrial septal aneurysm (ASA).
- PFO with ASA.
- Atrial septal defect, which is not associated with other congenital cardiac pathology with high primary risk for stroke.
- Mitral annular calcification or calcified aortic valve.
- Isolated left atrial smoke (no mitral stenosis or atrial fibrillation).
- Intracardiac thrombus without underlying causal structural pathology other than PFO/ASA or arrhythmia.

Possible or probable paradoxical embolism

- PFO plus deep venous thrombosis/pulmonary embolism preceding the stroke.
- PFO plus deep venous thrombosis/pulmonary embolism diagnosed after the stroke.

Small-vessel occlusion of unknown etiology

- MRI-DWI imaging evidence of a single clinically relevant acute infarction less than 20 mm in greatest axial diameter within the territory of basal ganglia, cerebellum, or pons penetrating arteries in the absence of any other pathology in the parent artery at the site of the origin of the penetrating artery (focal atheroma, parent vessel dissection, vasculitis, vasospasm, etc.) in a patient without known or newly diagnosed hypertension, diabetes or genetic small-vessel disease on initial hospitalization. Radiologic features suggestive of small-vessel disease include (1) one or several old or silent lacunar infarcts in territories different from the index stroke, (2) leukoaraiosis on MRI (FLAIR, T2), (3) microbleeds on MRI (T2* or SWI), and (4) dilatation of the perivascular spaces on MRI.

Examples of other conditions of uncertain causality

- Thrombocytosis without known essential thrombocytosis.
- Presence of any antiphospholipid antibody (lupus anticoagulant, and anticardiolipin-IgG and 2-glycoprotein-IgG antibodies) without existing diagnosis of antiphospholipid antibody syndrome according to current criteria. Due to the uncertainty of causality, the patient should be included and followed-up even if criteria for antiphospholipid syndrome were fulfilled at any later time point.
- Genetic coagulopathies: e.g. deficits of antithrombin, protein C, or protein S, elevated factor VIII, factor V G1691A mutation, factor II G20210A mutation, factor XIII mutation, familial dysfibrinogenemia, plasminogen deficiency, hyperhomocysteinemia (MTHFR C677T mutation).
- Oral contraceptive use or hormone replacement therapy.
- Inflammatory bowel disease.
- Stroke in a patient with migraine, even if IHS criteria was met for migrainous infarction: The present attack in a patient with migraine with aura is (A) typical of previous attacks except that one or more aura symptoms persists for >60 minutes, (B) neuroimaging demonstrates ischemic infarction in a relevant area, and (C) the infarction is not attributed to another disorder.