Anticoagulation therapy with warfarin, a vitamin K antagonist (VKA), is known to reduce strokes by approximately 60% in patients with atrial fibrillation (AF). However, the risk of hemorrhagic complications generally increases together with a reduction in cardioembolic thromboembolism. Although direct oral anticoagulants (DOACs) can reduce the risk of major hemorrhage, especially intracranial hemorrhage, the risk of hemorrhagic complications does not completely disappear. Therefore, physicians, thus far, have taken into account the net clinical benefit that is the balance of the risk (i.e., hemorrhagic complications) and the benefit (i.e., prevention of thromboembolism) when anticoagulation therapy is indicated in accordance with risk stratification using the CHADS2 or CHA2DS2-VASc score in patients with AF. Nevertheless, net clinical benefit does not always represent the activities of daily living (ADL), quality of life (QOL), or life prognosis in patients with AF who receive anticoagulation therapy, even when accurate scoring of both thromboembolic and bleeding risks is performed using preexisting scores. Important factors associated with impaired ADL, QOL, and/or life prognosis such as cognitive decline, dementia, frailty, malnutrition, low body weight, severe renal dysfunction, and malignancy are not included in current risk scores. Because the prevalence of these patient conditions and comorbidities increases with age, physicians may want to pay more attention to these factors both before initiating and during anticoagulation therapy in patients with AF, especially in elders, to obtain good net clinical outcomes.

Association Between Cognitive Decline or Dementia, Stroke, and AF
Cognitive decline and dementia are the major causes of ADL and QOL impairments. Many researchers have investigated the association between cognitive decline or dementia and AF. Most reports suggested that AF is associated with accelerated cognitive decline and higher risk of dementia, but some studies showed no difference in cognitive decline between patients with and without AF. Overall, the risk ratios (RR) of cognitive decline in patients with AF have been reported as between 0.8 and 8.1 compared with those without AF. Duration of AF is an important factor for dementia. AF is also a strong risk factor of ischemic stroke and approximately 80% of embolic strokes are caused by non-valvular AF. On the other hand, stroke itself is a risk factor for cognitive decline and dementia. Although prior symptomatic stroke is thought to be part of the cause of dementia in patients with AF, the association between AF and cognitive decline was found even in patients without prior overt stroke. In addition, general risk factors for cardiovascular diseases such as hypertension, diabetes, and aging have much in common for the development of AF, stroke, and dementia, including Alzheimer’s disease and vascular dementia. Therefore, the CHADS2 and CHA2DS2-VASc scores, which originally determined the risk stratification of thromboembolism in patients with AF, are also significant predictors of dementia. The triangle including AF, stroke, and...
dementia is quite complicated, and these angles and common risk factors are able to become confounders of each other (Figure). Therefore, long-term vascular changes and the interaction of the degenerative duo to multiple factors are thought to be possible mechanisms of dementia in patients with AF. Silent cerebral infarction (SCI) could be a candidate for mediator of the onset of dementia.

Association Between AF and SCI
Although SCI and white matter lesions on brain magnetic resonance imaging (MRI) have been thought of as clinically unimportant in patients with old age, a meta-analysis revealed that white matter lesions are associated with dementia, subsequent stroke, and death. In this issue of the Journal, Senoo et al focus on the relationship between AF and SCI in a meta-analysis of 4 Asian and 6 non-Asian studies in which SCI was diagnosed with MRI. These authors demonstrate that AF was significantly associated with SCI in both the Asian (RR 2.24, 95% confidence interval [CI] 1.26–3.99) and non-Asian (RR 1.85, 95% CI 1.65–2.08) populations. Overall, the RR was 2.02 (95% CI 1.35–2.48) and no racial difference was found. Although the association between AF and cognitive decline or dementia is difficult to conclude directly from the present study, it can be easily speculated, because SCI is a risk factor of dementia. In addition, the authors also list microbleeds, impaired cardiac function, and subsequent reduced cerebral perfusion as possible mediating mechanisms of dementia in patients with AF.

Anticoagulation Therapy as a Therapeutic Target for Cognitive Decline or Dementia
Although the study by Senoo et al clearly demonstrated the association between AF and SCI, it remains unclear whether anticoagulation therapy with warfarin or DOAC can reduce the development of SCI in order to reduce the risk of cognitive decline or dementia. In previous studies in which warfarin was used did not always show a beneficial effect for reducing cognitive decline, because the effect of warfarin depended on the time in therapeutic range of the international normalized ratio of prothrombin time. A subsequent recent report from the Clinical Pharmacist Anticoagulation Service (CPAS) has shown promising results for DOAC reducing new-onset dementia in patients with AF. The incidence of stroke or transient ischemic attack (adjusted hazard ratio [HR] 0.47, 95% CI 0.32–0.68) and major hemorrhage (adjusted HR 0.70, 95% CI 0.57–0.80) in patients treated with DOAC was significantly lower than in those treated with warfarin. The long-term incidence of dementia in patients treated with DOAC was also lower than in those taking warfarin (0.3% vs. 0.7%, P=0.03). It seems hopeful, but all-cause death was not significantly different between the DOAC and warfarin groups. Because this study was observational, not a randomized clinical trial, the effect of DOAC for dementia cannot be referred. Further research is necessary to confirm whether dementia can be a novel therapeutic target of anticoagulation therapy in patients with AF and to determine if DOAC is really beneficial for reducing cognitive decline and preventing new-onset dementia.

Concluding Remarks
According to previous reports by investigators, use of anticoagulants, including warfarin, can bring about a positive net clinical benefit. However, important issues in an individual patient with AF who is receiving an anticoagulant must be the ADL, QOL, and/or life prognosis. Contemporary evidence of anticoagulants, including DOACs, has not yet sufficiently determined if anticoagulation therapy can give the best net clinical outcome to patients with AF.

Disclosures
Authors have potential conflicts of interest to disclose. E.K. has received remuneration from Ono Pharmaceutical and Bristol-Myers Squibb, and T.N. has received remuneration from Nippon Boehringer Ingelheim and Daiichi-Sankyo.

References