Patent Foramen Ovale and Cryptogenic Strokes in the Stroke in Young Fabry Patients Study

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Background and Purpose—A patent foramen ovale (PFO) is disproportionately prevalent in patients with cryptogenic stroke. Without alternative explanations, it is frequently considered to be causative. A detailed stratification of these patients may improve the identification of incidental PFO.

Methods—We investigated the PFO prevalence in 3497 transient ischemic attack and ischemic stroke patients aged 18 to 55 years in the prospective multicenter SIFAP1 study (Stroke in Young Fabry Patients 1) using the ASCO classification. Patients without an obvious cause for transient ischemic attack/stroke (ASCO 0) were divided into subgroups with and without vascular risk factors (ASCO 0+ and 0–). In addition, we looked for PFO-related magnetic resonance imaging lesion patterns.

Results—PFO was identified in 25% of patients. Twenty percent of patients with a definite or probable cause of transient ischemic attack/stroke (≥1 grade 1 or 2 ASCO criterion; n=1769) had a PFO compared with 29% of cryptogenic stroke patients (ASCO 0 and 3; n=1728; P<0.001); subdivision of cryptogenic strokes revealed a PFO in 24% of 978 ASCO 3 patients (n.s. versus ASCO 1 and 2) and a higher prevalence of 36% in 750 ASCO 0 cases (P<0.001 versus ASCO 3 and versus ASCO 1 and 2). PFO was more commonly observed in ASCO 0– (n=271) than in ASCO 0+ patients (n=479; 48 versus 29%; P<0.001). There was no PFO-associated magnetic resonance imaging lesion pattern.

Conclusions—Cryptogenic stroke patients demonstrate a heterogeneous PFO prevalence. Even in case of less conclusive diseases like nonstenotic arteriosclerosis, patients should preferably be considered to have a non-PFO-mediated stroke.

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Key Words: arteriosclerosis ■ ischemic stroke ■ MRI ■ patent foramen ovale ■ risk factors

The relevance of a patent foramen ovale (PFO) as a frequent cause of stroke is controversial.1-4 Because of its higher prevalence, it is generally considered causative in cryptogenic stroke patients aged <55 years.5,6 However, the term cryptogenic stroke itself is not well defined and comprises typically also patients with less distinctive diseases like...
nonstenotic arteriosclerosis or risk factors like arterial hypertension. Therefore, many PFOs in younger transient ischemic attack (TIA)/stroke patients might be incidental, as supported by the observed risk of recurrent cerebral ischemic events in patients, despite interventional closure of the PFO.22–24 Recently, analysis of data from 3 randomized trials25–27 and pooled analysis22,23 failed to demonstrate a significant benefit of PFO closure over optimal medical treatment alone, although the RESPECT trial (Randomized Evaluation of Recurrent Stroke Care: PFO Closure to Established Current Standard of Care Treatment) reported that there may be a beneficial effect based on the per-protocol analysis.25 The lack of benefit may at least in part be because of treatment of patients with non-PFO-mediated TIA or stroke. Therefore identification of patients with ischemic strokes most probably caused by paradoxical embolism, for example, with scoring systems, such as the Risk of Paradoxical Embolism (RoPE) score,16,17 is important.

The SIFAP1 study (Stroke in Young Fabry Patients) was a prospective, observational study in 5023 stroke patients aged 18 to 55 years in 47 centers and 15 countries in Europe.19,20 The study screened this cohort for the prevalence of Fabry disease, but also prospectively collected informations on vascular risk factors and stroke subtyping, including data about the presence of a PFO or an interatrial septal aneurysm (ASA). The aims of this substudy were to assess the prevalence of a PFO or ASA in patients aged ≤55 years in SIFAP1 study who had a TIA or ischemic stroke, according to subgroups categorized by the ASCO classification system. We hypothesized that the prevalence of a PFO or ASA would be high, especially, in patients with no other cause for their TIA or stroke based on the detailed ASCO classification system. Furthermore, we evaluated the utility of the RoPE scoring system in identifying patients who were most likely to have had a PFO-related cerebrovascular event. Finally, we analyzed the magnetic resonance imaging (MRI) lesion size and location to determine specific PFO-related stroke patterns.

Methods
The detailed design of the SIFAP1 study has been published previously.20 Inclusion criterion was an acute stroke or TIA in the 3-month period before study entry, which was diagnosed by a neurologist or confirmed on MRI, in patients aged 18 to 55 years. SIFAP1 study was performed in accordance with the declaration of Helsinki and received Local Research Ethics Committee approval at the leading center in Rostock and in each individual study center. Written informed consent was obtained from every patient or assent obtained from a legal representative according to local regulations.

General information collected included demographic data, lifestyle and vascular risk factors, the patients’ medical history, and medication intake. All patients were examined by a neurologist, and investigators were advised to request a set of laboratory tests.20 MRI of the brain was mandatory in SIFAP1 study. In addition, information about the diagnostic tests and neurovascular workup performed and regarding administered therapies were requested.

Information on PFO and Atrial Septum
The SIFAP questionnaire collected several data on tests in conjunction with the qualifying cerebrovascular event, including optional information on the detection of a PFO. Additionally, adjunct information was obtained regarding the applied investigational technique, for example, transesophageal echocardiography or transcranial Doppler sonography. Available data regarding shunt size across the PFO, classified as minimal, moderate, or severe according to the interatrial transseptal passage of a few bubbles, a cloud of contrast, or opacification of the left atrium, were collected. Finally, there was the possibility to add information about existing atrial septum defects and aneurysms. ASA was reported from 10 mm protrusion beyond the plane of the atrial septum.

ASCO Classification
Although the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification was originally used in SIFAP1 study, we retrospectively applied the ASCO classification to phenotype patients using available data from the SIFAP1 database for this particular study. ASCO is a phenotypic classification system for patients with TIA and ischemic stroke that allows a detailed assessment of the potential relevance of specific risk factors in the etiopathogenesis of cerebrovascular events. It comprises 4 stroke etiologies: large-artery atherosclerosis (A); small vessel disease (S); cardioembolism (C); and other causes (O). Each characteristic is graded as a definite (1), uncertain (2), or unlikely (3) cause for the index event according to the significance of the most important finding in the corresponding category. If a pathology is absent, the relevant category is scored as 0. PFO and ASA trigger a gradation in the cardioembolism (C) category of the ASCO classification. However, to evaluate the PFO and ASA prevalence, this direct PFO/ASA-mediated categorization was not used for this specific study. The group of patients with no ASCO-relevant disease category (grade 0 for all ASCO items) was further subdivided into patients with (ASCO 0+) and without (ASCO 0−) vascular risk factors, including arterial hypertension, hyperlipidemia, current smoking or diabetes mellitus, or an elevated glycated hemoglobin (HbA1c) (>6.5%).

In light of prior studies that found a lower prevalence of PFO in stroke patients with a clear etiology for their stroke compared with patients with no identified cause,21,22 we hypothesized that PFO prevalence would be higher in cryptogenic TIA/ischemic stroke patients graded ASCO 3 to ASCO 0+ and would be highest in the ASCO 0− subgroup.

RoPE Score Calculation
In addition, we performed RoPE scoring26 on the patients included in this study, using age, vascular risk factors, and neuroimaging features to assess the likelihood of a PFO being relevant to the etiology of the index TIA or stroke in SIFAP1 (score 0–10).

Imaging Analysis
Cerebral MRI was performed in all SIFAP1 patients. Participating sites were free to choose the sequences regularly used at their center, but the study protocol recommended T1/PD (proton density)-weighted or fluid-attenuated inversion recovery images and a diffusion-weighted imaging sequence as a minimum. The images were analyzed centrally as outlined in detail previously.24 The number of lesions, infarct location, size, and vascular territories involved were recorded for both acute and old infarcts. Multilocular stroke was defined as either acute bilateral lesions in the anterior or middle cerebral artery territories or acute lesions in both the anterior and posterior circulation. For the current analysis, MRI lesion patterns in patients with and without PFO in the different ASCO subgroups were compared.

Statistical Analysis
Comparisons of prevalences between groups were performed using logistic or ordinal regression models with random effects (random intercept) models accounting for center heterogeneity. P values were age adjusted if indicated. A 2-sided significance level of α=0.05 was considered to represent statistical significance. No adjustments for multiple comparisons were performed. All statistical analyses were conducted using IBM SPSS Statistics 22 (SPSS, Inc, IBM Company, 2013, Chicago, IL) and Stata 13 IC (StataCorp, 2013, Stata Statistical Software: Release 13; StataCorp LP, College Station, TX).
Results

The SIFAP1 study included 4467 patients aged between 18 and 55 years with a TIA or an ischemic stroke. Patients were investigated according to the routinely performed tests in their local stroke centers (see Table I in the online-only Data Supplement). Data on the presence of a PFO and ASA were given in 3497 patients (78% of the overall study population). A PFO was detected in 863 of 3497 patients (25%). For basic data of patients with and without PFO, see Table II in the online-only Data Supplement. Information on the technique used for PFO screening was available in >70% of these patients. Accordingly, transesophageal echocardiography was performed in 77% of the patients, whereas in 17.9% of patients, only transthoracic echocardiography was done (information about patients with and without transesophageal echocardiography is provided in Table III in the online-only Data Supplement). A transcranial doppler screening was performed in 10% of all cases. As PFO prevalence decreased with age (18–25 years, 42%; 26–35 years, 29%; 36–45 years, 28%; 46–55 years, 21%), patients with a PFO on average were 2 years younger than patients without a PFO (median age of 45 versus 47 years; interquartile range, 38–50 versus 41–51; \( P < 0.001 \)).

ASCO classification was possible in 3491 patients in whom a PFO was rated as present or absent. ASCO 1 (definite cause of stroke) was found in 965 (28%) cases and ASCO 2 (probable cause of stroke) in a further 806 patients (23%; see Figure 1A). In both groups, 20% of patients had a PFO (see Figure 2). Patients graded ASCO 3 (n=964; 27%) or ASCO 0 (n=756; 22%) are traditionally classified as having cryptogenic stroke (see Figure 1B). The prevalence of PFO was significantly higher in patients with cryptogenic events (ASCO 3 and 0 combined: 29%) than in patients with a definite or probable cause for stroke (ASCO 1 and 2: 20%; \( P < 0.001 \), age adjusted). However, post hoc tests between individual cryptogenic stroke subgroups and patients with a definite or probable cause of stroke revealed no significant difference in the PFO prevalence in ASCO 3 versus ASCO 1 (24% versus 20%; \( P = 0.117 \), age adjusted) and ASCO 3 versus ASCO 2 (24% versus 20%; \( P = 0.157 \), age adjusted). In contrast, a PFO was more frequently detected in patients with ASCO 0 versus ASCO 1 and 2 (36% versus 20%; \( P < 0.001 \), age adjusted; Figure 2). A sensitivity analysis restricted to the subgroup of patients with ischemic stroke by excluding TIA patients yielded nearly identical results.

PFO in ASCO 0 Subgroups With and Without Vascular Risk Factors

The ASCO 0 group was subdivided into patients with and without vascular risk factors like arterial hypertension, diabetes mellitus, or current smoking. Four hundred and eighty-five patients had at least 1 risk factor (see Table IV in the online-only Data Supplement) and were labeled as ASCO 0+, whereas the remaining 271 cases were classified as ASCO 0−. A PFO was identified more frequently in ASCO 0− patients than in ASCO 0+ patients (48% versus 29%; \( P < 0.001 \), age adjusted). Both subgroups revealed a higher PFO prevalence than ASCO 1 and 2 (\( P = 0.001 \) for ASCO 0+ and \( P < 0.001 \) for ASCO 0−).

Shunt Size

Data on PFO shunt grading were available in <60% of all PFO-positive patients. However, based on these available

Figure 1. A, ASCO distribution of the 3491 patients with information on patent foramen ovale (PFO) and ASCO grade according to their maximum grading in %: c(all) represents all patients typically classified as cryptogenic stroke, including patients labeled ASCO 3 and ASCO 0. B, ASCO distribution of the 1720 patients typically classified as cryptogenic stroke c(all) according to their maximum grading in %: ASCO 0 is stratified in patients with (ASCO 0+) and without (ASCO 0−) vascular risk factors.

Figure 2. Patent foramen ovale (PFO) prevalence according to the ASCO classification in %: significant difference in cryptogenic stroke patients (ASCO 3, 0+ 0−) is almost exclusively driven by ASCO 0− patients, while ASCO 3 do not show a significant higher prevalence of PFO compared with grade 1 and 2. (The highest ASCO grading of every patient was used. PFO and atrial septal aneurysm [ASA] were not used for ASCO grading for the purpose of this study. Cardiovascular risk factors were arterial hypertension, hyperlipidemia, or diabetes mellitus in the medical history of the patient or an elevated HbA1c [>6.6%] in the registered laboratory investigations or current smoking.) n=3491.
data, severe shunts were more commonly observed in patients classified as ASCO 3 or 0 than in patients classified as ASCO 1 or 2 (16.2 versus 10.8%; \( P = 0.002 \), age adjusted).

### Atrial Septal Aneurysm

An ASA was found in 225 of 3497 patients (6%). Nearly 3 quarters of ASAs were associated with a coexisting PFO. Isolated ASAs were recorded in 65 patients only (1.8%) and were similarly distributed in the different ASCO subgroups (range 1.7%–5.0%; \( P = 0.704 \)). The percentage of patients with a PFO who had an associated ASA was 20% in ASCO grades 2, 3, and 0 and 12% in ASCO grade 1 (see Figure I in the online-only Data Supplement; \( P = 0.194 \), age adjusted). Within patients with PFO and ASCO 1 or 2, 16% of patients had an ASA compared with 20% of patients with PFO and ASCO 3 or 0 (\( P = 0.200 \), age adjusted).

### MRI Patterns

MRI data were available in 3300 of the 3497 patients (94%). Diffusion-weighted imaging hyperintense lesions were present in 65% of the 3300 patients. There was no significant difference in lesion pattern between patients with versus those without a PFO (see Table 1).

Patients with a PFO generally had smaller lesions than those without PFO (10% versus 15% lesions more than half lobe, and 57% versus 54% lesions less than or equal to half lobe; \( P = 0.001 \), age adjusted). However, although significant, these differences were small (see Table 2).

Old ischemic stroke lesions were generally less frequent in patients with cryptogenic stroke, but this was PFO independent and not significant after age adjustment (see Table V in the online-only Data Supplement).

### Discussion

Despite a comprehensive workup, we found a particularly high number of strokes with undetermined etiology in this large multicenter study. Beyond the young age of our population, this might partly be assigned to different definitions of cryptogenic stroke in the different classification systems. By using the extended ASCO classification, we were able to separate cryptogenic stroke patients into those harboring cardiovascular risk factors or pathology that was unlikely to be the direct cause of the stroke, for example, nonstenotic arteriosclerosis and cryptogenic stroke patients without corresponding diseases. Only the latter ones demonstrated a considerable higher PFO prevalence, underlying the relevance of a PFO in causing paradoxical emboli in this specific subgroup. This information would help identify patients with a higher likelihood for an involvement of PFO in the pathogenesis of cerebrovascular events and facilitate the clinically relevant consideration for percutaneous mechanical closure. These results are in line with other studies,7,25 including the recently developed RoPE score,26 putting forward alternative mechanisms instead of paradoxical embolism in case of cryptogenic stroke patients with coexisting minor arteriosclerosis or cardiovascular risk factors.

In agreement with other studies,7,27,28 we were not able to identify any typical imaging patterns in young patients with versus those without PFOs. On the contrary to large and predominantly superficially located lesions in presumed PFO-mediated TIAs or strokes according to the RoPE study,18 patients with PFO and cryptogenic TIA or stroke in the SIFAP1 study had the smallest lesions, although the differences between groups were small and of doubtful clinical relevance. In contrast to other studies,15,18 there was no significant difference in the number of old ischemic lesions in SIFAP1 between patients with and without a PFO after age adjustment (see Table V in the online-only Data Supplement).

In contrast to data that suggested a higher risk when a PFO was associated with ASA29,30 but in accordance with several

### Table 1. Distribution of Different Acute Stroke Types in Percent of Patients With and Without PFO, n=3300 (Column Percentages)

<table>
<thead>
<tr>
<th>Lesion Size</th>
<th>PFO+ (n=828)</th>
<th>PFO− (n=2472)</th>
<th>P Value (Age Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacunar strokes</td>
<td>14.3</td>
<td>13.5</td>
<td>0.329</td>
</tr>
<tr>
<td>Cortico-subcortical</td>
<td>36.1</td>
<td>32.4</td>
<td>0.284</td>
</tr>
<tr>
<td>Multilocular stroke</td>
<td>8.6</td>
<td>8.1</td>
<td>0.828</td>
</tr>
</tbody>
</table>

PFO indicates patent foramen ovale.

### Association Between RoPE Scores and PFO

In cryptogenic strokes (ASCO 3 and 0), there was a linear trend, with a higher PFO prevalence associated with higher RoPE scores reaching 45% in the RoPE 9 and 10 categories (\( P < 0.001 \)). Limitation of the analysis to the ASCO 0− subgroup led to a slight increase of the PFO prevalence to 52% in these categories (see Table 3).

### Table 2. Size of Lesions in Percent of Patients With and Without PFO in the Different Subgroup of the ASCO Classification (Row Percentages)

<table>
<thead>
<tr>
<th>Lesion Size</th>
<th>( \leq 1 \text{ cm} ) (n=190)</th>
<th>&gt;1 cm ( \leq \frac{1}{2} \text{ lobe} ) (n=332)</th>
<th>&gt;( \frac{1}{2} ) lobe (n=57)</th>
<th>( \leq 1 \text{ cm} ) (n=490)</th>
<th>&gt;1 cm ( \leq \frac{1}{2} \text{ lobe} ) (n=826)</th>
<th>&gt;( \frac{1}{2} ) lobe (n=225)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCO 1</td>
<td>46.2</td>
<td>42.9</td>
<td>10.9</td>
<td>43.5</td>
<td>42.3</td>
<td>14.2</td>
</tr>
<tr>
<td>ASCO 2</td>
<td>46.8</td>
<td>48.4</td>
<td>4.8</td>
<td>39.7</td>
<td>54.5</td>
<td>5.7</td>
</tr>
<tr>
<td>ASCO 3</td>
<td>27.3</td>
<td>64.5</td>
<td>8.1</td>
<td>23.2</td>
<td>60.9</td>
<td>15.9</td>
</tr>
<tr>
<td>ASCO 0+</td>
<td>25.8</td>
<td>60.8</td>
<td>13.4</td>
<td>18.8</td>
<td>62.9</td>
<td>18.3</td>
</tr>
<tr>
<td>ASCO 0−</td>
<td>18.5</td>
<td>70.7</td>
<td>10.9</td>
<td>15.7</td>
<td>61.4</td>
<td>22.9</td>
</tr>
</tbody>
</table>

Lesions size in patients with PFO is significantly smaller (\( P < 0.001 \)) after adjustment for age and ASCO grade. n=2120. PFO indicates patent foramen ovale.
other studies,\textsuperscript{31–33} we neither found higher numbers of concomitant ASAs in cryptogenic strokes nor encounter any imaging patterns depending on a PFO with associated ASA. One limitation of our study is that it was not compulsory in our study to report data on the presence or absence of an ASA. Nevertheless, ASAs were reported in 6% of patients overall, including in 2.5% of patients without a PFO and in 18.5% of patients with a PFO; these findings are similar to the numbers reported in the literature to date.\textsuperscript{22,34} Therefore, we do not think that we missed a relevant amount of ASAs in our patients. In this study, the prevalence of a PFO was higher for patients with higher RoPE scores, although the proportion of PFO-positive patients in SIFAP1 study did not reach the high percentage rates of \( \leq 73\% \) reported by Kent et al.\textsuperscript{16} Even the exclusion of patients with minor pathology like nonstenotic arteriosclerosis and patients with hyperlipidemia as an additional risk factor to the RoPE score did not result in similar high ranges. This might be because of differences in the definition of cryptogenic stroke and differences in age profile between the study populations. Although PFO screening in SIFAP study was not mandatory, we got data from nearly 80% of all patients. Finally, the rates of PFO in our cryptogenic stroke cohort are in accordance with those of several other studies,\textsuperscript{21,35,36} making underreporting because of a lack of information or overestimation by PFO screening unblinded to the clinical situation\textsuperscript{27} unlikely. In agreement with other studies,\textsuperscript{25} even in SIFAP1 study, the PFO prevalence was generally higher in younger patients. However, when we examined only cryptogenic strokes without minor disease or risk factors, patients with and without PFO did not differ in terms of age (see Table VI in the online-only Data Supplement). While the RoPE score is heavily influenced by age, our data are, therefore, in line with several other studies, favoring a less age-dependent role of PFO in truly cryptogenic strokes.\textsuperscript{21,38}

### Conclusions

In our large SIFAP1 study population, no higher prevalence of PFO was identified in patients with cryptogenic stroke and vascular risk factors or subclinical atherosclerosis. In these patients, preferentially other mechanisms of stroke should be taken into account. In contrast, cryptogenic stroke patients without similar conditions provide a higher PFO prevalence. Therefore, further trials on PFO occlusion should focus on these patients because they may be the most informative group in PFO closure versus best medical treatment alone.

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### Disclosures

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### References


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on behalf of the Stroke in Young Fabry Patients (SIFAP) Investigators

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Patent Foramen Ovale and cryptogenic strokes in the Stroke in Young Fabry Patient study

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Düsseldorf/Germany, University: S Jander, HP Hartung, M Siebler, C Böttcher, A Köhne, J Platz, TC Brosig, V Rothhammer, C Henseler

Frankfurt am Main/Germany, University: T Neumann-Haefelin, OC Singer, U Ermis, IMRM dos Santos, C Schuhmann, S van de Loo

Giessen/Germany, University: M Kaps, J Allendörfer, C Tanislav, M Brandtner

Glasgow/United Kingdom, University: K Muir, K Dani, N MacDougall, W Smith, A Rowe, A Welch

Graz/Austria, Medical University: F Fazekas, G Schrotter, U Krenn, S Horner, B Pendl, A Pluta-Fuerst, U Trummer

Greifswald/Germany, University: C Kessler, M Chatzopoulos, Bettina v Sarnowski, Ulf Schminke, T Link, A Khaw, E Nieber

Halle/Germany, University: S Zierz, T Müller, N Wegener, K Wartenberg, C Gaul, D Richter

Hamburg/Germany, University: M Rosenkranz, AC Krützelmann, J Hoppe, CU Choe, S Narr, TU Magnus, G Thomalla, F Leypoldt, D Otto

Heidelberg/Germany, University: C Lichy, W Hacke, RJ Barrows

Helsinki/Finland, University: T Tatlisumak, J Putaala, S Curtze, M Metso

Innsbruck/Austria, University: J Willeit, M Furtner, M Spiegel, MH Knoflach, B Prantl

Jena/Germany, University: OW Witte, D Brämer, A Günther, T Prell, C Herzau, K Aurich

Kiel/Germany, University: G Deuschl, F Wodarg, P Zimmermann, CC Eschenfelder, M Levens

Klagenfurt/Austria, University: JR Weber, SM Marecek

Leipzig/Germany, University: D Schneider, D Michalski, W Kloppig, L Küppers-Tiedt, M Schneiders, A Schulz, P Matzen, C Weise, C Hobohm, H Meier, R Langos, D Urban, I Gerhardt

Leuven/Belgium, University: V Thijs, R Lemmens, E Marcelis, C Hulsbosch

Linz/Austria, University: F Aichner, HP Haring, E Bach

Lisbon/Portugal, University: J Machado Candido, AA e Silva, M Lourenco, AIM de Sousa

Lyon/France, University: L Derex, TH Cho

Madrid/Spain, University: E Díez-Tejedor, B Fuentes, P Martínez-Sanchez, MI Pérez-Guevara

Marburg/Germany, University: H Hamer, A Metz, K Hallenberger, P Müller

Milan/Italy, University: P Baron, A Bersano, M Gattinoni
Msida/Malta, University: N Vella, M Mallia

Mühlhausen/Thüringen/Germany: M Jauss, L Adam, F Heidler, C Gube, M Kiszka

Munich/Germany, University: M Dichgans, A Karpinska, Y Mewald, V Straub, A Dörr, A Zollver

Münster/Germany, University: EB Ringelstein, M Schilling, A Borchert, N Preuth, T Duning, G Kuhlenbäumer, D Schulte to Bühne

Oxford/United Kingdom, University: PM Rothwell, L Marquardt

Regensburg/Germany, University: F Schlachetzki, S Boy, J Mädl, GM Ertl, NPR Fehm, C Stadler

Rostock/Germany, University: R Benecke, A Dudesek, S Kolbaske

Salzburg/Austria, University: G Lardurner, C Sulzer, A Zerbs, S Lilek, AM Walleczech, D Sinadinowska

Tbilisi/Georgia, University: M Janelidze, M Beridze, N Lobjanidze, A Dzagnidze

Tübingen/Germany, University: A Melms, K Horber, I Fink, B Liske

Ulm/Germany, University: AC Ludolph, R Huber, K Knauer, C Hendrich, S Raubold

Warsaw/Poland, University: A Czlonkowska, A Baranowska, B Blazejewska-Hyzorek

Wien/Austria: W Lang, W Kristoferitsch, J Ferrari, E Ulrich, A Flamm-Horak, A Lischka-Lindner, W Schreiber

Zagreb/Croatia, University: V Demarin, Z Tranjec, M Bosner-Puretic, MJ Jurašić, V Basic Kes, M Budisic, L Kopacevic
Supplemental Table I. Frequency of different diagnostic methods for stroke evaluation. Hypercoagulability screening was comprising a test of at least one variable out of blood coagulation factor II or V, ANA, ANCA or Antiphospholipid-antibodies.

<table>
<thead>
<tr>
<th>Method</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR-Angiography head</td>
<td>2276 (65.1)</td>
</tr>
<tr>
<td>CT-angiography head/neck</td>
<td>527 (15.1)</td>
</tr>
<tr>
<td>Conventional angiography</td>
<td>468 (13.4)</td>
</tr>
<tr>
<td>Extracranial duplex</td>
<td>3146 (90.0)</td>
</tr>
<tr>
<td>Transcranial duplex</td>
<td>2334 (66.7)</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>3133 (89.6)</td>
</tr>
<tr>
<td>Hypercoagulability screening</td>
<td>1352 (38.7)</td>
</tr>
<tr>
<td></td>
<td>PFO (n=863)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
</tr>
<tr>
<td><strong>Sex (Male in %)</strong></td>
<td>58.6</td>
</tr>
<tr>
<td><strong>Age</strong> years median (IQR)</td>
<td>45 (38-50)</td>
</tr>
<tr>
<td><strong>Stroke entity in %</strong></td>
<td></td>
</tr>
<tr>
<td>TIA</td>
<td>19.0</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>81.0</td>
</tr>
<tr>
<td><strong>Stroke severity</strong></td>
<td></td>
</tr>
<tr>
<td>NIHSS median (IQR)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td><strong>Risk factors in %</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>31.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.4</td>
</tr>
<tr>
<td><strong>MRI findings in %</strong></td>
<td></td>
</tr>
<tr>
<td>Acute stroke</td>
<td>71.1</td>
</tr>
<tr>
<td>Old vascular lesions</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Supplemental Table II: Demographical, clinical and imaging data of patients with and without PFO. IQR refers to interquartile range, TIA refers to transient ischaemic attack. NIHSS refers to National institute of Health stroke scale.

\(^a\) age adjusted

\(^b\) p-values adjusted for centre heterogeneity
<table>
<thead>
<tr>
<th>TEE (n=1915)</th>
<th>TEE no or n/a (n=1582)</th>
<th>( p^b )</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong> Male (%)</td>
<td>60.7</td>
<td>59.1</td>
</tr>
<tr>
<td><strong>Age</strong> median years (IQR)</td>
<td>46 (40-51)</td>
<td>47 (41-51)</td>
</tr>
<tr>
<td><strong>Stroke entity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA (%)</td>
<td>19.1</td>
<td>26.9</td>
</tr>
<tr>
<td>ischemic stroke (%)</td>
<td>80.9</td>
<td>73.1</td>
</tr>
<tr>
<td><strong>Stroke severity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS median (IQR)</td>
<td>3 (1-5)</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>45.1</td>
<td>48.9</td>
</tr>
<tr>
<td>Diab. mell. (%)</td>
<td>9.3</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>MRI findings</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Stroke (%)</td>
<td>70.4</td>
<td>59.2</td>
</tr>
<tr>
<td>Old Stroke (%)</td>
<td>26.8</td>
<td>26.9</td>
</tr>
<tr>
<td><strong>Acute Stroke localisation</strong></td>
<td>(n=1285)</td>
<td>(n=873)</td>
</tr>
<tr>
<td>Left hemispheric (%)</td>
<td>48.2</td>
<td>45.3</td>
</tr>
<tr>
<td>Right hemispheric (%)</td>
<td>41.2</td>
<td>43.3</td>
</tr>
<tr>
<td>Bilateral (%)</td>
<td>10.1</td>
<td>10.9</td>
</tr>
<tr>
<td><strong>Infarct size</strong></td>
<td>(n=1258)</td>
<td>(n=864)</td>
</tr>
<tr>
<td>&lt;1 cm (%)</td>
<td>32.4</td>
<td>31.5</td>
</tr>
<tr>
<td>≤ half of a lobe (%)</td>
<td>55.2</td>
<td>53.6</td>
</tr>
<tr>
<td>&gt; half of a lobe (%)</td>
<td>12.3</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Supplemental Table III. Demographic and clinical data of patients with TEE (n=1915) and of all other patients (n=1582), which either had no TEE (n=561) or the information about the PFO-screening method performed was not indicated (n=1021). Imaging parameters were analysed whenever possible.

\( a \) age adjusted
\( b \) p-values adjusted for centre heterogeneity
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker (n=756)</td>
<td>37.7</td>
</tr>
<tr>
<td>Hypertension (n=754)</td>
<td>28.5</td>
</tr>
<tr>
<td>Hyperlipidemia (n=728)</td>
<td>26.8</td>
</tr>
<tr>
<td>Diabetes mell. (n=753)</td>
<td>5.3</td>
</tr>
<tr>
<td>Elevated HbA1c (&gt;6.5%) (n=371)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Supplemental Table IV. Vascular risk factors determining a classification as ASCO 0+ in % of ACSO 0 patients (n=756). Numbers in brackets represent the number of valid data for each field.
<table>
<thead>
<tr>
<th></th>
<th>PFO - (n=2355)</th>
<th>PFO + (n=802)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-35y</td>
<td>72.1</td>
<td>76.2</td>
<td>0.227 (age adjusted)</td>
</tr>
<tr>
<td>36-55y</td>
<td>70.7</td>
<td>74.2</td>
<td></td>
</tr>
<tr>
<td>ASCO 1</td>
<td>66.2</td>
<td>65.8</td>
<td>0.619 PFO- vs PFO+ (age adjusted)</td>
</tr>
<tr>
<td>ASCO 2</td>
<td>73.6</td>
<td>74.6</td>
<td></td>
</tr>
<tr>
<td>ASCO 3</td>
<td>67.1</td>
<td>70.2</td>
<td></td>
</tr>
<tr>
<td>ASCO 0+</td>
<td>86.9</td>
<td>92.1</td>
<td></td>
</tr>
<tr>
<td>ASCO 0-</td>
<td>91.5</td>
<td>87.9</td>
<td></td>
</tr>
</tbody>
</table>

Supplemental Table V. Lesion-free patients prior to the index event are displayed in %. Older lesions are comparably frequent in Patients with and without PFO in general (p=0.227) and in all ASCO-subgroups (p=0.619).
<table>
<thead>
<tr>
<th>All</th>
<th>PFO+</th>
<th>PFO-</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>N=3497</td>
<td>N=863</td>
<td>n=2634</td>
</tr>
<tr>
<td>Age</td>
<td>46 (41-51)</td>
<td>45 (38-50)</td>
<td>47 (41-51)</td>
</tr>
<tr>
<td>ASCO1</td>
<td>N=965</td>
<td>N=197</td>
<td>N=768</td>
</tr>
<tr>
<td>Age</td>
<td>48 (42-52)</td>
<td>47 (41-51)</td>
<td>48 (42-52)</td>
</tr>
<tr>
<td>ASCO2</td>
<td>N=806</td>
<td>N=165</td>
<td>N=641</td>
</tr>
<tr>
<td>Age</td>
<td>47 (42-51)</td>
<td>45 (40-49)</td>
<td>47 (42-52)</td>
</tr>
<tr>
<td>ASCO3</td>
<td>N=964</td>
<td>N=229</td>
<td>N=735</td>
</tr>
<tr>
<td>Age</td>
<td>47 (42-51)</td>
<td>46 (41-50)</td>
<td>48 (42-51)</td>
</tr>
<tr>
<td>ASCO 0+</td>
<td>N=485</td>
<td>N=141</td>
<td>N=344</td>
</tr>
<tr>
<td>Age</td>
<td>44 (38-49)</td>
<td>42 (34-48)</td>
<td>45 (39-50)</td>
</tr>
<tr>
<td>ASCO 0-</td>
<td>N=271</td>
<td>N=130</td>
<td>N=141</td>
</tr>
<tr>
<td>Age</td>
<td>39 (31-46)</td>
<td>39 (31-46)</td>
<td>39 (31-46)</td>
</tr>
</tbody>
</table>

Supplemental Table VI. Age of patients with and without PFO (median, IQR in brackets). Patients with PFO are 2 years younger on average (p < 0.001). However there was almost no difference in terms of age concerning patients classified ASCO 0-. 
Supplemental Figure I. ASA-prevalence in % of PFO+ patients according to the ASCO classification. N=862 PFO + patients with info on ASA