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EDITORIAL COMMENT

Aspirin for Primary Prevention

The Importance of the Regional Difference of Drug Effect*

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Aspirin is the mainstream drug for established ischemic heart disease. For patients with myocardial infarction and the patients receiving coronary intervention regardless of stent use, aspirin is widely prescribed, often with other more potent drugs like $P2Y_{12}$ inhibitors to prevent secondary cardiovascular events.[1-3] However, aspirin use for primary prevention in high-risk patients has been discussed for a long time.[4] When receiving aspirin therapy, the benefit of decreasing cardiovascular events is expected, but there is a concern about the increase in bleeding. Therefore, for patients to receive the merit, the risk reduction of cardiovascular events commensurate with the risk increased bleeding is a prerequisite for antithrombotic therapy.

Diabetic or elderly patients, who are associated with a higher risk of experiencing cardiovascular events, have been the subject of a clinical trial evaluating the primary prevention with aspirin.[5-7]

The risk difference between ethnicities for Asians and Westerners was well known as the "East-Asian paradox": the incidence of ischemic disease or cardiovascular events in Asia is reported lower than that in United States or Europe, and on the other hand, the incidence of bleeding events is higher, the prevalence of CYp2C19 poor metabolizer is reported.[8] The appropriate intensity of antithrombotic therapy in East Asia might be lower than that amount that is applied to Westerners. However, the hypothesis is derived from reviews or comparisons of each clinical research, and there is limited solid evidence supporting it.[9] There is no evidence comparing ethnicities around primary prevention.

In this issue of *JACC: Asia*, Kim et al[10] reported the result of a meta-analysis focused on the difference in the effect of aspirin for primary prevention between East Asians and Westerners. The authors conducted a systematic review of the research evaluating the effect of low-dose (≤100 mg daily) aspirin on the cardiovascular endpoints for patients without a previous history of cardiovascular disease including heart failure. After the full review, 11 studies (2 from East Asia and 9 from Western countries) were finally included in the analysis, and the involved number of patients was over 130,000. As a result, aspirin use was associated with a significant 10% risk reduction of major cardiac adverse events, driven by the 11% risk reduction of myocardial infarction and stroke, with the cost of major bleeding, which is a relative increase of 58% bleeding, including a 31% increase of intracranial hemorrhage and a 76% increase of gastrointestinal bleeding.

As for the difference between ethnicities, the risk reduction of cardiovascular events was comparable between East Asians and Westerns (P interaction = 0.721); on the other hand, the increased risk of bleeding events was more evident in East Asians compared with Westerners, and there was a significant interaction (P interaction < 0.001). With the simple addition of the beneficial risk difference of aspirin for cardiovascular events to the harmful risk difference for a bleeding event, the net number needed to treat was 124 in East Asians and 1,389 in Westerners; both were on the side of harmful effect increasing bleeding events and indicate the number of treated patients associated with 1 bleeding event increase.

There are some limitations of the current study. The number of studies included on East Asians was small and not well balanced to compare with Westerns. Moreover, because the 2 studies included were both reports from Japan, there is a concern about handling the current data as "East Asians"; to demonstrate the effect of low-dose aspirin in this

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region, studies from countries other than Japan, such as China or Korea, must be added. The Japanese are unique even in Asian countries for the small stature and the more prevalence of hypertensive patients. The approved dosage of $P2Y_{12}$ inhibitors is different from other countries, eg, the maintenance dose of prasugrel is 3.75 mg in Japan, which is one-third the dose of other countries.[11] The lower event rate and the smaller number of patients included in the study of East Asians were associated with the wider CI, and the study is comparably underpowered to describe the risk difference, especially each component of a cardiovascular event. Another point to note is that the effect of aspirin varies depending on the time when each clinical trial is conducted and the concomitant use of other drugs. In the older study, drugs that prevent the progression of atherosclerosis like high-intensity statins or more effective hypoglycemic agents were thought to currently not be widely used. Such drugs might have led to an attenuating effect of the primary prevention of aspirin.

In the area of post-percutaneous coronary intervention antithrombotic therapy, there is some evidence favoring early discontinuation of aspirin and monotherapy of $P2Y_{12}$ inhibitor after percutaneous coronary intervention, and in patients requiring anticoagulation therapy, the dual antithrombotic therapy with oral anticoagulants and $P2Y_{12}$ inhibitors omitting aspirin demonstrated less clinical events.[12-14] The role of aspirin in secondary prevention as well as primary prevention is diminishing. However, we do not know the effect of aspirin on the patients between primary and secondary prevention, ie, patients who have already moderate coronary stenosis that has not led to myocardial infarction or revascularization.

The effect of antithrombotic therapy is different 1 by 1, related to ethnicity, gender, body weight or body mass index, liver dysfunction, and other comorbidities. Different from statins or other medications with fewer side effects, antithrombotic therapy always has to worry about the inevitable side effects of bleeding, and the appropriate strategy should be considered carefully in East Asians. Clinical research for the local population is required, and we have to continue the research for the patients in front of us.

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