# Prasugrel or clopidogrel for long-term secondary stroke prevention?

See Articles page 238

After a transient ischaemic attack or ischaemic stroke, the risk of stroke remains high despite antithrombotic therapy, risk-factor control, and in some patients, carotid revascularisation and patent foramen ovale closure. After non-cardioembolic transient ischaemic attack or ischaemic stroke, antiplatelet therapy is the preferred antithrombotic treatment strategy because any protective effect of anticoagulation with vitamin K antagonists (target international normalised ratio 2·0–3·0) or direct oral anticoagulants (rivaroxaban at 15 mg/day) against ischaemic events is offset by increased bleeding.[1] Among the antiplatelet therapies, immediate treatment with aspirin reduces the proportion and severity of early recurrent stroke in the first 6–12 weeks by half. Addition of clopidogrel to aspirin for the first 3 weeks after a transient ischaemic attack or mild ischaemic stroke provides additional net benefit,[2] whereas triple therapy with aspirin, clopidogrel, and dipyridamole increases major bleeding.

In the long term, clopidogrel or aspirin and extended-release dipyridamole have equal efficacy,[3] and greater efficacy than aspirin alone, but are not optimal. Dipyridamole has to be discontinued in at least 5% of patients because of headache;[3] aspirin increases major bleeding in older individuals (ie, ≥75 years); and the antiplatelet effect of aspirin might be compromised by patient non-adherence, decreased drug absorption, genetic polymorphisms, increased platelet turnover, increased platelet reactivity to other agonists, and exogenous thromboxane A2 from activated leukocytes or endothelium. Non-responsiveness to clopidogrel is also an issue for some individuals because clopidogrel is a prodrug that requires bioactivation by cytochrome P-450 (CYP) isoenzymes to the active compound. Common reduced-function CYP2C19-2 and CYP2C19-3 polymorphisms and drug–drug interactions (eg, proton pump inhibitors) interfere with its bioactivation and antiplatelet effects. Other limitations of clopidogrel include a delayed onset and irreversibility of its antiplatelet effects. More effective therapies are therefore needed.

Prasugrel is a newer, third-generation, oral thienopyridine P2Y12 ADP receptor inhibitor but also a prodrug. It is hydrolysed rapidly by esterases to an intermediate metabolite, which undergoes CYP-dependent oxidation to the active compound. However, genetic variation in CYP isoenzymes do not retard its biotransformation; hence, prasugrel has a more consistent platelet response than clopidogrel. Prasugrel at a maintenance dose of 10 mg/day has proven superior to clopidogrel at 75 mg/day in preventing ischaemic events in patients with acute coronary syndromes scheduled for percutaneous coronary intervention, but led to increasing bleeding.[4] Prasugrel at 10 mg/day has not proved superior to clopidogrel in patients with unstable angina or myocardial infarction without ST-segment elevation treated medically.[5] Prasugrel has now been compared with clopidogrel for secondary prevention of recurrent stroke in the large, phase 3, non-inferiority PRASTRO-I trial by Akira Ogawa and colleagues, published in *The Lancet Neurology*.[6]

In the PRASTRO-I trial, 3747 Japanese patients older than 75 years and weighing more than 50 kg with recent (1–26 weeks previously) non-cardioembolic ischaemic stroke were randomly allocated to double-blind treatment with prasugrel at 3·75 mg/day or clopidogrel at 75 mg/daily.[6] The low dose of prasugrel (3·75 mg) was chosen to avoid the bleeding complications reported at higher doses (10 mg).[4,5] The target sample size of 3600 patients was based on estimated primary outcome event rates of 4·3% with clopidogrel and 3·6% with prasugrel at 2 years (15% relative risk reduction). After a median observation period of approximately 96 weeks in both groups, the primary outcome was similar (73 [4%] of 1885 patients in the prasugrel group *vs* 69 [4%] of 1862 patients in the clopidogrel group, risk ratio [RR] 1·05, 95% CI 0·76–1·44), failing to confirm the non-inferiority of prasugrel to clopidogrel because the upper 95% CI of the RR was 1·44, exceeding the pre-defined non-inferiority margin of an upper confidence limit of 1·35.[6] The primary result was consistent among all patient subgroups, including the 17% of participants with reduced function of CYP2C19 (300 of 1742 in the prasugrel group, and 300 of 1719 in the clopidogrel group). There was also no safety benefit of low-dose prasugrel compared with clopidogrel; the proportions of patients with bleeding were similar.

Clopidogrel therefore remains an antiplatelet regimen of choice for the secondary prevention of recurrent ischaemic stroke in Japan. There appears to be no benefit from routine CYP2C19 genetic testing to guide the selection of prasugrel over clopidogrel. However, the generalisability of the findings to Japanese people older than 75 years or weighing less than 50 kg (the subject of the ongoing PRASTRO-II trial [JapicCTI-121901]), Japanese women (who comprised only 21% [797 of 3747] of participants in the PRASTRO-I trial), or other non-Japanese populations is unclear. Whether the results are applicable to higher doses of prasugrel, as used in other countries, is also unclear.

The quest continues for more effective antithrombotic therapies to reduce the proportion and severity of recurrent stroke. The thienopyridine ticagrelor has the advantage over clopidogrel and prasugrel of acting directly (without biotransformation) and binding reversibly to the platelet P2Y12 receptor for ADP. It prevents stroke in individuals with vascular risk factors[7] and might have a role in long-term secondary stroke prevention. A large trial (NCT03354429) is testing the safety and efficacy of adding ticagrelor to aspirin for prevention of new early stroke after acute transient ischaemic attack or ischaemic stroke. A trial of the combination of cilostazol with aspirin or clopidogrel compared with aspirin or clopidogrel alone for the long-term prevention of recurrent ischaemic stroke in 1884 Japanese high-risk patients with non-cardioembolic ischaemic stroke is due to report its results soon (NCT01995370). Combining long-term, low-dose anticoagulation (rivaroxaban at 2·5 mg, twice per day) with low-dose antiplatelet therapy (aspirin at 100 mg/day) is another promising antithrombotic strategy of secondary stroke prevention, given that it substantially reduced the rate of stroke, compared with aspirin monotherapy, in patients with stable peripheral and coronary artery atherosclerosis, including in a subgroup of patients with previous non-lacunar ischaemic stroke.[8] Other treatment paradigms that target the metabolic causes of plaque accumulation, the inflammatory causes of plaque instability and rupture,[9] and the activated form of coagulation factor XI (XIa),[10] an enzyme involved in thrombus propagation and stabilisation, are under investigation.

*Graeme J Hankey*
Medical School, Faculty of Health and Medical Sciences, The University of Western Australia, Harry Perkins Institute of Medical Research, QEII Medical Centre, Nedlands, Perth 6009, Australia
graeme.hankey@uwa.edu.au

GJH reports personal honoraria from Bayer, Bristol-Myers Squibb, Medscape, and the American Heart Association.

1 Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018; **378:** 2191–201.
2 Hao Q, Tampi M, O'Donnell M, Foroutan F, Siemieniuk RA, Guyatt G. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. *BMJ* 2018; **363:** k5108.
3 Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med* 2008; **359:** 1238–51.
4 Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007; **357:** 2001–15.
5 Roe MT, Armstrong PW, Fox KA, et al. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. *N Engl J Med* 2012; **367:** 1297–309.
6 Ogawa A, Toyoda K, Kitagawa K, et al. Comparison of prasugrel and clopidogrel in patients with non-cardioembolic ischaemic stroke: the PRASTRO-I randomised trial. *Lancet Neurol* 2019; **18:** 238–47.
7 Malhotra K, Goyal N, Kasunich AS, et al. Ticagrelor for stroke prevention in patients with vascular risk factors: A systematic review and meta-analysis. *J Neurol Sci* 2018; **390:** 212–18.
8 Sharma M, Hart RG, Connolly S, et al. Stroke outcomes in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. *Circulation* 2019 (in press).
9 Kelly PJ, Murphy S, Coveney S, et al. Anti-inflammatory approaches to ischaemic stroke prevention. *J Neurol Neurosurg Psychiatry* 2018; **89:** 211–18.
10 Gill D, Georgakis MK, Laffan M, et al. Genetically determined FXI (factor XI) levels and risk of stroke. *Stroke* 2018; **49**: 2761–63.

# Dementia risk after transient ischaemic attack and stroke

See **Articles** page 248

About 20% of patients who are admitted to hospital for stroke develop dementia within the first year after the event; incidence is higher in those with recurrent stroke and lower in those with first-ever stroke.[1] Furthermore, roughly one in ten patients with first-ever stroke already has dementia at event onset.[1] As survival rates after stroke increase, dementia has become a growing concern for patients, families, and health-care providers. Previous studies have identified predictors of post-stroke dementia, including age, low educational attainment, previous stroke, stroke severity, dysphasia, diabetes, atrial fibrillation, and leucoaraiosis on brain imaging.[1–3] However, this information mostly originates from hospital-based studies, which are prone to selection bias and other biases, including attrition. There are few data for dementia risk after transient ischemic attack or