Most of the previous observational studies suggest that estrogen replacement therapy reduces cardiovascular risks, but meta-analysis of randomized clinical trials showed increased risk of hormone replacement therapy for cardiovascular events. Both hypercoagulability and upregulation of inflammation-sensitive proteins could underlie the increased risk of estrogen treatment in coronary artery disease (CAD) and ischemic stroke. Recent selective estrogen receptor modulators (SERMs) have been widely used for prevention of breast cancer and bone fracture related to osteoporosis. These SERMs include tamoxifen, raloxifene, arzoxifene and lasofoxifene. In meta-analysis, women receiving any SERM had a lower rate of cardiovascular events.

Figure. Effect of selective estrogen receptor modulators (SERMs) on cardiovascular disease is mediated through protective and adverse actions. Protective action can be mediated by lowering the levels of low-density lipoprotein-cholesterol and high-sensitivity C-reactive protein. These effects are presumably antiatherogenic and diminish plaque inflammation, as well as reducing the risk of cardiovascular events. In contrast, adverse action is mediated mainly by coagulopathy, as shown in the increase in D-dimer. Coagulopathy will increase the risk of atherothrombosis, particularly ischemic stroke through thrombus formation in the left atrium in atrial fibrillation and the patent foramen ovale in the presence of deep vein thrombosis. Overall, the effect of SERM on cardiovascular events will be determined by the relationship between these 2 actions.
breast cancers than those receiving a placebo. All SERMs have been shown to increase the risk of venous thrombosis, but it remains controversial whether SERMs are beneficial or adverse for cardiovascular events. Furthermore, there are few reports in Asian women receiving a SERM for cardiovascular risks.

In this issue of the Journal, Yang et al report that tamoxifen use was associated with reduced risk of cardiovascular events in 3,690 female subjects in Taiwan, which is in contrast with a previous meta-analysis showing that women with breast cancers who were treated with tamoxifen had an 82% increased risk of ischemic stroke. What causes this discrepant result about tamoxifen treatment for cardiovascular disease?

The relationship between antithrombotic or antiatherosclerotic factors and procoagulant activity would explain the effect of SERMs on cardiovascular events (Figure). In fact, estrogen replacement treatment has been shown to increase both C-reactive protein (CRP), a marker of vessel inflammation, and D-dimer, a marker of coagulopathy. In contrast, neither tamoxifen or raloxifene treatment has shown any effect on D-dimer levels. Furthermore, Cushman et al showed that tamoxifen treatment reduced CRP by 26% and fibrinogen by 22%. In addition, tamoxifen was found to be a potent inhibitor of acyl-CoA:cholesterol acyltransferase (ACAT1), thus decreasing the level of low-density lipoprotein cholesterol (LDL-C). Therefore, it seems likely that SERMs have a better influence on atherothrombosis than estrogen replacement therapy.

However, a recent meta-analysis of SERMs showed that treatment had no effect on cardiovascular events, but all SERMs were associated with increased risk of venous thromboembolic events. Only lasofoxifene treatment has been shown to reduce major cardiovascular events in postmenopausal women with osteoporosis. In the PEARL study, 8,556 women with a mean age of 67 years were allocated to placebo or lasofoxifene (0.25 or 0.5 mg/day) and followed for 5 years. Treatment with lasofoxifene 0.5 mg/day significantly reduced the risk of both CAD and stroke by approximately 30%. Lasofoxifene treatment also significantly reduced the LDL-C and high-sensitivity CRP (hsCRP) levels by 10–15%. Although it remains unclear why only lasofoxifene among the SERMs showed beneficial effects on stroke and CAD in randomized control trials, Yang et al suggest that not only lasofoxifene but also tamoxifen and other SERMs may have beneficial effects on atherothrombosis.

When we consider the mechanisms underlying the effect of SERMs on cardiovascular events, the difference in etiology between CAD and stroke has to be taken into account. In CAD, atherothrombosis plays central role in disease development, thus reduction of LDL-C and the inflammation marker, hsCRP, is an important strategy. However, stroke includes ischemic and hemorrhagic types, and ischemic stroke also consists of cardioembolic, atherothrombotic and lacunar infarction. Atrial fibrillation is the major risk factor in ischemic stroke, but not myocardial infarction, and hypercoagulability could enhance thrombus formation in the left atrium in atrial fibrillation. The presence of deep vein thrombosis in patients with SERM treatment could cause paradoxical embolic cerebral infarction, but it rarely leads to CAD. Because approximately 15% of the general population has a patent foramen ovale, previous findings that estrogen and tamoxifen treatment increase the risk of ischemic stroke could be explained in part by the presence of atrial fibrillation, deep vein thrombosis and paradoxical cerebral embolism.

In clinical practice, patients who receive SERMs need to be carefully managed for deep vein thrombosis. The D-dimer level could predict both risk and severity of cardiac embolism in atrial fibrillation and reflect the anticoagulation status. Thus, measurement of not only D-dimer but also LDL-C and hsCRP levels would be recommended for prevention of CAD and stroke. Patients with a high level of D-dimer at baseline should be carefully treated with a SERM because these patients are likely to have accelerated thrombus formation and increased risk of deep vein thrombosis and ischemic stroke after SERM treatment. We do not have therapeutic strategies specific for inhibition of vessel inflammation. If SERM treatment inhibits plaque inflammation through a specific mechanism, SERMs might be a potential regimen for prevention of atherothrombosis.

References