Thromboembolism is central to atrial fibrillation (AF)–related morbidity. The pathogenesis of intracardiac thrombus formation in AF is linked to each component of Virchow’s triad including atrial stasis, endothelial dysfunction, and a systemic hypercoagulable state. Although embolism of cardiac thrombi can involve any vascular territory, there has been a historical focus on cerebral embolism, an outcome associated with substantial disability and mortality. In contrast to the well-characterized risk and sequelae of cerebral embolism, much less is known regarding the clinical risk factors and outcomes associated with systemic embolic events (SEEs) in AF.

In this issue of Circulation, Bekwelem and colleagues improve our understanding of the epidemiology and prognostic implications of systemic embolism in AF. They retrospectively pooled data from 4 published randomized trials of antiplatelet or anticoagulant therapy in AF patients encompassing a total of 37,973 individuals (Table). The investigators readjudicated suspected SEEs by using a harmonized classification scheme. A SEE was defined by both clinical and objective evidence of the sudden loss of end-organ perfusion. They then examined the risks of both 30-day and long-term morbidity in relation to SEEs.

Overall, 221 SEEs occurred in 219 individuals during a mean follow-up of 2.4 years. The incidence of SEEs (0.24/100 person-years) was lower than that of cerebral embolism (1.92/100 person-years) and comprised 12% of clinically recognized thromboembolic events. Anatomically, ≈60% of SEEs involved the lower extremities, whereas ≈30% occurred in the visceral-mesenteric system, and only 11% occurred in the upper extremities. Most patients underwent an invasive procedure as part of their clinical management. SEEs were associated with similar and significant 30-day mortality in comparison with stroke alone (24% versus 25%). SEEs were associated with ≈4-fold increased risk of long-term mortality, in comparison with a ≈7-fold increased risk of mortality associated with ischemic stroke.

This study has a number of strengths that distinguish it from previous literature. Collation of readily available, ethically diverse patient cohorts yielded the largest reported assessment of AF-related SEEs to date. Careful end point ascertainment and independent readjudication of events with prespecified diagnostic criteria enhance the validity of the results. Comprehensive clinical descriptions of SEEs, including anatomic distribution and diagnostic methodology, provide a detailed understanding of the different arterial beds commonly affected by peripheral embolism in AF.

The findings of Bekwelem et al should be interpreted in the context of the cohorts included and study design. First, although the collated studies have similar baseline characteristics (Table), there was significant heterogeneity in therapeutic exposure (anticoagulant versus antiplatelet) and relatively short follow-up time. Thus, the reported SEE rate represents a blended rate among patients taking either anticoagulation or antiplatelet therapy and does not reflect the long-term natural history of AF. Second, given the relatively low incidence of SEEs, the study was likely underpowered for several of the subgroup analyses presented, including age, sex, and location of peripheral embolism. Third, the reliance on clinically evident end-organ ischemia is practical, although it likely underestimates the true incidence of systemic embolism, particularly to abdominal visceral organs that have a rich network of collateral circulation which may mitigate the ischemic insult of embolic phenomenon. Fourth, some peripheral embolic events could reflect lower baseline vascular reserve (eg, related to previous SEEs, atherosclerotic burden, or anatomic smaller vessels) or more significant embolic burden. This may explain the identification of previous SEEs and peripheral arterial disease as risk factors for incident SEEs and may confound analyses of mortality.

Systemic Embolism in AF – Unique Events or Additional Embolic Destinations?

Should a SEE be regarded as a distinct AF outcome or as yet another embolic destination? Given that the vast majority of patients with thromboembolism in this study experienced either stroke or an SEE alone (≈97% of embolic events), one might speculate that patients are uniquely predisposed to either incident stroke or SEEs. The authors identify several clinical characteristics more prevalent in patients with incident SEEs in comparison with stroke including female sex, white ethnicity history of smoking, previous myocardial infarction, previous SEEs, and peripheral arterial disease. Female sex and SEEs have been linked previously, and others have identified increasing age, severe left ventricular dysfunction, and echocardiographic...
evidence of left atrial appendage thrombi as additional risk factors for SEEs in comparison with stroke in AF.12

The incidence and anatomic location associated with cardioembolism may also be related to other factors. Anatomic distribution is generally influenced by the character of arterial branching and the course of blood flow.1,6 Increased thrombus size has been reported to favor a peripheral rather than cerebral embolic destination.12 Limited histological comparison of central versus peripheral thrombi in AF suggest a differing biology, with in situ thrombi composed primarily of amorphous debris and fibrin, in contrast to embolic thrombi composed of fibrin and platelets.13 Regardless of whether patients are predisposed to specific embolic destinations, the contribution by Bekwelem and colleagues underscores the substantial morbidity associated with embolism of any kind.

Clinical and Therapeutic Implications of Identifying SEE Risk in AF

Given that several SEE risk factors (eg, female sex, peripheral vascular disease, previous myocardial infarction) are included in stroke prediction algorithms, it is unlikely that the report by Bekwelem et al7 will significantly modify the decision to initiate anticoagulation. Indeed, the CHA2DS2-VASc score demonstrated similar discrimination and reclassification of clinical outcomes when risk was defined either as stroke-alone or a composite of stroke and SEEs.14

**Table.** Baseline Characteristics, Therapeutic Comparison, and Embolic End Points in Included Studies

<table>
<thead>
<tr>
<th>Therapeutic comparison</th>
<th>Clopidogrel + ASA vs ASA</th>
<th>Clopidogrel + ASA vs VKA</th>
<th>Apixaban vs ASA*</th>
<th>Dabigatran (110 mg vs 150 mg)† vs VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>71±10</td>
<td>70±9</td>
<td>70±10</td>
<td>71±9</td>
</tr>
<tr>
<td>CHADS2</td>
<td>2.0±1.1</td>
<td>2.0±1.1</td>
<td>2.0±1.1</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>Male sex</td>
<td>58</td>
<td>66</td>
<td>59</td>
<td>64</td>
</tr>
<tr>
<td>History of stroke/TIA, %</td>
<td>13</td>
<td>15</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>Peripheral arterial disease, %</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>End points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, median</td>
<td>3.6 y</td>
<td>1.3 y</td>
<td>1.1 y</td>
<td>2.0 y</td>
</tr>
<tr>
<td>Stroke, all</td>
<td>2.4 vs 3.3%/y</td>
<td>2.4 vs 1.4%/y</td>
<td>1.6 vs 3.4%/y</td>
<td>1.4 vs 1.0 vs 1.6%/y</td>
</tr>
<tr>
<td>Stroke, ischemic</td>
<td>1.9 vs 2.8%/y</td>
<td>2.2 vs 1.0%/y</td>
<td>1.1 vs 3.0%/y</td>
<td>1.3 vs 0.9 vs 1.2%/y</td>
</tr>
<tr>
<td>SEE</td>
<td>0.4 vs 0.4%/y</td>
<td>0.4 vs 0.1%/y</td>
<td>0.1 vs 0.4%/y</td>
<td>0.1 vs 0.1 vs 0.1%/y</td>
</tr>
</tbody>
</table>

Continuous measures are reported as mean±standard deviation. ACTIVE indicates The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events; AF, atrial fibrillation; ASA, aspirin; AVERROES, Apixaban versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; RE-LY, Randomized Evaluation of Long-Term Anticoagulation Therapy; SEE, systemic embolic event; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

*ASA dose was >61 mg in 35% of study patients.
†Dabigatran dose was either 110 mg or 150 mg.

Pre-Diagnosis | AF Diagnosis | Post-Diagnosis
--- | --- | ---
? Enhanced Surveillance | **Thromboembolism Prophylaxis** |  
| | SEE | Stroke
| | i. | ii. |
| | Vascular reserve (peripheral)  | Vascular reserve (cerebral)  |
| | i. Opioid burden  | i. Aortic plaque  |
| | ii. Female  | ii. Smoking  |

† AF Risk  
- Age
- CHADS2 score

† Risk of Stroke  
- CHA2DS2-VASc score
- Cryptogenic stroke

† Risk of SEE  
- History of SEE
- Peripheral arterial disease
- Smoking

Figure. Schematic representation of risk assessment in AF. Prediagnosis, the role of enhanced surveillance may be considered for patients at increased risk of AF, stroke, and SEEs. The CHARGE-AF score (inclusive of age, race, height, weight, blood pressure, smoking status, use of antihypertensive medication, diabetes mellitus, history of myocardial infarction and heart failure) has demonstrated discrimination in the prediction of AF.15 Postdiagnosis, risk assessment and implementation of thromboembolism prophylaxis is often guided by the CHA2DS2-VASc algorithm.16 The circles display the relatively increased incidence of stroke in comparison with SEE. Enclosed in the circles are risk factors that may selectively predispose to either stroke or SEE. AF indicates atrial fibrillation; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; and SEE, systemic embolic event.
Nevertheless, the study suggests that current efforts being considered for stroke prevention might have extended value for SEE prevention. For example, given the morbidity attributable to SEEs, should cardiac rhythm monitoring be implemented to identify subclinical AF in patients with SEE risk factors such as peripheral arterial disease (Figure)?15,16 Such initiatives may be cost-effective for stroke prevention17 and are currently being evaluated.18–20 Similarly, would enhanced cardiac rhythm monitoring to detect AF alter management in patients with visceral embolism or peripheral ischemia without known AF, akin to efforts to identify a cause for cryptogenic stroke?21 At what expense would AF prevention prove cost-effective altogether for the reduction of embolic morbidity, if it were achievable? Practically, answering such questions may be challenging owing to the relatively low event rates and large sample sizes necessary. Therefore, at present, it appears prudent to exercise increased vigilance for AF detection in patients either at high risk for systemic embolic events or with unexplained peripheral ischemia that may be of embolic origin.

Bekwelem and colleagues have contributed significantly to our understanding of the spectrum of thromboembolic risk in patients with AF. Their report provides us with estimates of the incidence of SEEs, the arterial beds most commonly affected, and the morbidity associated with such events. By opening our eyes, these data help us “SEE” embolic risk more clearly. Ultimately such clarity will guide more effective application of therapies to stem the rising tide of AF22 and thromboembolic morbidity.

Disclosures

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References


Key Words: Editorials || arrhythmias, cardiac || atrial fibrillation || atrial flutter || embolism
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