



Long-term (> 10-year) clinical follow-up after young embolic stroke/TIA of undetermined source

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Abstract

Background: To date, the pathophysiology of first-ever and recurrent stroke/TIA still remains unclear in young patients with embolic stroke/TIA of undetermined source (ESUS). Clinical studies with long-term follow-up in young ESUS patients are necessary to investigate the underlying pathophysiology of first-ever and recurrent stroke/TIA in this patient population, in particular the role of new-onset atrial fibrillation.

Aims: Our aim was to study the long-term (> 10-year) clinical outcome of young patients (< 50 years) with ESUS.

Methods: This cohort study included all patients aged ≤ 50 years who underwent transoesophageal echocardiography for diagnostic work-up of ESUS during 1996–2008 from one tertiary center. All patients were contacted by telephone between September–November 2018 to update clinical information from medical records. The clinical outcomes of this study were incidence rates of all-cause and cardiovascular mortality, recurrent stroke/TIA, new-onset clinical AF, and ischemic vascular events.

Results: In total, 108 patients (57% female, mean age 40 ± 7.2 years [range 19–50 years], $n = 72$ stroke) were included. Across clinical follow-up (median 13 [IQR 10–16] years), 24 patients died ($n = 14$ cardiovascular). The 15-year incidence rate of recurrent stroke/TIA was 15% (incidence rate = 1.09 [95%CI 0.54–1.65]/100 patient-years) and a 5.5% incidence of new-onset clinical AF (incidence rate = 0.44 [95%CI 0.09–0.79]/100 patient-years) following ESUS.

Conclusions: The incidence of recurrent stroke/TIA is relatively high during long-term clinical follow-up of young patients with ESUS. In contrast, new-onset clinical AF is relatively low and therefore may not play an important part in the pathophysiology of first-ever and recurrent stroke/TIA of these patients.

Keywords

Embolic strokes of undetermined source, atrial fibrillation, stroke, transient ischemic attack, cryptogenic, young stroke

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Introduction

Embolic strokes of undetermined source (ESUS) are defined as non-lacunar ischemic strokes without major cardio-embolic sources despite thorough diagnostic evaluation, and comprise $\sim 40\%$ of all ischemic strokes in patients aged < 50 years.¹ To date, the pathophysiology of first-ever and recurrent stroke/TIA still remains unclear in the young ESUS population. Although they have the lowest risk of recurrent stroke compared to other first-ever ischemic stroke types,² the impact of any stroke/TIA at such a young age cannot be ignored. Silent atrial fibrillation (AF) has been implicated as a key factor in the etiology of ESUS for its risk of arterial embolism;³ however, AF is generally

associated with older age.⁴ Clinical studies with long-term follow-up in young ESUS patients are necessary to investigate the underlying pathophysiology of

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first-ever and recurrent stroke/TIA in this subgroup of patients.

Aims

Our aim was to study the long-term (>10-year) clinical outcome of young patients (<50 years) with ESUS.

Methods

For this retrospective cohort study, all consecutive patients aged < 50 years between 1996 and 2008 were screened if they were referred to our tertiary center for diagnostic work-up of ESUS in < 50-year-old patients, which routinely included a diagnostic transoesophageal echocardiography (TOE) as part of unexplained non-lacunar ischemic stroke/TIA. The clinical protocol included brain imaging and cervical/transcranial duplex Doppler ultrasound, TOE, and 24-h Holter ambulatory electrocardiographic monitoring. Patients received antiplatelet therapy according to the prevailing clinical protocol. The study cohort comprised patients with TIA or non-lacunar stroke in the absence of a major-risk cardio-embolic source or $\geq 50\%$ luminal stenosis in arteries supplying the ischemic area, or other possible causes (systemic vascular disease, dissection, etc.) according to the Cryptogenic Stroke/ESUS International Working Group definitions.⁵

The clinical outcomes of this study were incidence rates of all-cause and cardiovascular mortality, recurrent stroke/TIA, new-onset clinical AF, and peripheral ischemic events across follow-up after the index event (stroke/TIA) in patients aged < 50 years. Patient baseline characteristics and incident cardiovascular risk factors during follow-up were gathered from medical records. Clinical outcomes were updated from patient contact by telephone between September–November 2018 or alternatively gathered from last medical follow-up. Patient-reported events were adjudicated using source documents of treating hospitals or general practitioners. Data on mortality were acquired via the Cause of Death Registry of Statistics Netherlands. All deaths were marked cardiovascular unless an unequivocal non-cardiac cause could be established. This study complies with the declaration of Helsinki and national legislation; the local medical ethical committee approved the study and all patients provided verbal informed consent.

Statistical analyses were performed on R v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS v.23 (IBM Corp., Armonk, NY, USA). Data are presented as frequencies (percentage), mean \pm standard deviation, or median [25th–75th percentile]. Incidence rates of the outcomes were calculated using Poisson regression. For recurrent stroke/TIA

and AF, cumulative incidence functions are shown as Kaplan–Meier estimates of time-to-event analyses from the index event, with all-cause mortality as competing risk event. Follow-up was censored at the time of last telephone contact or, if unavailable, at last medical contact. Hazard ratios for presence of baseline risk factors were determined using Cox regression. Incident risk factors during follow-up were included as time-dependent variables. A *P*-value < 0.05 was considered statistically significant.

Results

The study cohort consisted of 108 patients (57% female, mean age 40 ± 7.2 years [range 19–50 years], $n = 72$ stroke; Table 1) with a total median follow-up duration of 13[10–16] years.

Death occurred in 24 patients ($n = 10$ non-cardiovascular, $n = 14$ cardiovascular). In total, 63(75%) of the surviving patients could be contacted by telephone to update clinical information (median follow-up 14[11–18] years). Twenty patients could not be contacted due to emigration ($n = 2$) or untraceable telephone number with unknown general practitioner ($n = 18$) (median follow-up 14[6.8–18] years).

The incidence rates of all clinical events across follow-up are summarized in Table 2. Recurrent stroke/TIA

Table 1. Baseline characteristics of the study cohort

	N = 108
Demographics	
Age at index event, y	40 \pm 7.2
Female	61 (57)
Cardiovascular risk factors	
Hypertension	20 (19)
Diabetes mellitus	7 (7)
Hypercholesterolemia	13 (12)
Current smoking	24 (22)
Pack years	19 \pm 2.3
Minor cardio-embolic risk factors^a	
Patent foramen ovale	16 (15)
Atrial septal aneurysm	5 (5)
Spontaneous echo contrast in atrial appendage	1 (1)

Note: Data presented as mean \pm SD or frequencies (%).

^aEchocardiographic findings at index event.

Table 2. Incidence rates of clinical events during follow-up after index stroke/TIA

	N of events	Patient-years	Incidence rates (95% CI) per 100 patient-years
All-cause mortality	24	1372	1.75 (1.14–2.54)
Cardiovascular	14	1372	1.02 (0.57–1.65)
Recurrent stroke/TIA	15	1241	1.21 (0.69–1.93)
Recurrent stroke	14	1307	0.54 (0.23–1.04)
Recurrent TIA	1	1292	0.70 (0.33–1.25)
Atrial fibrillation	6	1350	0.44 (0.18–0.90)
Other cardiovascular events			
Myocardial infarction	2	1362	0.15 (0.02–0.45)
Pulmonary embolism	2	1358	0.15 (0.02–0.45)
Deep venous thrombosis	2	1356	0.07 (0.004–0.32)
Peripheral arteriopathy ^a	2	1361	0.15 (0.02–0.45)

^aPeripheral arteriopathy = acute abdominal aortic aneurysm ($n = 1$), brachial artery occlusion ($n = 1$).

occurred in 15 patients (incidence rate = 1.21[95%CI 0.69–1.93]/100 patient-years) and new-onset AF was diagnosed in 6 patients (incidence rate = 0.44[95%CI 0.18–0.90]/100 patient-years). The estimated cumulative incidence of recurrent stroke/TIA and AF across 20-year follow-up is shown in Figure 1.

Explorative analyses showed that presence of ≥ 1 conventional cardiovascular risk factor at baseline was not associated with higher risk of recurrent stroke/TIA (HR 1.47[95%CI 0.53–4.07]; $P = 0.45$), nor presence of a patent foramen ovale or atrial septal aneurysm (HR 0.86[95%CI 0.19–3.79]; $P = 0.84$). In a time-dependent Cox analysis, new-onset diabetes ($n = 15$) was significantly associated with a higher risk of recurrent stroke/TIA (HR 5.9[95%CI 1.85–18.6]; $P = 0.003$). Regarding possible predictors of AF, regression analyses showed that new-onset AF was not associated with presence of conventional cardiovascular risk factors at baseline (Table 1) (HR 0.41[95%CI 0.05–3.70]; $P = 0.39$).

Discussion

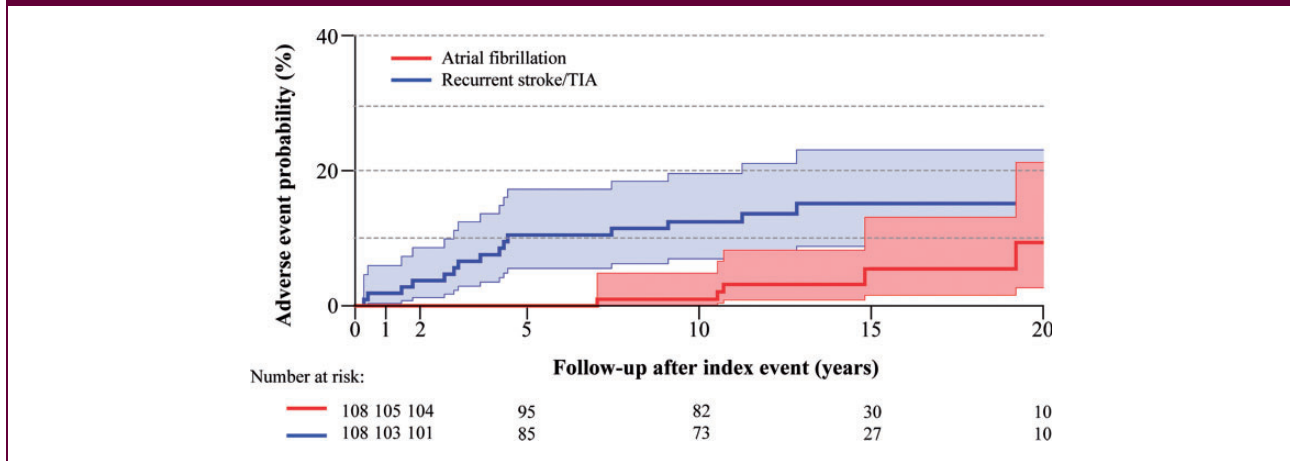
This study reports an incidence of 15% for recurrent stroke/TIA and a 5.5% incidence of new-onset clinical AF in a young patient cohort across 15-year follow-up following stroke/TIA of undetermined source. Baseline cardiovascular and cardioembolic risk factors were not associated with increased risk of recurrent stroke/TIA;

only new-onset diabetes seemed to increase risk of recurrent stroke/TIA.

In this study, the 15-year cumulative incidence rate for recurrent stroke/TIA was 15%, which is comparable to the 19.5% stroke rate reported in young ESUS patients in a Finnish registry study by Martinez-Majander et al.² Although young ESUS patients have the lowest risk of recurrent stroke compared to other first-ever ischemic stroke types,² such a recurrence rate is still of high importance considering that these patients are in the prime of life. Evidence-based interventions to optimize secondary prevention are currently lacking since the pathophysiology of recurrent stroke/TIA still remains unclear. In this study's explorative analyses, which should be interpreted with caution given the number of events, no association between baseline conventional cardiovascular risk factors and recurrent stroke/TIA was found, nor did presence of a PFO/ASD. Only new-onset diabetes seemed to increase risk of recurrent stroke/TIA, presumably by diabetic vascular disease. Some studies suggest a common pathophysiological mechanism with the TOAST-classified cardioembolic strokes including AF.^{6,7} In the current data, the low clinical AF rate did not allow for time-dependent analysis of the association between new-onset clinical AF and recurrent stroke/TIA.

In a population-based prospective cohort study, the natural 15-year incidence of clinical AF in < 55 year old

Figure 1. Cumulative incidence of AF and recurrent stroke/TIA. Estimated cumulative incidence functions with corresponding 95% confidence intervals for new-onset AF and recurrent stroke/TIA after the first-ever stroke/TIA of undetermined source at age ≤ 50 years, with all-cause mortality as competing event (median follow-up 13[10–16] years).



was 2.9%–5.4%,⁸ similar to the incidence in our study cohort. Although a cardio-embolic mechanism is speculated,⁷ a temporal association between device-detected AF and embolic events has not been established yet.^{9,10} Current studies on new-onset AF in the ESUS patient population primarily comprise older patients as well as subclinical device-detected AF, resulting in a significantly higher incidence rate of AF than reported in the present study.^{11,12} Even though the present study only reports clinical AF, the estimated subclinical AF in this study cohort is expected to be low given that device-detected AF is known to progress to clinical AF.^{13–15} In a pooled analysis of two studies,¹⁰ the risk of clinical AF during follow-up (≤ 2.5 years) was 5.7(95%CI 4.0–8.0; $P < 0.001$) times higher in patients with device-detected AF. Considering both the relatively low incidence rate of clinical AF and the lengthy follow-up period in the present study, the prevalence of subclinical AF during the index event can therefore be assumed to be also low in this young population. For this reason, AF seems less likely to be an important etiological factor in the first-ever stroke/TIA of young ESUS patients.

This study is one of the very few which investigated long-term clinical outcome of ESUS patients aged ≤ 50 years. The study strength lies in the lengthy follow-up, providing unique data in this patient population as well as sufficient time to detect clinical AF that might potentially have caused the index event. Limitations of this study include this single-center cohort size, a limited but potential selection bias from diagnostic work-up through TOE, cervical/transcranial Doppler to assess vasculature, and absence of subclinical AF assessment. Active patient telephone follow-up in a significant number of patients did provide thorough event reporting and adjudication.

In conclusion, the incidence of recurrent stroke/TIA is relatively high during long-term clinical follow-up of young patients with ischemic stroke/TIA of undetermined source considering their age. In contrast, new-onset clinical AF is relatively low and therefore may not play an important part in the pathophysiology of first-ever and recurrent stroke/TIA of these patients. Future studies are warranted to improve our understanding of the underlying mechanism of first-ever stroke/TIA in this population.

Declaration of conflicting interests


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References

1. Yang H, et al. Cardiac diagnostic work-up of ischaemic stroke. *Eur Heart J* 2018; 39: 1851–1860.
2. Martinez-Majander N, et al. Embolic strokes of undetermined source in young adults: baseline characteristics and long-term outcome. *Eur J Neurol* 2018; 25: 535–541.

3. Marini C, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke* 2005; 36: 1115–1119.
4. Go AS, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001; 285: 2370–2375.
5. Hart RG, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014; 13: 429–438.
6. Adams HP Jr, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24: 35–41.
7. Boeckh-Behrens T, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. *Stroke* 2016; 47: 1864–1871.
8. Heeringa J, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J* 2006; 27: 949–953.
9. Brambatti M, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014; 129: 2094–2099.
10. Mahajan R, et al. Subclinical device-detected atrial fibrillation and stroke risk: a systematic review and meta-analysis. *Eur Heart J* 2018; 39: 1407–1415.
11. Gladstone DJ, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014; 370: 2467–2477.
12. Sanna T, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; 370: 2478–2486.
13. de Vos CB, et al. Progression from paroxysmal to persistent atrial fibrillation clinical correlates and prognosis. *J Am Coll Cardiol* 2010; 55: 725–731.
14. Healey JS, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012; 366: 120–129.
15. Glotzer TV, et al. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MODe Selection Trial (MOST). *Circulation* 2003; 107: 1614–1619.