

Supplemental Table I. Examples of findings or conditions when the patient usually is eligible for SECRETO.

Examples of large-artery atherosclerosis of uncertain causality

Atherosclerotic carotid or vertebral artery plaque or low-grade stenosis (<50%) in a relevant artery
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

Examples of cardiac findings of uncertain causality or presumed paradoxical embolism

Patent foramen ovale (PFO)
Atrial septal aneurysm (ASA)
PFO with ASA
Atrial septal defect not associated with other congenital cardiac pathology with high primary risk for stroke
Mitral annular calcification or calcified aortic valve
Isolated left atrial thrombus (no mitral stenosis or atrial fibrillation)
Intracardiac thrombus (intra-atrial, atrial appendage, intraventricular, attached to PFO channel or ASA) without underlying structural pathology other than PFO/ASA or arrhythmia
Presumed paradoxical embolism in the setting of PFO/ASA (or pulmonary arteriovenous fistula) with concomitant deep venous thrombosis or pulmonary embolism (newly diagnosed or history of)

Small-vessel occlusion of unknown/uncertain etiology

MRI diffusion-weighted imaging evidence of a single clinically relevant acute infarction less than 20 mm in greatest (axial) diameter within the territory of basal, 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 or diabetes on initial hospitalization, and supportive radiologic features including (1) one or several old or silent lacunar infarcts in territories different from the index stroke, (2) white-matter hyperintensities on MRI (FLAIR, T2), (3) microbleeds on MRI (T2* or SWI), and (4) dilatation of the perivascular spaces.

Examples of other conditions of uncertain causality

Thrombocytosis *without* known essential thrombocytosis
Presence of any antiphospholipid antibody (lupus anticoagulant, and anticardiolipin-IgG and β_2 -glycoprotein-IgG antibodies) *without existing diagnosis* of antiphospholipid syndrome according to current criteria. *Importantly, the patient should be included and followed-up even if criteria for antiphospholipid syndrome¹ were fulfilled at any later time point.*
Coagulopathies: e.g. deficits of antithrombin, protein C, or protein S, elevated factor VIII, factor V G1691A or factor II G20210A mutations, factor XIII mutation, familial dysfibrinogenemia, plasminogen deficiency, hyperhomocysteinemia (methylenetetrahydrofolate reductase 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 infarction²: 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.

MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery, SWI, susceptibility-weighted imaging; IHS, International Headache Society.

¹Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4:295-306.

²Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia.* 2013 Jul;33(9):629-808.

Supplemental Table II. Potential physical, chemical, and psychological triggers and recent temporal events studied in SECRETO.

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- Valsalva-inducing activity during the 1-2 hours preceding the stroke
 - Heavy physical exertion during the 1-2 hours preceding the stroke
 - Sudden posture changes, heavy eating, sudden temperature change, exposure to heavy traffic, sexual activity, or anger during the 1-2 hours preceding the stroke
 - Stimulant ingestion during the 24 hours preceding the stroke, including alcohol, coffee, tea, cola and energy drinks
 - Illicit drug use during the 24 hours preceding the stroke
 - Recent changes in medication (registration period 4 weeks preceding the stroke)
 - Recent infections (registration period 3 months preceding the stroke)
 - Recent stressful life-events (registration period 6 months preceding the stroke)
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Supplemental Table III. Standardized scales and questionnaires, and their adaptations, which are used to collect clinical information from study participants. Some of the scales or their items are stroke-specific and not asked from controls.

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- Oslo Social Support Scale
 - Physical and chemical triggers, preceding infections, reproductive health, and migraine screen (questionnaires/forms developed for this study)
 - Anger Onset Scale
 - Interview for Recent Life Events
 - Perceived Stress Scale
 - Alcohol Use Disorders Identification Test
 - WHO Alcohol, Smoking and Substance Involvement Screening Test
 - International Physical Activity Questionnaire
 - Mediterranean Diet Score
 - Short form DSM-IV questionnaire
 - Family history (form developed for this study)
 - Finnish Migraine Specific Questionnaire (used in Finnish patients with migraine in the screening questionnaire).
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WHO, World Health Organization; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition.

Supplemental Table IV. Preliminary key figures of the SECRETO study population as of October 2016.

Study procedures	Patients (n=123)	Controls (n=76)
Brain MRI	123 (100)	NA
DWI positive lesion(s)	123 (100)	NA
Angiography of extra- and intracranial arteries	123 (100)	NA
Prolonged ECG	123 (100)	NA
Per-protocol TTE/TEE	111 (90) / 109 (89)	63 (83) / 57 (75)
TCD bubble test	83 (67)	57 (75)
TEE or TCD	113 (92)	72 (95)
Baseline blood samples obtained	122 (99)	76 (100)
Clinical oral examination	76 (62)	58 (76)
Orthopantomography	76 (62)	58 (76)
3-month follow-up visit completed	107 (87)	NA
3-month blood samples obtained	103 (84)	NA
12-month follow-up completed	72 (59)	NA
24-month follow-up completed	26 (21)	NA
Study population characteristics		
Vascular comorbidity*	29 (24)	16 (21)
Current smoking	39 (32)	19 (25)
Physical inactivity	8 (7)	3 (4)
Migraine with aura	48 (39)	8 (10)
Migraine without aura	4 (3)	6 (7)
Recent infection†	44 (36)	22 (29)
Right-to-left shunt in TEE or TCD	68 (55)	24 (32)
NIH Stroke Scale score	4 (0-6)	NA
Intravenous thrombolysis	26 (21)	NA
Mechanical thrombectomy	6 (5)	NA
Valsalva inducing trigger	23 (19)	NA

Data are median (interquartile range) or n (%).

MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; ECG, electrocardiogram; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; TCD, transcranial Doppler ultrasound; NIH, National Institutes of Health; NA, not applicable.

*Any of hypertension, type 1 or 2 diabetes, diabetes, coronary heart disease, peripheral arterial disease, or aneurysm.

†Within 4 weeks prior to stroke in patients or before the interview in controls.