Recurrent Stroke while on Antiplatelet Therapy

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KEYWORDS

• Recurrence • Ischemic stroke • Antiplatelets • Resistance • Treatment failure

KEY POINTS

- One-third to one-half of patients who experience a recurrent stroke are already on antiplatelet medications.
- Multiple reasons exist for a breakthrough stroke to occur while on antiplatelets, and we prefer not to use the term treatment failure. Nonadherence is the most common cause for laboratory antiplatelet resistance, and not all recurrent strokes have laboratory evidence of antiplatelet resistance.
- When recurrence occurs, the need to correctly identify the cause and mechanism of stroke cannot be overemphasized.
- At present, there is no good indication for antiplatelet resistance testing in ischemic stroke, or for adjusting medications based on its results.
- Choice of antiplatelet regimen to prevent recurrence depends on timing. A combination of aspirin and clopidogrel may be superior to a single antiplatelet agent in the first 3 months after a mild ischemic stroke. There is no benefit for dual antiplatelet therapy for long-term secondary prevention.

INTRODUCTION

Approximately 795,000 adults in United States experience a new or recurrent ischemic stroke each year, and an additional estimated 240,000 adults experience a transient ischemic attack (TIA).[1] In addition to the significant morbidity resulting from a stroke, survivors are at a high risk of recurrent ischemic events. A recurrent stroke carries twice the probability of death and increased cardiovascular complications compared with the first stroke and as such can be serious.[2] The annual risk of a recurrent ischemic event after an initial ischemic stroke or TIA is on average approximately 3% to 4%.[3]

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Although the benefit of antiplatelet agents is uncertain for primary prevention,[4] drugs such as aspirin, clopidogrel, or the combination of aspirin and extended-release dipyridamole are mainstays for secondary prevention in patients who have experienced a noncardioembolic stroke or TIA.[5] The recurrence of cerebrovascular ischemic events in patients on antiplatelets is a problem commonly encountered by vascular neurologists. Treatment failure is commonly attributed to pharmacologic resistance but has multiple causes, including vascular factors causing increased platelet activation or failure to uncover the true cause and mechanism of stroke. Clinicians are faced with options of switching to a new antiplatelet medication or using a combination of antiplatelet medications in the acute setting and for long-term secondary stroke prevention, balancing future protective benefit and increased hemorrhagic risks. This article discusses the incidence of recurrent stroke while on antiplatelets, its causes, and available evidence on appropriate management strategies to prevent further events.

INCIDENCE

With remarkable advances in cardiovascular and stroke secondary prevention therapies, the current average annual rate of future stroke of ≈ 3% to 4% is at an all-time low.[3] For noncardioembolic strokes, recent clinical trials suggest that the annual risk may be as low as 3%, although this may underestimate the community-based rate.[6–10] Multiple factors influence the risk of an individual patient's risk for recurrent stroke, including age, comorbidities, type of events, stroke subtype, and medication adherence. Recurrent stroke is associated with a greater number of risk factors and a higher incidence of large-artery atherosclerosis than the first stroke.[11] Of the ≈795,000 strokes each year, 185,000 are recurrent attacks. Approximately a third to half of them develop while on antiplatelet therapy,[1] which represents a significant management challenge.

ANTIPLATELET TREATMENT FAILURE

The US Food and Drug Administration (FDA) has approved aspirin, clopidogrel, combination aspirin/dipyridamole, and ticlopidine for prevention of vascular events in patients with stroke or TIA. Overall, these medications reduce the relative risk (RR) of stroke, myocardial infarction (MI), or death by ≈22%.[12] Aspirin is the most widely used agent for secondary prevention and offers an RR reduction of 15% for any type of stroke.[13] Therefore, thrombotic events occur despite being on antiplatelet therapy and this has produced the concept of antiplatelet treatment failure. Other terms used commonly and often interchangeably are clinical antiplatelet failure, antiplatelet resistance, antiplatelet nonresponsiveness, and inadequate efficacy.[14]

There is a lack of uniform definitions, and a lot of variability exists in the manner in which resistance and failure are defined. In the strictest sense, antiplatelet resistance refers to laboratory evidence of insufficient inhibition of platelet aggregation by antiplatelet agents in vitro. Therefore, aspirin resistance is defined as a failure to achieve reduction in platelet thromboxane A2 (TXA2) formation following inhibition of platelet cyclooxygenase (COX)-1 enzyme, and thienopyridine resistance refers to the inability to attain reduction in adenosine diphosphate–mediated platelet aggregation after blockade of P2Y12 receptor signaling. In contrast, clinical resistance and treatment failure refer to the failure of antiplatelets to prevent atherothrombotic events. We prefer not to use the term antiplatelet treatment failure. It is well known that platelets have multiple pathways for activation and aggregation, and a single antiplatelet may not inhibit all of them.[15] For example, aspirin reduces TXA2 synthesis through the inhibition of the COX-1 enzyme. However, COX-2 enzyme is inducible under conditions