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ORIGINAL RESEARCH ARTICLE

Systemic Embolic Events in Atrial Fibrillation: An Individual Patient Data Meta-analysis of 71 683 Participants Randomized to NOAC Versus Warfarin

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BACKGROUND: Systemic embolic events (SEEs) are a serious but underrecognized complication of atrial fibrillation. Although non–vitamin K antagonist oral anticoagulants prevent ischemic stroke (IS), their efficacy in SEE and the clinical characteristics of patients who experience SEE remain poorly understood.

METHODS: We analyzed individual patient data from 4 pivotal randomized trials enrolling patients between 2005 and 2010 comparing non–vitamin K antagonist oral anticoagulants versus warfarin in atrial fibrillation. We characterized the incidence, clinical features, management, and outcomes of clinically overt SEE and compared results in these patients with patients who had an IS.

RESULTS: Among 71 683 patients, 188 experienced SEE (26 with concurrent IS), yielding an annualized event rate of 0.13% per patient-year, compared with 1.25% per patient-year for IS (n=1797). Among 171 patients with SEE as their first event, median age was 75 years (interquartile range, 68–80), 49.7% were female, and mean±SD CHA_2DS_2-VASc score was 4.7±1.5. Compared with IS, patients with SEE had higher rates of peripheral arterial disease (PAD, 16.5% versus 5.4%; $P<0.001$), previous myocardial infarction (24% versus 17%; $P=0.02$), previous vitamin K antagonist exposure (57% versus 46%; $P=0.007$), worse renal function (median creatinine clearance 58 versus 62 mL/min; $P=0.02$), and higher incidence of nonparoxysmal atrial fibrillation (86% versus 80%; $P=0.047$). Interventions (surgical or percutaneous) were performed in 62 patients (31%) with SEE. Standard-dose non–vitamin K antagonist oral anticoagulants reduced the risk of SEE by 29% compared with warfarin over a median follow-up of 25.2 months (interquartile range, 17.5–32.0; hazard ratio, 0.71 [95% CI, 0.51–0.99]; $P=0.04$). Thirty-day mortality after SEE was similar to IS (18% versus 17%), and SEE was associated with a nearly 3-fold increased risk of long-term mortality compared with patients without SEE or IS (hazard ratio, 2.85 [95% CI, 2.11–3.85]). Independent predictors of SEE included peripheral artery disease, smoking, nonparoxysmal atrial fibrillation, female sex, previous myocardial infarction, previous stroke or transient ischemic attack, vitamin K antagonist experience, and renal dysfunction.

CONCLUSIONS: In this large individual patient data meta-analysis, non–vitamin K antagonist oral anticoagulants significantly reduced the risk of SEE compared with warfarin. Although SEEs were approximately one-tenth as frequent as IS, they were associated with comparable mortality and substantial morbidity.

Key Words: atrial fibrillation ■ NOACs ■ systemic embolic events ■ warfarin

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Clinical Perspective

What Is New?

- In 71 683 patients with atrial fibrillation, systemic embolic events (SEEs) accounted for approximately 10% of thromboembolic events and had mortality rates comparable with ischemic stroke.
- Standard-dose non–vitamin K oral anticoagulants reduced SEE risk by approximately 30% versus warfarin, a benefit not seen for ischemic stroke.
- Predictors of SEE differed from ischemic stroke and included peripheral artery disease, previous myocardial infarction, renal dysfunction, female sex, and smoking.

What Are the Clinical Implications?

- SEE is an underrecognized yet severe complication of atrial fibrillation with substantial morbidity and mortality.
- Standard-dose non–vitamin K oral anticoagulants are superior to warfarin in the prevention of SEE, reinforcing guideline-recommended anticoagulation.
- Modifiable predictors of SEE include renal dysfunction, current smoking, and nonparoxysmal atrial fibrillation, which can help identify patients for targeted interventions to lower the risk of SEE.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
ARISTOTLE	Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation
COMBINE AF	A Collaboration Between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation
ENGAGE AF–TIMI 48	Effective Anticoagulant With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48
HR	hazard ratio
IQR	interquartile range
IS	ischemic stroke
LD	lower dose
MI	myocardial infarction
NOAC	non–vitamin K antagonist oral anticoagulant
PAD	peripheral artery disease
RE-LY	Randomized Evaluation of Long-Term Anticoagulation Therapy
ROCKET AF	Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation
SEE	systemic embolic event
TIA	transient ischemic attack
VKA	vitamin K antagonist

Atrial fibrillation (AF) is a leading cause of arterial thromboembolic events, with a predominant focus on ischemic stroke (IS) in research and clinical practice.[1,2] However, extracranial systemic embolic events (SEEs), which account for approximately 10% of all arterial thromboembolic events in AF, remain underrecognized and undercharacterized, despite their potential to cause severe, often life-threatening complications.[3–6] The challenges in detecting and managing SEEs, compared with IS, contribute to this gap in knowledge.[6] Although non–vitamin K antagonist oral anticoagulants (NOACs) have proven effective in preventing IS,[7–12] their role in reducing the risk of SEE in particular has not been thoroughly evaluated. This leaves a critical knowledge gap that hinders optimal clinical management of patients with AF. To address this knowledge gap, we pooled individual patient-level data from the pivotal randomized trials comparing NOACs with warfarin in patients with AF. We assessed the efficacy of NOACs in preventing SEE and characterized the incidence, management, and associated short- and long-term mortality.

METHODS

Study Design and Data Source

We used individual participant data from COMBINE AF (A Collaboration Between Multiple Institutions to Better Investigate Non–Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation), a dataset that included 4 pivotal phase 3 international randomized controlled trials comparing the efficacy and safety of NOACs versus warfarin for stroke prevention in patients with atrial fibrillation[11,13]: RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy; dabigatran),[7] ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation),[8] ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation),[9] and the ENGAGE AF–TIMI 48 study (Effective Anticoagulant With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; edoxaban)[10] (see Figure S1 for the study flow diagram). Patient enrollment occurred from December 2005 to December 2007 (RE-LY), December 2006 to June 2009 (ROCKET AF), December 2006 to April 2010 (ARISTOTLE), and November

2008 to November 2010 (ENGAGE AF–TIMI 48). Details and baseline characteristics of patients included in COMBINE AF have been published elsewhere.[11,13] For the present analyses, a standard-dose NOAC treatment strategy was defined as dabigatran 150 mg twice daily (RE-LY), rivaroxaban 20 mg (or 15 mg if dose reduction criteria were met) once daily (ROCKET AF), apixaban 5 mg (or 2.5 mg if dose reduction criteria were met) twice daily (ARISTOTLE), or edoxaban 60 mg (or 30 mg if dose reduction criteria were met) once daily (ENGAGE AF–TIMI 48). A lower-dose (LD) NOAC treatment strategy was defined as dabigatran 110 mg twice daily (RE-LY) or edoxaban 30 mg (in patients without dose reduction criteria) or 15 mg (if dose reduction criteria were met) once daily (ENGAGE AF–TIMI 48). Patients in our meta-analyses were analyzed according to their randomization group regardless of whether they were treated with dose reduction by individual trial criteria. The trial protocols were approved by the relevant ethics committees at all participating sites. We encourage parties interested in data sharing to contact the corresponding author. This study was conducted and reported in accordance with the PRISMA-IPD guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data), and the completed checklist is provided in the Supplemental Material.

Outcomes

The primary efficacy end point was the time to the first SEE, a component of the primary composite end point of stroke or SEE in all included trials of stroke or SEE.[7–10] An SEE was defined as an abrupt episode of arterial insufficiency associated with either clinical or radiographic evidence of arterial occlusion that occurred in the absence of other likely mechanisms that included atherosclerosis or instrumentation.[5–10] Arterial embolic events to the central nervous system (including the eye), coronary, and pulmonary arterial circulation were classified as stroke/transient ischemic attack, myocardial infarction (MI), and pulmonary embolism, respectively, rather than SEE.[5–10] In patients with atherosclerotic peripheral artery disease (PAD), the diagnosis of an SEE to the lower extremities required arteriographic evidence of abrupt arterial occlusion.[5–10] An independent clinical end point events committee, blinded to the study drug assignment, adjudicated all suspected SEEs, strokes, and causes of death.[5–10]

Statistical Analysis

Descriptive statistics of baseline characteristics were given as frequency and percentages, medians with 25th and 75th percentiles, or means with SDs. Baseline characteristics were compared using the χ^2 test for categorical variables or Kruskal-Wallis test for continuous variables. Kruskal-Wallis tests were used for all continuous variables, regardless of whether they were summarized using means with SDs or medians with interquartile ranges (IQRs). The baseline characteristics were shown for patients with SEE as a first event and compared with those with IS as first events and then with patients with neither SEE nor IS. In addition, baseline characteristics were shown for patients who had SEE alone, IS alone, both SEE and IS, or none of these events during follow-up. Two authors independently reviewed deaths occurring within 30 days of SEE to identify fatal SEE. In addition, we independently assessed post-SEE procedures to determine their relatedness to the SEE event.

To evaluate the impact of SEE and IS on mortality beyond the acute phase, we used an interval censoring approach that allowed us to estimate long-term mortality associated with these events. Long-term mortality was defined as death occurring beyond 30 days after the index event, assessed over the entire follow-up period (median, 25.2 months; IQR, 17.5–32.0). For patients whose first event was an SEE or IS, time zero was defined as the time of that event. Cox proportional hazards models, stratified by trial, were used to estimate the effects of SEE alone, IS alone, and both SEE and IS on all-cause mortality. Individuals who did not experience either event served as the reference group.

In this modeling framework, patients were represented by 2-time intervals: (1) from baseline to the first occurrence of SEE or IS (or censoring if no event occurred), and (2) from the time of the event to either death or censoring. This interval-based approach captures the impact of SEE and IS on mortality beyond the immediate 30-day window—thus referred to as long-term mortality. The Cox proportional hazards assumption was assessed using Schoenfeld residuals, and no violations were detected. The models were adjusted for the individual components of the CHA_2DS_2-VASc score at baseline: congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack/SEE, vascular disease (previous MI, coronary artery disease without infarction, and PAD), and sex.

We used an interval censoring approach whereby the variable in the model reflects the patient's final status (event-free as the reference). The timing of death is based on intervals, in which a patient has one interval from being event-free to experiencing an event, and another interval from the event to either death or censoring. This approach better quantifies the impact of the event on mortality by focusing on the time periods before and after the occurrence of SEE or IS. In addition, we performed an analysis combining standard-dose and LD NOAC versus warfarin.

We examined discontinuation patterns by event type to evaluate the association between study drug interruption and subsequent ischemic events. Discontinuation was defined as permanent cessation of study drug before the occurrence of the event of interest. In sensitivity analyses, patients were classified as off treatment if discontinuation occurred >3 days before an event; discontinuations within 1 to 3 days of the event were considered on treatment. We calculated the proportion of patients off study drug at the time of any SEE (with or without IS) and IS alone. For context, discontinuation rates were also assessed among patients without SEE or IS. Time off study drug before an event was summarized using mean, median, and IQRs by event type. Last, annualized event rates of SEE and IS were compared between patients who discontinued study drug before an event and those who remained on therapy or discontinued after the event.

All analyses were performed on the intention-to-treat population from randomization until the end of the treatment period. Cox proportional hazards models were stratified by trial to account for differences in baseline risk and event rates across studies. To evaluate treatment strategies, we compared hazard ratios (HRs) with 95% CIs for standard-dose or LD NOACs versus warfarin. Heterogeneity across trials was assessed using the estimated SD of random effects.

To identify clinical predictors of SEE, a multivariable Cox proportional hazards model was constructed. Candidate variables were selected a priori based on clinical relevance and included creatinine clearance, body mass index, AF type

(nonparoxysmal versus paroxysmal), previous vitamin K antagonist (VKA) use (experienced versus naïve), age, sex, congestive heart failure, previous stroke or transient ischemic attack, MI, PAD, and current smoking. Backward stepwise selection was performed using the Akaike Information Criterion to derive the final model.[14] Missing data were minimal and handled using a complete case approach; no imputations were performed. For the prediction model, only patients with complete data for all candidate variables were included in the Cox model selection. All statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Baseline Characteristics

Of the 71 683 patients in this analysis (median [IQR] age, 72 [65–77] years; 26 714 [37.3%] women), 188 patients experienced at least 1 SEE. Among these, 9 patients had multiple SEEs resulting in a total of 198 SEEs in 188 patients. Only the first SEE per patient was included in all primary analyses, consistent with the time-to-first-event framework (Figure S2). These 188 first SEEs represented 9.59% of all arterial thromboembolic events. The annualized event rate for SEE was 0.13% per patient-year (1.3 events per 1000 patient-years), compared with 1.25% per patient-year (12.5 events per 1000 patient-years) for IS.

Of the 188 patients with an SEE, 162 (86%) had SEE only, and 9 (5%) had SEE, then developed IS; 16 (9%) had IS, then developed SEE, and 1 had SEE and IS simultaneously (Figure S2). Among the 171 patients with SEEs as first events, the median (IQR) age was 75 (68–80) years, 49.7% were women, median (IQR) of body mass index was 27.5 (23.5–30.7) kg/m^2, and mean (SD) CHA_2DS_2-VASC score was 4.7 (1.5). Compared with IS (n=1789), patients with SEE were more likely to have PAD (16.5% versus 5.4%; $P<0.001$), have previous MI (24% versus 17%; $P=0.02$), be VKA-experienced (57% versus 46%; $P=0.007$), and have worse renal function (median creatinine clearance [IQR], 58 [46–74] versus 62 [48–81] mL/min; $P=0.02$) and less likely to have paroxysmal AF (14% versus 20%; $P=0.047$) (Table). The baseline characteristics of patients with SEE alone and IS alone and those with both SEE and IS are shown in Table S1.

Management of SEEs

Among the 188 patients with SEEs, a total of 203 procedures were performed. These included 38 percutaneous interventions (19%), 24 surgical procedures (12%), and 15 embolectomies (7%). Of note, 11 patients (6%) underwent >1 procedure. As shown in Figure 1, most procedures were performed in the extremities (92%; n=71), with a minority in visceral territories (8%; n=6). Among the 24 surgical procedures, 50% (n=12) were amputations, 29% (n=7) were peripheral arterial bypass surgeries, 8% (n=2) were laparotomies, and 13% (n=3) were other procedures (1 each of ileal resection, hemicolectomy with enterectomy, and open embolectomy).

Relative Efficacy of Standard-Dose NOAC Compared With Warfarin

There was a 29% reduction (HR, 0.71 [95% CI, 0.51–0.99]; $P=0.04$) in SEE with NOACs (n=61 events; 0.10%/year) compared with warfarin (n=85 events; 0.15%/year). In the warfarin group, 16 (0.03%/year) SEEs were fatal, and 69 (0.12%/year) were nonfatal, compared with 7 (0.01%/year) fatal and 54 (0.09%/year) nonfatal events in the standard-dose NOAC group (Figure 2A).

Relative Efficacy of LD NOAC Compared With Warfarin

Across 2 trials that included a LD NOAC arm, there were 42 (0.15%/year) SEEs with LD NOACs and 42 (0.15%/year) with warfarin (HR, 0.99 [95% CI, 0.65–1.52]; $P=0.97$). In the warfarin group, 8 (0.03%/year) SEEs were fatal and 34 (0.12%/year) were nonfatal, compared with 10 (0.03%/year) fatal and 32 (0.11%/year) nonfatal events in the LD NOAC group (Figure 2B).

Relative Efficacy of Standard-Dose NOAC Compared With LD NOAC

Standard-dose NOAC was associated with numerically lower rates of any SEE compared with LD NOAC, with a significant reduction in fatal SEE favoring standard-dose NOAC (Figure S3).

Thirty-Day Mortality After SEE

The 30-day mortality rate was similar between patients with SEE (18%) and those with IS (17%) (Table S2). Among the 33 deaths within 30 days after SEE, the majority (91%; n=30) were cardiovascular, whereas 6% (n=2) were caused by infection, and 3% (n=1) were hemorrhagic. When excluding the 26 patients who had both SEE and IS, the 30-day mortality rate was 16% in patients with SEE alone, comparable with 17% in those with IS alone. However, in the 26 patients who experienced both SEE and IS, the 30-day mortality rate was 36%, more than twice that observed in patients with either event alone (Table S3).

Long-Term Mortality After SEE

SEEs were associated with a nearly 3-fold increased risk of long-term mortality—defined as death occurring beyond 30 days after the index event—compared with

Table. Comparison of Clinical Characteristics in Patients With Systemic Embolic Events Versus Ischemic Stroke Versus Neither (First Event Only)

Characteristic	SEE (n=171)	IS (n=1789)	Neither (n=69 630)	*P* value for comparison of 3 groups	*P* value, SEE vs IS
Age, years, median (IQR)	75 (68–80)	74 (68–79)	72 (65–77)	<0.001	0.24
Female sex, n (%)	85 (49.7)	766 (42.8)	25 808 (37.1)	<0.001	0.082
Race, White, n (%)	137 (80.1)	1329 (74.3)	55 910 (80.3)	<0.001	0.094
CrCl (mL/min), median (IQR)	57.8 (46–74)	61.9 (48.4–80.9)	70.1 (54–90.8)	<0.001	0.018
BMI (kg/m^2), median (IQR)	27.5 (23.5–30.7)	27.5 (24.4–31.1)	28.4 (25.2–32.2)	<0.001	0.15
Paroxysmal AF	24 (14)	363 (20.4)	16 198 (23.3)	<0.001	0.050
CHA_2DS_2-VASC score, mean (SD)	4.7 (1.5)	4.6 (1.5)	4 (1.5)	<0.001	0.74
Congestive heart failure, n (%)	89 (52)	877 (49)	32 253 (46.3)	0.026	0.45
Hypertension, n (%)	152 (88.9)	1580 (88.3)	61 045 (87.7)	0.64	0.82
Age ≥75 years, n (%)	86 (50.3)	849 (47.5)	26 639 (38.3)	<0.001	0.48
Diabetes, n (%)	49 (28.7)	585 (32.7)	21 405 (30.7)	0.17	0.28
Stroke/TIA, n (%)	66 (38.6)	824 (46.1)	19 220 (27.6)	<0.001	0.061
Coronary artery disease, n (%)	59 (34.5)	584 (32.6)	20 788 (29.9)	0.017	0.62
Previous myocardial infarction, n (%)	41 (24)	298 (16.7)	10 130 (14.6)	<0.001	0.016
PCI, n (%)	13 (10.2)	115 (8.2)	4175 (8)	0.66	0.44
CABG, n (%)	15 (11.7)	87 (6.2)	3589 (6.9)	0.057	0.016
History of PAD	28 (16.5)	96 (5.4)	3114 (4.5)	<0.001	<.001
Age 65–74 years, n (%)	56 (32.7)	626 (35)	26 111 (37.5)	0.043	0.55
Valvular heart disease	40 (23.4)	383 (21.4)	13 246 (19)	0.015	0.55
Current smoker, n (%)	20 (11.7)	140 (7.8)	5023 (7.2)	0.049	0.078
Weight ≤60 kg, n (%)	35 (20.5)	291 (16.3)	7261 (10.4)	<0.001	0.16
VKA naïve, n (%)	74 (43.3)	968 (54.1)	35 758 (51.4)	0.007	0.007
Medication at randomization, n (%)					
Aspirin	56 (32.7)	608 (34)	23 530 (33.8)	0.95	0.74
Thienopyridine	4 (2.3)	71 (4)	2097 (3)	0.058	0.29

This table includes participants with SEE as a first event and therefore does not include all participants with SEEs. AF indicates atrial fibrillation; CrCl, creatinine clearance; IS, ischemic stroke; PAD, peripheral arterial disease; SEE, systemic embolic event; and TIA, transient ischemic attack.

patients who experienced neither SEE nor IS (HR, 2.85 [95% CI, 2.11–3.85]). In contrast, IS conferred an even higher long-term mortality risk (HR, 3.58 [95% CI, 3.26–3.92]) (Figure 3). When excluding patients who had both SEE and IS, the HR for mortality was 2.83 (95% CI, 2.08–3.85) in patients with SEE alone and 3.52 (95% CI, 3.21–3.86) in those with IS alone. The HR was markedly higher at 8.24 (95% CI, 4.78–14.22) in patients with both SEE and IS, relative to patients without either event alone (Figure S4). Cause-of-death analysis showed a higher proportion of vascular and other cardiovascular deaths in patients with both SEE and IS, which

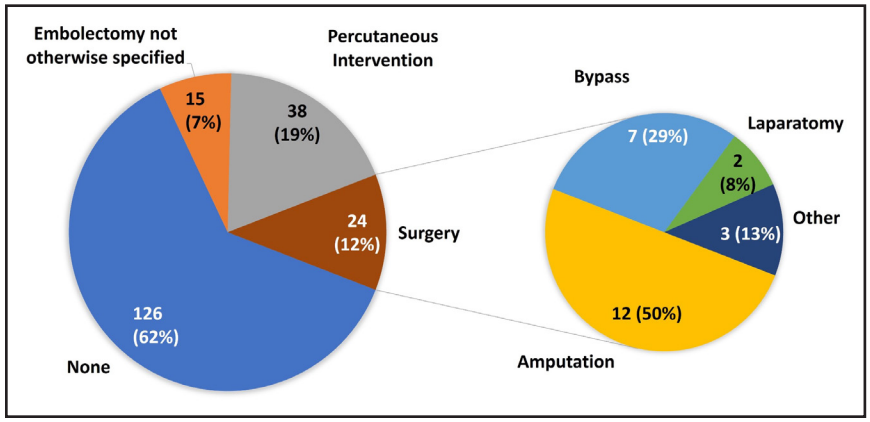

Figure 1. Management of patients with systemic embolic events. Distribution of various management approaches for patients with systemic embolic events.

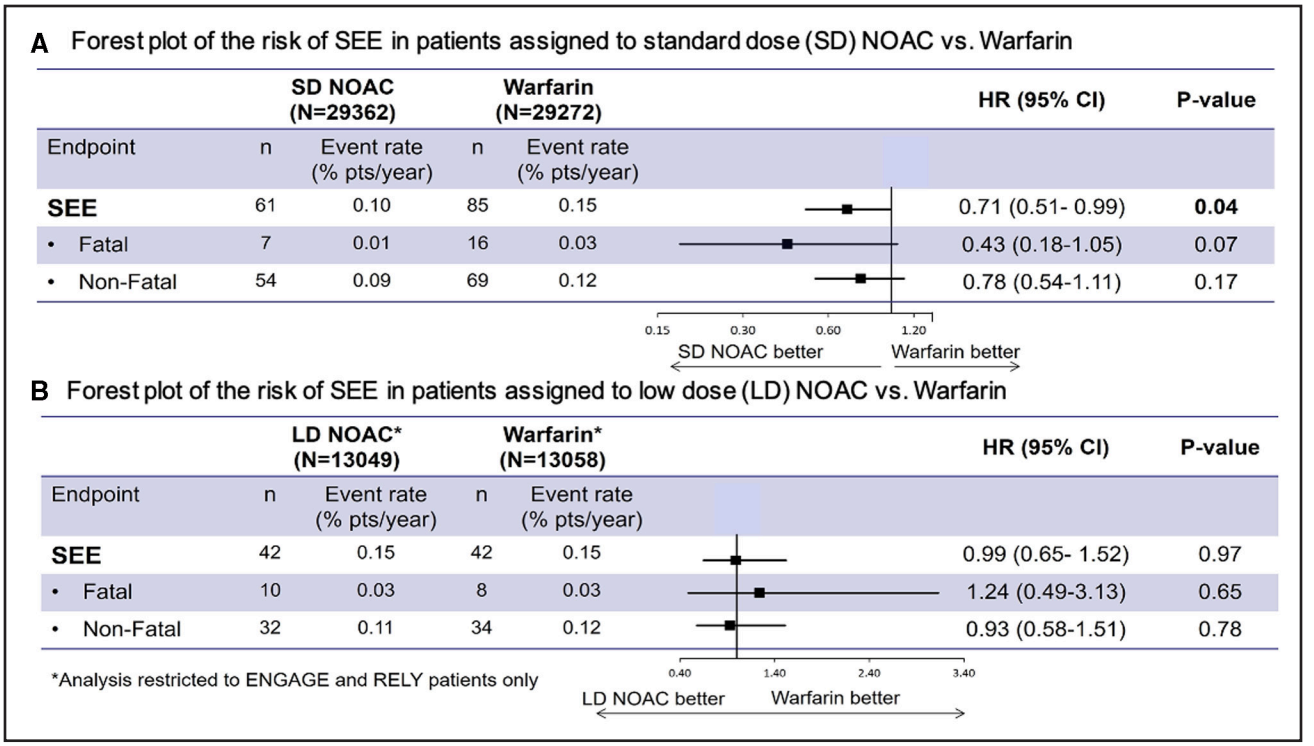

Figure 2. Systemic embolic events with non–vitamin K antagonist oral anticoagulant versus warfarin.
A, Forest plot of the risk of SEE in patients assigned to standard-dose (SD) NOAC vs warfarin. **B**, Forest plot of the risk of SEE in patients assigned to low-dose (LD) NOAC vs warfarin. AF indicates atrial fibrillation; ENGAGE, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48; HR, hazard ratio; NOAC, non–vitamin K antagonist oral anticoagulant; pts, patients; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; and SEE, systemic embolic event.

may partly explain the increased mortality observed in this subgroup (Table S4).

Anticoagulation Discontinuation Patterns and Risks of Ischemic Events and Mortality

Permanent discontinuation of study anticoagulant occurred in 29% of patients overall and was more frequent among those who experienced SEE (35%) than for IS (26%) (Table S5). Among patients who permanently discontinued anticoagulation and then experienced a thromboembolic event, the median time to an event after discontinuation was 17 days for any SEE and for IS.

Annualized event rates for SEE and IS were higher after discontinuation of study anticoagulant compared with rates in patients who did not discontinue (any SEE, 0.20 versus 0.11 per 100 patient-years; IS, 1.53 versus 1.18 per 100 patient-years; Table S6). After SEE, patients who discontinued therapy had more than twice the mortality rate compared with those who continued anticoagulation (32% versus 14%), highlighting the potential risks associated with treatment cessation after an event.

Independent Predictors of SEE

In a multivariable Cox proportional hazards model, several baseline clinical characteristics were independently associated with the risk of SEE. These included lower creatinine clearance (HR per mL/min, 0.98 [95% CI, 0.97–0.99]), nonparoxysmal AF (HR, 1.91 [95% CI, 1.12–3.25]), female sex (HR, 1.99 [95% CI, 1.34–2.94]), history of stroke or transient ischemic attack (HR, 1.88 [95% CI, 1.30–2.73]), previous MI (HR, 1.78 [95% CI, 1.14–2.79]), PAD (HR, 3.18 [95% CI, 1.87–5.39]), current smoking (HR, 2.26 [95% CI, 1.25–4.06]), and previous use of a VKA (HR, 1.45 [95% CI, 0.996–2.12]). Full model estimates are presented in Table S7.

DISCUSSION

By pooling individual patient-level data from 71 683 patients across 4 pivotal randomized trials, this study represents the largest randomized controlled trial–based analysis of SEE in patients with AF and offers a unique opportunity to evaluate this underrecognized but clinically important thromboembolic complication. There were 4 key findings from these analyses.

First, our study supports previous findings indicating that approximately 10% of arterial thromboembolic complications in patients with AF can be attributed to SEEs.[4,6,15–17] However, it is important to note that the percentage of SEEs may be an underestimation of the overall thromboembolic burden because arterial emboli to the brain are more likely to be clinically evident, whereas a similar size

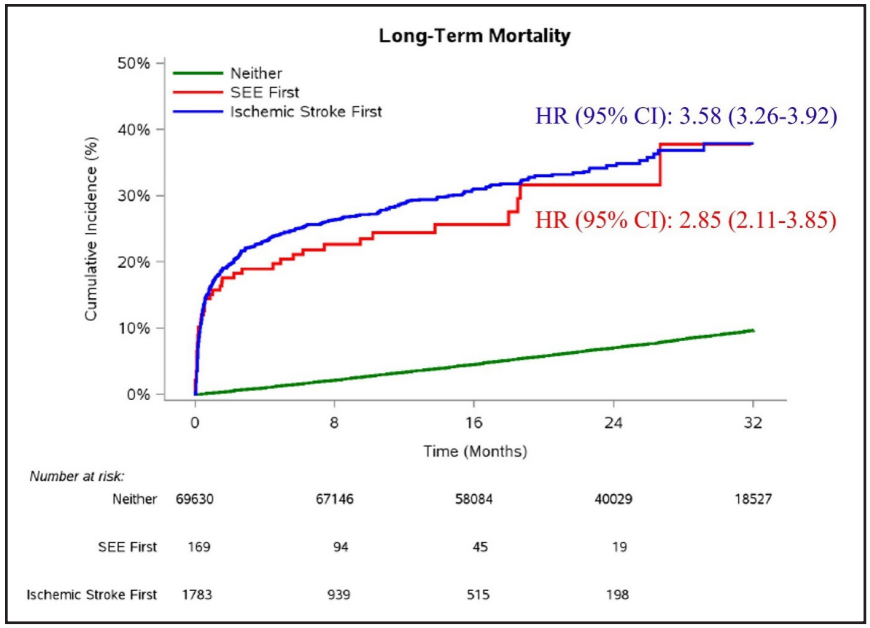

Figure 3. Long-term mortality incidence after the first SEE or ischemic stroke while on anticoagulation (NOAC or warfarin). Each curve represents the Kaplan-Meier estimated cumulative mortality incidence after the first occurrence of each of the 2 clinical events (SEE or ischemic stroke). The hazard ratios represent the risk of death in patients after a first ischemic stroke (blue font) and in patients after a first SEE (red font) compared to patient with neither event. IS indicates ischemic stroke; NOAC, non–vitamin K antagonist oral anticoagulant; and SEE, systemic embolic event.

thrombus in peripheral arteries may be asymptomatic or attributed to another cause.[3,5] Although clinically recognized SEE accounts for approximately one-tenth of the frequency of IS in patients with AF, it is associated with significant morbidity and mortality and often requires surgical or percutaneous intervention to restore blood flow.

Second, we demonstrated that standard-dose NOACs are superior to warfarin in reducing the risk of SEE in patients with AF. The relative efficacy of NOACs in reducing SEE has not been well established. Individual trials were underpowered for SEE alone as it represents <10% of the primary composite end point of all-cause stroke or SEE.[7–12] Although warfarin has been shown to effectively halve the incidence of SEE compared with antiplatelet therapy,[18,19] our findings suggest that NOACs reduced the risk of SEE by an additional 29% compared with warfarin. This benefit appears to be more pronounced in preventing fatal SEE. In contrast, there was no significant reduction in IS with NOACs versus warfarin in COMBINE-AF.[11] One potential explanation for the significant benefit of NOACs in preventing SEE compared with IS is that the adjudication of SEE might have captured more accurately events of "cardioembolic" origin, which are most effectively prevented by anticoagulation.[14] In contrast, IS has varied pathogeneses (embolic, cardioembolic, nonthrombotic) that anticoagulation may or may not prevent. Although NOACs appear superior to warfarin in preventing thromboembolic events, they may not confer as much advantage over warfarin in preventing local ischemic or atherosclerotic events.[5]

Third, our analysis of 30-day mortality after SEE revealed a comparable rate to that observed for IS. Most deaths within 30 days of SEE (91%) were cardiovascular deaths, highlighting the substantial cardiovascular burden of these events. Over long-term follow-up, SEE was associated with a nearly 3-fold increased mortality compared with patients without SEE or IS, although IS conferred an even higher risk. These findings align with previous reports indicating increased long-term mortality after SEE; however, our estimates suggest a lower risk than earlier studies, which reported up to a 4-fold increase in mortality after an SEE and a 7-fold increase in mortality after an IS.[6] One potential explanation for the lower mortality risk after an SEE or IS is that our study analyzed a more homogeneous patient population, all of whom were receiving anticoagulation (NOAC or warfarin), whereas previous studies included patients on antiplatelet therapy, which might have influenced outcomes.[6] An important finding of this study is the impact of anticoagulation discontinuation on subsequent ischemic events. We observed that a substantial proportion of SEE and IS occurred after patients had been off anticoagulation for >3 days. Patients who discontinued therapy also experienced higher event rates and markedly increased mortality after SEE. These findings underscore that even brief interruptions in anticoagulation are associated with elevated thromboembolic risk and worse outcomes, highlighting the critical importance of maintaining continuous therapy in patients with AF.

Our fourth key finding highlights that, although SEE and IS share some demographic and risk factor similarities, they have distinct profiles, supporting previous observations.[3,6] Compared with patients with IS, those with SEE were more likely to have PAD, a history of MI, previous VKA exposure, worse renal function, and nonparoxysmal AF. In a multivariable analysis, we identified several independent predictors of SEE, including PAD, current smoking, nonparoxysmal AF, female sex, previous MI, previous stroke or transient ischemic attack, previous VKA use, and impaired renal function. These comorbidities may not only increase the risk of

thromboembolism but also raise the likelihood that an embolic event becomes clinically apparent, particularly in vascular territories already compromised by atherosclerosis. Therefore, some of the observed differences in risk profiles between SEE and IS may reflect detection bias rather than fundamentally distinct mechanisms. Because our analysis included only symptomatic and adjudicated events, it reflects clinically overt SEEs, and subclinical embolic events likely went undetected.

Limitations

Participants in the 4 included trials were subject to trial-specific eligibility criteria and may not fully represent the broader AF population seen in clinical practice. It is important to note that only symptomatic, clinically overt SEEs were captured, likely underestimating the total burden of embolic events. Emboli in vascular beds with poor collateral circulation or underlying atherosclerosis—such as in PAD—are more likely to present with symptoms and be detected, introducing potential detection bias and contributing to differences in baseline characteristics between SEE and IS patients. Systematic imaging (eg, brain magnetic resonance imaging or vascular ultrasound) was not mandated across the trials, limiting our ability to definitively exclude coexisting silent IS in patients with SEE, or silent SEE in those with IS. Therefore, subclinical coexisting embolic events cannot be excluded, and comparisons between SEE and IS should be interpreted with caution. Although all events were adjudicated by an independent clinical events committee blinded to treatment assignment, based on clinical data, imaging, and procedural reports, the possibility of undetected overlapping embolic events remains. In addition, anatomical site information for SEE was not consistently available across trials and could not be analyzed. Information on postrandomization interventions such as catheter ablation, antiarrhythmic drug use, lifestyle modification, or left atrial appendage closure was not systematically collected across trials and could not be accounted for in this analysis. These therapies may have influenced long-term outcomes and represent an important area for future study. In our cohort, the prevalence of previous ablation was ≤3.3% across all subgroups. Distinguishing SEE from local atherosclerotic limb events is especially challenging in patients with PAD. To reduce misclassification, all events were adjudicated with predefined criteria to exclude alternative mechanisms such as nonembolic acute limb ischemia or chronic limb-threatening ischemia. We also observed that nearly one-third of SEE events were preceded by anticoagulation discontinuation, which was associated with worse outcomes. However, residual confounding—particularly confounding by contraindication—remains a concern, as discontinuation may reflect frailty, bleeding risk, or clinical deterioration. Analyses of events after drug discontinuation are inherently complex and were not fully characterized in these trials. Therefore, these findings should be interpreted cautiously, and further prospective studies are warranted to better understand the consequences of anticoagulation interruptions. Last, although this study provides the largest individual patient-level dataset on SEE to date, future research incorporating systematic imaging and biomarker data is warranted to elucidate underlying mechanisms, identify subclinical events, and refine risk stratification.

CONCLUSIONS

In patients with AF treated with oral anticoagulation, SEE occurred at a rate of 0.13% per patient-year—approximately one-tenth the frequency of IS—yet the 2 entities were associated with similarly high mortality. SEE events were also associated with significant morbidity and often required surgical or endovascular intervention. Standard-dose NOACs were significantly more effective than warfarin in preventing SEE, in contrast with IS, where these treatments had similar benefit. Nearly one-third of SEE events occurred after anticoagulation discontinuation, and these patients experienced higher event rates compared with those who remained on therapy, highlighting the importance of treatment continuity in high-risk patients. SEE may have a distinct clinical profile from IS, and these findings support further research into improved detection, tailored prevention strategies, and deeper understanding of embolic risk in patients with AF.

ARTICLE INFORMATION

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Supplemental Material

Supplemental Tables S1–S7
Supplemental Figures S1–S4
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Checklist

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