The prevalence of PFO is about 25% in the general population. In patients with stroke of unknown cause (cryptogenic stroke), the prevalence of PFO increases to approximately 40%. To date, epidemiologic studies have not shown thromboembolic events more frequently in persons with PFO, and therefore no special primary prevention is needed. However, the question on prevention arises in patients with stroke and emboli to other organs. Prospective cohort studies and a single randomized trial have shown that treatment with aspirin or warfarin reduces the risk of recurrent stroke in the average patient with PFO to the same risk as in patients without PFO. Aspirin was as effective as anticoagulation. Among patients with PFO, those with spontaneous or large right-to-left shunts, with a coinciding atrial septal aneurysm (ASA) or multiple ischemic events prior to the PFO diagnosis are at higher risk of recurrent stroke than the average PFO patient. Percutaneous device closure (PDC) becomes therefore a challenging alternative to medical treatment in such patients. Several observational case series have reported 0% to 3.4% recurrence rates of stroke or TIA in patients treated by PDC, but data from randomized controlled trials (RCT) comparing the effect of PDC with medical therapy only are still missing. The results from ongoing RCTs in Europe and the USA are not to be expected in the near future, mainly because of slow enrolment and low overall event rates. Data of indirect comparisons of patients treated medically and patients treated with PDC have shown an advantage for PDC compared to medical treatment, and the ESO guidelines 2008 state: It is recommended that endovascular closure of PFO be considered in patients with cryptogenic stroke and high-risk PFO (Evidence Class IV, GCP). Better evidence pending I advocate that PFO in stroke patients should be closed.