

A new antiplatelet agent Cilostazol — what is the evidence for its use and tolerability?

Shaista Anwar Siddiqi,¹ Ayeesha Kamran Kamal²

Stroke Fellow,¹ Stroke Program,² Section of Neurology, Department of Medicine, Aga Khan Hospital, Karachi.

What is Cilostazol?

Cilostazol is an antiplatelet agent that inhibits phosphodiesterase III in platelets and vascular endothelium. It has also been shown to improve serum lipid profile by lowering triglycerides and increasing high-density lipoprotein cholesterol. Apart from cardiovascular or peripheral artery disease, Cilostazol has been used in ischaemic stroke patients to reduce recurrent stroke.

What is the data on efficacy of Cilostazol versus placebo in prevention of atherothrombosis?

A meta-analysis of Cilostazol versus placebo in atherothrombotic diseases including cardiovascular, cerebrovascular or peripheral artery disease showed that Cilostazol was associated with significant reduction (14%) in occurrence of all atherothrombotic events. Of all these vascular events, the major reduction was seen in cerebrovascular events (42%) with only 1% reduction in the cardiac events. In addition, this effect was not associated

with any increased risk of bleeding complications.

What is the data on efficacy of Cilostazol versus Aspirin in secondary prevention of stroke?

Till date, two large trials of Cilostazol have been done versus aspirin to address its role in secondary prevention of stroke. These are CSPS II and CASISP which were done on Japanese and Chinese patients respectively.

CASISP recruited 720 patients (mean age 60 years, over 60% male) with an ischaemic stroke within 1-6 months and randomized these patients to receive either Cilostazol or aspirin. The average follow up was 12-18 months. All patients had ischaemic infarctions (more than one in 60% cases in both the groups) on the MRI while 39% patients had evident cerebral microbleeds. Overall, the bleeding events were 4% and 9% in Cilostazol and aspirin respectively. Both symptomatic and asymptomatic cerebral haemorrhages were seen more in the aspirin group than Cilostazol group. Notably, all the symptomatic

haemorrhages were noted at the site of previous microbleeds. In the initial 6 months, both drugs have the same effect on reduction of stroke recurrence but after 6 months, Cilostazol was more effective than aspirin causing 38% relative risk reduction in stroke. Of all the recurrent stroke events, 25% in the aspirin group and 8% in the Cilostazol group were related to cerebral haemorrhage.

CSPS II recruited 2757 patients with an established non-cardio embolic ischaemic infarction within past 26 weeks. These patients were randomized to receive either Cilostazol or aspirin and were followed up for a mean of 29 months. Overall, lacunar infarction was more common and 30% patients were randomized within 28 days of index event. Over half of the patients in both the groups were receiving aspirin at the time of randomization. The primary endpoint i.e. the first occurrence of new stroke (cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage) as well as the secondary composite endpoint (stroke, transient ischaemic attack, angina pectoris, myocardial infarction, heart failure or hospitalization for haemorrhage) was significantly less in Cilostazol group than aspirin group. Cilostazol reduced the composite outcome by 20% as compared to aspirin. Also, the haemorrhagic events (cerebral haemorrhage, subarachnoid haemorrhage, haemorrhage requiring hospitalization) were also more common in aspirin group than Cilostazol group.

In a recent metanalysis performed by this group, Cilostazol was found to be beneficial especially due to its side effect profile in the reduction of intracerebral haemorrhage.

Conclusion

Cilostazol is promising as an option for the secondary prevention of vascular events after a non-cardio

embolic ischaemic stroke and in patients who do not have active concurrent cardiac ischaemia. It may be useful in patients who are at increased risk of CNS haemorrhage. Studies have also been done in broader populations with atherothrombotic disease which have shown modest efficacy. However, the cost and the tolerability of the drug may limit its use as a routine antiplatelet agent. Additional studies are needed in South Asian and other populations to further the evidence on its routine applicability .

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Suggested reading

1. Y Huang, Y Cheng, J Wu, Y Li, E Xu, Z Hong, on behalf of the Cilostazol versus aspirin for secondary ischaemic stroke prevention (CASISP) cooperation investigators. Cilostazol as an alternative to aspirin after ischaemic stroke: a randomised, double-blind, pilot study. *Lancet Neurol* 2008; 7: 494-9.
2. Y Shinohara, Y Katayama, S Uchiyama, T Yamaguchi, S Handa, K Matsuoka, for the CSPS 2 group. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol* 2010; 9: 959-68.
3. S Uchiyama, BM Demaerschalk, S Goto, Y Shinohara, F Gotoh, WM Stone et al. Stroke Prevention by Cilostazol in Patients with Atherothrombosis: Meta-analysis of Placebo-controlled Randomized Trials. *J Stroke and Cerebrovascul Dis* 2009; 18: 482-90.
4. 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. Issue 1.