Expanding antiplatelet use for patients with stroke

The case for stroke of unknown type

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Stroke occurs in approximately 16.9 million people worldwide annually.[1] It is the second cause of death[2] and the third leading cause of disability-adjusted life-years lost to disease.[3] The greatest burden is in low and middle income countries (LMIC), where approximately 69% of these strokes occur.[1]

Aspirin is of benefit in reducing in-hospital death and recurrence in patients with suspected ischemic stroke.[4] However, it is unclear whether aspirin treatment could also be beneficial in people with stroke of undetermined type, mostly due to concerns regarding bleeding risks in patients who may have intracerebral hemorrhage (ICH) or subarachnoid hemorrhage (SAH). This is important to understand as in many regions of LMIC brain imaging is either not available or unaffordable, and so large proportions of people have strokes of unknown type. For example, in the Trivandrum Stroke Registry, 31.2% of patients were not imaged, more of these being in the rural population (43.6%) than the urban population (28.1%).[5] Similarly, in a prospective CT scan study of patients with acute stroke in Nigeria, only 101 patients out of 1,122 (9%) could afford the CT scan.[6] Finding ways to prevent mortality, stroke recurrence, and disability in these nonimaged patients would be of great benefit, particularly in regions where resources are scant and social welfare safety nets are usually inadequate or nonexistent.[7]

In the current issue of *Neurology*®, Berkowitz et al.[8] carry out a decision analysis to assess the effects of aspirin therapy on the risk of in-hospital stroke recurrence and death among patients with acute stroke who do not undergo brain imaging. They used data from a meta-analysis of 2 large clinical trials of early initiation of aspirin therapy following stroke.[4] These data were useful because aspirin therapy was not only provided to patients following an ischemic stroke, but was also inadvertently provided to 733 patients with ICH. This enabled assessment of the effects of aspirin therapy in people with both ischemic stroke and ICH. Since the proportion of people with ICH is unknown in many populations, the authors undertook sensitivity analyses of in-hospital stroke recurrences and death in patient groups where the proportion of ICH ranged from 9% up to 60%. When the proportion of strokes that were ICH was 34%, the authors found that aspirin use would be likely to reduce in-hospital mortality or stroke recurrence by 13 per 1,000. This means that only 77 patients would need to be treated for one to benefit. Furthermore, aspirin was beneficial even when the proportion of strokes that were ICH was as high as 60%, a value that is likely higher than what is expected for most populations. Based on this analysis and similar previous observations,[9] it seems reasonable to recommend that acute stroke patients of unknown type receive aspirin therapy (160 mg/day to 320 mg/day) at least 25–48 hours after onset of symptoms and during their hospitalization for a period of up to 4 weeks. As the bleeding risk in ICH is highest during the first 24 hours, administering aspirin within this period is not recommended. This finding is highly important for clinicians who work in low-resource settings where imaging is either unavailable or unaffordable to patients, but is also relevant to clinicians in other settings. However, as the authors recommend, it seems prudent to exclude from aspirin therapy those patients whose clinical presentation suggests ICH or SAH. This includes those presenting with any of the following: sudden-onset headache, seizures, coma, neck stiffness, vomiting, or diastolic blood pressure greater than 110 mm Hg.[10]

How does this translate to benefits in LMIC? Using data from the Global Burden of Disease (2010) study, approximately 11.6 million strokes occur in LMIC annually.[1] If we estimate that 20% (2.32 million) of these patients are not imaged and apply the prediction that aspirin use in these patients would avert 13 deaths or second strokes per 1,000 patients treated, over 30,000 patients would be expected to have improved in-hospital outcomes every year. Given that the proportion of patients not imaged is likely to be greater than 20%, the

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potential effect of administering aspirin in these patients is likely to be even better.

What remains unknown is whether this translates into improved long-term outcomes, as the analysis was limited to in-hospital mortality and recurrence. Furthermore, it remains unclear whether these patients should be discharged on antiplatelet agents. Despite these limitations, the use of aspirin in those with unknown stroke subtype who lack signs or symptoms suggestive of ICH or SAH is an important message for those regions where imaging is less available. Further decision analysis based on the findings of studies with long-term outcomes and aspirin use would substantially add to our knowledge of how to manage patients who do not have access to imaging.

AUTHOR CONTRIBUTIONS

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