Stent-Retriever Thrombectomy for Stroke

TO THE EDITOR: In their report on the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial, Saver et al. (June 11 issue)\(^1\) provide additional evidence on the effectiveness of endovascular therapy for acute ischemic stroke.\(^2\) In phase 3 stroke trials, the functional outcome on the modified Rankin scale is typically regarded as an important and valid measure. In the SWIFT PRIME trial, the effect of treatment on this functional outcome was impressively large. However, the blinding of this partly subjective assessment is crucial to minimizing bias. In this study, patients and their proxies were aware of the treatment they received, and the blind may easily have been broken. In the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN),\(^5\) we created masked structured reports, which were assessed by an independent committee. In the SWIFT PRIME trial, local investigators were responsible for the assessment of outcomes, even if they were not otherwise involved with the trial. This factor may have influenced the score on the modified Rankin scale.

In this otherwise very well conducted trial, the treatment effect on secondary outcomes pointed in the desired direction, which corroborates the observed effect on the primary outcome. Nevertheless, we have to remain aware that any outcome assessment that is not properly blinded, particularly in stroke trials, may lead to an overestimation of the treatment effect.

Olvert A. BERKHEMER, M.D.
Academic Medical Center
Amsterdam, the Netherlands
o.a.berkhemer@amc.uva.nl

Wim H. van Zwam, M.D., Ph.D.
Maastricht University Medical Center
Maastricht, the Netherlands

Diederik W.J. Dippel, M.D., Ph.D.
Erasmus University Medical Center
Rotterdam, the Netherlands

for the MR CLEAN Investigators

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1508744

TO THE EDITOR: In the editorial accompanying the article by Saver et al., Furlan\(^1\) concludes that in patients with acute ischemic stroke, endovascular therapy is superior to the use of intravenous tissue plasminogen activator (t-PA). Since five recently published randomized trials that he cites support this conclusion, even skeptics of endovascular therapy will be convinced, according to the editorialist.

However, in the comparison between these two treatments, there is one point that has not been fully addressed. In all five of the randomized trials that Furlan describes, patients in the
control group were assigned to receive intravenous t-PA, but the temporal window for enrollment showed some differences among the studies and, more important, was extended up to a time limit (from 4.5 to 12 hours) that exceeded the interval that is recognized as an effective window for intravenous t-PA. Although effectiveness has been shown when intravenous t-PA is administered within 3 to 4.5 hours after the onset of symptoms, current evidence indicates that thrombolysis is ineffective when it is administered beyond this temporal window. In our view, a full demonstration of superiority of endovascular therapy would require a more selective design of the trials, in which the two treatments would be administered within 3 to 4.5 hours after symptom onset.

Sabrina Trippoli, Pharm.D.
Valeria Fadda, Pharm.D.
Andrea Messori, Pharm.D.
Tuscany Region Health Service
Florence, Italy
andrea.messori.it@gmail.com

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMct1508744

THE AUTHORS REPLY: We believe that the larger treatment effect in SWIFT PRIME than in MR CLEAN reflects vascular biology, not assessment methodology. Both trials were assessed in a blinded manner with respect to the score on the modified Rankin scale. In our study, we used the more stringent assessment method that included in-person examination of the patients, multiple informants, and explicit decision rules. In MR CLEAN, investigators used an older approach that relied on telephone interviews with a single person (a technique that is vulnerable to informant bias) and no explicit decision rules (introducing noise). The concern arises that improperly blinded assessments potentially caused an underestimation of the treatment effect in MR CLEAN. Indeed, among the five trials cited by Berkhemer et al. showing the positive effects of endovascular therapy, the absolute difference between the endovascular group and the medical group in the frequency of functional independence (a score of 0 to 2 on the modified Rankin scale) at 90 days ranged from 13.5 to 31.4 percentage points. MR CLEAN was the outlier on the low end of the range (13.5 percentage points), whereas SWIFT PRIME was squarely in the middle (24.7 percentage points).

However, almost certainly, the source of these differences in treatment effect lies not in the techniques for ascertainment on the modified Rankin scale but in the trial differences in patient populations, imaging-selection strategies, reperfusion success, and treatment alacrity. Outcome differences across the five trials correlate tightly with the reperfusion rate (r=0.87) and speed (r=0.89). Among patients in SWIFT PRIME, as compared with those in MR CLEAN, reperfusion occurred more frequently (88% vs. 59%) and more quickly (252 minutes vs. 332 minutes). The powerful collective message of these studies is: to maximize benefit to patients, we must open up arteries fast and well.

Jeffrey L. Saver, M.D.
University of California, Los Angeles
Los Angeles, CA
jsaver@mednet.ucla.edu

Mayank Goyal, M.D.
University of Calgary
Calgary, AB, Canada

Hans-Christoph Diener, M.D., Ph.D.
University of Essen
Essen, Germany

for the SWIFT PRIME Investigators

Since publication of their article, Drs. Goyal and Diener report no further potential conflict of interest. Dr. Saver reports that the Regents of the University of California have received funding for his services to Neuravi as a scientific consultant regarding trial design and conduct. No further potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMct1508744
THE EDITORIALIST REPLIES: The recent endovascular trials have shown the superiority of endovascular therapy over intravenous t-PA alone in patients with large-vessel occlusion. The benefit of intravenous t-PA as a bridge to endovascular therapy remains unproven. The initiation of t-PA while a patient is awaiting endovascular therapy does not appear to increase risk and may provide some additional benefit. A trial comparing intravenous t-PA with endovascular therapy in patients with large-vessel occlusion within 4.5 hours after symptom onset will probably never be done. First, any intravenous or intraarterial reperfusion therapy will be more efficacious when started sooner. Second, all the patients in the cited trials received intravenous t-PA before undergoing endovascular therapy — in other words, recanalization had not occurred after t-PA alone. Third, the comparison would have to be restricted to patients who had received a diagnosis of large-vessel occlusion. The evidence is now overwhelming that in patients with large-vessel occlusion, endovascular therapy has superior rates of recanalization and clinical efficacy. The use of intravenous t-PA is better than no therapy, but hospitals need a strategy to access endovascular therapy for the treatment of patients with occluded large vessels.

Anthony J. Furlan, M.D.
University Hospitals Case Medical Center
Cleveland, OH
anthony.furlan@uhhospitals.org

Since publication of his article, the author reports no further potential conflict of interest.

DOI: 10.1056/NEJMc1507644

Trends in Mental Health Care among Children and Adolescents

TO THE EDITOR: Amidst concerns about the dearth of mental health services, it is encouraging that outpatient mental health treatment in youth increased in the United States between 1996–1998 and 2010–2012, per Olfson et al. (May 21 issue). The fact that this increase in treatment use paralleled a decline in severe mental health impairment raises a few questions. First, it would be interesting to see whether the increased use of mental health services at earlier stages of illness had slowed the progression of illness and resulted in lower levels of mental health impairment. Second, the use of a measure based on parents’ reporting (Columbia Impairment Scale) to assess mental health impairment may have resulted in underdetection of internalizing disorders and substance abuse, especially in adolescents. A youth self-reporting measure is more likely to capture impairment due to these issues accurately.

Overall, the finding that fewer than half the severely impaired youths received services should guide mental health providers to redouble efforts to raise levels of awareness and improve access to care.

Deepika Shaligram, M.D.
Newton–Wellesley Hospital
Newton, MA

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1507642

TO THE EDITOR: Olfson et al. found increases in the percentage of youths receiving psychotherapy and psychotropic medications in the United States between 1996–1998 and 2010–2012. However, the interpretation of these results may be compromised by the fact that psychotherapy use was defined as one or more psychotherapy visits. Although it is acknowledged that no information on the quality or effectiveness of care is provided, an additional major limitation may result from the definition of psychotherapy itself. Psychotherapy is a treatment method that aims to ameliorate symptoms and functional impairment through focus on the patient’s behavior, thoughts, and affect; the social context; and possibly the therapeutic relationship. In parallel with psychotropic medication, the presence of an “active ingredient” is a sine qua non of psychotherapeutic treatment. Whatever this specified or unspecified ingredient may be, its production cannot occur in very few visits. Undoubtedly, the increase in outpatient treatment among U.S. youths is of great importance and may reflect better public awareness and fewer barriers to accessing care. Still, it remains to be proved whether this trend also reflects an increase in the use of psychotherapy.

Trends in Mental Health Care among Children and Adolescents

TO THE EDITOR: Amidst concerns about the dearth of mental health services, it is encouraging that outpatient mental health treatment in youth increased in the United States between 1996–1998 and 2010–2012, per Olfson et al. (May 21 issue). The fact that this increase in treatment use paralleled a decline in severe mental health impairment raises a few questions. First, it would be interesting to see whether the increased use of mental health services at earlier stages of illness had slowed the progression of illness and resulted in lower levels of mental health impairment. Second, the use of a measure based on parents’ reporting (Columbia Impairment Scale) to assess mental health impairment may have resulted in underdetection of internalizing disorders and substance abuse, especially in adolescents. A youth self-reporting measure is more likely to capture impairment due to these issues accurately.

Overall, the finding that fewer than half the severely impaired youths received services should guide mental health providers to redouble efforts to raise levels of awareness and improve access to care.

Deepika Shaligram, M.D.
Newton–Wellesley Hospital
Newton, MA

No potential conflict of interest relevant to this letter was reported.


DOI: 10.1056/NEJMc1507642

TO THE EDITOR: Olfson et al. found increases in the percentage of youths receiving psychotherapy and psychotropic medications in the United States between 1996–1998 and 2010–2012. However, the interpretation of these results may be compromised by the fact that psychotherapy use was defined as one or more psychotherapy visits. Although it is acknowledged that no information on the quality or effectiveness of care is provided, an additional major limitation may result from the definition of psychotherapy itself. Psychotherapy is a treatment method that aims to ameliorate symptoms and functional impairment through focus on the patient’s behavior, thoughts, and affect; the social context; and possibly the therapeutic relationship. In parallel with psychotropic medication, the presence of an “active ingredient” is a sine qua non of psychotherapeutic treatment. Whatever this specified or unspecified ingredient may be, its production cannot occur in very few visits. Undoubtedly, the increase in outpatient treatment among U.S. youths is of great importance and may reflect better public awareness and fewer barriers to accessing care. Still, it remains to be proved whether this trend also reflects an increase in the use of psychotherapy.