PFO closure may become first-line preventive therapy for patients with cryptogenic stroke

Percutaneous closure of patent foramen ovale: long-term follow-up shows benefit

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The foramen ovale is a door-like opening of the interatrial septum framed by the septum primum and septum secundum. *In utero* it serves as a pathway for oxygenated blood to shunt from the right to the left atrium, thereby bypassing the nonfunctional lungs. After birth a right-to-left shunt is undesirable and the foramen ovale closes. However, in a quarter of the population no permanent closure occurs, and the patent foramen ovale (PFO) may allow particulate or chemical material to pass from the venous to the arterial circulation, especially during increased right atrial pressure (e.g., Valsalva manoeuvre). A PFO has been associated with cryptogenic stroke, myocardial infarction, migraines, sleep apnoea, platypnoea-orthodeoxia, diving-associated decompression illness and high-altitude pulmonary oedema. Nevertheless, the majority of humans with a PFO live without experiencing a PFO-related medical condition [1]. Therefore, the PFO does not qualify as a screening target in the general population [2] and primary prophylactic PFO closure in asymptomatic individuals is not recommended.

Stroke is one of the most feared and devastating health disorders. One third of strokes are so-called cryptogenic because no apparent cause is found. The prevalence of a PFO in patients suffering a cryptogenic stroke is higher than in patients with known stroke causes [3, 4]. Nonetheless, in a large number of patients with cryptogenic stroke, no PFO is found [4]. Given the high background prevalence of PFO in the general population, many PFOs detected in patients with cryptogenic stroke are incidental. However, PFO patients who suffered a paradoxical embolism may represent a higher risk cohort and may benefit more from PFO closure compared with medical management, especially when an atrial septal aneurysm or large shunt is present.

In the 1970s and 1980s percutaneous closure of interatrial connections was developed. On the basis of mostly nonrandomised, observational data, PFO closure was advocated for patients with cryptogenic stroke [5]. However, three major randomised controlled trials [6–8] did not meet their predefined primary endpoint to establish the superiority of percutaneous PFO closure over medical management in patients with cryptogenic stroke. Meanwhile, 17 meta-analyses based on these results [9] have been published. The lack of long-term follow-up and controversies about intention-to-treat analyses versus device-in-place analyses have modified interpretation of randomised data. Indeed, short-term observations suffer from low recurrence rates. Adjudicating events occurring before PFO closure in the device arm, by obstinately following the intention-to-treat principle, is not helpful in defining the effect of PFO closure. Long-term follow-up in the as-treated cohort may finally establish percutaneous PFO closure as the preferred therapy for the prevention of recurrent paradoxical embolism in patients with cryptogenic stroke [10].

Accordingly, in this edition of the journal, Andreas Wahl et al. report the long-term outcome of PFO closure with the Sideris Buttoned Occluder. The authors should be congratulated for their persistence in following-up their patients for more than 10 years. The study tested the long-term safety of the device and showed a low stroke recurrence rate after PFO closure. The periprocedural complication rate in this cohort is somewhat historical, and in the meantime percutaneous PFO closure has become a relatively simple and safe procedure. Given the unsatisfactory closure rate with the Sideris Buttoned Occluder it is understandable that the authors stopped using this device and prefer others with higher closure rates and a better safety and efficacy profile (e.g., the AMPLATZER™ PFO Occluder).

This manuscript coincides with the long-term follow-up results of the RESPECT trial [6], which were recently reported at Transcatheter Cardiovascular Therapeutics 2015 in San Francisco. Extended follow-up

analysis of this randomised trial showed that PFO closure reduced the relative risk of recurrent cryptogenic stroke by 70% compared with medical therapy (1.5 to 4.3%; p = 0.004). As paradoxical embolism is excluded after successful PFO closure and conservatively treated patients face a persistently increased bleeding risk due to continuous antithrombotic medication, it is expected that event-curves for safety and efficacy will continue to separate over the years. However, with increasing age the susceptibility to noncryptogenic stroke increases. Therefore, during long-term follow-up the effect of PFO closure becomes blurred by events unrelated to the PFO. In this setting, paradoxical embolism has to be discriminated from events caused by atherosclerotic plaque rupture, which becomes more prevalent with age. The scrutiny of scientific researchers is mandatory to dissect the various causes of ischaemia in an aging cohort and tease out the group that may benefit from PFO closure by sound analyses and adequately powered randomised controlled trials. The identification of cofactors such as hypercoagulability, deep vein thrombosis or cardiac anatomical peculiarities (e.g., atrial septal aneurysm or large shunt) may further transform the PFO from an innocent bystander to a vicious facilitator.

Long-term follow-up – as reported by Andreas Wahl et al. – solidifies the biological impact of PFO closure so that it may become first-line therapy for the prevention of paradoxical embolism in patients with cryptogenic stroke.

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