ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International
Editor-in-Chief: Nancy E. Epstein, MD, NYU Winthrop Hospital, Mineola, NY, USA.
SNI: Review of Randomized Controlled Trials Editor
Benjamin W. Y. Lo, MD
Departments of Neurosurgery and Neurointensive Care, Lenox Hill Hospital, New York

SNI
Open Access

Editorial

Review of Toyoda K, *et al*. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischemic stroke in Japan. Lancet Neurol. 2019 Jun;18(6):539-548

Benjamin W. Y. Lo[1], Satoru Miyawaki[2], Hitoshi Fukuda[3], Masaomi Koyanagi[4]

[1]Departments of Neurosurgery and Neurointensive Care, Lenox Hill Hospital, New York, [2]Department of Neurosurgery, Faculty of Medicine, The University of Tokyo, Tokyo, [4]Department of Neurosurgery, Kokura Memorial Hospital, Fukuoka, [3]Department of Neurosurgery, Kochi University, Kochi, Japan

E-mail: *Benjamin W. Y. Lo - lo_benjamin@hotmail.com; Satoru Miyawaki - satorumiyawaki@gmail.com; Hitoshi Fukuda - fukudaharpseal@gmail.com; Masaomi Koyanagi - koyanagm@gmail.com

***Corresponding author:**
Benjamin W. Y. Lo, MD,
Departments of Neurosurgery and Neurointensive Care,
Lenox Hill Hospital,
100 E 77th Street,
New York, NY 10075.

lo_benjamin@hotmail.com

Received : 03 March 20
Accepted : 04 March 20
Published : 28 March 20

DOI
10.25259/SNI_83_2020

Quick Response Code:

ABSTRACT

Background: Prior meta-analyses showed that treatment with cilostazol, with or without aspirin, significantly reduced the incidence of recurrent ischemic stroke, occurrence of hemorrhagic stroke, and frequency of other serious vascular adverse events.

Methods: This review highlights the value of the randomized controlled trial (RCT) by Toyoda *et al.* entitled, "Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischemic stroke in Japan: a multicenter, open-label, randomized controlled trial." Here, dual therapy consisting of cilostazol and another antiplatelet agent was used to prevent secondary ischemic stroke in high-risk Japanese patients.

Results: Patients on dual therapy consisting of cilostazol/aspirin or cilostazol/clopidogrel had significantly lower frequencies of recurrent stroke. However, there were significant differences in the incidence of attendant hemorrhagic complications utilizing mono or dual therapy.

Conclusion: This RCT demonstrated the safety of dual therapy, consisting of cilostazol/aspirin or cilostazol/clopidogrel, in preventing secondary ischemic stroke in a high-risk Japanese population. Further studies are required to generalize these findings to other patient populations worldwide.

Keywords: Antiplatelet agent, Cilostazol, Stroke

UTILITY OF CILOSTAZOL

Prior meta-analyses showed cilostazol with/without aspirin therapy, approved for the prevention of secondary stroke in Asia, significantly reduced the incidence of recurrent ischemic stroke, occurrence of hemorrhagic stroke, and serious vascular events (e.g. myocardial infarction and/or vascular deaths).[1,2] Here, we reviewed the randomized controlled trial (RCT) by Toyoda *et al.* entitled, "Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischemic stroke in Japan: a multicenter, open-label, randomized controlled trial".

This study highlights the value of cilostazol combined with other antiplatelet agents (e.g., aspirin or clopidogrel) in the secondary prevention of ischemic stroke in high-risk patients in Japan.

PHYSIOLOGY OF CILOSTAZOL

Cilostazol is a selective phosphodiesterase 3A inhibitor which prevents platelet aggregation through increased intracellular cAMP that inhibits phospholipase and cyclooxygenase activities, reducing thromboxane A2 production, and platelet aggregation. Increased cAMP and protein kinase A levels in vascular smooth muscle cells also prevent myosin light chain kinase-mediated vasoconstriction. Further, cilostazol also improves endothelial function, reendothelialization, and vascular smooth muscle cell proliferation.[1]

METABOLISM OF CILOSTAZOL

Cilostazol is metabolized by the cytochrome P450 system. Inhibitors of cytochrome P450 system (such as omeprazole, diltiazem, erythromycin, itraconazole, and ketoconazole) increase active metabolites of this medication, necessitating cilostazol dosage reduction.

SIDE EFFECTS OF CILOSTAZOL

Cilostazol's most common side effects are headaches, tachycardia (contraindicated for those with heart failure), diarrhea, and heat intolerance.

Exclusion criteria

Exclusion criteria for using cilostazol included: (1) cardioembolic disease, (2) use of other anticoagulants, (3) contraindications to obtaining MRI scans, (4) prior non-traumatic intracranial hemorrhage, (5) other hemorrhagic diseases, and/or (6) other blood clotting disorders/diatheses.

Cilostazol stroke prevention study (CSPS) trial

The CSPS trial was a multicenter, open-label RCT involving 292 hospitals across Japan (2013–2017).[3] This RCT evaluated the safety of cilostazol as an antiplatelet agent with vasodilatory effects, which, when combined with aspirin or clopidogrel, beneficially impacted the incidence of recurrent stroke and hemorrhage. With 1879 enrolled patients, ranging in age from 20 to 85, they diagnosed those with non-cardioembolic strokes on MRI (e.g., 90% lacunar or atherosclerotic strokes). Inclusion criteria included at least 50% stenosis of intracranial and/or extracranial arteries and at least two major vascular risk factors (e.g., age ≥65, hypertension, diabetes, chronic kidney disease, peripheral artery disease, history of ischemic heart disease, and/or current smoking).

Randomized trial

Patients underwent block randomization; each block required at least six subjects per participating hospital. There were 932 patients randomized to dual therapy consisting of cilostazol (e.g., titrated to 100 mg twice daily over 2 weeks to prevent side effects of headaches and/or palpitations), combined with either aspirin or clopidogrel. Alternatively, 947 patients received monotherapy; aspirin 81 mg or 100 mg daily (for weight over 50 kg) or clopidogrel 50 mg or 75 mg daily (for weight over 50 kg). No placebos were used in this open-label study. Further, patients were not blinded to their therapy.

Hemorrhagic complications of RCT utilizing dual therapy versus monotherapy

There were no significant differences in hemorrhagic complications between the dual and monotherapy groups. In addition, blood pressure was equally controlled in both populations. At 1.4 years, 29/932 (3%) patients on dual therapy experienced stroke recurrence versus 64/947 (7%) on monotherapy (HR 0.49, 95% CI 0.31–0.76, $P = 0.001$); 5/932 (<1%) versus 7/947 (<1%) experienced hemorrhagic strokes; 8/932 (<1%) versus 13/947 (1%) experienced severe intracranial hemorrhage; and 9/947 (<1%) versus 9/932 (<1%) experienced gastrointestinal bleeding.

Study limitations

This study methodological limitation includes: (1) delays in study recruitment, (2) 344/1879 enrolled discontinued trial medications, withdrew consent, or were lost to follow-up, and (3) 14 patients in the monotherapy group crossed over to the dual therapy arm.

CONCLUSION

This RCT, by Toyoda *et al.* demonstrated the safety of dual therapy, consisting of cilostazol/aspirin or cilostazol/clopidogrel, in preventing secondary ischemic stroke in the Japanese population. Further studies are needed to determine whether these findings would generalize to other populations worldwide.

Declaration of patient consent

Patient consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Disclaimer

Otsuka Pharmaceutical Company, the maker of cilostazol, funded this study and declared that it had no role in the study design, data collection, analysis, or interpretation. Authors of this review have no affiliations with Otsuka Pharmaceutical Company, or involvement with its medication trials, or entity with any financial interest in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Noma K, Higashi Y. Cilostazol for treatment of cerebral infarction. Expert Opin Pharmacother 2018;19:1719-26.
2. Niu PP, Guo ZN, Jin H, Xing YQ, Yang Y. Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: An updated network meta-analysis. BMJ Open 2016;6:e009013.
3. Toyoda K, Uchiyama S, Yamaguchi T, Easton JD, Kimura K, Hoshino H, *et al*. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischaemic stroke in Japan: A multicentre, open-label, randomised controlled trial. Lancet Neurol 2019;18:539-48.

How to cite this article: Lo BW, Miyawaki S, Fukuda H, Koyanagi M. Review of Toyoda K, *et al*. Dual antiplatelet therapy using cilostazol for secondary prevention in patients with high-risk ischemic stroke in Japan. Lancet Neurol. 2019 Jun;18(6):539-548. Surg Neurol Int 2020;11:53.