

## Clinical update

# Percutaneous closure of patent foramen ovale: an underutilized prevention?

Fabian Nietlispach<sup>1\*</sup> and Bernhard Meier<sup>2</sup>

<sup>1</sup>Department of Cardiology, University Heart Center Zurich, Zurich, Switzerland; and <sup>2</sup>Department of Cardiology, Bern University Hospital, Bern, Switzerland

Received 27 March 2015; revised 13 July 2015; accepted 21 July 2015; online publish-ahead-of-print 6 August 2015

Stroke is a devastating event for patients and their families. Paradoxical embolism through a patent foramen ovale (PFO) is a recognized cause of stroke. Percutaneous PFO closure is a simple and safe procedure. The debate on PFO closure is far from settled. This is, in part, due to the fact that the three published randomized controlled trials (RCTs) on PFO closure vs. medical therapy were negative regarding their primary endpoint; however, as-treated and per-protocol analyses as well as several meta-analyses report a benefit of PFO closure. In our opinion, PFO closure is underutilized and the results of the three RCTs are not adequately reflected in the current guidelines.

### Keywords

PFO closure • Percutaneous • Stroke • Prevention • Paradoxical embolism

## Case vignettes

A 37-year-old nurse and mother of two teenage boys suffered from migraine for many years. She was admitted to the hospital with a stroke that left her with permanent aphasia. It took 2 years before her patent foramen ovale (PFO) was looked for and closed, which improved her migraine.

It was the evening of 18 December 2005. Ariel Sharon, prime minister of Israel, was on his way home, when he suddenly had difficulties articulating. He was diagnosed with a transient ischaemic attack (TIA) and recovered quickly. A plausible reason for his TIA was identified: a PFO. He was slated to undergo percutaneous PFO closure after the Holidays on 5 January 2006. Until the procedure, the prime minister was treated with low-molecular-weight heparin. Tragically, the day before the scheduled procedure he collapsed at home and was hospitalized. Haemorrhagic stroke was the diagnosis. He never recovered from this incident and remained in a coma for 8 years until his death in January 2014.

The two patients are exemplary for PFO-associated events in several regards: first, a causative relation between a PFO and a particular event is always hypothetical. Secondly, PFO-associated events can have devastating sequelae. Thirdly, anticoagulation is the only valuable alternative to PFO closure, but bears a relevant lifetime risk of bleeding. And last but not least, migraine is associated with PFO and PFO closure for migraine includes the potential of preventing stroke.

## Patent foramen ovale closure, still a wallflower

Interventional cardiology has to weigh the benefits against the risks of a procedure in a particular patient. The more effective and the safer an intervention, the higher the adoption in clinical practice. Patent foramen ovale closure is the simplest intervention in interventional cardiology. A single operator can safely and virtually painlessly perform the procedure using local groin anaesthesia. It takes ~15 min and the patient can leave the hospital a few hours later without any physical restrictions. Nonetheless, many still question that the safety of PFO closure be outweighed by its effectiveness as a preventive intervention.

On a more global perspective, the annual incidence of stroke in the western world (Western Europe and North America) amounts to ~1.6 million; 1% of these strokes are recurrent strokes and 15% of these recurrent strokes are presumably caused by a PFO.<sup>1</sup> If all PFOs were closed for secondary prevention (240 000 PFO closures that is), 1150 strokes could theoretically be prevented annually when compared with a scenario where all patients with recurrent strokes and PFO were treated medically (assuming an 80% efficacy of PFO closure with a 60% relative risk reduction when compared with medical therapy).

The benefit may be even greater when looking at the data from a randomized controlled trial (RCT)<sup>2</sup>: only 25 PFOs needed to be

\* Corresponding author. Tel: +41 44 255 85 99, Fax: +41 44 255 44 01, Email: [fabian.nietlispach@usz.ch](mailto:fabian.nietlispach@usz.ch), [nietlispach@aol.com](mailto:nietlispach@aol.com)

Published on behalf of the European Society of Cardiology. All rights reserved. © The Author 2015. For permissions please email: [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

closed for secondary prevention in order to avoid one stroke within 5 years. In a population at an average age of 60 years, only about five PFOs need to be closed to prevent one stroke; less with PFO closure at a younger age.

## Current evidence

In addition to numerous registry analyses and non-randomized comparisons, three RCTs on PFO closure vs. medical therapy for secondary prevention of stroke have been published. The CLOSURE-1 trial (Evaluation of the STARFlex Septal Closure System in Patients with a Stroke and/or Transient Ischemic Attack due to Presumed Paradoxical Embolism through a Patent Foramen Ovale)<sup>3</sup> randomized 909 patients to either PFO closure (using the no longer available STARFlex device from NMT Medical, Boston, MA, USA) or medical therapy (vitamin K antagonist or acetylsalicylic acid). The PC trial (Percutaneous Closure of Patent Foramen Ovale in Cryptogenic Embolism)<sup>4</sup> enrolled 414 patients and the RESPECT trial (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment)<sup>2</sup> enrolled 980 patients to undergo PFO closure using the Amplatzer PFO Occluder (St Jude Medical, Plymouth, MN, USA) or medical therapy (vitamin K antagonist or antiplatelet therapy). Mean follow-up ranged from 2 to 4 years.

## Safety of patent foramen ovale closure

Safety of PFO closure emerges from the non-randomized and randomized trials, equally. Neither in the PC nor in the RESPECT trial were adverse events more common in the closure group than in the medical group (PC: 21 vs. 18%,  $P = 0.37$ ; RESPECT: 23 vs. 22%,  $P = 0.65$ ). Importantly, none of the adverse events resulted in either death or permanent disability.

Patent foramen ovale closure is associated with an increased incidence of atrial fibrillation. In the PC trial, the incidence of atrial fibrillation after PFO closure was 2.9% in the device group vs. 1.0% in the medical group ( $P = 0.17$ ). In the CLOSURE-1 trial using the obsolete STARFlex device, the difference was more marked and significant (5.7 vs. 0.7%,  $P > 0.001$ ). The three RCTs were likely underpowered for the occurrence of adverse events. Given the three- and eight-fold increases, respectively, in the incidence of atrial fibrillation, a potential harm of the intervention cannot be excluded. It seems, however, that device choice plays an important role in the occurrence of atrial fibrillation and it is furthermore important to note that two-thirds of these events in the device group happened within the first 2 weeks and only a few patients needed treatment for conversion or oral anticoagulation. This represents therefore a relatively harmless form of atrial fibrillation regarding stroke risk compared with the chronic forms in the elderly patients.

To reduce the small potential risk of device-induced atrial fibrillation, data suggest to use Amplatzer(-like) devices as a first choice.

The difference in the safety profile of different PFO closure devices was confirmed in a randomized study comparing the Amplatzer, STARFlex, and Helex (W.L. Gore & Associates, Inc., Flagstaff, AZ, USA) devices.<sup>5</sup> Procedural complications (device embolization, air embolism, or cardiac tamponade) happened most frequently with the use of the Helex device, whereas the STARFlex device had the worst safety profile during follow-up (atrial fibrillation in 12.3% and device thrombus in 5.0%).

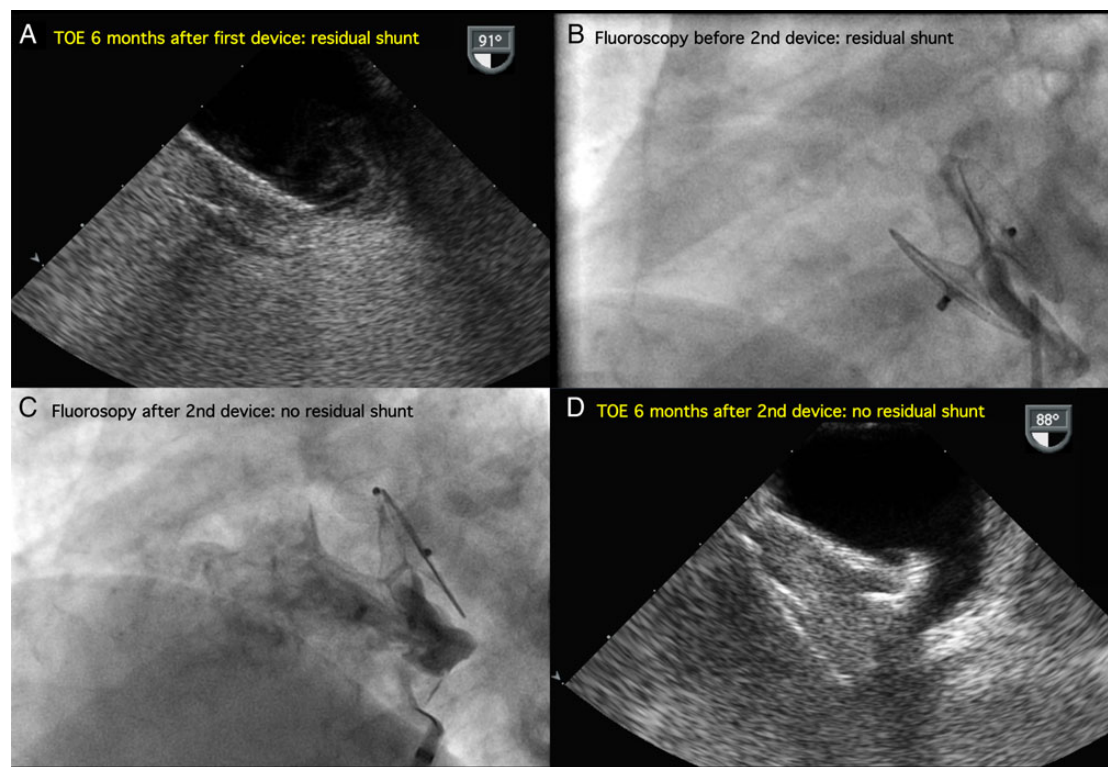
## Efficacy of patent foramen ovale closure

Rates of complete PFO closure were  $>95$  and  $>93\%$ , respectively, in the Amplatzer trials, but only 86% in the CLOSURE-1 trial. Closure rates matter since residual shunts have been associated with more recurrent events.<sup>6</sup> Residual shunts can be successfully treated with a second procedure (Figure 1).<sup>7</sup> Yet, re-closure with a second device is rarely performed, presumably also due to a prevailing overly complex approach to PFO closure, implying general anaesthesia and peri-procedural guidance with transoesophageal echocardiography (TOE).

## Underpowered trials and meta-analyses

All three RCTs are statistically not significant on their own with regard to the intention-to-treat analyses. Notwithstanding, all three RCTs point into the same direction with numerically less events in the PFO closure arm. In CLOSURE-1, the composite endpoint of stroke, TIA, death within 30 days, or death due to neurological causes from day 31 to 2 years occurred over 2 years in 5.5% of patients in the closure arm and 6.8% of patients in the medical arm [hazard ratio (HR) 0.78; 95% CI 0.45–1.35;  $P = 0.37$ ]. In the PC trial, the composite endpoint of death, non-fatal stroke, TIA, or peripheral embolism within 4 years occurred in 3.4 and 5.2% in the PFO closure and the medical arm, respectively (HR 0.63; 95% CI 0.24–1.62;  $P = 0.34$ ). In the RESPECT trial, 0.66 vs. 1.38 recurrent strokes per 100 patient-years occurred in the respective groups (HR 0.49; 95% CI 0.22–1.11;  $P = 0.08$ ). This indicates that the three RCTs were most likely underpowered regarding patient number or follow-up duration. The PC trial assumed the incidence of recurrent events in the medical therapy group to be 3% per year, when in fact it was roughly 1% per year. In the CLOSURE-1 trial, the incidence of the primary endpoint at 2 years was assumed to be 6% for the medical therapy arm and 3% in the PFO closure arm. After slow recruitment and when additional data on the incidence of recurrent strokes became available, the statistical analysis was revised during the conduction of the trial and the projected incidence in the device arm was reduced to 2% (thereby curtailing the sample size from 1600 to 800 patients). The observed incidence in the trial, however, was only 3.4% in the medical arm and 2.8% in the device arm. It were therefore mostly the patients in the medical treatment arm who performed better than assumed.

One possible way to overcome the limitation of underpowered trials is the analysis per treatment, which was significantly in favour of PFO closure in the RESPECT trial.<sup>2</sup> Another is to perform a meta-analysis. Several meta-analyses confirmed the superiority of PFO closure over medical therapy (Figure 2).<sup>8,9</sup> Rengifo-Moreno *et al.*<sup>8</sup> found a significant relative risk reduction for TIA or stroke of 41% (95% CI 0.36–0.97,  $P = 0.04$ ) and for death, neurological events, and peripheral embolism of 33% (95% CI 0.44–1.00,  $P = 0.05$ ) in favour of PFO closure. A device-specific analysis of all available RCTs reported a significant 61% relative risk reduction, when only randomized trials with the Amplatzer device were included (95% CI 0.17–0.84). Including the STARFlex or the Helex devices blunts the benefit somewhat.<sup>10</sup> The authors of the latter meta-analysis further calculated the probability of each treatment to be the best to prevent stroke. It was 77% for the Amplatzer device and only 0.4% for medical therapy.



**Figure 1** Second device for residual leak at follow-up of patent foramen ovale closure. A 70-year-old man with stroke was found on transoesophageal echocardiography (TOE) to have a significant residual leak 6 months after patent foramen ovale closure with a 30 mm Cribriform Amplatzer Occluder (A). The residual shunt was angiographically confirmed (B) and a second device (18 mm Amplatzer PFO Occluder) was implanted (C) with complete closure documented by TOE 6 months later (D).

The two randomized Amplatzer trials (PC<sup>4</sup> and RESPECT<sup>2</sup>) showed some strong trends, all in favour of PFO closure. In the PC trial, when using the contemporary stroke definition of the RESPECT trial, only one stroke occurred in the closure arm in contrast to seven strokes in the medical arm (HR 0.14, 95% CI 0.02–1.17,  $P = 0.07$ ). This corroborates the results of the RESPECT trial (HR 0.49, 95% CI 0.22–1.11,  $P = 0.08$ ). In the RESPECT trial, the risk reduction was even more pronounced when the composite of stroke and cardiovascular death was looked at (HR 0.17, 95% CI 0.02–1.47,  $P = 0.07$ ).

Recurrent strokes after PFO closure occurred exclusively early after PFO closure in the PC trial. No temporal pattern could be identified in the medical group where recurrent strokes occurred at random throughout the study period. Longer follow-up will show whether the curves keep diverging. Importantly, recurrent strokes were moderate to massive in the majority of patients in the medical treatment group, whereas only in a minority of patients in the PFO closure group (63 vs. 14%,  $P = 0.06$ ). This suggests that recurrent strokes may be less severe after PFO closure than after medical therapy.

### Per-protocol and as-treated analyses

Intention-to-treat analyses come with their own limitations in medical device trials: for instance, two patients suffered a TIA in the

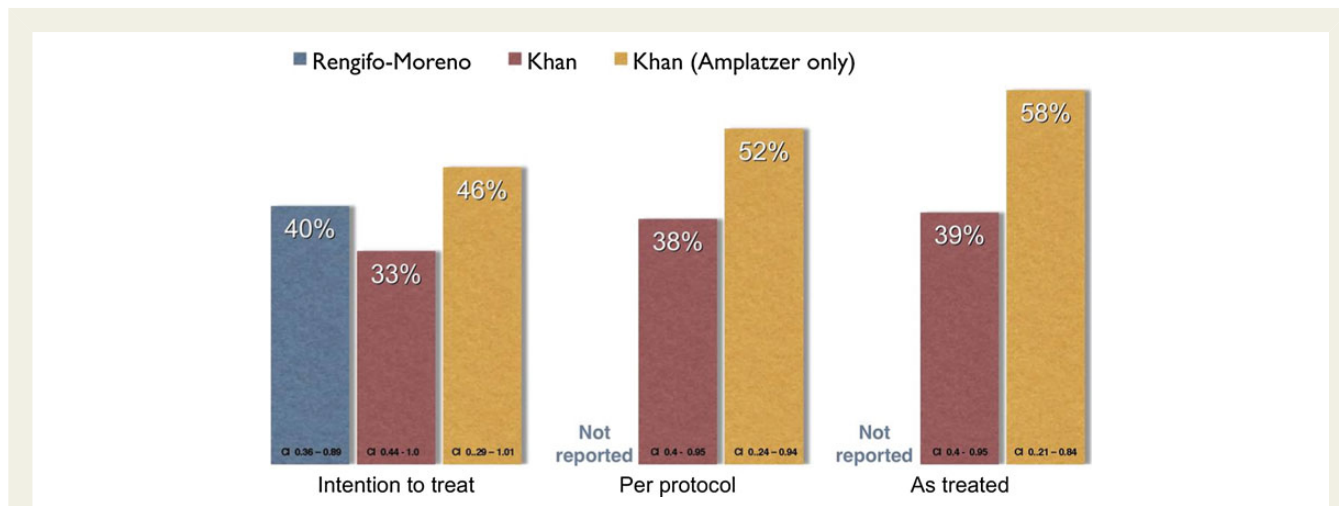
CLOSURE-1 trial while awaiting PFO closure. In the intention-to-treat analysis, these events are counted as events in spite of PFO closure.

The RESPECT trial reported a trend favouring PFO closure in the intention-to-treat analysis (9 vs. 16 events with a HR with closure of 0.49, 95% CI 0.22–1.11,  $P = 0.08$ ). Patent foramen ovale closure was significantly better than medical therapy in the per-protocol (6 vs. 14 events, HR 0.37, 95% CI 0.14–0.96,  $P = 0.03$ ) and the as-treated analyses (5 vs. 16 events, HR 0.39, 95% CI 0.10–0.75,  $P = 0.007$ ).

### Subgroup analyses and very long-term follow-up

In the subgroup analyses of the RESPECT trial, there was a significant benefit of PFO closure when compared with patients treated medically with acetylsalicylic acid alone (1.4 vs. 3.6%, HR 0.34, 95% CI 0.12–0.94,  $P = 0.03$ ). Vitamin K antagonists performed as well as PFO closure (3.0 vs. 2.5%, HR 1.14, 95% CI 0.26–5.1,  $P = 0.86$ ). Therefore, the only alternative to PFO closure is lifelong oral anticoagulation with its accruing and ever-increasing risk of bleeding.

Having this in mind and the fact that strokes occurred throughout the study period with medical therapy, one can expect an accumulating benefit with PFO closure with growing follow-up. This was indeed shown in an observational study of 308 patients with >10 years of follow-up<sup>11</sup>: a lower risk for stroke was found for patients



**Figure 2** Relative risk reduction in different meta-analyses.<sup>8,9</sup> Superiority of patent foramen ovale closure over medical therapy was confirmed with relative risk reduction for recurrent stroke/transient ischaemic attack of 33–58%. Left: superiority of patent foramen ovale closure in the intention-to-treat analyses (hazard ratio 0.54–0.67). Middle: superiority of patent foramen ovale closure in the per-protocol analyses (hazard ratio 0.48–0.62). Right: superiority of patent foramen ovale closure in the as-treated analyses (hazard ratio 0.42–0.61). CI, confidence interval.

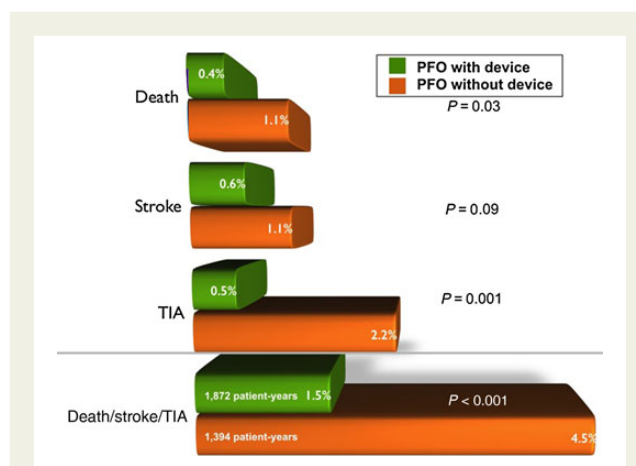
who underwent PFO closure when compared with medical therapy. Even more impressive, a mortality benefit during years after PFO closure when compared with years before or without PFO closure was observed. Patent foramen ovale closure resulted in a significant 64% relative risk reduction for death (Figure 3). Moreover, a propensity-matched analysis of about 200 patients was performed. It showed a significant reduction in the composite endpoint of stroke, TIA, or peripheral embolism in favour of PFO closure.

Patients with a significant right-to-left shunt or an atrial septal aneurysm at TOE not only have a more dangerous PFO, but they were also identified as a subgroup of patients to have a significant benefit of PFO closure in the RESPECT trial with a risk reduction of 82 and 81%, respectively (HR = 0.18, 95% CI 0.04–0.81, P = 0.01 with P-value for interaction 0.07 and HR = 0.19, 95% CI 0.04–0.87, P = 0.02 with P-value for interaction 0.10).

In summary, evidence suggests that the PFO is less dangerous regarding repeat cerebral events than suggested in the neurological literature of the 1980s. This has led to underpowered trials and the fact that strictly evidence-based medicine does not recommend PFO closure over medical therapy. The numerous sub-analyses or meta-analyses, however, invariably favour PFO closure. Although statistically not as powerful as the intention-to-treat analysis of a RCT, the additional analyses all point into the same direction and should not be ignored. Moreover, a single small percutaneous intervention appears more attractive than lifelong blood thinners even in case of equality rather than superiority.

### Current guidelines

In the most recent American guidelines,<sup>12</sup> PFO closure without evidence for deep venous thrombosis is not supported and in the presence of deep venous thrombosis only received a class IIb/level of evidence C recommendation. The European Stroke Organisation guidelines<sup>13</sup> only consider PFO closure in patients with cryptogenic stroke and a high-risk PFO and were written in 2008 when the



**Figure 3** Ten-year outcome of patients after patent foramen ovale (PFO) closure (patent foramen ovale with the device) compared with those on medical treatment (patent foramen ovale without the device) in terms of yearly risk of death, stroke, or transient ischaemic attack. There is a significant survival benefit with patent foramen ovale closure.<sup>11</sup>

current evidence was yet not available. Therefore, the current evidence needs to be more adequately reflected in the current guidelines (Table 1).

So far, guidelines only consider PFO closure in the setting of a ‘cryptogenic’ stroke. ‘Cryptogenic stroke’ is a misnomer, since it excludes PFO as an established cause of stroke in contrast to atrial fibrillation or carotid atherosclerosis. The presence of a PFO in patients with stroke/TIA should prompt PFO closure to eliminate at least one of the potential stroke causes. Patent foramen ovale closure should be withheld only if another indication for ongoing oral

**Table 1** Patients with an ischaemic stroke/TIA and the presence of a PFO

AHA/ASA Guidelines <sup>12</sup>	ESO Guidelines <sup>13</sup>	Suggested guidelines
Without DVT → data do not support PFO closure (class III, level A)	With high-risk PFO (ASA, EV, and CN) → PFO closure is considered (class IV)	PFO closure is recommended, even in the presence of other potential causes of stroke.
With DVT → PFO closure might be considered	In patients with more than one stroke → PFO closure is considered (class IV)	In patients with contraindication to PFO closure, oral anticoagulation is recommended
		PFO closure for primary prevention can be considered in patients at high risk for paradoxical embolism due to tendency for venous thrombosis, vocational or recreational activities fostering right to left shunts, or aggravating PFO attributes (ASA, EV, CN, etc.), or those who can expect a collateral benefit (e.g. patients suffering from migraine)
		For PFO closure, Amplatzer(-like) devices should be preferably used

TIA, transient ischaemic attack; ASA, atrial septal aneurysm; CN, Chiari network; DVT, deep venous thrombus; EV, Eustachian valve; PFO, patent foramen ovale.

anticoagulation (e.g. mechanical heart valve) or a contraindications exist.

## Time for patent foramen ovale closure for primary prevention?

Bearing in mind a small excess of atrial fibrillation caused by PFO closure, primary prevention should address high-risk patients.

### Patent foramen ovale properties

As shown in multiple studies, the probability that a PFO is the cause of an embolic event is higher in patients with a 'dangerous' PFO (PFO associated with an atrial septal aneurysm, an Eustachian valve or Chiari network, or a large spontaneous shunt)—therefore, anatomical findings (particularly on TOE) help to define a high-risk population.<sup>14</sup> Younger and otherwise healthy patients with a PFO have a higher relative risk of the PFO being responsible for an embolic event, although the absolute PFO risk increases with age and disease burden (more thrombi in the venous system).

### Patent foramen ovale and migraine

Migraine patients may experience collateral benefit of PFO closure in the form of prevention of paradoxical embolism in addition to possible migraine alleviation. The 37-year-old nurse suffered from migraine before experiencing a devastating embolic stroke. If her migraine had led to screening for a PFO with the intention to close it for the potential benefit on migraine, the subsequent catastrophic stroke would likely have been avoided. Evidence confirms an association of migraine and PFO. In an observational study on > 600 consecutive PFO closures,<sup>15</sup> one-fourth of patients suffered from concomitant migraine, whereof 64% suffered from severe migraine with aura. After PFO closure, migraine was cured in 34% and improved in 85% of these patients. Patients suffering from migraine with aura had a particularly favourable improvement of their symptoms with 39% of these patients being cured from their migraine after PFO closure. Therefore, patients suffering from migraine have a high chance to experience improvement of their symptoms

by PFO closure—as a 'collateral benefit' they will also be protected from paradoxical embolism. They may therefore be a target for PFO closure for primary stroke prevention.

### Screening for patent foramen ovale

Similar to patients with migraine, other conditions are associated with PFO and have a worthwhile chance to improve after PFO closure. Besides, persons with high-risk activities and persons at high risk for venous thrombosis, the prerequisite of paradoxical embolism could be considered for primary preventive PFO closure. A simple screening transthoracic echocardiography (TTE) bubble study may miss small PFOs, but likely identifies persons with a 'dangerous' PFO. They represent ~5% of the population. *Table 2* lists conditions and people that consider reasonable subjects to undergo such a screening test.<sup>16</sup>

### Possible strategies to support patent foramen ovale closure for primary prevention

It must be stressed that there are currently no data supporting PFO closure for primary prevention. However, it seems reasonable to give it due thought at least for PFOs with aggravating attributes in light of the devastating consequences a PFO-associated event can cause.

Given the slow recruitment and the long follow-up that was needed to complete the RCTs on PFO closure for secondary stroke prevention, it is unlikely that a RCT on primary prevention will be conducted in the near future. Nation-wide or multinational registries on primary prevention may therefore add valuable evidence. Also, company-initiated worldwide registries would be welcomed.

Screening of young people with a life expectancy of > 50 years for a PFO has to be considered, as only two PFOs need to be closed to avoid one stroke, assuming a comparable risk reduction for primary prevention in high-risk patients as for secondary prevention.

Closing all PFOs for secondary prevention and even more so if primary prevention in a subgroup of patients was considered, the financial burden for the health-care system would be considerable.

**Table 2** Conditions and people justifying screening for PFO

- Conditions associated with PFO
  - Migraine
  - Sleep apnoea
  - High altitude pulmonary oedema
  - Platypnoea orthodeoxia or exercise desaturation
- High-risk activities
  - Weight lifters, brass musicians, glass blowers, tile setters (frequent Valsalva manoeuvres)
  - Frequent flyers, pilots (high-risk for deep venous thrombosis)
  - Deep sea divers, military pilots, astronauts (risk of venous gas formation or microcavitations)
- Pacemaker- and internal cardioverter-defibrillator carriers (clots on cables)<sup>16</sup>

PFO, patent foramen ovale.

On the other hand, prevention pays back at least in part by avoiding costly clinical events. A more pro-active role of health-care authorities with regard to PFO closure seems therefore justified. In some individuals, tremendous suffering can be avoided.

## Conclusions

Stroke is among the most devastating diseases for patients and their families. It can cause loss of self-determination and independence. In a society where life expectancy of the general population is steadily increasing, it is the role of physicians to take every effort not only to prolong life, but also to preserve quality of life.

The role of cardiology is crucial to achieve this goal. Cardiology has to offer many therapies that prolong life and increase quality of life for patients. Patent foramen ovale closure is one of them. It is a simple, safe, and effective treatment that can make a difference for patients. It is a once-in-a-lifetime intervention and has therefore been referred to as a mechanical vaccination against some forms of stroke, myocardial infarction, and other systemic embolism.<sup>17</sup>

The current evidence does not seem to be sufficiently reflected in the European and American guidelines and a more pro-active role in PFO closure for secondary prevention and for high-risk patients appears justified. A simple screening test, perhaps building on ear-lobe oximetry,<sup>18</sup> is direly needed.

## Authors' contributions

Conceived and designed the research: F.N. and B.M.; drafted the manuscript: F.N.; made critical revision of the manuscript for key intellectual content: B.M.

**Conflict of interest:** F.N. and B.M. received proctor fees from St Jude Medical. B.M. received research grants to the institution and speaker fees from St Jude Medical.

## References

1. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007;**357**:2262–2268.
2. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;**368**:1092–1100.
3. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, Raizner A, Wechsler L. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;**366**:991–999.
4. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, Wahl A, Windecker S, Juni P. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med* 2013;**368**:1083–1091.
5. Hornung M, Bertog SC, Franke J, Id D, Taaffe M, Wunderlich N, Vaskelyte L, Hofmann I, Sievert H. Long-term results of a randomized trial comparing three different devices for percutaneous closure of a patent foramen ovale. *Eur Heart J* 2013;**34**:3362–3369.
6. Windecker S, Wahl A, Chatterjee T, Garachemani A, Eberli FR, Seiler C, Meier B. Percutaneous closure of patent foramen ovale in patients with paradoxical embolism: long-term risk of recurrent thromboembolic events. *Circulation* 2000;**101**:893–898.
7. Schwerzmann M, Windecker S, Wahl A, Nedeltchev K, Mattle HP, Seiler C, Meier B. Implantation of a second closure device in patients with residual shunt after percutaneous closure of patent foramen ovale. *Catheter Cardiovasc Interv* 2004;**63**:490–495.
8. Rengifo-Moreno P, Palacios IF, Junpaparp P, Witzke CF, Morris DL, Romero-Corral A. Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2013;**34**:3342–3352.
9. Khan AR, Bin Abdulhak AA, Sheikh MA, Khan S, Erwin PJ, Tleyjeh I, Khuder S, Eltahawy EA. Device closure of patent foramen ovale versus medical therapy in cryptogenic stroke: a systematic review and meta-analysis. *JACC Cardiovasc Interv* 2013;**6**:1316–1323.
10. Stortecky S, da Costa BR, Mattle HP, Carroll J, Hornung M, Sievert H, Trelle S, Windecker S, Meier B, Juni P. Percutaneous closure of patent foramen ovale in patients with cryptogenic embolism: a network meta-analysis. *Eur Heart J* 2015;**36**:120–128.
11. Wahl A, Juni P, Mono ML, Kalesan B, Praz F, Geister L, Raber L, Nedeltchev K, Mattle HP, Windecker S, Meier B. Long-term propensity score-matched comparison of percutaneous closure of patent foramen ovale with medical treatment after paradoxical embolism. *Circulation* 2012;**125**:803–812.
12. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;**45**:2160–2236.
13. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008;**25**:457–507.
14. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke: incidental or pathogenic? *Stroke* 2009;**40**:2349–2355.
15. Wahl A, Praz F, Tai T, Findling O, Walpoth N, Nedeltchev K, Schwerzmann M, Windecker S, Mattle HP, Meier B. Improvement of migraine headaches after percutaneous closure of patent foramen ovale for secondary prevention of paradoxical embolism. *Heart* 2010;**96**:967–973.
16. DeSimone CV, Friedman PA, Noheria A, Patel NA, DeSimone DC, Bdeir S, Aakre CA, Vaidya VR, Slusser JP, Hodge DO, Ackerman MJ, Rabinstein AA, Asirvatham SJ. Stroke or transient ischemic attack in patients with transvenous pacemaker or defibrillator and echocardiographically detected patent foramen ovale. *Circulation* 2013;**128**:1433–1441.
17. Meier B. Closure of the patent foramen ovale with dedicated Amplatzer occluders: closing in on a mechanical vaccination. *Catheter Cardiovasc Interv* 2008;**72**:80–81.
18. Billinger M, Schwerzmann M, Rutishauser W, Wahl A, Windecker S, Meier B, Seiler C. Patent foramen ovale screening by ear oximetry in divers. *Am J Cardiol* 2013;**111**:286–290.