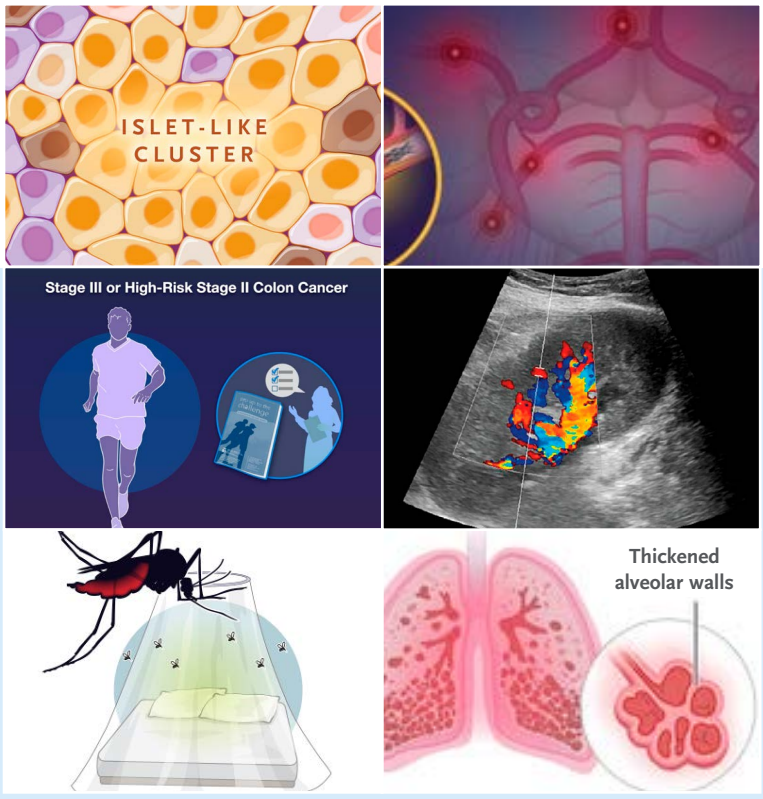
The NEW ENGLAND JOURNAL of MEDICINE

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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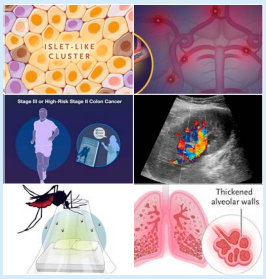
Progress comes gradually in many diseases. Pulmonary fibrosis has been a particularly difficult area. But in two companion trials, the drug nerandomilast, a phosphodiesterase 4B inhibitor, showed promise in reducing the rate of decrease in forced vital capacity. While neither curing nor halting the disease, 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.

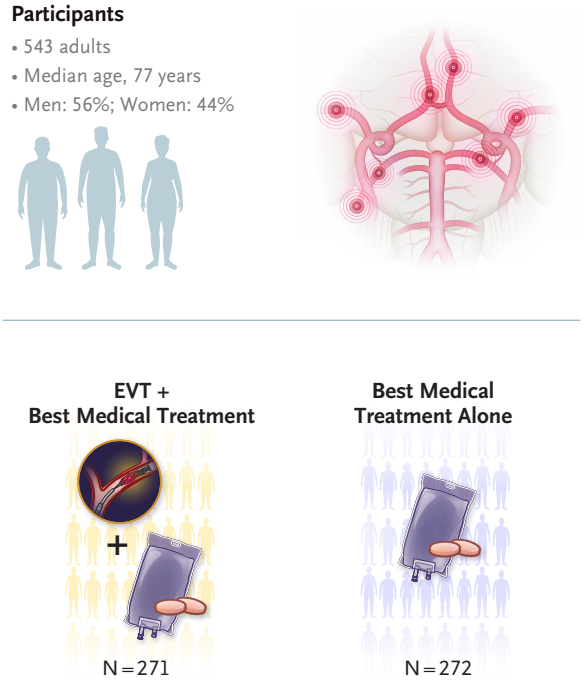
LIMITATIONS AND REMAINING QUESTIONS

- 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

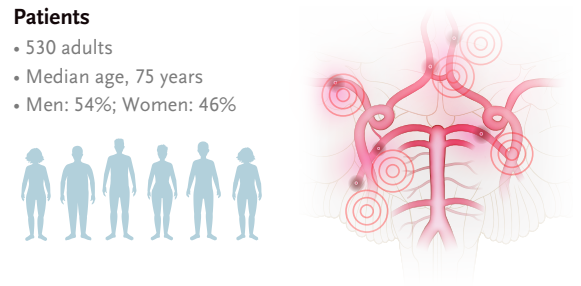
Functional outcomes at 90 days were similar in the two groups. Mortality at 90 days (a secondary outcome) appeared to be higher in the EVT group than in the usual-care group. Serious adverse events, including symptomatic intracranial hemorrhage, occurred more frequently in the EVT group than in the usual-care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

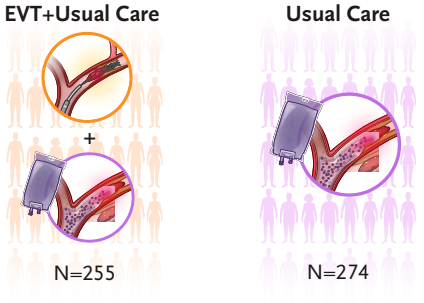
LIMITATIONS AND REMAINING QUESTIONS

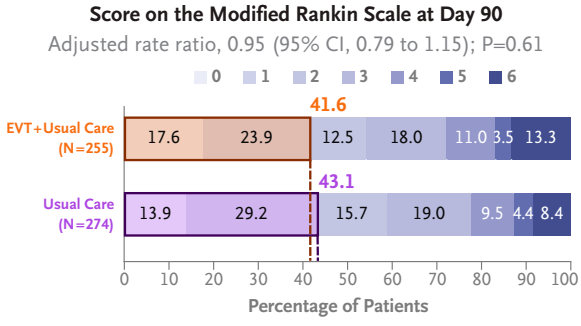
- No information is available on how many patients were treated with EVT outside the trial. It is possible that treatment of patients with EVT outside the trial biased the result toward the null.
- Individual neurointerventionalists were not credentialed for the trial, which may have influenced technical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

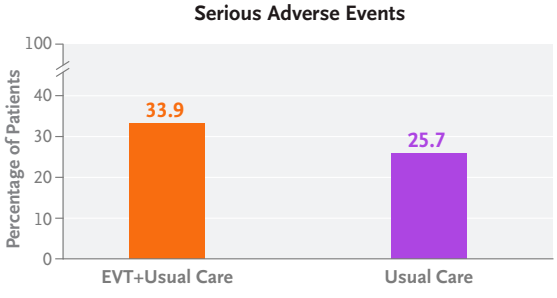
CONCLUSIONS

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.
2. Psychogios M, Brehm A, Ribo M, et al. Endovascular treatment for stroke due to occlusion of medium or distal vessels. N Engl J Med. DOI: 10.1056/NEJMoa2408954.
3. Menon BK, Hill MD, Davalos A, et al. Efficacy of endovascular thrombectomy in patients with M2 segment middle cerebral artery occlusions: meta-analysis of data from the HERMES Collaboration. J Neurointerv Surg 2019;11:1065-9.
4. Saber H, Desai SM, Haussen D, et al. Endovascular therapy vs medical management for patients with acute stroke with medium vessel occlusion in the anterior circulation. JAMA Netw Open 2022;5(10):e2238154.
5. National Library of Medicine. PubMed search results: "medium vessel occlusion stroke thrombectomy" (https://pubmed.ncbi.nlm.nih.gov/?term=medium+vessel+occlusion+stroke+thrombectomy).
6. National Library of Medicine. PubMed search results: "distal vessel occlusion stroke thrombectomy" (https://pubmed.ncbi.nlm.nih.gov/?term=distal+vessel+occlusion+stroke+thrombectomy).
7. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387:1723-31.
8. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med 2015;372:2285-95.
9. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med 2015;372:1019-30.

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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

Sandy Feng, M.D., Ph.D.[1]

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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1. Montgomery RA, Griesemer AD, Segev DL, Sommer P. The decedent model: a new paradigm for de-risking high stakes clinical trials like xenotransplantation. Am J Transplant 2024;24:526-32.
2. Montgomery RA, Stern JM, Lonze BE, et al. Results of two cases of pig-to-human kidney xenotransplantation. N Engl J Med 2022;386:1889-98.
3. Porrett PM, Orandi BJ, Kumar V, et al. First clinical-grade porcine kidney xenotransplant using a human decedent model. Am J Transplant 2022;22:1037-53.
4. Kawai T, Williams WW, Elias N, et al. Xenotransplantation of a porcine kidney for end-stage kidney disease. N Engl J Med 2025;392:1933-40.
5. Anand RP, Layer JV, Heja D, et al. Design and testing of a humanized porcine donor for xenotransplantation. Nature 2023;622:393-401.
6. Loupy A, Goutaudier V, Giarraputo A, et al. Immune response after pig-to-human kidney xenotransplantation: a multimodal phenotyping study. Lancet 2023;402:1158-69.
7. Griffith BP, Goerlich CE, Singh AK, et al. Genetically modified porcine-to-human cardiac xenotransplantation. N Engl J Med 2022;387:35-44.
8. Bobier C, Hurst DJ, Rodger D. Xenotransplantation under the Food and Drug Administration's Expanded Access pathway. Am J Transplant 2024;24:1911-2.
9. Griffith BP, Grazioli A, Singh AK, et al. Transplantation of a genetically modified porcine heart into a live human. Nat Med 2025;31:589-98.

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The NEW ENGLAND JOURNAL of MEDICINE

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Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis

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ABSTRACT

BACKGROUND

Bacterial vaginosis affects one third of reproductive-aged women, and recurrence is common. Evidence of sexual exchange of bacterial vaginosis–associated organisms between partners suggests that male-partner treatment may increase the likelihood of cure.

METHODS

This open-label, randomized, controlled trial involved couples in which a woman had bacterial vaginosis and was in a monogamous relationship with a male partner. In the partner-treatment group, the woman received first-line recommended antimicrobial agents and the male partner received oral and topical antimicrobial treatment (metronidazole 400-mg tablets and 2% clindamycin cream applied to penile skin, both twice daily for 7 days). In the control group, the woman received first-line treatment and the male partner received no treatment (standard care). The primary outcome was recurrence of bacterial vaginosis within 12 weeks.

RESULTS

A total of 81 couples were assigned to the partner-treatment group, and 83 couples were assigned to the control group. The trial was stopped by the data and safety monitoring board after 150 couples had completed the 12-week follow-up period because treatment of the woman only was inferior to treatment of both the woman and her male partner. In the modified intention-to-treat population, recurrence occurred in 24 of 69 women (35%) in the partner-treatment group (recurrence rate, 1.6 per person-year; 95% confidence interval [CI], 1.1 to 2.4) and in 43 of 68 women (63%) in the control group (recurrence rate, 4.2 per person-year; 95% CI, 3.2 to 5.7), which corresponded to an absolute risk difference of –2.6 recurrences per person-year (95% CI, –4.0 to –1.2; P<0.001). Adverse events in treated men included nausea, headache, and metallic taste.

CONCLUSIONS

The addition of combined oral and topical antimicrobial therapy for male partners to treatment of women for bacterial vaginosis resulted in a lower rate of recurrence of bacterial vaginosis within 12 weeks than standard care. (Funded by the National Health and Medical Research Council of Australia; StepUp Australian New Zealand Clinical Trials Registry number, ACTRN12619000196145.)

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*The StepUp Team members are listed in the Supplementary Appendix, available at NEJM.org.

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Male-Partner Treatment to Prevent Recurrence of Bacterial Vaginosis

A Research Summary based on Vodstrcil LA et al. | 10.1056/NEJMoa2405404 | Published on March 6, 2025

WHY WAS THE TRIAL DONE?

Studies have shown that men may harbor bacterial species associated with bacterial vaginosis in the distal urethra and subpreputial space and that the penile microbiota is predictive of a woman's risk of bacterial vaginosis. Evidence of sexual exchange of bacterial vaginosis–associated organisms suggests that treating partners could increase the likelihood of cure.

HOW WAS THE TRIAL CONDUCTED?

Women with bacterial vaginosis who were in a monogamous relationship with a male partner received first-line recommended antimicrobial agents; their male partners were assigned to receive either partner treatment — oral metronidazole and 2% clindamycin cream applied to penile skin — or no partner treatment. The primary efficacy outcome was recurrence of bacterial vaginosis within 12 weeks.

TRIAL DESIGN

- Open-label
- Randomized
- Controlled
- Location: Five health centers in three Australian states

RESULTS

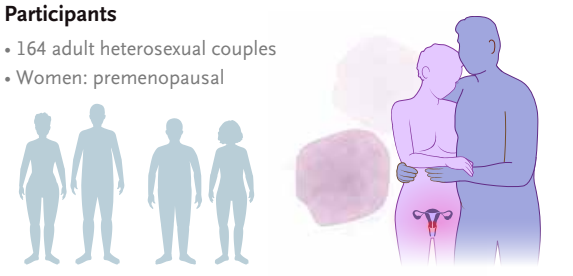
The trial was stopped early after an interim analysis showed that treating only the female partner was inferior to treating both partners with respect to recurrence of bacterial vaginosis by week 12. Adverse events were reported by nearly half the treated male partners; the incidence of systemic adverse events in treated men was similar to that in the women. Common adverse events included nausea, headache, and metallic taste.

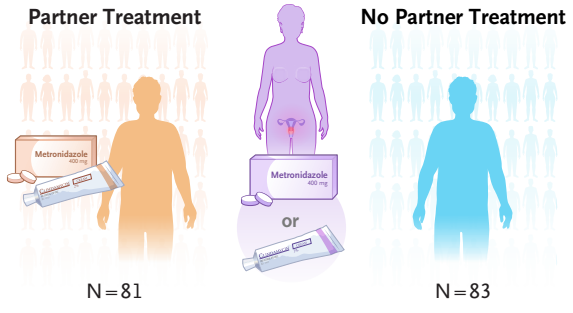
LIMITATIONS AND REMAINING QUESTIONS

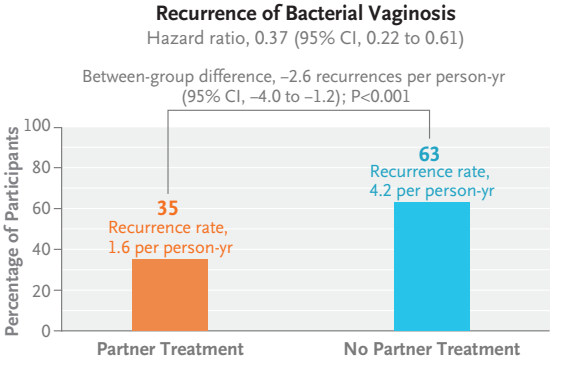
- Placebo cream was not given to any male partners, owing to concern that any topical cream might alter the penile microbiome.
- Participants and clinicians knew the trial-group assignments, but the laboratory staff and microscopist assessing the primary outcome did not.
- Most of the trial participants attended a single sexual health center in urban Australia, which may affect the generalizability of the results.

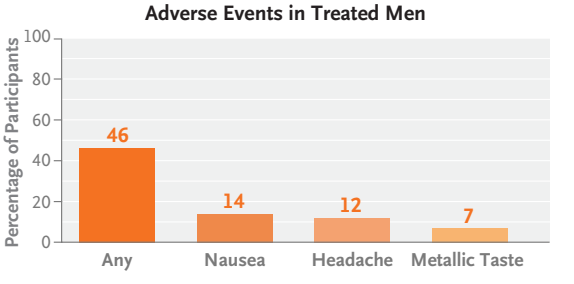
CONCLUSIONS

Treating male partners with oral metronidazole and topical clindamycin, in addition to treating female patients, resulted in a lower incidence of recurrent bacterial vaginosis within 12 weeks than treating only women.









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EDITORIALS

Bacterial Vaginosis — Time to Treat Male Partners

Christina A. Muzny, M.D., M.S.P.H.,[1] and Jack D. Sobel, M.D.[2]

Bacterial vaginosis, the most common cause of vaginal discharge in reproductive-age women,[1] is associated with multiple consequential adverse outcomes, including an increased risk of adverse birth outcomes, acquisition of human immunodeficiency virus and other sexually transmitted infections (STIs), pelvic inflammatory disease, and a high incidence of symptomatic recurrence.[2] Bacterial vaginosis is characterized as a polymicrobial vaginal dysbiosis due to a decrease in protective lactobacillus species and an increase in facultative and strictly anaerobic bacteria.[3] The incidence of symptomatic recurrence after treatment can be as high as 60% at 12 months.[4]

Despite substantial data supporting the role of sexual transmission of bacterial vaginosis–associated bacteria,[2,5] bacterial vaginosis is still unfortunately not accepted as an STI by practitioners. This situation is primarily attributable to a lack of agreement regarding the inciting agent or agents (although hypothetical models have been proposed[6]), the absence of a disease counterpart in men, and the erroneous belief that a first episode of bacterial vaginosis can occur in women without a history of sexual activity.[7] This prevailing perspective has been sustained by the failure of virtually all previous trials of male-partner treatment to show that such treatment prevents recurrence of bacterial vaginosis in women.[8,9] Critical gaps in knowledge of the pathogenesis of bacterial vaginosis have impeded advances in treatment and prevention, to the frustration of clinicians and patients.

In this context, Vodstrcil et al.[10] report in this issue of the *Journal* the results of a multicenter, randomized trial of combination oral metronidazole and topical clindamycin antimicrobial therapy for regular (monogamous) male partners at the time their female partner was treated for bacterial vaginosis, as compared with treatment of the woman alone, in an attempt to reduce recurrence of bacterial vaginosis. At 12 weeks, recurrence was documented in 24 of 69 women (35%) in the partner-treatment group (recurrence rate, 1.6 per person-year; 95% confidence interval [CI], 1.1 to 2.4) and in 43 of 68 women (63%) in the control group (recurrence rate, 4.2 per person-year; 95% CI, 3.2 to 5.7). These findings corresponded to an absolute risk difference of −2.6 recurrences per person-year (95% CI, −4.0 to −1.2). The trial design differed from that of previous failed trials of male-partner treatment[8,9] (which used oral antimicrobial therapies only) by using a combination of oral and topical antimicrobial therapy for male partners in an attempt to clear cutaneous penile and urethral carriage of bacterial vaginosis–associated bacteria.

The results of this trial are timely and important. They provide substantial evidence supporting the role of sexual transmission of bacterial vaginosis–associated bacteria, particularly within regular sexual partnerships. They also signify a need for a major change to the treatment approach of women with bacterial vaginosis with respect to how women should be counseled regarding the origin of their infection and to the need to engage their male partners in sharing responsibility for transmission and treatment.

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To date, there have been no effective strategies to prevent sexual transmission of bacterial vaginosis–associated bacteria, apart from consistent use of condoms.[2]

The major paradigm shift that this trial represents will require clinicians to educate their patients on the role of sexual transmission of bacterial vaginosis–associated bacteria when the pathogenesis of bacterial vaginosis is incompletely understood and the precise etiologic agent of this polymicrobial infection is not yet identified. It will also require a willingness of male partners to commit to taking both oral and topical medications, once notified by their female partner that she has bacterial vaginosis and that it is probably sexually transmitted. In the trial by Vodstrcil et al., 14% of the men in the intervention group reported taking less than 70% of their prescribed doses of medication, an early signal that male partner buy-in could be challenging in some situations. Nevertheless, adverse events related to topical clindamycin were uncommon among the men, and systemic side effects of oral metronidazole were similar to those in women and were no more common.

Some limitations of the trial affecting generalizability warrant mention. The trial, which was conducted in Australia, included a majority of persons of Western Pacific and European ethnic background. Substantial racial and ethnic disparities in the prevalence of bacterial vaginosis have been documented, with prevalence among Black women in North America being particularly high.[1] In addition, a majority of the male partners in both groups (80%) were uncircumcised and more than a quarter of women were using an intrauterine device (28% in the intervention group and 33% in the control group); both factors confer a predisposition to carriage of bacterial vaginosis–associated bacteria and an increased risk of relapse.[2] Reassuringly, the results appeared to be similar in subgroup analyses with stratification according to these factors, although the trial was not powered for these subgroups or to explore the association between these factors and recurrence of bacterial vaginosis. The trial overall was relatively small, but it was stopped early for efficacy. Finally, results apply specifically to women with regular male partners. Similar trials are needed in diverse populations to confirm and extend these findings.

Despite these limitations, this trial provides data critical to educating clinicians and patients about the role of sexual transmission of bacterial vaginosis–associated bacteria and the benefit of male-partner treatment. It is time to start the conversation.

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

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1. Peebles K, Velloza J, Balkus JE, McClelland RS, Barnabas RV. High global burden and costs of bacterial vaginosis: a systematic review and meta-analysis. Sex Transm Dis 2019;46:304-11.
2. Muzny CA, Balkus J, Mitchell C, et al. Diagnosis and management of bacterial vaginosis: summary of evidence reviewed for the 2021 Centers for Disease Control and Prevention sexually transmitted infections treatment guidelines. Clin Infect Dis 2022;74:Suppl_2:S144-S151.
3. Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. N Engl J Med 2005;353:1899-911.
4. Bradshaw CS, Morton AN, Hocking J, et al. High recurrence rates of bacterial vaginosis over the course of 12 months after oral metronidazole therapy and factors associated with recurrence. J Infect Dis 2006;193:1478-86.
5. Fethers KA, Fairley CK, Hocking JS, Gurrin LC, Bradshaw CS. Sexual risk factors and bacterial vaginosis: a systematic review and meta-analysis. Clin Infect Dis 2008;47:1426-35.
6. Muzny CA, Taylor CM, Swords WE, et al. An updated conceptual model on the pathogenesis of bacterial vaginosis. J Infect Dis 2019;220:1399-405.
7. Bump RC, Buesching WJ III. Bacterial vaginosis in virginal and sexually active adolescent females: evidence against exclusive sexual transmission. Am J Obstet Gynecol 1988;158:935-9.
8. Mehta SD. Systematic review of randomized trials of treatment of male sexual partners for improved bacteria vaginosis outcomes in women. Sex Transm Dis 2012;39:822-30.
9. Schwebke JR, Lensing SY, Lee J, et al. Treatment of male sexual partners of women with bacterial vaginosis: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis 2021;73(3):e672-e679.
10. Vodstrcil LA, Plummer EL, Fairley CK, et al. Male-partner treatment to prevent recurrence of bacterial vaginosis. N Engl J Med 2025;392:947-57.

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The NEW ENGLAND JOURNAL of MEDICINE

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Lepodisiran — A Long-Duration Small Interfering RNA Targeting Lipoprotein(a)

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ABSTRACT

BACKGROUND

Elevated lipoprotein(a) concentrations are associated with atherosclerotic cardiovascular disease. The safety and efficacy of lepodisiran, an extended-duration, small interfering RNA targeting hepatic synthesis of lipoprotein(a), are unknown.

METHODS

We randomly assigned participants in a 1:2:2:2:2 ratio to receive lepodisiran at a dose of 16 mg, 96 mg, or 400 mg at baseline and again at day 180, lepodisiran at a dose of 400 mg at baseline and placebo at day 180, or placebo at baseline and at day 180, all administered by subcutaneous injection. Data from the two groups that received lepodisiran at a dose of 400 mg at baseline were pooled for the primary analysis. The primary end point was the time-averaged percent change from baseline in the serum lipoprotein(a) concentration (lepodisiran difference from placebo [i.e., placebo-adjusted]) during the period from day 60 to day 180.

RESULTS

A total of 320 participants underwent randomization; the median baseline lipoprotein(a) concentration was 253.9 nmol per liter. The placebo-adjusted time-averaged percent change from baseline in the serum lipoprotein(a) concentration from day 60 to day 180 was −40.8 percentage points (95% confidence interval [CI], −55.8 to −20.6) in the 16-mg lepodisiran group, −75.2 percentage points (95% CI, −80.4 to −68.5) in the 96-mg group, and −93.9 percentage points (95% CI, −95.1 to −92.5) in the pooled 400-mg groups. The corresponding change from day 30 to day 360 was −41.2 percentage points (95% CI, −55.4 to −22.4), −77.2 percentage points (95% CI, −81.8 to −71.5), −88.5 percentage points (95% CI, −90.8 to −85.6), and −94.8 percentage points (95% CI, −95.9 to −93.4) in the 16-mg, 96-mg, 400-mg–placebo, and 400-mg–400-mg dose groups, respectively. Serious adverse events, none of which were deemed by investigators to be related to lepodisiran or placebo, occurred in 35 participants. Dose-dependent, generally mild injection-site reactions occurred in up to 12% (8 of 69) of the participants in the highest lepodisiran dose group.

CONCLUSIONS

Lepodisiran reduced mean serum concentrations of lipoprotein(a) from 60 to 180 days after administration. (Funded by Eli Lilly; ALPACA ClinicalTrials.gov number, NCT05565742.)

Author affiliations are listed at the end of the article. Dr. Nissen can be contacted at nissens@ccf.org or at C5Research, Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH, 44195.

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

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The NEW ENGLAND JOURNAL of MEDICINE

Lepodisiran — A Long-Duration siRNA Targeting Lipoprotein(a)

A Research Summary based on Nissen SE et al. | 10.1056/NEJMoa2415818 | Published on March 30, 2025

WHY WAS THE TRIAL DONE?

Elevated serum concentrations of lipoprotein(a) are associated with risk of atherosclerotic cardiovascular disease, aortic stenosis, and death from any cause. Traditional approaches to cardiovascular risk reduction have minimal effects on lipoprotein(a). Lepodisiran — a long-duration small interfering RNA (siRNA) that inhibits hepatic production of apolipoprotein(a) — showed promise for serum lipoprotein(a) reduction in a previous phase 1 study. Additional data are needed.

HOW WAS THE TRIAL CONDUCTED?

Adults 40 years of age or older who had a serum lipoprotein(a) concentration of at least 175 nmol per liter were assigned to receive subcutaneous injections of lepodisiran at a dose of 16 mg, 96 mg, or 400 mg at baseline and again at day 180; lepodisiran at a dose of 400 mg at baseline and placebo at day 180; or placebo at both time points. The primary end point was the time-averaged percent change from baseline in the serum lipoprotein(a) concentration (lepodisiran difference from placebo [i.e., placebo-adjusted]) during the period from day 60 to day 180 (i.e., before the second injection).

TRIAL DESIGN

- Phase 2
- Randomized
- Placebo-controlled
- Location: 66 centers in 10 countries

RESULTS

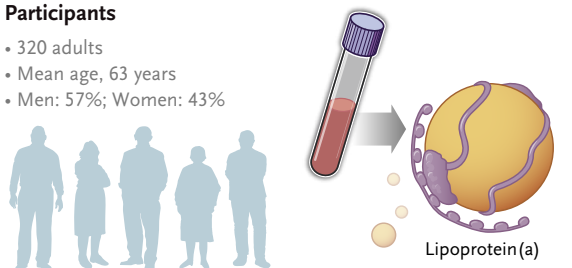
Lepodisiran at all doses was associated with reductions in the serum lipoprotein(a) concentration at 60 to 180 days after administration. During 540 days of follow-up, no serious adverse events related to lepodisiran were reported. Injection-site reactions, which were generally mild, occurred most often with the highest dose of lepodisiran.

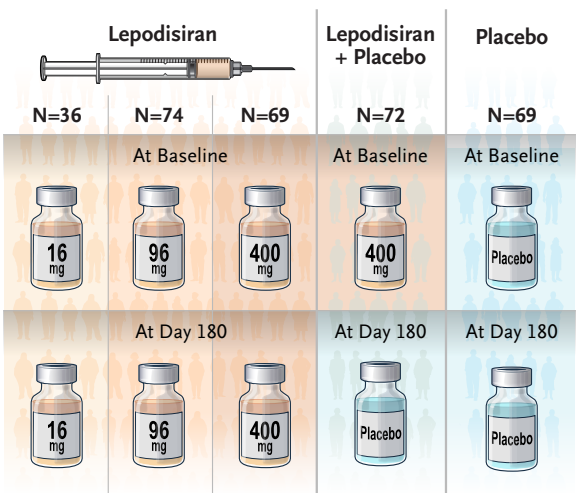
LIMITATIONS AND REMAINING QUESTIONS

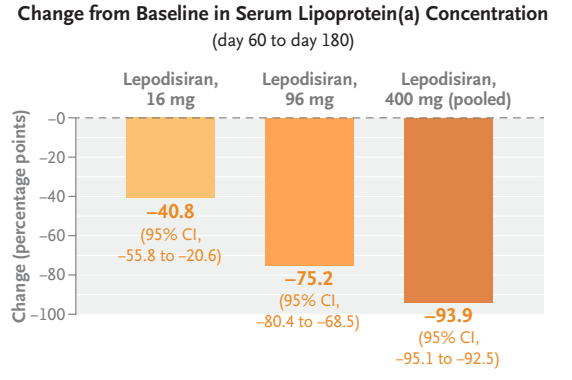
- Only 2% of participants were Black. Elevated lipoprotein(a) concentrations are more common in Black people than in White people, so further study in this population is necessary.
- Only two doses of lepodisiran were administered in this trial. The effect of additional doses is not known.

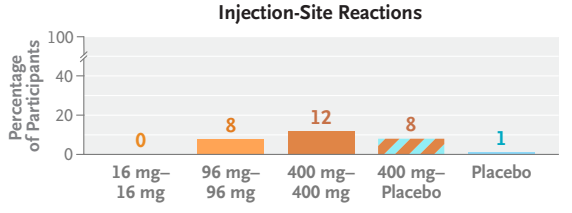
CONCLUSIONS

In adults with elevated serum lipoprotein(a) concentrations, a single injection of lepodisiran substantially reduced lipoprotein(a) from baseline to days 60 to 180 after administration.









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EDITORIALS

Targeting Lipoprotein(a) — the Next Frontier in Cardiovascular Disease

Daniel J. Rader, M.D.[1]

Intervention to reduce the levels of circulating low-density lipoprotein (LDL) cholesterol and its major protein, apolipoprotein B, is one of the most effective ways to reduce the risk of cardiovascular events. However, even with aggressive lowering of the LDL cholesterol level, the risk of cardiovascular disease is not eliminated. One of the important factors contributing to such residual risk is lipoprotein(a).[1] Lipoprotein(a), which was first described in 1963, is a circulating lipoprotein similar to LDL but with a unique protein called apolipoprotein(a), which is bound to apolipoprotein B. Numerous epidemiologic studies have shown a significant association between lipoprotein(a) levels and atherosclerotic cardiovascular disease or calcific aortic stenosis.[1] Levels of lipoprotein(a) are highly genetically determined, and the most important genetic variants affecting lipoprotein(a) levels are in the gene *LPA*, which encodes apolipoprotein(a). The finding that *LPA* variants that increase lipoprotein(a) levels are also strongly associated with cardiovascular outcomes was evidence of causality and provided the impetus for the development of therapies to lower lipoprotein(a) levels.[1,2]

The regulation of lipoprotein(a) metabolism is markedly different from that of LDL, and the LDL receptor plays only a minor role, if any, in its catabolism. Levels of lipoprotein(a) are regulated primarily by the rate of apolipoprotein(a) synthesis by the liver.[1] Lipoprotein(a) is a major carrier of oxidized phospholipids, which appear to be one of the key mediators of vascular disease.[3] Targeting the production of apolipoprotein(a) by the liver is a promising approach to reducing lipoprotein(a) production, circulating levels of lipoprotein(a) (as well as oxidized phospholipids), and the risk of cardiovascular disease.

The advent of antisense oligonucleotides and RNA interference ushered in an era of therapeutic gene silencing through the targeting of specific messenger RNAs, with the liver a prime target. The field quickly turned to these technologies to silence apolipoprotein(a) production in order to reduce lipoprotein(a) levels, and these approaches have shown remarkable success in lowering lipoprotein(a) levels. Pelacarsen, an antisense oligonucleotide, has been reported to reduce lipoprotein(a) levels by more than 90%,[4] and three different small interfering RNAs (siRNAs) — olpasiran, lepodisiran, and zerlasiran — have all been reported to reduce lipoprotein(a) by more than 90% as well.[5-7] In this issue of the *Journal*,[8] Nissen et al. report findings from a phase 2 trial involving 320 persons with high lipoprotein(a) levels (≥175 nmol per liter) in whom lepodisiran was administered subcutaneously at doses of 16 mg, 96 mg, or 400 mg. Treatment with lepodisiran led to a sustained time-averaged placebo-adjusted reduction from baseline in lipoprotein(a) levels of up to 94 percentage points (at the 400-mg dose) during the period from day 60 to day 180. The magnitude of lipoprotein(a) reduction is similar to that observed with the other siRNAs, whereas the duration of the effect appears to exceed that of the other agents. The reductions in lipoprotein(a) levels seen with these agents in persons with a high risk of cardiovascular events and elevated lipoprotein(a) levels at baseline would be expected to result in a substantial reduction in cardiovascular events.[2]

Three of these lipoprotein(a)-lowering therapies

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Table 1. Large Trials Assessing the Effect of Lipoprotein(a) Reduction on Cardiovascular Outcomes.*

Drug (Mechanism)	Trial, Status, ClinicalTrials.gov number	No. of Patients	Baseline Lipoprotein(a) Level	Main Inclusion Criteria	Primary End Point	Start Date, Estimated Completion Date
Pelacarsen (ASO)	Lipoprotein(a)-HORIZON, phase 3, NCT04023552	8323 (enrolled)	≥70 mg/dl or approx. ≥175 nmol/liter	MI, ischemic stroke, or revascularized PAD	MACE†	2019, early 2026
Olpasiran (siRNA)	OCEAN(a), phase 3, NCT05581303	7297 (enrolled)	≥200 nmol/liter	MI or coronary revascularization with percutaneous coronary intervention and at least 1 additional risk factor	MACE†	2022, late 2026
Lepodisiran (siRNA)	ACCLAIM-lipoprotein(a), phase 3, NCT06292013	12,500 (planned)	≥175 nmol/liter	ASCVD or age >55 yr with high risk of first ASCVD event	MACE†	2024, 2029

* ASCVD denotes atherosclerotic cardiovascular disease, ASO antisense oligonucleotide, MI myocardial infarction, PAD peripheral artery disease, and siRNA small interfering RNA.
† MACE (major adverse cardiovascular event) is a composite of death from a cardiovascular cause, nonfatal myocardial infarction, nonfatal stroke, or urgent coronary revascularization. The primary end point of the olpasiran trial did not include nonfatal stroke.

are currently being studied in large trials assessing cardiovascular outcomes (Table 1). The trials involve patients with high lipoprotein(a) levels (≥70 mg per deciliter or 175 to 200 nmol per liter), most of whom have established atherosclerotic cardiovascular disease, though the ACCLAIM-lipoprotein(a) trial of lepodisiran also includes some persons without atherosclerotic cardiovascular disease but with a combination of other risk factors. The ACCLAIM-lipoprotein(a) trial is the largest of the three trials assessing cardiovascular outcomes, with a planned enrollment of 12,500 participants, and will conclude in approximately 4 years, whereas the other two trials are slated to conclude in 2026. Whether intervention to substantially reduce lipoprotein(a) levels will reduce the risk of cardiovascular events to a clinically relevant degree is one of the biggest questions in cardiovascular medicine — and the answer will determine whether a new class of drugs that addresses a major cardiovascular risk factor will eventually be approved and become part of the recommended treatment regimen. In addition, an oral small molecule lipoprotein(a) inhibitor is in clinical development, and two efforts to target the *LPA* gene through gene editing are in preclinical development.[9]

It has been estimated that approximately one in five Americans has high lipoprotein(a) levels and an associated increased risk of cardiovascular disease. However, despite the ready availability of clinical tests for lipoprotein(a) levels, less than 1% of these persons have had lipoprotein(a) levels measured.[9,10] A number of guidelines and societies have recommendations that incorporate clinical measurement of lipoprotein(a) levels, with some recommending that all adults have these levels measured once.[9] Beyond atherosclerotic cardiovascular disease, lipoprotein(a) is a major causal risk factor for calcific aortic stenosis, a condition for which there is no medical therapy. If lowering lipoprotein(a) levels is effective in reducing cardiovascular events, a future goal will be to test its effect on calcific aortic stenosis.

The story of lipoprotein(a) began more than 60 years ago with epidemiology, biochemistry, and molecular physiology and has accelerated remarkably in recent years with genetics and novel drug technology; its story may culminate in the identification of a major causal risk factor for atherosclerotic cardiovascular disease and the development of highly effective and targeted interventions. The entire field of cardiovascular medicine awaits the next chapter — one that is likely to have reverberations for the practice of medicine for decades.

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

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1. Boffa MB, Koschinsky ML. Lipoprotein(a) and cardiovascular disease. Biochem J 2024;481:1277-96.
2. Burgess S, Ference BA, Staley JR, et al. Association of LPA variants with risk of coronary disease and the implications for

lipoprotein(a)-lowering therapies: a Mendelian randomization analysis. JAMA Cardiol 2018;3:619-27.
3. Gilliland TC, Liu Y, Mohebi R, et al. Lipoprotein(a), oxidized phospholipids, and coronary artery disease severity and outcomes. J Am Coll Cardiol 2023;81:1780-92.
4. Tsimikas S, Karwatowska-Prokopczuk E, Gouni-Berthold I, et al. Lipoprotein(a) reduction in persons with cardiovascular disease. N Engl J Med 2020;382:244-55.
5. O'Donoghue ML, Rosenson RS, Gencer B, et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. N Engl J Med 2022;387:1855-64.
6. Nissen SE, Linnebjerg H, Shen X, et al. Lepodisiran, an extended-duration short interfering RNA targeting lipoprotein(a): a randomized dose-ascending clinical trial. JAMA 2023;330:2075-83.
7. Nissen SE, Wolski K, Watts GF, et al. Single ascending and multiple-dose trial of zerlasiran, a short interfering RNA targeting lipoprotein(a): a randomized clinical trial. JAMA 2024;331:1534-43.
8. Nissen SE, Ni W, Shen X, et al. Lepodisiran — a long-duration small interfering RNA targeting lipoprotein(a). N Engl J Med 2025;392:1673-83.
9. Reyes-Soffer G, Yeang C, Michos ED, Boatwright W, Ballantyne CM. High lipoprotein(a): actionable strategies for risk assessment and mitigation. Am J Prev Cardiol 2024;18:100651.
10. McGowan M, Wilemon K, Ahmed C, Myers K, MacDougall D. Characterization of lipoprotein(a) measurement in a large US healthcare dataset. J Clin Lipidol 2022;16(3):e36-e37 (https://www.lipidjournal.com/article/S1933-2874(22)00108-8/abstract).

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Nonoperative Management of Mismatch Repair–Deficient Tumors

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ABSTRACT

BACKGROUND

Among patients with mismatch repair–deficient (dMMR), locally advanced rectal cancer, neoadjuvant checkpoint blockade eliminated the need for surgery in a high proportion of patients. Whether this approach can be extended to all early-stage dMMR solid tumors, regardless of tumor site, is unknown.

METHODS

We conducted a phase 2 study in which patients with stage I, II, or III dMMR solid tumors that were amenable to curative-intent surgery were treated with neoadjuvant dostarlimab, a programmed cell death 1 (PD-1) blocking agent, for 6 months. The response to treatment was assessed in two cohorts: patients in cohort 1 had dMMR, locally advanced rectal cancer, and patients in cohort 2 had dMMR nonrectal solid tumors. Patients with a clinical complete response could elect to proceed with nonoperative management; those with residual disease were to undergo resection. In this analysis, the primary end point, assessed in cohort 1, was a sustained clinical complete response at 12 months. Recurrence-free survival and safety were evaluated.

RESULTS

A total of 117 patients were included in the analysis. In cohort 1, all 49 patients who completed treatment had a clinical complete response and elected to proceed with nonoperative management. A total of 37 patients had a sustained clinical complete response at 12 months, a finding that met the criterion for efficacy. In cohort 2, a total of 35 of 54 patients who completed treatment had a clinical complete response, and 33 elected to proceed with nonoperative management. Among the 103 patients who completed treatment across both cohorts, 84 had a clinical complete response, and 82 did not undergo surgery. Among the 117 total patients, recurrence-free survival at 2 years was 92% (95% confidence interval, 86 to 99); the median follow-up for recurrence was 20.0 months (range, 0 to 60.8). The majority of patients (95%) had reversible, grade 1 or 2 adverse events (60%) or had no adverse events (35%). The option for curative resection was not compromised during or after treatment in any of the patients.

CONCLUSIONS

Among patients with early-stage dMMR solid tumors that were amenable to curative-intent surgery, neoadjuvant PD-1 blockade led to organ preservation in a high proportion of patients. (Funded by Swim Across America and others; ClinicalTrials.gov number, NCT04165772.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Cercek can be contacted at cerceka@mskcc.org, and Dr. Diaz at diaz15@mskcc.org; Drs. Cercek and Diaz can be contacted at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

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EDITORIALS

Nonoperative Management of dMMR Tumors — A Patient-Centered Approach

Elena Elez, M.D., Ph.D.[1]

In the treatment of patients with mismatch repair–deficient (dMMR), metastatic solid tumors, checkpoint blockade has ushered in a revolutionary change, marked by profound and, more importantly, durable responses.[1-3] As neoadjuvant therapy, programmed cell death 1 (PD-1) blockade alone or in combination with cytotoxic T-lymphocyte–associated antigen 4 blockade has had unprecedented results in patients with colorectal cancer. The recent Neoadjuvant Immune Checkpoint Inhibition and Novel Immuno-oncology Combinations in Early-Stage Colon Cancer 2 (NICHE-2) study showed that a major pathological response occurred in a high proportion of patients with dMMR colon cancer who were treated with dual checkpoint inhibition for 1 month before surgery, with no recurrences observed in those followed for at least 36 months.[4]

In this issue of the *Journal*, Cercek and colleagues report the results from their study evaluating the use of PD-1 blockade in patients with early-stage dMMR solid tumors, with the ultimate goal of nonoperative management.[5] This approach represents an advance in patient care, given that surgery may be mutilating in some patients, and associated long-term sequelae may adversely affect their quality of life. In this prospective, single-group, phase 2 study, two cohorts of patients were treated with a PD-1 inhibitor (dostarlimab) for 6 months: cohort 1 included patients with dMMR, locally advanced rectal cancer, and cohort 2 included patients with dMMR nonrectal solid tumors. Patients who had a clinical complete response could elect to proceed with nonoperative management.

The results of the study are remarkable and unexpected (at least to many of us). Deep and long-lasting responses were observed in both cohorts, enabling most of the patients to successfully avoid surgical intervention. Five patients had a recurrence, and grade 3 adverse events were uncommon; only one patient had a grade 4 adverse event. The option for curative-intent surgery was not compromised during the trial in any of the patients, and three patients with rectal cancer went on to conceive and deliver healthy infants. Moreover, the study compared various methods for response assessment, including liquid biopsy (measurement of circulating tumor DNA), tumor biopsy, and imaging, underscoring the potential for a monitoring strategy incorporating a range of techniques.

PD-1 blockade could represent a life-changing approach for patients with dMMR solid tumors. However, some important points should be noted. In considering whether mismatch-repair deficiency is a tumor-agnostic biomarker, which would indicate that treatment may be effective across dMMR solid tumors regardless of histologic subtype, we cannot overlook response heterogeneity according to subtype. The new findings confirmed outstanding outcomes among patients with rectal cancer, which had been reported previously by the investigators.[6] In cohort 1, all 49 patients who completed treatment had a clinical complete response and elected to proceed with nonoperative management. In cohort 2, a total of 54 patients completed treatment, and a high proportion of those with colon, urothelial, or hepatobiliary cancer had a clinical complete response.

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However, the benefit was more modest among patients with upper gastrointestinal, gynecologic, or prostate cancer.

These findings are consistent with a trend observed in a "basket" study conducted by Hyman et al.,[7] which was one of the first studies to apply a histology-independent strategy. The study evaluated BRAF inhibition in patients with tumors harboring a *BRAF* V600E mutation, including various histologic subtypes. Efficacy was observed for all histologic subtypes except colorectal cancer, for which dual BRAF–EGFR inhibition (the combination of a BRAF inhibitor and anti–epithelial growth factor receptor antibodies) was provided. Such observations reaffirm that histologic and tumor-intrinsic biologic features remain key determinants of clinical response, even in the context of a shared molecular feature. The immune context is even more complex. Emerging evidence suggests that each histologic subtype across dMMR solid tumors has a specific signature of microsatellite instability and that these tumors can be stratified according to specific neoantigen profiles.[8] In addition, the response to immunotherapy may vary according to whether the tumor has epigenetic silencing of MLH1 (a mismatch-repair protein) or the patient has genetic loss of MLH1.[4]

The multidisciplinary nature of this treatment strategy must be considered. A neoadjuvant approach for limited-stage tumors would require timely coordination across multiple disciplines and commitment from tumor boards in refining care pathways and adapting traditional working cultures involving sparing surgery or chemoradiation therapy for locally advanced rectal cancer. A fundamental aspect of the strategy would be appropriate imaging-based staging and follow-up procedures. Given the inflammation of tumors with microsatellite instability, some clinically node-positive cases might reflect an inflammatory reaction rather than true tumor spread, and there is a risk of overtreatment among patients who could be cured with less-invasive, straightforward surgical resection similar to that performed for T1 tumors. To further inform the overall approach, results from multicenter, randomized, controlled trials are awaited.

Treatment duration is another relevant issue. Although the likelihood of a pathological complete response increases with the number of cycles, so does the risk of immune-related adverse events and the financial burden.[9] In this study, the median time to a negative biopsy was 1.5 months, whereas the median time to a complete response on imaging was 6.1 months. Additional strategies such as liquid biopsy could help in defining the appropriate treatment duration. However, some patients with a relapse had a 3-month decline in the level of circulating tumor DNA, which underscores the need for cautious interpretation. Relying solely on liquid biopsy could lead to false negative results. Integration of the information from various types of response assessment may be the answer but would require the implementation of new techniques and processes.

Finally, and perhaps most importantly, shared decision making remains fundamental to patient-centered care. Although PD-1 blockade could become an important option for patients with early-stage dMMR tumors, averting surgical resection in some cases, patients and their physicians should collaborate to reach an agreement on the most appropriate treatment option, with patient values and preferences incorporated into treatment decisions.[10]

Collectively, the results from the study by Cercek et al. appear to position anti–PD-1 therapy as a potentially curative, organ-preserving option for patients with dMMR, locally advanced rectal cancer and also offer promise for those with other dMMR solid tumors. Longer follow-up data and additional evidence will determine whether its application can be extended more broadly across solid tumors.

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

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1. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
2. André T, Shiu K-K, Kim TW, et al. Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. N Engl J Med 2020;383:2207-18.
3. Andre T, Elez E, Van Cutsem E, et al. Nivolumab plus ipilimumab in microsatellite-instability–high metastatic colorectal cancer. N Engl J Med 2024;391:2014-26.
4. Chalabi M, Verschoor YL, Tan PB, et al. Neoadjuvant immunotherapy in locally advanced mismatch repair–deficient colon cancer. N Engl J Med 2024;390:1949-58.
5. Cercek A, Foote MB, Rousseau B, et al. Nonoperative management of mismatch repair–deficient tumors. N Engl J Med 2025;392:2297-308.
6. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair–deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363-76.

7. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with *BRAF* V600 mutations. N Engl J Med 2015;373:726-36.
8. Hause RJ, Pritchard CC, Shendure J, Salipante SJ. Classification and characterization of microsatellite instability across 18 cancer types. Nat Med 2016;22:1342-50.
9. Rousseau B, White JR, Cercek A, Diaz LA Jr The duration of immunotherapy for mismatch repair–deficient cancers. N Engl J Med 2025;392:824-6.
10. Soukup T, Sevdalis N, Green JSA, Lamb BW, Chapman C, Skolarus TA. Making tumor boards more patient-centered: let's start with the name. JCO Oncol Pract 2021;17:591-3.

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BRIEF REPORT

Patient-Specific In Vivo Gene Editing to Treat a Rare Genetic Disease

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SUMMARY

Base editors can correct disease-causing genetic variants. After a neonate had received a diagnosis of severe carbamoyl-phosphate synthetase 1 deficiency, a disease with an estimated 50% mortality in early infancy, we immediately began to develop a customized lipid nanoparticle–delivered base-editing therapy. After regulatory approval had been obtained for the therapy, the patient received two infusions at approximately 7 and 8 months of age. In the 7 weeks after the initial infusion, the patient was able to receive an increased amount of dietary protein and a reduced dose of a nitrogen-scavenger medication to half the starting dose, without unacceptable adverse events and despite viral illnesses. No serious adverse events occurred. Longer follow-up is warranted to assess safety and efficacy. (Funded by the National Institutes of Health and others.)

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Dr. Musunuru and Ms. Grandinette contributed equally to this article.

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EDITORIALS

Progress in the Development of N-of-1 Therapy

Peter Marks, M.D., Ph.D.[1]

Musunuru and colleagues[1] describe in the *Journal* an innovative approach in which gene editing is applied in the treatment of a very rare disease, the severe urea-cycle disorder carbamoyl-phosphate synthetase 1 (CPS1) deficiency, which is usually fatal in early infancy in approximately half the infants who receive the diagnosis. In an accompanying Science behind the Study editorial, Gropman and Komor[2] describe the nature of CPS1 deficiency, the gene-editing technology of base editing, and the methods Musunuru et al. used to develop and deliver a base editor to an infant with CPS1 deficiency. To summarize briefly, after quickly identifying a genetic abnormality (a compound heterozygous defect) in a newborn, Musunuru et al., with diligent attention to scientific, regulatory, and ethical standards, rapidly developed a specific adenine base editor to be delivered intravenously in the form of a messenger RNA (mRNA) encapsulated in lipid nanoparticles. To address the issue of the presumed cross-reactive immunologic material–negative status of the infant and possible antibody formation, a thoughtfully chosen immunosuppressive regimen was initiated a few days before the first dose of the therapy was administered; a second, higher dose of the therapy was ultimately delivered 3 weeks after the initial dose. Although very early results at 7 weeks after the initial treatment are described in the study by Musunuru et al., they may indicate a solution to the vexing problem of personalized (N-of-1) therapy for rare diseases.

It is currently estimated that there are more than 7000 rare diseases affecting approximately 30 million people in the United States and 300 million people worldwide.[3] Although not all rare diseases may be eligible for a gene-editing approach with available technology, there could be hundreds to thousands of diseases that could be treated through an approach similar to the one described by Musunuru et al. That is, the combination of rapid diagnosis though genome sequencing and expedited individualized product development, followed by administration of the therapy and careful monitoring of safety and efficacy outcomes, could remarkably improve the lives of persons affected by these rare disorders. Although additional work will need to be conducted to reproducibly deliver gene-editing products to target tissues other than the liver, progress is being made in targeting bone marrow, T cells, and the brain.[4] Moreover, with the application of a forward-leading, science-based regulatory approach, this clustered regularly interspaced short palindromic repeats (CRISPR)–based method could potentially provide a solution to the commercial challenges that currently limit the ability to apply such an approach broadly to N-of-1 disorders.

In the United States, the "platform technologies" provision was enacted in late 2022.[5] The development of gene-editing products to address N-of-1 disorders with the use of mRNA encapsulated in lipid nanoparticles represents one of the most obvious opportunities for the application of a platform-technology approach that could be transformational. The platform in this case would consist of the following elements: the backbone mRNA construct encoding the "editor" enzyme (so far, CRISPR-associated protein 9 [Cas9] or a variant of Cas9 has been used in most clinical studies); the procedure for the development of an appropriate guide RNA sequence that minimizes

the potential for off-target effects; the design of the lipid nanoparticle, including any organ-specific targeting modifications; the manufacturing information for the overall product; the quality-control procedures to be used during the manufacture of the products; and the standardized method to be used for immune suppression in conjunction with the administration of the product.

A regulatory approach that leverages the information that is used repeatedly from product to product, while allowing for the required customization (in the case of the CRISPR constructs, just a short stretch of guide RNA), could be transformational for N-of-1 disorders. Such an approach would greatly simplify the process and markedly reduce the complexity and cost of product development. One could envision that it might be possible for companies to develop products targeting rare genetic abnormalities that lead to the absence of the expression of a protein in a specific tissue and then obtain regulatory approval for the overall approach (e.g., for a given backbone mRNA combined with a delivery system), rather than having to obtain regulatory approval for many unique disease-specific products. Facilitating such a process could transform N-of-1 therapy into N-of-many therapies, thus leading to commercial viability of these products for rare diseases — a development that would ultimately benefit many persons with great unmet medical need. Although the results are very early, the approach taken by Musunuru et al. for the treatment of a genetic defect causing CPS1 deficiency shows the potential strength of the application of cutting-edge science and technology with a forward-leaning regulatory approach to safely expedite the development and availability of life-saving medicines.

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

[1]Washington, DC.

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1. Musunuru K, Grandinette SA, Wang X, et al. Patient-specific in vivo gene editing to treat a rare genetic disease. N Engl J Med 2025;392:2235-43.
2. Gropman AL, Komor AC. Personalized gene editing to treat an inborn error of metabolism. N Engl J Med 2025;392:2273-6.
3. The Lancet Global Health. The landscape for rare diseases in 2024. Lancet Glob Health 2024;12(3):e341.
4. Tsuchida CA, Wasko KM, Hamilton JR, Doudna JA. Targeted nonviral delivery of genome editors in vivo. Proc Natl Acad Sci U S A 2024;121(11):e2307796121.
5. Niazi SK. The United States Food and Drug Administration's platform technology designation to expedite the development of drugs. Pharmaceutics 2024;16:918.

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EDITORIAL

SCIENCE BEHIND THE STUDY

Personalized Gene Editing to Treat an Inborn Error of Metabolism

Andrea L. Gropman, M.D.,[1] and Alexis C. Komor, Ph.D.[2-4]

Musunuru et al.[1] report in the *Journal* the development of a personalized gene-editing strategy to treat a single infant with carbamoyl-phosphate synthetase 1 (CPS1) deficiency: they treated the infant when he was approximately 7 months of age. As discussed by Marks in an accompanying editorial,[2] this article is a milestone in the evolution of personalized therapies for rare and ultrarare inborn errors of metabolism. However, one must be sensitive to concerns about the evidentiary standards applied in such early interventions.

WHAT IS CPS1?

CPS1 is a mitochondrial enzyme that catalyzes the first and rate-limiting step of the urea cycle: the conversion of ammonia and bicarbonate to carbamoyl phosphate (Fig. 1). This is a crucial detoxification step that occurs primarily in hepatocytes. Without functional CPS1, ammonia accumulates rapidly in the bloodstream and causes hyperammonemia, which is toxic to the brain and can lead to coma or death if untreated.

CPS1 deficiency is an autosomal recessive inborn error of metabolism and one of the most severe and rarest urea-cycle disorders: its estimated incidence is approximately 1 in 800,000 to 1 in 1,300,000 live births. It typically manifests as profound hyperammonemia in the first 24 to 48 hours after birth. Clinical interventions are limited and may include dialysis, ammonia scavengers, protein restriction, and, later in life, liver transplantation, but neurologic outcomes are often poor. Gene editing presents a compelling therapeutic opportunity for infants with CPS1 deficiency and certain other urea-cycle disorders.

KEY CONCEPTS

Base-pair
Two nitrogenous bases paired together in double-stranded DNA by weak bonds. Specific pairing of these bases (adenine with thymine and guanine with cytosine) facilitates accurate DNA replication.

CRISPR-Cas9 editing
A process in which clustered regularly interspaced short palindromic repeats (CRISPR) — small remnants of viral DNA from previous viral infection that are embedded in bacterial DNA — generate guide RNAs, which are used together with a DNA-cutting enzyme (Cas9) by the bacterium to defend against viral infection. With synthetic guide strands and an exogenous Cas enzyme, this technology can be used in eukaryotic cells to modify DNA or RNA for the purpose of gene editing.

Hepatocyte
A primary cell of the liver. Hepatocytes make up 70 to 80% of the liver's mass and are involved in many of the liver's key functions, including detoxification and the metabolism of carbohydrates and lipids. In addition, they are involved in the production of proteins, such as albumin, clotting factors and various complement factors, and bile. They can be infected by hepatotropic viruses including hepatitis A, B, C, D, and E viruses. The liver has a remarkable ability to regenerate because hepatocytes can reenter the cell cycle from a quiescent phase. Nevertheless, in the context of chronic liver disease, such as chronic hepatitis B virus infection, they are slowly displaced by fibrous tissue, eventually leading to cirrhosis, liver failure, and liver cancer.

Nonsense variant
A single DNA nucleotide that has been altered such that an amino acid codon becomes a stop codon, leading to truncation of the encoded protein.

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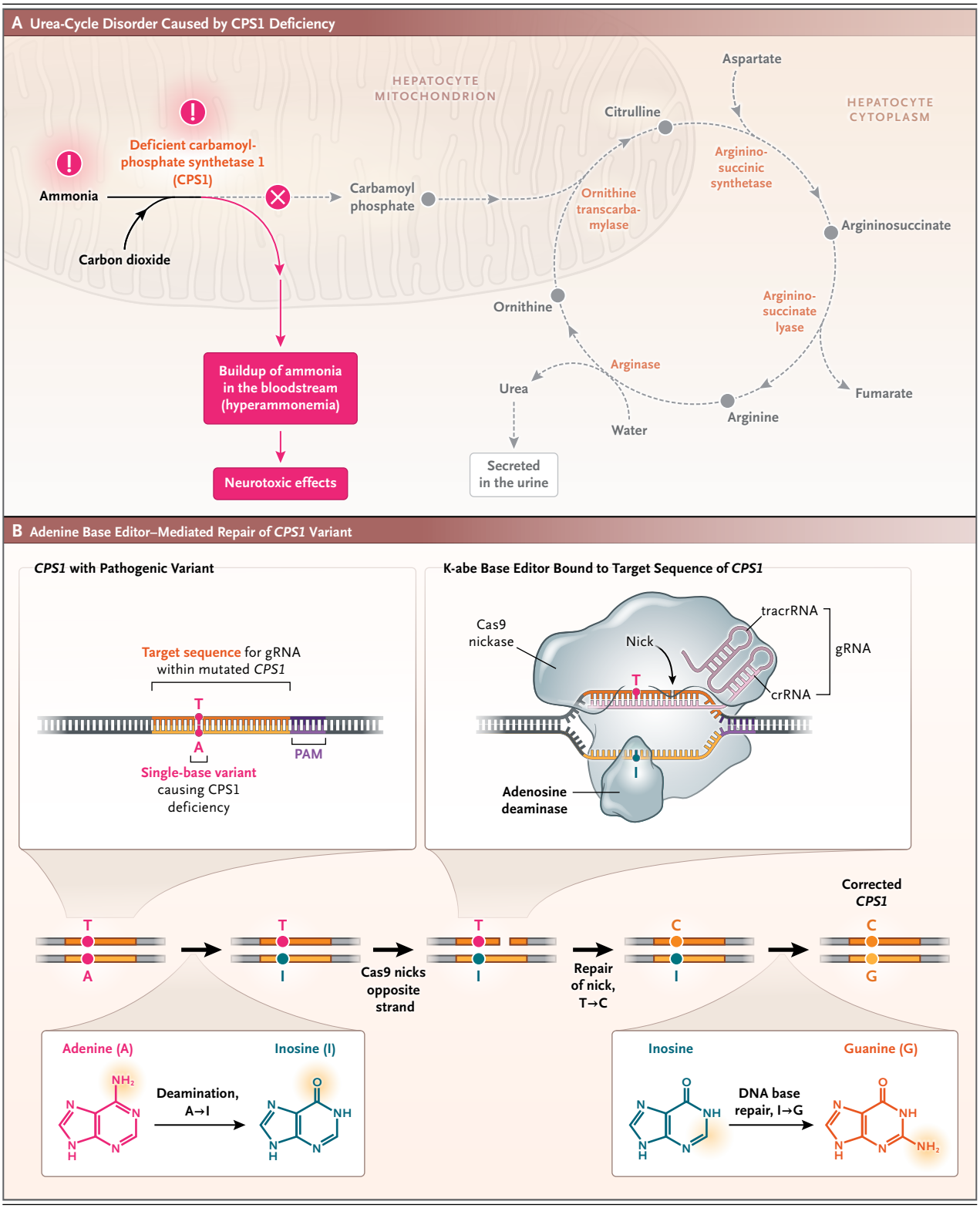

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Figure 1 (facing page). A Strategy to Treat CPS1 Deficiency through Base Editing.

Deficiency of carbamoyl-phosphate synthetase 1 (CPS1) is a recessive urea-cycle disorder caused by damaging or null variants in the gene *CPS1*. The CPS1 enzyme catalyzes the first step in the urea cycle, which takes place in the hepatocyte (Panel A). This step involves the combination of ammonia and carbon dioxide to produce carbamoyl phosphate, thus converting a neurotoxin (ammonia) into a substrate of the urea cycle (carbamoyl phosphate). The product of this cycle, urea, is excreted from the body in the urine. In the absence of adequate levels of CPS1, ammonia levels increase. An infant described by Musunuru et al.[1] presented with symptoms within 2 days after birth. Within 7 months, Musunuru et al. generated and carried out preclinical studies of an adenine base editor (kayjayguran abengcemeran, or k-abe) (Panel B), designed to correct one of the infant's pathogenic *CPS1* variants. The editor is made up of a modified clustered regularly interspaced short palindromic repeats–associated protein 9 (Cas9) enzyme (which does the editing) and a guide RNA (gRNA, which guides the Cas9 enzyme to the mutant *CPS1* nucleotide). In preclinical experiments, k-abe changed (or "edited") the mutant adenine into an inosine (which resembles guanine) on the noncoding strand, which resulted in the correction of the thymine to cytosine on the coding strand and permitted synthesis of full-length CPS1. Reduced levels of ammonia in the infant's plasma after treatment with k-abe is consistent with correction of the pathogenic *CPS1* variant. The term crRNA denotes CRISPR (clustered regularly interspaced short palindromic repeats) RNA, PAM protospacer adjacent motif, and tracrRNA trans-activating CRISPR RNA.

HOW TO TREAT CPS1 DEFICIENCY WITH A GENETIC MEDICINE?

CPS1 is encoded by a particularly large gene, which complicates its delivery with common vectors such as adeno-associated virus. In addition, the risk of vector dilution due to hepatocyte turnover in neonates may further reduce the efficacy of conventional gene therapy.

Moreover, because only a handful of patients worldwide have the same ultrarare disease, it is challenging to assemble robust preclinical and clinical data. Natural-history registries are therefore valuable in this context. Among patients with the same variant, there may be variable expressivity, and clinical presentation may vary widely, which complicates outcome measures. And CPS1 deficiency is genetically heterogeneous: it is caused by a variety of different mutations. With respect to gene editing, each mutation would require its own unique editing strategy, the development of which is costly and can take years to identify and sufficiently customize.

WHAT IS BASE EDITING?

Base editing is a method that can be used to install single variants into the genome of live cells in a targeted, precise, and efficient manner. Thus, one can revert a pathogenic stop codon to the "original," nonmutant sequence, allowing the synthesis of a full-length, functional protein. Musunuru et al. used an adenine base editor (ABE), which comprises an enzyme (a clustered regularly interspaced short palindromic repeats–associated protein 9 [Cas9] nickase [Cas9n]–adenosine deaminase fusion) and a piece of RNA called a guide RNA (gRNA). The Cas9n enzyme is guided to a specific 20 base-pair (see Key Concepts) protospacer sequence (in this case, the region of the patient's paternal *CPS1* gene that harbors the mutation) with the gRNA. The protospacer must be next to a three-base motif, called the protospacer adjacent motif (PAM), which the Cas9n protein recognizes and binds tightly to. Once bound, the adenosine deaminase domain deaminates adenines within the protospacer, leading to the conversion of a specific A–T base pair into a G–C base pair. Base editing is therefore more precise than clustered regularly interspaced short palindromic repeats [CRISPR]–Cas9 editing, which disrupts genes by cutting the DNA rather than targeting a single base pair for mutation.

HOW CAN IT TREAT CPS1 DEFICIENCY?

Musunuru et al. developed a base-editing strategy to correct the *CPS1* Q335X "stop" variant, a nonsense G-to-A variant on the noncoding strand. They started out by testing several different gRNAs that target overlapping protospacers. With each gRNA, the pathogenic A variant is in a slightly different position and orientation with respect to the positioning of the adenosine deaminase domain, once the ABE has bound to the PAM and protospacer.

Increasing the potential for patient-specific customization, each gRNA can be combined with an ABE variant: ABE variants differ in their preferences for specific DNA motifs. Numerous

ABE:gRNA combinations were individually generated and tested to identify the combination with the greatest efficiency and precision. Further complicating the testing process is that it must be carried out with the use of cells that harbor the pathogenic variant and that are the same or a similar cell type to the target tissue (in the case of CPS1 deficiency, a hepatocyte) and are easy to culture and grow in the laboratory. For some rare diseases, it can take months to a year to generate such a cell line.

HOW WAS GENE-EDITOR CUSTOMIZATION ACCELERATED?

To obtain a suitable cell line for testing ABE:gRNA combinations, Musunuru et al. inserted a 100 base-pair segment representing the patient's mutated *CPS1* (generated through DNA-synthesis technology) into the genome of a human hepatocyte cell line. Overall, the generation of the cell line and ABE:gRNA screening took 2 months to complete. Preclinical studies of the adenine base editor (named kayjayguran abengcemeran, or k-abe) were then conducted in two different transgenic mouse models and in nonhuman primates.

WHAT'S NEXT?

The ability to intervene at the genomic level and to directly correct the underlying genetic defect in a patient's liver shows the promise of CRISPR-based medicine. Limitations of the study include the fact that the mouse model, although carrying the patient's pathogenic *CPS1* variants, does not have a CPS1 deficiency phenotype and so is unsuitable for testing therapeutic efficacy.

This study must be balanced against the current limitations of an N-of-1 experience in a rare or ultrarare condition. Although the authors noted clinical stabilization in the short term, the absence of direct molecular confirmation of gene editing by means of liver biopsy leaves questions unanswered, such as the durability of the therapeutic effect, the extent of mosaicism of editing, and the risks of off-target events or immune responses. Longer-term follow-up of this patient will be critical to obtaining answers.

The development of minimally invasive biomarkers in lieu of liver biopsy to assess editing success and expansion to small, well-controlled cohorts should be considered. One could consider ureagenesis studies that use stable isotope tracers, cell-free DNA assays, or quantitative metabolomics. Further customization of delivery platforms and enhancement of editing efficiency will be key to translating this singular success into reproducible and scalable therapy. Moreover, the path from proof of concept to standard of care will require careful ethical and regulatory stewardship. For patients with CPS1 deficiency and similar ultrarare disorders, the findings of Musunuru et al. offer hope and yet require validation through treatment of the second patient, the third, and beyond.

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

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1. Musunuru K, Grandinette SA, Wang X, et al. Patient-specific in vivo gene editing to treat a rare genetic disease. N Engl J Med. DOI: 10.1056/NEJMoa2504747.
2. Marks P. Progress in the development of N-of-1 therapy. N Engl J Med. DOI: 10.1056/NEJMe2505704.

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The NEW ENGLAND JOURNAL of MEDICINE

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Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis

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ABSTRACT

BACKGROUND

Nerandomilast (BI 1015550) is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory effects. In a phase 2 trial involving patients with idiopathic pulmonary fibrosis, treatment with nerandomilast stabilized lung function over a period of 12 weeks.

METHODS

In this phase 3, double-blind trial, we randomly assigned patients with idiopathic pulmonary fibrosis in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo, with stratification according to background antifibrotic therapy (nintedanib or pirfenidone vs. none). The primary end point was the absolute change from baseline in forced vital capacity (FVC), measured in milliliters, at week 52.

RESULTS

A total of 1177 patients underwent randomization, of whom 77.7% were taking nintedanib or pirfenidone at enrollment. Adjusted mean changes in FVC at week 52 were −114.7 ml (95% confidence interval [CI], −141.8 to −87.5) in the nerandomilast 18-mg group, −138.6 ml (95% CI, −165.6 to −111.6) in the nerandomilast 9-mg group, and −183.5 ml (95% CI, −210.9 to −156.1) in the placebo group. The adjusted difference between the nerandomilast 18-mg group and the placebo group was 68.8 ml (95% CI, 30.3 to 107.4; P<0.001), and the adjusted difference between the nerandomilast 9-mg group and the placebo group was 44.9 ml (95% CI, 6.4 to 83.3; P=0.02). The most frequent adverse event in the nerandomilast groups was diarrhea, reported in 41.3% of the 18-mg group and 31.1% of the 9-mg group, as compared with 16.0% in the placebo group. Serious adverse events were balanced across trial groups.

CONCLUSIONS

In patients with idiopathic pulmonary fibrosis, treatment with nerandomilast resulted in a smaller decline in the FVC than placebo over a period of 52 weeks. (Funded by Boehringer Ingelheim; FIBRONEER-IPF ClinicalTrials.gov number, NCT05321069.)

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*A complete list of investigators in the FIBRONEER-IPF trial is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

Nerandomilast in Patients with Idiopathic Pulmonary Fibrosis

A Research Summary based on Richeldi L et al. | 10.1056/NEJMoa2414108 | Published on May 18, 2025

WHY WAS THE TRIAL DONE?

Current therapies for idiopathic pulmonary fibrosis do not halt disease progression, and their gastrointestinal side effects often interfere with treatment. In a phase 2 trial, nerandomilast — an orally administered preferential inhibitor of phosphodiesterase 4B — stabilized lung function over 12 weeks and had an acceptable safety profile in patients with idiopathic pulmonary fibrosis. Additional data are needed.

HOW WAS THE TRIAL CONDUCTED?

Patients 40 years of age or older with idiopathic pulmonary fibrosis were assigned to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo. The primary end point was the absolute change in forced vital capacity (FVC) from baseline to week 52.

TRIAL DESIGN

- Phase 3
- Double-blind
- Randomized
- Placebo-controlled
- 332 sites in 36 countries

RESULTS

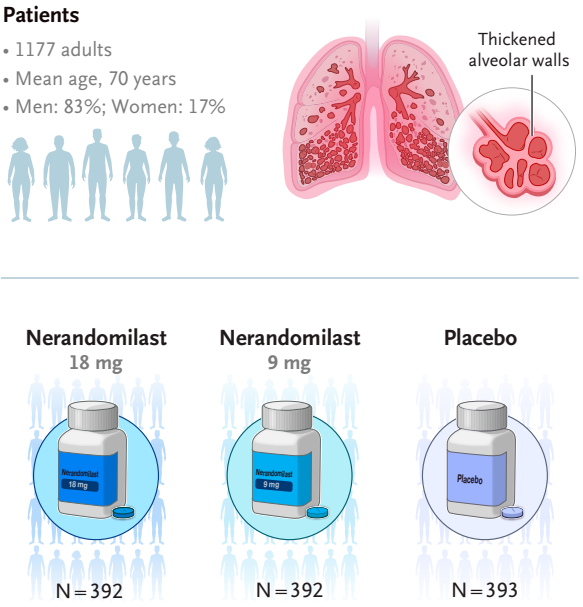
Nerandomilast at either dose resulted in a significantly smaller decline in the FVC than placebo. The most common adverse event with nerandomilast was diarrhea. The incidence of serious adverse events was similar across the groups.

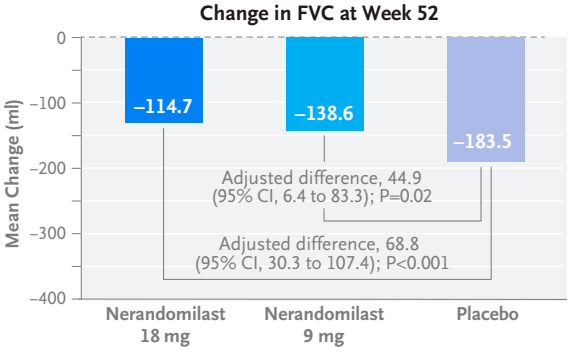
LIMITATIONS AND REMAINING QUESTIONS

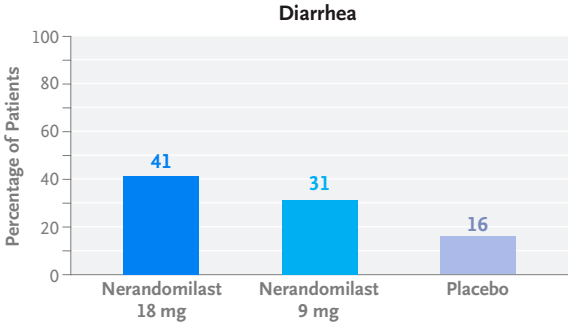
- The trial was not powered to evaluate nerandomilast in subgroups.
- The duration of follow-up did not allow for assessment of the effect of nerandomilast on long-term mortality.
- Approximately three fourths of the patients used background antifibrotic therapy. Discontinuations, initiations, and changes in dose administration of antifibrotic therapy may have affected the differences observed between the nerandomilast and placebo groups.

CONCLUSIONS

Among adults with idiopathic pulmonary fibrosis, twice-daily treatment with nerandomilast led to a smaller decline in the FVC than placebo over 52 weeks.







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ORIGINAL ARTICLE

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M. Maher, M.D.,[1,2] Shervin Assassi, M.D.,[3] Arata Azuma, M.D.,[4,5] Vincent Cottin, M.D.,[6] Anna-Maria Hoffmann-Vold, M.D.,[7,8] Michael Kreuter, M.D.,[9,10] Justin M. Oldham, M.D.,[11] Luca Richeldi, M.D.,[12] Claudia Valenzuela, M.D.,[13] Marlies S. Wijsenbeek, M.D.,[14] Emmanuelle Clerisme-Beaty, M.D.,[15] Carl Coeck, M.D.,[16] Hui Gu, Ph.D.,[17] Ivana Ritter, M.D.,[15] Arno Schlosser, M.Sc.,[18] Susanne Stowasser, M.D.,[15] Florian Voss, Ph.D.,[19] Gerrit Weimann, M.D.,[15] Donald F. Zoz, M.D.,[20] and Fernando J. Martinez, M.D.,[21] for the FIBRONEER-ILD Trial Investigators*

ABSTRACT

BACKGROUND

Nerandomilast (BI 1015550) is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory properties. Nerandomilast has been shown to slow the progression of idiopathic pulmonary fibrosis, but an assessment of its effects in other types of progressive pulmonary fibrosis is needed.

METHODS

In a phase 3, double-blind trial, we randomly assigned patients with progressive pulmonary fibrosis in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo, with stratification according to background therapy (nintedanib vs. none) and fibrotic pattern on high-resolution computed tomography (usual interstitial pneumonia-like pattern vs. other patterns). The primary end point was the absolute change from baseline in the forced vital capacity (FVC), measured in milliliters, at week 52.

RESULTS

A total of 1176 patients received at least one dose of nerandomilast or placebo, of whom 43.5% were taking background nintedanib therapy at baseline. The adjusted mean change in the FVC at week 52 was –98.6 ml (95% confidence interval [CI], –123.7 to –73.4) in the nerandomilast 18-mg group, –84.6 ml (95% CI, –109.6 to –59.7) in the nerandomilast 9-mg group, and –165.8 ml (95% CI, –190.5 to –141.0) in the placebo group. The adjusted difference between the nerandomilast 18-mg group and the placebo group was 67.2 ml (95% CI, 31.9 to 102.5; P<0.001), and the adjusted difference between the nerandomilast 9-mg group and the placebo group was 81.1 ml (95% CI, 46.0 to 116.3; P<0.001). The most frequent adverse event was diarrhea, reported in 36.6% of the patients in the nerandomilast 18-mg group, 29.5% of those in the nerandomilast 9-mg group, and 24.7% of those in the placebo group. Serious adverse events occurred in similar percentages of patients in the trial groups.

CONCLUSIONS

In patients with progressive pulmonary fibrosis, treatment with nerandomilast led to a smaller decline in the FVC than placebo over a period of 52 weeks. (Funded by Boehringer Ingelheim; FIBRONEER-ILD ClinicalTrials.gov number, NCT05321082.)

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*A complete list of investigators in the FIBRONEER-ILD trial is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

A Research Summary based on Maher TM et al. | 10.1056/NEJMoa2503643 | Published on May 19, 2025

WHY WAS THE TRIAL DONE?

Nerandomilast is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory properties. This agent slows the progression of idiopathic pulmonary fibrosis, but an assessment of its effects in other types of progressive pulmonary fibrosis is needed.

HOW WAS THE TRIAL CONDUCTED?

Patients with progressive pulmonary fibrosis were randomly assigned in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo twice daily, with stratification according to background therapy (nintedanib vs. none) and fibrotic pattern on high-resolution CT. The primary end point was the absolute change in the forced vital capacity (FVC) at week 52.

TRIAL DESIGN

- Phase 3
- Randomized
- Double-blind
- Placebo-controlled
- Location: 403 sites in 44 countries

RESULTS

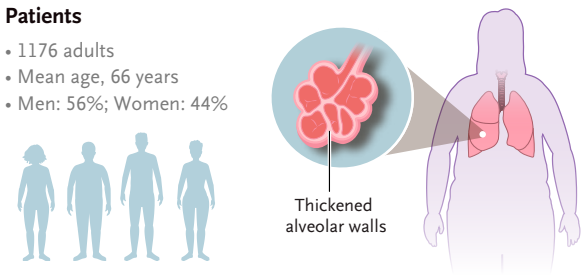
At week 52, the absolute decline in the FVC was significantly smaller with either dose of nerandomilast than with placebo. The most common adverse event was diarrhea, which occurred more frequently in the nerandomilast groups.

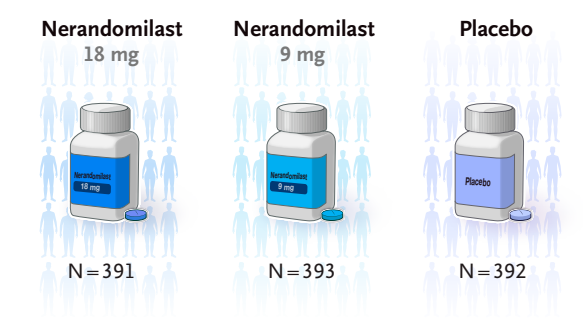
LIMITATIONS AND REMAINING QUESTIONS

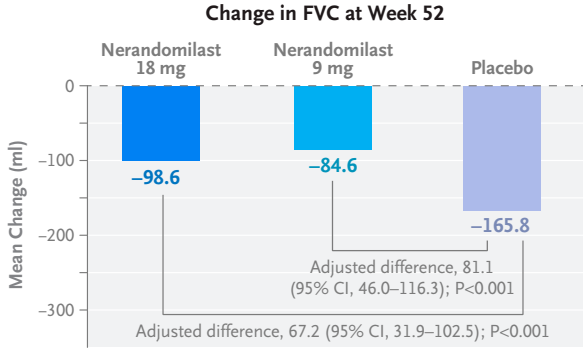
- The trial was not powered to evaluate nerandomilast in specific subgroups, including those based on interstitial lung disease diagnosis.
- Patients taking some medications, notably mycophenolate, that are commonly used for treatment of autoimmune diseases were excluded.

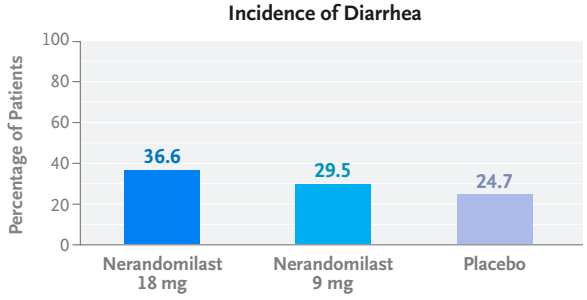
CONCLUSIONS

In patients with progressive pulmonary fibrosis, nerandomilast at a dose of 18 mg twice daily or 9 mg twice daily resulted in a smaller decline in the FVC than placebo over a period of 52 weeks.









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EDITORIALS

Progress through Persistence — Turning the Page in Pulmonary Fibrosis Clinical Trials

Joyce S. Lee, M.D.[1]

The field of pulmonary fibrosis has come a long way in the past 25 years, with the approach to patient care evolving from a predominantly experience-based decision-making model to a more data-driven model. Along that journey, we have learned that certain practices that were considered to be standards of care were harmful to patients with idiopathic pulmonary fibrosis (IPF)[1] and that many promising therapeutics were ineffective.[2,3] Progress was finally achieved when two medications, nintedanib and pirfenidone, were approved in 2014 for the treatment of IPF. Both agents were shown to reduce the decline from baseline to week 52 in the forced vital capacity (FVC) by approximately 50%, but many patients had challenging side effects.[4,5]

Since the approval of these two medications, there has been a series of disappointing clinical trials in our field, with no new therapies entering the clinic. Now in the *Journal*, Richeldi et al.[6] and Maher et al.[7] turn the page and report the results of two phase 3 randomized clinical trials involving patients with pulmonary fibrosis. Both trials assessed the efficacy and safety of nerandomilast (BI 1015550), a preferential inhibitor of phosphodiesterase 4B that showed antifibrotic and immunomodulatory effects in preclinical models of pulmonary fibrosis.

In the FIBRONEER-IPF trial, Richeldi et al. assigned 1177 patients with IPF to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo.[6] The majority of the patients (77.7%) were taking background nintedanib or pirfenidone therapy at enrollment. The nerandomilast groups differed significantly from the placebo group with regard to the primary end point of the absolute change from baseline to week 52 in the FVC (measured in milliliters) (Table 1). The reduction in the decline in the FVC at week 52 with nerandomilast as compared with placebo appeared to be consistent among all prespecified subgroups except the group that was taking 9 mg of nerandomilast and background pirfenidone therapy, a finding that was probably due to an interaction between the two agents that reduced plasma concentrations of nerandomilast. The authors did not observe significant differences between the nerandomilast groups and the placebo group with regard to the key secondary end point of a first acute exacerbation, hospitalization for a respiratory cause, or death, assessed in a time-to-event analysis over the duration of the trial.

In the FIBRONEER-ILD trial, Maher et al. assigned 1176 patients with non-IPF interstitial lung disease (ILD) and a progressive pulmonary fibrosis (PPF) phenotype to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo.[7] The PPF criteria were the same as those in the phase 3 INBUILD trial of nintedanib in patients with PPF.[8] A minority of the patients (43.5%) were taking background nintedanib therapy, and several of the more frequently used immunosuppressive medications were not permitted. A significant difference with regard to the primary end point of the absolute change from baseline to week 52 in the FVC was observed between both nerandomilast groups and the placebo group. The results of prespecified subgroup analyses of the differences between the nerandomilast groups and the placebo group with regard to the primary end

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Table 1. Trial End-Point Analyses with Nerandomilast as Compared with Placebo.*

Analysis	FIBRONEER-IPF		FIBRONEER-ILD	
	Nerandomilast, 18 mg, vs. Placebo	Nerandomilast, 9 mg, vs. Placebo	Nerandomilast, 18 mg, vs. Placebo	Nerandomilast, 9 mg, vs. Placebo
Primary end-point analysis				
Adjusted difference in mean absolute change in FVC at wk 52 (95% CI) — ml	68.8 (30.3 to 107.4)	44.9 (6.4 to 88.3)	67.2 (31.9 to 102.5)	81.1 (46.0 to 116.3)
Key secondary end-point analysis				
Hazard ratio for first acute exacerbation, hospitalization for respiratory cause, or death (95% CI)	1.17 (0.86 to 1.59)	1.03 (0.75 to 1.41)	0.77 (0.59 to 1.01)	0.88 (0.68 to 1.14)
Other secondary end-point analyses†				
Adjusted difference in mean absolute change at wk 52				
Percentage of predicted FVC (95% CI) — percentage points	1.73 (0.68 to 2.78)	1.17 (0.13 to 2.22)	1.9 (0.9 to 3.0)	2.2 (1.2 to 3.2)
Percentage of predicted DLco (95% CI) — percentage points	1.7 (0 to 3.4)	2.5 (0.8 to 4.2)	−0.5 (−2.5 to 1.5)	−0.9 (−2.9 to 1.1)
Living with Pulmonary Fibrosis questionnaire‡				
Dyspnea score (95% CI)	−0.6 (−2.8 to 1.6)	−1.0 (−3.2 to 1.2)	−1.3 (−3.7 to 1.2)	−0.9 (−3.3 to 1.5)
Cough score (95% CI)	−0.6 (−3.4 to 2.3)	0 (−2.9 to 2.8)	0.1 (−3.1 to 3.4)	−1.9 (−5.1 to 1.3)
Fatigue score (95% CI)	0.5 (−2.0 to 2.9)	0.2 (−2.2 to 2.7)	0.9 (−1.6 to 3.5)	0.1 (−2.5 to 2.6)
Hazard ratio for acute exacerbation or death (95% CI)	1.11 (0.75 to 1.65)	1.12 (0.76 to 1.67)	0.59 (0.41 to 0.84)	0.78 (0.56 to 1.08)
Hazard ratio for hospitalization for respiratory cause or death (95% CI)	1.13 (0.82 to 1.56)	0.98 (0.70 to 1.36)	0.75 (0.56 to 1.00)	0.83 (0.63 to 1.10)
Hazard ratio for death (95% CI)	0.81 (0.46 to 1.43)	1.03 (0.60 to 1.76)	0.48 (0.30 to 0.79)	0.60 (0.38 to 0.95)
Hazard ratio for absolute decline in percentage of predicted FVC of >10 percentage points or death (95% CI)	0.84 (0.64 to 1.10)	0.96 (0.74 to 1.25)	0.74 (0.57 to 0.95)	0.71 (0.55 to 0.91)
Hazard ratio for absolute decline in percentage of predicted DLco of >15 percentage points or death (95% CI)	0.88 (0.62 to 1.26)	0.98 (0.69 to 1.41)	1.03 (0.73 to 1.45)	0.89 (0.64 to 1.25)
Hazard ratio for initiation of supplemental oxygen (95% CI)	0.91 (0.62 to 1.33)	0.63 (0.42 to 0.96)	NR	NR

* In the FIBRONEER-IPF and FIBRONEER-ILD trials, patients were randomly assigned in a 1:1:1 ratio to receive nerandomilast at a dose of 18 mg twice daily, nerandomilast at a dose of 9 mg twice daily, or placebo twice daily. CI denotes confidence interval, DLco diffusing capacity of the lungs for carbon monoxide, FVC forced vital capacity, and NR not reported.
† The widths of confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.
‡ Scores on the Living with Pulmonary Fibrosis questionnaire range from 0 to 100, with higher scores indicating worse symptoms.

point, which included assessments according to ILD diagnosis and background use of nintedanib therapy, were generally consistent with those in the overall population. The differences between the nerandomilast groups and the placebo group with regard to the key secondary end point of a first acute exacerbation, hospitalization for a respiratory cause, or death, assessed in a time-to-event analysis over the duration of the trial, were not significant.

In both trials, there were no apparent differences in measures of health-related quality of life across the nerandomilast and placebo groups. Adverse events were generally similar in the two trials. Diarrhea was the most frequently reported adverse event and occurred in up to 41% of the patients who were receiving nerandomilast and in up to 62% of those who were receiving nerandomilast and background nintedanib therapy.

These trials present a wealth of data to consider. One key takeaway is that IPF and PPF continue to progress with ongoing loss of lung function despite our current standard of care. Second, data from the current trials suggest that although nerandomilast slowed the decline in the FVC in both IPF and PPF, the decline continued. Third, although no dose–response relationship was observed in the nerandomilast groups and the between-group differences with respect to the key secondary end point were not significant in either trial, the mortality findings in the FIBRONEER-ILD trial deserve additional exploration. Fourth, as in previous trials of pharmacologic interventions for IPF or PPF,[4,5] nerandomilast did not improve health-related quality of life as compared with placebo. Fifth, the frequency of diarrhea was higher in the nerandomilast groups than in the placebo group, and proactive management of this adverse event will be needed in patients receiving nerandomilast.

The current clinical trials represent a meaningful advancement in the treatment landscape for persons living with IPF and progressive ILD other than IPF. Important issues that our community of clinicians will need to address moving forward nonetheless remain — decisions regarding the choice of first-line therapy, indications for up-front combination therapy as compared with add-on therapy, and the role of immunosuppression in patients with non-IPF ILD and a PPF phenotype. Furthermore, a shift toward early identification and treatment of ILD should be a priority to prevent or slow the development of clinically significant disease. We must remain persistent in our efforts to find better therapies for our patients — therapies that not only modify (and potentially improve) disease behavior but also improve the quality of life for our patients living with these devastating diseases.

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

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1. The Idiopathic Pulmonary Fibrosis Clinical Research Network. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med 2012;366:1968-77.
2. King TE Jr, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184:92-9.
3. Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004;350:125-33.
4. King TE Jr, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2083-92.
5. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med 2014;370:2071-82.
6. Richeldi L, Azuma A, Cottin V, et al. Nerandomilast in patients with idiopathic pulmonary fibrosis. N Engl J Med 2025; 392:2193-202.
7. Maher TM, Assassi S, Azuma A, et al. Nerandomilast in patients with progressive pulmonary fibrosis. N Engl J Med 2025; 392:2203-14.
8. Flaherty KR, Wells AU, Cottin V, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019; 381:1718-27.

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The NEW ENGLAND JOURNAL of MEDICINE

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Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

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ABSTRACT

BACKGROUND

Preclinical and observational studies suggest that exercise may improve cancer outcomes. However, definitive level 1 evidence is lacking.

METHODS

In this phase 3, randomized trial conducted at 55 centers, we assigned patients with resected colon cancer who had completed adjuvant chemotherapy to participate in a structured exercise program (exercise group) or to receive health-education materials alone (health-education group) over a 3-year period. The primary end point was disease-free survival.

RESULTS

From 2009 through 2024, a total of 889 patients underwent randomization to the exercise group (445 patients) or the health-education group (444 patients). At a median follow-up of 7.9 years, disease-free survival was significantly longer in the exercise group than in the health-education group (hazard ratio for disease recurrence, new primary cancer, or death, 0.72; 95% confidence interval [CI], 0.55 to 0.94; P=0.02). The 5-year disease-free survival was 80.3% in the exercise group and 73.9% in the health-education group (difference, 6.4 percentage points; 95% CI, 0.6 to 12.2). Results support longer overall survival in the exercise group than in the health-education group (hazard ratio for death, 0.63; 95% CI, 0.43 to 0.94). The 8-year overall survival was 90.3% in the exercise group and 83.2% in the health-education group (difference, 7.1 percentage points; 95% CI, 1.8 to 12.3). Musculoskeletal adverse events occurred more often in the exercise group than in the health-education group (in 18.5% vs. 11.5% of patients).

CONCLUSIONS

A 3-year structured exercise program initiated soon after adjuvant chemotherapy for colon cancer resulted in significantly longer disease-free survival and findings consistent with longer overall survival. (Funded by the Canadian Cancer Society and others; CHALLENGE ClinicalTrials.gov number, NCT00819208.)

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

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The NEW ENGLAND JOURNAL of MEDICINE

Structured Exercise after Adjuvant Chemotherapy for Colon Cancer

A Research Summary based on Courneya KS et al. | 10.1056/NEJMoa2502760 | Published on June 1, 2025

WHY WAS THE TRIAL DONE?

For patients with stage III or high-risk stage II colorectal cancer, standard management includes surgery and adjuvant chemotherapy. However, 20 to 40% of patients have recurrent disease, and side effects of treatment undermine their quality of life. New interventions that improve survival and quality of life are needed.

HOW WAS THE TRIAL CONDUCTED?

Patients who had undergone complete resection of stage III or high-risk stage II colon cancer and had completed adjuvant chemotherapy in the previous 2 to 6 months were randomly assigned to participate in a structured exercise program (behavioral-support sessions and supervised exercise sessions held every 2 weeks or monthly for 3 years) or to receive health-education materials only. The primary end point was disease-free survival.

TRIAL DESIGN

- Phase 3
- Randomized
- Controlled
- Location: 55 sites (mostly in Canada and Australia)

RESULTS

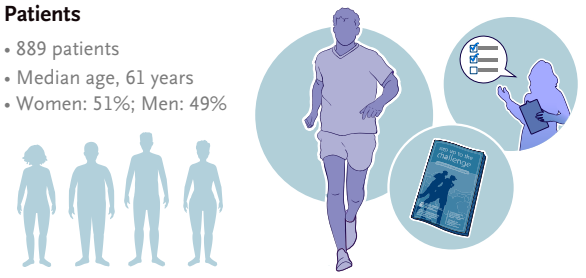
During a median follow-up of approximately 8 years, disease-free survival was significantly longer in the exercise group than in the health-education group. Musculoskeletal adverse events occurred more often in the exercise group than in the health-education group.

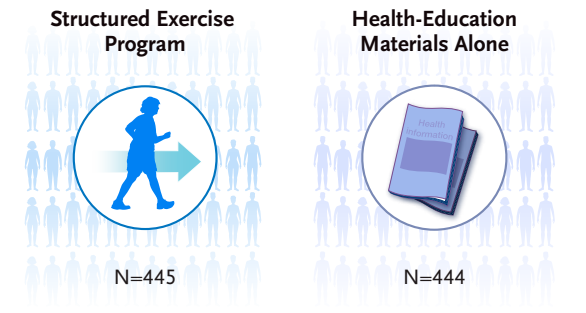
LIMITATIONS AND REMAINING QUESTIONS

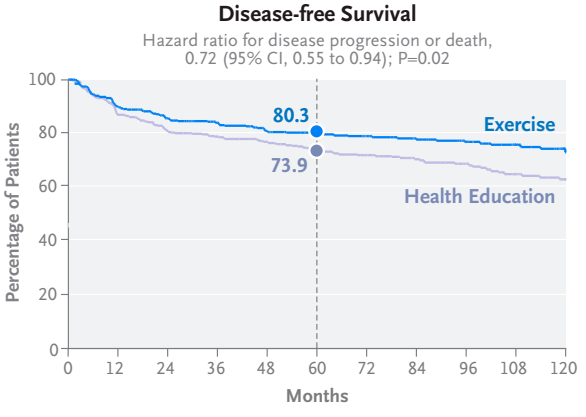
- Recruitment of patients was slow and spanned 15 years.
- Disease-free survival at 3 years was higher than expected, probably in part because of a selection bias toward higher-functioning patients.
- Whether beginning an exercise intervention earlier in the treatment course would further improve outcomes remains to be determined.

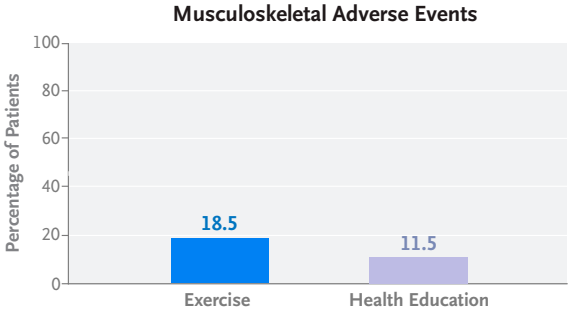
CONCLUSIONS

Among patients who had recently completed adjuvant chemotherapy for colon cancer, a 3-year structured exercise program led to significantly longer disease-free survival than health education alone.









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EDITORIALS

Extending Cancer Survival with Exercise — Time for Oncology to Act

Melinda L. Irwin, Ph.D., M.P.H.[1]

In 2006, a prospective observational study first showed that physical activity after a colon cancer diagnosis was linked to a decreased risk of recurrence and death.[1] Since then, numerous observational studies across various cancers have shown similar survival benefits.[2] However, some observers have argued that such studies could not prove causation and might reflect confounding factors, such as a higher likelihood that healthier patients would exercise or had biologically less aggressive tumors. Other observational studies have shown that physically active people have a lower risk of cancer than more sedentary people.[2] Preclinical research supports that exercise can slow tumor growth,[3] and small trials involving participants with and without cancer have shown that exercise improves metabolic, inflammatory, and immune markers[4] and may improve adherence to cancer treatment.[5] Despite these findings and national guidelines recommending increased physical activity,[6,7] exercise has yet to be widely integrated into cancer care, perhaps because of a lack of definitive evidence from large randomized trials.

Oncology has reached a turning point. In this issue of the *Journal*, Courneya and colleagues present the final results from the phase 3 Colon Health and Lifelong Exercise Change (CHALLENGE) trial.[8] In this trial, investigators randomly assigned patients who had undergone complete resection of stage III or high-risk stage II colon cancer to receive health-education materials alone or to participate in a 3-year aerobic exercise intervention. All the patients had completed adjuvant chemotherapy within the previous 2 to 6 months. The primary end point was disease-free survival.

At a median follow-up of 7.9 years, the risk of disease recurrence, a new primary cancer, or death was 28% lower in the exercise group than in the health-education group, and overall mortality was lower by 37%. At 8 years, overall survival was 90.3% in the exercise group and 83.2% in the health-education group — an absolute difference in benefit of 7.1 percentage points. These remarkable findings were due to fewer recurrences of colon cancer and fewer new primary cancers, mainly of the breast, prostate, and colon.

This trial of the effects of exercise on disease-free survival in patients with colon cancer provides definitive evidence that exercise offers additional benefits to overall survival beyond surgery and chemotherapy, while also enhancing the patients' quality of life. The magnitude of benefit is similar to that of many approved cancer therapies. Ongoing trials are evaluating the effect of exercise, nutrition, and diet-induced weight loss on disease-free survival in patients with breast or ovarian cancer, studies that may help to clarify the role of these approaches across different cancer types.[9,10]

The 3-year, partially supervised aerobic exercise program in the trial was feasible for the patients, who had a median age of 61 years, with one third over the age of 65 years; 51% of the patients were women, and 90% had stage III colon cancer. Patients in the exercise group maintained significantly greater increases in physical activity (ranging from 1.5 to 2.5 additional hours per week), cardiorespiratory fitness, and physical func-

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tion than did those in the health-education group. The primary effect of exercise was consistent across patient and treatment subgroups, which suggested that regardless of age or disease status, exercise can improve outcomes for patients with colon cancer.

Although the median body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) at enrollment was 28 and one third of the patients had a BMI of more than 30, no weight change was noted in either group over the 3-year period, which suggests that the disease-free survival benefit of exercise was independent of weight loss. Future research and clinical care for patients with cancer must include exercise interventions, given that obesity is linked to an increased risk of the development of (and death from) 13 types of cancer.[11] Moreover, emerging antiobesity medications show promise in reducing the risk of chronic disease but arouse concern about muscle loss.[12]

Despite the importance of the CHALLENGE trial, it is striking that it took 15 years to recruit 889 patients from 55 centers across six countries — averaging 59 patients per year, or about 1 patient per center annually. Although eligibility criteria were broad and applicable to most patients with stage II or III colon cancer, slow accrual probably stemmed from a limited geographic base, with 94% of the patients recruited from Canada and Australia. Moreover, many clinical-trial cooperative groups have limited infrastructure support for conducting behavioral trials, as compared with drug trials. In the United States, the National Clinical Trials Network does not provide funding for lifestyle or behavioral intervention–associated costs.

The CHALLENGE findings underscore the need to integrate exercise into cancer care. Although current guidelines already recommend physical activity before, during, and after treatment,[6,7] few adults — whether healthy or diagnosed with cancer — meet the recommended 2.5 hours per week of moderate-intensity activity, such as brisk walking.[13] Without systems-level changes, physical activity levels are unlikely to increase. Although implementation studies are needed to identify the best strategies for integrating exercise into care, we should not wait. Clinicians can refer patients to community-based exercise programs and use or adapt existing services such as cardiac rehabilitation. Trained exercise counselors should be embedded within oncology care teams, with services covered by insurance. As oncology continues to advance, exercise must become a standard part of care. The time to act is now.

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

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1. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with stage III colon cancer: findings from CALGB 89803. J Clin Oncol 2006;24:3535-41.
2. McTiernan A, Friedenreich CM, Katzmarzyk PT, et al. Physical activity in cancer prevention and survival: a systematic review. Med Sci Sports Exerc 2019;51:1252-61.
3. Eschke RK, Lampit A, Schenk A, et al. Impact of physical exercise on growth and progression of cancer in rodents — a systematic review and meta-analysis. Front Oncol 2019;9:35.
4. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Mol Oncol 2021;15:790-800.
5. Schmitz KH, Brown JC, Irwin ML, et al. Exercise and nutrition to improve cancer treatment-related outcomes (ENICTO). J Natl Cancer Inst 2025;117:9-19.
6. Campbell KL, Winters-Stone KM, Wiskemann J, et al. Exercise guidelines for cancer survivors: consensus statement from international multidisciplinary roundtable. Med Sci Sports Exerc 2019;51:2375-90.
7. Ligibel JA, Bohlke K, May AM, et al. Exercise, diet, and weight management during cancer treatment: ASCO guideline. J Clin Oncol 2022;40:2491-507.
8. Courneya KS, Vardy JL, O'Callaghan CJ, et al. Structured exercise after adjuvant chemotherapy for colon cancer. N Engl J Med 2025;393:13-25.
9. Delahanty LM, Wadden TA, Goodwin PJ, et al. The Breast Cancer Weight Loss trial (Alliance A011401): a description and evidence for the lifestyle intervention. Obesity (Silver Spring) 2022;30:28-38.
10. Thomson CA, Crane TE, Miller A, et al. Lifestyle intervention in ovarian cancer enhanced survival (LIVES) study (NRG/GOG0225): recruitment, retention and baseline characteristics of a randomized trial of diet and physical activity in ovarian cancer survivors. Gynecol Oncol 2023;170:11-8.
11. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer — viewpoint of the IARC Working Group. N Engl J Med 2016;375:794-8.
12. Linge J, Birkenfeld AL, Neeland IJ. Muscle mass and glucagon-like peptide-1 receptor agonists: adaptive or maladaptive response to weight loss? Circulation 2024;150:1288-98.
13. Arem H, Mama SK, Duan X, Rowland JH, Bellizzi KM, Ehlers DK. Prevalence of healthy behaviors among cancer survivors in the United States: how far have we come? Cancer Epidemiol Biomarkers Prev 2020;29:1179-87.

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ORIGINAL ARTICLE

Omitting Regional Nodal Irradiation after Response to Neoadjuvant Chemotherapy

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ABSTRACT

BACKGROUND

The benefit of regional nodal irradiation in the treatment of breast cancer is well established for patients with pathologically positive axillary nodes, but whether it is also beneficial for patients whose nodes become pathologically tumor free (ypN0) after neoadjuvant chemotherapy remains unclear.

METHODS

We evaluated whether regional nodal irradiation improves outcomes in patients with biopsy-proven, node-positive breast cancer who reach ypN0 status after neoadjuvant chemotherapy. Patients with breast cancer with a clinical stage of T1 to T3 (tumor size, ≤2 cm to >5 cm), N1, and M0 (indicating spread to movable, ipsilateral level I and II axillary lymph nodes but no distant metastasis) who had ypN0 status after neoadjuvant chemotherapy were randomly assigned to receive regional nodal irradiation or no regional nodal irradiation. The primary end point was the interval of freedom from invasive breast cancer recurrence or death from breast cancer (invasive breast cancer recurrence–free interval). Secondary end points included the locoregional recurrence–free interval, the distant recurrence–free interval, disease-free survival, and overall survival. Safety was also assessed.

RESULTS

A total of 1641 patients were enrolled in the trial; 1556 were included in the primary-event analysis: 772 in the irradiation group and 784 in the no-irradiation group. After a median follow-up of 59.5 months, 109 primary end-point events (50 in the irradiation group and 59 in the no-irradiation group) had occurred. Regional nodal irradiation did not significantly increase the invasive breast cancer recurrence–free interval (hazard ratio, 0.88; 95% confidence interval, 0.60 to 1.28; P=0.51). Point estimates of survival free from the primary end-point events were 92.7% in the irradiation group and 91.8% in the no-irradiation group. Regional nodal irradiation did not increase the locoregional recurrence–free interval, the distant recurrence–free interval, disease-free survival, or overall survival. No deaths related to the protocol-specified therapy were reported, and no unexpected adverse events were observed. Grade 4 adverse events occurred in 0.5% of patients in the irradiation group and 0.1% of those in the no-irradiation group.

CONCLUSIONS

The addition of adjuvant regional nodal irradiation did not decrease the risk of invasive breast cancer recurrence or death from breast cancer in patients who had negative axillary nodes after neoadjuvant chemotherapy. (Funded by the National Institutes of Health; NSABP B-51–Radiation Therapy Oncology Group 1304 ClinicalTrials.gov number, NCT01872975.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Mamounas can be contacted at terry.mamounas.md@adventhealth.com or at AdventHealth Cancer Institute, 2501 N. Orange Ave., Orlando, FL 32804.

Drs. Mamounas and White contributed equally to this article.

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Omitting Regional Nodal Irradiation after Response to Chemotherapy

A Research Summary based on Mamounas EP et al. | 10.1056/NEJMoa2414859 | Published on June 5, 2025

WHY WAS THE TRIAL DONE?

Among patients with breast cancer, the benefit of regional nodal irradiation is well established in cases of pathologically positive axillary lymph nodes. Whether regional nodal irradiation can benefit patients whose nodes become tumor-free after neoadjuvant chemotherapy is unclear.

HOW WAS THE TRIAL CONDUCTED?

Patients with operable breast cancer with positive axillary nodes that became pathologically tumor-free after at least 8 weeks of neoadjuvant chemotherapy were randomly assigned to receive adjuvant regional nodal irradiation or no regional nodal irradiation after mastectomy or lumpectomy. The primary end point was the invasive breast cancer recurrence–free interval, defined as the time to invasive locoregional recurrence, distant recurrence, or death from breast cancer.

TRIAL DESIGN

- Phase 3
- Prospective
- Randomized
- Multicenter

RESULTS

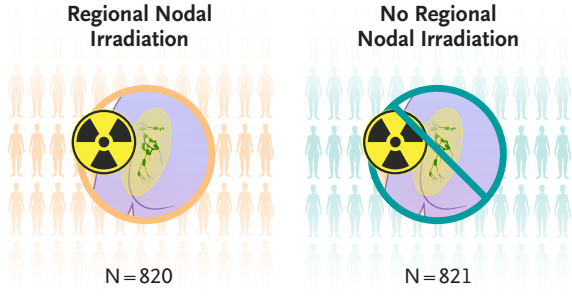
During a median 5 years of follow-up, regional nodal irradiation after surgery did not significantly increase the invasive breast cancer recurrence–free interval. No unexpected adverse events occurred, and few patients had grade 4 adverse events.

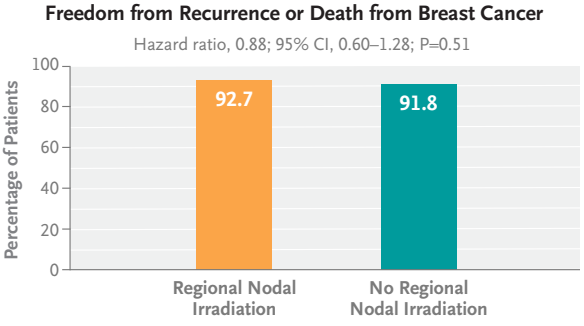
LIMITATIONS AND REMAINING QUESTIONS

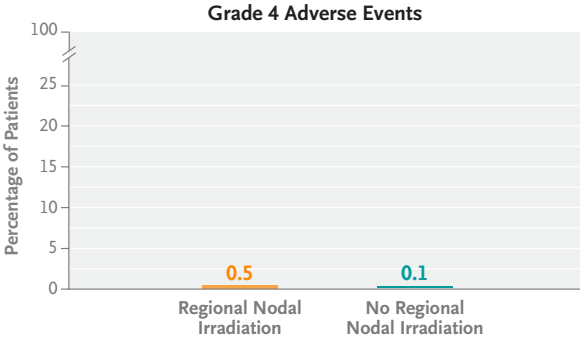
- The observed incidence of invasive breast cancer recurrence or death from breast cancer (8.2%) was approximately 40% lower than expected.
- Patients with negative axillary nodes after surgery were eligible for the trial even if they had isolated tumor cells remaining. However, the researchers did not collect information on the presence of residual tumor cells at trial enrollment, so the proportion of these patients and their specific outcomes are unknown.
- Patient follow-up is ongoing.

CONCLUSIONS

Among patients with breast cancer whose positive axillary nodes became free of tumor in response to neoadjuvant chemotherapy, regional nodal irradiation after surgery did not decrease the risk of invasive breast cancer recurrence or death from breast cancer.







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ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist, in Early Type 2 Diabetes

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ABSTRACT

BACKGROUND

Orforglipron is a small-molecule, nonpeptide glucagon-like peptide-1 (GLP-1) receptor agonist in clinical development for type 2 diabetes and weight management. Additional data on the efficacy and safety of orforglipron are needed.

METHODS

In this phase 3, double-blind, placebo-controlled trial, we randomly assigned participants in a 1:1:1:1 ratio to receive orforglipron at one of three doses (3 mg, 12 mg, or 36 mg) or placebo once daily for 40 weeks. Participants had type 2 diabetes treated only with diet and exercise, a glycated hemoglobin level of at least 7.0% but no more than 9.5%, and a body-mass index (the weight in kilograms divided by the square of the height in meters) of at least 23.0. The primary end point was the change from baseline to week 40 in the glycated hemoglobin level. A key secondary end point was the percent change in body weight from baseline to week 40.

RESULTS

A total of 559 participants underwent randomization. The mean glycated hemoglobin level at baseline was 8.0%. At week 40, the estimated mean change from baseline in the glycated hemoglobin level was −1.24 percentage points with the 3-mg dose, −1.47 percentage points with the 12-mg dose, −1.48 percentage points with the 36-mg dose, and −0.41 percentage points with placebo. All three doses of orforglipron were superior to placebo with respect to the primary end point; the estimated mean difference from placebo was −0.83 percentage points (95% confidence interval [CI], −1.10 to −0.56) with the 3-mg dose, −1.06 percentage points (95% CI, −1.33 to −0.79) with the 12-mg dose, and −1.07 percentage points (95% CI, −1.33 to −0.81) with the 36-mg dose (P<0.001 for all comparisons). The mean glycated hemoglobin level at week 40 was 6.5 to 6.7% with orforglipron. The percent change in body weight from baseline to week 40 was −4.5% with the 3-mg dose, −5.8% with the 12-mg dose, −7.6% with the 36-mg dose, and −1.7% with placebo. The most common adverse events were mild-to-moderate gastrointestinal events, most of which occurred during dose escalation. No episodes of severe hypoglycemia were reported. Permanent discontinuation of orforglipron or placebo due to adverse events occurred in 4.4 to 7.8% of participants receiving orforglipron and 1.4% of participants receiving placebo.

CONCLUSIONS

In adults with early type 2 diabetes, orforglipron significantly reduced the glycated hemoglobin level over a period of 40 weeks. (Supported by Eli Lilly; ACHIEVE-1 ClinicalTrials.gov number, NCT05971940.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Rosenstock can be contacted at juliorosenstock@dallasdiabetes.com.

*A list of the principal ACHIEVE-1 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

Orforglipron in Early Type 2 Diabetes

A Research Summary based on Rosenstock J et al. | 10.1056/NEJMoa2505669 | Published on June 21, 2025

WHY WAS THE TRIAL DONE?

For patients with type 2 diabetes, subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonists are well-established, effective treatments. However, many patients prefer oral formulations over injectables. In a phase 2 trial, orforglipron — an oral, small-molecule, nonpeptide GLP-1 receptor agonist — led to meaningful reductions in the glycated hemoglobin level and body weight in patients with type 2 diabetes. However, additional data are needed.

HOW WAS THE TRIAL CONDUCTED?

Adults with type 2 diabetes that was inadequately controlled with diet and exercise alone, a glycated hemoglobin level between 7.0% and 9.5%, and a body-mass index of at least 23.0 were assigned to receive oral orforglipron at one of three maintenance doses (3 mg, 12 mg, or 36 mg) or placebo once daily for 40 weeks. The primary end point was the change in the glycated hemoglobin level from baseline to week 40.

TRIAL DESIGN

- Phase 3
- Double-blind
- Randomized
- Placebo-controlled
- Location: China, India, Japan, Mexico, and the United States

RESULTS

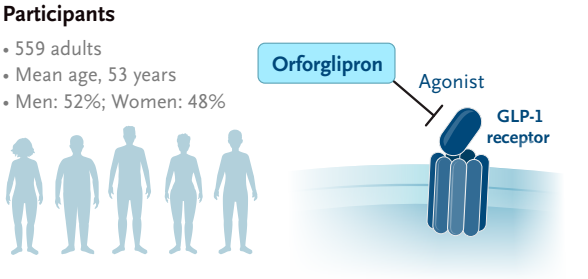
All three doses of orforglipron were associated with a statistically significant reduction in the glycated hemoglobin level; all the doses led to a greater reduction than placebo. The adverse events most often reported with orforglipron were mild-to-moderate gastrointestinal events, most of which occurred during dose escalation. The percentage of participants who discontinued their regimen because of adverse events was higher in the orforglipron groups than in the placebo group.

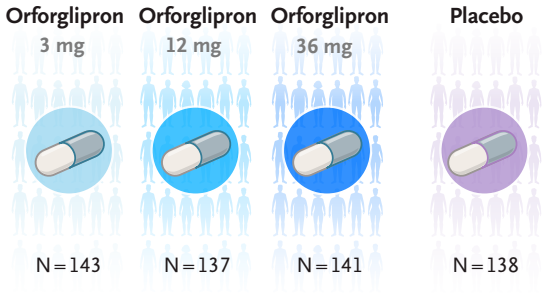
LIMITATIONS AND REMAINING QUESTIONS

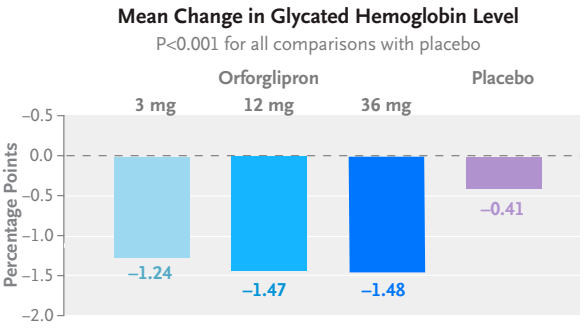
- The trial enrolled participants who were being treated only with diet and exercise at baseline; over 60% had not received any previous glucose-lowering medications. Thus, the findings cannot be generalized to patients receiving other background antihyperglycemic medications.
- The trial was relatively short. Data on long-term efficacy and safety are needed.

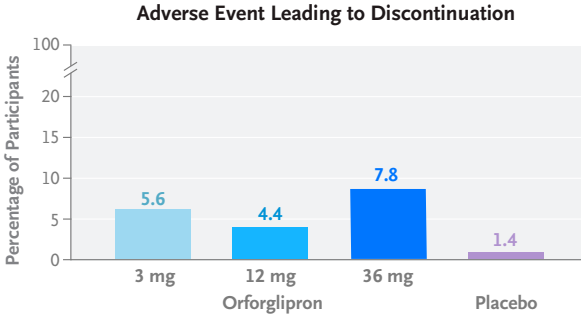
CONCLUSIONS

In adults with type 2 diabetes that was inadequately controlled with diet and exercise alone, once-daily orforglipron lowered the glycated hemoglobin level significantly more than placebo at 40 weeks.









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EDITORIALS

Mimicking Complex Receptor Actions with Small(ish) Molecules

Derek B. Lowe, Ph.D.[1]

As a therapeutic area, type 2 diabetes includes a wide range of treatment options in several mechanistic classes (although metformin has multiple classifications). One of the best therapies, however, is and has always been weight loss through diet and exercise.

On the face of it, a weight-loss strategy involving diet and exercise is theoretically available to any patient at any time at relatively low cost. But practitioners know all too well what almost invariably happens after such a recommendation — not much, and not enough. Thus, drug developers have sought pharmacologic mechanisms for weight loss in patients with type 2 diabetes, as well as in others, for decades, but the long list of failed projects and withdrawn products (for the few that reached the market) has been discouraging. This landscape has changed dramatically with the advent of incretin hormone receptor ligands, the efficacy of which is now beyond doubt. The benefits conferred by these agents in patients with type 2 diabetes (and other diagnoses) are clear, and an entire medical subfield is growing around their further effects.

The incretins, like many peptide hormones, are fairly small as proteins go — a few dozen amino acids long. But that makes them gigantic as compared with small-molecule drugs. Their molecular weights are at least 10 times as high as the 300 to 500 mass units that medicinal chemists have traditionally aimed for, and being peptides, they have generally undesirable properties as well. Many have short half-lives in the circulation, which can be a desirable feature for endogenous peptides but is nowhere near what is needed for the administration of a once-daily dose. In addition, they are generally digested swiftly if administered orally and are thus given as injections. Fixing these problems by modifying the peptide structure itself is not impossible, but it is a slow, empirical, and invariably expensive process with no guarantee of success.

So replacing the peptide entirely with a more resilient small molecule would seem to be an attractive strategy, but the aforementioned size discrepancies between peptides and small-molecule agents may send research teams off into the wilderness for years. The receptors for the peptide hormones tend to have similarly large, complex binding sites, so for a small molecule to recapitulate the effects of an endogenous ligand by occupying a small-molecule–sized territory within a receptor may be a formidable challenge. As an example, there is no small-molecule replacement available at the insulin receptor binding site itself, despite uncounted failed attempts.

In this issue of the *Journal*, Rosenstock and colleagues[1] report the results of a pivotal trial of orforglipron, which is, in fact, a small molecule that manages to mimic the effects of glucagon-like peptide-1 (GLP-1) at the GLP-1 receptor. Orforglipron was discovered at Chugai Pharmaceutical during the 2010s. Cryoelectron micros-

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copy studies have shown that orforglipron works through an unexpected mechanism: rather than occupying the deeper regions of the binding pocket, it binds farther out, in the outer-facing extracellular domain of the receptor. Orforglipron interacts with one of the extracellular loops and several of the transmembrane helices, and occupation of this newly appreciated pocket moves those helices into an arrangement similar to that induced by GLP-1 binding itself.[2]

As compared with the natural ligand, orforglipron is best described as a partial agonist, but its signaling is so strong at the GLP-1 receptor that this level of activity is clearly enough for physiological effects. Indeed, orforglipron led to meaningful improvement in glycemic control — similar to results seen in trials of other GLP-1 agonists — accompanied by major weight loss. The gastrointestinal side effects were those expected with GLP-1 compounds as well. All in all, orforglipron appears to mimic GLP-1 (and the synthetic peptidic GLP-1 agonists) at the structural biology level all the way up to the level of clinical results in patients. The trial by Rosenstock and colleagues did not appear to show noticeable hepatotoxicity, a feature that has ended the development of other small-molecule GLP-1 drug candidates such as danuglipron.[3] The reasons for such differences are as yet unknown and will be of great interest.

Lead compounds with such mechanisms are discovered by screening. We are approaching an era when computational methods can deal with the coordinated motions of whole receptor proteins in response to ligand binding, a very difficult and labor-intensive problem. One must add to the required assay development work the considerable efforts of a large team of medicinal chemists, because "small molecule" is not a term that earlier research teams would have applied to a complex structure such as orforglipron. It would indeed have been rejected at one time as "undruglike," but that sort of mistake will not be repeated as medicinal chemists have been staking out ever-more-complex territory. Drugs are as drugs work.

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

[1]American Association for the Advancement of Science, Washington, DC.

1. Rosenstock J, Hsia S, Nevarez Ruiz L, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist, in early type 2 diabetes. N Engl J Med 2025;393:1065-76.
2. Kawai T, Sun B, Yoshino H, et al. Structural basis for GLP-1 receptor activation by LY3502970, an orally active nonpeptide agonist. Proc Natl Acad Sci U S A 2020;117:29959-67.
3. Griffith DA, Edmonds DJ, Fortin J-P, et al. A small-molecule oral agonist of the human glucagon-like peptide-1 receptor. J Med Chem 2022;65:8208-26.

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ORIGINAL ARTICLE

Ivermectin to Control Malaria — A Cluster-Randomized Trial

C. Chaccour,[1-3] M. Maia,[4,5] M. Kariuki,[6] P. Ruiz-Castillo,[1] C. Wanjiku,[4] L. Kasiwa,[4] A. Brazeal,[4] A. Casellas,[1] M. Ngama,[6] T. Onyango,[4] E. Elobolobo,[7] K. Kazungu,[4] M. Mael,[1] W. Wangari,[4] K. Nuru,[4] R. Otuko,[4] A. Sanz,[1] I. Ringera,[4] A. Matano,[6] S. Mitora,[6] M. Ribes,[1] J. Brew,[7] N. Gorski,[1] P. Nicolas,[1] S. Stanulovic,[1] I. Omondi,[4] J. Furnival-Adams,[1] L. Túnez,[1] J. Mbarak,[6] V. Vegove,[8] E. Yaa,[6] S. Mramba,[6] Y. Kibet,[6] N. Nyambura,[6] C. Rotich,[6] S. Wanjiru,[6] M. Vura,[6] F. Wanjiku,[6] L. Sam,[9] L. Collins,[10] K. Xia,[11] F. Hammann,[12] F. Saúte,[13] M. Rudd,[14] C. Rist,[11] C. Jones,[4,5] J. Mwangangi,[6,15] and N.R. Rabinovich[1,16]

ABSTRACT

BACKGROUND

Malaria control and elimination is threatened by the spread of insecticide resistance and behavioral adaptation of vectors. Whether mass administration of ivermectin, a broad-spectrum antiparasitic drug that also kills mosquitoes feeding on treated persons, can reduce malaria transmission is unclear.

METHODS

We conducted a cluster-randomized trial in Kwale, a county in coastal Kenya in which malaria is highly endemic and coverage and use of insecticide-treated nets are high. Clusters of household areas were randomly assigned in a 1:1 ratio to receive mass administration of ivermectin (400 μg per kilogram of body weight) or albendazole (400 mg, active control) once a month for 3 consecutive months at the beginning of the "short rains" season. Children 5 to 15 years of age were tested for malaria infection monthly for 6 months after the first round of treatment. The two primary outcomes were the cumulative incidence of malaria infection (assessed among children 5 to 15 years of age) and of adverse events (assessed among all eligible participants). Analyses were performed with generalized estimating equations in accordance with the intention-to-treat principle.

RESULTS

A total of 84 clusters comprising 28,932 eligible participants underwent randomization. The baseline characteristics of the participants were similar in the trial groups. Six months after the first round of treatment, the incidence of malaria infection was 2.20 per child-year at risk in the ivermectin group and 2.66 per child-year at risk in the albendazole group; the adjusted incidence rate ratio (ivermectin vs. albendazole) was 0.74 (95% confidence interval [CI], 0.58 to 0.95, P=0.02). The incidence of serious adverse events per 100 treatments did not differ significantly between the trial groups (incidence rate ratio, 0.63; 95% CI, 0.21 to 1.91).

CONCLUSIONS

Among children 5 to 15 years of age who were living in an area with high coverage and use of bed nets, ivermectin, administered once a month for 3 consecutive months, resulted in a 26% lower incidence of malaria infection than albendazole. No safety concerns were identified. (Funded by Unitaid; BOHEMIA ClinicalTrials.gov number, NCT04966702; Pan African Clinical Trial Registry number, PACTR202106695877303.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Dr. Chaccour can be contacted at cchaccour@unav.es or at the Navarra Center for International Development, Edificio de Bibiotecas 2a Planta, Universidad de Navarra, 31009 Pamplona, Spain.

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The NEW ENGLAND JOURNAL of MEDICINE

Ivermectin to Control Malaria — A Cluster-Randomized Trial

A Research Summary based on Chaccour C et al. | 10.1056/NEJMoa2411262 | Published on July 24, 2025

WHY WAS THE TRIAL DONE?

Progress in malaria control has stalled in recent years owing to emerging resistance to insecticides and behavioral adaptations among anopheles mosquitoes. Whether mass administration of ivermectin, a broad-spectrum antiparasitic drug that also kills mosquitoes feeding on treated persons, can reduce malaria transmission is unclear.

HOW WAS THE TRIAL CONDUCTED?

Clusters of households in areas with high use of insecticide-treated bed nets were randomly assigned to receive either oral ivermectin (400 μg per kilogram of body weight) or albendazole (400 mg; control) once monthly for 3 months, beginning in October 2023 at the start of the "short rains" season. The two primary outcomes were the cumulative incidence of malaria infection (assessed monthly for 6 months after the first round of treatment among children 5 to 15 years of age) and of adverse events (assessed among all eligible participants).

TRIAL DESIGN

- Open-label
- Blinded assessment
- Cluster-randomized
- Controlled
- Location: Kwale County, Kenya

RESULTS

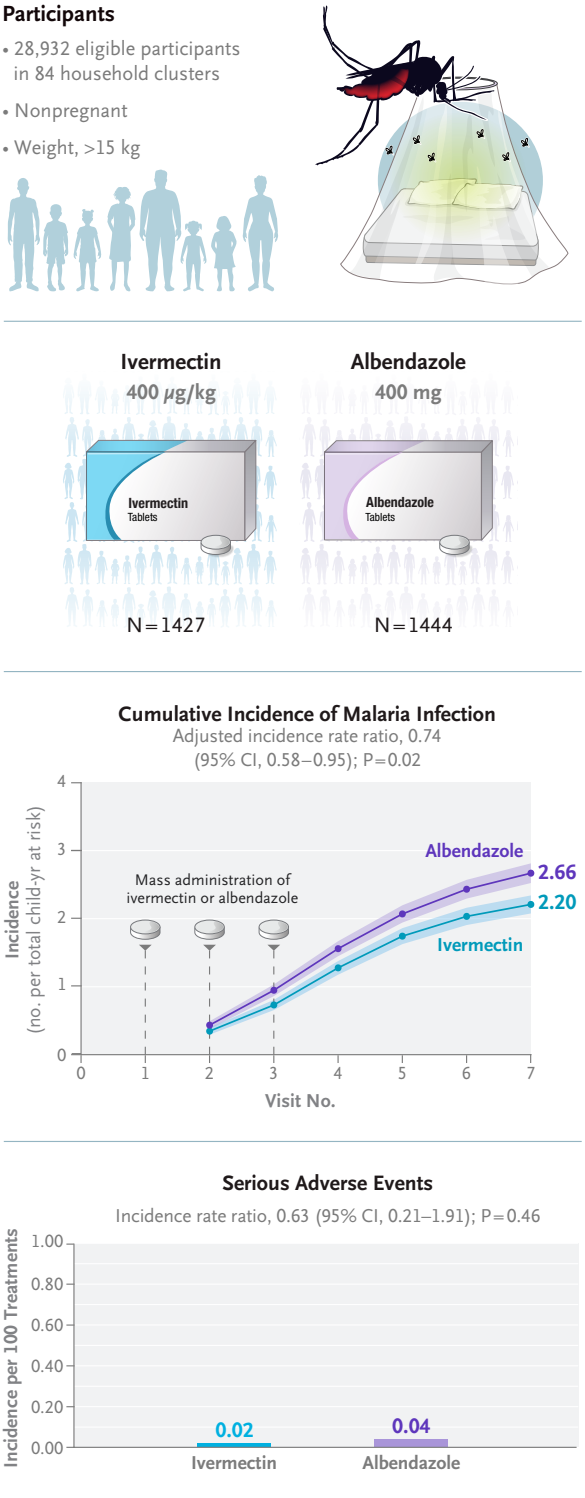
The cumulative incidence of malaria infection at 6 months was significantly lower with ivermectin than with albendazole. The incidence of serious adverse events was similar in the two groups.

LIMITATIONS AND REMAINING QUESTIONS

- Data on the incidence of transmission of malaria infection in the cluster areas before the intervention were lacking.
- The real effect of ivermectin was probably underestimated, given that children in the cohort received a full course of artemether–lumefantrine whenever an infection was detected, which resulted in more frequent use of artemether–lumefantrine in the albendazole group.
- The safety of ivermectin in children weighing less than 15 kg and in potentially pregnant women warrants study.

CONCLUSIONS

In an area of Kenya with high use of insecticide-treated bed nets, mass administration of a 400-μg/kg dose of ivermectin once per month for 3 consecutive months at the start of the short rains season led to a significantly lower incidence of malaria infection among children 5 to 15 years of age than albendazole.



Funding for this Research Summary is provided by the Doris Duke Foundation, committed to building a creative, equitable, and sustainable future.

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EDITORIALS

Ivermectin against Malaria — Good News in Bad Times

Richard W. Steketee, M.D., M.P.H.[1]

Twenty-five years ago,[1] international organizations, philanthropic foundations, governments of donor nations (especially the United States), and health ministries in countries where malaria is endemic united to invest in an enhanced approach to malaria control that included a scale-up of an evidence-based intervention "package" featuring new diagnostics and drugs (to reduce the incidence of malaria-related illness and death) and vector control with insecticide-treated mosquito nets (to kill mosquitoes and stop transmission of infection).[1] Many countries where malaria is endemic delivered the package with high coverage and achieved remarkable progress. In the 25 years that followed, elimination of local malaria transmission was reported in 26 countries and certified by the World Health Organization in 18 countries.[2] Between 2000 and 2023, an estimated 2.2 billion malaria infections and 12.7 million malaria-related deaths were prevented worldwide.[3] However, malaria remains a public health challenge, with the most recent annual estimates showing 263 million cases and 597,000 deaths in 2023.[3] Of these, 95% of cases and deaths occurred in 34 countries (30 in Africa), and each of these countries reported more than a million cases per year.[3] Faced with intense transmission due to climates favoring mosquito habitats, porous or unscreened houses, large reservoirs of human parasite infection, and limited national health budgets, these 34 countries need additional tools designed specifically to reduce infection transmission.

In this issue of the *Journal*, Chaccour and colleagues[4] describe a well-conducted trial of ivermectin, a low-cost, oral endectocide that is given to all residents of a community to kill mosquitoes when they ingest human blood containing drug concentrations above a lethal threshold. This cluster-randomized trial was conducted in coastal Kenya, where malaria transmission remains persistent and intense despite high levels of reported use of insecticide-treated mosquito nets (77% of the residents in the intervention clusters) and access to malaria treatment. In short intervals of mass drug administration, all eligible residents in the clusters were given a single monthly oral dose of ivermectin (the investigational drug, at a dose of 400 μg per kilogram of body weight) or albendazole (the comparison drug, at a dose of 400 mg) for 3 consecutive months at the start of the "short rains" season. Among children 5 to 15 years of age (the primary efficacy analysis population), the incidence of malaria infection was shown to be 26% lower with ivermectin than with albendazole. These findings were not unexpected[5] but were the first to show that seasonal mass administration of ivermectin on a monthly schedule could be performed in alignment with other malaria or health interventions and provide a further substantial reduction in transmission. The investigators recognized that the monthly dose would kill mosquitoes for only 10 days after administration and have no killing effect for the remaining two thirds of the month.[6] It is conceivable that doses could be given more frequently (a challenge for program delivery) or that a longer-acting endectocide could be identified through future research, thereby leading to a greater reduction in transmission that exceeds the observed 26%.

The trial participants received the 400-μg-per-

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kilogram dose of ivermectin with no unacceptable side effects, a finding that is consistent with the known safety profile of the drug after more than 4 billion doses had been given for other parasitic diseases (e.g., onchocerciasis, filariasis, and strongyloidiasis). The ability of ivermectin to kill bedbugs, lice, and scabies mites, as well as its approval by multiple regulatory agencies, could facilitate its acceptance in a community and incorporation into malaria programs.[7]

Research on other interventions to decrease parasite transmission continues. For example, a recent trial in Kenya[8] showed that household diffusers that released a mosquito repellent containing transfluthrin reduced the incidence of malaria infection in communities reporting high use of insecticide-treated mosquito nets, with approximately the same degree of reduction as that with mass administration of ivermectin in the trial by Chaccour et al. Other strategies designed specifically to reduce transmission are being explored, such as mosquito nets treated with a combination of insecticides, longer-lasting antimalarial agents, the addition of low-dose primaquine to antimalarial treatment regimens, genetic modification of mosquitoes, monoclonal antibodies, and vaccines that prevent malaria transmission (the two approved malaria vaccines reduce illness but not parasite transmission). Could these new tools ultimately complement current malaria interventions?

Unfortunately, news of this encouraging intervention comes at a dire moment for global public health. Radical funding cuts in staff, commodities, program operations, and research have devastated existing malaria programs in Africa, Asia, and the Americas, as well as the many supporting organizations (e.g., the Agency for International Development, the Centers for Disease Control and Prevention, the National Institutes of Health, the World Health Organization, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria). Until these resources are restored, continued deployment of currently effective interventions should be prioritized to prevent the undoing of progress and the likely resurgence of malaria. As the trial by Chaccour et al. shows, new and exciting opportunities will arise. During the current pause in funding, planning and support should focus on basic research of longer-acting endectocides and on implementation research of methods to scale up delivery of ivermectin, as well as its potential codelivery with other new transmission reduction measures such as home-based repellent diffusers. If these new strategies are effective, practical, and affordable, they could boost the value of future packages to prevent malaria transmission, illness, and death, especially in the 34 countries that need them most.

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

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1. Nabarro D. Roll back malaria. Parassitologia 1999;41:501-4.
2. World Health Organization. Global malaria programme: countries and territories certified malaria-free by WHO. January 15, 2025 (https://www.who.int/teams/global-malaria-programme/elimination/countries-and-territories-certified-malaria-free-by-who).
3. World Health Organization. World malaria report 2024: addressing inequality in the global malaria response. December 11, 2024 (https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024).
4. Chaccour C, Maia M, Kariuki M, et al. Ivermectin to control malaria — a cluster-randomized trial. N Engl J Med 2025;393:362-75.
5. Slater HC, Foy BD, Kobylinski K, et al. Ivermectin as a novel complementary malaria control tool to reduce incidence and prevalence: a modelling study. Lancet Infect Dis 2020;20:498-508
6. Kamau Y, Tuwei M, Wanjiku C, et al. Mosquitocidal efficacy and pharmacokinetics of single-dose ivermectin versus three-day dose regimen for malaria vector control compared with albendazole and no treatment: an open-label randomized controlled trial. Int J Infect Dis 2024;148:107236
7. Crump A. Ivermectin: enigmatic multifaceted 'wonder' drug continues to surprise and exceed expectations. J Antibiot (Tokyo) 2017;70:495-505.
8. Ochomo EO, Gimnig JE, Awori Q, et al. Effect of a spatial repellent on malaria incidence in an area of western Kenya characterised by high malaria transmission, insecticide resistance, and universal coverage of insecticide treated nets (part of the AEGIS Consortium): a cluster-randomised, controlled trial. Lancet 2025;405:147-56

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BRIEF REPORT

Survival of Transplanted Allogeneic Beta Cells with No Immunosuppression

Per-Ola Carlsson, M.D., Ph.D.,[1,2] Xiaomeng Hu, Ph.D.,[3] Hanne Scholz, Ph.D.,[4-6] Sofie Ingvast, B.Sc.,[6] Torbjörn Lundgren, M.D., Ph.D.,[7] Tim Scholz, M.D., Ph.D.,[8] Olof Eriksson, Ph.D.,[9] Per Liss, M.D., Ph.D.,[8] Di Yu, Ph.D.,[6] Tobias Deuse, M.D.,[10] Olle Korsgren, M.D., Ph.D.,[6] and Sonja Schrepfer, M.D., Ph.D.[3]

SUMMARY

The need to suppress a patient's immune system after the transplantation of allogeneic cells is associated with wide-ranging side effects. We report the outcomes of transplantation of genetically modified allogeneic donor islet cells into a man with long-standing type 1 diabetes. We used clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated protein 12b (Cas12b) editing and lentiviral transduction to genetically edit the cells to avoid rejection; the cells were then transplanted into the participant's forearm muscle. He did not receive any immunosuppressive drugs and, at 12 weeks after transplantation, showed no immune response against the gene-edited cells. C-peptide measurements showed stable and glucose-responsive insulin secretion. A total of four adverse events occurred, none of which were serious or related to the study drug. (Funded by the Leona M. and Harry B. Helmsley Charitable Trust; EudraCT number, 2023-507988-19-00; ClinicalTrials.gov number, NCT06239636.)

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Drs. Hu and H. Scholz contributed equally to this article.

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EDITORIALS

SCIENCE BEHIND THE STUDY

Replacement of Beta Cells for Type 1 Diabetes

Kevan C. Herold, M.D.,[1,2] and Jordan S. Pober, M.D., Ph.D.[1,2]

For more than 100 years, replacing insulin by injection has been the only treatment for clinical stage 3 (symptomatic) type 1 diabetes (see Key Concepts). Advanced techniques for insulin delivery still lack the precision, rapid kinetics, and flexibility that endogenous insulin-producing beta cells can achieve. Despite initial successes with the transplantation of cadaver-derived islets,[1] the requirement for multiple donors and failure to maintain insulin independence prompted further research to identify alternative sources of beta cells and new antirejection strategies.[2] In this issue of the *Journal*, Reichman et al.[3] and Carlsson et al.[4] report advances on each front.

MAKING BETA CELLS FROM STEM CELLS

Reichman et al. report results from patients with type 1 diabetes who received zimislecel, clusters of islet cells differentiated from a line of human embryonic stem cells[5] (Fig. 1). They administered the clusters of differentiated islet cells by infusion into the portal vein, coupled with glucocorticoid-free immunosuppression. The transplant achieved the primary objective of eliminating severe hypoglycemia; it improved glucose control (i.e., lowered the glycated hemoglobin level) and, in 10 of the 12 participants, eliminated the need for exogenous insulin. Cadaver-derived islets that are introduced in this manner are likely to lodge within the hepatic sinusoids and depend on diffusion for nutrients. In the normal pancreas, the islet microvasculature furnishes nutrients to cells throughout the islet, and the vascular basement membrane, vascular cells, and pericytes are implicated in beta-cell function, proliferation, and responses to inflammation. The absence of microvessels in the islet clusters may partly shield the transplanted beta cells from host immune responses; sustained immunosuppression is required to prevent rejection, increasing the risk of infection (infection caused the death of one patient in the study) and cancer. Whether the transplanted clusters will survive over the long term remains to be seen, and the regimen that was used does not obviously prevent progressive chronic rejection, which involves immune mechanisms distinct from those that mediate acute rejection.[7]

BELOW THE RADAR OF ADAPTIVE IMMUNITY?

Carlsson et al. describe a "three-hit" approach to evade acute rejection. Through genetic engineering, they created "hypoimmune islets" and tested them in a single patient. Intact islets were isolated from a pancreas donor with blood type O, dispersed into single cells, and genetically disrupted (with the use of nuclease Cas12b [clustered regularly interspaced short palindromic repeats {CRISPR}–CRISPR-associated protein 12b] and guide RNAs[8]) to eliminate the expression of class I and II major histocompatibility complex (MHC) molecules (Fig. 1). In the single participant, there was sustained production of insulin by the graft without the need for immune suppressants. MHC molecules are the most polymorphic proteins encoded by the human genome, and two unrelated persons are unlikely to share all six alleles encoding the three class I loci and the

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KEY CONCEPTS

Immunosuppression
The inhibition of unwanted immune responses. In the context of allotransplantation, it is used to suppress immune responses that would otherwise result in the rejection of a foreign (or histoincompatible) organ or cellular graft. Immunosuppressive drugs are also used to treat autoimmune and inflammatory diseases. These drugs eliminate or block the activity of immune cells and soluble mediators secreted by immune cells (e.g., cytokines and antibodies) that recruit other immune cells. Immunosuppression can also occur as an unwanted side effect of drugs used in chemotherapy and as a consequence of an underlying pathologic process (e.g., cancer).

Induced pluripotent stem cell
A type of pluripotent stem cell derived from a nonpluripotent cell, typically an adult somatic cell such as a fibroblast, by transfection and the forced expression of stem-cell–associated genes.

Major histocompatibility complex (MHC)
A complex of linked genes encoding cell-surface proteins that display peptides produced by cleavage of intracellular proteins (in the case of class I MHC) or extracellular proteins that are processed (in the case of class II MHC). These molecules help T cells recognize foreign or mutated proteins. The human form of MHC is referred to as HLA.

Natural killer (NK) cell
A type of cytotoxic lymphocyte critical to the function of the innate immune system.

Type 1 diabetes
A chronic autoimmune disease caused by the immune-mediated destruction of insulin-producing pancreatic beta cells. It is one of the most common chronic diseases of childhood but can manifest at any age. Once beta cells are destroyed, they do not recover, and lifelong insulin replacement is required. Approaches involving the transplantation of insulin-producing beta cells are under clinical investigation.

An illustrated glossary is available at NEJM.org

three class II loci. Physiologically, these proteins serve as scaffolds that display antigens (peptides derived from other proteins) to T cells. In the context of a transplant, they are the major targets of rejection by the recipient's immune response.[9]

MUTING MHCI

CD8+ killer T cells may directly recognize nonself class I MHC molecules (HLA-A, -B, and -C) on graft islet cells, triggering beta-cell loss. β_2-microglobulin is an invariant component of class I MHC molecules; disrupting the gene that encodes it (*B2M*) prevents all class I molecules from being expressed. Carlsson et al. therefore sought to inactivate *B2M* through disrupting this gene.

MUTING MHCII

In organ transplantation, matching MHC alleles between donor and recipient weakens the allogeneic immune response, but even "fully matched" graft beta cells may be vulnerable to autoimmune destruction. This vulnerabity occurs because CD4+ effector T cells contribute to rejection by activating CD8+ T cells, antibody-producing B cells, and innate immune cells. To do so, CD4+ T cells must recognize antigens presented by class II MHC molecules on the surface of specialized antigen-presenting cells. In the context of a transplant, CD4+ T cells may cross-react to class II MHC on the cells of the graft (direct recognition) or shed intact graft class II MHC displayed on host dendritic cells (semi-direct recognition) or even peptides from degraded graft cells that can bind to self class II MHC on host dendritic cells and trigger CD4+ T-cell activation (indirect recognition). Carlsson et al. therefore set about inactivating all three class II MHC proteins (HLA-DR, -DP, and -DQ) by disrupting a single gene, *CIITA*, which encodes a protein essential for the synthesis of MHC class II proteins.

Finally, in addition to acute T-cell–mediated rejection, allogeneic cells are also subject to antibody-mediated rejection by preexisting or de novo (post-transplantation) antidonor antibodies. Because these antibodies primarily target nonself MHC molecules on donor cells, eliminating expression of class I and II MHC molecules should be protective.[10]

WHAT ABOUT INNATE IMMUNITY?

Innate immune cells may also attack foreign

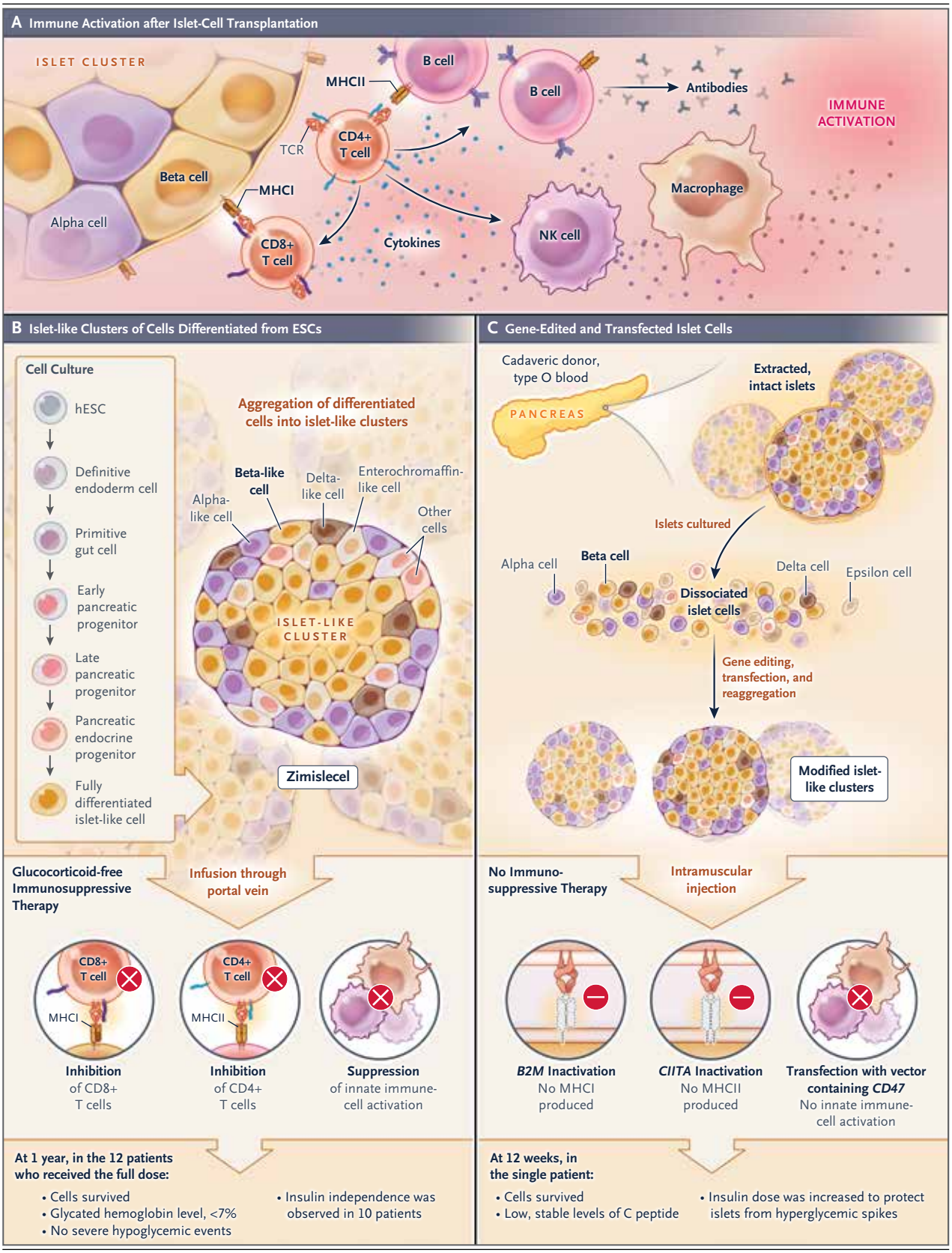

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Figure 1 (facing page). Overcoming Barriers to Replacement of Beta Cells.

Immune recognition of transplanted cells involves the coordinated activity of adaptive and innate immune cells (Panel A). CD8+ T cells can recognize class I major histocompatibility complex (MHC) molecules and kill the graft, but there is also presentation of antigens that are derived from the graft and of class II MHC molecules to CD4+ T cells, with release of cytokines, activation of B cells that can produce antibodies against MHC molecules on the graft, and innate immune cells. Reichman et al.[3] describe the derivation of differentiated isletlike clusters from a line of human embryonic stem cells (hESC) line, involving culture with specific agents and associations with specific gene-expression signatures as they pass through six stages (Panel B).[6] They then infused the clustered islet cells into the portal vein of patients with type 1 diabetes. To prevent rejection of the transplanted clusters through the recognition of the cells by the recipients' immune systems, the study participants were given immunosuppressive therapy before receiving the cells and as a maintenance therapy after infusion. Carlsson et al.[4] harvested islets of Langerhans from the pancreas from an organ donor, dissociated the cells, and then altered them to render them resistant to rejection by the recipient's immune system (Panel C). More specifically, they shut down the expression of class I and II MHC genes through the inactivation of the genes *B2M* and *CIITA* and then transfected the edited cells with a gene encoding *CD47*, which inhibits innate immune cells. These "hypoimmune islets" produced insulin for 12 weeks in the absence of immunosuppression in one patient after implantation in the forearm muscle. ESC denotes embryonic stem cell, NK natural killer, and TCR T-cell receptor.

cells and contribute to rejection in the absence of T-cell–mediated or antibody-mediated activation. Macrophages may recognize and attack foreign cells with the use of leukocyte-like immunoglobulin receptor. Natural killer (NK) cells may attack foreign cells when their inhibitory killer immunoglobulin-like receptors sense the absence of self HLA-C or -B (i.e., missing self). To limit this, Carlsson et al. transfected the disbursed islet cells with a lentiviral vector containing *CD47*, which encodes a protein that induces an inhibitory ("don't eat me") signal to myeloid cells (Fig. 1).[11] The transfected cells rebuffed both blood monocytes and NK cells of the transplant recipient in studies in vitro.

The modified islets were introduced by intramuscular injection rather than portal-vein infusion and continued to function with no immunosuppression for the 12-week duration of the study. Although many of the islet cells showed only partial modifications or no modification (i.e., had a subset or even none of the intended genetic changes), the treatment was sufficient to limit host antigraft immune responses as assessed by post-transplant assays of cytotoxicity mediated by T cells, antibodies, and innate immune cells. Still, 12 weeks is short, and the extent of perfusion of the islets after intramuscular injection is unknown.

WHAT'S NEXT?

These studies are encouraging but preliminary. Additional and careful follow-up is essential to establish long-term efficacy and safety. The potential clinical benefits are substantial. Reichman et al. found that severe hypoglycemia was prevented in participants who received the full dose of zimislecel, a potentially limitless source of islets. The experience with hypoimmune islets was with a single participant who received less than 10% of the number needed for insulin independence; here, the methods of islet isolation and preparation are limiting. The genetic engineering used by Carlsson et al. could be applied to stem cells to obviate the need for immune suppression.[12] An alternative strategy to prevent transplant allorejection would be to use islet organoids obtained from induced pluripotent stem cells derived from the patient.[13]

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

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1. Shapiro AMJ, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230-8.
2. Makhlouf L, Kishimoto K, Smith RN, et al. The role of autoimmunity in islet allograft destruction: major histocompatibility complex class II matching is necessary for autoimmune destruction of allogeneic islet transplants after T-cell costimulatory blockade. Diabetes 2002;51:3202-10.
3. Reichman TW, Markmann JF, Odorico J, et al. Stem cell–derived, fully differentiated islets for type 1 diabetes. N Engl J Med 2025;393:858-68.
4. Carlsson P-O, Hu X, Scholz H, et al. Survival of transplanted allogeneic beta cells with no immunosuppression. N Engl J Med 2025;393:887-94.
5. Pagliuca FW, Millman JR, Gürtler M, et al. Generation of functional human pancreatic β cells in vitro. Cell 2014;159:428-39.
6. Hogrebe NJ, Maxwell KG, Augsornworawat P, Millman JR. Generation of insulin-producing pancreatic β cells from multiple human stem cell lines. Nat Protoc 2021;16:4109-43.
7. Kloc M, Ghobrial RM. Chronic allograft rejection: a significant hurdle to transplant success. Burns Trauma 2014;2:3-10.

8. Strecker J, Jones S, Koopal B, et al. Engineering of CRISPR-Cas12b for human genome editing. Nat Commun 2019;10:212.
9. Lakkis FG, Lechler RI. Origin and biology of the allogeneic response. Cold Spring Harb Perspect Med 2013;3(8):a014993.
10. Piemonti L, Everly MJ, Maffi P, et al. Alloantibody and autoantibody monitoring predicts islet transplantation outcome in human type 1 diabetes. Diabetes 2013;62:1656-64.
11. Logtenberg MEW, Scheeren FA, Schumacher TN. The CD47-SIRPα immune checkpoint. Immunity 2020;52:742-52.
12. Maxwell KG, Augsornworawat P, Velazco-Cruz L, et al. Gene-edited human stem cell-derived β cells from a patient with monogenic diabetes reverse preexisting diabetes in mice. Sci Transl Med 2020;12:12.
13. Wang S, Du Y, Zhang B, et al. Transplantation of chemically induced pluripotent stem-cell-derived islets under abdominal anterior rectus sheath in a type 1 diabetes patient. Cell 2024;187(22):6152-6164.e18.

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The NEW ENGLAND JOURNAL of MEDICINE

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Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

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ABSTRACT

BACKGROUND

Aldosterone dysregulation plays an important pathogenic role in hard-to-control hypertension. In several studies, baxdrostat, an aldosterone synthase inhibitor, reduced the seated systolic blood pressure of patients with uncontrolled or resistant hypertension.

METHODS

In this phase 3, multinational, double-blind, randomized, placebo-controlled trial, we recruited patients with a seated systolic blood pressure of between 140 mm Hg and less than 170 mm Hg despite the receipt of stable treatment with two antihypertensive medications (uncontrolled hypertension) or three or more such medications (resistant hypertension), including a diuretic. After a 2-week placebo run-in period, we randomly assigned patients with a seated systolic blood pressure of 135 mm Hg or more in a 1:1:1 ratio to receive baxdrostat at a dose of 1 mg, baxdrostat at a dose of 2 mg, or placebo once daily for 12 weeks. The primary end point was the change in seated systolic blood pressure from baseline to week 12.

RESULTS

A total of 796 patients underwent randomization and 794 received 1-mg baxdrostat (264 patients), 2-mg baxdrostat (266 patients), or placebo (264 patients) in addition to background therapy. At 12 weeks, the change from baseline in the least-squares mean seated systolic blood pressure was –14.5 mm Hg (95% confidence interval [CI], –16.5 to –12.5) with 1-mg baxdrostat, –15.7 mm Hg (95% CI, –17.6 to –13.7) with 2-mg baxdrostat, and –5.8 mm Hg (95% CI, –7.9 to –3.8) with placebo. The estimated difference from placebo (placebo-corrected difference) was –8.7 mm Hg (95% CI, –11.5 to –5.8) with 1-mg baxdrostat and –9.8 mm Hg (95% CI, –12.6 to –7.0) with 2-mg baxdrostat ($P<0.001$ for both comparisons). A potassium level of more than 6.0 mmol per liter was reported in 6 patients (2.3%) with 1-mg baxdrostat, in 8 patients (3.0%) with 2-mg baxdrostat, and in 1 patient (0.4%) with placebo.

CONCLUSIONS

Among patients with uncontrolled or resistant hypertension, the addition of baxdrostat to background therapy resulted in a significantly lower seated systolic blood pressure at 12 weeks than placebo. (Funded by AstraZeneca and others; BaxHTN ClinicalTrials.gov number, NCT06034743.)

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*The investigators in the BaxHTN trial are listed in the Supplementary Appendix, available at NEJM.org.

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The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

A Research Summary based on Flack JM et al. | DOI: 10.1056/NEJMoa2507109 | Published on August 30, 2025

WHY WAS THE TRIAL DONE?

Hard-to-control hypertension is often driven by aldosterone dysregulation. Baxdrostat is a highly selective, potent aldosterone synthase inhibitor that has been associated with mixed results in trials involving patients with uncontrolled or resistant hypertension. Additional data are needed.

HOW WAS THE TRIAL CONDUCTED?

Adults with hard-to-control hypertension despite treatment with maximally tolerated doses of either two antihypertensive medications (uncontrolled hypertension) or three or more such medications (resistant hypertension) were enrolled. After a 2-week placebo run-in period, patients who had a seated systolic blood pressure of 135 mm Hg or more were assigned to receive baxdrostat (1 mg or 2 mg) or placebo once daily for 12 weeks. The primary efficacy end point was the change in seated systolic blood pressure from baseline to week 12.

TRIAL DESIGN

- Phase 3
- Multinational
- Double-blind
- Randomized
- Placebo-controlled

RESULTS

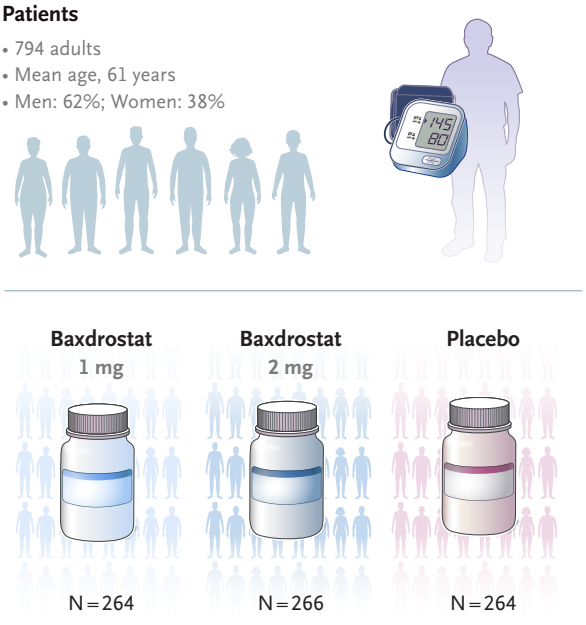
At 12 weeks, seated systolic blood pressure had decreased significantly more with each dose of baxdrostat than with placebo. A potassium level of more than 6.0 mmol per liter was reported more often with baxdrostat than with placebo.

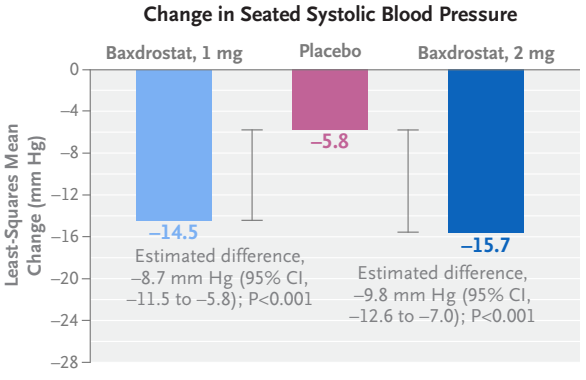
LIMITATIONS AND REMAINING QUESTIONS

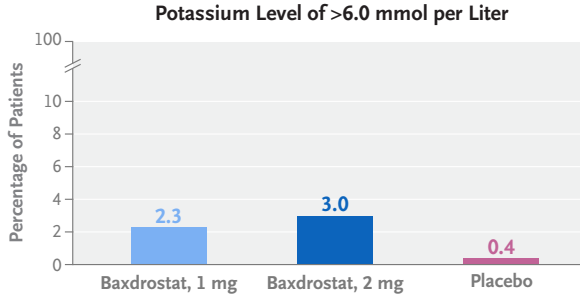
- Ambulatory blood pressure was measured in only a small number of patients.
- The percentages of women and Black patients were smaller than those in the general population with hypertension, which limits the generalizability.
- Medication adherence was not measured directly by objective methods throughout the trial.

CONCLUSIONS

In adults with uncontrolled or resistant hypertension, the addition of once-daily baxdrostat to background antihypertensive therapy resulted in significantly greater reductions in seated systolic blood pressure at 12 weeks than placebo.







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EDITORIAL

Aldosterone Synthase Inhibition for Hypertension

Tomasz J. Guzik, M.D., Ph.D.,[1,2] and Maciej Tomaszewski, M.D.[3-5]

Hypertension is described as resistant if a patient who is taking three or more antihypertensive agents, including a diuretic, at the maximum recommended doses maintains a blood pressure of 140/90 mm Hg or more during an office visit, after pseudo-resistance and secondary causes have been excluded.[1] This condition affects nearly 1 in 10 patients with hypertension[1] and carries a disproportionate global burden of cardiovascular risk.[2,3]

In many cases, resistant hypertension represents a salt-retaining, low-renin state driven by inappropriate, renin-independent aldosterone secretion. An excess of aldosterone drives sodium and water retention, along with fibrosis, inflammation, and vascular injury, which amplifies the risk beyond blood-pressure elevation.[4] Mineralocorticoid-receptor antagonists (MRAs) counter these effects,[3] yet their use as antihypertensives is constrained by hyperkalemia, reduced safety and efficacy in advanced kidney disease, and sex hormone–related side effects.[5] Moreover, MRAs trigger a compensatory increase in aldosterone with downstream consequences.

Direct inhibition of aldosterone synthase lowers aldosterone levels, which in turn reduces mineralocorticoid receptor–mediated activity of the epithelial sodium channel, which limits distal sodium reabsorption and promotes natriuresis (Fig. 1). However, early attempts at development of aldosterone synthase inhibitors were hindered by the structural homology between aldosterone synthase and 11β-hydroxylase, which resulted in the risk of off-target cortisol suppression. Subsequently, structural resolution revealed exploitable active-site and entry-channel differences, thereby enabling the design of heteroaryl scaffolds with chiral and steric optimization.[5] These advances have resulted in the development of aldosterone synthase inhibitors, including baxdrostat and lorundrostat.[6,7] The use of these drugs has enabled broader protection, with improvement in blood-pressure control and mitigation of aldosterone-driven fibrosis, vascular injury, and renal damage, along with avoidance of cortisol effects.[5,7]

In a trial report now published in the *Journal*, Flack and colleagues[8] describe the primary findings of the BaxHTN trial, in which they studied whether selective aldosterone synthase inhibition with daily baxdrostat (at a dose of 1 mg or 2 mg) would deliver a sustained, safe reduction

Figure 1 (facing page). Aldosterone Synthase Inhibition in the Renin–Angiotensin–Aldosterone System.

Angiotensin II stimulates zona glomerulosa cells to produce aldosterone in the adrenal cortex in a reaction catalyzed by aldosterone synthase (CYP11B2). Aldosterone activates mineralocorticoid receptors in the distal nephron, which increases the activity of the epithelial sodium channel (ENaC), leading to sodium and water retention, potassium loss, and elevated blood pressure. Beyond its epithelial effects, aldosterone promotes oxidative stress, vascular stiffening, cardiac fibrosis and remodeling, heart failure with preserved ejection fraction, and renal fibrosis. Inhibitors of the renin–angiotensin–aldosterone system (RAAS) — including angiotensin-converting–enzyme (ACE) inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptors — act upstream or at the receptor level but may leave aldosterone levels elevated. Selective aldosterone synthase inhibitors (ASIs), such as baxdrostat and lorundrostat, directly suppress aldosterone production, which reduces sodium retention and end-organ fibrosis while sparing cortisol synthesis and offers a mechanistically distinct complement to RAAS blockade. ROMK denotes renal outer medullary potassium channel.

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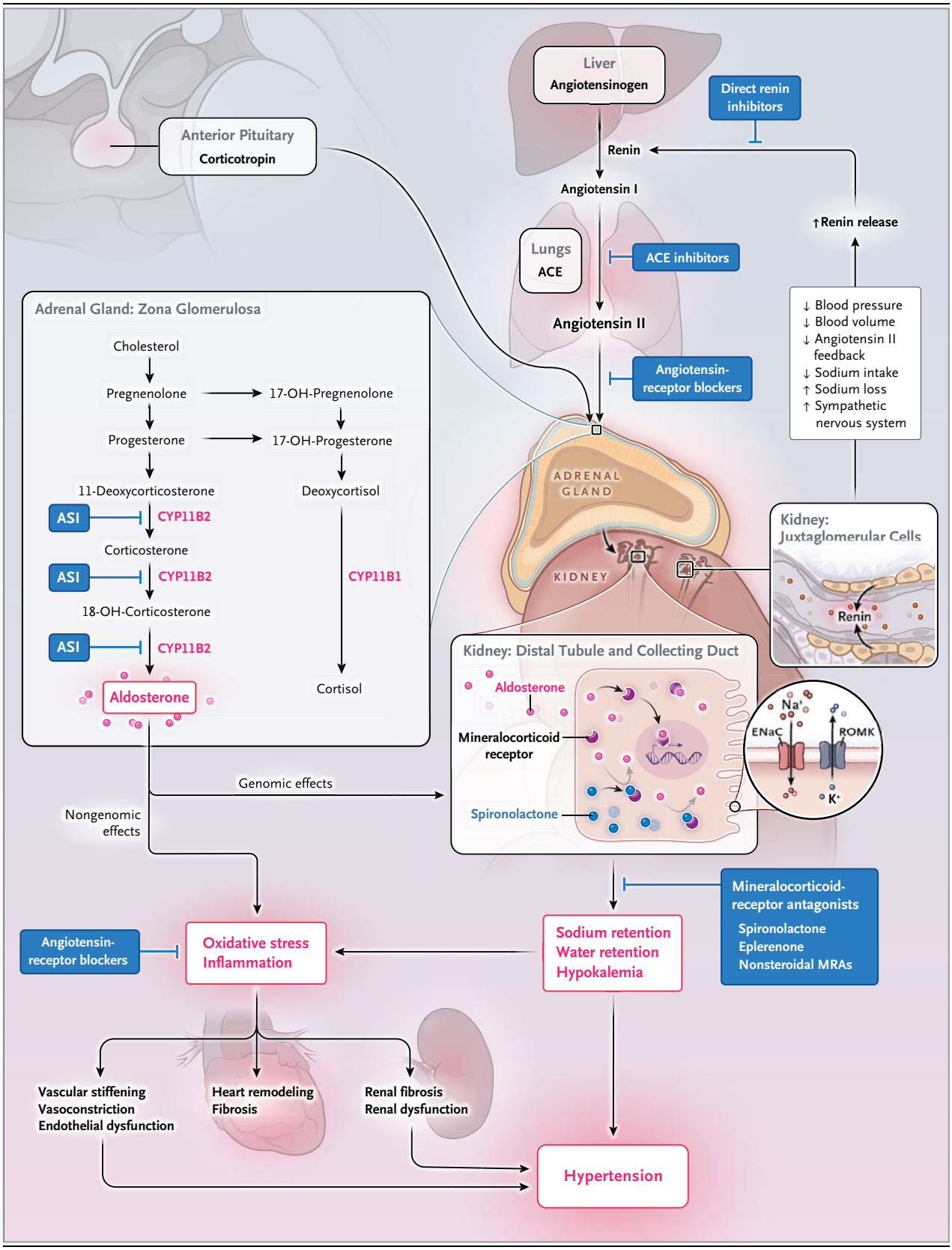

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in blood pressure in adults with uncontrolled or resistant hypertension, along with at least two additional antihypertensive agents, including a diuretic. A large percentage (approximately 90%) of the patients were taking an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, nearly all were taking a diuretic, and many were taking a calcium-channel blocker.

The trial consisted of four parts: part 1, a 12-week randomized, placebo-controlled trial of 1 mg of baxdrostat, 2 mg of baxdrostat, or placebo; part 2, a 12-week open-label phase that was designed to collect safety data and serve as a run-in to part 3; part 3, an 8-week (weeks 32 to 52) randomized-withdrawal phase; and part 4, an ongoing 20-week open-label phase to collect additional safety data regarding 2-mg baxdrostat. The primary end point was the change in the seated systolic blood pressure from baseline to week 12.

At the end of the 12-week randomized, double-blind period, the patients who received baxdrostat had a clinically important placebo-corrected change in the systolic blood pressure of –8.7 mm Hg in the 1-mg group and –9.8 mm Hg in the 2-mg group from a mean baseline of 149/87 mm Hg across groups. The percentage of patients with a controlled seated systolic blood pressure (<130 mm Hg) at week 12 was 39.4% with 1-mg baxdrostat, 40.0% with 2-mg baxdrostat, and 18.7% with placebo. In the randomized-withdrawal phase, there was a gradual offset in the least-squares mean seated systolic blood pressure of –3.7 mm Hg in the 2-mg baxdrostat group and a minimal rebound of 1.4 mm Hg in the placebo group, a finding that was consistent with the possible resetting of natriuretic action and long-term vascular or neurohumoral effects of baxdrostat.

Exploratory analyses confirmed the reductions in aldosterone levels, increases in plasma renin activity, and concordant reductions in ambulatory systolic blood pressure. Changes in electrolytes and the estimated glomerular filtration rate (eGFR) followed expected trajectories in the renin–angiotensin–aldosterone system (RAAS), which stabilized after early shifts. However, these descriptive findings remain hypothesis-generating only.

Clinical adoption of baxdrostat will depend in part on the safety profile that emerges. In the BaxHTN trial, most electrolyte abnormalities occurred within the first 2 weeks. Confirmed potassium levels of more than 6.0 mmol per liter occurred in 1.1% of the patients in the 1-mg baxdrostat group, in 1.1% of those in the 2-mg baxdrostat group, and in 0% of those in the placebo group. Hyponatremia (<135 mmol per liter) occurred in 19 to 23% of the patients receiving baxdrostat and rarely required intervention. An early decrease in the eGFR (approximately 7 ml per minute per 1.73 m^2 of body-surface area) was reversed with treatment withdrawal. These class-predictable adverse effects suggest a favorable risk–benefit balance, particularly for the 1-mg dose, with disciplined monitoring.

The BaxHTN trial delivers three clear clinical messages. First, regarding efficacy, baxdrostat lowered the seated systolic blood pressure by approximately 9 to 10 mm Hg relative to placebo, a result that was evident by week 4 and was sustained to week 12 — an action that was similar to that of spironolactone and other aldosterone synthase inhibitors. The effect occurred on top of existing RAAS blockade and near-universal diuretic use, which highlights the potential of aldosterone synthase inhibitors to overcome aldosterone breakthrough in salt-retaining hypertension. Second, regarding safety, adverse biochemical changes (shifts in potassium, sodium, and eGFR) emerged within 2 weeks and were monitored by laboratory checks at baseline, at 1 to 2 weeks, and after 4 weeks. Discontinuations for hyperkalemia were rare. Third, regarding durability, in the randomized-withdrawal phase, blood pressure rose only modestly despite drug clearance, which suggests a physiological reset of sodium balance or vascular tone. If these results are confirmed in longer studies, they could support steadier blood-pressure control and reduced rescue therapy.

The positioning of baxdrostat in the antihypertensive armamentarium will be clarified with accumulating evidence. Currently, MRAs, especially spironolactone, remain guideline recommended for resistant hypertension, with the PATHWAY-2 trial showing superiority over bisoprolol and doxazosin.[4] As the two selective aldosterone synthase inhibitors that are presently available, baxdrostat and lorundrostat have been found to consistently lower blood pressure in patients with resistant or uncontrolled hypertension.[8,9] Unlike MRAs, which raise levels of

renin and aldosterone and miss the nonreceptor aldosterone actions, aldosterone synthase inhibitors directly suppress aldosterone, which mechanistically complements the RAAS blockade (Fig. 1).

With sodium sensitivity common in older patients and in those with obesity or chronic kidney disease, natriuresis has central clinical relevance. By reducing aldosterone-driven sodium reabsorption, aldosterone synthase inhibitors augment the proven natriuretic strategies in patients with cardiovascular disease, such as thiazide diuretics, MRAs, sodium–glucose cotransporter 2 inhibitors, and neprilysin inhibitors. Collectively, aldosterone synthase inhibitors provide a mechanistically distinct, clinically validated, and synergistic option for patients with hard-to-control hypertension.

Altogether, the BaxHTN trial showed clear efficacy when added to standard therapy, a manageable safety profile, and mechanistic plausibility within sodium-driven hard-to-control hypertension. The next steps will include defining which patients are likely to have the best response for precision therapy, clarifying the use of these drugs as compared with MRAs, standardizing early monitoring, and providing long-term data on durability and event reduction. Success would shift aldosterone synthase inhibition from a promising adjunct to a central pillar of therapy for difficult-to-control hypertension, thereby reinforcing a broader renaissance of natriuretic strategies in blood-pressure control.

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

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1. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH guidelines for the management of arterial hypertension The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension: endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens 2023;41:1874-2071.
2. Tian Z, Vollmer Barbosa C, Lang H, Bauersachs J, Melk A, Schmidt BMW. Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis. Cardiovasc Res 2024;120:108-19.
3. Schutte AE, Jafar TH, Poulter NR, et al. Addressing global disparities in blood pressure control: perspectives of the International Society of Hypertension. Cardiovasc Res 2023;119:381-409.
4. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet 2015;386:2059-68.
5. Leopold JA, Ingelfinger JR. Aldosterone and treatment-resistant hypertension. N Engl J Med 2023;388:464-7.
6. Shimizu H, Tortorici MA, Ohta Y, et al. First-in-human study evaluating safety, pharmacokinetics, and pharmacodynamics of lorundrostat, a novel and highly selective aldosterone synthase inhibitor. Clin Transl Sci 2024;17(8):e70000.
7. Freeman MW, Halvorsen Y-D, Marshall W, et al. Phase 2 trial of baxdrostat for treatment-resistant hypertension. N Engl J Med 2023;388:395-405.
8. Flack JM, Azizi M, Brown JM, et al. Efficacy and safety of baxdrostat in uncontrolled and resistant hypertension. N Engl J Med 2025;393:1363-74.
9. Laffin LJ, Kopjar B, Melgaard C, et al. Lorundrostat efficacy and safety in patients with uncontrolled hypertension. N Engl J Med 2025;392:1813-23.

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ORIGINAL ARTICLE

Zalunfiban at First Medical Contact for ST-Elevation Myocardial Infarction

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Abstract

BACKGROUND Zalunfiban is a glycoprotein IIb/IIIa (integrin αIIbβ3) inhibitor designed for subcutaneous administration on first medical contact with patients with suspected ST-segment elevation myocardial infarction (STEMI).

METHODS An international, double-blind, placebo-controlled trial randomly assigned patients with STEMI in a 1:1:1 ratio to receive a single subcutaneous injection of zalunfiban (0.11 mg/kg or 0.13 mg/kg) or placebo. The primary efficacy end point was a hierarchical proportional odds model ranking seven end points from worst to best: all-cause death, stroke, recurrent myocardial infarction, acute stent thrombosis, new-onset or rehospitalization for heart failure, larger infarct size, or no end point through 30 days. The primary safety end point was the occurrence of severe or life-threatening bleeding as per the global use of strategies to open occluded coronary arteries (GUSTO) criteria.

RESULTS The trial randomly assigned 2467 patients (853 to zalunfiban 0.11 mg/kg, 818 to zalunfiban 0.13 mg/kg, and 796 to placebo). The primary efficacy end point was significantly improved by zalunfiban (adjusted odds ratio 0.79; 95% confidence interval, 0.65 to 0.98; P=0.028). GUSTO severe bleeding was similar between those who received zalunfiban versus placebo (1.2% vs. 0.8%; P=0.40), but GUSTO mild to moderate bleeding was increased (6.4% vs. 2.5%; P<0.001). Angiography showed faster coronary blood flow with zalunfiban versus placebo (corrected frame count of the infarct-related artery 109 [interquartile range 35 to 176] vs. 176 [interquartile range 40 to 176]; P=0.012).

CONCLUSIONS In patients with STEMI, zalunfiban administered at first medical contact significantly improved preintervention infarct-related patency and reduced the likelihood of a worse 30-day multicomponent hierarchical clinical end point. Zalunfiban was not associated with increased severe or life-threatening bleeding but was associated with increased mild to moderate bleeding. (Funded by CeleCor Therapeutics; CELEBRATE ClinicalTrials.gov number, NCT04825743.)

**The authors' full names and academic degrees are listed in the Supplementary Appendix. A list of all emergency medical services and participating sites is also provided.*

The author affiliations are listed at the end of the article.

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EDITORIAL

Subcutaneous Glycoprotein IIb/IIIa Inhibitor for ST-Elevation Myocardial Infarction — Teaching an Old Drug New Tricks

Marc-André d'Entremont, M.D., M.P.H.,[1,2] and Sanjit S. Jolly, M.D., M.Sc.[1]

In this issue of *NEJM Evidence*, van't Hof et al. report the results of the CeleCor Blinded Randomized Trial in ST-Elevation Myocardial Infarction (STEMI) (CELEBRATE) trial.[1] The investigators demonstrated that a novel subcutaneous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor administered at first medical contact in patients with STEMI, who were candidates for percutaneous coronary intervention (PCI), significantly decreased the odds of a major adverse composite clinical end point, but also increased nonsevere bleeding compared with placebo at 1 month.

Current STEMI guidelines recommend early upstream dual antiplatelet therapy — typically aspirin and a P2Y12 inhibitor — to reduce ischemic events.[2] However, commonly used P2Y12 inhibitors, such as ticagrelor and prasugrel, only achieve maximal platelet inhibition 4 to 6 hours after administration.[3] Before the introduction of these potent P2Y12 inhibitors, several randomized controlled trials investigated the role of using adjunctive GPIIb/IIIa inhibitors in patients with STEMI. For example, in the Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up (ADMIRAL) trial, patients randomly assigned to abciximab had a lower incidence of a composite end point of death, reinfarction, or urgent revascularization at 30 days compared with placebo.[4] Similarly, in the Ongoing Tirofiban in Myocardial Evaluation (ON-TIME 2) trial, the use of tirofiban increased post-PCI ST-segment resolution compared with placebo.[5] In the larger Facilitated Intervention with Enhanced Reperfusion Speed to Stop Events (FINESSE) trial, a three-group trial that randomly assigned more than 2000 patients with STEMI to half-dose reteplase with abciximab, abciximab alone, or placebo, there was no difference between groups in a composite clinical end point inclusive of mortality, ventricular arrhythmias, and heart failure at 90 days. However, there was an increase in Thrombolysis in Myocardial Infarction (TIMI) major and minor bleeding in both groups with GPIIb/IIIa inhibitors compared with placebo.[6] Conventional GPIIb/IIIa inhibitors require a continuous intravenous infusion, making them impractical for prehospital administration. Rapid, short-acting platelet inhibition in patients with STEMI, from first medical contact to maximal platelet inhibition with P2Y12 inhibitors, is therefore an unmet clinical need.[7]

Zalunfiban (RUC-4) is a novel subcutaneous single-dose GPIIb/IIIa inhibitor that achieves 90% platelet inhibition within 15 minutes of administration with a plasma half-life of 1 hour.[8] In the CELEBRATE trial, a total of 2467 patients with STEMI who were candidates for primary PCI, were randomly assigned at first medical contact to placebo or zalunfiban at doses of 0.11 mg/kg or 0.13 mg/kg in a 1:1:1 ratio. The investigators prespecified an

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analysis comparing the pooled zalunfiban groups to the placebo. When compared with patients receiving the placebo, patients who had received zalunfiban had 21% lower odds of a hierarchical composite outcome of all-cause death, stroke, recurrent myocardial infarction (MI), acute stent thrombosis, new-onset heart failure, rehospitalization for heart failure, or large MI (defined as a high-sensitivity troponin T level more than 30 times the upper limit of normal) with most outcomes measured at 30 days. Although there was no difference in severe bleeding (defined using global use of strategies to open occluded coronary arteries [GUSTO] criteria) between patients randomly assigned to receive zalunfiban or placebo (1.2% vs. 0.8%, respectively), there was a significant increase in GUSTO-defined mild to moderate bleeding in the zalunfiban group (6.4%) compared with the placebo (2.5%).

The investigators should be commended for completing a complex yet well-executed prehospital STEMI trial of a GPIIb/IIIa inhibitor in the era of potent P2Y12 inhibitors. A few points merit discussion. First, the efficacy results in favor of zalunfiban compared with a placebo were primarily driven by a reduction in the incidence of acute stent thrombosis (0.2% vs. 1.1%), heart failure (6.5% vs. 8.1%), and large MI (85.4% vs. 88.5%). Given that the efficacy results appeared to be driven mainly by a reduction in the large MI outcome — which the trial investigators specified as the least important by clinical hierarchy — we would encourage caution regarding the interpretation of the efficacy of zalunfiban in reducing hard ischemic outcomes. Second, while GUSTO-defined severe or life-threatening bleeding was not significantly different between the zalunfiban and placebo groups, GUSTO-defined mild and moderate bleeding was significantly higher in the zalunfiban group, despite 95% of study participants undergoing radial access for PCI. Importantly, even minor bleeding events have been linked to increased 1-year mortality in patients undergoing PCI, albeit with a weaker association than that observed for major bleeding.[9,10] Third, it must be underlined that the median time between administration of the trial drug and PCI was 50 minutes, the median time from symptom onset to angiography was 130 minutes, and 95% of trial participants received heparin and a potent P2Y12 inhibitor (ticagrelor) before primary PCI. Demonstrating an incremental clinical benefit beyond pretreatment with potent P2Y12 inhibition in such a short time frame is promising as a future therapeutic avenue.

In conclusion, the CELEBRATE trial brings back a treatment option that has been set aside for over a decade by transforming a hospital-based infusion into a field-ready subcutaneous injection with ideal pharmacokinetic properties for pretreatment. If subsequent randomized controlled trials confirm its effectiveness for hard clinical outcomes, similar agents could reestablish GPIIb/IIIa inhibition as an effective upstream therapy in patients with STEMI, with balanced and careful consideration for ischemic benefits and bleeding risks.

Disclosures

Author disclosures are available at evidence.nejm.org.

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References

1. Van't Hof AWJ, Gibson CM, Rikken SAOF, et al. Zalunfiban at first medical contact for ST-segment elevation myocardial infarction. NEJM Evid 5(1);2025. DOI: 10.1056/EVIDoa2500268.
2. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC guidelines for the management of acute coronary syndromes: developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J 2023;44:3720-3826. DOI: 10.1093/eurheartj/ehad191.
3. Parodi G, Valenti R, Bellandi B, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) primary PCI study. J Am Coll Cardiol 2013;61:1601-1606. DOI: 10.1016/j.jacc.2013.01.024.
4. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. N Engl J Med 2001;344:1895-1903. DOI: 10.1056/nejm200106213442503.
5. Van't Hof AWJ, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. Lancet 2008;372:537-546. DOI: 10.1016/s0140-6736(08)61235-0.
6. Ellis SG, Tendera M, de Belder MA, et al. Facilitated PCI in patients with ST-elevation myocardial infarction. N Engl J Med 2008;358:2205-2217. DOI: 10.1056/NEJMoa0706816.
7. Montalescot G, van't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. N Engl J Med 2014;371:1016-1027. DOI: 10.1056/NEJMoa1407024.
8. Bor WL, Zheng KL, Tavenier AH, et al. Pharmacokinetics, pharmacodynamics, and tolerability of subcutaneous administration of a novel glycoprotein IIb/IIIa inhibitor, RUC-4, in patients with

ST-segment elevation myocardial infarction. EuroIntervention 2021;17:e401-e410. DOI: 10.4244/EIJ-D-21-00287.

9. Mehran R, Pocock S, Nikolsky E, et al. Impact of bleeding on mortality after percutaneous coronary intervention: results from a patient-level pooled analysis of the REPLACE-2 (randomized evaluation of PCI linking angiomax to reduced clinical events), ACUITY (acute catheterization and urgent intervention triage strategy), and HORIZONS-AMI (harmonizing outcomes with revascularization and stents in acute myocardial infarction) trials. JACC Cardiovasc Interv 2011;4:654-664. DOI: 10.1016/j.jcin.2011.02.011.

10. De Luca G, Navarese E, Marino P. Risk profile and benefits from Gp IIb-IIIa inhibitors among patients with ST-segment elevation myocardial infarction treated with primary angioplasty: a meta-regression analysis of randomized trials. Eur Heart J 2009;30:2705-2713. DOI: 10.1093/eurheartj/ehp118.

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NEJM AI

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ORIGINAL ARTICLE

Randomized Trial of a Generative AI Chatbot for Mental Health Treatment

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Abstract

BACKGROUND Generative artificial intelligence (Gen-AI) chatbots hold promise for building highly personalized, effective mental health treatments at scale, while also addressing user engagement and retention issues common among digital therapeutics. We present a randomized controlled trial (RCT) testing an expert–fine-tuned Gen-AI–powered chatbot, Therabot, for mental health treatment.

METHODS We conducted a national, randomized controlled trial of adults (N=210) with clinically significant symptoms of major depressive disorder (MDD), generalized anxiety disorder (GAD), or at clinically high risk for feeding and eating disorders (CHR-FED). Participants were randomly assigned to a 4-week Therabot intervention (N=106) or waitlist control (WLC; N=104). WLC participants received no app access during the study period but gained access after its conclusion (8 weeks). Participants were stratified into one of three groups based on mental health screening results: those with clinically significant symptoms of MDD, GAD, or CHR-FED. Primary outcomes were symptom changes from baseline to postintervention (4 weeks) and to follow-up (8 weeks). Secondary outcomes included user engagement, acceptability, and therapeutic alliance (i.e., the collaborative patient and therapist relationship). Cumulative-link mixed models examined differential changes. Cohen's d effect sizes were unbounded and calculated based on the log-odds ratio, representing differential change between groups.

RESULTS Therabot users showed significantly greater reductions in symptoms of MDD (mean changes: −6.13 [standard deviation {SD}=6.12] vs. −2.63 [6.03] at 4 weeks; −7.93 [5.97] vs. −4.22 [5.94] at 8 weeks; d=0.845–0.903), GAD (mean changes: −2.32 [3.55] vs. −0.13 [4.00] at 4 weeks; −3.18 [3.59] vs. −1.11 [4.00] at 8 weeks; d=0.794–0.840), and CHR-FED (mean changes: −9.83 [14.37] vs. −1.66 [14.29] at 4 weeks; −10.23 [14.70] vs. −3.70 [14.65] at 8 weeks; d=0.627–0.819) relative to controls at postintervention and follow-up. Therabot was well utilized (average use >6 hours), and participants rated the therapeutic alliance as comparable to that of human therapists.

CONCLUSIONS This is the first RCT demonstrating the effectiveness of a fully Gen-AI therapy chatbot for treating clinical-level mental health symptoms. The results were promising for MDD, GAD, and CHR-FED symptoms. Therabot was well utilized and received high user ratings. Fine-tuned Gen-AI chatbots offer a feasible approach to delivering personalized mental

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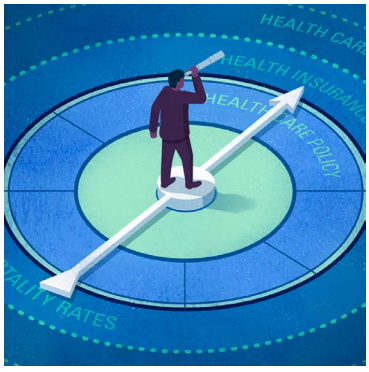
IN DEPTH

Using Mortality and Years-of-Life-Lost Metrics to Evaluate Health System Performance and Inform Health Care Policy



Elizabeth A. McGlynn, PhD, Laura Dwyer-Lindgren, PhD, MPH, Anna C. Davis, PhD, Zhuochen Li, MS, John L. Adams, PhD, Ali H. Mokdad, PhD

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Health plans in the United States have not typically examined the overall mortality outcomes of their enrollees. Kaiser Permanente (KP) collaborated with the Institute for Health Metrics and Evaluation (IHME) at the University of Washington to augment KP's existing suite of quality measures with estimates of mortality rates and years-of-life-lost (YLL) rates for KP members. This work was designed to inform whether or not KP was meeting its strategic goal of improving the health outcomes of its members and to stimulate a national dialogue about how different system designs contribute to the health of populations for which systems are responsible. Results for KP members are compared with non-members in the communities in which KP operates, and with the general population of the United States. The authors examine trends for all three populations during the 10-year period from 2010 to 2019, preceding the Covid-19 pandemic, and from 2019 to 2022 for KP and the United States only; community estimates were not available beyond 2019. Over the 10-year initial study period, KP members had lower rates of mortality and YLL and experienced greater declines over that time than non-members living in the communities in which KP operates ("the community"); similarly, the community had lower mortality and YLL rates and experienced greater declines over time than the overall United States population. Mortality rates among KP members were lower than in the community for all racial and ethnic groups. The magnitude of the

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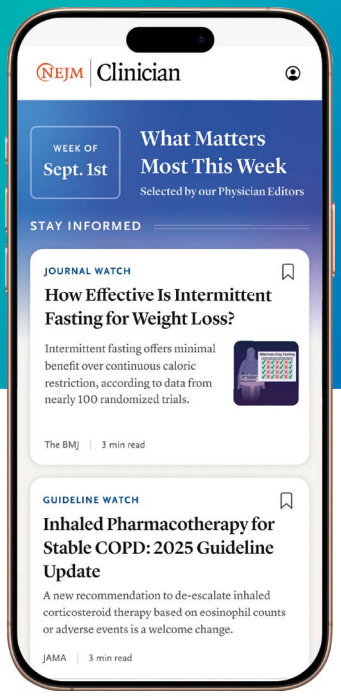

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