The benefits of aspirin in early secondary stroke prevention

Aspirin is considered an affordable and widely available, if only modestly effective, thromboprophylactic for secondary stroke prevention. The two large randomised controlled trials of aspirin in acute ischaemic stroke reported that aspirin reduced the odds of early recurrent stroke at 2–4 weeks by about 12% (odds ratio [OR] 0·88, 95% CI 0·79–0·97) and the odds of death or dependency at the end of follow-up by about 5% (OR 0·95, 0·91–0·99). The ten trials of aspirin for long-term secondary prevention in patients with previous transient ischaemic attack (TIA) or ischaemic stroke reported that aspirin reduced the risk of any recurrent stroke over 3 years by about 17% (relative risk [RR] 0·83, 95% CI 0·72–0·96). However, non-randomised observational studies have suggested that urgent medical treatments, including aspirin, in acute TIA and mild ischaemic stroke reduced the risk of recurrent stroke by up to 80%.

In The Lancet, Peter Rothwell and colleagues report findings from an analysis of the individual patient data from all randomised controlled trials of aspirin after ischaemic stroke or TIA, giving fresh insights into the effect of aspirin on the timing and severity of recurrent stroke and challenging our understanding of the role of aspirin in secondary stroke prevention.

Rothwell and colleagues found that in the three trials of aspirin versus control in acute ischaemic stroke (n=40531), the overall effect of aspirin was indeed modest. However, there was significant heterogeneity according to baseline stroke severity (p_m=0·014). Aspirin appeared far more effective in reducing the 14 day risk of recurrent ischaemic stroke in patients with mild (OR 0·51, 95% CI 0·34–0·75) and moderate (0·65, 0·44–0·98) neurological damage after stroke, than for those with severe deficits (OR 1·10, 0·77–1·58). Also, the reduction in recurrent stroke among patients with mild and moderate stroke was as great as half to two-thirds within the first 2–6 days.

Moreover, among the 12 trials of secondary prevention of stroke in 15778 patients with TIA or ischaemic stroke randomised to aspirin or control, aspirin reduced the 12 week risk of any stroke by half (hazard ratio 0·49, 95% CI 0·40–0·60), disabling or fatal ischaemic stroke by two-thirds (0·34, 0·25–0·46), and acute myocardial infarction by two-thirds (0·30, 0·17–0·52). The effect of aspirin was consistent among the trials and independent of patient characteristics, stroke aetiology, and aspirin dose. The effect of aspirin was however, greater in the first 6 weeks after randomisation (indeed greatest in the first 2 weeks) than the second 6 weeks, and attenuated further to be of limited long-term benefit thereafter.

Among seven trials of dipyridamole plus aspirin versus aspirin in 9437 patients, the addition of dipyridamole to aspirin had no effect on the risk or severity of recurrent ischaemic stroke within 12 weeks, but did reduce risk thereafter, particularly of disabling or fatal ischaemic stroke.

These results suggest that we might have underestimated the effect of aspirin in preventing early recurrent stroke and myocardial infarction after TIA and ischaemic stroke, overestimated the effect of aspirin in preventing long-term recurrent stroke, been unaware of the benefits of aspirin in reducing the severity of early recurrent ischaemic stroke, and underestimated the effect of dipyridamole in preventing long-term recurrent stroke. These results have implications for clinical practice.

First, patients with suspected TIA or ischaemic stroke require urgent assessment and intervention. These people have a high early risk and ongoing long-term risk of recurrent stroke and other vascular events unless the underlying cardiovascular cause and its potential consequences are appropriately treated. Second, aspirin is the first-line antithrombotic of choice and should be administered immediately. The benefits in reducing the risk and severity of early recurrent stroke are greater than previously recognised. The potential risks associated with administering aspirin before brain imaging to exclude intracerebral haemorrhage (ICH) are likely to be low because this is a rare cause of transient or mild focal neurological symptoms, and the few randomised trials of antithrombotic therapy in such patients, or patients with intracerebral haemorrhage, have not reported adverse outcomes. However, a larger body of observational evidence suggests that antiplatelet therapy at the time of intracerebral haemorrhage might increase mortality. Hence, caution and further research are warranted in this setting. Similarly, although observational studies suggest no detrimental effect of prior antiplatelet use in patients with ischaemic
stroke who subsequently require thrombolysis, further research is required.

The implications of these results for public education are to raise awareness of the nature of the symptoms and signs of TIA and stroke, the high risk of early recurrent stroke even if symptoms have subsided, and the need to seek medical attention immediately. For individuals with stroke-like symptoms that are transient and resolve within minutes to an hour or so, self-administration of aspirin, while awaiting medical assessment, is likely to be safe and of benefit in preventing a recurrent ischaemic event of the brain. For individuals with persistent stroke-like symptoms that could possibly be due to intracerebral haemorrhage, the overall benefits of self-administration of aspirin are also likely to offset the risks, but further evaluation of such a public policy is recommended.

Rothwell and colleagues are now reviewing the individual patient data from other trials of antiplatelet therapy and will shortly report on factors that could modify the effects of antiplatelet drugs, and the long-term benefits, risks, and costs of continuing versus stopping specific antiplatelet drugs in patient subgroups. Meanwhile, the quest continues to identify antiplatelet and anticoagulant regimens that are even more effective than aspirin in preventing recurrent stroke, and their optimum timing and duration. Although there is no significant benefit of early ticagrelor compared with aspirin, the early short-term use of clopidogrel and aspirin in combination is more effective than aspirin monotherapy in select populations. Trials of dual antiplatelet therapy (eg, adding clopidogrel or cilostazol to aspirin) and triple antiplatelet therapy (adding clopidogrel and dipyridamole to aspirin) are ongoing in other populations, and trials of a potent selective protease-activated receptor-4 (PAR4) antagonist and new direct oral anticoagulants are planned. Future trials should measure the severity, as well as the incidence, cause, and timing of recurrent vascular events.

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GJH has received honoraria from AC Immune for chairing the data safety monitoring committee of two clinical trials of vaccines for Alzheimer’s disease, from Bayer for lecturing about stroke prevention in atrial fibrillation at sponsored scientific symposia, and from Medscape, Web MD, for participating in a discussion about stroke prevention in atrial fibrillation at theheart.org.

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