Aspirin’s Benefits Were Previously Underestimated and Are Primarily Accrued in the Acute Setting

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Urgent management of transient ischemic attack (TIA) or minor stroke within 24 hours of symptom onset can reduce the 3-month risk of stroke by ≤80%.1,2 This risk had been previously estimated at 10% to 12% or more based on data from the 1990s and early 2000s,3,4 but more recent data suggest that this risk may now be <3%.1,2,3 Guidelines recommend urgent assessment and treatment, including risk factor control, carotid endarterectomy or stenting, and immediate oral anticoagulation for documented atrial fibrillation or aspirin therapy for most other cases.6,9 Because the risk of recurrent stroke is highest in the first few days,3,4 urgent TIA clinics, such as those reported in the SOS-TIA (SOS-Transient Ischemic Attack) or EXPRESS studies (Early Use of Existing Preventative Strategies for Stroke),1,2 have used dual antiplatelet therapy in the acute setting based on meta-analyses of previous trials. In SOS-TIA,1 the referring physician was instructed by telephone to immediately initiate a 300 mg loading dose of aspirin even before the initial evaluation or hospital admission and before any brain imaging. Whether this immediate empirical antiplatelet regimen partly explains the low recurrence rates observed in the SOS-TIA and EXPRESS studies is not clear because no randomized trial has yet validated this approach for TIA and minor ischemic stroke.

In a recent article of The Lancet, Rothwell et al10 report the results of a new meta-analysis of 12 randomized controlled trials of aspirin versus control for TIA or minor stroke that was focused on the time course of benefit from aspirin therapy. While the overall benefits of aspirin for secondary stroke prevention are well-established, this analysis demonstrated that the overall beneficial effects of aspirin have been underestimated because the aspirin’s benefits are largely limited to the first 12 weeks post-randomization and do not continue to accrue beyond 12 weeks. Aspirin reduced the 6-week risk of stroke, myocardial infarction, and vascular death by ~60% (hazard ratio, 0.42; 95% confidence interval, 0.32–0.55; P<0.001) and reduced disabling or fatal stroke by 70% (Figure). Nearly 70% of the stroke/myocardial infarction/death events occurred during the first 6 weeks. In addition to aspirin’s effect on recurrence risk, aspirin also resulted in a dramatic 60% reduction in stroke severity based on a modified Rankin Scale shift analysis. A further reduction in recurrent stroke risk continued to accrue between week 6 and week 12, but not subsequently (hazard ratio, 0.97; P=0.99), with a significant heterogeneity in the treatment effect observed in the first 12 weeks of aspirin treatment compared to beyond 12 weeks. This effect was independent of the aspirin dose or baseline patient characteristics. In contrast, the addition of dipyridamole to aspirin was ineffective during the first 12 weeks, but did reduce the risk of recurrence beyond week 12, particularly for disabling stroke.

The efficacy of aspirin in the first 12 weeks compared to placebo or controls, such as dipyridamole, clopidogrel, or cilostazol, might reflect the lack of a clinically significant antiplatelet effect of dipyridamole (the long-term benefit of this drug, already observed in ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial),11 has also been attributed to a blood pressure-lowering effect) or a decrease in the antiplatelet effect of clopidogrel among subpopulations with certain CYP19A alleles that result in poor or absent metabolism of clopidogrel into its active form.12 Of note, in CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events), there was no reduction in disabling/fatal stroke in the clopidogrel plus aspirin arm compared with aspirin only arm13; in CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), there was an increase in the severity of recurrent stroke in the clopidogrel arm14; and in PRoFESS (Prevention Regimen For Effectively Avoiding Second Strokes), aspirin plus dipyridamole was superior to clopidogrel in reducing early severe recurrent strokes.15 In contrast, the most recent SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) showed no difference between ticagrelor and aspirin within the first 90 days,16 although there was a trend toward the superiority of ticagrelor over aspirin overall (P=0.067) and at 8 days (nominal P value =0.01), without a between-group difference in disabling stroke (albeit again trending in favor of ticagrelor).

The central questions are why aspirin’s benefit was only observed acutely and subacutely and tended to disappear after 12 weeks and what the implications of this finding are on our understanding of the mechanisms of action for aspirin and dipyridamole and on the optimal medication management during the acute and chronic phase. Mechanistic explanations could involve platelet adaptation to chronic aspirin therapy.
via upregulation of non-COX-1 mediated pathways, the relative effects of aspirin on activated platelets specifically, or the gradual acetylation of other proteins that may act through other important pathways. If chronic use of aspirin induces aspirin resistance because of an adaptation to treatment, then stopping aspirin after 12 weeks of treatment and switching to another antiplatelet agent (or continuing another antiplatelet agent in the case of acute dual antiplatelet therapy) could be warranted. Discontinuation of aspirin could effectively reset the patient’s memory of aspirin exposure and, thus, allow a subsequent rechallenge with aspirin to result in restored acute clinical efficacy after a new acute event though this provocative hypothesis has yet to be validated.10

Given the high risk after a TIA or a minor ischemic stroke, dual antiplatelet therapy has been and is being tested in randomized controlled trials within the first 12 weeks after a TIA or a minor stroke. Hence, the findings by Rothwell et al10 would impose aspirin as the initial obligatory acute antiplatelet agent to which another agent may be added to further improve its efficacy. This approach was evaluated in CHANCE (though it is interesting to note that patients randomized to the dual antiplatelet arm of CHANCE were converted to clopidogrel monotherapy without aspirin for days 22–90 after randomization) and is currently being tested in the POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; NCT00991029; clopidogrel plus aspirin versus aspirin during 90 days) and hopefully in a future trial of ticagrelor plus aspirin versus aspirin. However, Rothwell et al’s10 findings suggest that after the first few weeks of dual antiplatelet therapy, aspirin should be preferentially discontinued rather than the second agent, provided that the other drug has already proven efficacy compared with aspirin in the long-term, as has been demonstrated for clopidogrel and dipyridamole.

Unfortunately, in this meta-analysis, few patients were randomized within the first 7 days after stroke onset, but the pooled analysis of over 40,000 individuals from CAST (Chinese Acute Stroke Trial),17 IST (International Stroke Trial),18 and one other small trial (MAST-I [Multicentre Acute Stroke Trial–Italy]19) showed that aspirin reduced the severity of recurrent stroke during the first 14 days. Once again, the maximum effect occurred within the first days, and those who had received aspirin before randomization and were allocated to continue aspirin had maximal benefit within the first 24 hours postrandomization.

Hence, although there is no randomized controlled evidence for prehospital acute administration of aspirin and the feasibility of a trial to evaluate such an approach may be limited, this meta-analysis may provide enough compelling evidence to advocate having patients immediately self-administer aspirin for suspected TIA or minor stroke, even before presenting for medical attention. A self-administered loading dose of aspirin for transient symptoms is likely to be safe given how rare hemorrhagic stroke is identified among patients with transient symptoms and the lack of effect of aspirin on progression of hemorrhagic stroke and may be justified given the large early benefit observed in Rothwell et al’s10 meta-analysis. Therefore, immediate self-administration of a loading dose of aspirin for suspected TIA or minor ischemic stroke during the period of maximal efficacy and before early events can occur may now be justified.

Figure. Event rates in aspirin and control group overtime with proportion of disabling and fatal and nondisabling stroke. Reprinted from Rothwell et al10 Copyright © 2016, (see: http://creativecommons.org/licenses/by/4.0/).

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