Silent Cerebral Infarction in East Asian vs. Non-Asian Atrial Fibrillation Patients
— Meta-Analysis —

Keitaro Senoo, MD; Yusuke Kondo, PhD; Yoshio Kobayashi, PhD; Gregory YH Lip, MD

Background: Atrial fibrillation (AF) is the most common arrhythmia in the ageing population in East Asia. Silent cerebral infarction (SCI) is defined as cerebral infarction in the absence of corresponding clinical symptoms, and is a highly prevalent and morbid condition in AF. SCI is increasingly being recognized as a risk factor for future stroke, which can lead to cognitive decline or dementia. The latter is an increasingly common health problem in East Asia.

Methods and Results: We conducted a meta-analysis to compare the association of AF and SCI between East Asian and non-Asian patients. AF was associated with SCI in patients with no symptomatic stroke history (relative risk [RR], 2.24; 95% CI: 1.26–3.99, I²=83%; P=0.006) although the prevalence varied widely between studies (P for heterogeneity<0.001). In non-Asian patients, the prevalence of SCI in AF is higher than that in controls (RR, 1.85; 95% CI: 1.65–2.08, I²=17%; P<0.001). There was no significant racial difference between Asian and non-Asian studies (P=0.53).

Conclusions: In East Asia, AF was significantly associated with SCI and no racial difference was seen between East Asian and non-Asian patients. The present findings offer clinicians new insights into the association between AF and SCI.

Key Words: Asia; Atrial fibrillation; Silent cerebral infarction

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major cause of stroke. The estimated global prevalence of AF is approximately 1–2%. In Asia, the prevalence of AF has been reported to be slightly lower than that in Western populations. Due to the much larger population in Asia, the burden of AF is estimated to be much greater in Asian than in Western populations. Indeed, it has been estimated that in 2050 there will be 72 million patients with AF in Asia, more than double the combined number of patients from Europe and the USA. Therefore, it is particularly important that AF is effectively managed in the ageing population of Asia.

Silent cerebral infarction (SCI) is defined as the presence of cerebral infarction with the absence of corresponding clinical symptoms. In a recent meta-analysis, AF was associated with SCI predicting subsequent clinically overt stroke. Thus, the prevalence of SCI and its effect as a risk factor for overt stroke are important considerations during the evaluation of AF.

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AF is also a well-established risk factor for dementia. For example, Liao et al reported a consistently higher rate of cognitive decline and risk of dementia in patients with AF. These associations are partly due to the increased risk of clinical stroke in AF, but other mechanisms are likely to contribute, including the occurrence of SCI and microbleeds. Current evidence is not sufficient to support a trend of increased prevalence of dementia in East Asia over the last few decades, but AF may contribute to dementia risk. We conducted a meta-analysis to compare the association of AF and SCI between East Asian and non-Asian patients.

Methods

Data Sources
PubMed were searched from their inception to 7 October 2017. No language restriction was applied. To ensure a comprehensive search of the literature, we also manually

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Exclusion criteria included inappropriate study design (e.g., reviews, editorials, letters, case series, case reports, and conference proceedings); evaluation of SCI after a procedure, such as catheter ablation, coronary artery bypass graft surgery, or cardioversion, in patients with AF; and conflicting and inconsistent data.

Data Extraction and Quality Assessment
Following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines,14 studies were initially screened on the basis of titles and abstracts. Data were extracted by 2 reviewers independently and disagreements were resolved by consensus or, if necessary, by a third reviewer. We searched the reference lists of the included studies and previously published systematic reviews and meta-analyses. We contacted the authors when required data were ambiguous or missing.

Study Selection
The PRISMA statement for reporting systematic reviews and meta-analyses of studies13 was used for the method of the present study.

The search terms for AF and SCI included each of the following individually and in combination: “atrial fibrillation”, “silent cerebral infarction”, and “silent stroke”, and returned 217 citations.

Table. SCI Studies in East Asian vs. Non-Asian AF Patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>Country</th>
<th>AF (n)</th>
<th>NSR (n)</th>
<th>Diagnosis method</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Kim et al17</td>
<td>South Korea</td>
<td>12</td>
<td>394</td>
<td>MRI</td>
</tr>
<tr>
<td>2012</td>
<td>Kobayashi et al18</td>
<td>Japan</td>
<td>71</td>
<td>71</td>
<td>MRI</td>
</tr>
<tr>
<td>2014</td>
<td>Saito et al19</td>
<td>Japan</td>
<td>131</td>
<td>112</td>
<td>MRI</td>
</tr>
<tr>
<td>2014</td>
<td>Cha et al20</td>
<td>South Korea</td>
<td>400</td>
<td>800</td>
<td>MRI</td>
</tr>
<tr>
<td>2003</td>
<td>Vermeer et al18</td>
<td>Netherlands</td>
<td>32</td>
<td>983</td>
<td>MRI</td>
</tr>
<tr>
<td>2008</td>
<td>Das et al19</td>
<td>USA</td>
<td>45</td>
<td>1,995</td>
<td>MRI</td>
</tr>
<tr>
<td>2013</td>
<td>Gaita et al20</td>
<td>Italy</td>
<td>180</td>
<td>90</td>
<td>MRI</td>
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<tr>
<td>2013</td>
<td>Stefansdottir et al21</td>
<td>Iceland</td>
<td>330</td>
<td>3,921</td>
<td>MRI</td>
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<tr>
<td>2013</td>
<td>Marfella et al22</td>
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<td>288</td>
<td>MRI</td>
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<tr>
<td>2014</td>
<td>Chen et al23</td>
<td>USA</td>
<td>48</td>
<td>887</td>
<td>MRI</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; MRI, magnetic resonance imaging; NSR, normal sinus rhythm; SCI, silent cerebral infarction.

Figure 1. Meta-analysis of silent cerebral infarction (SCI) studies in East Asian vs. non-Asian atrial fibrillation (AF) patients. M-H, Mantel-Haenszel method.
prevalence of SCI in AF was higher than that in controls (RR, 1.85; 95% CI: 1.65–2.08, I²=17%; P<0.001). There was no significant racial difference between Asian and non-Asian studies (P=0.53; Figure 1).

Discussion

Silent Cerebral Infarction and AF

The precise mechanisms underlying the association between AF and SCI are not completely understood. Kobayashi et al showed that a high rate of cortical/subcortical and deep white matter SCI was observed in patients with AF, which is thought to arise from a synergistic effect of microthrombi and hemodynamic abnormalities. Sugioka et al reported that left atrial abnormalities and complex arch plaques diagnosed on transesophageal echocardiography were independent risk factors for SCI.

In a meta-analysis using general population data, SCI was an independent predictor of incident stroke (hazard ratio [HR], 2.08; 95% CI: 1.69–2.56; P<0.001). In a subgroup analysis pooling 9,483 stroke-free individuals from large population-based studies, SCI was present in 18% of participants and remained a strong predictor of future stroke (HR, 2.06; 95% CI: 1.64–2.59; P<0.01).

Of note, SCI was found to be associated with dementia, probably because patients continue to have additional brain infarcts, both silent and symptomatic. SCI and the Risk of Dementia and Cognitive Decline

In East Asia, the increased life expectancy and the considerable number of older people has led to increasing occurrence of diseases. Of these, dementia is the most prominent and poses major challenges to health-care systems. The prevalence of dementia in Asia has previously been reported to be lower than that in Western populations, but age-specific prevalence rates are similar globally. Overall, dementia prevalence is expected to rise dramatically across Asia due to increasingly elderly populations.

Main Image

The 217 articles retrieved from the searches were first screened based on the title and abstract, and 205 studies were excluded because they were obviously irrelevant to the review. Two studies (1 in East Asia and 1 in non-Asia) were then excluded because no AF data were seen. Finally, we separately performed meta-analysis of 4 studies in East Asia and 6 studies in non-Asia and evaluated racial difference in the prevalence of SCI between East Asia and non-Asia (Table).

In East Asia, the prevalence of SCI diagnosed on magnetic resonance imaging (MRI) in patients with AF ranges from 25% to 49.3%. In the present meta-analysis, AF was associated with SCI compared to patients with no symptomatic stroke history (RR, 2.24; 95% CI: 1.26–3.99, I²=83%; P=0.006) although the prevalence varied widely between studies (P for heterogeneity<0.001). In non-Asia, the prevalence of SCI in AF was higher than that in controls (RR, 1.85; 95% CI: 1.65–2.08, I²=17%; P<0.001). There was no significant racial difference between Asian and non-Asian studies (P=0.53; Figure 1).

Results

The 217 articles retrieved from the searches were first screened based on the title and abstract, and 205 studies were excluded because they were obviously irrelevant to the review. Two studies (1 in East Asia and 1 in non-Asia) were then excluded because no AF data were seen. Finally, we separately performed meta-analysis of 4 studies in East Asia and 6 studies in non-Asia and evaluated racial difference in the prevalence of SCI between East Asia and non-Asia (Table).
the association between AF and cognitive decline in patients with or without history of stroke, AF was significantly associated with the risk for cognitive decline (RR, 1.40; 95% CI: 1.19–1.64, P<0.001).12 In East Asia, 4 studies have explored the impact of AF on cognition and dementia risk.11,20 24 The study by Liao et al was consistent with the result of the global meta-analysis, even in patients without any underlying disease (adjusted HR, 1.420; 95% CI: 1.394–1.448, P<0.001).11 Both CHADS2 (congestive heart failure, hypertension, age, diabetes and stroke) (c-index, 0.589; 95% CI: 0.586–0.592) and CHA2DS2-VASc (congestive heart failure, hypertension, age, diabetes, stroke, vascular disease and sex) (c-index, 0.611; 95% CI: 0.608–0.614) scores were significant predictors of dementia in AF patients. At present, a simple easy way to predict incident dementia in AF is lacking, so both CHADS2 and CHA2DS2-VASc scores might be useful for screening of dementia in AF subjects.

An obvious pathway linking AF with cognitive decline or dementia is the elevated risk of stroke in patients with AF. AF is associated with at least a doubling of stroke risk,33 and the effects of stroke on cognitive function are well established. Elevated stroke risk per se, however, does not completely account for the increased risk of dementia and cognitive decline associated with AF.12 Therefore, further studies are necessary in order to clarify the relationship between AF and cognitive decline.

Pathophysiological Considerations
Several potential mechanisms could explain the association between AF, SCI and cognitive decline (Figure 2). Vermeer et al showed that the presence of SCI visualized on MRI doubled the risk of dementia (HR, 2.26; 95% CI: 1.09–4.70).34 The presence of SCI on baseline MRI was associated with worse performance on neuropsychological tests and a steeper decline in global cognitive function. Second, microbleeds may also partially explain the association between AF and cognitive decline. Microbleeds are relatively frequent and have been linked to an increased risk of cerebral hemorrhage, lacunar infarcts, and degenerative changes of the brain matter.34 Oral anticoagulation in patients with AF can increase the risk of microbleeds or worsen the impact of existing ones on cognitive function. In the Rotterdam study, patients on warfarin had a higher prevalence and incidence of microbleeds, especially those with greater variability in anticoagulation control.35 Lee et al also suggested that underlying microbleeds are independently associated with an incidence of warfarin-related intracerebral hemorrhage.36 Nowadays, non-vitamin K antagonist oral anticoagulants (NOAC) have come into widespread use for cardiogenic embolism prevention in place of warfarin. In 1 study, NOAC did not increase microbleeds in AF patients longitudinally over 1 year.37 Longer follow-up in large samples would evaluate the impact of NOAC on the progression of microbleeds.38

Third, AF could increase dementia risk through its impact on cardiac function. Patients with AF have been found to have reduced cerebral perfusion.39 Indeed, restoration of sinus rhythm in patients with AF through cardioversion or ablation leads to improved cerebral blood flow.40 41 Reduced diastolic function and low cardiac index, both potential consequences of AF, have also been associated with incident dementia in prospective studies.42 43 Finally, shared risk factors, such as hypertension, coronary disease, and diabetes, which tend to accumulate with ageing, would explain the association between AF and cognitive decline.44

Potential of OAC for SCI
Although anticoagulation can reduce symptomatic stroke or transient ischemic attack significantly in patients with AF, the impact on prevention of SCI is unclear. Further studies are needed to determine whether anticoagulation influences SCI and to identify patients who benefit from anticoagulation. Differences in cognitive decline in AF patients between those on warfarin, aspirin, or no treatment were not observed,45 and warfarin cannot reduce brain volume loss in AF patients.21 This supports the possibility that chronic over-anticoagulation or under-anticoagulation may produce repeated microemboli and microbleeds that are below the detection threshold of standard brain imaging, but that eventually contribute to dementia.

Kobayashi et al showed that the CHADS2 score was not associated with the number of SCI except in cortex/subcortex,3 and Gaia et al also reported that 60% of SCI patients had a CHA2DS2-VASc score ≤1.29 If OAC can prevent SCI in AF patients, MRI screening in AF patients with CHA2DS2-VASc score ≤1 should be discussed.

Conclusions
In East Asia, AF was significantly associated with SCI and no racial difference was seen between East Asian and non-Asian patients. The present findings offer clinicians new insights into the association between AF and SCI.

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Conflict of Interests
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References

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