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A systematic transoesophageal echocardiography study of suture-mediated percutaneous patent foramen ovale closure

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Introduction

Percutaneous patent foramen ovale (PFO) closure has proven to be superior to medical therapy for secondary prevention in selected patients with cryptogenic stroke[1]. Furthermore, percutaneous PFO closure prevents decompression sickness and platypnoea-orthodeoxia syndrome, and may play a role in patients with migraine[2]. However, despite their recognised efficacy, PFO occluders carry a potential risk of early and late complications and may represent an obstacle for future transseptal left-sided catheter-based interventions[3]. As the vast majority of PFO closure interventions are carried out for preventive purposes in a young population, the concept of "deviceless" PFO closure has become increasingly attractive and has been tested for over a decade, but with poor results[3]. Recently, a suture-mediated approach to percutaneous PFO closure has been proposed. Early data demonstrated feasibility in different anatomical conditions, with a high device success rate and no device-related complications[4,5]. Nevertheless, post-procedural PFO patency and device-related complications at follow-up have only been assessed using a transthoracic echocardiography (TTE) microbubble test, which provides limited sensitivity, leading to uncertainty regarding actual device performance[6,7]. Therefore, we conducted the present study to evaluate the efficacy and safety of suture-mediated PFO closure by transoesophageal echocardiography (TEE), which has been shown to have higher sensitivity than TTE for detection of residual shunt and characterisation of device-related complications[1].

Methods

Between July 2017 and July 2020, 80 consecutive patients underwent percutaneous suture-mediated PFO closure with the NobleStitch EL device (HeartStitch) at our institution and were included in this prospective observational registry. The study design is provided in **Supplementary Figure 1**. Inclusion and exclusion criteria are discussed in **Supplementary Appendix 1**. TEE was performed at baseline and between 3 and 6 months post procedure to evaluate residual right-to-left shunt (RLS), predictors of device failure, and device-related complications. Details of the TEE examination protocol

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and procedural steps are illustrated in **Supplementary Figure 2** and **Supplementary Appendix 2**. The primary efficacy outcome was effective PFO closure at TEE follow-up (residual RLS grade ≤1 at microbubble test). Secondary efficacy outcomes were procedural success (correct device delivery followed by negative intraprocedural contrast injection and TTE microbubble test) and complete PFO closure (residual RLS grade 0 at TEE follow-up). Secondary safety outcomes were procedure-related adverse events (access-site complications, bleeding, pericardial effusion or cardiac tamponade, arrhythmias), and in-hospital and follow-up device-related adverse events (device detachment, device embolisation, device thrombosis, or atrial septal damage). Other outcomes and the statistical analysis are discussed in **Supplementary Appendix 3** and **Supplementary Appendix 4**.

Results

BASELINE CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS

The median PFO tunnel length and width were 10 mm (interquartile range [IQR]=6-12 mm) and 4 mm (IQR=3-5 mm), respectively. Atrial septal aneurysm was encountered in 9% of patients, while a prominent Eustachian valve or Chiari network was identified in 11% of patients. A stretched PFO anatomy was reported in 31% of cases. The microbubble test was positive in all patients during the Valsalva manoeuvre and in 54% of patients at baseline during normal respiration; 44% of patients presented with a moderate RLS (grade 2) and 56% with a severe RLS (grade 3) **(Supplementary Table 1)**.

PROCEDURAL AND IN-HOSPITAL OUTCOMES

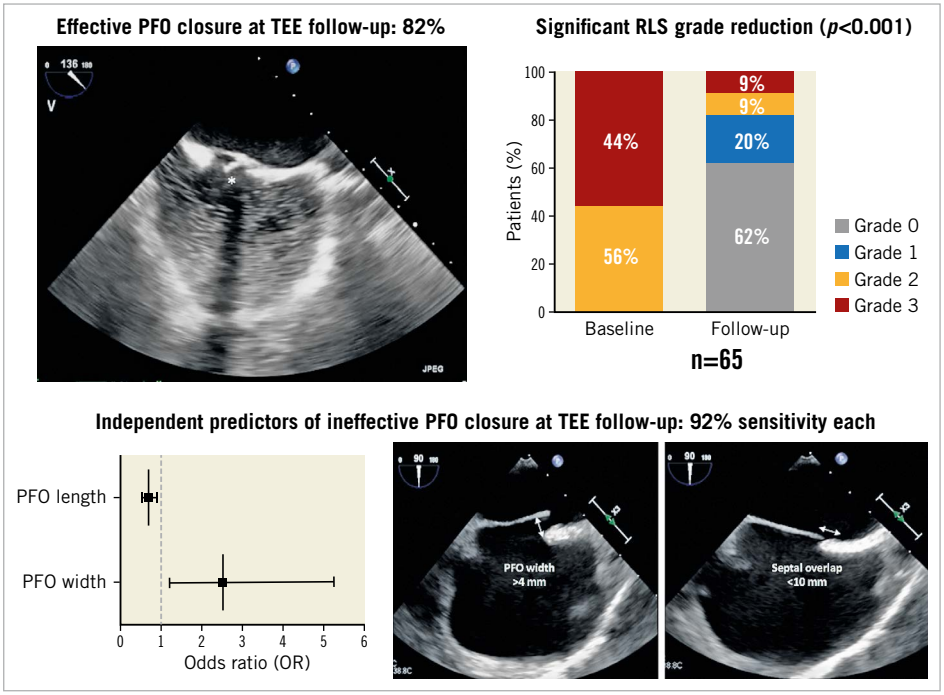
Percutaneous suture-mediated PFO closure was successfully carried out in 94% of patients. In 6 patients intraprocedural contrast injection and a TTE microbubble test demonstrated significant residual RLS that was addressed by an additional stitch delivery in 1 case, and by AMPLATZER PFO Occluder (Abbott) implantation in the remaining 5 cases. Procedural complications occurred in 8 (10%) patients. No device-related complications were observed. The majority of patients received one-month single antiplatelet therapy at discharge **(Supplementary Table 2)**.

TRANSOESOPHAGEAL ECHOCARDIOGRAPHY FOLLOW-UP

Of the 75 successfully treated patients, 65 (87%) underwent 3- to 6-month TEE follow-up. The mean TEE follow-up time was 142±96 days **(Supplementary Table 3)**. The primary efficacy outcome of effective PFO closure occurred in 82% of patients. Complete PFO closure occurred in 62% of patients **(Supplementary Figure 3)**. Overall, a significant reduction in RLS at the TEE microbubble test follow-up was observed (p<0.001). Residual RLS was present in 25 (38%) patients: 13 (20%) grade 1, 6 (9%) grade 2 and 6 (9%) grade 3 **(Central illustration)**.

PREDICTORS OF INEFFECTIVE PFO CLOSURE

A comparison of baseline clinical characteristics, echocardiographic features and procedural variables was performed between patients with effective PFO closure and those without **(Supplementary Table 4)**. **Supplementary Table 5** shows the results of the univariate analysis. Multivariable logistic regression analysis identified



Central illustration. *Suture-mediated percutaneous patent foramen ovale closure with the NobleStitch EL device: efficacy and failure predictors at transoesophageal echocardiography follow-up. PFO: patent foramen ovale; RLS: right-to-left shunt ; TEE: transoesophageal echocardiography*

PFO length (odds ratio [OR] 0.69, 95% confidence interval [CI]: 0.52-0.92, p=0.012) and PFO width (OR 2.52, 95% CI: 1.21-5.25, p=0.014) as independent predictors of ineffective PFO closure at TEE follow-up, with a good accuracy of the regression model (C-statistic 0.867) **(Table 1)**. Receiver operating characteristic (ROC) curve analysis identified a cut-off of 10 mm for PFO length (area under the curve [AUC] 0.788, sensitivity 92%) and of 4 mm for PFO width (AUC 0.800, sensitivity 92%) for the detection of incomplete PFO closure with the NobleStitch EL device at TEE follow-up **(Table 1)**. No cases of device detachment or embolisation were reported. A case of device thrombosis was documented in a patient with thrombotic diathesis which was managed with oral anticoagulation. A case of atrial septal defect was observed and treated with repeat percutaneous PFO closure using an AMPLATZER PFO Occluder[8].

CLINICAL FOLLOW-UP

Clinical follow-up was available for all 65 patients who underwent TEE follow-up **(Supplementary Table 6)**.

Discussion

Despite the lack of specific patient selection criteria, suture of the atrial septum with the NobleStitch EL device has shown encouraging results in terms of successful implantation, effective PFO closure and safety[4,5]. In this study, we adopted a systematic TEE-based strategy to evaluate device efficacy at 3- to 6-month follow-up in order to improve detection of residual RLS and to identify reliable functional and anatomical predictors of device failure and device-related complications, which should be carefully assessed during the initial clinical experience with every new technology. Effective closure was defined as residual RLS grade ≤1 at TEE follow-up, according to the definition adopted in the majority of clinical trials on PFO closure with traditional devices[9]. The rate of effective PFO closure with the NobleStitch EL device evaluated at 3- to 6-month TEE follow-up was 82%. This result appears to be in line with previously reported TTE data for the NobleStitch EL, but lower than TEE data for traditional PFO closure devices **(Supplementary Table 7)**. Despite different endpoint definitions derived from different RLS grading scores, and the lack of direct comparisons, the lower rates of effective PFO closure observed with the suture-mediated technique in currently available registries might have been influenced by inadequate patient selection criteria[1-5]. Among baseline TEE anatomical features, multivariable logistic regression analysis identified PFO length and PFO width as independent predictors of ineffective PFO closure at TEE follow-up. PFO length <10 mm and PFO width >4 mm showed 92% sensitivity for the identification of suboptimal anatomy for PFO closure with the NobleStitch EL device **(Figure 1)**. These results highlight the importance of careful anatomical assessment of the fossa ovalis by preprocedural baseline TEE to identify those patients who could benefit the most from suture-mediated PFO closure. Although commonly described as a tunnel, PFO has a semilunar shape that requires multiple 2D views or ideally 3D multiplanar imaging reconstruction to be fully characterised **(Supplementary Figure 4)**. Whether advanced procedural imaging guidance could improve outcomes remains to be determined. Real-time 3D TEE or intracardiac imaging of the fossa ovalis could guide septal suture placement and orientation during the procedure in order to achieve optimal sealing. As immediate post-procedure residual RLS has been shown to predict late shunt after PFO closure, the implementation of intraprocedural TEE assessment at the time of index procedure could help to identify a significant proportion of patients who would have presented with ineffective PFO closure at follow-up[10]. Finally, our data confirm the safety profile of the NobleStitch EL device, despite an increased sensitivity in device-related complication detection provided by the use of TEE at follow-up, with a rate of device thrombosis and atrial septal damage of 2% at 3 to 6 months.

Limitations

All the procedures were performed at a single centre by highly experienced operators, thus our results need further confirmation in order to be generalisable. Microbubble injections at baseline and follow-up were performed from the upper extremity, potentially affecting the sensitivity of the test. The lack of another PFO closure device for direct comparison, together with the relatively small sample size and short follow-up length, does not allow the

Table 1. Transoesophageal echocardiographic independent predictors and proposed cut-off values for the prediction of ineffective PFO closure.

Independent predictors of ineffective PFO closure						
Variables	**OR (95% CI)**	***p*-value**	**C-statistic**			
PFO length	0.69 (0.52-0.92)	0.012	0.867			
PFO width	2.52 (1.21-5.25)	0.014				
Cut-off values for the prediction of ineffective PFO closure						
Variable	**95% CI**	***p*-value**	**AUC**	**Cut-off**	**Sensitivity**	**Specificity**
PFO length	0.64-0.93	0.002	0.788	<10 mm	0.92	0.62
PFO width	0.68-0.92	0.002	0.800	>4 mm	0.92	0.50

Multivariate binary logistic regression analysis for predictors of ineffective PFO closure (residual RLS ≥grade 2) at follow-up with the NobleStitch EL device and receiver operating characteristic (ROC) curve analysis for the identification of PFO length and width cut-off values to predict ineffective PFO closure (residual RLS ≥grade 2) at follow-up with the NobleStitch EL device. AUC: area under the curve; CI: confidence interval; PFO: patent foramen ovale

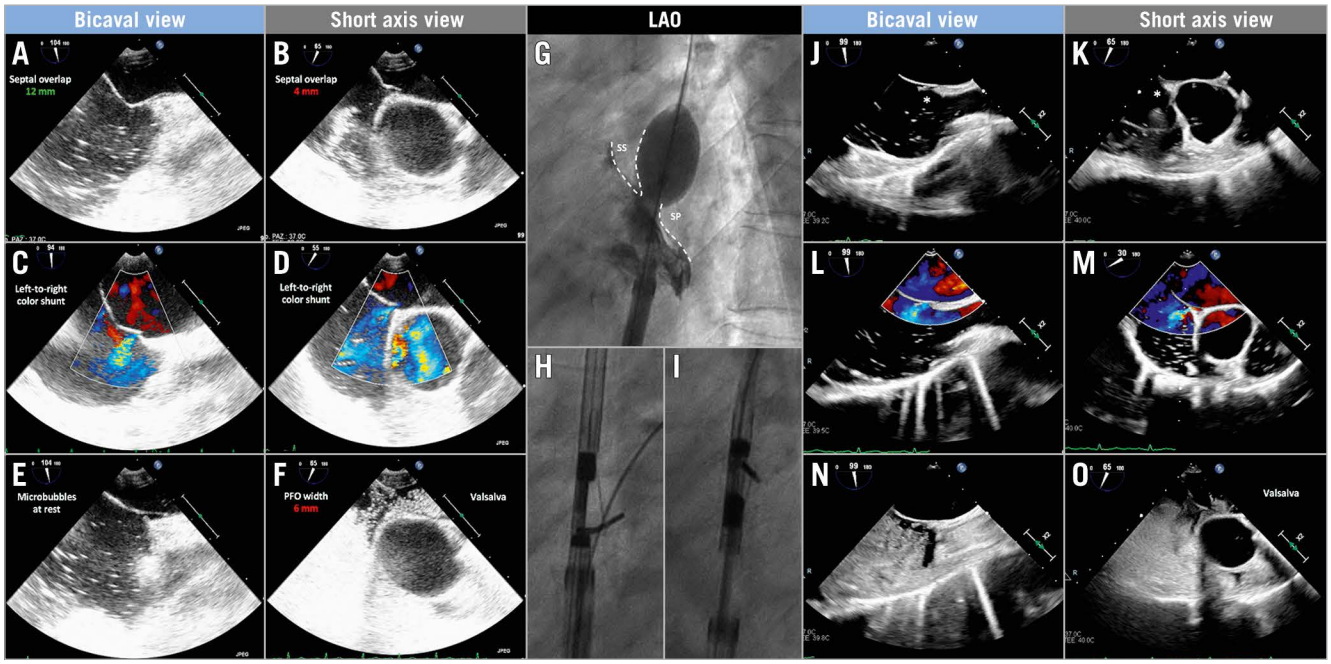


Figure 1. *Transoesophageal echocardiographic anatomical assessment of patent foramen ovale (PFO). Baseline TEE anatomical assessment in multiple 2D views showing favourable septal overlap in the bicaval view (A) that reduces to 4 mm in the short-axis view (B), baseline colour left-to-right shunt (stretched PFO) in both views (C & D), microbubble passage at rest even before the complete filling of the right atrium (E) and wide PFO opening with severe right-to-left shunt during Valsalva manoeuvre (F). Sizing balloon interrogation of the atrial septum demonstrating minimum overlap between septum secundum (SS) and septum primum (SP) (G). Percutaneous PFO closure using the NobleStitch device: delivery of septum secundum (H) and septum primum (I) sutures. Follow-up TEE evaluation at three months showing the KwiKnot (asterisk) in place (J & K) and demonstrating incomplete closure of the PFO with residual left-to-right colour shunt (L & M) and residual right-to-left shunt during Valsalva manoeuvre (N & O). LAO: left anterior oblique*

discrimination of efficacy in terms of recurrent cerebrovascular event reduction.

Conclusion

Suture-mediated PFO closure with the NobleStitch EL device currently provides lower rates of effective PFO closure than traditional devices with a favourable safety profile at 3- to 6-month TEE follow-up. PFO width and length at baseline TEE are relevant selection criteria that might improve the outcomes of the procedure. Further studies on larger populations are warranted to assess whether the proposed anatomical selection criteria and procedural imaging could improve the outcomes of percutaneous suture-mediated PFO closure and to establish more fully the role of the NobleStitch EL in the complex landscape of percutaneous PFO closure devices.

Impact on daily practice

Suture-mediated percutaneous PFO closure provides 82% effective PFO closure with a low rate of device-related complications at 3- to 6-month TEE follow-up. PFO length <10 mm and PFO width >4 mm identify patients with an unsuitable anatomy for the procedure.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Study design and patient population.

Supplementary Appendix 2. Transoesophageal echocardiographic examination.

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Supplementary Appendix 4. Statistical analysis.

Supplementary Table 1. Baseline clinical and transoesophageal echocardiography characteristics.

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Supplementary Table 5. Transoesophageal echocardiographic univariate predictors of ineffective PFO closure.

Supplementary Table 6. Follow-up clinical outcomes.

Supplementary Table 7. Comparison of device efficacy in different PFO closure studies.

Supplementary Figure 1. Study design.

Supplementary Figure 2. Percutaneous patent foramen ovale closure with the NobleStitch EL device: procedural steps.

Supplementary Figure 3. Complete closure of patent foramen ovale with the NobleStitch EL device: baseline, procedure and follow-up transoesophageal echocardiography.

Supplementary Figure 4. Three-dimensional transoesophageal echocardiography assessment of the fossa ovalis.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00242

Supplementary data

Supplementary Appendix 1. Study design and patient population

A cohort of 182 consecutive patients was evaluated for suture-mediated PFO closure with the NobleStitch EL device (HeartStitch, Inc., Fountain Valley, CA, USA) at our institution between July 2017 and July 2020. Of these, 102 patients were excluded because of reluctance to undergo TEE follow-up (27.5%) or unsuitable anatomy at baseline TEE evaluation: atrial septal defect (13%), multi-fenestrated atrial septum (26.5%), and atrial septal aneurysm with extremely floppy tissue (33%). Overall, 80 patients underwent suture-mediated PFO closure with the NobleStitch EL device and were included in this prospective observational registry. Patients were considered eligible if they had experienced a documented cryptogenic cerebrovascular accident (CVA), including ischaemic stroke or transient ischaemic attack (TIA), or if they complained of intractable migraine, or were exposed to the risk of decompression sickness, or suffered from platypnoea-orthodeoxia syndrome, and had evidence of PFO with significant right-to-left shunt (RLS). All patients underwent complete neurological and cardiological examination as appropriate, including neuroimaging, 24-hour Holter-ECG monitoring, carotid artery Doppler ultrasound, and PFO documentation by contrast-enhanced transcranial Doppler or TTE. Baseline TEE was performed in all the cases. Ischaemic stroke and TIA were defined as previously described [3]. The index CVA was defined as cryptogenic after other identifiable causes had been ruled out [3]. The risk of paradoxical embolism (RoPE) score was calculated for each patient to evaluate the likelihood of PFO being associated with the index cryptogenic CVA [20]. Data regarding procedural technical details and in-hospital outcomes were prospectively collected. After discharge, patients were followed-up by outpatient visits or phone calls at 1, 3 and 6 months after the procedure, and a follow up TEE microbubble test was scheduled at 3 to 6 months to evaluate residual RLS. The study design is illustrated in **Supplementary Figure 1**.

Supplementary Appendix 2. Transoesophageal echocardiographic examination

All patients underwent comprehensive TEE examination according to ASE recommendations [21]. In all patients, multiple planes including short-axis view and bicaval view were systematically evaluated to identify the best projection for PFO shunt detection and anatomical assessment. According to current guidelines, PFO was diagnosed when microbubbles were found in the left atrium within three cardiac cycles after their appearance in the right atrium either at rest or during the Valsalva manoeuvre release phase [21]. Baseline and follow-up RLS was graded on a standard scale based on the maximum number of microbubbles detected in the left atrium in any single frame during the first three cardiac cycles after their appearance in the right atrium, according to the definition used in the RESPECT trial: the presence of no microbubbles was indicated as grade 0 (no RLS), 1-9 microbubbles as grade 1 (mild RLS), 10-20 microbubbles as grade 2 (moderate RLS), and >20 bubbles as grade 3 (severe RLS) [3]. The following anatomical features were systematically assessed at baseline: PFO length (minimum overlap between septum primum and secundum), PFO width (maximum opening), presence of atrial septal aneurysm (excursion of the septal tissue of >10 mm from the plane of the atrial septum into the right or left atrium or a combined total excursion right and left of ≥15 mm), presence of stretched PFO (baseline colour Doppler left-to-right shunt, resulting from stretching of the superior limbic band of the septum secundum by atrial dilation and remodelling without a true deficiency of the atrial septal tissue), presence of prominent Eustachian valve or Chiari network. Preprocedural images were assessed by an interventional cardiologist and an echocardiographer, both highly experienced in structural heart interventions.

Supplementary Appendix 3. Suture-mediated percutaneous PFO closure

The NobleStitch EL system consists of three elements that are sequentially introduced inside the heart through the femoral vein. After crossing the PFO with a multipurpose or similar catheter, a

0.035'' stiff guidewire is placed in the left upper pulmonary vein and a straightened 14 Fr Mullins sheath (PTS-X; NuMED, Hopkinton, New York, NY, USA) is advanced in the right atrium. Sizing balloon interrogation of the PFO during contrast injection is performed to determine the anatomy of the septum secundum (SS) and septum primum (SP). The 0.035'' stiff guidewire is exchanged for a 0.032'' guidewire and an additional 0.018" guidewire is placed into the distal superior vena cava. The NobleStitch S and NobleStitch P dedicated suture delivery catheters are sequentially advanced and contrast injections are carried out to obtain optimal engagement of the SS and SP. After each NobleStitch needle has been pierced through the septum to capture and retrieve the 4-0 polypropylene suture from the suture-carrying arm, the system is removed along with the wire, leaving the sutures free. The suture ends are then gently pulled together to draw the SP towards the right atrium. Finally, the KwiKnot catheter is advanced over the sutures to approximate both septa, achieving an "S" shape closure of the PFO by securing the stitch and trimming the excess suture material, leaving a radiopaque polypropylene knot on the right side of the atrial septum. Contrast injection and a TTE saline microbubble test were performed in all patients to assess the acute result by injection from the inferior vena cava. In case of device failure (any residual RLS), the use of a second stitch or a bail-out traditional PFO closure device was permitted. Procedural details are illustrated in **Figure 1**. The procedure was performed under local anaesthesia and fluoroscopic guidance. The first 3 cases were performed using TEE monitoring, under general anaesthesia. Prophylactic antibiotics were administered in all patients. Patients were pre-treated with a single antiplatelet agent (aspirin 100 mg daily) in the absence of other indications, and received unfractionated heparin to achieve and maintain an activated clotting time >250 seconds during the procedure. During in-hospital stay, patients received 24-hour ECG monitoring after the procedure. Antithrombotic therapy at discharge consisted of a single antiplatelet agent for ~~one~~1 month, in the absence of other indications.

Supplementary Appendix 4. Statistical analysis

Continuous variables were described as means and standard deviations (SD) or as medians and interquartile ranges (IQR), as appropriate. Normality was checked by the Kolmogorov-Smirnov test. Categorical variables were expressed as proportions and compared with the χ^2 test with Yates correction for continuity or the Fisher's exact test as appropriate. Comparison of independent groups was performed either with an unpaired t-test or with the Mann-Whitney U test or the sign test, as appropriate. The baseline and follow-up measurements were compared using a paired t-test or the Wilcoxon signed-rank test, as appropriate. Binary logistic regression was used to identify echocardiographic predictors of ineffective PFO closure (primary efficacy outcome). The results were reported as odds ratio (OR) with associated 95% confidence intervals (CI). The predictive accuracy of the logistic regression model was assessed by the concordance (c) statistics. Receiver operating characteristic (ROC) curve analysis for continuous anatomical variables was performed to identify the best cut-off value to predict effective PFO closure at TEE follow-up, assuming that sensitivity rather than specificity would be of higher clinical relevance in this context in order to minimise the risk of inadequate patient selection and eventually reduce the need for additional bail-out procedures. Two-sided p-values<0.05 were considered statistically significant. Statistical analyses were performed using SPSS software, Version 24 (IBM Corp., Armonk, NY, USA). Graphs were generated with GraphPad Prism software, version 6 (GraphPad, Inc, San Diego, CA, USA).

Supplementary Table 1. Baseline clinical and transoesophageal echocardiography characteristics.

Baseline clinical and transoesophageal echocardiography characteristics	Patients (N=80)
Age, years	48±12
Female	43 (54)
Medical history	
• Hypertension	20 (25)
• Dyslipidaemia	24 (30)
• Current smoker	11 (14)
• Diabetes	2 (3)
Reason for PFO closure	
• Cryptogenic CVA	72 (90)
• Intractable migraine	6 (7)
• Other	2 (3)
Type of recurrent cryptogenic CVA	
• Ischaemic stroke	50 (69)
• TIA	22 (31)
Disabling stroke (modified Rankin scale* ≥3 at 6 months)	0 (0)
RoPE score†	6 (5-7)
PFO length, mm	10 (6-12)
PFO width, mm	4 (3-5)
Atrial septal aneurysm‡	7 (9)
Prominent Eustachian valve	9 (11)
Baseline colour shunt (stretched PFO)§	25 (31)
Valsalva colour shunt	10 (12)
Baseline positive microbubble test	43 (54)
Valsalva positive microbubble test	80 (100)
Right-to-left shunt severity	
• Grade 2 shunt	35 (44)
• Grade 3 shunt	45 (56)
High-risk PFO‖	80 (100)

Data are presented as absolute numbers and percentages (for categorical variables) or median value (IQR) or mean value±SD (for continuous variables), as appropriate.
* The modified Rankin scale is a measure of disability. Scores range from 0 (no symptoms) to 6 (death). A score of 3 or higher indicates at least moderate disability, with the need for some help in daily affairs.
† Risk of paradoxical embolism (RoPE) is a score index used to indicate whether a PFO in cryptogenic CVAs is stroke/TIA-related or incidental. Scores range from 0 to 10, with larger values representing a higher probability that a PFO is related to cryptogenic CVA.
‡ Atrial septal aneurysm was defined as excursion of the septal tissue of >10 mm from the plane of the atrial septum into the right or left atrium or a combined total excursion right and left of ≥15 mm.

§ Stretched PFO derives from stretching of the superior limbic band of the septum secundum by atrial dilation and remodelling, without a true deficiency of the atrial septal tissue, resulting in baseline colour Doppler left-to-right shunt.
|| High-risk PFO is defined as the presence of atrial septal aneurysm and/or moderate to severe shunt (grade ≥2) and refers to the risk of paradoxical embolisation.

Supplementary Table 2. Procedural and in-hospital outcomes.

Procedural and in-hospital outcomes	Patients (N=80)
Successful PFO closure*	75 (94)
Second stitch delivery	1 (1.5)
Bail-out traditional device†	5 (6)
Transoesophageal echocardiography guidance	3 (4)
Procedural time, min	40 (31-64)
Radiation exposure, Gy·cm^2	60 (40-116)
Contrast media volume, mL	140 (100-175)
Procedure-related complications	
• Access-site minor bleeding‡	3 (4)
• Retroperitoneal haemorrhage	1 (1.5)
• Arteriovenous fistula	1 (1.5)
• Cardiac tamponade	0 (0)
• Pericardial effusion	0 (0)
• Atrial fibrillation or supraventricular tachycardia	3 (4)
Device-related complications	
• Device detachment or embolisation	0 (0)
• Device thrombosis	0 (0)
• Atrial septal damage	0 (0)
Hospitalisation length, days	2.7±0.9
In-hospital all-cause death	0 (0)
Antithrombotic therapy at discharge	
• Aspirin	44 (55)
• Clopidogrel	10 (12)
• DAPT	21 (26)
• NOAC	2 (3)
• None	3 (4)

Data are presented as absolute numbers and percentages (for categorical variables) or median value (IQR) or mean value±SD (for continuous variables), as appropriate.
* Successful PFO closure was defined as correct delivery of the septal sutures followed by negative intraprocedural contrast injection and/or TEE or TTE microbubble test.
† Amplatzer PFO Occluder (Abbott Vascular, Santa Clara, CA, USA) was used as bail-out device in all 3 cases.
‡ Bleeding severity was defined according to BARC classification.

Supplementary Table 3. Follow-up transoesophageal echocardiography outcomes.

Transoesophageal echocardiography outcomes	Patients (N=65)
Follow-up time, days	142±96
Device-related complications	
• Device detachment or embolisation	0 (0)
• Device thrombosis	1 (2)
• Atrial septal tear*	1 (2)
Baseline colour shunt	5 (8)
Valsalva colour shunt	4 (7)
Baseline positive microbubble test	12 (18)
Valsalva positive microbubble test	25 (38)
Right-to-left shunt severity	
• Grade 0 shunt	40 (62)
• Grade 1 shunt	13 (20)
• Grade 2 shunt	6 (9)
• Grade 3 shunt	6 (9)
Complete PFO closure†	40 (62)
Effective PFO closure‡	53 (82)

Data are presented as absolute numbers and percentages (for categorical variables) or mean value±SD (for continuous variables), as appropriate.
* Diamond-shaped atrial septal defect with left-to-right shunt.
† Complete closure was defined as a residual RLS grade 0 at follow-up.
‡ Effective closure was defined as a residual RLS grade ≤1 at follow-up.

Supplementary Table 4. Baseline and procedural characteristics of the patients with and without significant residual right-to-left shunt (grade ≥2) at transoesophageal follow-up.

	Effective closure (N=53)	Ineffective closure (N=12)	*p*-value
Age, years	49±11	51±12	0.348
Female	30 (57)	5 (42)	0.349
Reason for PFO closure			
• Cryptogenic ischaemic stroke	35 (67)	6 (50)	0.513
• Cryptogenic TIA	12 (23)	5 (42)	0.273
• Intractable migraine	4 (7)	1 (8)	0.309
• Other	2 (3)	0 (0)	1.000
RoPE score†	5 (4-6)	5 (4-8)	0.522
PFO length, mm	11 (7-12)	6.5 (4.5-8)	0.002
PFO width, mm	4 (3-4.5)	5 (4-5.5)	0.005
Atrial septal aneurysm	4 (7.5)	2 (17)	0.305
Prominent Eustachian valve	6 (11)	2 (17)	0.634
Baseline colour shunt (stretched PFO)	6 (11)	5 (42)	0.024
Valsalva colour shunt	5 (9)	2 (17)	0.604
Baseline microbubble test positivity	23 (43)	11 (92)	0.003
Right-to-left shunt severity			
• Grade 2 shunt	26 (49)	4 (33)	0.324
• Grade 3 shunt	27 (51)	8 (67)	0.324
Transoesophageal echocardiography guidance	2 (3)	0 (0)	1.000
Procedural time, min	48 (31-65)	37 (27-54)	0.236
Radiation exposure, Gy·cm^2	58 (40-109)	69 (40-171)	0.393
Contrast media volume, mL	150 (102-180)	100 (80-130)	0.010

Data are presented as absolute numbers and percentages (for categorical variables) or mean value±SD (for continuous variables), as appropriate. Echocardiographic and clinical follow-up length were not significantly different between the two groups

Supplementary Table 5. Transoesophageal echocardiographic univariate predictors of ineffective PFO closure.

Univariate predictors	OR (95% CI)	*p*-value
PFO length	0.67 (0.50-0.88)	0.004
PFO width	2.37 (1.29-4.38)	0.006
Atrial septal aneurysm	2.45 (0.39-15.25)	0.336
Prominent Eustachian valve	1.56 (0.27-8.92)	0.613
Baseline colour shunt (stretched PFO)	5.59 (1.32-23.33)	0.018
Valsalva colour shunt	1.92 (0.32-11.33)	0.476
Baseline positive microbubble test	12.50 (1.49-104.61)	0.020
Right-to-left shunt grade 2	0.52 (0.14-1.93)	0.329
Right-to-left shunt grade 3	1.92 (0.52-7.10)	0.329

Univariate binary logistic regression analysis for predictors of ineffective PFO closure (residual RLS ≥grade 2) at follow-up with the NobleStitch EL device.

Supplementary Table 6. Follow-up clinical outcomes.

Clinical outcomes	Patients (N=65)
Clinical follow-up time, days	226±112
All-cause death	0 (0)
Recurrent ischaemic stroke	0 (0)
Recurrent TIA	2 (3)
Recurrent migraine*	6 (9)
Holter ECG or ILR monitoring	16 (25)
Detected arrhythmias	0 (0)
Repeated PFO closure with traditional device†	6 (9)

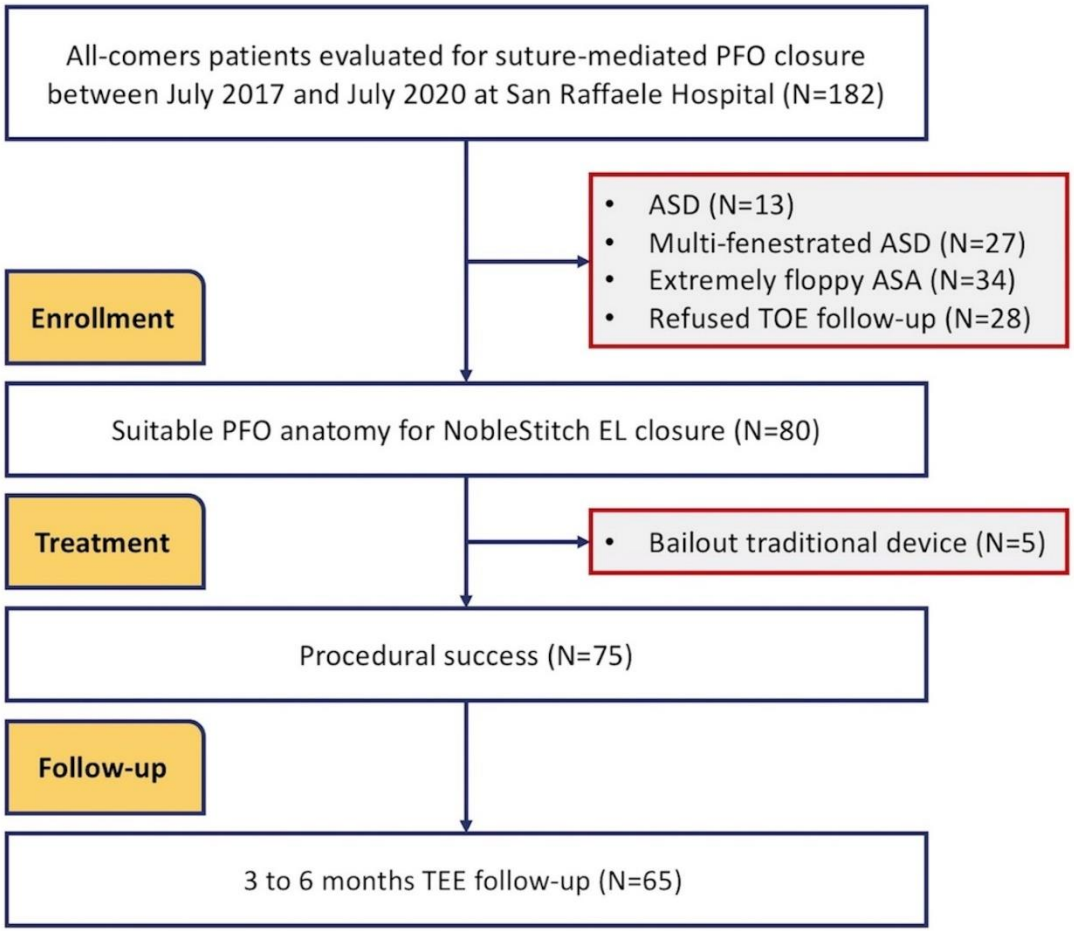
Data are presented as absolute numbers and percentages (for categorical variables) or mean value±SD (for continuous variables), as appropriate.
* In patients with available follow-up, recurrent migraine was reported in 2 out of 6 (33%) in whom it was considered as the primary indication for PFO closure.
† Amplatzer PFO Occluder (Abbott Vascular, Santa Clara, CA, USA) was used as bail-out device in 2 cases.

Supplementary Table 7. Comparison of device efficacy in different PFO closure studies.

	Closure-I (2012)	PC trial (2013)	RESPECT (2013)	CLOSE (2017)	Gore REDUCE (2017)	DEFENSE PFO (2018)	Italian registry (2018)	Gaspardone et al (2020)
Study design	RCT	RCT	RCT	RCT	RCT	RCT	Prospective registry	Prospective registry
Patients (N)	447	204	499	238	441	60	192	230
Study device	STARFlex Septal Closure System	Amplatzer PFO Occluder	Amplatzer PFO Occluder	Different devices*	HELEX or GSO	Amplatzer PFO Occluder	NobleStitch EL	NobleStitch EL
Procedural success (%)†	89.4	95.9	96.1	99.6	98.8	100	96	96
Follow-up strategy	TEE	TEE	TEE	TEE	TEE	TTE	TTE	TTE
Follow-up time (months)	6	6	6	12	12	1**	12	3-6
Complete PFO closure (%)‡	-	-	72.7	-	75.6	-	75	62
Effective PFO closure (%)¶	86.1	95.9	93.5	93	94.5	93.3	89	84

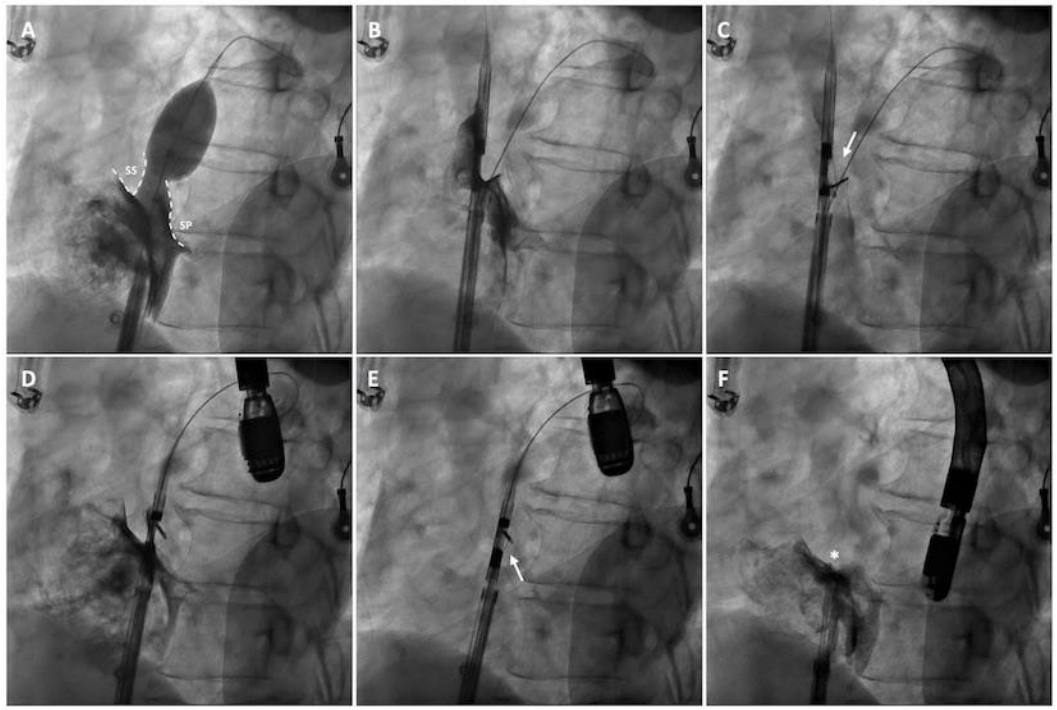
Data are reported as absolute numbers or percentages, as indicated.
† Procedural success was defined as correct device implantation and retention or suture delivery, as appropriate.
‡ Complete closure was defined as a residual right-to-left shunt grade 0 at follow-up.
¶ Effective closure was defined as a residual right-to-left shunt grade ≤1 at follow-up in all the studies, except for the Gore REDUCE trial in which it was defined as a residual right-to-left shunt grade <3 at follow-up.
In RCTs, shunt grading varied according to study definitions. In Gaspardone et al[5], shunt grading followed the RESPECT trial scale.
* In the CLOSE trial the Amplatzer PFO Occluder device was used in 51.5% of cases.

** In the DEFENSE PFO trial follow-up TTE was performed 1 day after the procedure.
Amplatzer PFO Occluder (Abbott Vascular, Santa Clara, CA, USA), HELEX Septal Occluder and CARDIOFORM Septal Occluder (Gore Medical, Flagstaff, AZ, USA), NobleStitch EL (HeartStitch Inc., Fountain Valley, CA, USA); STARFlex Septal Closure System (NMT Medical, Boston, MA, USA).
PFO: patent foramen ovale; RCT: randomised controlled trial; TEE: transoesophageal echocardiography; TTE: transthoracic echocardiography

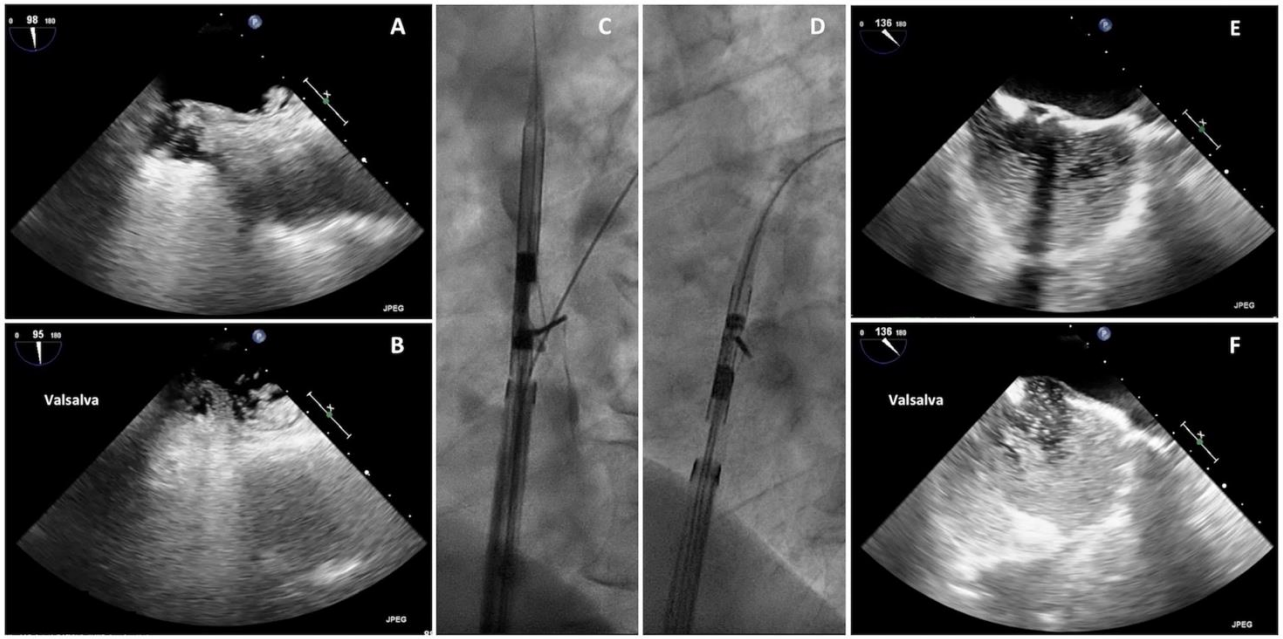


Supplementary Figure 1. Study design.

Overview of patient selection, enrolment, treatment and follow-up.

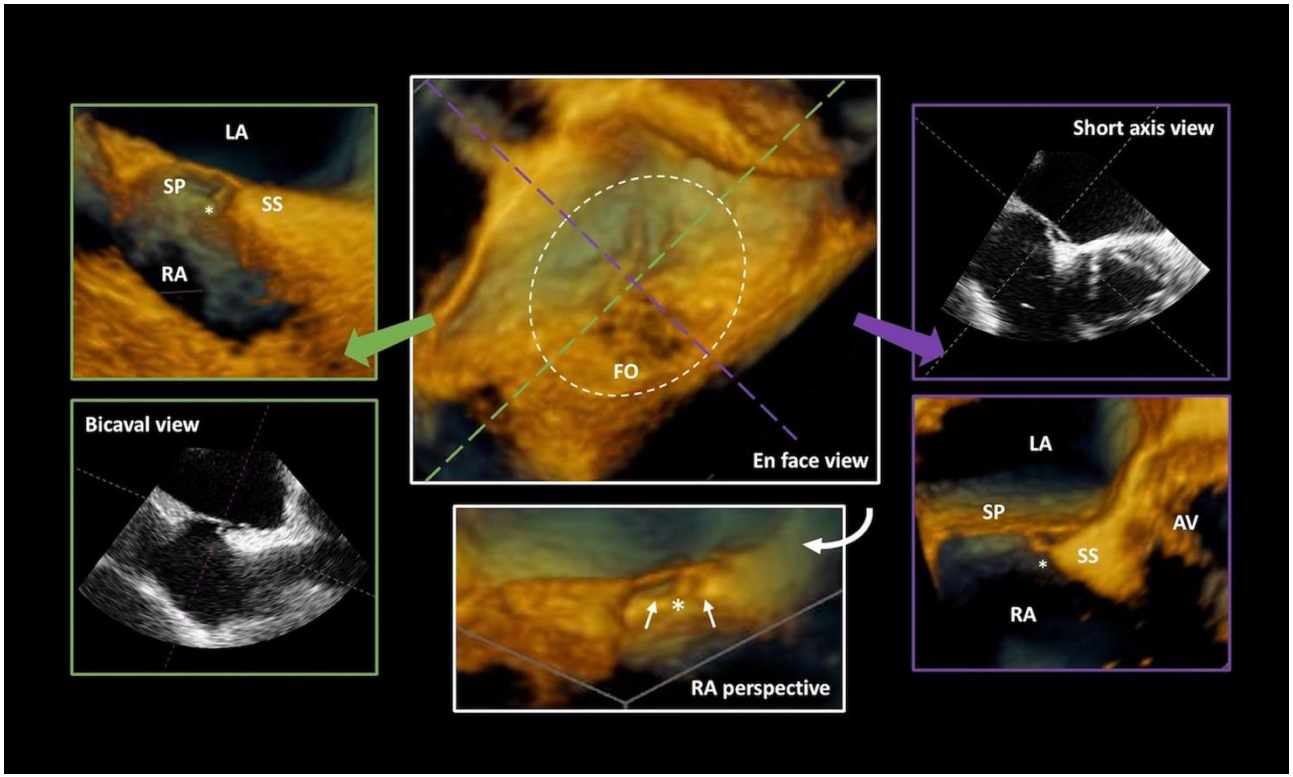


Supplementary Figure 2. Percutaneous patent foramen ovale closure with the NobleStitch EL device: procedural steps.
Sizing balloon interrogation of the PFO to determine the anatomy of the septum secundum (SS) and septum primum (SP) during contrast injection (A). NobleStitch S and P sequential advancement and needle firing (white arrows) through the septum secundum (B & C) and the septum primum (D & E), suturing the septum primum at the level of the nadir of the septum secundum, in order to fold it back over the septum secundum. Final contrast injection showing the KwiKnot in place at the right side of the atrial septum (asterisk) and no residual shunt (F).



Supplementary Figure 3. Complete closure of patent foramen ovale with the NobleStitch EL device: baseline, procedure and follow-up transoesophageal echocardiography.

Baseline TEE microbubble test during normal respiration (A) and during the Valsalva manoeuvre (B) showing severe right-to-left shunt: >25 microbubbles within three cardiac cycles after appearance in the right atrium (arrows). Percutaneous PFO closure using the NobleStitch device: delivery of septum secundum (C) and septum primum (D) sutures. Repeat microbubble test at three months TEE follow-up showing the KwiKnot (asterisk) in place and demonstrating complete closure of the PFO without any residual right-to-left shunt at rest (E) and during the Valsalva manoeuvre (F).



Supplementary Figure 4. Three-dimensional transoesophageal echocardiography assessment of the fossa ovalis.

TEE follow-up real-time 3D volume rendering of the fossa ovalis showing an *en face* view from the left atrium and right atrium perspective (white boxes). Multiplanar reconstruction identifying the bicaval view (green boxes) and short-axis view (purple boxes). Despite the suture (*) being placed in the middle of the PFO, there is a large opening on both sides (arrows).