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Embolic stroke of unknown source (ESUS) in patients with atrial septum defect and patent foramen ovale: difference and similarities

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Embolic stroke of unknown source (ESUS) in patients with atrial septum defect and patent foramen ovale: difference and similarities

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Abstract

Introduction
Paradoxical embolism from right-to-left shunt through a patent foramen ovale (PFO) is a well-characterized cause of embolic strokes of undetermined source (ESUS). In order to better understand the pathogenic role of atrial septum defects (ASD), we compared them with ESUS of high and low likelihood of being related to PFO.

Methods
In the Acute STroke Registry and Analysis of Lausanne (ASTRAL), we calculated prevalence of PFO and ASD in ESUS patient undergoing echocardiography, and odds ratios (OR) when to compared to non-cryptogenic strokes. Using the Risk of Paradoxical Embolism (RoPE) score, we divided cryptogenic PFO patients in high (HL-PFO, RoPE 8-10) and low-likelihood (LL-PFO, RoPE 0-4) PFO-related stroke. We then performed univariate comparison of epidemiological, clinical and radiological variables of both group with ESUS ASD patients.

Results
Among all ESUS, prevalence for ASD and PFO were 1.3% and 36.8% respectively. When compared to non-cryptogenic stroke, ASD and PFO were associated with ESUS (OR of 5.2, CI= 1.6-16.6, and 2.8, CI= 2.1-3.8). Compared with HL-PFO, ASD were older, more often female, had more cardiovascular risk factors (CVRF) and silent strokes. Compared with LL-PFO, ASD group was significantly younger, more often female, and had less CVRF. No differences were found for clinical and radiological characteristics and outcome.

Conclusion
In ESUS, ASD seems to be a rare but significant stroke risk factor. Given that characteristics of such patients lie in-between high and low-likelihood paradoxical PFO-stroke, a thorough workup for other stroke mechanisms is warranted in ASD patients before routine ASD closure.

Key words
Atrial septal defect - Patent foramen ovale - Paradoxical embolism - Embolic stroke of undetermined source

Introduction

Stroke is a major cause of mortality and disability worldwide. Patients with stroke are at high risk of further cerebrovascular events, making the identification of the etiology essential for secondary prevention. A large majority of ischemic stroke is caused by well-defined mechanism, each associated with a particular presentation, recurrence risk, and a specific secondary prevention (1,2). Despite technological progress, around 25% of all ischemic strokes remain of unknown, or "cryptogenic" origin (3–5). Given that most such strokes are due to thromboembolic events, the term Embolic Strokes of Undetermined Source (ESUS) has been created and defined as non-lacunar brain infarct without proximal arterial stenosis, major-risk cardio embolic source, or any specific cause of stroke (6). Paradoxical embolism through a right-to-left shunt is a well-recognized candidate for ESUS (7). The most common paradoxical embolization occurs through a patent foramen ovale (PFO), which acts as a flap-like valve, allowing transient right-to-left shunt during Valsalva or early systole. Many case of direct visualization of thrombus in transit through the PFO have been reported. Atrial septal defect (ASD) with a persistent, but invertible left-to-right shunt is a much rarer cause, but has a potentially higher recurrence rate (7,8).

The pathogenicity of a PFO in patients with cryptogenic stroke and recurrence risk have recently been better defined with the Risk of Paradoxical Embolism (RoPE) score (9–11). Also, PFO related strokes have some particular radiological presentation, ie. they tend to be large, radiologically apparent, superficially located or unassociated with prior radiological infarcts (12). On the other hand, the available literature on ASD is much less clear regarding its pathogenic role and recurrence risk in stroke. Currently, most ASD in patients with cryptogenic stroke are closed, also because of the increased risk of such patients for cardiac insufficiency, pulmonary hypertension and arrhythmia (13,14).

Assuming that patients with a high likelihood of PFO-related stroke constitute a model of a paradoxical stroke with epidemiological, clinical and radiological patterns, we compared such patients with cryptogenic ASD stroke patients in order to better understand the potential pathogenicity of ASD. Knowledge from such analyses may be useful to determine whether stroke in patients with ASD need further work-up for other causes of ESUS, and aggressive treatment such as ASD closure.

Methods

We used the data from the Acute STroke Registry and Analysis of Lausanne (ASTRAL) which is a registry cohort of all acute ischemic stroke (AIS) patients admitted since 2003 to the stroke unit and/or intensive care unit of the CHUV within 24 hours after last-well time, as published previously (3). To enrich the ASD population, we also added patients with ischemic stroke and imaging positive transient ischemic attack (TIA) from the parallel registry called « ASTRAL-E » containing all patients excluded from ASTRAL because of arrival >24 hours after stroke onset or TIA. Furthermore, we added patients diagnosed with ASD and stroke during the same observation period by one of the co-authors (AD, cardiologist) at the neighbouring Morges county hospital.

For the ASD group, we selected all ASTRAL, ASTRAL-E and Morges hospital patients with ASD on transthoracic (TTE), transoesophageal echocardiography (TEE), or both. All echocardiographic images were reanalyzed by one of the authors (AD) to confirm the presence of the ASD. ASD was defined as a tissue defect in the septum primum with either spontaneous left to right shunting, and/or with right to left shunting with microbubbles injection. Microbubble injection was not required for ASD diagnosis. Occasionally, the ASD was only diagnosed at the time of closure of a presumed PFO based on intracardiac or transoephageal imaging. PFO was defined as right to left passage of microbubbles after their intravenous injection, either spontaneously or with a Valsalva maneuver, through a lack of apposition of the septum primum. Simultaneous presence of ASD and PFO was also searched. ASA was defined as a more than 11 mm excursion of the interatrial septum on TTE and/or TEE.

In all patients (ASTRAL and other), a large range of parameters were collected and then analyzed retrospectively: demographics, cardiovascular risk factors, clinical symptoms and examination, and other features of the stroke (affected side, vascular territory, brain structures affected, cortical vs. subcortical involvement, The National Institutes of Health Stroke Scale (NIHSS) score at admission). Acute brain imaging on admission consisted mostly of multimodal CT imaging including CT-perfusion (64 detectors since 2005), and in selected patients acute or subacute MRI and repeat CT scan. Experiences neuroradiologists reviewed all neuroimages for the topography of the stroke lesions (cortical, subcortical, brainstem) and for silent stroke lesions. At least one arterial study of cervical and cerebral arteries (usually CT-angiography on admission) was obtained in all patients and a minimum of 24 hour continuous cardiac monitoring

for search of stroke causes. Additional exams for rare causes of stroke were performed if clinically indicated. Stroke and TIA recurrences and the modified Rankin score (mRS) were assessed by mRS-certified personnel in an unblinded manner at the outpatient clinic or with a structured telephone interview at 3 and 12 months. Outcome was considered favorable if the mRS was ≤2 in patients with a prestroke mRS ≤2.

In order to calculate the overall prevalence of ASD and PFO in an ischemic stroke population, we used all patients undergoing echocardiography in ASTRAL and calculated odds ratios (OR). We then calculated OR for ASD and PFO prevalence in patients with a defined stroke cause vs. ESUS.

In order to see whether ASD patients resembled patients with PFO related stoke, we compared their demographic and radiological characteristics with patients having a high or low likelihood of paradoxical embolism: we used the RoPE score in order to divide cryptogenic PFO patients in ASTRAL in high (HL-PFO, RoPE 8-10, PFO attributable fraction of 84% to 88%) and low-likelihood (LL-PFO, RoPE 0-4, PFO attributable fraction of 0% to 38%) of PFO related stroke (10). We removed patients with an intermediate RoPE score of 5-7 (attributable fraction of 34% to 72%) (10). Patients with both an ASD and a PFO were kept in the ASD group for the overall analyses, but the comparison with the HL-PFO was also repeated with the ASD-only patients.

Nominal variables were expressed as absolute number and percent, and continuous variables as median and interquartile range (IQR). Given the limited number of ASD patients available, we did univariate comparison of epidemiological, clinical and radiological variables of the ESUS ASD patients with the HL-PFO and with the LL-PFO group. Statistical analysis was performed using STATA 14.0 statistical software. Results were expressed as odds ratios and 95% confidence Intervals. P-value <0.05 was considered as significant.

The local ethics committee approved the protocol of this study.

Results

Between January 2003 and October 2014, 2367/3517 (67.4%) of all AIS in ASTRAL had a TTE, TEE or both and were included in our analysis. 993 of all strokes (28.2%) were of undetermined origin according to TOAST criteria, including 755 (76.0%) who underwent echocardiography.

We identified 12 AIS in 11 patients with an ESUS and an ASD. 10 of these were ASDs only, and two had a simultaneous PFO on microbubble testing. Six other patients with an ASD were excluded from the cryptogenic ASD group because of another definite cause of stroke (n=4) or because of imaging negative TIA (n=2) (Figure 1). None of the ASD patients had a permanent right-to-left shunt.

Misdiagnosis of atrial septum pathology initially occurred in 5 patients: one patient first diagnosed as PFO was reclassified as ASD because of a permanent septal tissue defect; conversely 4 "ASD" patients were reclassified as PFO because of the opposite situation. 9 of the 12 events in ESUS ASD patients were reported in women (75%) and their median age was 50 years. When excluding the 2 events with an ASD-associated PFO from the cryptogenic ASD group, 8 of the 10 patients were women (80%), and the median age was 50 years. Baseline characteristics of ASD patients are summarized in Table 2.

In the 2367 ASTRAL patients undergoing echocardiography, PFO were searched with microbubbles injection in 827 patients. Among these patients, the overall PFO prevalence was 36.8% (304/827). Among cryptogenic stroke, it was 48.5% (194/400) and among non-cryptogenic strokes 25.3% (101/400). Comparing cryptogenic with non-cryptogenic patients, the OR was 2.8 (2.07 – 3.76, p<0.01) to find a PFO.

Using the data from ASTRAL (14 AIS, of which 10 were cryptogenic), the prevalence of ASD in all strokes (cryptogenic or not) examined with echocardiography was 0.59% (14/2367). In patients with cryptogenic strokes, this frequency was 1.33% (10/754) and it was 0.26% (4/1551) in non-cryptogenic stroke (Table 1). Comparing cryptogenic with non-cryptogenic patients, the OR for the presence of an ASD was 5.2 (Figure 2). The ASD-only group exhibited an OR of 4.15 for the presence of ASD in cryptogenic vs. non-cryptogenic stroke (8/754 vs. 4/1551). When we compared the proportion of cryptogenic vs. non-cryptogenic stroke within ASD patients (10 vs. 4) vs. PFO patients (194 vs.101), we found an OR of 1.30 (Figure 2, non-significant).

Among the cryptogenic patients with PFO, the HL-PFO contained 55 events and the LL-PFO group 42. In the HL-PFO population, median age was 29.6 with 38.2% women. The LL-PFO had a median age of 72.3 years and consisted of 57.1% woman. Baseline characteristics of HL-PFO and LL-PFO are summarized in Table 2.

When comparing ASD with the HL-PFO, the former were older, more often female, and had more cardiovascular risk factors (CVRF) (Tables 2 and 3). Half of the

ASD patients had 2 CVRF or more, with a particularly high prevalence of arterial hypertension and hyperlipidemia. In keeping with the higher CVRF profile, three patients in the ASD group had a previous unexplained clinical stroke or TIA, but only one in the HL-PFO group (p=0.02). The prevalence of concomitant ASA was comparable in both groups. When applying the ROPE score to the cryptogenic ASD patients (7; IQR 5-8), their median score was lower than in the HL-PFO (8; IQR 8-9, p<0.01). Median admission NIHSS and territory affected by the stroke were similar in both groups. Younger age in the HL-PFO group may explain its somewhat higher proportion of favorable outcome at 3 and 12 months. Stroke or TIA recurrence at 12 months was low in ASD and HL-PFO (1/12; 8% and 1/55; 2% respectively) and statistically not different. Radiological stroke localization from the ASD group tended to be more in the brainstem and less cortical, but these differences didn't reach statistical significance. Silent strokes were borderline more frequently found in ASD group (2/12; 17% vs. 1/55; 2%, p=0.07).

When comparing the ASD-only patients with HL-PFO, we found the same results concerning demographics, PFO features, prevalence of major risk factors, preceding cerebrovascular events, stroke characteristic, outcome, and territory topography. The two patients with simultaneous ASD and PFO very similar to the other 10 ASD events: there was one female and one male of 46 and 43 years respectively, a ROPE-score of 8 and no silent strokes on imaging.

The higher prevalence of silent strokes in ASD patients (20% vs. 2%, p=0.05) remained borderline. One ASD patient had two chronic lesions of embolic appearance in the each PICA territory and the second a lacunar lesion above the left lenticular nucleus. The only HL-PFO patient with a silent stroke lesion had an embolic appearing left occipital lobe scar.

When comparing the ASD group with the LL-PFO group, the former were significantly younger and had less cardiovascular risk factors (Tables 2 and 3). The ROPE score was significantly higher in the ASD than the LL-PFO (7; IQR 5-8 vs. 3.5; IQR 3-4, p<0.01). No differences were found concerning presence of ASA. There were no significant differences concerning previous clinical stroke or TIA, outcome at 3 and 12 months, mortality, arterial territory and topography, except for a tendency of more strokes in the brainstem and less in the cortex in the ASD group. We found no statistical differences concerning presence of silent strokes.

Discussion

In this retrospective study of a large AIS databank, we found a low prevalence of ASD; both ASD and PFO seemed to be associated with ESUS. When compared cryptogenic AIS with a high likelihood of a PFO-related stroke, cryptogenic stroke patients with ASD had a higher age and cardiovascular profile, including silent strokes on imaging. Stroke severity, clinical and radiological stroke location and clinical outcome were similar. When compared to cryptogenic AIS with a low likelihood of a PFO-related stroke, ASD patients were younger and had a more benign cardiovascular profile. Clinical, radiological, and prognostic factors were similar.

Prevalence of ASD in ESUS is low compared to PFO, in keeping with its low prevalence in the general population. Similar to PFO, its pathogenic role seems confirmed by our finding of a higher prevalence in ESUS than in stroke with a determined cause (OR of 5.2 for ASD, and 2.8 for PFO). Our OR for PFO is identical to the one in the meta-analysis of Alsheikh-Ali et al (15). The OR for ASD is non-significantly higher than for PFO in this small sample; to our knowledge, OR for ASD association with strokes has not been published previously.

When reviewing our ASD and PFO patients for this study, we found several misdiagnoses, in particular an overdiagnosis of ASD in PFO patients. This may be important if a center has a tendency to offer ASD closure to the majority of such patients.

The exact mechanism for the pathogenicity of ASD is not yet fully understood. Due to the permanent opening of the ASD, a left-to-right shunt is usually present in such patients. For paradoxical embolization, shunt inversion is required, which can occur transiently during Valsalva, and permanent in severe ASDs with pulmonary hypertension (“Eisenmenger syndrom”). Unlike in PFO, it is not clear whether other structural septum findings in ASD are associated with a particularly high stroke risk. However, a small size ASD has recently been associated with a greater risk of embolic events, similar to PFO (11,13). In our population, we found no difference concerning the presence of an ASA among the three populations.

When compared to HL-PFO, ASD patient are significantly older, and they are younger than LL-PFO. Also for other risk factors including preceding cerebrovascular events and silent infarctions, ASD patient with ESUS seems to be an intermediate population between patients with high and low probability of paradoxical embolism.

We report a female predominance of ASD in ESUS when compared to both LL-PFO and HL-PFO. This finding is likely explained by a higher prevalence of ASD in girls at birth, whereas PFO prevalence is similar in both sexes (16,17). These results are similar to a previous report comparing ASD and PFO patients referred for percutaneous closing (13).

Radiologically, PFO related stroke are typically large, apparent, superficially located or unassociated with prior radiological infarcts (12). Our results show no statistical differences in radiological presentation and stroke localization. Silent cerebral infarction were somewhat more present in ASD and LL-PFO than in the HL-PFO; this may be explained by the higher risk factor profile (as exemplified by an ASD with a silent lacunar lesion), or by a unproven higher tendency of ASD for recurrent embolic stroke.

Unadjusted functional outcome at 3 and 12 months seemed similar in all three groups and recurrence rates were too low for meaningful statistical comparisons, although HL-PFO seems to have the lowest risk, as is well known from previous studies (11,18).

The RoPE score has been designed for patients with PFO, in order to assess PFO pathogenicity, and consequently probability of paradoxical embolism. Assuming that paradoxical embolism from right-to-left shunt is the common mechanism in PFO and ASD related stroke, we also applied the RoPE score to our ASD patients. The intermediate value between HL- and LL-PFO groups are consistent with the intermediate age and risk factor profile in ASD patients, and support the notion that some but not all AIS in these patients are ASD related. Similar to LL-PFO patients, a significant proportion of ESUS in ASD patients may be related to other mechanisms such as covert paroxysmal atrial fibrillation or atherosclerotic sources (6,7). Therefore, a careful work-up by an experienced cerebrovascular center seems warranted before otherwise asymptomatic ASD closure is considered.

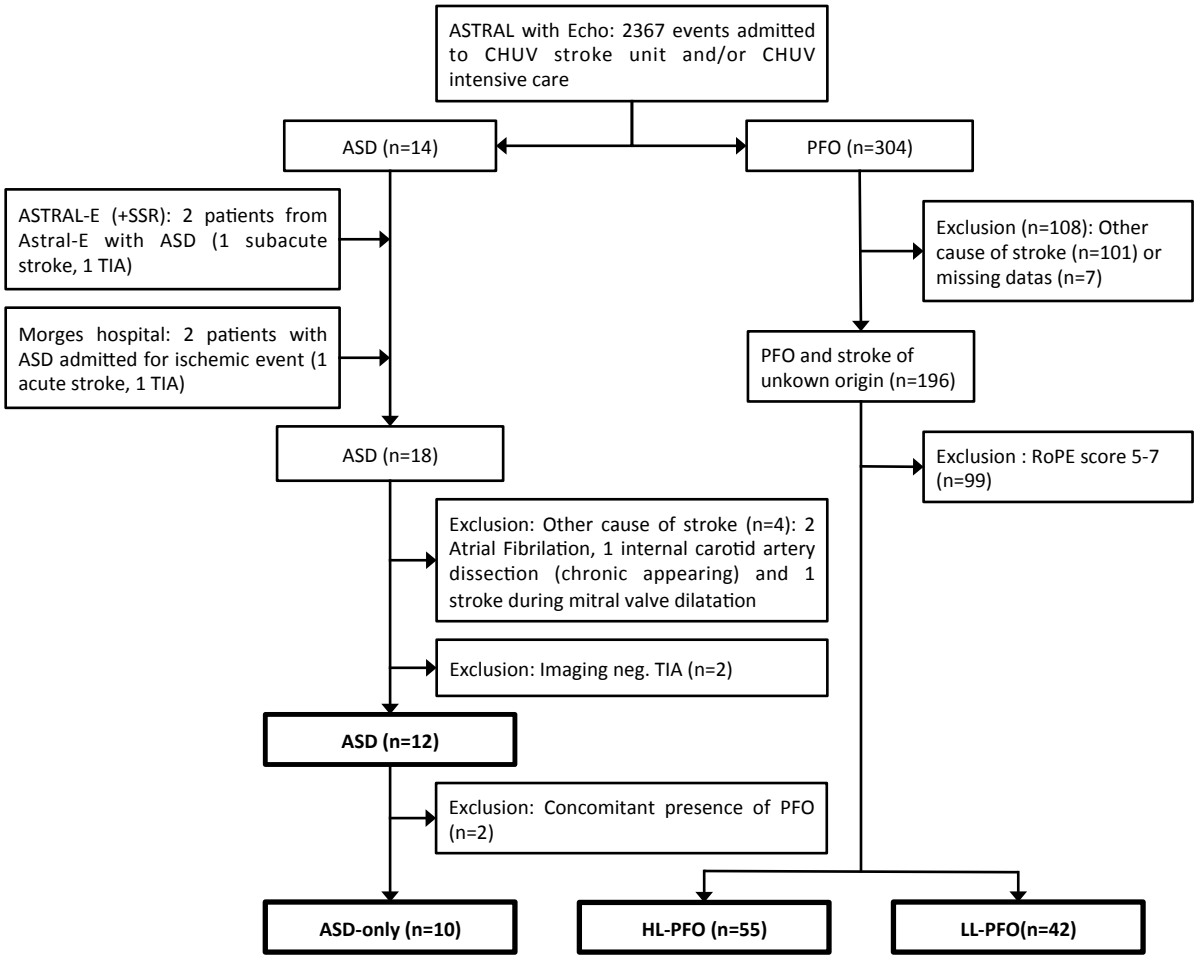
The most important limitation for this study is the low number of ASD patients, not allowing for a multivariate analysis. Secondly, the study design is retrospective, observational, and non-randomized. Moreover, this is a single center study, which may not have a population representative of other setting for acute stroke care.

In conclusion, in a limited number of ASD patients with ESUS, we confirmed a likely association of ASD and AIS, and found an intermediate likelihood of ASD being causally related to the stroke. This supports detailed etiological work-up of such

patients with selective closure of ASD. Further systematic study of ASD and ESUS and the applicability of the RoPE score in ASD are required in larger samples of patients.

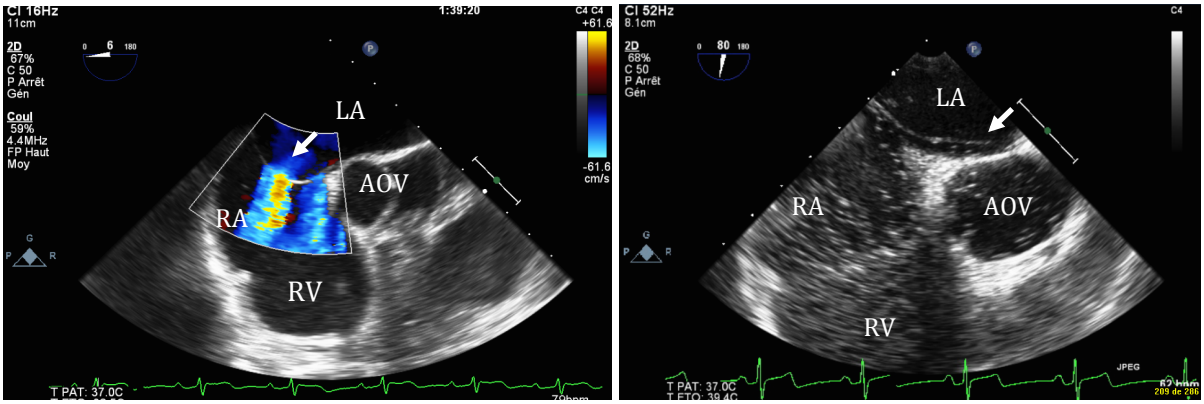
Tables and Figures

Figure 1. Inclusion and exclusion flow diagram



Final groups selected for the univariate comparison are bold surrounded. ASTRAL indicates acute stroke registry and analysis of Lausanne; ASD, atrial septal defect; CHUV, centre hospitalier universitaire vaudois, PFO, patent foramen ovale; ASTRAL-E, ASTRAL excluded; SSR, Swiss stroke registry; TIA, transient ischemic attack; RoPE, risk of paradoxical embolism; HL-PFO, high likelyhood of PFO related stroke; LL-PFO, low likelyhood of PFO related stroke.

Image 1. Transoesophageal echocardiography of ASD and PFO



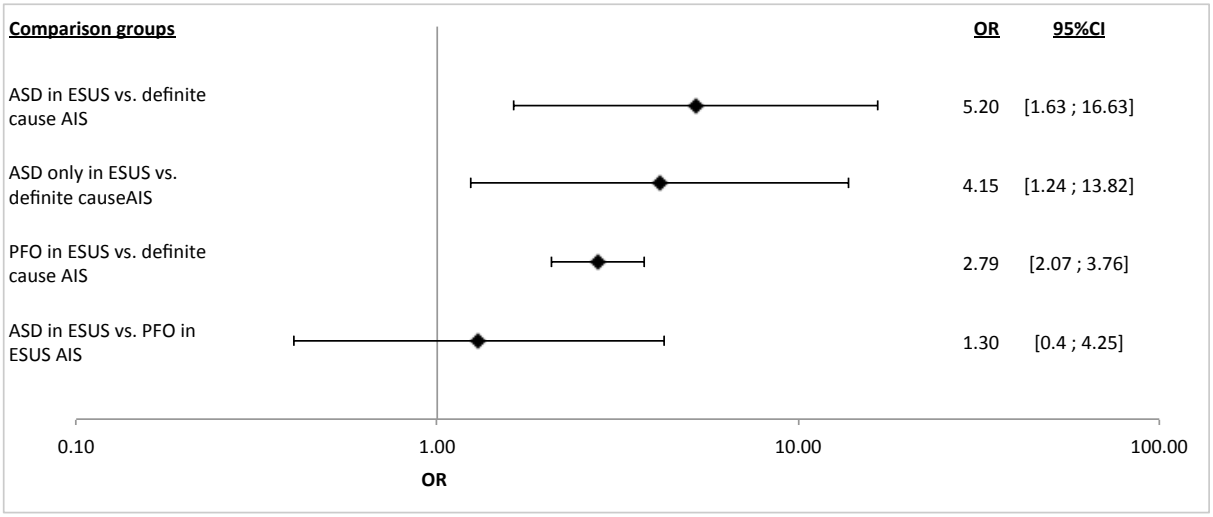
Transoesophageal echocardiography as used in this study for the initial diagnosis of atrial septum pathologies. Both images represent view in the vertical plane at the level of the interatrial septum. Left, view in a patient with an atrial septal defect, showing spontaneous passage of blood from the left to the right atrium at rest with Doppler through the atrial tissue defect (arrow). Right, view in a patient with a PFO, depicting passage of air microbubbles through the PFO (arrow) from the right into the left atrium during a Valsalva maneuver. PFO is characterized by the lack of apposition of the septum primum on septum secundum. LA indicates left atria; RA, right atrium; RV, right ventricle; AOV, aortic valve.

Table 1. ASD and PFO prevalence among ASTRAL patients

	ASD	PFO
Number of events	14	304
Reference population [a]	2367	827
Overall prevalence	0.59%	36.8%
Cryptogenic events	10	194
Prevalence among cryptogenic stroke	1.33%	48.5%
Definite cause	4	101
Prevalence among stroke of definite cause	0.26%	25.3%

[a] For overall prevalence, ASD patients were compared to all ASTRAL patients who had transthoracic and/or transoesophageal echocardiography, whereas PFO patients were compared to all ASTRAL patients who had echocardiography with injection of air microbubble.

Figure 2. ASD and PFO association with ESUS



Odd Ratio (OR) and 95% confidence interval (95%CI) of the different analyses are represented on a forest plot with a logarithmic scale. Odd Ratio (OR) superior to 1 are in favor of the first group of the comparison. Association is considered significant if 95%CI does not contain 1 (p-value <0.05). ESUS indicates embolic stroke of undetermined source; AIS, acute ischemic stroke.

Table 2. Baseline characteristics of ESUS patients with ASD and/or PFO

	ASD (n=12)	ASD-only (n=10)	HL-PFO (n=55)	LL-PFO (n=42)
Demographics				
Female sex	9 (75%)	8 (80%)	21 (38%)	24 (57%)
Age, y	49.5 (41.7-55.96)	49.98 (39.8-60.7)	29.64 (25.09-36.72)	72.29 (66.67-78.01)
PFO features				
RoPE	7 (5-8)	6.5 (5 to 7.75)	8 (8-9)	3.5 (3-4)
ASA	8 (67%)	7 (70%)	26 (47%)	17 (41%)
Major Risk Factor				
Hypertension	4 (33%)	4 (40%)	0	35 (83%)
Diabetes	0	0	1 (2%)	5 (12%)
Smoking	2 (17%)	2 (20%)	16 (29%)	10 (24%)
Hyperlipidemia	7 (58%)	6 (60%)	14 (26%)	33 (79%)
Atrial Fibrillation	0	0	0	0
CAD	1 (8%)	1 (10%)	0	0
BMI	6 (50%)	4 (40%)	13 (27%)	18 (45%)
Migraine	3 (25%)	2 (20%)	12 (22%)	2 (5%)
Previous stroke[a]	3 (25%)	3 (30%)	1 (2%)	19 (45%)
≥2 Risk Factors	6 (50%)	5 (50%)	9 (20%)	36 (92%)
Stroke characteristics				
Admission NIHSS	4 (3-13.25)	7.5 (3.5-13.75)	4 (1-9.5)	7 (4-10.75)
Anterior circulation	8 (67%)	7 (70%)	35 (64%)	31(74%)
Posterior circulation	4 (33%)	3 (30%)	20 (36%)	11 (26%)
Outcome				
Favorable at 3 months	7 (58%)	5 (50%)	35 (76%)	19 (49%)
Favorable at 12 months	7 (58%)	5 (50%)	36 (80%)	19 (49%)
Mortality at 12 months	0	0	0	2 (5%)
Recurrence over 12 months (stroke or TIA)	1 (8%)	1 (10%)	1 (2%)	3 (8%)
Radiology				
Territory Topography:				
Cortical	2 (17%)	1 (10%)	19 (35%)	15 (36%)
Subcortical	1 (8%)	1 (10%)	5 (9%)	5 (12%)
Cortical & subcortical	4 (33%)	4 (40%)	16 (29%)	14 (33%)
Brainstem (together)	5 (42%)	4 (40%)	15 (27%)	8 (19%)
Silent strokes	2 (17%)	2 (20%)	1 (2%)	15 (38%)

Continuous variables are presented as median±interquartile range. Nominal variables are presented as absolute number and percent (percent refers to recorded values only; missing values have been excluded). ASA, atrial septal aneurysm; CAD, coronary artery disease; BMI, body mass index; NIHSS, national institute of health stroke score.

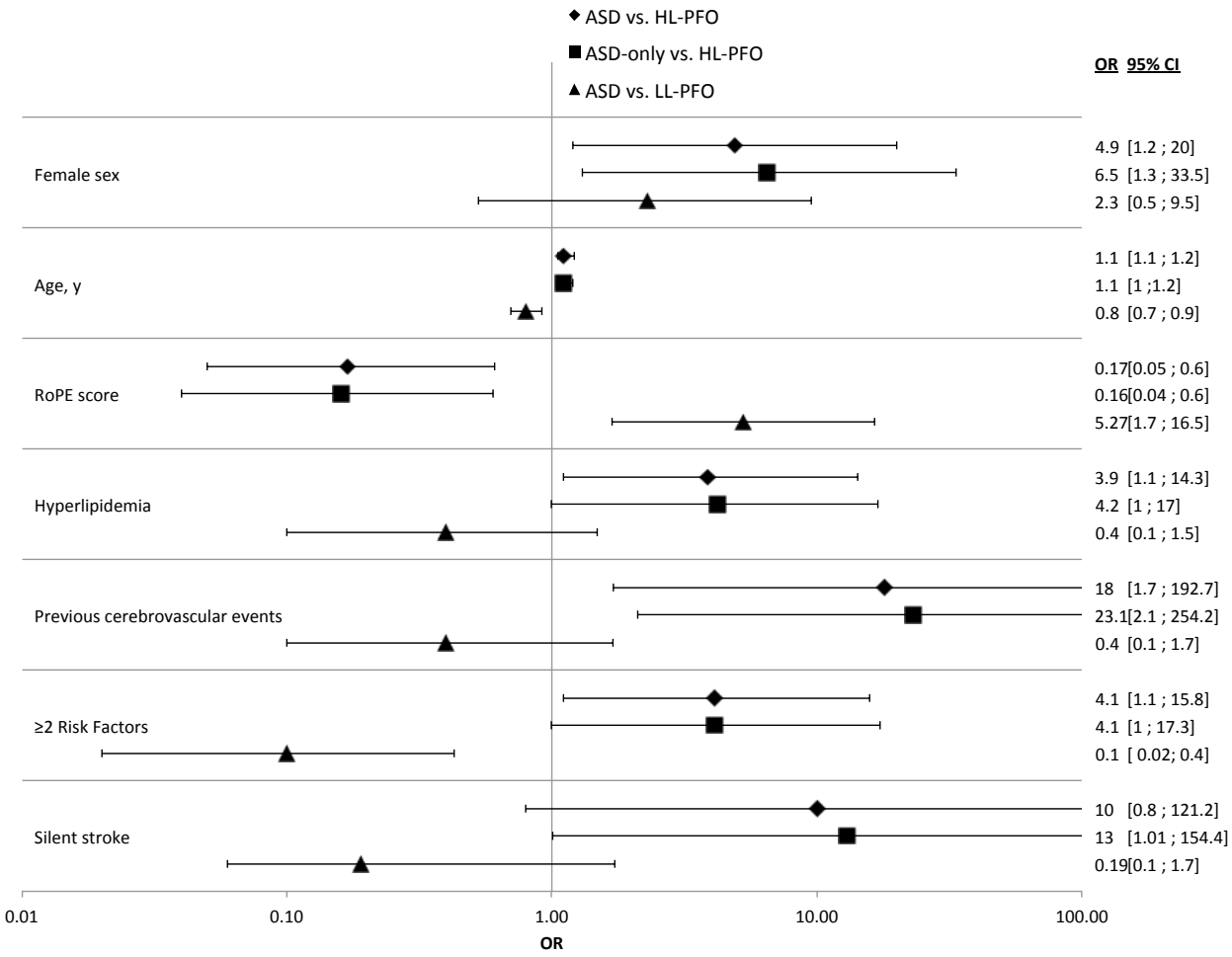
[a] Refers to previous clinical stroke or transient ischemic attack (TIA).

Table 3. Summary of results

	ASD vs. HL-PFO			ASD-only vs. HL-PFO			ASD vs. LL-PFO		
	OR	**OR-CI**	***p***	**OR**	**OR-CI**	***p***	**OR**	**OR-CI**	***p***
Demographics									
Female sex	4.9	1.2-20	<0.01	6.5	1.3-33.5	0.03	2.3	0.5-9.5	0.27
Age, y	1.1	1.1-1.2	<0.01	1.1	1.0-1.2	<0.01	0.8	0.7-0.9	<0.01
PFO features									
RoPE	0.2	0.05-0.6	<0.01	0.2	0.04-0.6	<0.01	5.3	1.7-16.5	<0.01
ASA	2.2	0.6-8.3	0.23	2.6	0.6-11.1	0.20	2.9	0.8-11.3	0.12
Major Risk Factor:									
Hypertension	NA	NA	<0.01	NA	NA	p<0.01	0.1	0.02-0.5	<0.01
Diabetes	NA	NA	0.82	NA	NA	0.74	NA	NA	0.39
Smoking	0.5	0.1-2.5	0.39	0.6	0.1-3.2	0.56	0.6	0.1-3.4	0.60
Hyperlipidemia	3.9	1.1-14.3	0.04	4.2	1.0-17.0	0.05	0.4	0.1-1.5	0.17
Atrial Fibrilation	NA	NA	NA	NA	NA	NA	NA	NA	NA
CAD	NA	NA	0.11	NA	NA	0.09	NA	NA	0.15
BMI	2.8	0.8-10.1	0.12	1.8	0.4-7.6	0.40	0.9	0.3-3.1	0.89
Migraine	1.2	0.3-5.0	0.84	0.9	0.2-4.7	0.88	6.7	0.97-45.9	0.05
Previous stroke [a]	18	1.7-192.7	0.02	23.1	2.1-254.2	0.01	0.4	0.1-1.7	0.22
≥2 risk factors	4.1	1.1-15.8	0.04	4.1	1.0 -17.3	0.05	0.1	0.02-0.4	<0.01
Stroke characteristics									
Admission NIHSS	1.0	0.95-1.1	0.57	1.0	0.96-1.1	0.34	1.0	0.9-1.1	0.77
Anterior circulation	1.1	0.3-4.3	0.84	1.3	0.3-5.7	0.70	0.7	0.2-2.8	0.63
Posterior circulation	0.9	0.2-3.3	0.84	0.8	0.2-3.2	0.70	1.4	0.35-5.6	0.63
Outcome									
Favorable at 3 months	0.4	0.1-1.7	0.23	0.3	0.1-1.3	0.11	1.5	0.4-5.45	0.56
Favorable at 12 months	0.4	0.1-1.4	0.13	0.3	0.1-1.1	0.06	1.5	0.4-5.45	0.56
Mortality at 12 months	NA	NA	0.52	NA	NA	0.47	NA	NA	0.75
Recurrence over 12 months (stroke or TIA)	4.0	0.2-69.1	0.52	4.9	0.3-85.6	0.28	1.1	0.1-11.6	0.94
Radiology									
Territory Topography:									
Cortical	0.4	0.1-1.9	0.24	0.2	0.02-1.79	0.15	0.4	0.1-1.9	0.22
Subcortical	0.9	0.1-8.6	0.93	1.1	0.1-10.7	0.93	0.7	0.1-6.4	0.73
Cortical & subcortical	1.2	0.3-4.6	0.77	1.6	0.4-6.5	0.49	1	0.3-3.9	1.00
Brainstem (together)	1.9	0.5-6.9	0.33	1.8	0.4-7.2	0.42	3.0	0.8-12.1	0.12
Silent strokes	10	0.8-121.2	0.07	13	1.01-154.4	0.05	0.3	0.1-1.7	0.19

Univariate comparison of epidemiological, clinical and radiological variables of the ESUS ASD patients with the high and low likelihood of PFO related stoke group (HL-PFO and LL-PFO group). NA indicates not available (OR cannot be calculated because of a value of zero in certain groups).

Figure 3. Forest plot summarizing significant results



Odd Ratio (OR) and 95% confidence interval (95%CI) of the different comparisons are represented on a forest plot with a logarithmic scale. Odd Ratio (OR) superior to 1 are in favor of ASD or ASD-only. Association is considered significant if 95%CI does not include 1 (p-value <0.05).

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