Embolic stroke of undetermined source: identification of patient subgroups for oral anticoagulation treatment

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Background: Embolic stroke of undetermined source (ESUS), a subtype of cryptogenic stroke, was defined as acute ischemic stroke displaying an embolic or non-lacunar brain infarct pattern on imaging without significant extra or intracranial ipsilateral vessel stenosis or without an identifiable cardioembolic source such as atrial fibrillation (AF) or left ventricular thrombi (Hart et al., 2014). ESUS patients tend to be younger than other stroke patients and have a lower incidence of traditional risk factors such as hypertension, diabetes and hypercholesterolemia, that are key contributors for the development of atherosclerosis, the substrate for small and large vessel disease. Two large clinical trials of embolic stroke of unknown source comparing the direct acting oral anticoagulants rivaroxaban and dabigatran to antiplatelet therapy for secondary stroke prevention, the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial *versus* aspirin to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) (Hart et al., 2018) and Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate *versus* Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RESPECT-ESUS) (Diener et al., 2019), showed not only no benefit for ESUS patients treated with oral anticoagulation to prevent recurrent strokes, but showed even higher risk of bleeding while treated with rivaroxaban. Consequently, the study hypothesis of prevention of recurrent stroke by oral anticoagulation with dabigatran and rivaroxaban in patients diagnosed with ESUS had to be rejected, keeping aspirin as primary secondary prevention treatment for this stroke subtype. Although the reasons for the negative study results are probably multifactorial, posthoc analysis and recent cardiac monitoring studies in ESUS patients suggested that AF may not account for the majority of stroke events in ESUS patients (for example see expert review on ESUS concept, etiology and diagnostic: Schäbitz et al., 2020). In addition to aspects of diagnosis and etiology of ESUS, this topical review will discuss recent evidence from prespecified subgroups of the NAVIGATE- and RESPECT-ESUS trials suggesting a benefit for patients treated with oral anticoagulation with regard to secondary stroke prevention.

ESUS etiology and diagnosis: Studies using continuous cardiac monitoring with implantable loop recorders in ESUS patients reported AF detection rates of 23.6% after one year and 42.1% after 3 years (Israel et al., 2017; Kitsiou et al., 2021). According to these data, AF is highly prevalent in ESUS patients, and when detected it normally triggers the administration of oral anticoagulation (Kitsiou et al., 2021). In addition, these findings raised the question of the stroke cause in the majority of ESUS patients in whom AF could not be detected. Indeed, recent studies shifted other stroke causes such as atherosclerosis of the aorta and the carotid arteries into focus (**Additional Table 1** for summary). The largest data set from a subgroup analysis of the NAVIGATE-ESUS trial showed carotid plaques to be present in up to 40% and mild carotid stenosis in up to 11% of ESUS patients (Ntaios et al., 2019c). Consistent with the hypothesis of atherosclerosis as stroke cause in ESUS patients, there was a trend towards a higher rate of ischemic stroke recurrence in patients with carotid plaques compared to those without (5.4 *vs.* 4.3/100 patient-years, hazard ratio, 1.23, 95% CI: 0.99–1.54). Another subgroup analysis from the NAVIGATE-ESUS trial showed in 509 (37%) of 1382 patients who had a transesophageal echocardiography, the presence of complex aortic arch atherosclerosis with plaques that were ulcerated or ≥ 4 mm in thickness or with a mobile thrombus present (Ntaios et al., 2019a). Again supporting the atherosclerosis hypothesis as stroke cause in ESUS patients, multi-territorial infarctions rather than single-territory infarctions tended to occur more often in patients with complex aortic arch atherosclerosis (21%) *versus* noncomplex (17%) *versus* no aortic arch atherosclerosis (13%) (Ntaios et al., 2019a). In addition to atherosclerosis of the aorta and the carotid arteries, potential causes of an ESUS include cardiac abnormalities of the left atrium and the ventricle such as atrial cardiopathy or left ventricular thrombus (**Additional Table 1**) (Takasugi et al., 2017; Tandon et al., 2019) Patent foramen ovale was a common finding in ESUS patients that occurred in 7.4% (in 534 patients out of 7213 enrolled patients in NAVIGATE ESUS) (Diener et al., 2019; Hart et al., 2019) and may represent a potential stroke cause particularly in patients in which another pathology such as atrial fibrillation, atherosclerotic disease of the brain supplying arteries and the aorta and any other structural cardiac abnormality could not be found (Kasner et al., 2018). Etiology in ESUS patients may be characterized by overlapping causes as potential embolic sources (Ntaios et al., 2019b).

The diagnostic workup for ESUS patients should not solely focus on rhythm monitoring for detection of atrial fibrillation, it must include an imaging of extra- or intracranial vessels to demonstrate significant stenosis (> 50%), transthoracic and/or transesophageal echocardiography to disclose cardioembolic sources and investigation for inherited or acquired coagulopathies at risk for thromboembolic events.

If this primary workup remains negative, an ESUS diagnosis can be made based on the current definition. Instead of accepting this diagnosis as final, investigators should consider the initiation of more comprehensive additional diagnostic. This includes three-dimensional transesophageal echocardiography, extra-intracranial vascular imaging including plaque measurement, long-term invasive cardiac monitoring by implanted loop recorders and even cardiac magnetic resonance imaging. After completion, the etiology has to be re-defined and the ESUS diagnosis potentially to be replaced by a specific etiology followed by treatment adaptation.

ESUS subgroups of elderly and renally impaired patients: Current evidence clearly fails to support the hypothesis that ESUS patients benefit from anticoagulation using dabigatran or rivaroxaban, and should therefore be treated with aspirin as most other cryptogenic stroke patients are. Subgroup analysis of the RESPECT-ESUS trial showed, however, that older and renally impaired patients and thus by design patients receiving the lower dose of dabigatran tended to benefit from anticoagulation.

In the RESPECT-ESUS trial, 16.4% of aspirin treated patients with a creatinine clearance between 30 to < 50 mL/min at baseline developed recurrent strokes compared to 10.2% of patients treated with dabigatran (hazard ratio 0.63, 95% CI: 0.37–1.07) (Diener et al., 2020). In the patient group with a creatinine clearance between 50 to < 80 mL/min at baseline, 8.3% had recurrent strokes when treated with aspirin compared to 5.7% in the dabigatran group (hazard ratio 0.68, 95% CI: 0.48–0.95). These findings are largely confirmed by data from the NAVIGATE-ESUS trial using rivaroxaban instead of dabigatran for oral anticoagulation, in which a trend was observed in the group of patients with a reduced GFR of less than 80 mL/min.: 4.9 % of patients treated with 15 mg rivaroxaban had recurrent strokes as compared to 5.8% treated with aspirin (hazard ratio 0.83, 95% CI: 0.62–1.12) (Hart et al., 2018).

The subgroup of patients older than 75

years in the RESPECT-ESUS trial showed a remarkable difference between aspirin and dabigatran treatment: 12.4% of patients treated with aspirin developed recurrent stroke compared to only 7.8% treated with dabigatran (hazard ratio 0.63, 95% CI: 0.43–0.94, interaction *P* = 0.097) (Diener et al., 2020). In patients with the combined risk factors age > 75 years and creatinine clearance < 50 mL/min, treatment with the lower dose of dabigatran (110 mg twice daily) resulted in only 7.4% of patients with recurrent stroke, whereas treatment with aspirin led to recurrent stroke in 13% of the patients (hazard ratio 0.57, 95% CI: 0.39–0.82, interaction *P* = 0.011). In the subgroup of patients randomized to study medication later than 91 days after index stroke, treatment with dabigatran led to a recurrent stroke in only 4.9% of patients as compared to 8% of patients treated with aspirin (hazard ratio 0.62, 95% CI: 0.37–1.04). Patients with highest CHA_2DS_2-VASc score (> 5) seamed to benefit from dabigatran treatment as well (7.7% recurrent stroke *versus* 9.6% in the aspirin treated patients, hazard ratio 0.79, 95% CI: 0.59–1.06). With regard to geographic regions, patients from Asia and central Europe seemed to benefit from dabigatran treatment with respect to stroke recurrence (6.0% *versus* 9.3%, hazard ratio 0.68; 95% CI: 0.44–1.03) and 4.3% *versus* 7.5% (hazard ratio 0.56, 95% CI: 0.30–1.06, respectively) compared to patients for North America or Western Europe.

Furthermore, these findings are supported by a sub-analysis of the Japanese cohort of the RESPECT-ESUS trial (Toyoda et al., 2020), in which recurrent strokes and ischemic strokes occurred with a lower relative risk in Japanese patients on treatment with dabigatran (6.8% and 6.8%, respectively) compared with treatment with aspirin (12.7% *vs.* 12.3%, hazard ratio 0.55 and 0.56, 95% CI: 0.32–0.94, 0.33–0.97, respectively). Life threatening bleeding and major intracranial hemorrhage occurred in the group of dabigatran treated Japanese patients in 2.0% and 1.7%, while treatment with aspirin led to a relative risk of life-threatening bleeding in 4.3% (hazard ratio 0.46, 95% CI: 0.17–1.21) or major intracranial hemorrhage in 3.0% of patients (hazard ratio 0.55, 95% CI: 0.18–1.65). Such favorable findings regarding bleeding rates correspond to the main trial which exhibited an almost similar bleeding rate between dabigatran and standard aspirin treated ESUS patients (Diener et al., 2029). Of note, comparing the patient baseline characteristics in the Japanese and Non-Japanese cohorts, there is a statistically significant difference in numbers of patients with a creatinine clearance of < 50 mL/min between these two cohorts. Whereas in the non-Japanese patient cohort only 6.7% of patients had impaired renal function, the Japanese cohort included 18.7% of these patients. In addition, the Japanese cohort was statistically significant older than the Non-Japanese cohort (67.4% *vs.* 63.8%, *P* < 0.0001). Thus, not the Japanese origin, but reduced renal function and older age appear to be important medical conditions in which treatment with reduced oral anticoagulation may prevent recurrent stroke, ischemic stroke and major intracranial hemorrhage. These findings in elderly and renally impaired ESUS patients are fully in line with epidemiological data displaying the hypothesis that elderly and renally impaired stroke patients have the highest risk for atrial fibrillation and subsequently exhibit the highest stroke recurrence risk over time (Reinecke et al., 2013).

Conclusion: The hypothesis ESUS patients may benefit from oral anticoagulation has been rejected, but evidence is mounting that in prespecified subgroups oral anticoagulation may have the potential to prevent recurrent embolic strokes. A dedicated diagnostic workup is crucial, not only to dissect the correct ESUS etiology but also to prevent harm from older and renally impaired patients with respect to treatments leading to life-threatening bleed or major intracranial hemorrhage.

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Additional files:
Additional file 1: *Open peer review report 1.*
Additional Table 1: *Underlying potential embolic sources of ESUS patients.*

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Additional Table 1 Underlying potential embolic sources of ESUS patients

Potential embolic sources	Prevalence	Population	Reference
Atrial fibrillation	up to 41.4%	German ESUS cohort, single center	Israel et al. (2017); Kitsiou et al. (2021)
Large arty disease	11% minor stenosis, 40% carotid plaques, 37% aortic plaques	NAVIGATE-ESUS cohort	Ntaios et al. (2019); Ntaios et al. (2019);
	48.5% (combination of the above)	Multicenter stroke registry	Ntaios et al. (2019)
Cancer	9.2%	Multicenter stroke registry	Ntaios et al. (2019)
PFO	7.4%	NAVIGATE-ESUS TTE/TOE cohort	Kasner et al. (2018)
Atrial cardiopathy	45%	Multicenter stroke registry	Ntaios et al. (2019)
Left ventricular disease	54.4%	Multicenter stroke registry	Ntaios et al. (2019)

ESUS: Embolic stroke of undetermined source; NAVIGATE-ESUS: New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus aspirin to Prevent Embolism in Embolic Stroke of Undetermined Source; PFO: patent foramen ovale; TOE: transesophageal echocardiography; TTE: transthoracic echocardiography.