Preface

Stroke is the leading cause of long-term disability worldwide, and represents an enormous emotional and socioeconomic burden not only for patients but also for families, caregivers and health services. In developed countries, about 80% of stroke events are attributed to focal ischemia caused by occlusion of the large or small vessels of the brain. Although treatment with intravenous recombinant tissue plasminogen activator in the hyperacute phase (<3 h of onset) and intensive care and management in stroke units by a specialist stroke team are widely recognized to significantly improve the outcome of stroke patients, the most important and effective measure to reduce such a burden is primary and secondary prevention of cardiovascular diseases including stroke among individuals who are at high risk.

The use of antiplatelet agents such as aspirin has been widely recognized to decrease the risk of cardiovascular events by 22% in high-risk patients. Based on the meta-analysis performed by the Antithrombotic Trialists' Collaboration, antiplatelet drugs are strongly recommended as the first-choice treatment, in addition to appropriate control of several cardiovascular risk factors such as hypertension, diabetes mellitus, or smoking. It has also been demonstrated, however, that antiplatelet therapy significantly increases the risk of bleeding, although benefits exceed hazards in most high-risk patients.

The ideal antiplatelet regimen for the prevention of atherothrombotic cardiovascular diseases should have the selective effect of suppressing platelet function without increasing bleeding tendencies. Roughly, there are 3 different types of antiplatelet drugs: one that just decreases platelet function, such as aspirin or clopidogrel, one that blocks the binding site of the platelet with fibrinogen,

such as GPIIb/IIIa inhibitors, and one that affects the platelet as well as the attachment of the platelet to the endothelium. Drugs of the third type are thought to be dipyridamole and cilostazol.

The report of the European Stroke Prevention Study demonstrated that the combination of low-dose aspirin and the extended-release form of dipyridamole was more effective than aspirin or dipyridamole alone without increasing hemorrhagic complications. The Cilostazol Stroke Prevention Study conducted in Japan reported that cilostazol (phosphodiesterase inhibitor, 100 mg, twice a day) significantly reduced the recurrence rate of ischemic stroke (relative risk reduction of 41.7%, $p = 0.0015$) as compared with inactive placebo during the mean follow-up of 2 years, and did not increase the incidence of intracerebral hemorrhage (4 intracerebral hemorrhages in the cilostazol group and 7 in the placebo group). It should be noted that more than 70% of the subjects in this trial had a history of lacunar infarction, which has a potential risk of intracerebral hemorrhage because of the presence of hypertensive vascular pathology such as angioneurosis. The reason for such favorable results is supposed to be due to protective effects of this drug on the endothelium, which have been found by animal experiments, in addition to platelet antiaggregant function. Such dual effects are expected to become a breakthrough for antiplatelet therapy. The results of a large-scale double-blind trial for a comparison with aspirin (CSPS-II), which is now being conducted in Japan, are eagerly awaited.

In this special supplement to *Cerebrovascular Diseases*, entitled 'Antiplatelet Therapy in Atherothrombosis', five distinguished guests are invited to give overviews

of or to review the state of the art of prevention of stroke and coronary artery disease with particular emphasis on antiplatelet therapy.

In the opening article of this issue, Dr. Caplan beautifully describes the history of the use of antiplatelet agents, and the mechanism and characteristics of each antiplatelet presently used. He concludes that effects on leukocytes and the endothelium may facilitate the capacity of agents or combinations to prevent brain infarction.

Dr. Uchiyama and his colleagues provide an overview of new modalities and aspects of antiplatelets, and refer to basic mechanisms of action of each agent, and to the limitation of effects of aspirin presenting their own data concerning aspirin resistance. They further describe future perspectives of antiplatelets that are expected to be more effective and safer for the prevention of atherothrombosis.

Dr. Shinohara reviews the regional differences in incidence and management of stroke around the world. He concludes that differences in stroke prevalence and the proportion of stroke subtypes between Japan and Western countries are getting smaller, probably due to changes in lifestyle in Japan, particularly in diet, although the difference in the ratio of stroke to ischemic heart dis-

eases is still present. He also emphasizes that recommended or appropriate doses of antithrombotic agents are lower in Japan than in Western countries.

As a contributor on coronary heart diseases, Dr. Holmes describes the importance of dual antiplatelet therapy, i.e. clopidogrel in addition to the standard of aspirin, in patients with acute coronary syndrome, particularly in those who undergo placement of intracoronary drug-eluting stents, which are used in approximately 90% of all interventional procedures. Dual antiplatelet therapy is recommended to continue for 3–6 months after stenting depending on the type of stents used.

The final article includes discussions on the polypill strategy and prevention clinics for stroke prevention by Dr. Amarenco. He emphasizes that the setup of comprehensive prevention clinics, in which well-trained specialized nurses play important roles in improving patients' compliance with taking drugs prescribed by doctors, may be more important and effective than general polypill distribution.

The editors hope the articles in this issue provide useful information for readers and are helpful in daily practice when treating atherothrombotic diseases.

T. Yamaguchi, Osaka