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EACVI Communication

EACVI survey on the management of patients with patent foramen ovale and cryptogenic stroke

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Aims The European Association of Cardiovascular Imaging (EACVI) Scientific Initiatives Committee performed a global survey to evaluate the current practice for the assessment and management of patients with suspected patent foramen ovale (PFO) and cryptogenic stroke.

Methods and results In total, 79 imaging centres from 34 countries across the world responded to the survey, which comprised 17 questions. Most non-invasive investigations for PFO were widely available in the responding centres, with the exception of transcranial colour Doppler which was only available in 70% of sites, and most commonly performed by neurologists. Standard transthoracic echocardiography, with or without bubbles, was considered the first-level test for suspected PFO in the majority of the centres, whereas transoesophageal echocardiography was an excellent second-level modality. Most centres would rule out atrial fibrillation (AF) as a source of embolism in all patients with cryptogenic stroke (63%), with the remainder reserving investigation for patients with multiple AF risk factors (33%). Cardiac magnetic resonance was the preferred tool for identifying other unusual aetiologies, like cardiac masses or thrombi. After PFO closure, there was variation in the use of antiplatelet therapy: a quarter recommended treatment for life, while only 12% recommended 5 years as stipulated in the guidelines (12%). Antibiotic prophylaxis prior to dental or endoscopic procedures was not recommended in 41% of centres, contrary to what the guidelines recommended.

Conclusion Our survey revealed a variable adherence to the current recommendations for the diagnosis and management of patients with cryptogenic stroke and PFO. Efforts should focus on optimizing and standardizing diagnostic tests and treatment of this condition.

Keywords patent foramen ovale • cryptogenic stroke • transoesophageal echocardiography/transcranial Doppler/survey/EACVI

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Introduction

The foetal connection between the left and right atria at the fossa ovalis remains open during adulthood in a quarter of the general population, with a higher prevalence in persons <30 years and lower in those >80 years old.[1] Patent foramen ovale (PFO) often remains undiagnosed but has been implicated in the aetiology of cryptogenic stroke due to paradoxical embolism through a right-to-left shunt. The management of PFO for stroke prevention has been the object of intense debate over the last few decades. The initial randomized trials of PFO closure in patients with cryptogenic stroke were neutral,[2–6] however, the most recent randomized clinical trials demonstrated benefit with PFO device closure compared with medical therapy in patients <60 years with cryptogenic stroke.[7–11]

In the midst of this controversy, considerable variation has emerged across different hospitals in the diagnostic and therapeutic pathways used to manage patients with a PFO and recent cryptogenic stroke. However, in 2018, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Scientific Documents and Initiatives Committee invited the European Association of Cardiovascular Imaging (EACVI), seven other European scientific societies, and a range of international experts to develop a shared and rational position statement on the management of PFO to help guide and standardize clinician decision-making.[12]

The aim of this survey from the EACVI Scientific Initiatives Committee was to assess current diagnostic and imaging processes employed in patients with suspected PFO, how they are managed in routine clinical practice, and to investigate adherence to the current position statement across Europe and beyond.

Methods

The present survey was conducted by the EACVI Scientific Initiative Committee from 16 March to 15 August 2020 according to the criteria previously described.[13–16] (www.escardio.org/eacvi/surveys).

Numerous imaging laboratories and members of the EACVI survey network, mainly based in Europe, were invited to complete an online survey investigating the diagnostic workup and use of imaging in patients with suspected PFO and how these patients are managed in routine clinical practice. The survey consisted of 17 multiple choice questions based on the recent EACVI guidelines, which were aimed at understanding the available facilities and workload of each centre, as well as the preferred imaging strategy including the use of transcranial colour Doppler (TCD) and transthoracic (TTE) and transoesophageal (TOE) echocardiography. The survey was also disseminated via social media.

Results

In total, 79 centres from 34 different countries responded to the survey. Responding centres were located in Australia (3), Austria (4), Belgium (1), Brazil (1), Colombia (1), Croatia (1), Cyprus (1), Czech Republic (1), Ecuador (1), Egypt (1), Estonia (1), Georgia (1), Germany (4), Greece (4), Hungary (1), Italy (19), Lebanon (2), Japan (1), Malta (2), Mexico (1), Netherlands (2), Norway (3), Oman (1), Portugal (2), Romania (2), Saudi Arabia (1), Serbia (1), Slovenia (4), Spain (5), Sweden (1), Switzerland (2), Turkey (1), Ukraine (2), and the UK (2). Most centres were tertiary centres or University Hospitals (58%), which provided a high-volume service.

Cardiac imaging availability and indications

Echocardiography techniques were widely available across the participating centres. However, nearly a third of centres did not perform transcranial Doppler in the institution. When performed, this test was most commonly carried out by neurologists (*Figure 1*).

Imaging investigations in patients with cryptogenic stroke and suspected PFO

Standard TTE, with (29.5%) or without (51.3%) bubbles, was considered the first-level test for suspected PFO in the majority of the centres, while TOE with bubbles was not usually the first diagnostic choice (only 6.4%). Conversely, TOE was a second-level modality, with 56% of respondents considering this imaging technique to be particularly useful in evaluating PFO anatomy (*Figure 2*).

TCD was considered the first-line imaging test only in 13% of centres. Respondents considered the advantages of TCD to include improved sensitivity (15.2%), its non-invasive nature (39%), and the ease with which a prolonged Valsalva manoeuvre can be performed without sedation (10%) (*Figure 2*). Of note, the threshold for a significant positive right-to-left shunt by TOE or TCD was 5 microbubbles in 39% and 10 microbubbles in 33% of centres.

Cardiac magnetic resonance imaging (MRI) was mainly used as a third-level diagnostic tool for identifying other potential aetiologies of cryptogenic stroke, like cardiac thrombi or masses (63%), aortic atheroma (41%), or pelvic deep vein thrombosis (21%). Other centres used TOE for this purpose.

Other investigations in patients with cryptogenic stroke

Most centres would rule out atrial fibrillation (AF) as a source of embolism in all subjects with crytogenic stroke (63%), while other respondents would only monitor for asymptomatic AF in patients >55 years old (20%), or with increased left atrial size (14%) or multiple risk factors for AF (33%) (*Figure 3*). In the large majority of centres (85%) AF screening is performed with 24/48 h of electrocardiogram (ECG) Holter monitoring. A quarter of respondents (30.4%) used implanting loop recorders in selected cases.

Only a small minority of centres performed routine thrombophilia screening for all patients with cryptogenic stroke. These thrombophilia screens were used mostly in young patients (<55 years old) with cryptogenic stroke (44% of centres), or in patients with recurrent deep vein thrombosis or pulmonary emboli (43%) (*Figure 4*).

Follow-up of patients with PFO

After being discharged from hospital, the large majority of centres offered routine follow-up of patients following PFO closure. Most commonly (45%) this was a regular cardiology outpatient clinic appointment including a bubble TTE at 6 months. Other institutions perform a baseline echocardiogram at discharge and a TCD at 1–6–12 months (21%); or a TCD in isolation at 6 months (20%). After the initial 6-month phase of recommended dual antiplatelet therapy,

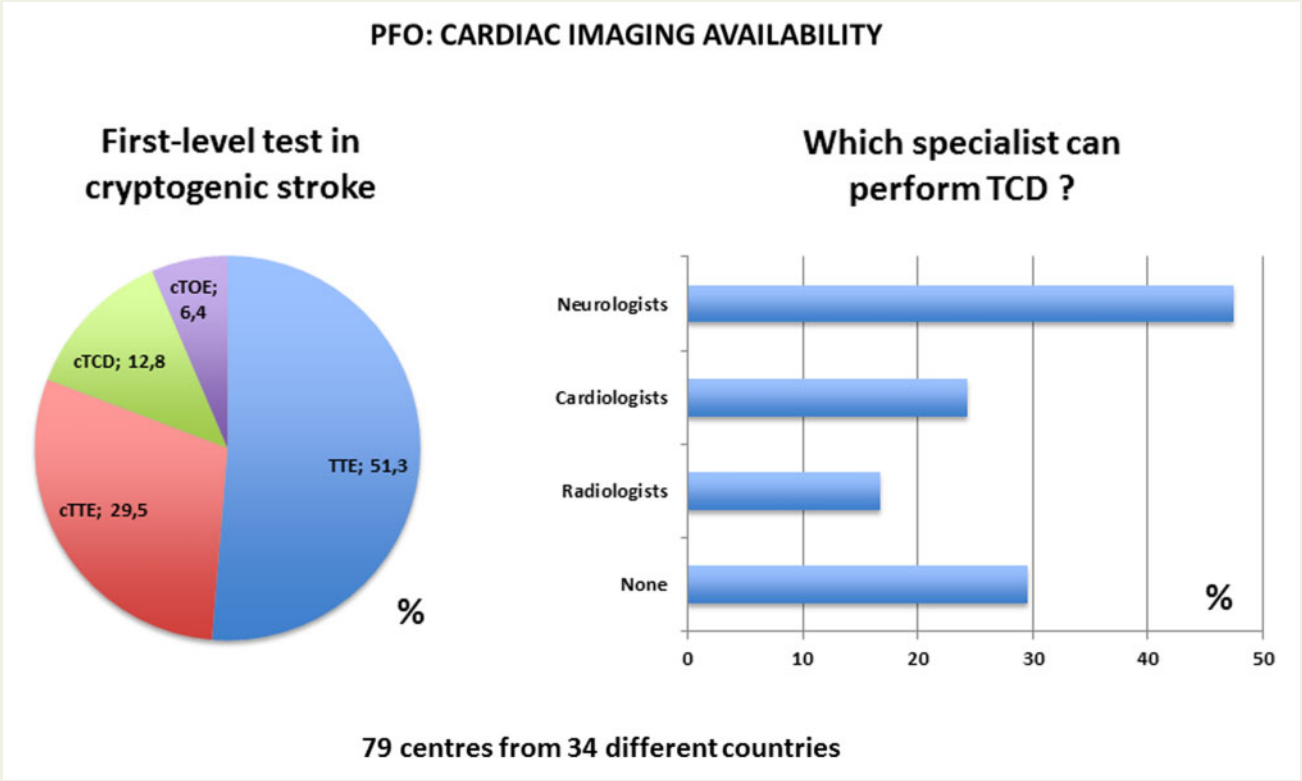

Figure 1 Pie chart (left) and bar chart (right) showing cardiac imaging availability in PFO patients with cryptogenic stroke in our survey centres.

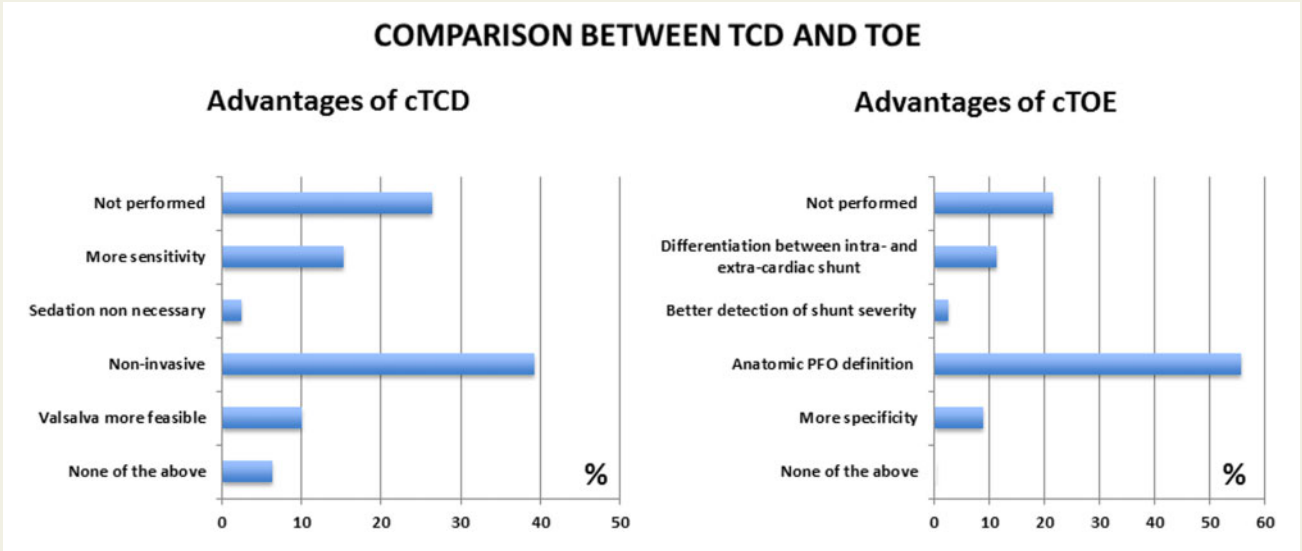

Figure 2 Bar charts showing the relative advantages of TCD (left) and TOE (right) imaging for PFO according to the survey respondents.

most centres suggested lifetime single-antiplatelet therapy (42%), while others limited it to 6 more months (36%) or for 5 years from the closure (12%) (*Figure 5*). Of note, antibiotic prophylaxis prior to dental or endoscopic procedures was not recommended in 41% of cases, while 37% recommended antibiotic prophylaxis only for 6 months after PFO closure. As for young patients with PFO not undergoing closure, most of the centres (44%) considered anatomical factors, such as atrial septal aneurysm or presence of Chiari network, as the most important factors associated with future recurrent cryptogenic stroke.

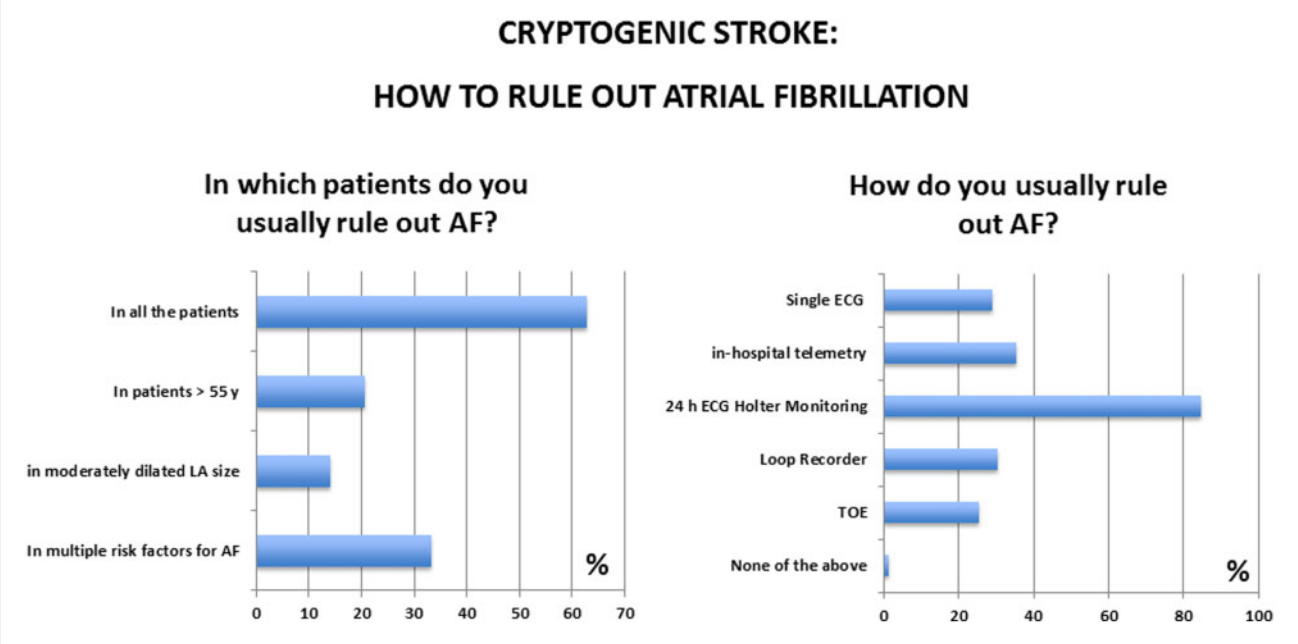

Figure 3 Bar charts showing when and how atrial fibrillation was ruled out as an embolic source in patients with cryptogenic stroke in our survey.

PFO assessment in patients with chronic migraine

The majority of centres (57%) did not routinely assess for a PFO in patients with recurrent migraines. However, 28% screened for a PFO if migraine patients had MRI evidence of white matter abnormalities in the brain (28%), while 14% would screen in the presence of focal neurological symptoms (14%) (*Figure 4*).

Discussion

This global survey provides an insight into the contemporary use of cardiac imaging in the assessment and management of patients with PFO and recent cryptogenic stroke.

Cardiac imaging availability and indications

Echocardiography holds the key position in both the diagnosis and management of patients with cryptogenic stroke and suspected PFO. Encouragingly, most ultrasound-based modalities were available in the large majority of centres. The exception was TCD, which was available in only 71% and was most commonly performed by neurologists rather than cardiologists (*Figure 1*). Further work is, therefore, required to improve the availability of TCD and to encourage the co-reporting of scans by cardiologists and neurologists.

Imaging investigations in patients with cryptogenic stroke

The use of non-invasive imaging in patients presenting for the first time with cryptogenic stroke is still controversial. EACVI recommendations reported that due to a lack of definitive evidence, no technique can be considered a gold standard and, in most cases, a precise diagnosis of PFO needs the combined use of different techniques, prescribed according to their different characteristics. As first-line investigations must warrant accuracy by minimizing false negative screenings, these guidelines proposed a diagnostic algorithm, with TCD or contrast-enhanced TTE as first-line test, and TOE as a second-level examination to be proposed only in cases of positive responses to the first-level tests.[12]

In this survey, these initial recommendations were followed in 94% of the responding centres. In particular, TTE with bubble contrast was the most popular initial non-invasive imaging technique. This technique has reported 99% specificity in the detection of PFO in previous studies. TOE with bubbles was the most popular second-line imaging test. This technique holds advantages in detecting PFO, defining PFO anatomy, and in identifying other potential causes of cryptogenic stroke, including cardiac masses and thrombi in the ventricles or atria.

Conversely, TCD appears to be less frequently used in clinical practice, despite being recommended as an alternative first-line imaging test for PFO, in some cases (poor acoustic window) being more feasible than TTE. TCD should not replace echocardiographic techniques to detect PFO and other shunt features; however, it can be used as a complementary and highly sensitive technique when performed by a properly trained and experienced operator.[17–26] TCD with emboli detection has been shown to be even more sensitive than TOE (96%) and just as specific compared with TTE or TOE. TOE has been reported to miss 15% of the shunts caught by TCD, 40% of which were large (Grade 3 and higher).[22] This perhaps reflects the importance of a prolonged Valsalva manoeuvre in shunt detection[23] an advantage of TCD that was noted by the respondents to our survey.

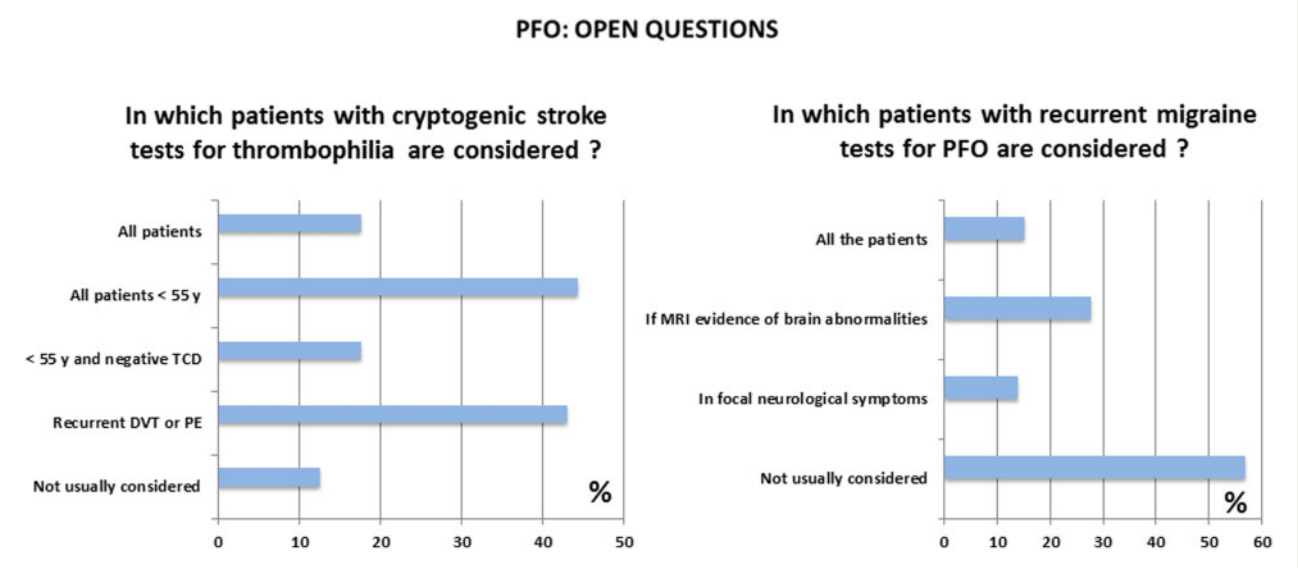

Figure 4 Bar charts showing thrombophilia (left) and recurrent migraine (right) management in PFO patients with cryptogenic stroke in the different institutions.

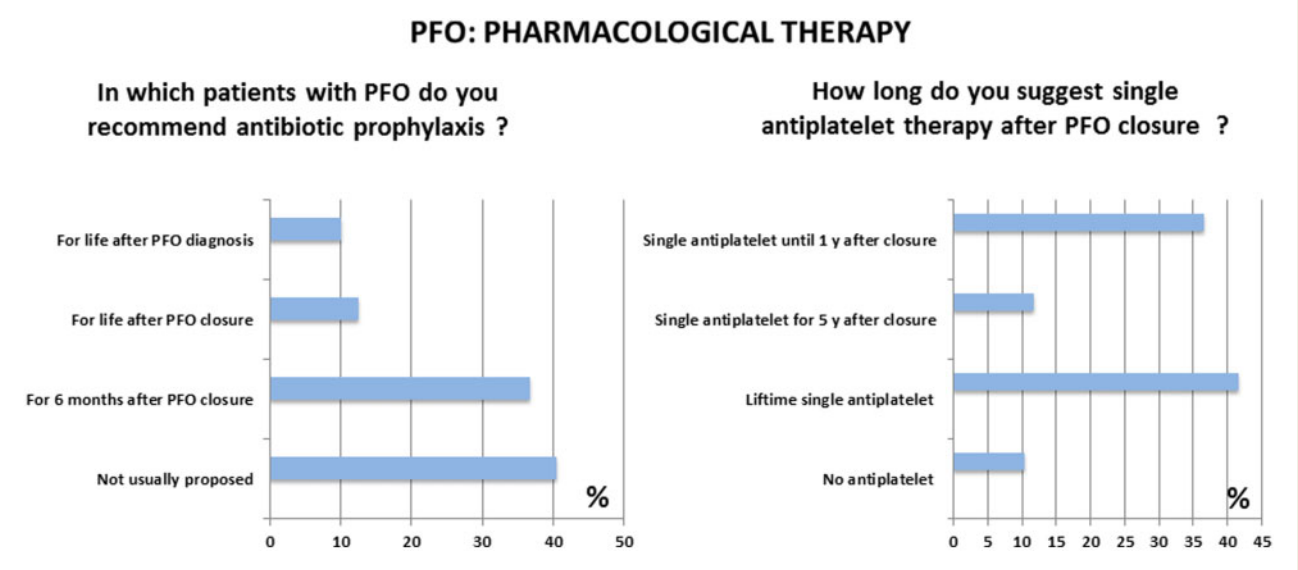

Figure 5 Bar charts showing antibiotic prophylaxis management (left) and antiplatelet therapy options (right) in our institutions.

This under-use and reduced availability of TCD should induce in different centres creation of a dedicated and skilled team, including also cardiologists, that could perform such exam in this clinical setting.

In this survey, 39% of respondents used 5 microbubbles as the threshold for a significant positive right-to-left shunt by TOE or TCD, while 33% used a threshold of 10 microbubbles. These results are not consistent with the recommendations of the recent EACVI/EAPCI position paper,[12] which suggested that the specificity of TCD was 100% when a threshold of 20 microbubbles on TTE or TOE or 10 high-intensity transient signals on TCD was used.[22] Better adherence to these cut-off values should be recommended.

Other investigations in patients with cryptogenic stroke

The guidelines also advocate interdisciplinary clinical assessments aimed at identifying AF in all patients with cryptogenic stroke. The recommended assessments were a routine 12-lead ECG alongside either in-patient cardiac telemetry or 24-h Holter monitoring.[12] The

results of the present survey are broadly consistent with these recommendations, although a third of centres do not routinely test for AF in all patients, instead of reserving investigation for patients >55 years old or with risk factors for AF (*Figure 3*).

MRI was mainly used in harmony with the current clinical guidelines in the diagnostic work-up of patients with PFO, for identifying other unusual aetiologies of cryptogenic stroke, like cardiac masses or pelvic deep vein thrombosis.

Retrospective studies investigated the association between inherited thrombophilias and PFO-related stroke with conflicting results.[27,28] In the EACVI/EAPCI position paper, routine laboratory tests for prothrombotic states[12] were therefore not recommended. This message was well received in our survey, with the majority of centres limiting thrombophilia testing to young patients (<55 years old) with cryptogenic stroke (*Figure 4*).

Follow-up of patients with PFO

Regarding the follow up of patients after successful percutaneous PFO closure, EACVI recommendations proposed: (i) a TTE prior to hospital discharge; (ii) a contrast TCD at least once beyond 6 months to assess effective PFO closure and thereafter, if residual shunt persists, annually until closure; (iii) contrast TOE or TTE in case of severe residual shunt at TCD, or recurrent events, or symptoms during follow-up.[12,29,30] Again the use of TCD for follow-up was limited, with only half of centres offering TCD follow-up post-PFO-closure as recommended, and 40% instead performing a bubble TTE at 6 months.

As for treatment, after the initial 6-month phase of recommended dual-antiplatelet therapy, EACVI/EAPCI protocols suggested single-antiplatelet therapy should be continued for at least 5 years. Centres in our survey varied in their response, with a quarter of the centres suggesting lifetime single-antiplatelet therapy and 36% recommending a further 6 months of therapy. Only 12% of the centres used the recommended 5 years of single-antiplatelet therapy after PFO closure (12%) (*Figure 5*).

Of note, antibiotic prophylaxis prior to dental or endoscopic procedures was not proposed in 41% of cases, despite the EACVI recommendations which suggested that it be considered routine in all cases for the first 6 months after the implantation and, prolonged beyond 6 months in patients with a residual shunt (*Figure 5*).[12]

Finally, in young patients with PFO not undergoing closure, most centres considered anatomical factors as the most important determinants of possible recurrent cryptogenic stroke.

PFO assessment in patients with recurrent migraine

The EACVI/EAPCI position paper suggested that in patients with recurrent migraine there is not enough evidence to support PFO closure at present.[12] In accordance with these recommendations, the vast majority of our institutions did not investigated migraine patients for PFO, limiting investigation to only those patients with brain MRI abnormalities or focal neurological symptoms (*Figure 4*).

Limitations

The majority of respondents worked in tertiary care centres or university hospitals. The survey findings may, therefore, not be generalizable to other types of care environments. The bulk of the survey respondents were cardiologists, and therefore, information on imaging practices and reporting may be incomplete. Lastly, there are differences between ESC and local national guidelines, which may have influenced the survey responses.

Conclusions

Our survey revealed variable adherence to current recommendation for most diagnostic and management strategies of patients with cryptogenic stroke and PFO. While TTE and TOE are the key imaging modalities in the assessment of patients with cryptogenic stroke and suspected PFO, the availability and use of contrast transcranial Doppler was relatively limited. Further effort is required to clarify and share optimal treatment strategies for patients post-PFO closure especially with regard to the duration of antiplatelet therapy and the use of antibiotic prophylaxis.

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Conflict of interest: In the last 3 years, H.C.D. received honoraria for participation in clinical trials, contribution to advisory boards or oral presentations from Abbott, Bayer Vital, BMS, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Pfizer, Portola, Sanofi-Aventis, and WebMD Global.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author and the EACVI.

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