SOCRATES-AF
Screening Of Patients after Cryptogenic Stroke to Prove Atrial Fibrillation and Detection of Silent Strokes in AF Patients - with Active Follow-up Controls.

SYNOPSIS

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Slovakian Heart Rhythm Association of (SASA)
in close cooperation with Slovakian Society of Neurology (SNeS)
Introduction:

Atrial fibrillation (AF) is a significant risk factor of different types of cerebral infarction. Number of AF dramatically increases with age (9 % of the population aged 80 years). Of the total number of ischemic strokes, cardioembolic infarction is represented in about 20 %, and is associated with a 2-fold increase in mortality. About 30 % of ischemic strokes are cryptogenic (indeterminate etiology). Another interesting type of stroke is „Silent Cerebral Infarction“ (SCI), which is mostly asymptomatic and can be detected by MR examination. There is a lack of clear diagnostic criteria for cardio-embolic SCI, such as necessary MR sequences or typical lesion patterns for SCI. It is known, that patients with AF have higher prevalence and number of areas of SCI per patient and worse cognitive performance than subjects in sinus rhythm, but a clear cardio-embolic pattern still need to be specified for MR lesions. Studies have shown that undiagnosed AF may be present in patients with unexplained cryptogenic or silent stroke and is not detected by 12-lead ECG examination. Following cryptogenic or silent cerebral infarction, Holter 24-hour ECG monitoring is routinely used. Paroxysms of AF may be episodic and may not be detected during routine ECG monitoring. It is estimated that by extending the monitoring to 3-7 days the detection of AF increases to 6 %. Reveal® ICM helps to improve detection of AF through long-term (3 years), continuous, automatic ECG monitoring. Detection of AF has a significant consequence on treatment in patients after cryptogenic or silent stroke: if AF is verified, the patient should get anticoagulation treatment, representing a 64 % relative risk reduction of stroke, compared to placebo. Large number of patients with AF after stroke clearly indicated on anticoagulants (AC) receive no treatment or are treated with antiplatelets (APT), as there is a lack of their interdisciplinary follow-up in Slovakia.

Prospective trial goals:

Identify new patients with atrial fibrillation and or stroke eligible for treatment with VKA/NOAC and optimize multidisciplinary cooperation between NEU↔CAR leading to improved management of patients. Screening of patients in particular arms is focused on confirmation of causality between AF and different types ischemic stroke (stroke, TIA, SCI). These patients clearly indicated on AC therapy will be enrolled into 3 arms:

Arm A): In this arm patients with AF /NVAF after stroke/TIA will be enrolled by neurologist and monitored through active FU controls in cooperation with cardiologist for the correct use of indicated AC treatment. Arm B): Detection of paroxysmal AF through long-term Reveal ECG monitoring in the population of patients with a history of cryptogenic stroke/TIA or silent cerebral infarction during 12/24 months. Arm C): Screening for silent cerebral infarctions (SCIs) in adult patients with confirmed paroxysmal AF or NVAF via MR examination. MR scans with positive SCI lesions will be independently analyzed by 2 specialists: 1 radiologists and 1 neurologist.

Patients with each arm with confirmed NVAF and stroke/TIA/SCI - will start anticoagulation treatment (VKA or NOAC) undergo a follow-up examination in neurologist or cardiologist to ensure the treatment is used as instructed. This will enable to improve interdisciplinary cooperation between cardiologist and neurologist. The participating neuro- and cardio-sites will be linked via virtual network with structured patient flow. Finally patient will be notified via sms or a phone call about exact date and time of each specialist appointment, what will help to standardize “patient care pathways”.
Scheme 1: Process of screening of AC management and active „follow-up“ controls in patients with stroke/AF

Scheme 2:
Summary of inclusion and exclusion criteria, arms A, B, C

OVD – organic valve disease; AF – atrial fibrillation; NVAF – non-valvular atrial fibrillation; TIA – transient ischaemic attack; SCI – Silent Cerebral Infarction; Reveal – implantable ECG monitor; MI – myocardial infarction, NMR – nuclear magnetic resonance; APT – antiplatelet treatment – e.g., ASA – aspirin or CLO - clopidogrel; mRS – Modified Rankin scale; TOAST - Trial of Org 10172 in Acute Stroke Treatment; VKA – vitamin K antagonist; NOAK – new oral anticoagulant
OAC initiation:

- In patients after stroke/TIA/SCI, there are no indication limitations.
- OAC (VKA or NOAC) as a first choice can be indicated by NEU, INT and CAR
- If the patient is not suitable for OAC ASA or APT can be considered (ASA, ASA+CLO)

* a,b,c,d criteria for OAC initiation post stroke/TIA/SCI:

a) Neurologist monitors the ischemic lesion for haemorrhagic transformation. According to it’s size as stated in points b,c,d.

b) Neurologist applies **3-6-12 days rule** (EHRA, 2013). In TIA/SCI initiates OAC immediately if the lesion is small (non-disabling stroke), in 3 days in moderate stroke in 6 days after severe stroke and in ≥12 days (2-3 weeks in massive stroke).

c) OAC is initiated as soon as possible after stroke/TIA/SCI

d) If OAC is not started during neurology hospitalization it is necessary to mention in discharge letter clear statement regarding OAC indication/contraindication and initiation. In the same time neurologist enrolls the patient in eCRF and refers for cardiologist FU.
Synopsis

Arm A

Consultants:
MUDr. Katarína Hatalová, cardiologist, Cardioconsult, Bratislava
MUDr. Daša Viszlayová, neurologist, Neurologická klinika FN Nitra a FSVaZ UKF Nitra

Methodology:
In arm A 600 patients will be screened for causality between stroke/TIA and AF by neurologist. Both stroke/TIA and AF must be confirmed (AF via 12 lead ECG). Each patient will be referred to cardiologist to undergo ECHO to exclude organic valve disease. Contraindications will be considered and the physician will indicate anticoagulation treatment. In the same time the patient data will be recorded in to eCRF with email notification of specialists and sms notification of patient regarding date and time of each scheduled appointment.

Inclusion and exclusion criteria are in the scheme 2, patient flow and FU harmonogram are in the scheme 3.

Detailed case report form exists as an electronic CRF (eCRF) and can be found in the synopsis attachment (printed eCRF for each follow-up visit in arm A in Slovak language)

Synopsis B:

ARM B

Consultants:
MUDr. Luboš Urban, PhD., arrhythmologist, OAKS, NÚSCH Bratislava
MUDr. Andrea Petrővičová, neurologist, Neurologická klinika FN Nitra a FSVaZ UKF Nitra

Methodology:
Detection of paroxysmal AF through long-term Reveal ECG monitoring in the population of patients with a history of cryptogenic stroke/TIA or silent cerebral infarction (SCI) during 12/24 months. Devices used for AF detection: 1. Reveal XT, 2. Reveal LINQ and MyCareLink home monitor. In total we will enroll 250 patients with acute cryptogenic stroke or TIA or at least 2 SCI lesions. Patients must have sinus rhythm during enrollment. In patients with suspected cardioembolic stroke we will monitor long term for AF. After discharge from neurology clinic patient will be referred to regional cardiology/internal medicine office for FU. In case of negative 12 lead ECG or Holter patient will be referred from regional cardiologist to Reveal implant center. Responsible investigator in Reveal ICM center will assess the patient suitability for implantation. Date of Reveal ICM implantation will be scheduled unless patient denies invasive AF monitoring and prefers other method of long-term ECG. Patients from selected Reveal ICM centers will be monitored for AF paroxysms via CareLink network. Carelink transmission can be provided manually through home monitor by patient or automatically via the same device. Patients without CareLink will attend office follow-up in Reveal ICM center at least once a year. In case the AF is detected and cryptogenic stroke or SCI is verified (TEE / NMR), OAC treatment will be started according to CHA2DS2-VASc and HAS-BLED score. After this, patient will be transferred to arm A for AT treatment FU. The expected rate of AF detection in patients after cryptogenic stroke with Reveal ICM is stated in Figure 1.
**Primary endpoints in arm B:**

1. Time to first documented AF episode during 12 months of observation in patients after cryptogenic stroke and in patients after verified silent cerebral infarction* (min 2 lesions of SCI)
2. Set-up of clear diagnostic criteria for cardio-embolic SCI, such as verification of required MR sequences and typical patterns of cardio-embolic SCI (Arm Bb). Positive MR scans will be independently analyzed by 2 specialists: 1 radiologist, 1 neurologist.

*There is very limited number of publications on this topic: where SCI is defined as focal, sharply demarcated, regularly or irregularly shaped areas hyper-intense on T2-weighted FLAIR images or isointense on T1-weighted images. T2-weighted FLAIR images will be used to differentiate gliotic ischemic lesions smaller than 3 mm from perivascular spaces and lacunae (hypointense on T2-weighted FLAIR images)

![Example of Brain magnetic resonance images in patient with paroxysmal AF without other risk factors: axial fluid-attenuated inversion recovery sequences demonstrate multiple small hyperintense lesions at the subcortical level in both hemispheres. Clusters (arrows) of small lesions are visible in the left frontal and temporoparietal regions (A), in the left frontal lobe (B), and in the right frontal lobe (C).](image)

**Secondary endpoints:**

1. Incidence of newly occurred ischemic stroke, silent cerebral infarctions and transient ischemic attack during 12 months of observation
2. Changes in the treatment under secondary prevention of acute stroke during 12 months of trial – VKA, apixaban, dabigatran, rivaroxaban, ASA, other APT, LMWH
3. Clinical outcome – NIHSS, modified Rankin Scale
4. Database of brain MR images with cardioembolic origin to improve diagnostic process

**Inclusion criteria**

Cryptog. stroke/TIA within 72 hours from symptoms onset (TOAST* classification of stroke) or min. 2 SCI lesions (silent cerebral infarction)

Sinus rythm on entry ECG

*mRS ≤ 4 during hospital discharge

**Exclusion criteria**

NOAC

Organic valve disease (OVD)

Contraindicated AT treatment – physician follows SmPC instructions for VKA/NOAK/ASA/other AA

Patient flow and FU harmonogram are in the scheme 3.
**TOAST**
Trial of Org 10172 in Acute Stroke Treatment

**mRS** - Modified Rankin Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>No significant disability. Able to carry out all usual activities, despite some symptoms.</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability. Requires some help, but able to walk unassisted.</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability. Requires constant nursing care and attention, bedridden, incontinent.</td>
</tr>
<tr>
<td>6</td>
<td>Dead.</td>
</tr>
</tbody>
</table>

Classification of stroke/TIA:
- Atherosclerosis of large arteries (embolus/thrombosis)
- Cardiogenic (high/medium risk)
- Occlusion of small arteries (lacune)
- Stroke of other determined etiology
- CMP of undetermined etiology (cryptogenic)
- Negative evaluation
- Uncompleted diagnosis
- Confirmed two or more causes

Cryptogenic stroke is without determined cause via following examinations: CT/MR, ECHO, duplex sono of extracranial arteries, arteriography, laboratory tests of prothrombotic conditions.

**Figure 1**

Detection of Atrial Fibrillation by 36 months

<table>
<thead>
<tr>
<th># at risk</th>
<th>Control</th>
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CRYSTAL-AF Clinical Trial (Continuous monitoring with Reveal ICM is superior to standard medical care for AF detection in patients with a cryptogenic stroke). Results: Reveal is superior to standard medical care for the detection of AF in patients with a cryptogenic stroke. CRYSTAL AF demonstrated that: ● Continuous monitoring detected over 7 times more patients with AF at the 12-month end point; ● When followed for 3 years, AF was detected at a rate of 30% in the ICM arm vs 3% in the standard follow-up arm; ● Short-term monitoring is not sufficient as the median time to AF detection over 12 months of follow-up was 84 days; ● 97% of patients who had AF detected were prescribed OAC. At 3 years, AF was detected at a rate of 30% in the Reveal ICM arm vs 3% in the standard follow-up arm, 8.8x more than in the standard monitoring arm.

Detailed case report form exists as an electronic CRF (eCRF) and can be found in the synopsis attachment (printed eCRF for each follow-up visit in arm Ba and arm Bb in Slovak language).
Synopsis C:

**ARM C**

**Consultants:**
MUDr. Peter Hlivák, PhD., arrhythmologist, OAKS, NÚSCH Bratislava
MUDr. Marek Krivošík, neurologist, Nemocnica akad. L. Dérera, UNB Bratislava

**Methodology**

Screening for silent cerebral infarctions (SCIs) in group of **150 adult patients** with confirmed paroxysmal AF or NVAF via MR examination. MR scans with positive SCI lesions will be independently analyzed by 2 specialists: 1 radiologist and 1 neurologist.

SCI = Silent Cerebral Infarctions defined as cerebral stroke verified through diagnostic imaging preferably (NMR) without anamnesis of acute neurologic dysfunction related to found lesion. According to anatomic-pathological criteria, areas of SCI lesions were defined as focal, sharply demarcated, regularly or irregularly shaped areas hyperintense on T2-weighted FLAIR images or isointense on T1-weighted images. T2-weighted FLAIR images were used to differentiate gliotic ischemic lesions smaller than 3 mm from perivascular spaces and lacunae (hypointense on T2-weighted FLAIR images).

In patients with confirmed NVAF and with suspected unrecognized embolization (vascular brain disease) cardiologist will refer the patients to neurologist to detect SCI with MRi.

Inclusion and exclusion criteria are in the scheme 2, patient flow and FU harmonogram are in the scheme 3.

Detailed case report form exists as an electronic CRF (eCRF) and can be found in the synopsis attachment (printed eCRF for each follow-up visit in arm C in Slovak language)

**Step 1** – **cardiologist** will exclude organic valve disease and will provide assessment of cognitive functions (MMSE questionnaire score ≤ 26 is required for patient enrollment). Based on MMSE score or clinical assessment that confirms clinical dysfunction cardiologist will refer patient to neurologist.

![MMSE Questionnaire Score](image-url)
Step 2 – NEUROLOGIST – will provide following examinations and refer patient to MRi:
  • Ultrasound examination of carotic and vertebral arteries to discover hemodynamically significant stenosis – standardization according European Carotid Surgery Trial
  • Detection of unstable atherosclerotic plaque and eventual MRi contraindication
  • MRi – all positive SCI lesions will be consulted with 2 independent specialists (NEU, RDG) and will be evaluated if SCI image is of cardioembolic origin

Step 3 – NEUROLOGIST after MRi examination – patients with confirmed NVAF regardless of their CHA2DS2-VASc score who can be indicated for reimbursed MRi scan will be monitored for SCI
  • minimal required sequences: T2, FLAIR, T1, DWI, ADC
  • definition of SCI lesion – hyperintense lesion at T2 and FLAIR sequences or isointense at T1 sequence while T2 and FLAIR image helps to differentiate lesions smaller than 3 mm from perivascular spaces (hypointense at T2 and FLAIR)
  • number and localization of SCI lesions

Step 4 – SCHEME 4 – patients with SCI verification will be indicated on NOAC treatment by neurologist cardiologist and transferred to arm A for active FU. Patients with undetected SCI will be managed by cardiologist according CHA2DS2-VASc score (0-no treatment, 1 – treatment with OAC/APT, >1 OAC treatment (1. VKA, 2. in VKA if 2 INRs out of 6 are out of range treatment with NOACs can be initiated).