Supplementary Methods

Study population

The Normandy Stroke Study is a prospective population-based study aiming to identify all residents of the Caen Normandie Metropole area (France, 411,797 residents in 2020) who developed a stroke or transient ischemic attack (TIA) starting from May 15th, 2017. The Normandy Stroke Study is approved by an ethics committee (Comité de Protection des Personnes, CPP 009/2017). As this study was purely observational, non-opposition was sought in accordance with French legislation, but written consent was not required. The complete methodology has been previously published and is designed to comply with the current gold standard for population-based studies in neuroepidemiology.[1] In brief, cerebrovascular events in hospitalized and non-hospitalized patients are identified through multiple prospective and retrospective overlapping sources, including: (1) prospective screening of all admissions to the neurovascular, neurology and neurosurgery units at the Caen University Hospital (only stroke unit in the area); (2) prospective screening of outpatient evaluations at the Caen University Hospital performed by vascular neurologists, vascular neurosurgeons, or neurogeriatricians; (3) review of selected diagnostic and procedural codes from emergency department evaluations and admissions to all departments of the Caen University Hospital, all other hospitals in the area, as well as two neighboring hospitals (including the procedural code for patent foramen ovale [PFO] closure); (4) review of radiology reports from all private imaging centers in the area and one public hospital (brain computed tomography [CT] and magnetic resonance imaging, head and neck CT angiogram, magnetic resonance angiogram); (5) review of emergency consultations in the community by SOS Médecins; and (6) review of autopsy reports.

Medical charts and imaging of all suspected stroke cases are evaluated by a vascular neurologist. Patients are included in the study if they meet the tissue-based criteria for ischemic stroke, TIA, intracerebral hemorrhage, subarachnoid hemorrhage, undetermined stroke, or cerebral venous thrombosis. An ischemic stroke was defined as an episode of neurological dysfunction caused by focal cerebral or retinal infarction, defined as symptoms lasting ≥24 hours or until death or lasting <24 hours and associated with imaging evidence of ischemic injury. An ischemic stroke was designated as cryptogenic when no specific cause was identified and PFO-associated if the event was cryptogenic, embolic (cortical, cerebellar, thalamic, or deep and >2 cm on diffusion-weighted imaging or >1.5 cm on fluid-attenuated inversion recovery or CT-scan), and met the PFO-Associated Stroke Causal Likelihood highly probable, probable or possible criteria.[2] Patients with an isolated deep infarct after endovascular thrombectomy for a large vessel occlusion stroke were categorized as having a cortical stroke.

PFO assessment

As the Caen University Hospital participated in the PFO CLOSE (Closure or Anticoagulants versus Antiplatelet Therapy to Prevent Stroke Recurrence) trial, contrast-enhanced transthoracic (cTTE) and transesophageal echocardiograms (cTEE) in the area are performed in accordance with the CLOSE protocol.[3] Agitated aerated saline injections (9 mL NaCl 0.9% and 1 mL air) and Valsalva maneuvers (before or at the time of injection) are used to increase sensitivity for PFO detection. Contrast-enhanced transcranial Dopplers are not routinely performed at our centre, but their results were included if they were performed at another center.

A PFO was defined as the presence of a right-left shunt within 3 cardiac cycles after opacification of the right atrium. If a contrast-enhanced study was not available, a PFO was defined as a transient low-velocity bidirectional or right-left jet flow across the fossa ovalis on color Doppler cTEE, in the absence of a visible atrial septal defect. The shunt was classified as large on echocardiography (cTTE or cTEE) if >20 microbubbles appeared in the left atrium within 3 cardiac cycles after opacification of the right atrium. In patients without a contrast-enhanced study, a large PFO was defined as a broad and persistent right-left flow extending into the left atrium, with a color Doppler-derived orifice diameter >2 mm. The presence of an atrial septal aneurysm was evaluated in patients who underwent a cTEE and was defined as an excursion of at least 10 mm from the plane of the atrial septum.

Analysis

The number of strokes prevented by the projected closures was estimated nationwide over 2 years, using the numbers needed to treat from the individual participant data meta-analysis of PFO closure trials.[4]

Supplementary References

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