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Stroke prevention trials should include patients with disabilities, study says

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Clinical trials for treatments to prevent recurring strokes typically only include participants who have little to no disability from a prior stroke. A new Yale study finds that leaving patients with such disability out of

trials may limit what can be concluded from their results.

Patients with stroke-induced disability—which might include being unable to walk or needing help with day-to-day activities—account for more than half of the stroke survivor population. Including them in trials would yield study cohorts that better reflect—and treatments that better support—the real-world population, researchers say.

The findings were published in *JAMA Network Open*.

For the study, researchers used data from two clinical trials that did include patients with moderate or severe disability: one that took place between 2003 and 2008 and included over 20,000 patients, and another that enrolled over 3,800 patients between 2005 and 2015.

Stroke-induced disability is measured by the modified Rankin Scale (mRS) on a scale of increasing severity from zero to five. The study categorized patients as having no symptoms (mRS score of zero), mild disability (mRS score of one or two), or moderate to severe disability (mRS score of three or greater).

For the new study, the researchers looked at the severity of patients' post-stroke disability and whether they later experienced another stroke or major cardiovascular event.

"We found that rates of both recurrent stroke and major cardiovascular events were significantly higher in the participants with more severe disability," said Dr. Adam de Havenon, an associate professor of neurology at Yale School of Medicine and lead author of the study.

In the larger trial, 7.2% of those with no disability, 8.7% of those with mild disability, and 10.6% of those with moderate to severe disability experienced a subsequent stroke. This pattern held true for the second

trial as well (6.4%, 9.0%, and 11.7%, respectively).

Similarly, rates of major cardiovascular events increased with greater disability, rising from 10.1% in patients with no disability to 17.2% in those with moderate to severe disability in the larger trial, and from 10.9% to 15.3% in the second one.

The findings suggest that patients with little to no stroke-induced disability may have less risk of recurrent stroke. By only including this group, clinical trials may not be capturing the full potential of any treatments being studied; conversely, the results of those trials may not extend to those with more severe disability.

"I approached this from the perspective of a clinician wanting to see research that generalizes to all the patients that I'm treating, not just some," said de Havenon. "But as a researcher I also began to wonder whether we were underrepresenting some demographics as a result of excluding patients with disability."

The study did reveal that patients with greater post-stroke disability were more likely to be female or from underrepresented racial and ethnic populations. Excluding individuals with more severe disability, therefore, would also reduce representation of these groups in trials.

"These findings are important because not only should we strive to have trials that are generalizable in terms of disability, but also in terms of gender, race, and ethnicity," said de Havenon.

Some trials may exclude participants with more severe disability due to concerns about protocol adherence or attrition rates. However, in their study, de Havenon and his colleagues found that straying from protocol or disenrolling occurred at similar rates across all levels of disability.

The takeaway, says de Havenon, is that trial designers should include participants with a range of disability.

"It is true that individuals with moderate to severe disability require extra considerations when thinking about a trial with long-term follow-up," said de Havenon. "But if you start thinking about those considerations and consult stroke survivors who have moderate disability as you design the trial, it's not such a challenge. Clinical trials for other disease states include participants with disability. There's no reason stroke trials shouldn't."

More information: Adam de Havenon et al, Disability and Recurrent Stroke Among Participants in Stroke Prevention Trials, *JAMA Network Open* (2024). DOI: 10.1001/jamanetworkopen.2024.23677

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