

Aspirin-clopidogrel no better than aspirin alone for patients with lacunar stroke

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Aspirin combined with the antiplatelet drug clopidogrel is no better than aspirin alone for stroke prevention in people with a history of lacunar strokes, and the combination carries a greater risk of gastrointestinal bleeding, according to results of a trial funded by the National Institutes of Health. Lacunar strokes occur due to chronic high blood pressure and typically produce small lesions deep within the brain.

The trial results also point to an overall improvement in [stroke](#) management during the past decade. Regardless of whether patients received [aspirin](#) alone or the dual therapy, their stroke risk was reduced more than three-fold from what it was 10 years ago.

[Antiplatelet drugs](#) such as aspirin are routinely prescribed to help prevent new strokes in people with a history of lacunar stroke. The [Secondary Prevention](#) of Small Subcortical Strokes (SPS3) trial was designed to determine if adding clopidogrel to aspirin would offer better protection than aspirin alone. The results appear in the Aug. 30th [New England Journal of Medicine](#). They show that the aspirin-clopidogrel combination was about equal to aspirin in reducing the risk of any type of stroke, but it almost doubled the risk of [gastrointestinal bleeding](#).

"For all stroke therapeutics, there is a need to balance the potential benefits against the risks. The SPS3 findings establish that for lacunar stroke, dual therapy with aspirin and clopidogrel carries significant risk and minimal benefit," said Walter Koroshetz, M.D., deputy director of National Institute of Neurological Disorders and Stroke (NINDS), part

of the National Institutes of Health.

The SPS3 trial is funded by NINDS and led by Oscar R. Benavente, M.D., research director of the Stroke and Cerebrovascular Health program at the University of British Columbia in Vancouver, British Columbia.

In addition to comparing dual [antiplatelet therapy](#) with aspirin, the trial was designed to test two levels of [blood pressure control](#). After an interim data analysis in August 2011, the antiplatelet component of the trial was stopped. NIH also issued a [clinical alert](#) warning that there was "little likelihood of benefit in favor of aspirin plus clopidogrel [for] recurrent stroke should the study continue to conclusion." The [blood pressure](#) component of the trial is ongoing, and the trial participants have been encouraged to continue taking aspirin without clopidogrel.

Strokes occur when blood vessels that supply the brain rupture or become blocked, such as by a blood clot. Antiplatelet drugs interfere with the formation of blood clots.

Lacunar strokes occur due to chronic high blood pressure, which in turn leads to progressive narrowing and finally blockage of small arteries that supply deep brain structures. They account for up to one-fifth of all strokes and are especially common among African-Americans, Hispanics and people with diabetes. Although lacunar strokes tend to produce relatively small lesions, they can cause disability depending on where they occur in the brain.

The SPS3 trial involves more than 3,000 participants at 82 clinical centers in North and South America and in Spain. The participants are age 30 and older, and all had a recent history of lacunar stroke prior to enrollment. About 52 percent are white, 31 percent Hispanic and 17 percent black.

For the antiplatelet component of the trial, about half of the participants received 325 milligrams of aspirin and 75 milligrams of clopidogrel daily, and the other half received aspirin and placebo. The participants were also randomly assigned to receive either standard control of systolic blood pressure (less than 130 mm Hg) or aggressive control (130-149 mm Hg).

After eight years of study, the annual risk of recurrent stroke was 2.7 percent in the aspirin-only group and 2.5 percent in the aspirin plus clopidogrel group. Most of the recurrent strokes in both groups were lacunar strokes. The rate of serious or life-threatening internal bleeding was 1.1 percent in the aspirin group and 2.1 percent in the dual therapy group. The difference was due mostly to a higher number of gastrointestinal bleeds in the dual therapy group. The percentage of brain bleeds in the two groups was not significantly different. Deaths from any cause were also higher in the aspirin-clopidogrel group.

For both groups, stroke recurrence was lower than the investigators had expected. When the SPS3 trial began in 2003, another large trial that tested warfarin vs. aspirin for [stroke prevention](#) had just ended. Warfarin is an anticoagulant, another class of drugs that interferes with blood clotting. That trial, called the Warfarin vs. Aspirin Recurrent Stroke Study (WARSS), found that patients with a history of lacunar strokes who took aspirin had an annual stroke recurrence rate of about 7 percent. (Warfarin and aspirin were about equal.)

This reflects a common trend, Dr. Benavente said. "What we see more and more often in stroke prevention [trials](#) is a significant decrease in stroke risk, compared to data from 10 years ago. We have better medications now to control stroke risk factors such as high blood pressure and cholesterol, and these are clearly having an impact."

In prior studies, antiplatelet drugs including aspirin or clopidogrel alone,

or a combination of aspirin and dipyridamole, have been shown to reduce stroke risk in patients with heart disease or prior stroke. In one trial, aspirin combined with clopidogrel was more effective than aspirin alone at reducing [stroke risk](#) in patients with atrial fibrillation, a type of abnormal heart rhythm. However, other trials involving broader stroke populations found no added benefit from combining aspirin and clopidogrel. Therefore, current practice guidelines recommend aspirin alone, clopidogrel alone, or aspirin plus dipyridamole for secondary prevention after most types of stroke. The SPS3 results are consistent with those guidelines.

Researchers continue to investigate whether the clopidogrel-aspirin combination might be beneficial for patients with other types of stroke, such as transient ischemic attack (TIA). This is a type of stroke in which symptoms fade away in less than 24 hours; it is also a warning that a more damaging stroke may be imminent. The Platelet-Oriented Inhibition in New TIA (POINT) trial is testing whether aspirin plus [clopidogrel](#) are effective at preventing major strokes when given within 12 hours of a TIA. That trial is also funded by NINDS.

More information: Benavente et al. for the SPS3 investigators. "Effects of clopidogrel added to aspirin in patients with recent lacunar stroke." *New England Journal of Medicine*, August 30, 2012. [DOI: 10.1056/NEJMoa1204133](#)

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