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Controversies in stroke: Antiplatelet therapy or not for asymptomatic/incidental lacunar infarction

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Asymptomatic lacunar infarcts represent the most common incidental finding on brain MRI in clinical practice. The estimated prevalence is 7%, and it rises steeply with age up to 25–30% in patients over 70 years of age. Although previously called ‘silent’ brain infarcts, it has become clear that asymptomatic lacunar infarcts are in fact associated with cognitive and motor deficits and are a risk factor for future stroke and cognitive decline.

Given the increased risk of subsequent stroke in patients with incidental lacunar infarcts, it could be argued that antiplatelet therapy should be initiated for prevention. However, evidence from randomised trials on the effectiveness and safety of antiplatelet therapy in asymptomatic lacunar infarcts is lacking, and consequently clinical practice varies.

We present 2 opposing viewpoints from clinicians on the question: “Should patients with asymptomatic/incidental lacunar infarcts be treated with antiplatelet therapy?”. Drs. Bilski and Gutierrez advocate in favor of treatment, while Dr. Aparicio proposes against antiplatelet therapy. Drs. Hilkens and de Leeuw provide this introductory text and the concluding remarks in their role as moderators.

Should antiplatelet therapy be prescribed for patients with an asymptomatic/incidental lacunar infarction? – NO

The purpose of initiating antiplatelet therapy upon finding an incidental lacunar infarction would be to prevent clinical outcomes of symptomatic stroke, atherosclerotic cardiovascular disease, cognitive decline, or death. However, the effectiveness of this intervention for these purposes has no support in the literature and the safety of the approach is questionable.

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The 2017 American Heart Association/American Stroke Association scientific statement on Prevention of Stroke in Patients with Silent Cerebrovascular Disease recommends following guidelines for primary prevention and does not recommend aspirin or antithrombotic therapy to prevent stroke because evidence of effectiveness has not been established.[1] A randomized, placebo controlled trial (RCT) at eight Italian centers of 83 adults age >45 years with silent brain infarct observed no difference in occurrence of stroke (1 event in the aspirin arm and 2 events in the controls); there were no differences in secondary endpoints of other cardiovascular events, change in cognition, or death.[2] The placebo group had more new silent brain infarcts on follow up MRI (6 vs. 1), which was part of the composite primary endpoint with ischemic stroke and TIA. However, 22 (27%) participants were lost to follow up or withdrew consent, contributing to attrition bias. The 2021 European Stroke Organization Guideline on covert cerebral small vessel disease similarly does not recommend antiplatelet drugs for incidental lacunar infarcts, citing insufficient and low-quality evidence.[3] A Cochrane review of three RCTs (3384 participants) that investigated antithrombotic therapy for prevention of cognitive decline in people with cerebral small vessel disease, lacunes, and subcortical infarcts found no evidence of any clinically relevant cognitive benefit.[4] No studies in this population have assessed for differences in the incidence of dementia or mortality.

Part of the reason we should question the use of antiplatelet therapy in persons with covert subcortical brain infarcts is the uncertainty about the natural history and underlying pathophysiology of these lesions. First, lacunar infarcts need to be carefully differentiated from, and can be mistaken for, small subcortical cystic structures, enlarged perivascular spaces, or previous hemorrhage.[5,6] Second, the timing of the infarction is uncertain. The incidence of ischemic stroke in early life is not rare, especially in newborns where incidence is estimated to be as high as 1 in 3500.[7] By midlife, the prevalence of covert brain infarction may be has high as 10–20%.[8,9] The benefit of initiating antiplatelet therapy after acute ischemic stroke is partly to prevent early recurrent stroke, where aspirin is started within 14 days of stroke onset.[10] The net benefit of antiplatelet treatment for secondary prevention is largely within the first month after stroke or TIA.[11,12] Third, small subcortical cavitated infarcts may result from mechanisms that are non-atherothrombotic, where platelet inhibition may have no role. Especially in children and young adults, atherosclerosis is much less likely to be the pathologic process in the absence of traditional cardiovascular risk factors. Even in older adults subcortical silent brain infarction may be secondary to mechanisms such as hypoperfusion, blood-brain barrier breakdown, or, rarely, embolism.[13,14] Non-atherosclerotic mechanisms may especially contribute to small subcortical infarcts in the cerebellum, medulla, thalamus, corona radiata, and striatocapsular regions. Acknowledging these uncertainties, guidelines for the secondary prevention of stroke (including antiplatelet initiation) are of unclear relevance to individuals with incidental brain infarction, especially younger patients.

Another concern is safety. Long-term administration of antiplatelet therapy carries risk. In primary prevention trials, aspirin increases the risk of intracranial bleeding by 31% and major extracranial bleeding by 53%[15]; in trials of secondary prevention for cardiovascular disease the risks are even higher.[16] In the primary prevention trial ASPREE [Aspirin in Reducing Events in the Elderly], among participants 70 years of age or older, rates of

major hemorrhagic events were 39% higher in the low-dose aspirin group compared to placebo (8.6 vs 6.2 events per 1000 person-years), while no difference was observed between groups with regards to cardiovascular events or incidence of dementia.[17,18] The U.S. Preventive Services Task Force recommends against initiating aspirin for primary prevention of cardiovascular disease in adults age 60 years or older. Older patients with asymptomatic lacunar infarction would seem to represent a higher risk group for incident stroke, where preventive treatment with antiplatelet medication may be compelling.[19] Yet in the SPS3 [Secondary Prevention of Small Subcortical Strokes] trial, major hemorrhages occurred at a rate of 1.1% per year among patients with lacunar stroke treated with aspirin, while the rate of recurrent stroke was 2.7% per year, with aspirin not conferring a large net benefit.[20] In a pooled analysis of 2 RCTs on aspirin use in patients with Alzheimer's dementia, another high-risk group, 3.2% developed intracerebral hemorrhage, although participants had advanced age and did not undergo MRI at baseline to evaluate for covert brain infarction.[21] It is not clear from this data that antiplatelet medication will confer a benefit among older, high-risk patients. Responsiveness to and risk associated with antiplatelet therapy may also vary between patients and by race/ethnicity.[22,23] Moreover, manifestations of cerebral small vessel disease can be both ischemic and hemorrhagic, for example the association of cerebral microbleeds with lacunar ischemic stroke.[24] Initiating antiplatelet medication for asymptomatic subcortical infarcts of unclear significance found on imaging has no evidence and may unintentionally cause harm.

Fortunately, there are other options to treat patients with covert lacunar infarction. First, the clinician should attempt to elicit a history of stroke-like symptoms related to the finding, in which case secondary prevention measures are indicated. Among persons without a previous diagnosis of stroke or TIA a history of stroke symptoms is surprisingly common, up to 18%.[25] Second, conditions such as hypertension, diabetes, and smoking should be assessed for and treated. The optimal systolic blood pressure treatment target for most high-risk adults, including at older age, is less than 130 mmHg for the primary prevention of cardiovascular disease and mortality.[26] Third, it is reasonable to take into consideration the presence of a covert lacunar infarction when deciding on treatment with statin medications. Current guidelines[27] recommend prescribing a statin for adults ages 40 to 75 with at least one vascular risk factor (i.e., hypertension, diabetes, smoking, or dyslipidemia) and an estimated 10-year cardiovascular disease risk[28] of 7.5% or greater, as long as low-density lipoprotein cholesterol levels are above 70 mg/dL. In addition, there is evidence that statin treatment may reduce the accrual of new covert brain infarcts among high-risk patients.[29] Finally, where available, clinicians should encourage patients to enroll in randomized clinical trials investigating the optimal medical management of covert lacunar infarction. Given the uncertainty about the underlying pathophysiology of these infarcts, patients with higher atherosclerotic cardiovascular risk should be carefully selected. Clinical trials can incorporate imaging markers, such as the presence of ischemic cerebral small vessel disease and the absence of prior hemorrhage, cortical superficial siderosis, or cerebral microbleeds, to mitigate risks.

Should antiplatelet therapy be prescribed for patients with an asymptomatic/incidental lacunar infarction? – YES

Lacunar infarcts account for 20–30% of all ischemic strokes and are traditionally defined as deep, small brain cavities, up to 15mm in diameter, located in the territory of penetrating arteries supplying the basal ganglia, deep cerebral white matter, or brainstem that occur as the result of occlusion of a small artery.[30,31,32] While it was originally thought that most lacunar infarcts had corresponding clinical syndromes, particularly the subcortical infarct syndromes first defined by C. Miller Fisher, the advancement of neuroimaging technology over the past several decades has led to the detection of incidental areas of gliosis on CT and MRI presumed to be infarcts without corresponding clinical neurologic signs or symptoms, thus referred to as incidental, covert or silent brain infarcts.[1,8,33,] We will (1) outline the prevalence of silent brain infarcts, (2) review the evidence on adverse outcomes associated with silent brain infarcts including increased risk of subsequent stroke, (3) highlight the similarities between silent and symptomatic lacunar infarcts including risk factor profile and pathophysiologic mechanism, and (4) discuss the existing data on the management of silent brain infarcts to ultimately suggest that the identification of silent brain infarcts on neuroimaging should prompt initiation of antiplatelet therapy for secondary stroke prevention.

It is estimated that approximately 25% of people 80 years of age or older have at least one silent brain infarct, more than 90% of which are lacunar infarcts, located subcortically.[8] The prevalence of these silent brain infarcts far exceeds the prevalence of symptomatic infarcts: incidentally found silent brain infarcts are estimated to be anywhere from 5 to 10 times more common than symptomatic infarcts presenting as a clinical stroke.[8,34] Interestingly, multiple neuroimaging studies have demonstrated that the prevalence of silent brain infarcts exceeds that of all other incidental imaging findings combined, including meningiomas and arachnoid cysts.[35,36] In addition to increased detection of silent brain infarcts, more precise neuroimaging has also resulted in the detection of white matter hyperintensities, defined as confluent areas that are typically bilateral and symmetric in hemispheric white matter, often associated with lacunar infarcts.[37] Though silent brain infarcts were named as such because they are found incidentally in the absence of clinical stroke symptoms, population-based epidemiologic studies have demonstrated that they are, in fact, not as silent as previously thought and are associated with adverse outcomes. Several studies have investigated the clinical manifestations of incidentally identified white matter lesions including silent brain infarcts on neuroimaging and have found that these lesions are associated with gait impairment and other subtle motor deficits, cognitive decline and dementia, psychiatric disorders, and impairments in activities of daily living.[1,32,38,39,40] The Rotterdam Scan Study found that the presence of silent brain infarcts was associated with worse baseline cognition and over time was associated with steeper decline in global cognition, more than doubling the risk of dementia.[41,42] This may be due to the possibility that silent brain infarcts and white matter hyperintensities can act synergistically in patients with initial stages of Alzheimer's pathology to promote progression to dementia.[43]

Silent brain infarcts have also been found to incur an increased risk of subsequent vascular events.[32,44] The Rotterdam Scan Study demonstrated that the presence of at least one silent brain infarct on baseline imaging increased the risk of a new silent brain infarct on follow-up imaging 5–6 years later up to 3-fold (odds ratio 2.9).[41] In the Northern Manhattan Study (NOMAS), we also reported an increased risk of vascular events and stroke among people with silent brain infarcts.[45,46] A meta-analysis of four additional population-based studies in the US and Europe compared the incidence of new strokes in patients with versus without silent brain infarcts defined on baseline MRI. Mean follow-up of these patients ranged from 3 to 15 years after baseline imaging, and all four studies found that silent brain infarcts are independent predictors of future strokes, with hazard ratios ranging from 1.5 to 3.3.[1] Another meta-analysis of thirteen studies by Gupta et al. demonstrated that the presence of silent brain infarcts in patients without a prior stroke confers a relative risk of subsequent stroke similar to that of prior stroke history. In this study, silent brain infarcts in patients without prior stroke had a hazard ratio of 2.06 for subsequent stroke. For reference, in patients with atrial fibrillation, a prior history of stroke is associated with a hazard ratio of 2.3 for recurrent stroke.[47] Silent brain infarcts and white matter hyperintensities also appear to have additive or synergistic effects; the extent of silent brain infarcts and white matter hyperintensities at the time of first stroke has been demonstrated to have significant prognostic implications for several outcomes, including the extent of disability and death.[32,48] The presence of silent brain infarcts also appears to negatively influence recovery of function after a stroke, likely by limiting brain plasticity rescue mechanisms.[49]

Silent lacunar infarcts share a similar risk factor profile to symptomatic lacunar infarcts, which includes increasing age, hypertension, diabetes, and smoking.[32,41,46] Some studies have also cited previous TIA, male gender and systemic vascular disease as other factors that increase risk for both silent and symptomatic lacunar infarcts.[1,50] The mechanism for both silent and symptomatic lacunar infarcts, as well as white matter hyperintensities, is presumed to be small vessel disease. Given the similarity in risk factor profile and pathophysiology of silent and symptomatic infarcts, it has been hypothesized that the determining factors in whether or not infarcts are clinically significant is related to the location and size of these infarct; perhaps silent infarcts do not manifest clinically given their small size in a non-eloquent location.[46,51] Given similar mechanisms responsible for silent and symptomatic lacunar infarcts, along with the adverse outcomes associated with silent brain infarcts including increased risk of subsequent stroke as described above, the American Heart Association/American Stroke Association published a scientific statement in 2017 on the prevention of stroke in patients with silent cerebrovascular disease, arguing that the approach to silent brain infarcts and symptomatic ischemic strokes should be the same, while acknowledging that there is a lack of robust data to support this recommendation.[1]

The current standard of care for secondary stroke prevention in patients with symptomatic lacunar infarcts attributed to small vessel disease is initiation of antiplatelet therapy, as recommended by the AHA/ASA.[52] However, there is currently no standard of care for secondary prevention in patients with silent lacunar infarcts and no large clinical trials have published data on this topic. A few smaller studies have begun to investigate antiplatelet use in prevention of silent brain infarcts. Maestrini et al. randomized patients ages 45 and older

with at least one silent brain infarct and no prior stroke to receive aspirin vs. placebo and had MRIs at baseline and after 4 years of treatment.[53] Although significance was not reached, there were more silent and symptomatic infarcts observed in the untreated group than in the group treated with aspirin. Additionally, there was no difference in adverse outcomes such as bleeding events from aspirin use between the groups.[53] Sato et al. investigated preventive effects of aspirin on silent brain infarcts in Japanese patients with non-valvular atrial fibrillation over 1 year and found that treatment with aspirin reduced the appearance of new silent lacunar infarcts in deep white matter and basal ganglia but not silent cortical infarcts.[54] The effect of antiplatelet in the reduction of silent brain infarcts is not restricted to aspirin. Other agents such as cilostazol,[55] are associated with lower risk of new silent brain infarcts compared with aspirin. It is worth noting that these patients had a clear indication for antiplatelet given prior stroke, however. There was no major bleeding side effects noted with antiplatelet administration in European (0%)[53] or Japanese (0%)[55,56] populations. It is worth noting that in general, aspirin is associated with a risk of between 0.2–1.0% per year for major bleeding,[57] but whether these results apply to populations with heavier risk factor burden or of various race/ethnic backgrounds need to be investigated further.

A few studies have also examined the effect of aspirin on preventing progression of white matter hyperintensities, which is relevant to this discussion since these lesions are presumed to have a similar pathophysiologic mechanism to silent brain infarcts. Fujita et al. assessed the effect of aspirin on preventing progression of white matter hyperintensities over a 4-year period.[58] 21 patients with platelet hyper-aggregability were treated with aspirin and compared to a group of 21 age- and white matter-matched controls without treatment during this time. They found that there was significant reduction in progression of white matter intensities in the group treated with aspirin: the relative risk reduction obtained by platelet hyper-aggregability correction with aspirin was 90% in periventricular hyperintensities and 67.1% in deep white matter hyperintensities.[58]

Despite paucity of existing data supporting the use of antiplatelets for secondary prevention in patients with silent brain infarcts, there is robust evidence that silent brain infarcts confer increased risk of subsequent symptomatic infarction. Initiation of antiplatelet therapy after identification of silent brain infarcts may reduce progression of white matter lesions and reduce risk of subsequent stroke without clear adverse risk of hemorrhage. Populations at a high risk of ischemic events (e.g. high risk factor burden, MRI evidence of white matter hyperintensities in addition to silent brain infarcts) might be best suited to show a benefit of antiplatelets in primary prevention that can offset the expected bleeding risk associated with antiplatelet. Furthermore, whether carrying out stroke etiology workup in patients with silent brain infarcts is cost-effective should be investigated.

Concluding remarks

In the absence of evidence from randomised clinical trials, the approach to a patient with asymptomatic/incidental lacunes should be guided by clinical reasoning and circumstantial evidence.

The key argument in favour of antiplatelet therapy is that presence of asymptomatic/incidental lacunes is a strong risk factor for future adverse outcomes, including stroke, cognitive decline and dementia. Furthermore, asymptomatic and symptomatic brain infarcts share similar risk factors and likely have a similar underlying pathophysiological mechanism – asymptomatic infarcts may simply not have caused distinct neurological symptoms because of their location. As such, the 'YES'-group advocates to treat patients with asymptomatic lacunes with antiplatelet drugs according to secondary prevention guidelines.

In contrast, the 'NO'-group proposes to follow primary prevention guidelines, arguing that antiplatelet therapy increases risk of serious bleeding, particularly in older individuals who are prone to bleeding and in whom bleeding is more often disabling or fatal. Moreover, patients with lacunar infarcts in the presence of other manifestations of small vessel disease may be more susceptible to intracerebral hemorrhage. Last, antiplatelet therapy is most effective in prevention of early recurrences after stroke, while the timing of initiation of antiplatelet therapy after an asymptomatic lacunar infarct is uncertain.

It might well be the case that optimal treatment of incidental lacunar infarcts is not uniform for all individuals. The potential benefit of antiplatelet therapy will likely depend on the burden of vascular risk factors, the etiology of the lacunar infarcts, the estimated risk of a future vascular event and the risk of bleeding. Patients at highest risk of vascular events may be selected for future trials. Irrespective of whether antiplatelet therapy is initiated, vascular risk factors should be adequately controlled to lower risk of cardiovascular disease, with hypertension being the strongest risk factor for both asymptomatic lacunar infarction and overt stroke.

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Non-standard Abbreviations and Acronyms

AHA/ASA	American Heart Association/American Stroke Association
RCT	randomized, placebo controlled trial
MRI	Magnetic Resonance Imaging
TIA	Transient Ischemic Attack
CT	Computed Tomography

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