

# Supplemental Material

## Data S1. Supplemental Results

We performed a post-hoc subgroup analysis dividing the patients into two age groups: 60-69 years and 70-80 years. The main results are shown below:

Proportion of patients with PFO among those with cryptogenic vs. non-cryptogenic strokes (P for interaction=0.28):

Age 60 to 69: 61/128 (47.7%) vs. 31/186 (16.7%), OR 4.55 (95%CI 2.71-7.65), P<0.0001

Age 70 to 80: 36/90 (40.0%) vs. 24/129 (18.6%), OR 2.92 (95%CI 1.58-5.38), P=0.0005

Proportion of patients with large PFO + ASA among those with cryptogenic vs. non-cryptogenic strokes:

Age 60 to 69: 21/61 (34.4%) vs. 4/31 (12.9%)

Age 70 to 80: 16/36 (44.4%) vs. 4/24 (16.7%)

Considering non-large PFO without ASA as reference, the OR for the association between large PFO + ASA and cryptogenic stroke was:

- OR 4.63 (95%CI 1.30-16.58) for patients aged 60 to 69
- OR 3.56 (95%CI 0.83-15.18) for patients aged 70 to 80
- P for interaction=0.85

**Table S1. Subgroup of patients with PFO: factors associated with cryptogenic or non-cryptogenic stroke.**

Variable	All (n=152)	Cryptogenic stroke (n=97)	Non-cryptogenic stroke (n=55)	P
<b>Age (years) mean (SD)</b>	68.4 (5.1)	68.0 (5.1)	69.1 (5.3)	0.21
<b>Male sex</b>	98 (64.5%)	63 (64.9%)	35 (63.6%)	0.87
<b>Hypertension</b>	74 (48.7%)	41 (42.3%)	33 (60.0%)	0.04
<b>Diabetes mellitus</b>	20 (13.2%)	9 (9.3%)	11 (20.0%)	0.06
<b>Current smoking</b>	27 (17.8%)	17 (17.5%)	10 (18.2%)	0.92
<b>Lipid lowering medication</b>	63 (41.4%)	39 (40.2%)	24 (43.6%)	0.68
<b>Antiplatelet medication</b>	52 (34.2%)	28 (28.9%)	24 (43.6%)	0.07
<b>Vitamin K Antagonists</b>	1 (0.7%)	1 (1.0%)		0.45
<b>DOAC or other anticoagulant</b>	5 (3.3%)	2 (2.1%)	3 (5.5%)	0.27
<b>Previous ischemic stroke</b>	22 (14.5%)	14 (14.4%)	8 (14.5%)	0.98
<b>Previous TIA</b>	18 (11.8%)	11 (11.3%)	7 (12.7%)	0.8
<b>Previous CHD</b>	16 (10.5%)	7 (7.2%)	9 (16.4%)	0.08
<b>Atrial fibrillation</b>	5 (3.3%)	1 (1.0%)	4 (7.3%)	0.04
<b>Previous DVT or PE</b>	7 (4.6%)	5 (5.2%)	2 (3.6%)	0.67
<b>Previous cancer</b>	25 (16.4%)	14 (14.4%)	11 (20.0%)	0.37
<b>NIHSS on admission median (IQR)</b>	1.0 (0.0, 3.0)	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	0.97
<b>MRI performed</b>	148 (97.4%)	94 (96.9%)	54 (98.2%)	0.64
<b>CEMRA performed</b>	134 (88.2%)	86 (88.7%)	48 (87.3%)	0.8
<b>CTA performed</b>	45 (29.6%)	25 (25.8%)	20 (36.4%)	0.18
<b>Ultrasound performed</b>	53 (34.9%)	27 (27.8%)	26 (47.3%)	0.02
<b>24-hr ECG monitoring</b>	31 (20.4%)	15 (15.5%)	16 (29.1%)	0.045
<b>Prolonged ECG Monitoring</b>	110 (72.4%)	79 (81.4%)	31 (56.4%)	<0.0001
<b>Anticoagulation at discharge</b>	27 (17.8%)	19 (19.6%)	8 (14.5%)	0.43
<b>Time between event and echocardiography (days) median (IQR)</b>	4.0 (3.0, 7.0)	4.0 (3.0, 6.0)	5.0 (3.0, 7.0)	0.2
<b>Dilated LA</b>	55 (36.2%)	30 (30.9%)	25 (45.5%)	0.07
<b>PFO characteristics</b>				0.02
<b>large PFO with ASA</b>	45 (29.6%)	37 (38.1%)	8 (14.5%)	
<b>large PFO without ASA</b>	38 (25.0%)	23 (23.7%)	15 (27.3%)	
<b>non-large PFO with ASA</b>	20 (13.2%)	11 (11.3%)	9 (16.4%)	
<b>non-large PFO without ASA</b>	49 (32.2%)	26 (26.8%)	23 (41.8%)	

DOAC: direct oral anticoagulant; TIA: transient ischemic attack; CHD: coronary heart disease; DVT: deep vein thrombosis; PE: pulmonary embolism; NIHSS: National Institute of Health Stroke Scale; MRI: magnetic-resonance imaging; CEMRA: Contrast-enhanced magnetic resonance angiography; CTA: computed tomography angiography; ECG: electrocardiogram; LA: left atrium; PFO: patent foramen ovale; ASA: atrial septum aneurysm.

**Table S2. From the ASCOD Classification: Detailed Causality Grades for Cardiac Pathology**

<b>C1 (potentially causal):</b> Cardiogenic stroke defined as acute, or recent and older bihemispheric or supra- and infratentorial territorial or cortical ischemic lesions and signs of systemic embolism with detection of at least one of the following potential causes:
(1) mitral stenosis (surface <1.5 cm <sup>2</sup> )
(2) mechanical valve
(3) myocardial infarction within 4 weeks preceding the cerebral infarction
(4) mural thrombus in the left cavities
(5) aneurysm of the left ventricle
(6) history or presence of documented atrial fibrillation – whether paroxysmal (>60 s), persistent or permanent – or flutter, with or without left atrial thrombus or spontaneous echo
(7) atrial disease (tachycardia-bradycardia syndrome)
(8) dilated or hypertrophic cardiomyopathies
(9) left ventricle ejection fraction <35%
(10) endocarditis
(11) intracardiac mass
<b>(12) PFO and thrombus in situ</b>
<b>(13) PFO and concomitant pulmonary embolism or proximal DVT preceding the index cerebral infarction</b>
(14) aforementioned cardiac pathologies (C1) with single or without obvious cerebral ischemic lesion
<b>C2 (causal link is uncertain):</b> Regardless of stroke pattern:
<b>(1) PFO + atrial septal aneurysm</b>
<b>(2) PFO and pulmonary embolism or proximal DTV concomitant but NOT preceding the index cerebral infarction</b>
(3) intracardiac spontaneous echo-contrast
(4) apical akinesia of the left ventricle and decreased ejection fraction (but >35%)
(5) history of myocardial infarction or palpitation and multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation)

(6) no direct cardiac source identified, but multiple brain infarction, repeated either bilateral or in two different arterial territories (e.g. both anterior and posterior circulation) and/or evidence of systemic emboli: renal or splenic or mesenteric infarction (on CT, MRI or autopsy) or embolism in peripheral artery supplying arm or leg

**C3 (causal link is unlikely, but the disease is present)** One of the following abnormalities present in isolation: PFO, ASA, strands, mitral annulus calcification, calcification aortic valve, nonapical akinesia of the left ventricle, transient atrial fibrillation <60 s, atrial hyperexcitability

**C0 (cardiac pathology not detected or not suspected)** Ruling out a cardiac source of embolism: minimum is negative ECG and examination by a cardiologist; maximum is negative ECG/telemetry/24-hour Holter ECG/long-term ECG recording (implantable device, transtelephonic ECG, loop recorder) and negative TEE for atrium, valves and septal abnormalities, negative TTE for PFO and assessment of left ventricle, negative cardiac CT/MRI, negative abdominal CT/MRI (search for old or simultaneous subdiaphragmatic visceral infarction)

**C9 (incomplete workup)** Minimum is ECG and examination by a trained cardiologist in the absence of cardiac imaging

Figure S1. Flow Chart

