

Extracranial Systemic Embolic Events in Patients With Nonvalvular Atrial Fibrillation Incidence, Risk Factors, and Outcomes

Wobo Bekwelem, MD, MPH; Stuart J. Connolly, MD; Jonathan L. Halperin, MD;
Selcuk Adabag, MD, MS; Sue Duval, PhD; Susan Chrolavicius, PhD; Janice Pogue, PhD;
Michael D. Ezekowitz, MB, ChB, DPhil; John W. Eikelboom, MBBS;
Lars G. Wallentin, MD, PhD; Salim Yusuf, MD, DPhil; Alan T. Hirsch, MD

Background—Nonvalvular atrial fibrillation is a major cause of thromboembolic events. In comparison with atrial fibrillation-related stroke, extracranial systemic embolic events (SEEs) remain poorly defined.

Methods and Results—All suspected SEEs reported among 37 973 participants of 4 large contemporary randomized clinical trials of anticoagulation in atrial fibrillation were independently adjudicated for clinical and objective evidence of sudden loss of perfusion of a limb or organ. Over 91 746 patient-years of follow-up, 221 SEEs occurred in 219 subjects. The SEE incidence was 0.24 of 100 and stroke incidence was 1.92 of 100 patient-years. In comparison with patients with stroke, those with SEE were more often female (56% versus 47%; $P=0.01$) and had comparable mean age (73.1 ± 8.5 versus 73.5 ± 8.8 years; $P=0.57$) and mean CHADS₂ scores (2.4 ± 1.3 versus 2.5 ± 1.2 ; $P=0.33$). SEEs more frequently involved the lower extremity (58%) than visceral-mesenteric (31%) or upper extremity (10%). SEE-related care involved clinic assessment alone in 5%, 30% were hospitalized without procedures, 60% underwent endovascular or surgical intervention, and 5% underwent amputation. Within 30 days, 54% of patients recovered fully, 20% survived with deficits, and 25% died. Thirty-day mortality was greater after visceral-mesenteric than lower- or upper-extremity SEE (55%, 17%, and 9%, respectively, $P\leq 0.0001$). The relative risk of death throughout follow-up was 4.33 (95% confidence interval, 3.29–5.70) after SEE versus 6.79 (95% confidence interval, 6.22–7.41) after stroke in comparison with patients without either event.

Conclusions—SEE constituted 11.5% of clinically recognized thromboembolic events in patients with atrial fibrillation and was associated with high morbidity and mortality. SEE mortality was comparable to that of ischemic stroke and varied by anatomic site. (*Circulation*. 2015;132:796–803. DOI: 10.1161/CIRCULATIONAHA.114.013243.)

Key Words: arrhythmias, cardiac ■ atrial fibrillation ■ embolism ■ peripheral artery disease ■ risk factors

Nonvalvular atrial fibrillation (AF) is a prevalent cardiac rhythm disturbance associated with systemic thromboembolic events.¹ Although the incidence and risk factors for ischemic stroke in patients with AF have been well studied, relatively little is known about the distribution, clinical features, and outcomes of extracranial systemic embolic events (SEEs) in this population.^{2–6} This is likely due, in part, to the difficulty in detecting SEE in comparison with ischemic stroke. Two previous reports^{7,8} have described the distribution and potential clinical significance of SEE. Abbott et al⁷ first described SEE cases that were evaluated over a 40-year period at a single US hospital from 1964 to 1980. This large case series observed that 74% were associated with AF, and affected patients had a

25% mortality rate. Frost et al⁸ evaluated the risk of SEE among patients discharged with AF from 1980 to 1993 in the Danish National Hospital Discharge Register. This study demonstrated that AF was associated a relative risk of incident SEE of 4.0 and 5.7 in men and women, respectively. Data from a contemporary prospective cohort that might define the risk and outcomes of both stroke and SEE have been unavailable.

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The factors that lead to clinically recognizable stroke and SEE are diverse, and the relative rates of these events can only be determined in clinical practice by careful case

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From Lillehei Heart Institute and Cardiovascular Division, University of Minnesota Medical School, Minneapolis (W.B., S.D., A.T.H.); Department of Medicine, McMaster University, Hamilton, Ontario (S.J.C., S.C., J.P., J.W.E., S.Y.); Mt. Sinai School of Medicine, New York (J.L.H.); Division of Cardiology, Minneapolis Veterans Administration Medical Center, MN (S.A.); Lankenau Institute for Medical Research, Wynnewood, PA (M.D.E.); and Uppsala Clinical Research Center, Sweden (L.G.W.).

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Correspondence Alan T. Hirsch, MD, Lillehei Heart Institute and Cardiovascular Division, University of Minnesota Medical School, 420 Delaware St SE, Minneapolis, MN 55455. E-mail hirsch005@umn.edu

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ascertainment. Also, the diverse mechanisms (ie, atherosclerosis, cardioembolism, differential arterial bed anatomy, and different end organ ischemic sensitivity) that contribute to these events may not be identical for stroke and SEE.^{9–11} The objectives of this study were to rigorously readjudicate all SEEs reported among participants in 4 recent large randomized trials of anticoagulation in patients with AF in >40 countries, describe the clinical characteristics, risk factors, vascular distribution, levels of care and outcomes of SEE, and compare the impact of these events to stroke in AF patients managed with antithrombotic therapy.

Methods

Data Sources

Clinical events were retrospectively examined from the databases of the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A, ACTIVE-W)^{12–14}; Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment study (AVERROES)¹⁵; and the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY)¹⁶ clinical trials. The ACTIVE trials evaluated the efficacy and safety of clopidogrel plus aspirin with or without irbesartan for the prevention of stroke and other vascular events in patients with nonvalvular AF.^{12–14}

Three separate interrelated trials composed the ACTIVE program. Patients eligible for and willing to take oral anticoagulation with a vitamin K antagonist were enrolled in ACTIVE-W, in which clopidogrel plus aspirin was compared with vitamin K antagonist therapy. Patients ineligible for or unwilling to take oral anticoagulation were enrolled in ACTIVE-A, in which clopidogrel was compared with placebo in patients receiving aspirin. ACTIVE-I was a randomized placebo-controlled trial of irbesartan in eligible patients from either ACTIVE-A or ACTIVE-W, based on a factorial design. ACTIVE-A enrolled 7554 patients in 580 centers in 33 countries.¹² ACTIVE-W enrolled 6706 patients randomly selected at 522 centers in 31 countries.¹³ The primary outcome was a composite of major vascular events including stroke, myocardial infarction (MI), SEE, or vascular death. Because all of the events were accumulated in the ACTIVE-A or ACTIVE-W databases, ACTIVE-I was not included in this analysis.¹⁴

AVERROES was a double-blind, double-dummy superiority trial of 5599 patients with AF for whom vitamin K antagonist therapy was deemed unsuitable. The study was conducted in 522 centers in 36 countries. Subjects were randomly assigned to receive apixaban (5 mg twice daily) or aspirin (81–324 mg daily) for the prevention of stroke or SEE.¹⁵

RE-LY was a randomized noninferiority trial of 18 113 patients with AF conducted in 951 centers in 44 countries. Subjects were randomly assigned to 1 of 2 fixed, blinded doses of dabigatran (110 mg or 150 mg twice daily), or unblinded adjusted-dose warfarin. The primary outcome was stroke or SEE.¹⁶

Study Design

To set forth standardized criteria that might be used to define SEE, all suspected SEE reported among participants in the ACTIVE-A, ACTIVE-W, AVERROES, and RE-LY trials were independently readjudicated by 4 clinicians for this analysis. Readjudication was blinded to treatment assignment. One reviewer initially reviewed the individual source documents, patient chronologies, and case report forms. Source documents that were not in English were translated. Based on prespecified criteria, the diagnosis of SEE was classified as definite, unknown, probably not, or definitely not. A random sample of the case dossiers (20%) was readjudicated in a blinded fashion by 2 other reviewers. There was 99% agreement among the reviewers for cases deemed definite SEE. For the 3 cases with discordant assessment, a fourth reviewer readjudicated the source documents to determine the final classification. Only cases considered definite SEE were included in the analyses reported here.

Definition of Terms and Outcomes

Verification of SEE required both clinical and objective evidence of sudden loss of perfusion of a limb or organ. Clinical evidence was contained in the narrative describing the acuity of the clinical event (example, new acute limb ischemia versus chronic peripheral artery disease [PAD]). Objective evidence included data derived from vascular imaging, ankle-brachial pressure index measurements, open surgical or endovascular procedures, laboratory tests, and autopsy findings. The clinical presentation, vascular anatomic distribution, method of detection, level of care, acute outcomes, and mortality throughout follow-up of each event were abstracted from the case report forms and source documents.

Level of care was defined by the use of clinical services as a consequence of the event. There were 4 categories defined a priori based on whether the patient required (1) an outpatient clinic visit only, (2) hospitalization without an invasive surgical or endovascular procedure, (3) surgical or endovascular procedure during hospitalization, or (4) amputation. The 30-day outcome was classified as full recovery, survival with deficit, or death.

Statistical Analyses

The unit of reporting of these data is the individual patient, except for the anatomic distribution of SEE which is reported by event. Baseline data are reported as mean±standard deviation for quantitative data and as percentages for categorical data. Data are presented for patients who had SEE alone, stroke alone, both SEE and stroke, or none of these events during follow-up. Percentages of clinical consequences and 30-day outcomes were collated. Comparisons between the location of SEE and the associated clinical consequences and outcomes were assessed by χ^2 tests or Fisher exact tests as appropriate. Early (30-day) mortality was assessed by logistic regression to compare outcomes according to subgroups of risk factors (age, sex, and CHADS₂ scores) and the anatomic location of events (upper extremity, lower extremity, visceral or mesenteric). Cox proportional hazards models, stratified by trial, were used to estimate the effects of SEE alone, stroke alone, and both SEE and stroke on death, using individuals with no events as the reference group. The models were adjusted for the individual components of CHA₂DS₂-VASC score at baseline: age, sex, hypertension, heart failure, diabetes mellitus, vascular disease (previous myocardial infarction, PAD, and coronary artery disease) and previous stroke/transient ischemic attack/systemic embolism. A time-dependent covariate was created to track the occurrence of

All suspected cases of extracranial systemic emboli in ACTIVE-A, ACTIVE-W, AVERROES, and RE-LY irrespective of adjudication status

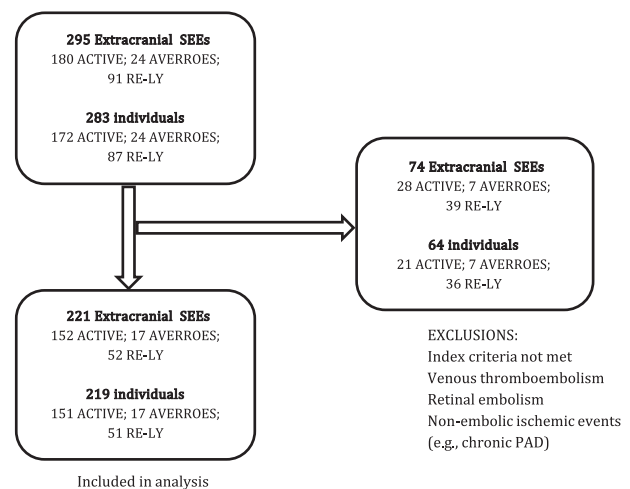


Figure 1. Extracranial systemic embolic events: inclusions and exclusions. PAD indicates peripheral artery disease; and SEEs, systemic embolic events.

Table 1. Baseline Characteristics of Study Patients in the ACTIVE-A, ACTIVE-W, AVERROES, and RE-LY trials, in Those With Extracranial SEEs Alone, Stroke Alone, Both Stroke and Extracranial SEEs, and Those With Neither of These Events

Characteristic	Event-Free Patients	Stroke	Extracranial SEE	Extracranial SEE + Stroke
n	36 077	1677	174	45*
Age, y, mean±SD†	70.7±9.3	73.5±8.8	73.1±8.5	74.4±9.1
Female sex, n (%)†‡	13 463 (37.3)	764 (45.6)	97 (55.7)	27 (60)
Race, white, n (%)‡	25 620 (71)	1132 (67.5)	134 (77)	26 (57.8)
High school education or greater, n (%)	10 955 (59.5)	599 (49.8)	73 (54.9)	16 (45.7)
Alcohol use, n (%)	11 420 (31.7)	448 (26.7)	45 (25.9)	8 (17.8)
Ever smoker, n (%)‡	18 068 (50.1)	740 (44.1)	94 (54)	19 (42.2)
AF type, n (%)§				
Permanent	17 531 (48.6)	1022 (61)	111 (63.8)	35 (77.8)
Paroxysmal	9954 (27.6)	328 (19.6)	28 (16.1)	3 (6.7)
Persistent	8552 (23.7)	326 (19.5)	35 (20.1)	7 (15.6)
AF duration, n (%)				
<3 mo	9784 (27.1)	397 (23.7)	44 (25.3)	10 (22.2)
3 mo to 2 y	7938 (22.1)	359 (21.4)	38 (21.8)	4 (8.9)
>2 y	18 336 (50.9)	921 (54.9)	92 (52.9)	31 (68.9)
History of hypertension, n (%)	29 471 (81.7)	1420 (84.7)	141 (81)	40 (88.9)
History of heart failure, n (%)	11 819 (32.2)	595 (35.5)	60 (34.5)	16 (35.6)
Diabetes mellitus, n (%)	7714 (21.4)	439 (26.2)	44 (25.3)	13 (28.9)
History of PAD, n (%)†‡	1181 (3.3)	85 (5.1)	16 (9.2)	6 (13.3)
History of ischemic heart disease, n (%)				
CAD	5464 (17.8)	164 (10.7)	20 (12.3)	2 (5)
Myocardial infarction†‡	4934 (16.1)	269 (17.6)	43 (26.5)	2 (5)
CABG‡	920 (7)	54 (5.1)	13 (10.7)	2 (6.7)
Previous stroke or transient ischemic attack, n (%)†	5890 (16.3)	450 (26.8)	44 (25.3)	15 (33.3)
Previous extracranial SEE, n (%)†‡	410 (2.3)	12 (2.6)	8 (19.5)	0 (0)
CHADS ₂				
Mean score±SD†	2.0±1.1	2.5±1.2	2.4±1.3	2.8±1.4
Score, n (%)				
0	877 (2.4)	18 (1.1)	4 (2.3)	1 (2.2)
1	12 113 (33.6)	383 (22.8)	41 (23.6)	9 (20)
≥2	23 077 (65.6)	1276 (76.9)	129 (75.9)	35 (79.5)
CHA ₂ DS ₂ -VASC Score, mean±SD†	3.4±1.4	3.9±1.6	4±1.5	4.3±1.8
HAS-BLED score, mean±SD†	3.1±1.1	3.7±1.1	3.5±1	3.8±1
Systolic blood pressure, mm Hg, mean±SD	132.3±17.9	136.6±19.2	134±19.1	136.7±20.5
Heart rate, beats/min, mean±SD	74.0±14.5	75.2±14.6	73.8±14.7	77.1±16.6
Medication use at baseline, n (%)				
ASA†	15 788 (43.8)	948 (56.5)	103 (59.2)	25 (55.6)
ACE-I or ARB†	15 114 (41.9)	401 (23.9)	36 (20.7)	8 (17.8)
β-Blocker	21 194 (58.8)	954 (56.9)	101 (58)	20 (44.4)
Amiodarone	2100 (6.2)	102 (6.2)	15 (8.8)	1 (2.2)
Digoxin	11 201 (31.1)	605 (36.1)	64 (36.8)	20 (44.4)
Calcium channel blocker	10 723 (29.7)	482 (28.7)	44 (25.3)	16 (35.6)
Statin†	13 788 (38.2)	532 (31.7)	51 (29.3)	8 (17.8)
Proton-pump inhibitor	2489 (14.1)	70 (14.9)	7 (17.1)	1 (10)
NSAIDs	18 484 (51.2)	637 (38)	69 (39.7)	14 (31.1)
Echocardiographic parameters				
Left atrial diameter, cm, mean (SD)	4.6 (1.9)	4.6 (0.8)	4.5 (0.5)	4.7 (0.5)
Ejection fraction, mean (SD)	53.7 (13.8)	54.1 (13.7)	54.2 (13.3)	56.4 (12.4)

(Continued)

Table 1. Continued

Characteristic	Event-Free Patients	Stroke	Extracranial SEE	Extracranial SEE + Stroke
Ejection fraction <50%, n (%)	4330 (29.6)	197 (28.7)	23 (27.4)	3 (20)
Renal function, eGFR, mL·min ⁻¹ ·1.73 m ⁻² , n (%)				
Normal, > 80 mL·min ⁻¹ ·1.73 m ⁻² †	7266 (25.2)	250 (18.1)	25 (16.7)	7 (21.2)
Mild impairment, 51–80 mL·min ⁻¹ ·1.73 m ⁻²	17 390 (60.2)	847 (61.2)	91 (60.7)	19 (57.6)
Moderate impairment, 31–50 mL·min ⁻¹ ·1.73 m ⁻²	3909 (13.5)	257 (18.6)	31 (20.7)	4 (12.1)
Severe impairment, ≤30 mL·min ⁻¹ ·1.73 m ⁻²	304 (1.1)	31 (2.2)	3 (2)	3 (9.1)

ACE-I indicates angiotensin-converting enzyme inhibitor; ACTIVE-A, ACTIVE-W, Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; AF, atrial fibrillation; ARB, angiotensin receptor blocker; ASA, aspirin; AVERROES, Apixaban Versus Acetylsalicylic Acid [ASA] to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment study; CABG, coronary artery bypass surgery; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral artery disease; RE-LY, the Randomized Evaluation of Long-Term Anticoagulation Therapy; SD, standard deviation; and SEE, systemic embolic event.

*Stroke occurred first in 24 of the 45 patients with both SEE and stroke.

†Significantly different between AF patients with SEE and those with no events ($P<0.05$).

‡Significantly different between AF patients with SEE and those with stroke ($P<0.05$).

§Classification of AF (permanent, paroxysmal, persistent): This sample does not sum to 100% because 41 patients had missing information.

SEE, stroke, or both SEE and stroke during the follow-up period. All patients were considered as no SEE or stroke at the beginning of the study. Patients who experienced either stroke or SEE thereafter were reclassified as stroke alone or SEE alone, respectively. They remained in that status throughout the rest of the follow-up period unless the other type of event occurred, in which case, the status was changed to both stroke and SEE. The long-term effects of stroke alone, SEE alone, both SEE and stroke were compared with no SEE or stroke by using hazard ratios (HRs; 95% confidence interval [CI]). The comparison of mortality risk between SEE and stroke was conducted by using the Wald test of parameter estimates between stroke alone and SEE alone groups in the above-mentioned Cox regression model with time-dependent covariates. Long-term mortality estimates for subgroups of sex, age, CHADS₂ scores, and location of SEE were also obtained by using Cox regression analysis. To evaluate time to death after an SEE and to illustrate how outcomes from SEE compare with other common clinical events, Kaplan–Meier estimates of time to all-cause mortality after the day of the first SEE, stroke, MI, or major bleeding were constructed. Per original trial protocols, all patients were followed from time of random assignment until these clinical events, and also until death or the end of the study. The median (25th and 75th percentile) overall length of follow-up was 1.2 years (0.5–2.1). Following events, the median (25th and 75th percentile) length of follow-up was 0.6 years (0.04–2.0). All analyses were performed with the use of SAS software, version 9.1 (SAS Institute Inc, Cary, NC). A 2-sided P value of <0.05 was considered statistically significant.

The study was approved by all appropriate national regulatory authorities and ethics committees. All patients provided written informed consent before entry into the individual studies. The authors of the article had full access to the data and planned the statistical analyses.

Results

Patient Selection

Among the 37 973 patients included in the 4 randomized trials and followed for a mean of 2.4 years, 295 suspected cases of SEE were reported in 283 individuals. Of these, 74 cases did not meet the specified criteria for SEE and were excluded from analysis. These were venous thromboembolic events (deep venous thrombosis and pulmonary embolism), retinal artery embolism, or symptoms due to chronic PAD without evidence of acute embolism. The remaining 221 SEE in 219 individuals were included in the analysis (Figure 1).

Baseline Characteristics

Baseline clinical characteristics of the study population are shown in Table 1. In comparison with patients with stroke, patients with SEE were more often female (56% versus 47%, $P=0.01$) and white (77% versus 67.5%, $P=0.01$), with a history of smoking (54% versus 44%, $P=0.01$), PAD (9% versus 5%, $P=0.02$), MI (26.5% versus 17.6%, $P=0.005$), or previous SEE (20% versus 3%, $P=0.0001$). Patients with SEE and those with stroke had similar mean ages (73.4 ± 8.6 versus 73.5 ± 8.9 years, respectively, $P=0.58$) and mean CHADS₂ scores (2.4 ± 1.3 versus 2.5 ± 1.2 , respectively, $P=0.33$). In comparison with patients with no events, patients with SEE were older, were more often female, and more often had a history of PAD or MI, previous stroke or SEE, and higher CHADS₂ and HAS-BLED risk scores. They were less likely to have normal renal function (estimated glomerular filtration rate >80 mL·min⁻¹·1.73 m⁻²) and less likely to have been treated with statins, aspirin, or inhibitors of the renin-angiotensin-aldosterone system at entry (Table 1).

Incidence, Distribution, and Outcomes of SEE

Over 91 746 patient-years (mean, 2.4 years) observation, 221 validated SEEs occurred in 219 individuals, an incidence of 0.24 of 100 patient-years. The rate of stroke during the same period was 1.92 of 100 patient-years (Table I in the online-only Data Supplement). SEEs thus encompassed 11.5% of all clinically recognized thromboembolic events in these patients

Table 2. Mode of Detection of Extracranial Systemic Embolic Events

Mode of Detection	n=219
Clinical symptoms, n (%)	219 (100)
Abnormal ABI, n (%)	2 (1)
Imaging (arterial duplex US, CT scan, or CT angiogram), n (%)	190 (86)
Endovascular procedure, n (%)	15 (7)
Surgical procedure, n (%)	10 (4)
Autopsy, n (%)	2 (1)

ABI indicates ankle brachial index; CT, computed tomographic; and US, ultrasound.

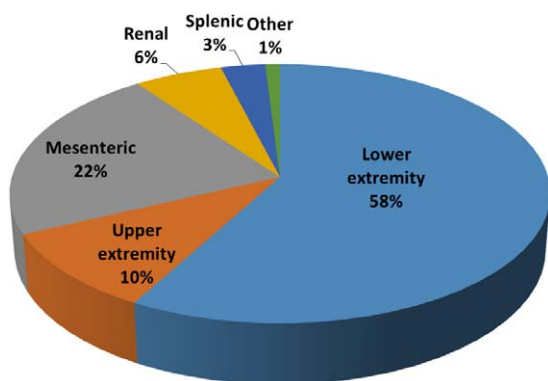


Figure 2. Anatomic distribution of extracranial systemic embolic events. Anatomic distribution is based on events and not individuals. There were 13 individuals that had systemic emboli to 2 different locations at the same presentation. Each presentation was considered 1 event even if there was >1 embolus to a limb or organ. There were a total of 221 events occurring in 219 individuals.

with nonvalvular AF. At presentation, all patients had acute ischemic symptoms. Evidence of acute ischemia was nearly always corroborated by imaging studies (86%). A small proportion of SEEs was identified based on abnormal ankle brachial index tests or direct findings observed during surgical or endovascular procedures, or at autopsy (Table 2). SEEs involved the lower-extremity (58%), visceral-mesenteric (31%), and upper-extremity (10%) vasculature (Figure 2). Of all individuals presenting with SEEs, 64% underwent interventional procedures or amputation, 31% were hospitalized without undergoing procedures, and only 5% were managed entirely on an outpatient basis (Table 3). The 30-day outcomes included full recovery in 54%, survival with deficit in 20%, and death in 25% (Table 4). In comparison with patients with upper-extremity SEE, those with lower-extremity SEE were more likely to undergo amputation. Patients with visceral-mesenteric SEE were more often hospitalized and underwent surgical or endovascular procedures (Table II in the online-only Data Supplement).

The 30-day mortality was similar in patients with SEE alone (42/174, 24%) or stroke alone (421/1677, 25%). SEEs involving the visceral-mesenteric arterial bed were more often associated with mortality within 30 days of the event than SEEs affecting the limbs (Table III in the online-only Data Supplement). There was no significant difference in 30-day mortality among patients with SEEs stratified by age, sex, or CHADS₂ score (Figure 3).

During long-term follow-up where events were treated as time-dependent covariates, after adjustment for components of the CHA₂DS₂-Vasc risk score, the HR for mortality was 4.33 (95% CI, 3.29–5.70) among patients with SEE alone, 6.79 (95% CI, 6.22–7.41) among patients with stroke alone, and 23.82 (95% CI, 16.02–35.43) among patients with both SEE and stroke, in comparison with patients with neither of these events. The HR for mortality from visceral or mesenteric SEE alone versus no event was 17.64 (95% CI, 11.07–28.10); and this was significantly worse than mortality among patients with stroke alone ($P<0.0001$). Mortality among patients with lower-extremity SEE (HR, 4.01; 95% CI, 2.81–5.73) and

upper-extremity SEE (HR, 1.50; 95% CI, 0.38–6.00) were lower in comparison with mortality among patients with stroke alone (P values of 0.004 and 0.033, respectively; Table IV in the online-only Data Supplement). In patients developing SEE, long-term mortality was similar in subgroups defined by sex and CHADS₂ score. Age >75 years (HR, 1.98; 95% CI, 1.08–3.60; $P=0.02$) and SEE involving the visceral-mesenteric vascular bed (HR, 3.68; 95% CI, 1.55–8.72; $P=0.00003$) were associated with higher long-term mortality rates, in comparison with individuals <75 years and upper-extremity SEE, respectively (Figure I in the online-only Data Supplement). Kaplan–Meier estimates of time to all-cause mortality after the first SEE, stroke, MI, or major bleeding showed a similar mortality risk for patients with SEE, stroke, and MI and this exceeded that related to major bleeding (Figure 4). The use of anticoagulation during follow-up was associated with a lower incidence of both SEE and stroke in comparison with no anticoagulation, but was associated with a greater reduction in SEE (HR, 0.32; 95% CI, 0.24–0.44) than in stroke (HR, 0.52; 95% CI, 0.47–0.57, P for heterogeneity 0.0064).

Discussion

A key objective in managing patients with AF is the prevention of thromboembolic events. To date, observational studies and randomized trials have focused almost entirely on stroke prevention. This analysis demonstrates that at least 11.5% of clinically recognized embolic events in patients with AF involve the extracranial vasculature. Depending on the SEE anatomic site, mortality after an SEE may be higher or lower than that observed in patients after ischemic stroke. Our finding that SEE predominantly affected the extremities (68%) and visceral-mesenteric circulation (31%), compares with 83% and 9%, respectively, in the US case series⁷ and 61% and 40%, respectively, in the Danish register.⁸ Our finding of 30-day mortality following an SEE (25%) is similar to what was reported in 1980.

Although SEE and stroke patients are characterized by some demographic and risk similarities (age and CHADS₂ score), they were not identical. In comparison with stroke patients, SEE patients were more often smokers, were female, had a previous history of PAD and previous SEE. The biological mechanisms underpinning these differences in clinical features cannot be determined from this analysis, but the data permit the generation of hypotheses for evaluation

Table 3. Level of Care Required at Presentation With Extracranial Systemic Embolic Events

Level of Care	n=219
Clinic visit only, n (%)	11 (5)
Hospitalization without surgical or endovascular procedure, n (%)	67 (31)
Surgical or endovascular procedure during hospitalization, n (%)	131 (60)
Amputation, n (%)	10 (4)

Patients were classified to a single highest level of care for each systemic embolic event. Hence, a patient who underwent a procedure was classified under the surgical or endovascular procedure during hospitalization group although they were also hospitalized; and a patient who was hospitalized was classified under the hospitalization without surgical or endovascular procedure group although they may have also been seen in clinic.

Table 4. Thirty-Day Outcomes After Extracranial Systemic Embolic Events

Outcome	n=219
Full recovery, n (%)	119 (54.3)
Survived with deficit, n (%)	44 (20)
Persistent cold limb, numbness, or limb pain	25
Limb loss	11
Colostomy	5
Chronic kidney disease	2
Nonhealing wound	1
Death, n (%)	54 (24.7)
Unknown, n (%)	2 (1)

in future studies. Smoking raises plasma levels of fibrinogen and factor XIII, which stabilize fibrin clots. Thus, a history of smoking may be associated with development of larger atrial thrombi that could be associated with clinically recognized SEEs.^{17–20} Although female sex is a risk factor for both stroke and SEE,^{21,22} it is unclear why female sex was associated with higher risk of SEE than stroke. One possible mechanism may be due to the smaller peripheral artery diameters of women that could predispose them to more severe limb ischemia when SEE occur.²² Alternatively, a greater degree of intra-atrial stasis may be present in women than in men,²³ which may increase the propensity to form larger intact atrial thrombi prone to embolism and SEE.

The observation that individuals with atherosclerotic PAD were more likely to experience SEEs is concordant with the population-based data used to develop the CHA₂DS₂VASc thromboembolism risk prediction schema, of which clinical PAD is a component.^{24,25} The presence of atherosclerosis may worsen clinical outcomes when SEEs occur in the regions with compromised arterial perfusion. The association of previous SEEs with increased incidence of subsequent SEEs is consistent with earlier observations that the risk of recurrent

ischemic stroke is 1.85 times higher in patients with previous stroke.²⁵ It is unknown if this observation is due to diagnostic suspicion bias in patients who have had previous SEEs or if it reflects interindividual differences in patterns of blood flow. Differences in these characteristics of patients who subsequently developed SEE rather than ischemic stroke may have implications for the prediction of the site of future events. To evaluate this properly, future studies should incorporate systematic assessment of the peripheral vasculature to better measure the true rate of SEE in patients with AF, as has been performed to establish a more precise estimate of the risk of stroke.

The higher incidence of SEEs in patients with more advanced forms of AF (63.8% in permanent versus 16.1% in paroxysmal) and longer duration of atrial fibrillation (52.9% with AF duration of >2 years versus 25.3% with AF duration <3 months) represents a key insight. These findings reinforce the concept that increasing AF burden is associated with worse clinical outcomes.²⁶

The 9-fold greater rate of ischemic stroke in comparison with SEE is unlikely to represent the true ratio of intracranial versus extracranial vascular events, because more extracranial events may be clinically silent or unrecognized. Mesenteric ischemic symptoms, in particular, are often overlooked or misdiagnosed, either because of redundant circulation, because smaller hepatic or splenic infarcts have relatively minor clinical consequences, or because renal arterial emboli may result in an asymptomatic decline in renal function that evolves insidiously over time.²⁷ Furthermore, limb ischemic events associated with PAD are often underrecognized,²⁸ as reflected in the baseline prevalence of PAD reported in these trials (ranging from 2.7% to 3.8%),^{12,13,15,16} in contrast to the 19% prevalence projected by a validated risk calculator²⁸ for individuals with a mean age of 71 years and high prevalence of atherosclerotic risk factors.

The purpose of this article was to describe the clinical characteristics of SEEs and not the effects of specific

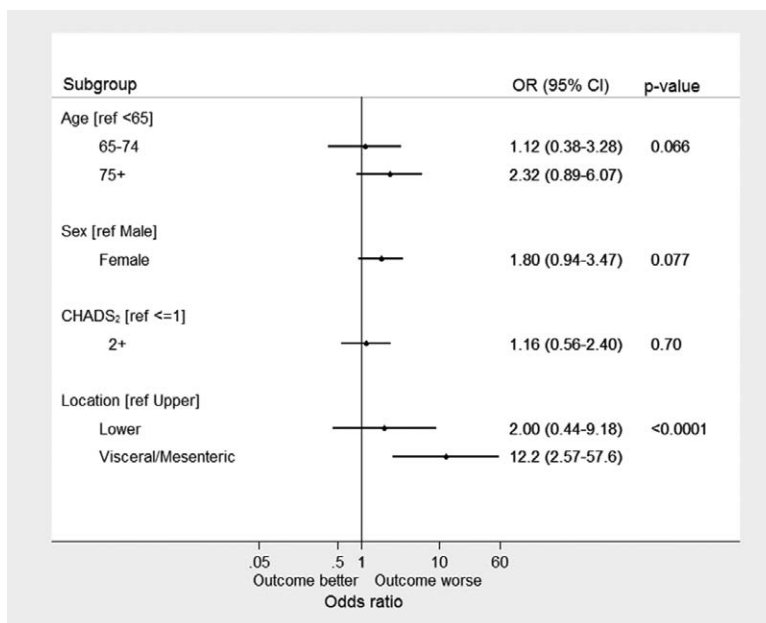


Figure 3. Thirty-day mortality among patients with extracranial systemic embolic events by clinical subgroups. *P* value is for the subgroup effect. CI indicates confidence interval; and OR, odds ratio.

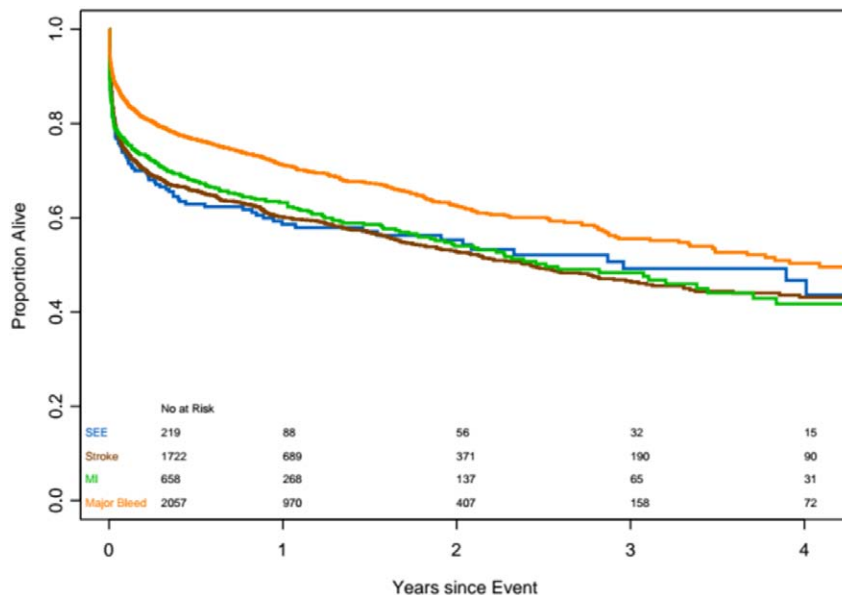


Figure 4. Long-term survival after the first extracranial systemic embolic event (SEE), stroke, myocardial infarction (MI), and major bleeding. Each curve represents the Kaplan–Meier estimated survival probability after the first occurrence of each of the 4 clinical events. The subsets of patients included in each curve are not mutually exclusive.

antithrombotic treatments on the differential rate of SEE and stroke thromboembolic events. Although these potentially different antithrombotic treatment effects are of clinical interest, these individual medication effects cannot be reliably determined from such a retrospective analysis pooling data from distinct trial populations and study designs. These medication-specific effects should be determined from an adequately designed prospective trial. Yet, to provide a preliminary estimate of the treatment impact of anticoagulation, we evaluated the event rates between individuals treated by any anticoagulant medication (warfarin, apixaban, or dabigatran) in comparison with individuals not treated by anticoagulant medications. For these trials, the comparator treatment was antiplatelet medication use (clopidogrel and aspirin or aspirin alone). This analysis demonstrated that anticoagulant medication use was associated with a lower incidence of both SEE and stroke in comparison with the use of antiplatelet medications. The use of anticoagulation was associated with a 30% greater reduction in SEE incidence than stroke.

The health economic cost of SEE has not been previously evaluated. In contrast, data from the National Stroke Association estimate that the cost for care during the first 90 days after stroke exceeds \$15 000.²⁹ The burden imposed by SEE on the individual is extremely high and the health economic impact is likely as large, because only 55% of patients in the trials we surveyed recovered without deficit, and mortality after SEE was comparable to that resulting from stroke depending on the anatomic site involved. Clearly, these events are not benign, and the adverse outcomes we observed suggest that SEE should be managed as aggressively as stroke.

Limitations

There are limitations to this retrospective analysis. First, although this is the first study to describe the vascular distribution, clinical features, and outcomes of SEE, all retrospective analyses are limited by the availability of source documents that adequately describe each clinical event. Thus, these data provide a conservative estimate of SEE rates. Second, it is

possible that such analyses might lead to misclassification of acute SEE events and not recognize the potential chronicity of regional arterial disease. For example, acute limb ischemia may arise from progression of chronic PAD but be first detected within an AF treatment trial and interpreted as an acute limb ischemic event. Yet, a rigorous adjudication process was designed to minimize such misclassification. This analysis included patients treated by a variety of anticoagulation medications. This design does not permit an accurate post hoc evaluation of the relative therapeutic benefit of the diverse antithrombotic interventions. Finally, patients evaluated within these 4 large randomized clinical trials may not be representative of individuals with AF who are treated within a community setting, and event rates would likely be higher in a less carefully managed community cohort.

Conclusions

SEE occurring in patients with AF enrolled in contemporary anticoagulation trials accounted for at least 11.5% of all thromboembolic events. These events were associated with considerable morbidity, and the clinical outcomes varied depending on the anatomic site involved. Risk factors for SEE differed from those associated with ischemic stroke, but depending on the SEE anatomic site, mortality after an SEE may be higher or lower than that observed in patients after ischemic stroke.

Disclosures

None.

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CLINICAL PERSPECTIVE

Although the incidence of and risk factors for ischemic stroke in patients with atrial fibrillation have been well studied, much less is known about the distribution, clinical features, and outcomes of extracranial systemic embolic events (SEEs) in this population. This study demonstrates that SEEs constituted at least 11.5% of clinically recognized thromboembolic events in patients with atrial fibrillation. These events are associated with high morbidity and mortality that was comparable to that of ischemic stroke. These data demonstrate that atrial fibrillation is associated with clinically important SEEs, and not merely stroke. These systemic events are not rare and merit clinical recognition because of their major impact on short-term health outcomes and death. Recognition of SEEs is more challenging than of stroke because nonstroke ischemic clinical presentations may seem to be due to comorbid disease. It is not yet known from prospective trials whether prompt recognition and treatment of SEEs would improve clinical outcomes. This knowledge gap is best evaluated by future investigations.

Extracranial Systemic Embolic Events in Patients With Nonvalvular Atrial Fibrillation: Incidence, Risk Factors, and Outcomes

Wobo Bekwelem, Stuart J. Connolly, Jonathan L. Halperin, Selcuk Adabag, Sue Duval, Susan Chrolavicius, Janice Pogue, Michael D. Ezekowitz, John W. Eikelboom, Lars G. Wallentin, Salim Yusuf and Alan T. Hirsch

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Supplemental Material

Supplemental Table 1. Distribution of extracranial systemic embolic events and stroke

Events	Total number of patients in analyses = 37973	% per 100 patient years
Extracranial systemic embolic events	* 219	0.24
Upper extremity	23	0.03
Lower extremity	135	0.15
Mesenteric	51	0.06
Renal	13	0.01
Spleen	6	0.01
Other	4	0.00
Stroke	1722	1.92

* There were 13 individuals that had two emboli to different organs/limbs at the same presentation

Supplemental Table 2. Comparison of location of extracranial systemic embolic events with clinical consequences

	Upper extremity		Lower extremity		Mesenteric(51), Renal (13), Spleen (6)		p-value
	N	%	N	%	N	%	
Non-CNS SEE	23	100.0	135	100.0	70	100.0	
Clinical Consequences							
Clinic Visit	1	4.3	10	6.7	1	1.6	0.28
Hospitalization	1	4.3	37	27.6	33	46.8	0.00024
Surgical Procedure	21	91.3	78	58.2	36	51.6	0.0017
Amputation	0	0.0	10	8.2	0	0.0	0.021

* There were 13 individuals that had two emboli to different organs/limbs at the same presentation

Supplemental Table 3. Classification of location of extracranial systemic embolic events by 30-day outcomes

Outcome	Location of extracranial systemic embolic events						p-value
	Upper extremity		Lower extremity		Mesenteric, Renal, Spleen		
	N = 23	%	N = 135		N = 70	%	
Full recovery	18	78.3	78	58.2	26	37.1	0.001
Survived with deficit	2	8.7	34	24.6	10	14.5	0.104
Death	2	8.7	22	16.4	34	48.4	0.000
Unknown	1	4.3	1	0.7	0	0.0	0.454

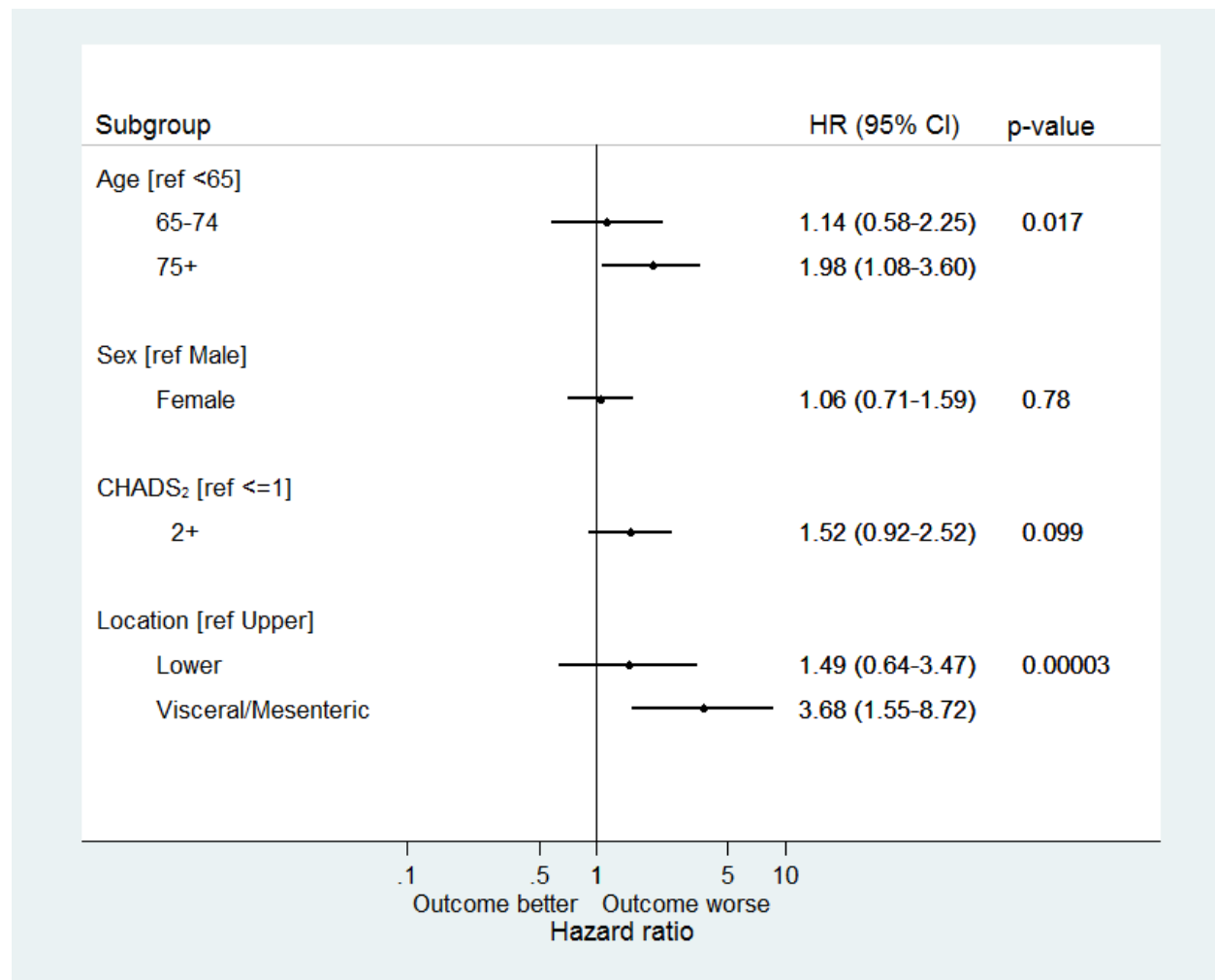
* There were 13 individuals that had two emboli to different organs/limbs at the same presentation

Supplemental Table 4. Comparison of the mortality risk between various locations of SEE and stroke

Risk group	Hazard ratio no stroke/SEE (ref:	p-value*
Stroke	6.78 (6.22-7.40)	
Upper extremity SEE	1.50 (0.38-6.00)	0.033
Lower extremity SEE	4.01 (2.81-5.73)	0.004
Visceral/mesenteric SEE	17.64 (11.07-28.10)	<0.0001

* P-value is calculated from Wald's test to compare hazard ratio of death with each location of SEE with hazard ratio of stroke

Supplemental Figure 1. Sub-group analysis of long term mortality during follow up among patients with extracranial systemic embolic events using Cox regression analysis.



*p-value is for the subgroup effect