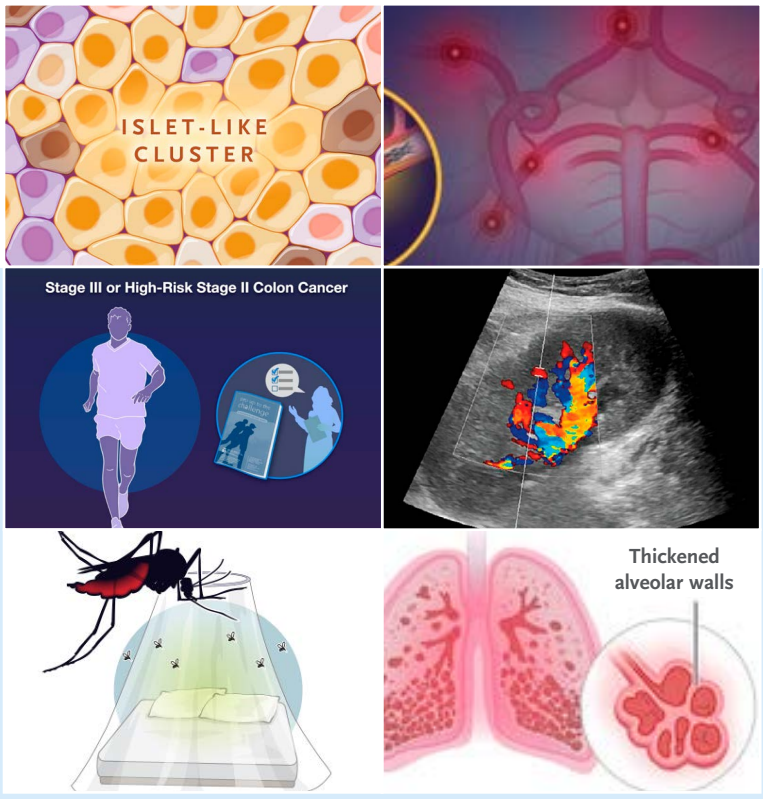
The NEW ENGLAND JOURNAL of MEDICINE

Notable Articles of 2025

A collection of articles from the *New England Journal of Medicine* selected by NEJM editors



NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2025

Dear Reader,

We're very lucky. As editors, we get to evaluate much of the research that immediately shapes patient care and help bring it to our readers. It's a mixture of high- and low-tech and ranges from enormous multinational studies to single patients. This year's Notable Articles represent a range of topics and approaches to give you an idea of the diversity of what we publish.

Bacterial vaginosis is associated with many consequences for women, including increased susceptibility to recurrent bacterial vaginosis, other infections, and problems with birth outcomes. And it's notoriously difficult to eradicate with high rates of recurrence even with monogamous male partners. The solution? Prevent recolonization by treating male sexual partners. Such treatment drops recurrence rates significantly and could substantially decrease the need for retreatment.

Can we extend the benefits of thrombolysis and thrombectomy in treating stroke to a larger group of patients? We published several stroke trials this year with decidedly mixed results. For example, a pair of studies showed that thrombectomy in medium-sized and smaller, more distal vessels failed to improve outcomes compared with medical therapy. Other studies suggested that thrombolysis in combination with thrombectomy was better than thrombectomy alone for large vessel strokes, indicating that these therapies might be extended to a larger group of patients. For physicians like me, who trained at the beginning of the era of thrombolysis for stroke, it's incredibly gratifying to have more options for these patients.

New ways to lower blood pressure and serum lipids hold great promise for reducing cardiovascular disease and stroke risk. Newer treatment targets and drugs hold promise for enlarging the therapeutic arsenal for hypertension and hyperlipidemia. These include inhibitors of aldosterone synthase (such as baxdrostat) and compounds that act on proteins important in lipoprotein synthesis and maintenance, such as lipoprotein(a), PCSK9, and ANGPTL3, all of which we published this year. It will be interesting to see how these newer agents get used together with existing drugs. Altogether, however, they show promise for treating hypertension and hyperlipidemia and further dropping rates of cardiovascular diseases.

Oncology has made great strides recently with the addition of a broad array of new agents. Not all advances are new drugs, however, and some are decidedly low-tech. For example, exercise can have a profound impact on disease-free survival among patients with colon cancer. But in other areas, sometimes less is more. In women who have breast cancer with positive nodes but respond well to neoadjuvant chemotherapy, nodal irradiation does not reduce recurrence rates or death from breast cancer but is associated with more adverse events. Of course, high-tech approaches also continue to be valuable. We now have further evidence that tumors that are mismatch repair deficient respond well to an immune checkpoint inhibitor that blocks the PD-1 protein, often to the extent that patients can avoid surgery.

The treatment of type 2 diabetes and obesity has been revolutionized by the development of drugs that bind to the GLP-1 receptor and related proteins. These drugs are all large lipopeptides that are expensive to produce and that generally need to be delivered parenterally. However, this year we've seen a phase 3 trial of an orally bioavailable small molecule GLP-1 receptor agonist. As small molecules should be easier to produce, store, and deliver, agents such as this hold promise for increasing the availability of these treatments.

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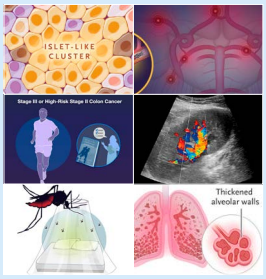
Progress comes gradually in many diseases. Pulmonary fibrosis has been a particularly difficult area. But in two companion trials, the drug nerandomilast, a phosphodiesterase 4B inhibitor, showed promise in reducing the rate of decrease in forced vital capacity. While neither curing nor halting the disease, more tools to help in this difficult field are welcome. Gene editing is coming into its own in a large variety of ways. This year we published on an engineered pig model with 69 genomic edits, which allowed a transplant of the engineered kidney into a human recipient without evidence of hyper rejection; CRISPR-Cas9 gene editing of patient cells to treat carbamoyl-phosphate synthetase 1 deficiency, a genetic disease with a high mortality rate in infancy; and CRISPR-Cas12b gene editing and lentiviral transduction of allogeneic donor islet cells to allow transplantation without immune suppression. We are still at the beginning of the uses of this methodology. Stay tuned!

Let me conclude with my own field, infectious disease. Ivermectin has many uses but one of the most common is to kill ectoparasites. Mosquitos are basically large ectoparasites, and they, too, can be killed by ivermectin. In a large cluster-randomized study, mass administration of ivermectin decreased the rate of malaria acquisition in children and adolescents in Kenya as compared with another antiparasitic drug, albendazole. Ivermectin could become a viable approach to malaria prevention.

One of the benefits of being an editor at NEJM is the chance to be among the first to review impactful studies. Already, we have exciting work coming up for 2026. I hope that you will enjoy it together with us.

Sincerely,
Eric J. Rubin, M.D., Ph.D.
Editor-in-Chief, *New England Journal of Medicine*



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BONUS CONTENT

Explore these bonus notable articles from ***NEJM Evidence***, ***NEJM AI***, and ***NEJM Catalyst Innovations in Care Delivery***.

ORIGINAL ARTICLE

Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels

M. Psychogios,[1,2] A. Brehm,[1] M. Ribo,[3,4] F. Rizzo,[3,4] D. Strbian,[5] S. Räty,[5] J.F. Arenillas,[6,7] M. Martínez-Galdámez,[8] S.D. Hajdu,[9] P. Michel,[10] J. Gralla,[11] E.I. Piechowiak,[11] D.P.O. Kaiser,[12,13] V. Puetz,[13,14] F. Van den Bergh,[15] S. De Raedt,[16] F. Bellante,[17] A. Dusart,[17] V. Hellstern,[18] A. Khanafer,[18] G. Parrilla,[19] A. Morales,[19] J.S. Kirschke,[20] S. Wunderlich,[21] J. Fiehler,[22] G. Thomalla,[23] R. Lemmens,[24] J.P. Peluso,[25] M. Bolognese,[26] A. von Hessling,[27] A. van Es,[28] N.D. Kruyt,[29] J.M. Coutinho,[30] C. Castaño,[31] J. Minnerup,[32,33] W. van Zwam,[34] E. Dhondt,[35] C.H. Nolte,[36] P. Machi,[37] C. Loehr,[38] H.P. Mattle,[39] J.-H. Buhk,[40] J. Kaesmacher,[11,41] T. Dobrocky,[11] P. Papanagiotou,[42,43] A. Alonso,[44] M. Holtmannspoetter,[45] A. Zini,[46] L. Renieri,[47] F. Keil,[48] I. van den Wijngaard,[29,49] G. Kägi,[39,50] M. Terceño,[51] M. Wiesmann,[52] S. Amaro,[53] N. Rommers,[54] L. Balmer,[1] I. Fragata,[55] M. Katan,[56] R.R. Leker,[57] J.L. Saver,[58] J. Staals,[59] and U. Fischer,[39,56] for the DISTAL Investigators*

ABSTRACT

BACKGROUND

Endovascular treatment (EVT) of stroke with large-vessel occlusion is known to be safe and effective. The effect of EVT for occlusion of medium or distal vessels is unclear.

METHODS

We randomly assigned participants with an isolated occlusion of medium or distal vessels (occlusion of the nondominant or codominant M2 segment of the middle cerebral artery [MCA]; the M3 or M4 segment of the MCA; the A1, A2, or A3 segment of the anterior cerebral artery; or the P1, P2, or P3 segment of the posterior cerebral artery) to receive EVT plus best medical treatment or best medical treatment alone within 24 hours after the participant was last seen to be well. The primary outcome was the level of disability at 90 days, as assessed with the modified Rankin scale score.

RESULTS

A total of 543 participants (women, 44%; median age, 77 years) were included in the analysis: 271 were assigned to receive EVT plus best medical treatment and 272 to receive best medical treatment alone. The median score on the National Institutes of Health Stroke Scale (range, 0 to 42, with higher scores indicating more severe symptoms) at admission was 6 (interquartile range, 5 to 9). Intravenous thrombolysis was given to 65.4% of the participants. The predominant occlusion locations were the M2 segment (in 44.0% of the participants), M3 segment (in 26.9%), P2 segment (in 13.4%), and P1 segment (in 5.5%). In the comparison between EVT plus best medical treatment and best medical treatment alone, no significant difference in the distribution of modified Rankin scale scores was observed at 90 days (common odds ratio for improvement in the score, 0.90; 95% confidence interval, 0.67 to 1.22; P=0.50). All-cause mortality was similar in the two groups (15.5% with EVT plus best medical treatment and 14.0% with best medical treatment alone), as was the incidence of symptomatic intracranial hemorrhage (5.9% and 2.6%, respectively).

CONCLUSIONS

In persons with stroke with occlusion of medium or distal vessels, EVT did not result in a lower level of disability or a lower incidence of death than best medical treatment alone. (Funded by the Swiss National Science Foundation and others; DISTAL ClinicalTrials.gov number, NCT05029414.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Psychogios can be contacted at marios.psychogios@usb.ch or at the Department of Diagnostic and Interventional Neuroradiology, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland. Dr. Fischer can be contacted at urs.fischer@insel.ch or at the Department of Neurology, University Hospital Bern, Rosenbühlgasse 25, 3010 Bern, Switzerland.

*A list of the DISTAL investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Psychogios and Brehm contributed equally to this article.

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The NEW ENGLAND JOURNAL of MEDICINE

Endovascular Treatment for Stroke Due to Occlusion of Medium or Distal Vessels

A Research Summary based on Psychogios M et al. | 10.1056/NEJMoa2408954 | Published on February 5, 2025

WHY WAS THE TRIAL DONE?

Endovascular treatment (EVT) is beneficial in persons with an acute ischemic stroke caused by a large-vessel occlusion, but its effect for treatment of stroke caused by occlusion of medium or distal vessels is unclear. Data from randomized, controlled trials are needed to fill this knowledge gap.

HOW WAS THE TRIAL CONDUCTED?

Adults with an acute ischemic stroke caused by a confirmed isolated occlusion of medium or distal vessels who had a National Institutes of Health Stroke Scale score of 4 or higher (range, 0 to 42, with higher scores indicating more severe symptoms) were assigned to receive EVT plus best medical treatment or best medical treatment alone within 24 hours after the participant was last seen to be well. The primary outcome was the level of disability at 90 days, as assessed with the modified Rankin scale score (range, 0 to 6, with higher scores indicating more severe disability).

TRIAL DESIGN

- Pragmatic
- Assessor-blinded
- Randomized
- Location: 55 hospitals in 11 countries (mostly European)

RESULTS

The distribution of the modified Rankin scale scores at 90 days did not differ significantly between the trial groups. There were no substantial between-group differences in prespecified safety outcomes, including symptomatic intracranial hemorrhage within 24 hours, death from any cause within 90 days, and serious adverse events within 90 days.

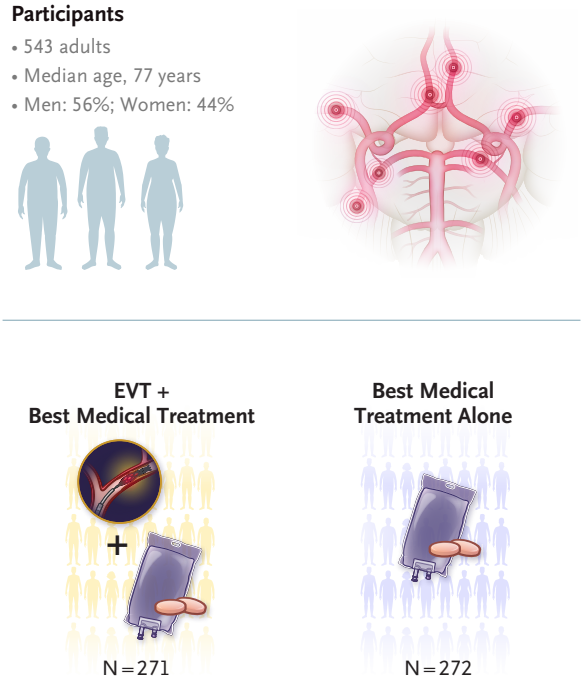
LIMITATIONS AND REMAINING QUESTIONS

- The pragmatic trial design is a potential limitation with its broad inclusion and exclusion criteria and allowance for interventionalists to use their own judgment when selecting techniques and materials.
- Some discrepancies were found between the site and core-laboratory ratings of the location of the vessel occlusion.

CONCLUSIONS

In persons with stroke due to occlusion of medium or distal vessels, EVT plus best medical treatment did not result in a lower level of disability or a lower incidence of death than best medical treatment alone.

NEJM QUICK TAKE | EDITORIAL



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ORIGINAL ARTICLE

Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion

M. Goyal,[1,2] J.M. Ospel,[1,2] A. Ganesh,[2] D. Dowlatshahi,[3,4] D. Volders,[5] M.A. Möhlenbruch,[6] M.A. Jumaa,[7,8] S.M. Nimjee,[9] T.C. Booth,[10,11] B.H. Buck,[12] J. Kennedy,[13] J.J. Shankar,[14] F. Dorn,[15] L. Zhang,[16] C. Hametner,[17] S. Nardai,[18] A. Zafar,[19] W. Diprose,[20] S. Vatanpour,[2] A. Stebner,[1] S. Bosshart,[1] N. Singh,[21] I. Sebastian,[2] K. Uchida,[22,23] K.J. Ryckborst,[2] R. Fahed,[3,4] S.X. Hu,[24] D.F. Vollherbst,[6] S.F. Zaidi,[7,8] V.H. Lee,[25] J. Lynch,[10] J.L. Rempel,[26] R. Teal,[27] A. Trivedi,[21] F.J. Bode,[28] A. Ogungbemi,[29] M. Pham,[30] P. Orosz,[18] M. Abdalkader,[31] C. Taschner,[32] J. Tarpley,[33] S. Poli,[34,35] R.-J. Singh,[36] R. De Leacy,[37] G. Lopez,[38,39] D. Sahlas,[40] M. Chen,[41] P. Burns,[42] J.D. Schaafsma,[43] R. Marigold,[44] A. Reich,[45] A. Amole,[46] T.S. Field,[47] R.H. Swartz,[48] F. Settecase,[49] G. Lenzsér,[50] S. Ortega-Gutierrez,[51-53] N. Asdaghi,[54] K. Lobotesis,[55] A.H. Siddiqui,[56] J. Berrouschot,[57] M. Mokin,[58,59] K. Ebersole,[60] H. Schneider,[61] A.J. Yoo,[62] J. Mandzia,[63] J. Klostranec,[64] C. Jadun,[65] T. Patankar,[66] E. Sauvageau,[67] R. Lenthall,[68] L. Peeling,[69] T. Huynh,[70] R. Budzik,[71] S.-K. Lee,[72] L. Makalanda,[73] M.R. Levitt,[74-78] R.J. Perry,[79] T. Hlaing,[80] B.S. Jahromi,[81] P. Singh,[82] A.M. Demchuk,[1,2,83] and M.D. Hill,[1,2,83,84] for the ESCAPE-MeVO Investigators*

ABSTRACT

BACKGROUND

Whether the large effect size of endovascular thrombectomy (EVT) for stroke due to large-vessel occlusion applies to stroke due to medium-vessel occlusion is unclear.

METHODS

In a multicenter, prospective, randomized, open-label trial with blinded outcome evaluation, we assigned patients with acute ischemic stroke due to medium-vessel occlusion who presented within 12 hours from the time that they were last known to be well and who had favorable baseline noninvasive brain imaging to receive EVT plus usual care or usual care alone. The primary outcome was the modified Rankin scale score (range, 0 [no symptoms] to 6 [death]) at 90 days, reported as the percentage of patients with a score of 0 or 1.

RESULTS

A total of 530 patients from five countries were enrolled between April 2022 and June 2024, with 255 patients assigned to the EVT group and 275 to the usual-care group. Most patients (84.7%) had primary occlusions in a middle-cerebral-artery branch. A modified Rankin scale score of 0 or 1 at 90 days occurred in 106 of 255 patien (41.6%) in the EVT group and in 118 of 274 (43.1%) in the usual-care group (adjuste rate ratio, 0.95; 95% confidence interval [CI], 0.79 to 1.15; P=0.61). Mortality at 90 da was 13.3% in the EVT group and 8.4% in the usual-care group (adjusted hazard rati 1.82; 95% CI, 1.06 to 3.12). Symptomatic intracranial hemorrhage occurred in 14 257 patients (5.4%) in the EVT group and in 6 of 272 (2.2%) in the usual-care grou

CONCLUSIONS

Endovascular treatment for acute ischemic stroke due to medium-vessel occlusion within 12 hours did not lead to better outcomes at 90 days than usual care. (Funded by the Canadian Institutes for Health Research and Medtronic; ESCAPE-MeVO ClinicalTrials.gov number, NCT05151172.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Hill can be contacted at michael.hill@ucalgary.ca or at the Calgary Stroke Program, Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Health Science Centre, 3330 Hospital Dr. NW, Rm. 2959, Calgary, AB T2N 2T9, Canada.

*A full list of the ESCAPE-MeVO investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Endovascular Treatment of Stroke Due to Medium-Vessel Occlusion

A Research Summary based on Goyal M et al. | 10.1056/NEJMoa2411668 | Published on February 5, 2025

WHY WAS THE TRIAL DONE?

In patients with acute ischemic stroke due to medium-vessel occlusion, nonrandomized studies suggest improvement in outcomes after endovascular thrombectomy (EVT). However, more-definitive data from prospective clinical trials specifically focused on the efficacy and safety of EVT for stroke due to medium-vessel occlusion are limited.

HOW WAS THE TRIAL CONDUCTED?

Adults with acute ischemic stroke due to medium-vessel occlusion who presented at an emergency department within 12 hours after the time they were last known to be well were assigned to receive EVT plus usual care or usual care alone. The primary outcome was the modified Rankin scale score (range, 0 [no symptoms] to 6 [death]) at 90 days, reported as the percentage of patients with a score of 0 or 1 (excellent functional outcome).

TRIAL DESIGN

- Phase 3
- Prospective
- Open-label
- Randomized
- Controlled
- Blinded outcome evaluation
- Location: 58 sites across 5 countries in North America and Europe

RESULTS

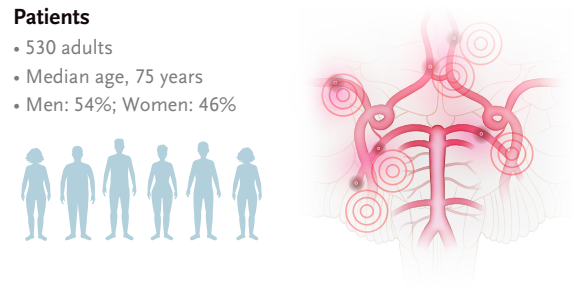
Functional outcomes at 90 days were similar in the two groups. Mortality at 90 days (a secondary outcome) appeared to be higher in the EVT group than in the usual-care group. Serious adverse events, including symptomatic intracranial hemorrhage, occurred more frequently in the EVT group than in the usual-care group.

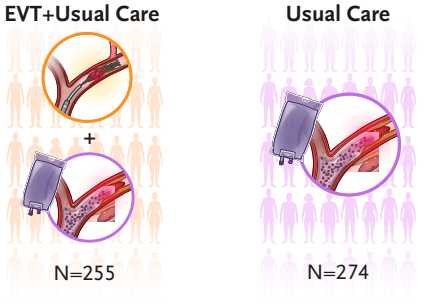
LIMITATIONS AND REMAINING QUESTIONS

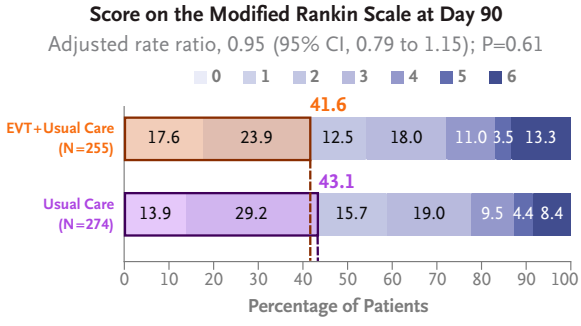
- No information is available on how many patients were treated with EVT outside the trial. It is possible that treatment of patients with EVT outside the trial biased the result toward the null.
- Individual neurointerventionalists were not credentialed for the trial, which may have influenced technical and safety outcomes.

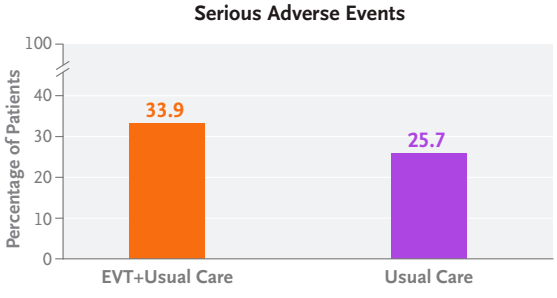
CONCLUSIONS

In adults with acute ischemic stroke caused by medium-vessel occlusion, endovascular thrombectomy within 12 hours did not lead to better outcomes at 90 days than usual care.









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EDITORIAL

Medium- and Distal-Vessel Occlusion — The Limit of Thrombectomy?

J Mocco, M.D.[1]

Few procedures have gone through a decade of practice-changing clinical trials as impressive as thrombectomy for stroke. Beginning in 2015 with multiple trials showing a benefit with thrombectomy in early large-vessel occlusion, followed by the extended-window trials in 2018 and then the large core trials in 2023, it seemed that no corner of the cerebrovasculature would not have a substantial benefit from a proper clot removal — until now.

The ESCAPE-MeVO (Endovascular Treatment to Improve Outcomes for Medium Vessel Occlusions) trial[1] and DISTAL (Endovascular Therapy plus Best Medical Treatment [BMT] versus BMT Alone for Medium Vessel Occlusion Stroke — A Pragmatic, International, Multicenter, Randomized Trial),[2] the results of which are now published in the *Journal*, provide data showing limits to the effectiveness of thrombectomy for ischemic stroke. Despite findings from post hoc analyses of previous trials[3] and observational cohorts[4] that have suggested a benefit with thrombectomy in stroke due to medium-vessel occlusion and possibly also to distal-vessel occlusion (defined, in combination, as occlusions beyond locations in the M1 segment [main trunk] of the middle cerebral artery or in the basilar artery), these two trials showed that thrombectomy added no clinical benefit as compared with best medical management alone. Furthermore, the ESCAPE-MeVO trial appeared to show higher mortality in the thrombectomy group than in the usual-care group (13.3% vs. 8.4%; adjusted hazard ratio, 1.82; 95% confidence interval [CI], 1.06 to 3.12), whereas mortality in DISTAL was 15.5% and 14.0%, respectively (odds ratio, 1.17; 95% CI, 0.71 to 1.90). These findings are fundamental to any future consideration of thrombectomy for stroke unrelated to large-vessel occlusion.

Thrombectomy for stroke unrelated to large-vessel occlusion (defined as thrombectomy beyond the M1 or basilar-artery locations) has become an increasingly accepted practice. The number of new publications listed in MEDLINE discussing the role of "medium vessel occlusion stroke thrombectomy" increased from 8 in 2020, to 38 in 2022, and to 99 in 2024[5]; with regard to "distal vessel occlusion stroke thrombectomy," the number increased from 83 in 2020, to 94 in 2022, and to 138 in 2024.[6] These increasingly common publications almost exclusively suggest a benefit with thrombectomy. With high-quality data from randomized, controlled trials in hand, we must critically and cautiously reexamine current practice.

The inclusion criteria of these two trials varied from those of previous randomized, controlled trials of thrombectomy, beyond criteria related to vessel location. Enrollment included patients with a baseline modified Rankin scale score of 2 or higher (on a scale from 0 [no symptoms] to 6 [death]), which was observed in 20% of the patients in DISTAL and in an unknown percentage in the ESCAPE-MeVO trial, which did not use the modified Rankin scale but excluded patients "requiring daily nursing care or assistance with activities of daily living." These broadened criteria may have reduced the potential benefit because of the difficulty in ameliorating baseline disability.

In addition, both trials enrolled patients with a National Institutes of Health Stroke Scale

(NIHSS) score of 5 or lower (on a scale from 0 to 42, with higher scores indicating more severe neurologic deficit) if a disabling deficit was present. The median NIHSS score in DISTAL was 6, with 41% of the patients presenting with an NIHSS score of 5 or lower. Given the increasing uptake of thrombectomy for ischemic stroke due to medium- or distal-vessel occlusion, it is possible that physicians chose intervention over randomization for potentially eligible patients with substantial deficits. Such potential bias may also explain the decade-older median ages in both trials (75 years in the ESCAPE-MeVO trial and 77 years in DISTAL) than in HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials)[7] and the SWIFT PRIME (Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment) trial[8] — a result that implies a possibility that physicians chose treatment rather than randomization for younger patients. The authors of DISTAL hypothesize that "physicians' beliefs regarding the efficacy of [endovascular thrombectomy] for occlusion of medium or distal vessels may have led to selective inclusion of participants," and the authors of the ESCAPE-MeVO trial consider that "it is possible that treatment of patients outside the trial biased the result toward the null."

Ultimately, these data provide important information on the current state of the field and where future efforts should focus. For instance, the percentage of patients with symptomatic intracranial hemorrhage was numerically higher in the thrombectomy group than in the usual-care group in each trial, and its occurrence was associated with death at 90 days in the ESCAPE-MeVO trial. The authors of that trial hypothesize that it is possible that "other technical approaches may be more effective." That trial required stent retrievers as a first-line approach, and although DISTAL did not mandate an approach, stent retrievers were used in 80% of the patients. Similarly, both trials showed lower percentages of patients with reperfusion (75.1% in the ESCAPE-MeVO trial and 71.7% in DISTAL) than has been seen in most previous trials. Whether this result is due to technical limitations of the chosen approaches or whether physician decision making for older patients, or for those with less-severe deficits, played a role is unclear.

In addition, these data confirm the importance of timing. The ESCAPE-MeVO authors hypothesize that "it is possible that decision making in stroke due to middle-vessel occlusion is more nuanced than that in stroke due to large-vessel occlusion" and that "additional time may have been needed … to arrange for general anesthesia." General anesthesia was used in 41.3% of the patients in the ESCAPE-MeVO trial, as compared with 9.1% in the original ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing [Computed Tomography] to Recanalization Times) trial.[9] The authors go so far as to consider whether pneumonia (a leading serious adverse event) and other infections "could be related to adjunct interventions such as the type of procedural sedation."

No matter how one considers these data, there is no question that they represent the current ground zero of evidence to inform decision making regarding the use of thrombectomy for stroke due to medium- and distal-vessel occlusion. The data clearly show that thrombectomy for distal-vessel occlusions should not be an assumed default care pathway.

Where do we go from here? The authors of the ESCAPE-MeVO trial correctly emphasize the importance of rigorously conducted randomized, controlled trials. The stroke community should not be complacent. Rather, we must thoroughly test appropriate questions, evaluate alternative approaches, and not allow bias to interfere with identifying the best treatment strategies for patients with stroke. Let us not forget that almost half of all the enrolled patients in these trials had substantial disability at 90 days. There remains a continuing mandate, with more work required, to study how we can improve outcomes in patients. These two trials prove that their patient populations did not have a benefit with thrombectomy, and as such, performance of thrombectomy for medium- or distal-vessel occlusion in a manner consistent with these trials is not evidence-based. Further effort, grounded in high-quality data science, is needed to evaluate alternative approaches for medium- or distal-vessel occlusion, be they medical or procedural.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

[1]Department of Neurosurgery, Icahn School of Medicine, Mount Sinai Health System, New York.

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1. Goyal M, Ospel JM, Ganesh A, et al. Endovascular treatment of stroke due to medium-vessel occlusion. N Engl J Med. DOI: 10.1056/NEJMoa2411668.
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BRIEF REPORT

Xenotransplantation of a Porcine Kidney for End-Stage Kidney Disease

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SUMMARY

Xenotransplantation offers a potential solution to the organ shortage crisis. A 62-year-old hemodialysis-dependent man with long-standing diabetes, advanced vasculopathy, and marked dialysis-access challenges received a gene-edited porcine kidney with 69 genomic edits, including deletion of three glycan antigens, inactivation of porcine endogenous retroviruses, and insertion of seven human transgenes. The xenograft functioned immediately. The patient's creatinine levels decreased promptly and progressively, and dialysis was no longer needed. After a T-cell–mediated rejection episode on day 8, intensified immunosuppression reversed rejection. Despite sustained kidney function, the patient died from unexpected, sudden cardiac causes on day 52; autopsy revealed severe coronary artery disease and ventricular scarring without evident xenograft rejection. (Funded by Massachusetts General Hospital and eGenesis.)

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EDITORIALS

Xenotransplantation — Long Awaited, Much Learned, Much More to Be Learned

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Despite vigorous efforts to expand the transplantation of organs from deceased and living donors, the gap between supply and demand persists. This lack of available organs has become a major factor in limiting the lifesaving potential of organ transplantation. Xenotransplantation, which has been hailed as the ultimate solution, seemed mirage-like until recently.

The dramatic breakthroughs that have been made in this field reflect the convergence of three major advances: successful genetic engineering of pigs with multiple gene knockouts (deletion of pig genes) and knock-ins (insertion of human genes); consistent survival of xenografts in nonhuman primate models for more than 1 year; and the emergence of the decedent model, in which xenotransplantation is performed and studied in humans who have been declared dead according to neurologic criteria.[1]

The survival and functioning of porcine kidneys that have been transplanted into decedent recipients without hyperacute rejection, as evidenced by the production of urine and decreased levels of serum creatinine,[2,3] paved the way for the Food and Drug Administration (FDA) to approve xenotransplantation into living recipients under its expanded-access protocol. To date, six approvals have been issued for such procedures (involving the transplantation of two hearts and four kidneys) performed between January 2022 and February 2025.

In this issue of the *Journal*, Kawai and colleagues report on kidney xenotransplantation performed in a living patient in March 2024.[4] The recipient was a 62-year-old man with end-stage kidney failure caused by diabetic nephropathy. The patient's relevant medical history included failed transplantation from a deceased donor, cardiovascular disease, and severe vasculopathy that limited dialysis-access options. The transplanted kidney had 10 genetic alterations (3 porcine gene deletions to eliminate expression of three glycan xenoantigens and 7 human gene additions to regulate complement, coagulation, and inflammation) and inactivation of porcine endogenous retroviruses.[5]

The patient received an immunosuppression regimen developed in the nonhuman primate model that consisted of three induction agents (antithymocyte globulin and anti-CD20 and anti-CD5 antibodies) and four maintenance agents (glucocorticoids, tacrolimus, mycophenolic acid, and anti-CD154 antibody). The kidney functioned immediately after transplantation. The serum creatinine level at first decreased but then rose, prompting biopsy that revealed T-cell–mediated rejection and complement protein C3 deposition. The patient was treated with standard antirejection therapy and a C3 inhibitor.

Over the ensuing 6 weeks, the patient had stable blood pressure, electrolyte profile, and kidney function, despite fluctuations in volume status. However, on postoperative day 52, the patient died from sudden cardiac arrest. The autopsy showed severe coronary artery disease with chronic sequelae, including cardiomegaly and diffuse myocardial fibrosis. The porcine kidney showed no apparent signs of rejection mediated by either T cells or antibodies or thrombotic microangiopathy.

This single case teaches much and raises many questions, with three key issues. First, the xenograft functioned well for 52 days, without sero-

logic or histologic evidence of antibody-mediated rejection. In contrast, biopsies of kidneys with a single rather than three gene knockouts that were performed 54 hours after transplantation into decedent recipients showed subtle signs of antibody-mediated responses, with microvascular inflammation and leukocytes within glomerular capillaries.[2] More sophisticated histoimmunologic phenotyping and bulk and spatial transcriptomic profiling confirmed antibody-mediated attack.[6] The patient in the current report had C3 deposition indicative of complement dysregulation, even with two human complement regulatory transgenes and early administration of a complement inhibitor. These observations open discussion as to the appropriate engineering of donor pigs — how many and which genes must be deleted or added. A corollary is the effect of these genetic alterations on the breeding potential of these pigs, a trait essential to achieving the primary goal of solving the organ shortage.

A second key lesson is that successful xenotransplantation clearly requires expanded immunosuppression regimens targeting T cells, B cells, and complement. Seven planned and two unplanned drugs were given to this xenograft recipient, as compared with the four drugs that are typically given to allograft recipients. Despite this intensified regimen, T-cell–mediated rejection occurred, necessitating further escalation. The 52-day time frame is simply insufficient to gauge the potentially deleterious effect of the profound immunosuppression that appears to be essential to sustaining a xenograft.

Finally, the patient's death, attributed to a fatal arrhythmia, raises diverse but related questions. The expanded-access, compassionate-use pathway has led to the selection of heart and kidney recipients who have extensive coexisting conditions and little physiologic reserve.[7-9] Although this patient's extensive history of cardiovascular disease and limited dialysis options facilitated a pathway to xenotransplantation, these issues undoubtedly increased the likelihood of life-threatening cardiovascular events. It is prudent to consider whether this vulnerability was exacerbated by abnormalities related to the metabolic control or hormonal responses of a porcine kidney.

In the wake of this and subsequent xenotransplantations, in February 2025, the FDA authorized two companies to initiate clinical trials in kidney xenotransplantation, including the approval of nine initial patients. Each xenotransplantation thus far has yielded a trove of invaluable insights. The next cases, together with ongoing investigations in nonhuman primate and decedent models, should provide crucial data about the safety, effectiveness, and viability of xenotransplantation as a solution to the current organ shortage.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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