Desirable antiplatelet therapy from the viewpoint of action mechanism—Antiplatelet effect achieved by functional preservation of endothelial cells—

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Platelets play an important role in the formation of arterial occlusive thrombi resulting the onset of atherothrombotic diseases such as ischemic stroke and acute myocardial infarction. Although accumulation of platelet at site of endothelial damage mostly due to rupture of atheroma under arterial blood flow condition is believed to be the initial event leading to the onset of atherothrombotic diseases, pre-conditioning state of platelets resulted by the interaction with endothelial cells in whole body is the important factor determining whether the thrombi grow big enough to occlude the arteries or not. So far, most of antiplatelet agents, including GPIIb/IIIa antagonists, were developed as direct inhibitor of platelet function. Since platelet also play crucial roles in the formation of hemostatic plug, strong antiplatelet agents always accompany with high risk of bleeding complication. If pre-conditioning of platelets, which is achieved by their interaction with endothelial cells expressing more adhesive proteins by various stimulation, can be prevented by preservation of endothelial cell functions, prevention of atherothrombotic disease without increased risk of bleeding can be expected because circulating blood contain full functioned but not partly activated platelet. Recently published clinical trial of cilostazol stroke prevention study done in Japan might suggest that cilostazol, which not only inhibit platelet function, but also improve endothelial cell function, can achieve strong antithrombotic effects without increase the risk of bleeding complication.

Evaluation of antiplatelet therapy—Event prevention and risk of hemorrhage

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Aspirin reduces the odds of the composite outcome of stroke, MI, or vascular death in all high-risk patients with symptomatic atherosclerosis by about 23%. It reduces the odds of stroke alone by about 25%. In trials limited to stroke/TIA patients, aspirin reduced the odds of the composite outcome of stroke, MI, or vascular death by only 16%. In stroke/TIA patients, ticlopidine is more effective than placebo, but has at least a 5% incidence of bothersome adverse effects, a 0.9% incidence of severe neutropenia and a small risk of TTP. The serious side effects of ticlopidine have led many experts to largely abandon its use. In stroke patients clopidogrel produces a benefit similar to aspirin for prevention of stroke or the outcome cluster of stroke, MI, or vascular death. The safety profile of clopidogrel is comparable to aspirin and safer than ticlopidine. Compared to placebo, dipyridamole in combination with aspirin reduces the risk of the composite outcome of stroke, MI, or vascular death in patients with symptomatic atherosclerosis by about 30%. In comparison with placebo, extended-release dipyridamole in combination with aspirin reduced the risk of stroke in patients with stroke/TIA by 37% in ESPS-2, which is nearly identical to the 38% stroke risk reduction that was obtained with the combination of standard dipyridamole and aspirin in a previous similar trial (ESPS-1). When compared with aspirin, the combination of extended-release dipyridamole produced a 23% reduction in stroke. Although inadequately studied, the combination does not appear to provide benefit over aspirin alone for reducing MI.

No study has performed a direct comparison of clopidogrel with the combination of

extended-release dipyridamole and aspirin. However, each of these two therapies has been directly compared with aspirin in cerebrovascular patients. The comparisons of these antiplatelet trials and drugs are indirect and thus must be interpreted far more cautiously than direct comparisons. The performance of antiplatelet drugs in separate trials varies because patient populations and protocols differ, and unrecognized biases may exist. No trial has performed a direct comparison between these alternative agents and physicians must make comparisons and clinical judgments based on the available data. Clearly, the relative benefit and safety of the various antiplatelet drugs, for various patients and vascular events, will remain uncertain unless very large trials directly comparing them are conducted.

No clinical trials have directly addressed the issue of subsequent therapy for patients who experience recurrent episodes of brain ischemia while taking aspirin. Many experts select an alternative antiplatelet drug. Although some experts add clopidogrel to aspirin, the benefits and safety of this combination for long-term therapy in stroke patients has been tested in the MATCH trial which arose concerns about the safety of this association in patients with ischemic stroke.

MATCH was a secondary prevention trial in patients with ischemic stroke or brain infarction with TIA within 3 months of randomization and with one of the following entry criteria : diabetes mellitus, past coronary heart disease, recurrent stroke on aspirin, peripheral arterial disease. Aspirin (A) was tested against placebo on the background of clopidogrel (C) in both arms. So it was C + A vs. C. As a consequence of the entry criteria stipulating the presence of multiple vascular risk factors, the MATCH population included 70% diabetics, 54% with lacunar stroke (small vessel disease) plus 10% strokes of unknown cause (both at low risk of recurrence). Only 30% of patients had large artery atherosclerotic disease. Few pa-

tients (5%) had a past history of coronary heart disease because most cardiologists had difficulty with the idea that their patients were maintained on a single antiplatelet agent. The primary end-point (MI, ischemic stroke, vascular death and rehospitalization for acute ischemic events) after 18 months was 16.73% in the C arm and 15.70% in the C + A arm, yielding a nonsignificant RRR of 6.4% (-4.6 to 16.3%) ($p = 0.244$) in favor of C + A. The same pattern was seen in all subgroups, including the large artery atherosclerotic group. On treatment analysis showed a RRR of 9.5% (-2.0 to 19.6%) favouring C + A ($p = 0.10$). On the safety side, there was an increase in life-threatening bleeding (any fatal bleeding, symptomatic intracranial hemorrhage, drop in hemoglobin of more than 5g/dl, or significant hypotension with the need of inotropes, or requiring transfusion of more than 4 units of RBC or equivalent of whole blood) with 1.3% in the C arm and 2.6% in the C + A arm (absolute difference of 1.26% (0.64 to 1.88) $p < 0.001$) ; there were 25 symptomatic intracranial bleeds in the C arm and 40 in the C + A arm.

Several issues have been discussed about the MATCH trial design. The trial may not have been adequately powered to found the difference the investigators were looking for because the event rate was lower than expected, 20% of patients recruited may have been resistant to aspirin, 70% of patients were diabetics (a population in which antiplatelet therapy has never been proven effective, and in which the effect of antihypertensive therapy is so important in terms of event reductions that adding any other treatment may lead to a ceiling effect), 54% of patients had lacunar stroke (a low risk population, more prone to intracranial bleeding).

Therefore, because of the very special population included in MATCH, and because of important positive results in other populations with high thrombogenicity such as PCI, the hypothesis of a favorable net benefit of C + A over

A or over W still needs to be thoroughly tested in other stroke or high risk populations.

The Cilostazol Stroke Prevention Study (CSPS) was a placebo-controlled double-blind trial for secondary prevention of 1067 patients with cerebral infarction, which included 75% of lacunar stroke patients. After a 3-year follow-up, the primary outcome (recurrence of cerebral infarction) was reduced by 41.5% on cilostazol compared to placebo ($p=0.015$) with a positive interaction with the lacunar stroke patient subgroup.

Current western country guidelines do not include yet these results. In patients who have experienced a non-cardioembolic stroke or TIA (i.e., atherothrombotic, lacunar or cryptogenic) the recommended treatment is an antiplatelet agent (Grade 1A). Aspirin at a dose of 50 – 325 qd, the combination of aspirin, 25 mg and extended-release dipyridamole, 200 mg bid, or clopidogrel (75 qd) are all acceptable options for initial therapy.

For patients who are allergic to aspirin, the recommended treatment is clopidogrel (Grade 1C+), but recent data have shown that aspirin plus esomeprazole is preferable to clopidogrel alone, but this study did not evaluate the benefit of clopidogrel plus omeprazole in that situation.

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