Cilostazol Versus Aspirin for Secondary Prevention of Vascular Events After Stroke of Arterial Origin

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For the secondary prevention of stroke of arterial origin, aspirin is the most widely studied and prescribed agent the world over. Cilostazol is both an antiplatelet and vasodilating agent. This agent has been used mainly in Asian populations with noncardioembolic stroke and no clinically evident cardiac disease.

Methods

Objectives

The objective of this review was to determine the relative effectiveness and safety of cilostazol compared directly with aspirin in the prevention of stroke and other serious vascular events in patients at high vascular risk for subsequent stroke, those with previous transient ischemic attack, or ischemic stroke of arterial origin.

Search Strategy

We searched the Cochrane Stroke Group Trials Register (last searched September 2010), the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2009, Issue 4), MEDLINE (1950 to May 2010), and EMBASE (1980 to May 2010). In an effort to identify further published, ongoing, and unpublished studies, we searched journals, conference proceedings, and ongoing trial registers; scanned reference lists from relevant studies; and contacted trialists and Otsuka Pharmaceutical Co Ltd.

Selection Criteria

We selected all randomized controlled trials comparing cilostazol with aspirin in which participants were treated for at least 1 month and followed systematically for development of vascular events (stroke, myocardial infarction, or vascular death).

Data Collection and Analysis

Two review authors independently selected trials for inclusion, extracted the data, and assessed trial quality. We calculated the treatment effect for each outcome in terms of risk ratio by using the Mantel-Haenszel method.

Results

We included 2 trials from Japan and China, which included a total of 3477 participants with a history of ischemic stroke of arterial origin. These trials were of good quality. Compared with aspirin, cilostazol was associated with a significantly lower risk of composite outcome of vascular events (stroke, myocardial infarction, or vascular death; relative risk, 0.72; 95% CI, 0.57 to 0.91; Figure). The proportional benefit of cilostazol over aspirin on the outcome of "strokes of any type (ischemic or hemorrhagic)" was 33% (95% CI, 14% to 48%) compared with aspirin.

In relation to hemorrhagic stroke during follow-up, cilostazol was associated with a risk reduction of 74% (95% CI, 45% to 87%) compared with aspirin. In safety analyses, aspirin overall caused more bleeds with extracranial hemorrhage significantly higher in patients on aspirin compared with cilostazol (relative risk, 0.74; 95% CI, 0.61 to 0.90). Cilostazol was significantly associated with minor adverse effects, namely headache, gastrointestinal intolerance, palpitation, dizziness, tachycardia, angina, and cardiac failure.

Conclusions

This review of the available trials in the Asian population shows cilostazol to be superior to aspirin in the secondary prevention of vascular events (stroke, myocardial infarction, or vascular death), strokes of all type (ischemic or hemorrhagic), and hemorrhagic stroke subtype alone after stroke of arterial origin. Cilostazol is associated with fewer major bleeding events than aspirin.

Implications for Practice

Cilostazol is a useful agent for the secondary prevention of stroke of arterial origin in Asians who do not have significant

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Figure. Meta-analysis of randomized trials comparing aspirin versus cilostazol in patients with ischemic stroke of arterial origin. Results are expressed as Mantel-Haenszel risk ratios and 95% CI with fixed-effects model. Relative risk $<1$ suggests that cilostazol was better than aspirin. From Kamal AK, Naqvi I, Husain MR, Khealani BA. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. Cochrane Database Syst Rev. 2011;1:CD008076. Reproduced with permission from John Wiley & Sons, Ltd. CASISP indicates Cilostazol vs Aspirin for Secondary Ischemic Stroke Prevention; CSPS II, Cilostazol Stroke Prevention Study 2; MI, myocardial infarction.
overt cardiac disease. It has a favorable major side effect profile (lower risk of intracranial hemorrhage compared with aspirin). This must be balanced against the daily cost of cilostazol, which is more expensive than aspirin, an important consideration when prescribing lifelong medications in low- and middle-income country patients.

**Implications for Research**
Future randomized trials in patients with ischemic stroke are needed to determine whether the benefit observed in reduction of vascular events after stroke applies in non-Asian populations as well and across all ischemic stroke subtypes.

**Disclosures**
None.

**Key Words:** antiplatelet agents ■ Asians ■ aspirin ■ cilostazol ■ ischemic stroke ■ secondary prevention ■ recurrent vascular events
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