



ARTICLE OF THE MONTH

Dabigatran For Prevention of Stroke After Embolic Stroke of Undetermined Source

*Diener HC, Sacco RL, Easton JD, et al.
N Engl J Med 2019; 380: 1906 – 1917*

Welcome to the August edition of SNACC's Article of the Month. This month we highlight a prospective trial investigating a possible role for the anticoagulant dabigatran in secondary prevention after cryptogenic stroke. Commentary is provided by Drs. Hemanshu Prabhakar, Charu Mahajan, and Indu Kapoor of the All India Institute of Medical Sciences in New Delhi, India.

Dr. Hemanshu Prabhakar MD, PhD is a professor in the Department of Neuroanaesthesiology and Critical Care at the All India Institute of Medical Sciences. He was awarded a PhD from the same department in 2016. He has edited several books on neuroanesthesia and neurocritical care. He is an active SNACC Member for past 8 years and has enthusiastically involved himself in several committees of SNACC. His special interests are neuromonitoring, neuroendoscopies and pituitary surgeries.

Dr. Charu Mahajan is an assistant professor in the Department of Neuroanaesthesiology and Critical Care at the All India Institute of Medical Sciences. Her areas of interest are anesthetic management of subarachnoid hemorrhage, awake craniotomy and ERAS.

Dr. Indu Kapoor is an assistant professor in the Department of Neuroanaesthesiology and Critical Care at the All India Institute of Medical Sciences. Her areas of interest are neuropharmacology, pediatric neuroanesthesia, robot-assisted neurosurgery and ultrasonography in neuroanesthesia.

As always, we encourage our readers' input on this topic on the SNACC [Twitter](#) feed, or on [Facebook](#).

Nina Schloemerkerper, MD; Adrian Pichurko, MD; and Oana Maties, MD

Commentary

By Drs. Hemanshu Prabhakar, Charu Mahajan, and Indu Kapoor

It has been shown that nearly 20 – 30% of ischemic strokes are cryptogenic, of which many are embolic strokes and their source remains undetermined. [1] Guidelines for secondary prevention of stroke in patients with a history of cryptogenic stroke recommend administration of antiplatelet agents. The treatment may include aspirin, a combination of extended-

release dipyridamole and aspirin, or clopidogrel and aspirin. [2] The authors in the present study hypothesized that oral anticoagulant dabigatran etexilate is more effective than aspirin for secondary stroke prevention in patients in this setting. [3] The investigators called their trial RE-SPECT ESUS (Randomized, double-blind, evaluation in secondary stroke prevention comparing the efficacy and safety of the oral thrombin inhibitor dabigatran etexilate versus acetylsalicylic acid in patients with embolic stroke of undetermined source.)

In this large multicenter trial conducted at 564 sites in 42 countries, over a period from December 2014 through January 2018, 5390 patients were enrolled and randomly assigned to receive dabigatran (2695 patients) or aspirin (2695 patients). Patients older than 60 years of age were eligible for enrollment. Patients were randomly assigned to receive either dabigatran (150 mg twice daily or 110 mg twice daily in patients older than 75 years) plus aspirin placebo or aspirin (100 mg once daily) and dabigatran placebo. The primary efficacy outcome was recurrent stroke of ischemic, hemorrhagic or unspecified type, assessed in a time-to-event analysis. The two main secondary outcomes were ischemic stroke and composite of nonfatal stroke, nonfatal myocardial infarction, or death from cardiovascular causes, with both outcomes evaluated in time-to-event analyses. Other secondary outcomes were disabling recurrent stroke and death from any cause.

During a median follow-up of 19 months (interquartile range 13 to 27 months), recurrent stroke occurred in 177 patients (6.6%) in the dabigatran group (4.1% per year) and in 207 patients (7.7%) in the aspirin group (4.8% per year) (hazard ratio, 0.85; 95% confidence interval [CI], 0.68 to 1.03; $p = 0.10$). Ischemic strokes occurred in 172 patients (4% per year) and 203 patients (4.7% per year) in dabigatran and aspirin groups, respectively (hazard ratio, 0.84; 95% CI, 0.68 to 1.03). Major bleeding occurred in 77 patients (1.7% per year) in the dabigatran group and in 64 patients (1.4% per year) in the aspirin group (hazard ratio 1.19; 95% CI 0.85 to 1.66). Clinically relevant nonmajor bleeding occurred in 70 patients (1.6% per year) and 41 patients (0.9% per year) in the dabigatran and aspirin groups, respectively.

The RE-SPECT ESUS trial showed no significant difference between the effect of dabigatran and that of aspirin on the risk of recurrent stroke among patients with embolic stroke of undetermined source. An interesting post hoc analysis suggested dabigatran may have had an effect on stroke recurrence after one year, which could possibly be due to an increase in undetected atrial fibrillation or other cardiac sources over time. The authors also report that their detection rate of atrial fibrillation was similar to previous two trials – CRYSTAL – AF (Cryptogenic stroke and underlying atrial fibrillation) [4] and FIND – AF (Finding atrial fibrillation in stroke) [5], which showed detection rates of atrial fibrillation of approximately 10 – 15% per year. In the present trial, the authors did not extend ECG monitoring to all their patients and so do not have a systematic assessment of occurrence of atrial fibrillation.

The authors consider the large sample size and broad distribution of international centers as the biggest strength of this trial. They believe that the results of this study can be generalized and they were able to successfully reach the prespecified recurrent stroke rates. The authors conclude that dabigatran was not superior to aspirin in preventing recurrent strokes in patients who had an embolic stroke of undetermined origin. They found more clinically relevant nonmajor bleeding events in the dabigatran group.

References

1. Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens Stroke Registry: a descriptive analysis. *Stroke* 2015; 46: 176 – 81
2. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014; 45: 2160 – 236
3. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019; 380: 1906 – 1917
4. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014; 370: 2478 – 2486
5. Wachter R, Groschel K, Gelbrich G, et al. Holter-electrocardiogram-monitoring in patients with acute ischemic stroke (FIND – AF randomised): open-label randomized controlled trial. *Lancet Neurol* 2017; 16: 282 – 290