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LETTERS TO THE EDITORS

The best DEFENSE for high-risk patent foramen ovale: An updated meta-analysis of six randomized trials

La meilleure DEFENSE pour les Foramen Ovales Perméables a haut risque : une méta-analyse des 6 essais randomisés

Keywords Patent foramen ovale; Cryptogenic stroke; Ischaemic stroke; Percutaneous close; Meta-analysis
Mots clés Perméable ; AIC cryptogénique ; AIC ; Fermeture percutanée ; Méta-analyse

Patent foramen ovale (PFO) is a potential cause of cryptogenic stroke. In September 2017, two new randomized controlled trials (RCTs) — CLOSE and Gore REDUCE — were published simultaneously with the extended follow-up results of the RESPECT trial, comparing percutaneous closure with antiplatelet and/or anticoagulant therapy [1—3]. Percutaneous closure was shown to be associated with decreased rates of stroke and an increased risk of new-onset atrial fibrillation, contrary to the findings of previously published trials on the topic (CLOSURE I and PC), which showed no difference [4,5]. In a recent meta-analysis of 3440 patients conducted by our group, PFO closure significantly decreased the risk of a new ischaemic stroke [6]. The benefit was more prominent among high-risk patients, such as those with septal aneurysm and large shunt [6].

The results from a new trial — DEFENSE-PFO — were published in March 2018 [7]. This is the sixth RCT on the topic and, to our knowledge, has not been included in any published meta-analyses. The DEFENSE-PFO study was an investigator-initiated multicentre randomized open-label superiority trial conducted in Korea, and included patients with a high-risk PFO [7]. The researchers defined patients with high-risk PFO as having one of the following characteristics: atrial septal aneurysm; hypermobility of the septum (''phasic septal excursion into either atrium $\geq$ 10 mm''); or large PFO size, defined as maximum separation of the septum primum from the secundum during the Valsalva manoeuvre $\geq$ 2 mm on transoesophageal echocardiography. A total of 120 patients were randomized, 60 to each group, and the median follow-up was 2.8 years. The two groups were similar overall, but there was a trend towards an older population in the medical therapy group ($P = 0.06$), although statistical significance was not reached. There were no ischaemic strokes in the percutaneous closure group versus five ischaemic strokes in the medical therapy group. There were three major bleeding events, all in the medical therapy arm.

We performed an updated meta-analysis of all six RCTs ($n = 3560$) to assess the efficacy and safety of transcatheter PFO closure versus medical therapy for these patients. The method has been described previously [6]. Our results show that percutaneous closure is still associated with a reduced risk of new ischaemic stroke (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.19—0.81; $I^2 = 52.8\%$). The other outcomes are presented in Fig. 1. We also conducted a subgroup analysis for patients with high-risk PFO. Because of high heterogeneity in the way that high-risk PFO was defined in the trials, we decided to include in this subgroup the patients with a large shunt from the first five trials and the whole DEFENSE-PFO population. Patients with high-risk PFO had a significant benefit in terms of reduced risk of new ischaemic stroke when treated with percutaneous closure versus medical therapy (OR 0.27, 95% CI—0.14 to 0.51). However, patients with a small shunt did not benefit significantly from percutaneous closure (OR 0.86, 95% CI 0.26—1.46).

Our new analysis presented here, in combination with the results from the DEFENSE-PFO and CLOSE trials, which enrolled only this subgroup, suggest that percutaneous closure should be preferred, as it is beneficial for patients with either septal aneurysm and/or large shunt [1,6,7]. Thus, closure might be the best defence for high-risk PFOs. On the other hand, it remains questionable whether patients with small shunts actually benefit from PFO closure ($I^2 = 0$). We therefore believe that it is of paramount importance to carefully select patients who meet the eligibility criteria for this therapeutic option, as proposed in the algorithm published recently by Mojadidi et al. [8]. Future studies should continue to examine the specific subpopulations of patients who will benefit most, as it is currently clear that percutaneous closure is not beneficial for everybody (e.g. those with small shunts and the elderly).

Abbreviations: CI, confidence interval; OR, odds ratio; PFO, patent foramen ovale; RCT, randomized controlled trial.

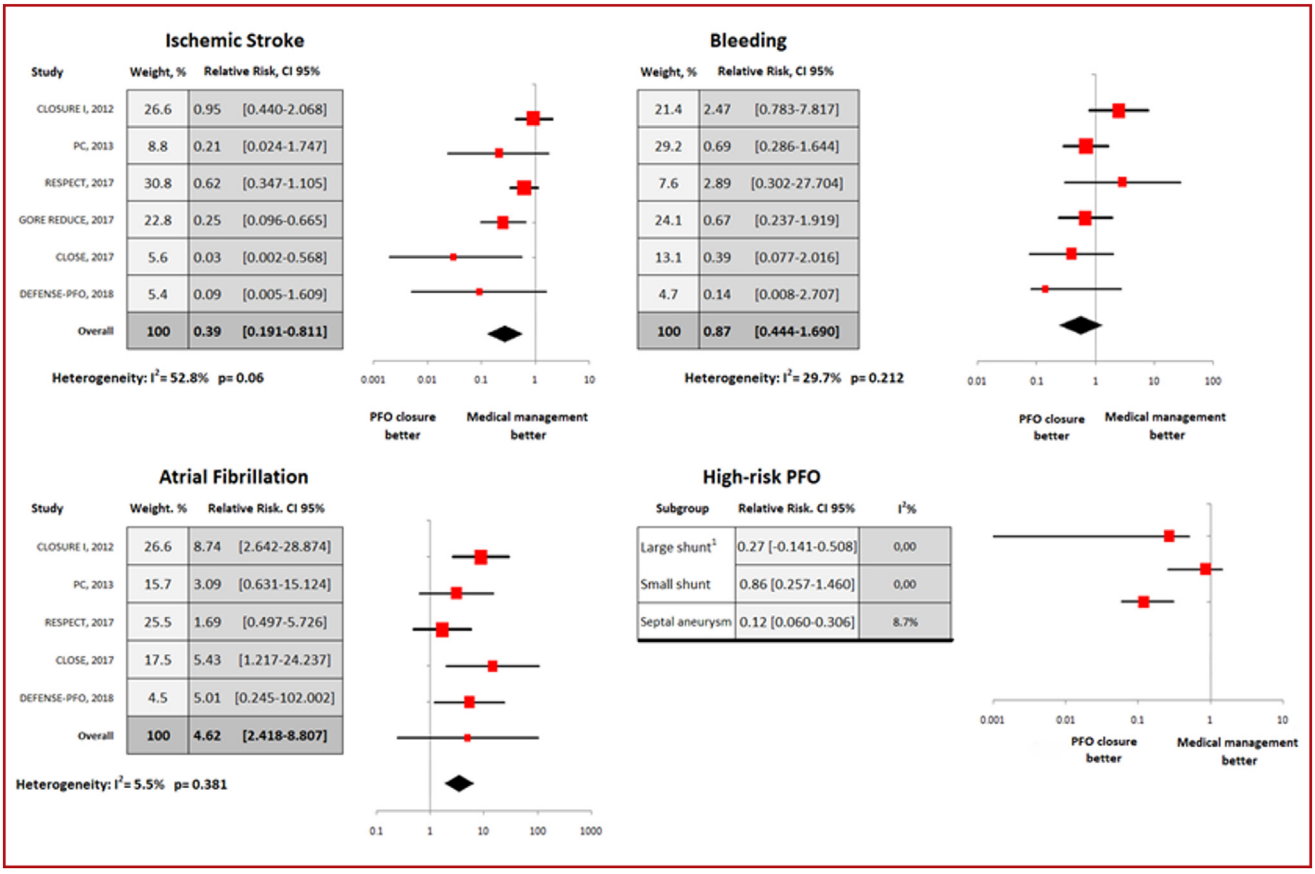

Figure 1. Meta-analyses of the six randomized clinical trials. Patent foramen ovale (PFO) closure was better at preventing a new ischaemic stroke (odds ratio [OR] 0.39, 95% confidence interval [CI] 0.19—0.81; $I^2 = 52.8\%$). No difference in bleeding risk was found between the two strategies (OR 0.87, 95% CI 0.44—1.69; $I^2 = 29.7\%$). Closure devices were associated with a higher risk of new-onset atrial fibrillation (OR 4.62, 95% CI 2.42—8.81; $I^2 = 5.5\%$), although this difference was not significant in the subgroup analysis for patients treated with Amplatzer™ (St. Jude Medical, St. Paul, MN, USA) devices only (OR 2.29, 95% CI 0.91—5.76; $I^2 = 0$). Percutaneous closure was associated with reduced stroke rates (OR 0.27, 95% CI—0.14 to 0.51; $I^2 = 0$) among the subgroup of patients with high-risk PFOs (large shunt + DEFENSE-PFO). Patients with a small shunt did not have a benefit (OR 0.86; 95% CI 0.26—1.46).

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Disclosure of interest

The authors declare that they have no competing interest.

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