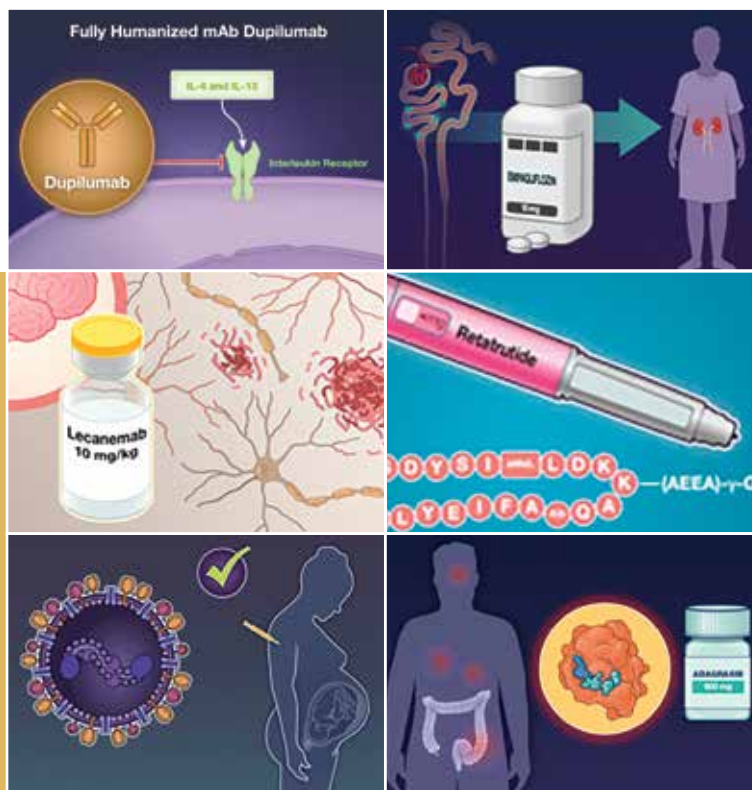




The NEW ENGLAND  
JOURNAL of MEDICINE

# Notable Articles of 2023

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





# The NEW ENGLAND JOURNAL of MEDICINE

December 2023

Dear Reader,

In December, as our attentions turn to the new year ahead, I always find it interesting to reflect on the studies we've published in the past year and evaluate their contribution to the ever-evolving practice of medicine.

While the last couple of years have been dominated by Covid-19 news, this year our Notable Articles collection focuses on new approaches to diverse diseases. I've highlighted several new interventions, including advances in oncology, such as “universal” CAR-T cells that have undergone gene editing to allow them to be used off-the-shelf without having to be derived uniquely for each host, an approach that could bring therapy to a much broader range of patients. New antitumor targets, such as *KRAS* containing the G12C mutation, are now accessible with inhibitors, and we are seeing the first evidence that this class of agents is active in a variety of tumors in combination with other antitumor strategies. New targets are also emerging in kidney diseases, including aldosterone synthase, which can be inhibited to effectively treat hypertension, and *APOL1*, whose variants are associated with proteinuria. Moreover, existing drugs, such as the sodium–glucose transporter 2 (SGLT2) inhibitor empagliflozin, can reduce disease progression and cardiovascular disease in patients with chronic kidney disease. And we published more in a series of studies examining the effects of antibodies that bind to the Ab protein and clear amyloid. Some, such as a study of lecanemab, have shown positive, though small, effects in early Alzheimer's disease.

We have also seen new applications for other agents. Dupilumab, an antibody that blocks type 2 inflammation, reduces the number of exacerbations and improves the quality of life of patients with COPD who have high eosinophil counts. GLP-1 agonists, which were developed to treat diabetes, also reduce obesity and improve heart failure in obese individuals. And we have seen the first drug, retatrutide, that not only acts at GLP-1 but also at two other receptors, glucose-dependent insulinotropic polypeptide (GIP) and the glucagon receptor. Treatment with retatrutide results in dramatic weight loss in obese and overweight subjects. Ketamine, a dissociative anesthetic, proved to be noninferior to electroconvulsive therapy in treatment-resistant depression.

My list this year contains two important trials in infectious disease. Using a new treatment strategy, investigators found that the majority of patients with antibiotic-sensitive tuberculosis could be cured in as little as two months, a substantial shortening from the standard six month regimen. This was also the year that the first successful vaccine against respiratory syncytial virus was shown to be active, both in older adults (in studies not included in the list) and in pregnancy. When pregnant women are vaccinated, their children are protected by maternal antibody. And, speaking of pregnancy, a bundle of interventions decreased the rate and severity of postpartum hemorrhage in four African countries.

On behalf of the editorial team, we hope you enjoy reading this collection of studies that we believe stand out among the year's most notable and impactful in clinical medicine. As we look forward to the new year, we at the *Journal* remain committed to publishing only the most valuable, peer-reviewed studies — studies you can trust to inform and guide the care you provide to your patients.

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



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# The NEW ENGLAND JOURNAL of MEDICINE

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SEPTEMBER 21, 2023

VOL. 389 NO. 12

## Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

M.N. Kosiborod, S.Z. Abildstrøm, B.A. Borlaug, J. Butler, S. Rasmussen, M. Davies, G.K. Hovingh, D.W. Kitzman, M.L. Lindegaard, D.V. Møller, S.J. Shah, M.B. Treppendahl, S. Verma, W. Abhayaratna, F.Z. Ahmed, V. Chopra, J. Ezekowitz, M. Fu, H. Ito, M. Lelonek, V. Melenovsky, B. Merkely, J. Núñez, E. Perna, M. Schou, M. Senni, K. Sharma, P. Van der Meer, D. von Lewinski, D. Wolf, and M.C. Petrie, for the STEP-HFpEF Trial Committees and Investigators\*

### ABSTRACT

#### BACKGROUND

Heart failure with preserved ejection fraction is increasing in prevalence and is associated with a high symptom burden and functional impairment, especially in persons with obesity. No therapies have been approved to target obesity-related heart failure with preserved ejection fraction.

#### METHODS

We randomly assigned 529 patients who had heart failure with preserved ejection fraction and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The dual primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in the 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

#### RESULTS

The mean change in the KCCQ-CSS was 16.6 points with semaglutide and 8.7 points with placebo (estimated difference, 7.8 points; 95% confidence interval [CI], 4.8 to 10.9;  $P < 0.001$ ), and the mean percentage change in body weight was  $-13.3\%$  with semaglutide and  $-2.6\%$  with placebo (estimated difference,  $-10.7$  percentage points; 95% CI,  $-11.9$  to  $-9.4$ ;  $P < 0.001$ ). The mean change in the 6-minute walk distance was 21.5 m with semaglutide and 1.2 m with placebo (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1;  $P < 0.001$ ). In the analysis of the hierarchical composite end point, semaglutide produced more wins than placebo (win ratio, 1.72; 95% CI, 1.37 to 2.15;  $P < 0.001$ ). The mean percentage change in the CRP level was  $-43.5\%$  with semaglutide and  $-7.3\%$  with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72;  $P < 0.001$ ). Serious adverse events were reported in 35 participants (13.3%) in the semaglutide group and 71 (26.7%) in the placebo group.

#### CONCLUSIONS

In patients with heart failure with preserved ejection fraction and obesity, treatment with semaglutide (2.4 mg) led to larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss than placebo. (Funded by Novo Nordisk; STEP-HFpEF ClinicalTrials.gov number, NCT04788511.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Kosiborod can be contacted at [mkosiborod@saint-lukes.org](mailto:mkosiborod@saint-lukes.org) or at Saint Luke's Mid America Heart Institute, 4401 Wornall Rd., Kansas City, MO 64111.

\*A list of the STEP HFpEF trial committees and investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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## RESEARCH SUMMARY

# Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Kosiborod MN et al. DOI: 10.1056/NEJMoa2306963

**CLINICAL PROBLEM**

Patients with heart failure with preserved ejection fraction often have obesity, a condition that is associated with a greater burden of heart failure–related symptoms, worse functional capacity, and more impaired quality of life. Whether therapies that target obesity in such patients can alleviate symptoms and physical limitations is unknown.

**CLINICAL TRIAL**

**Design:** A multinational, double-blind, randomized, placebo-controlled trial evaluated whether treatment with semaglutide — a glucagon-like peptide 1 receptor agonist approved for long-term weight management — would reduce heart failure–related symptoms and improve physical function, in addition to inducing weight loss, in adults with heart failure with preserved ejection fraction and obesity.

**Intervention:** 529 patients with a body-mass index of  $\geq 30$  were assigned to receive subcutaneous semaglutide (2.4 mg) or placebo once weekly for 52 weeks. The dual primary end points were the change in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS), which quantifies heart failure–related symptoms and physical function, and the change in body weight from baseline to week 52.

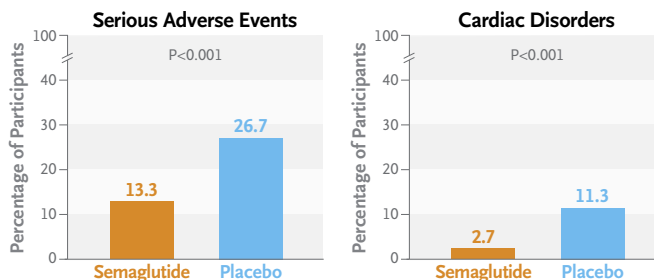
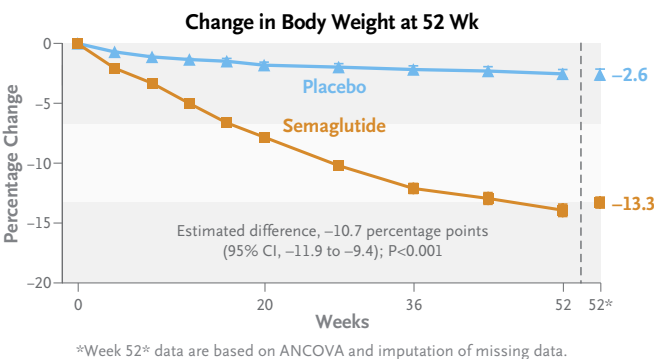
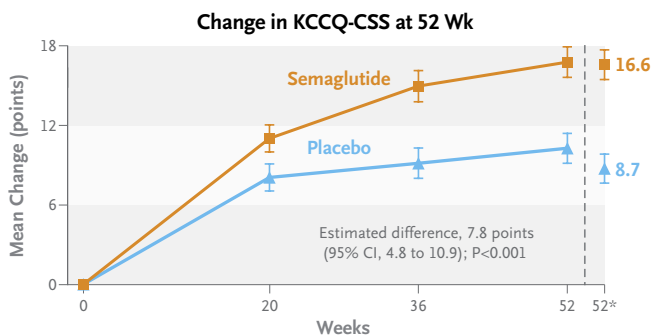
**RESULTS**

**Efficacy:** The mean change in KCCQ-CSS and the mean percentage change in body weight were significantly greater with semaglutide than with placebo.

**Safety:** Serious adverse events occurred less often with semaglutide than with placebo, primarily because fewer cardiac disorders occurred in the semaglutide group. Adverse events leading to treatment discontinuation were more common with semaglutide.

**LIMITATIONS AND REMAINING QUESTIONS**

- The number of non-White trial participants was low.
- The trial was not sufficiently powered to evaluate the effects of semaglutide on clinical events, such as hospitalization for heart failure.
- Whether the observed effects of semaglutide would last beyond 1 year is unknown.

**CONCLUSIONS**

In adults with heart failure with preserved ejection fraction and obesity, once-weekly treatment with semaglutide was associated with greater reductions in heart failure–related symptoms and physical limitations and greater weight loss than placebo over 52 weeks.

## EDITORIAL



## Heart Failure with Preserved Ejection Fraction — A Metabolic Disease?

Yigal M. Pinto, M.D., Ph.D.

The classification of heart failure is based on its accompanying ejection fraction: when the ejection fraction is below 40%, it is categorized as heart failure with reduced ejection fraction, and when the ejection fraction is above 50%, it is classified as heart failure with preserved ejection fraction. Heart failure with an ejection fraction between 40% and 50% is considered to be mid-range. Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction share many signs and symptoms that are attributable to increased intracardiac pressures, a hallmark of both conditions.

In contrast to the similarity of the presentations, the management of these entities could hardly differ more. Indeed, interventions that have been shown in trials to have benefit for patients with heart failure with reduced ejection fraction have not been shown to be effective for treating heart failure with preserved ejection fraction. Current concepts that have been used to explain the discrepancy note that multiple coexisting conditions define both symptoms and outcomes in heart failure with preserved ejection fraction, since patients with this form of heart failure tend to be older and to have more accompanying metabolic disease.<sup>1</sup> Consonant with this thinking, the first therapy to show benefit in patients with this condition was sodium–glucose cotransporter 2 (SGLT2) inhibitors.<sup>2</sup>

As Kosiborod et al. now report in the *Journal*,<sup>3</sup> semaglutide, a glucagon-like peptide 1 (GLP-1) agonist, has entered the arena to combat heart failure with preserved ejection fraction. In this relatively small trial, semaglutide provided a benefit for patients with heart failure with preserved ejection fraction through an upstream intervention that addressed metabolic drivers and differed from earlier treatment approaches that aimed to reduce

myocardial load or induce neurohumoral blockade. These positive results suggest that changes within myocytes may not be the main drivers in heart failure with preserved ejection fraction; rather, the multisystem pathologic processes that have long been associated with the condition are also drivers of its clinical manifestations and outcomes.

Semaglutide was first approved to treat diabetes mellitus and obesity. GLP-1 agonism seems to be particularly beneficial when patients with insulin resistance have low endogenous levels of GLP-1.<sup>4</sup> However, GLP-1 agonism has broad effects — it redistributes fat, decreases inflammation, inhibits glucagon production, and delays gastric emptying.<sup>5</sup> GLP-1 receptors have not yet been clearly identified on human cardiac myocytes,<sup>6</sup> which argues against a direct effect of GLP-1 agonism on cardiac myocytes.

In this trial, Kosiborod et al. found that once weekly semaglutide at a dose of 2.4 mg administered for 1 year decreased body weight (13.3% loss vs. 2.6% in the placebo group) and significantly improved the Kansas City Cardiomyopathy Questionnaire clinical summary score and the 6-minute walk distance.<sup>3</sup> Patients with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher were eligible for the trial if they had symptoms and objective signs of elevated intracardiac pressures and a left ventricular ejection fraction of at least 45%. Most of the 529 participants (84%) had an ejection fraction of 50% or higher. The median N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at baseline in the trial population was 451 pg per milliliter. Although this level seems moderately elevated, one should bear in mind that NT-proBNP levels are lower in persons with obesity.<sup>7</sup>

An important question is whether semaglutide also lowered intracardiac pressures. Kosiborod et al. reported that the percentage decrease in NT-proBNP levels was approximately 15 percentage points greater with semaglutide than with placebo. Given that NT-proBNP levels decrease with increasing BMI, in the absence of any effect, one would have expected that a 13% weight loss would actually increase NT-proBNP. Therefore, the measured decrease in NT-proBNP levels may underestimate its true decline. The trial was not powered for the analysis of hard end points (e.g., death from any cause) but showed a nonsignificantly lower number of hospitalizations or urgent visits for heart failure in the semaglutide group than in the placebo group, and the numbers of deaths in this trial were quite low (7 of the 529 participants, or 1.3%).

Another question the results raise is whether mere weight loss, by whatever means, could also suffice to improve the condition of patients with heart failure with preserved ejection fraction. A small previous trial showed that weight loss with the use of liraglutide did not improve echocardiographic measures of diastolic function.<sup>8</sup> In addition, severe caloric restriction and concomitant robust weight loss (mean of 13 kg) alone did not improve diastolic function.<sup>9</sup>

One may propose that the success of SGLT2 inhibition and now of GLP-1 agonism suggests that an important part of heart failure with preserved ejection fraction is driven by metabolic abnormalities. However, SGLT2 inhibition is also known to be beneficial in patients with heart failure with reduced ejection fraction. Whether GLP-1 agonism is also beneficial in these patients has not yet been directly addressed, but a meta-analysis suggested that GLP-1 agonists have modest benefits for heart failure end points.<sup>10</sup> If indeed SGLT2 inhibition and GLP-1 agonism prove beneficial in patients with heart failure regardless of whether the ejection fraction is reduced or preserved, then the two forms of heart failure might have more in common than is often assumed. In that case, the two conditions may well be rather similar to one another, but heart failure with preserved ejection fraction may lack the myocardial component of heart failure with reduced ejection fraction. If that were true, then both conditions would be syndromes caused by a plethora of metabolic and inflammatory changes; however, in the case of heart failure with reduced ejection fraction, a local myocardial com-

ponent is added, so that an intrinsic myocardial load-to-capacity mismatch makes that condition sensitive to treatment that improves that mismatch, whereas heart failure with preserved ejection fraction (which lacks the load-to-capacity mismatch) is affected only by treatments that address the metabolic and inflammatory abnormalities.

The encouraging findings for semaglutide in patients with heart failure with preserved ejection fraction reported here potentially add a much-needed extra option for these patients and provide another upstream treatment for patients with signs of this condition plus a high BMI. How these findings translate to hard end points remains to be established and will be important in determining the role of GLP-1 agonism as compared with SGLT2 inhibition in patients with heart failure with preserved ejection fraction.

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

From the Departments of Clinical Cardiology and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Amsterdam.

This editorial was published on August 25, 2023, at NEJM.org.

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## ORIGINAL ARTICLE

# Base-Edited CAR7 T Cells for Relapsed T-Cell Acute Lymphoblastic Leukemia

Robert Chiesa, M.D., Christos Georgiadis, Ph.D., Farhatullah Syed, Ph.D., Hong Zhan, Ph.D., Annie Etuk, Ph.D., Soragia Athina Gkazi, Ph.D., Roland Preece, Ph.D., Giorgio Ottaviano, M.D., Toni Braybrook, M.Bio., Jan Chu, M.Sc., Agnieszka Kubat, B.Sc., Stuart Adams, Ph.D., Rebecca Thomas, Ph.D., Kimberly Gilmour, Ph.D., David O'Connor, M.B., Ch.B., Ajay Vora, M.B., B.S., and Waseem Qasim, M.B., B.S., Ph.D., for the Base-Edited CAR T Group\*

## ABSTRACT

**BACKGROUND**

Cytidine deamination that is guided by clustered regularly interspaced short palindromic repeats (CRISPR) can mediate a highly precise conversion of one nucleotide into another — specifically, cytosine to thymine — without generating breaks in DNA. Thus, genes can be base-edited and rendered inactive without inducing translocations and other chromosomal aberrations. The use of this technique in patients with relapsed childhood T-cell leukemia is being investigated.

**METHODS**

We used base editing to generate universal, off-the-shelf chimeric antigen receptor (CAR) T cells. Healthy volunteer donor T cells were transduced with the use of a lentivirus to express a CAR with specificity for CD7 (CAR7), a protein that is expressed in T-cell acute lymphoblastic leukemia (ALL). We then used base editing to inactivate three genes encoding CD52 and CD7 receptors and the  $\beta$  chain of the  $\alpha\beta$  T-cell receptor to evade lymphodepleting serotherapy, CAR7 T-cell fratricide, and graft-versus-host disease, respectively. We investigated the safety of these edited cells in three children with relapsed leukemia.

**RESULTS**

The first patient, a 13-year-old girl who had relapsed T-cell ALL after allogeneic stem-cell transplantation, had molecular remission within 28 days after infusion of a single dose of base-edited CAR7 (BE-CAR7). She then received a reduced-intensity (nonmyeloablative) allogeneic stem-cell transplant from her original donor, with successful immunologic reconstitution and ongoing leukemic remission. BE-CAR7 cells from the same bank showed potent activity in two other patients, and although fatal fungal complications developed in one patient, the other patient underwent allogeneic stem-cell transplantation while in remission. Serious adverse events included cytokine release syndrome, multilineage cytopenia, and opportunistic infections.

**CONCLUSIONS**

The interim results of this phase 1 study support further investigation of base-edited T cells for patients with relapsed leukemia and indicate the anticipated risks of immunotherapy-related complications. (Funded by the Medical Research Council and others; ISRCTN number, ISRCTN15323014.)

From Great Ormond Street Hospital for Children NHS Trust (R.C., G.O., T.B., J.C., S.A., R.T., K.G., D.O., A.V., W.Q.) and the UCL Great Ormond Street Institute of Child Health (C.G., F.S., H.Z., A.E., S.A.G., R.P., A.K., W.Q.) — both in London. Dr. Qasim can be contacted at w.qasim@ucl.ac.uk or at Great Ormond Street Hospital, 20 Guilford St., London, WC1N 1DZ, United Kingdom.

\*A list of members of the Base-Edited CAR T Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Chiesa and Georgiadis contributed equally to this article.

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This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

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## EDITORIAL

## SCIENCE BEHIND THE STUDY

Elizabeth G. Phimister, Ph.D., *Editor*

## Engineering CAR T Cells for Off-the-Shelf Use

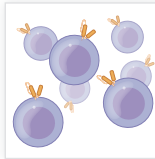
Dan L. Longo, M.D.

In this issue of the *Journal*, Chiesa et al.<sup>1</sup> report a proof-of-principle clinical experience: the eradication of measurable residual disease in a girl with T-cell lymphoblastic leukemia with tumoricidal chimeric antigen receptor (CAR) T cells (see Key Concepts) generated from allogeneic base-edited cells. The patient had had disease relapses and had residual tumor cells after the last round of salvage treatment (Fig. 1). The goal was to eliminate the residual disease to allow her to undergo bone marrow transplantation while she was in complete remission, a situation that maximizes the efficacy of transplantation.

## WHAT ARE CAR T CELLS?

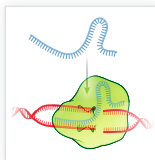
CAR T cells are T cells into which DNA encoding an antibody with specificity for a tumor-cell target has been introduced.<sup>2</sup> The CAR-expressing T cells then attack and kill cells expressing the target (i.e., the **tumor-associated antigen**). CAR T cells have been shown to have high levels of activity in hematologic cancers<sup>3</sup> and are beginning to show activity in solid tumors.<sup>4</sup> Typically, they are generated from the patient's own T cells. Challenges to the use of CAR T cells include the fact that it takes a few weeks to generate them for each patient and that usually only enough cells are generated to treat the patient once. In some patients, tumors progress while the CAR T cells are in preparation. And in some patients, the response is partial, and one wonders whether partial responses could become complete with another round or two of treatment. A goal, therefore, is to have sufficient numbers of ready-made effector cells available to treat the patient immediately and to support repeated treatment. Perhaps allogeneic donors could be the source of such cells. However, the use of allogeneic donor cells for the generation of CAR T cells is complicated by the fact that the host will recognize "foreign" cells through their **major histocompatibility complex (MHC)** and try to reject them. Reciprocally, the transferred T cells will see the host as foreign and mediate graft-versus-host reactions.

## Key Concepts



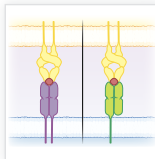
## Chimeric antigen receptor T cells

Engineered T cells that target a specific cell-surface antigen, such as one expressed by a tumor cell. The specific targeting is mediated by a chimeric antigen receptor (CAR), so called because it combines the specificity of an antibody (the extracellular part) with the T-cell-activating function of a T-cell receptor (the intracellular part). Its forced expression on the surface of the T cell (through genetic means) augments specificity, function, and metabolism.



## CRISPR-Cas9

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.



## Major histocompatibility complex

A complex of linked genes encoding cell-surface proteins that display peptides produced by cleavage of intracellular proteins; these proteins help T cells recognize foreign or mutant proteins. The human form of MHC is referred to as HLA, and the porcine counterpart as SLA.



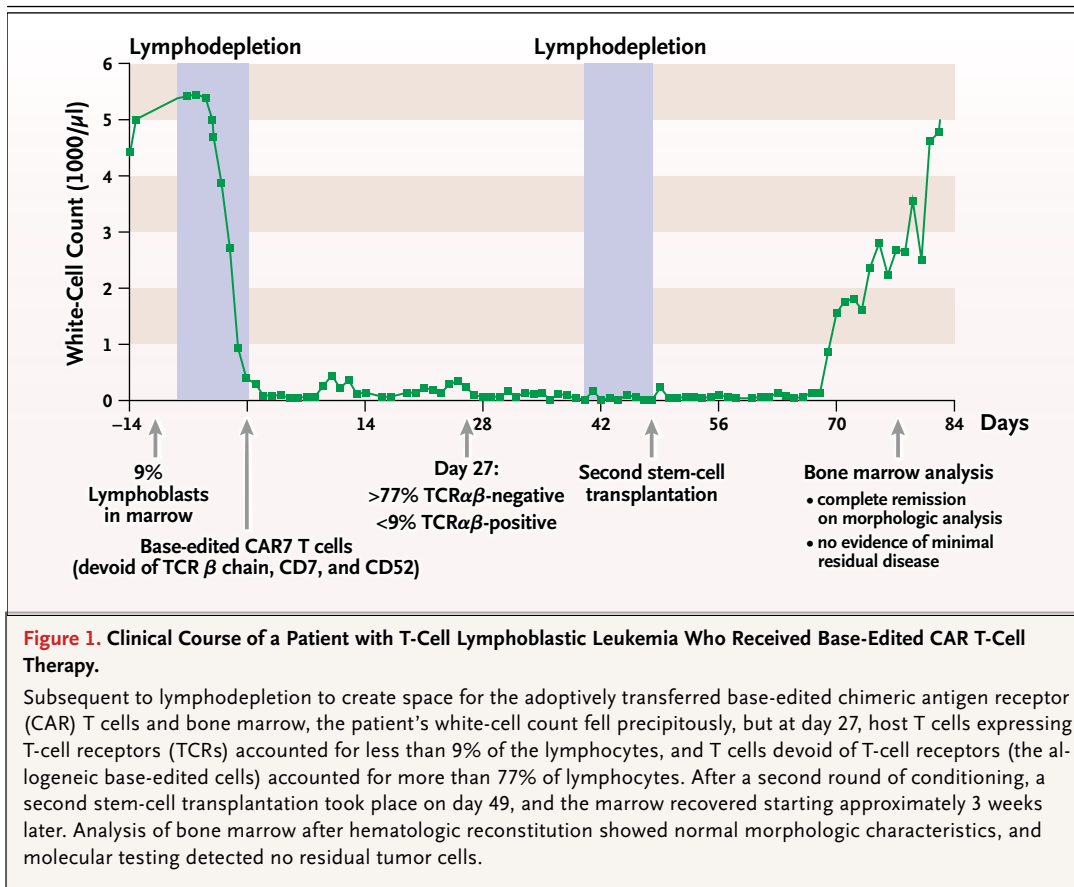
## Tumor-associated antigen

A molecule that is expressed exclusively by tumor cells or is expressed to a greater extent by tumor cells than by cells of normal tissues and that is targeted by an antibody or antibody-bearing cell.

 An expanded illustrated glossary is available at [NEJM.org](https://www.nejm.org)

## HOW CAN HISTOCOMPATIBILITY ISSUES BE OVERCOME?

The prevention of rejection of foreign adoptively transferred cells by the host is routinely accomplished in clinical medicine during allogeneic



bone marrow transplantation through immunosuppression of the host. (More on this later.) To prevent graft-versus-host disease, Chiesa et al. “disabled” the cell-surface receptor on the cells to be adoptively transferred that recognizes foreign (albeit host, in this case) MHC molecules: the T-cell receptor.

#### CAN GENES BE SILENCED IN CAR T CELLS?

Yes. New tools that are based on **CRISPR (clustered regularly interspaced short palindromic repeats)–Cas9** technology have made it possible to target particular sequences in the genome with high specificity.<sup>5</sup> Site specificity is accomplished by inserting a complex of protein and nucleic acids into dividing cells. The complex comprises a fragment of RNA (called single guide RNA) complementary to the sequence of the target site and a scaffold sequence for the binding of Cas9, an enzyme that cuts the DNA at the target site (a gene), disrupting the gene. In the current study, Chiesa et al. used a modified version of this method to generate, from third-party donors, CAR T cells with altered gene expression that

#### Figure 2 (facing page). Comparison of Cas9 Editing and Base Editing.

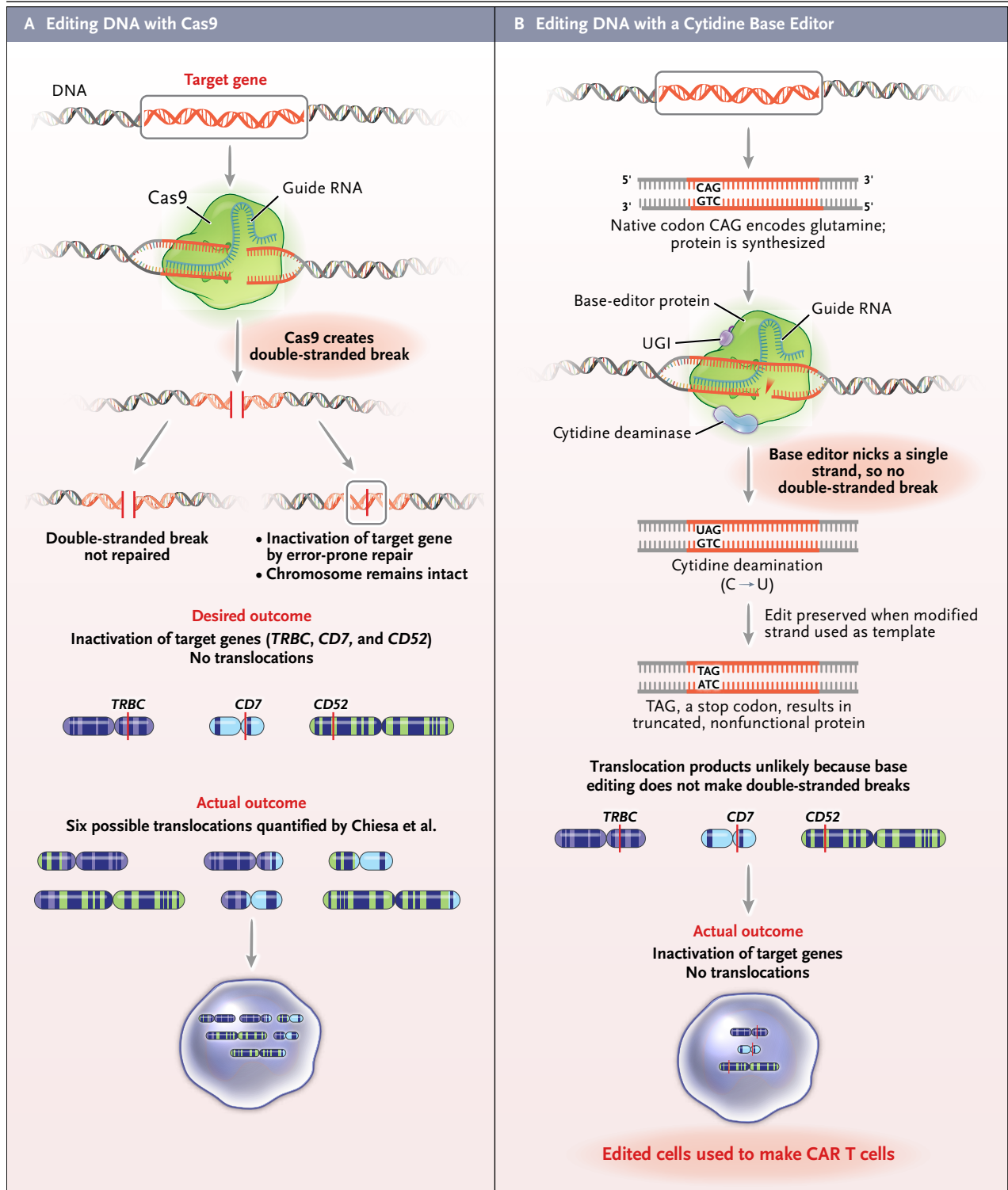
Panel A illustrates the steps of Cas9-mediated gene silencing. The guide RNA directs the Cas9 complex to the targeted gene or genes, and the Cas9 induces a double-stranded DNA break. The break is either not repaired or repair is attempted with an error-prone mechanism such as nonhomologous end joining. Typically, the targeted genes are inactivated, but aberrant translocations can occur when the broken DNA is recombined with a distinct chromosomal segment. Chiesa et al.<sup>1</sup> detected six translocations after editing *TRBC* (encoding the  $\beta$  chain of the T-cell receptor), *CD7*, and *CD52* using “standard” Cas9 and guide RNAs targeting these genes. Panel B illustrates the steps of Cas9-mediated cytidine base editing. The complex, formed by guide RNA and Cas9 (modified to include the functions of cytidine deaminase and uracil glycosylase inhibitor), binds to a specific locus of the target gene, owing to complementarity in sequence between the locus and the guide RNA. The modified Cas9 nicks (but does not cleave) the DNA. The deaminase then converts distal cytidines within a 5-bp window (positions 4 through 8) to uridines. This step leads to thymidines replacing cytidines and either introduces stop codons or alters the signals for messenger RNA splicing, either of which will interfere with expression of the gene. Chiesa et al. detected no abnormal translocations using the base-editing method.



have specificity for a tumor-associated antigen but do not express T-cell receptors, thereby making them unable to mediate allogeneic graft-versus-host effects.

**HOW DID THEY DO IT?**

The method is called base editing,<sup>6,7</sup> and Chiesa et al. used a particular type of editing, called C-to-T base editing. To achieve this exquisitely



precise level of editing (at the level of a single base!), they used a modified version of the Cas9 protein with new properties, one of which is the ability to deaminate cytidines. Thus, the modified Cas9 removes an amine group from the pyrimidine ring of cytidine, thereby converting it to uridine. Uridine becomes methylated to thymidine, which pairs with adenine. Thus, cytidine deaminase introduces a thymidine residue, replacing cytidine, and alters the sequence. This C-to-U-to-T conversion can be used to introduce a stop codon to prevent transcription or to alter specific messenger RNA splice sites to prevent protein production. The second property of the modified Cas9 is the inhibition of uracil glycosylase, thus preventing repair of the uridine.

During editing with a “regular” unmodified Cas9 enzyme, the Cas9 makes a double-stranded cut in the DNA at the site to which it is shepherded by the guide RNA. In the base-editing scheme, the altered Cas9 enzyme does not make a double-stranded break but instead nicks one strand of DNA. Any cytidine within a 5-base window distal to the nick and on the opposite strand becomes “unmasked” and altered by the deaminase. Chiesa et al. used activated T cells pooled from unrelated donors because the process works best in dividing cells. And so, through base editing, the authors inactivated both alleles encoding the T-cell receptor  $\beta$  chain and prevented expression of the T-cell receptor and thus the capacity of the CAR T cell to mediate graft-versus-host effects.

#### HOW TO PREVENT REJECTION OF ALLOGENEIC CAR T CELLS?

The authors certainly did not want the half-life of the effector cells shortened through rejection of the CAR T cells by the host. In other contexts that involve the administration of allogeneic hematopoietic cells, the rejection of the cells by the recipient is controlled with the use of immunosuppressive drugs. Chiesa et al. used an immunosuppressive chemoimmunotherapy regimen that includes a potent lymphocyte-killing antibody, alemtuzumab (anti-CD52). However, this creates another problem: CAR T cells normally express CD52, making them susceptible to elimination by alemtuzumab. Therefore, the authors used C-to-T gene editing to silence *CD52* in the allogeneic T cells from which the CAR T

cells were made, making them less vulnerable to the immunosuppressive regimen.

#### WHAT IS THE TUMOR TARGET OF THE CAR T CELLS?

In this study, the CAR T cells recognize CD7, a cell-surface protein on the neoplastic T-cell leukemia cells of the patient. The recognition unit (the CAR) was introduced to the allogeneic base-edited T cell by a lentivirus vector. But the CD7 target introduces another layer of complexity, because the effector CAR T cells themselves express CD7. One does not want the effector cells killing one another rather than the tumor, and so Chiesa et al. silenced *CD7* in the allogeneic T cells using C-to-T base editing. Chiesa et al. therefore simultaneously silenced three genes — encoding the T-cell receptor  $\beta$  chain, CD7, and CD52 — in the allogeneic T cells before the cells were transduced with DNA encoding a CAR to facilitate the recognition of CD7 on host leukemia cells.

#### DOUBLE-STRANDED DNA BREAKS ARE DANGEROUS, NO?

Yes, they are, and a relative strength of base editing is that it leaves the chromosome intact. When a cell is exposed to multiple double-stranded DNA breaks (as is the case when three edits are made simultaneously), DNA-repair mechanisms are activated to try to repair them, which sometimes leads to serious genetic damage from translocations of chromosomes, which occurs through the fusion of two “broken” chromosomes. Indeed, when Chiesa et al. used unmodified Cas9 and the same guide RNAs to target *TRBC*, *CD7*, and *CD52*, they detected six translocated chromosomes in the edited cells (Fig. 2).

#### ARE THERE OTHER METHODS TO GENETICALLY MODIFY EFFECTOR CELLS?

Two other experimental methods to edit base sequences are in development. Both use nucleases that introduce DNA breaks: zinc-finger nucleases and transcription activator–like effector nucleases (TALENs). One clinical study that used TALENs was halted because of chromosome translocations thought to be related to the intervention.<sup>8</sup>

#### WHAT'S NEXT?

The study by Chiesa et al. is continuing. In addition to the patient described above, another pa-

tient has had morphologic and molecular remission, and one has died. The long-term outcomes of the two surviving patients and those of the others in this study, which has a projected enrollment of 10 patients, will be of interest.

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

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## ORIGINAL ARTICLE

# Triple–Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

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## ABSTRACT

**BACKGROUND**

Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its dose–response relationships with respect to side effects, safety, and efficacy for the treatment of obesity are not known.

**METHODS**

We conducted a phase 2, double-blind, randomized, placebo-controlled trial involving adults who had a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 or higher or who had a BMI of 27 to less than 30 plus at least one weight-related condition. Participants were randomly assigned in a 2:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The primary end point was the percentage change in body weight from baseline to 24 weeks. Secondary end points included the percentage change in body weight from baseline to 48 weeks and a weight reduction of 5% or more, 10% or more, or 15% or more. Safety was also assessed.

**RESULTS**

We enrolled 338 adults, 51.8% of whom were men. The least-squares mean percentage change in body weight at 24 weeks in the retatrutide groups was –7.2% in the 1-mg group, –12.9% in the combined 4-mg group, –17.3% in the combined 8-mg group, and –17.5% in the 12-mg group, as compared with –1.6% in the placebo group. At 48 weeks, the least-squares mean percentage change in the retatrutide groups was –8.7% in the 1-mg group, –17.1% in the combined 4-mg group, –22.8% in the combined 8-mg group, and –24.2% in the 12-mg group, as compared with –2.1% in the placebo group. At 48 weeks, a weight reduction of 5% or more, 10% or more, and 15% or more had occurred in 92%, 75%, and 60%, respectively, of the participants who received 4 mg of retatrutide; 100%, 91%, and 75% of those who received 8 mg; 100%, 93%, and 83% of those who received 12 mg; and 27%, 9%, and 2% of those who received placebo. The most common adverse events in the retatrutide groups were gastrointestinal; these events were dose-related, were mostly mild to moderate in severity, and were partially mitigated with a lower starting dose (2 mg vs. 4 mg). Dose-dependent increases in heart rate peaked at 24 weeks and declined thereafter.

**CONCLUSIONS**

In adults with obesity, retatrutide treatment for 48 weeks resulted in substantial reductions in body weight. (Funded by Eli Lilly; ClinicalTrials.gov number, NCT04881760.)

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\*A full list of the Retatrutide Phase 2 Obesity Trial Investigators is provided in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

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RESEARCH SUMMARY

# Triple-Hormone-Receptor Agonist Retatrutide for Obesity — A Phase 2 Trial

Jastreboff AM et al. DOI: 10.1056/NEJMoa2301972

**CLINICAL PROBLEM**

Obesity is projected to affect nearly one quarter of the world population by 2035. Retatrutide, a single peptide with agonism toward three receptors — the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors — showed promise for weight reduction in an early trial involving patients with type 2 diabetes, but its effects in patients without diabetes are unknown.

**CLINICAL TRIAL**

**Design:** A phase 2, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of retatrutide in adults without diabetes but with obesity or overweight plus ≥1 weight-related condition.

**Intervention:** 338 adults 18 to 75 years of age with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) of 30 to 50 or a BMI of 27 to <30 plus ≥1 weight-related condition were assigned to receive subcutaneous retatrutide with the dose adjusted to reach one of four maintenance doses or placebo once weekly for 48 weeks. All participants also took part in a lifestyle intervention. The primary end point was the percentage change in weight from baseline to 24 weeks.

**RESULTS**

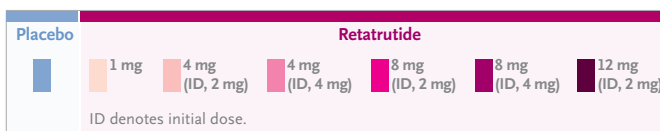
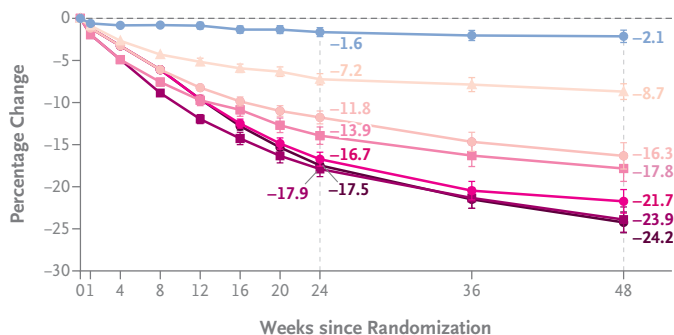
**Efficacy:** The percentage change in weight at 24 weeks at all doses of retatrutide was greater than that with placebo. Weight loss with retatrutide was dose-dependent, with weight decreasing further by week 48.

**Safety:** Gastrointestinal adverse events occurred substantially more often with retatrutide than with placebo; these events were usually mild to moderate in severity and were more common at higher doses of retatrutide.

**LIMITATIONS AND REMAINING QUESTIONS**

- Participants were all from the United States, and 88% were White.
- Because only 4% of the participants had overweight (BMI, 27 to <30) plus an obesity-related condition, the results may not be generalizable to this population.

Changes in Body Weight



Adverse Events

Events	Assigned Maintenance						
	Placebo (N=70)	1 mg (N=69)	4 mg ID, 2 mg (N=33)	4 mg ID, 4 mg (N=33)	8 mg ID, 2 mg (N=35)	8 mg ID, 4 mg (N=35)	12 mg ID, 2 mg (N=62)
Nausea	8 (11)	10 (14)	6 (18)	12 (36)	6 (17)	21 (60)	28 (45)
Diarrhea	8 (11)	6 (9)	4 (12)	4 (12)	7 (20)	7 (20)	9 (15)
Vomiting	1 (1)	2 (3)	4 (12)	4 (12)	2 (6)	9 (26)	12 (19)
Constipation	2 (3)	5 (7)	5 (15)	2 (6)	4 (11)	4 (11)	10 (16)
Antidrug antibodies during treatment	1 (1)	3 (4)	4 (12)	5 (16)	5 (16)	2 (6)	11 (18)

Data are number of participants (percent). Data on antidrug antibodies were missing for 10 patients.

**CONCLUSIONS**

In adults with obesity without diabetes, once-weekly treatment with subcutaneous retatrutide led to substantial, dose-dependent reductions in weight at 24 and 48 weeks.

## EDITORIAL

## Triple G Agonists — A Home Run for Obesity?

Mary Elizabeth Patti, M.D.

The buzz was palpable at the 2023 American Diabetes Association Scientific Sessions as multiple new nutrient-stimulated, hormone-based therapies for obesity and type 2 diabetes took center stage. Among these therapies, the triple-hormone-receptor agonist retatrutide — the subject of a phase 2 trial by Jastreboff et al., the results of which are published in this issue of the *Journal*<sup>1</sup> — showed unprecedented efficacy in treating obesity, with 24% weight loss over 48 weeks.

Hormonal responses to nutrient intake are key regulators of metabolism. The best known is insulin secretion in response to postprandial increases in levels of glucose or amino acids, promoting nutrient storage and maintaining normoglycemia. In addition, intestinal hormonal responses to food intake further magnify insulin secretion (e.g., the “incretin effect” mediated by glucagon-like peptide-1 [GLP-1] and glucose-dependent insulinotropic polypeptide [GIP]) and modulate satiety, food intake, and other aspects of prandial metabolism (mediated by, e.g., GLP-1, GIP, peptide tyrosine tyrosine [PYY], and amylin). Incretin-mimetic GLP-1 agonists have already gained widespread acceptance for the management of type 2 diabetes and obesity. The addition of GIP receptor agonism, as with the dual GLP-1–GIP agonist tirzepatide, further enhances weight loss.

What is the new “triple G” hormone receptor agonist? Retatrutide is a single peptide that activates three G-protein–coupled receptors — GLP-1, GIP, and glucagon (GCG) receptors.<sup>2,3</sup> Engaging the GCG receptor might seem counterintuitive; GCG is best recognized as a counterregulatory hormone released from pancreatic  $\alpha$  cells during hypoglycemia, increasing blood glucose. However, GCG also has potent catabolic effects, in that it stimulates adipose lipolysis, reduces food intake, slows gastric emptying, and increases energy expenditure.<sup>4</sup> Thus, incorporating GCG receptor agonism may further enhance weight loss, while simultaneous incretin-mimetic action of GLP-1–GIP signaling can balance the potential adverse glycemic effects of GCG. Preclinical studies showed that triple G agonists were superior to single or dual agonists for achieving weight loss,

reducing hepatic steatosis, and normalizing glucose levels.<sup>2</sup>

Jastreboff et al. performed a double-blind, randomized trial of weekly subcutaneous retatrutide as compared with placebo in 338 adults without diabetes who had either class 1 obesity (a body-mass index [BMI, the weight in kilograms divided by the square of the height in meters] of  $\geq 30$ ) or overweight (a BMI of 27 to  $<30$ ) with associated coexisting conditions. Doses of retatrutide ranged from 1 to 12 mg. All the participants received dietary counseling.

Among the participants treated with retatrutide per protocol, the mean weight loss at the highest dose was 18% at 24 weeks and 24% at 48 weeks, as compared with approximately 2% at both time points among the participants who received placebo. At the highest dose, 26% of the participants had weight loss of 30% or more at 48 weeks. Weight reductions occurred across the BMI spectrum but were greater among the participants with a BMI of at least 35. In this relatively short-term trial, the effect of retatrutide on cardiovascular events could not be determined, but several measures of cardiometabolic risk improved, including blood pressure and levels of glycated hemoglobin, fasting glucose, insulin, total and low-density lipoprotein cholesterol, and triglycerides. Modest increases in heart rate occurred, similar to findings in previous studies of incretin analogues.

As with GLP-1–GIP agonists, the side effects of retatrutide were dose-dependent and predominantly gastrointestinal, with nausea occurring in 45 to 60% of the participants at higher doses, mostly during early dose escalation. Adverse events led to drug discontinuation in 16% of the participants at the highest dose, but serious adverse events were few.

The trial included only participants without diabetes. Although weight loss is typically lower in persons with type 2 diabetes, another recently published study of retatrutide involving patients with type 2 diabetes<sup>5</sup> reported 17% weight loss at 36 weeks, with a 2% decrease in the glycated hemoglobin level. Likewise, the benefits of triple agonism extended to treatment of nonalcoholic



fatty liver disease; in a subgroup of 98 persons in the trial who had nonalcoholic fatty liver disease,<sup>6</sup> fat content normalized in 90% of participants at the highest doses of retatrutide.

Together, these data offer further optimism about the idea that effective pharmacologic management of obesity and related disorders is possible. However, larger and longer-term studies are needed to expand the generalizability of the results, to confirm lasting safety and health outcomes, and to determine the protocols for clinical care. For example, it will be essential to identify the magnitude and rate of weight loss and the lifestyle and dietary interventions that will ensure adequate nutrition and minimize the loss of lean body mass. In addition, we will need to know the best options for the prevention of weight regain should the medication be discontinued because of side effects or as a result of changes in insurance coverage or drug availability.

The advent of highly effective therapy for obesity raises many questions both for clinicians and for public policy decision makers. Because obesity is a chronic disease (analogous to hypertension), it is necessary to manage it with long-term therapy. Clinicians and patients alike will need to carefully consider the available options for obesity; potential treatments include dietary and lifestyle interventions and long-term pharmacologic therapy, as well as bariatric metabolic surgery, which leads to an even greater magnitude of sustained weight loss and metabolic control than retatrutide.<sup>7-9</sup> Triple G agonists could provide a bridge to more permanent surgical weight loss or potentially augment surgical efficacy. Given the estimated 42% prevalence of obesity among adults in the United States,<sup>10</sup> the substantial costs of achieving successful obesity care with triple G agonists and other agents need to be balanced against anticipated cost savings

that would be realized by preventing obesity-related complications.

Finally, a key challenge and societal imperative will be to ensure affordability and equitable access to effective antiobesity therapies, especially in underserved populations that carry the highest burden of disease. Only then will obesity management truly hit a home run.

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

From Joslin Diabetes Center, Boston.

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## Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

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### ABSTRACT

#### BACKGROUND

In some patients with chronic obstructive pulmonary disease (COPD), type 2 inflammation may increase exacerbation risk and may be indicated by elevated blood eosinophil counts. Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4 and interleukin-13, key drivers of type 2 inflammation.

#### METHODS

In a phase 3, double-blind, randomized trial, we assigned patients with COPD who had a blood eosinophil count of at least 300 per microliter and an elevated exacerbation risk despite the use of standard triple therapy to receive dupilumab (300 mg) or placebo subcutaneously once every 2 weeks. The primary end point was the annualized rate of moderate or severe exacerbations of COPD. Key secondary and other end points that were corrected for multiplicity were the change in the prebronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) and in the scores on the St. George's Respiratory Questionnaire (SGRQ; range, 0 to 100, with lower scores indicating a better quality of life) and the Evaluating Respiratory Symptoms in COPD (E-RS-COPD; range, 0 to 40, with lower scores indicating less severe symptoms).

#### RESULTS

A total of 939 patients underwent randomization: 468 to the dupilumab group and 471 to the placebo group. The annualized rate of moderate or severe exacerbations was 0.78 (95% confidence interval [CI], 0.64 to 0.93) with dupilumab and 1.10 (95% CI, 0.93 to 1.30) with placebo (rate ratio, 0.70; 95% CI, 0.58 to 0.86;  $P < 0.001$ ). The prebronchodilator FEV<sub>1</sub> increased from baseline to week 12 by a least-squares (LS) mean of 160 ml (95% CI, 126 to 195) with dupilumab and 77 ml (95% CI, 42 to 112) with placebo (LS mean difference, 83 ml; 95% CI, 42 to 125;  $P < 0.001$ ), a difference that was sustained through week 52. At week 52, the SGRQ score had improved by an LS mean of  $-9.7$  (95% CI,  $-11.3$  to  $-8.1$ ) with dupilumab and  $-6.4$  (95% CI,  $-8.0$  to  $-4.8$ ) with placebo (LS mean difference,  $-3.4$ ; 95% CI,  $-5.5$  to  $-1.3$ ;  $P = 0.002$ ). The E-RS-COPD score at week 52 had improved by an LS mean of  $-2.7$  (95% CI,  $-3.2$  to  $-2.2$ ) with dupilumab and  $-1.6$  (95% CI,  $-2.1$  to  $-1.1$ ) with placebo (LS mean difference,  $-1.1$ ; 95% CI,  $-1.8$  to  $-0.4$ ;  $P = 0.001$ ). The numbers of patients with adverse events that led to discontinuation of dupilumab or placebo, serious adverse events, and adverse events that led to death were balanced in the two groups.

#### CONCLUSIONS

Among patients with COPD who had type 2 inflammation as indicated by elevated blood eosinophil counts, those who received dupilumab had fewer exacerbations, better lung function and quality of life, and less severe respiratory symptoms than those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; BOREAS ClinicalTrials.gov number, NCT03930732.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Bhatt can be contacted at sbhatt@uabmc.edu or at the Division of Pulmonary, Allergy, and Critical Care Medicine, University of Alabama at Birmingham, 1900 University Blvd., Tinsley Harrison Tower, Ste. 422, Birmingham, AL 35294, and Dr. Rabe can be contacted at k.f.rabe@lungenclinic.de or at LungClinic Grosshansdorf, Wöhrendamm 80, 22927 Grosshansdorf, Germany.

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

Drs. Bhatt and Rabe contributed equally to this article.

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RESEARCH SUMMARY

# Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts

Bhatt SP et al. DOI: 10.1056/NEJMoa2303951

**CLINICAL PROBLEM**

Some patients with chronic obstructive pulmonary disease (COPD) have elevated eosinophil counts, a marker of type 2 inflammation, which may increase the risk of disease exacerbations. Patients with type 2 inflammation commonly have elevated levels of interleukin-4 and interleukin-13. Dupilumab is a fully humanized monoclonal antibody that blocks the shared receptor component for these two interleukins.

**CLINICAL TRIAL**

**Design:** In a phase 3, international, double-blind, randomized, placebo-controlled trial, the efficacy and safety of dupilumab were evaluated in patients with COPD and an absolute blood eosinophil count of  $\geq 300$  per microliter.

**Intervention:** 939 current or former smokers 40 to 80 years of age, who had symptomatic COPD and were at increased risk for exacerbations despite the use of standard inhaled triple therapy, received add-on therapy with either subcutaneous dupilumab (300 mg) or placebo every 2 weeks for 52 weeks. The primary end point was the annualized rate of moderate or severe exacerbations of COPD during the trial.

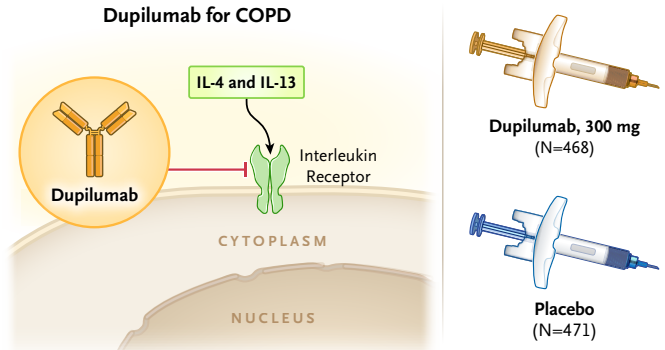
**RESULTS**

**Efficacy:** Treatment with dupilumab resulted in a lower annualized rate of moderate or severe exacerbations of COPD than placebo.

**Safety:** The percentages of patients with adverse events and serious adverse events during treatment were similar in the two groups.

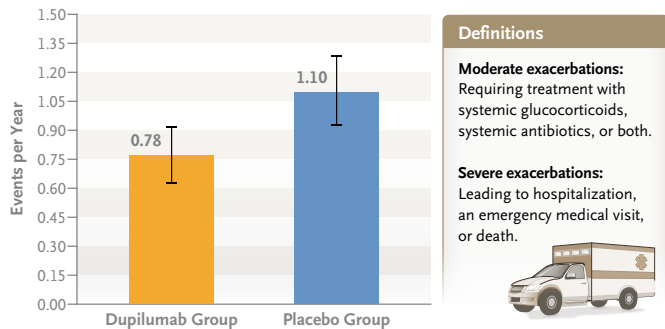
**LIMITATIONS AND REMAINING QUESTIONS**

- The trial was conducted during the coronavirus disease 2019 pandemic, which may have affected patient behaviors, exposures, and frequencies of exacerbations of COPD.
- Patients who identified as Black were underrepresented in the trial.
- Randomization was not stratified according to smoking status.

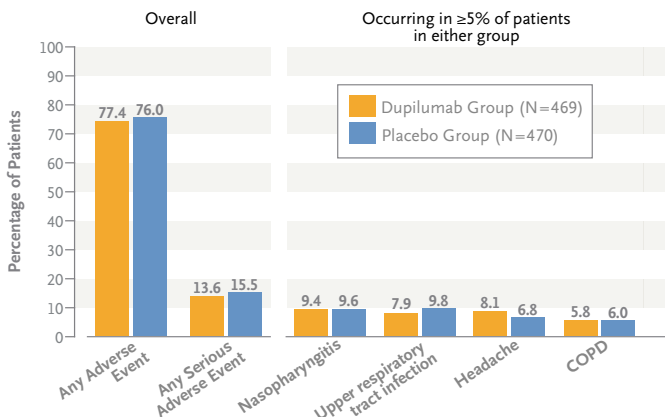


**Adjusted Annualized Rate of Moderate or Severe Exacerbations of COPD**

Rate ratio, 0.70; 95% CI, 0.58–0.86;  $P < 0.001$



**Adverse Events**



**CONCLUSIONS**

In patients with COPD who had type 2 inflammation as indicated by elevated eosinophil counts, add-on treatment with dupilumab resulted in a lower annualized rate of moderate or severe exacerbations than placebo.

## EDITORIAL



## Biologics for COPD — Finally Here

Alvar Agusti, M.D., Ph.D.

The use of biologic therapies, including monoclonal antibodies, has revolutionized the treatment of many human diseases. In respiratory medicine, monoclonal antibodies have already transformed the management of severe asthma.<sup>1</sup> By contrast, previous trials of biologic agents targeting interleukin-5 have yielded potentially relevant but mostly inconclusive results in patients with chronic obstructive pulmonary disease (COPD).<sup>2,3</sup> Fortunately for patients with COPD, things are changing, and biologic treatment is finally here for them.

In this issue of the *Journal*, Bhatt et al.<sup>4</sup> report the results of a 52-week, phase 3, multicenter, double-blind, randomized trial (the BOREAS trial), which involved 939 patients who had COPD and a blood eosinophil count of at least 300 per microliter (a marker of type 2 inflammation). Treatment with dupilumab administered subcutaneously once every 2 weeks at a dose of 300 mg, in addition to ongoing treatment with inhaled triple therapy (a long-acting  $\beta_2$ -agonist, a long-acting antimuscarinic agent, and an inhaled glucocorticoid), resulted in a lower incidence of exacerbations of COPD, better lung function and health status, and less severe respiratory symptoms than placebo.<sup>4</sup> These results provide clear evidence that type 2 airway inflammation is involved in exacerbations and airflow limitation in this specific subgroup of patients with COPD.

Several aspects of this important trial, however, deserve comment. First, dupilumab is a fully human monoclonal antibody that blocks the effects of both interleukin-13 and interleukin-4 by binding to a component of the interleukin-4 receptor  $\alpha$  shared by both cytokines,<sup>1</sup> whereas previous trials targeted the interleukin-5 pathway with mepolizumab<sup>2</sup> or benralizumab.<sup>3</sup> The broader inhibition of type 2 inflammation that was achieved with dupilumab than with mepolizumab or ben-

ralizumab, along with a possibly greater effect on airway mucus and airway smooth muscle, may account for the clearer evidence of efficacy that was seen with dupilumab.<sup>1</sup>

Second, Bhatt et al. studied a carefully selected subgroup of patients with COPD — those with a blood eosinophil count of at least 300 per microliter.<sup>4</sup> High circulating levels of eosinophils in patients with COPD identify those patients at increased risk for exacerbations of COPD as well as those who are more likely to have a response to the preventive effects of an inhaled glucocorticoid.<sup>5</sup> Therefore, the results of the BOREAS trial cannot be generalized automatically to all patients with COPD. Further studies are needed to evaluate whether these clinical effects are also seen in patients with lower levels of circulating eosinophils.

Third, it is noteworthy that these effects were observed when dupilumab treatment was added to inhaled triple therapy, since inhaled triple therapy itself is known to reduce exacerbations of COPD and alleviate symptoms in many patients with COPD, regardless of the level of circulating eosinophils.<sup>6</sup> Thus, the incremental effect of treatment with dupilumab in combination with the established standard treatment with inhaled triple therapy in these patients fills an important unmet need. However, we do not know whether there was a differential effect among various inhaled triple-therapy combinations. Furthermore, post hoc analyses would be of interest and may help guide future investigations to refine the appropriate target patient populations.

The BOREAS trial also raises relevant questions that require further research. The first is the potential effect of dupilumab treatment (in combination with inhaled triple therapy) on other key outcomes such as death and disease progression. Other trials have clearly shown that triple therapy reduces all-cause mortality among patients

with COPD who have frequent exacerbations of COPD,<sup>7,8</sup> but Bhatt et al. do not report data on deaths (or disease progression); such data would potentially be of great clinical relevance.

In addition, as discussed above, it is important to realize that these results are from a very specific subpopulation of patients with COPD that was identified by an easy-to-obtain biomarker (blood eosinophil count). This approach is fully in line with the so-called treatable-traits strategy, which advocates addressing the complexity of COPD in particular — and chronic airway diseases in general — by targeting specific phenotypic characteristics (in this case, exacerbation of COPD), on the basis of validated biomarkers (the eosinophil count) of specific biologic mechanisms or endotypes (type 2 inflammation).<sup>9</sup> As such, the BOREAS trial is an exemplar for future drug development in COPD, with the target of treatment being a measured driving mechanism rather than an arbitrary diagnostic label or an unrelated physiological measure.

Finally, it is noteworthy that the mean age of the patients in the BOREAS trial was 65 years.<sup>4</sup> It is now well established that there are various lung-function trajectories through life that can lead to COPD in adulthood and that early life events that limit lung growth and development are critical factors determining respiratory health later in life.<sup>10</sup> It is possible, therefore, that the diagnosis and treatment of COPD at a younger age may yield better results. The recently released Global Initiative for Chronic Obstructive Lung Disease (GOLD) report clearly emphasizes the need to study COPD in young patients.<sup>6</sup>

The results of the BOREAS trial should be most welcome because they finally open a new era in the treatment of patients with COPD. Hopefully, new biologic therapies will be illuminated soon, and this new era will offer patients with COPD new and more effective remedies for their disease.

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

From Cátedra de Salud Respiratoria, University of Barcelona, the Respiratory Institute, Hospital Clinic of Barcelona, and the August Pi Sunyer Biomedical Research Institute — all in Barcelona; and Centro de Investigación Biomédica en Red de Enfermedades Respiratorias, Madrid.

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# The NEW ENGLAND JOURNAL of MEDICINE

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## Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

I. Gallos, A. Devall, J. Martin, L. Middleton, L. Beeson, H. Galadanci, F. Alwy Al-beity, Z. Qureshi, G.J. Hofmeyr, N. Moran, S. Fawcus, L. Sheikh, G. Gwako, A. Osoti, A. Aswat, K.-M. Mammoliti, K.N. Sindhu, M. Podeseck, I. Horne, R. Timms, I. Yunas, J. Okore, M. Singata-Madliki, E. Arends, A.A. Wakili, A. Mwampashi, S. Nausheen, S. Muhammad, P. Latthe, C. Evans, S. Akter, G. Forbes, D. Lissauer, S. Meher, A. Weeks, A. Shennan, A. Ammerdorffer, E. Williams, T. Roberts, M. Widmer, O.T. Oladapo, F. Lorencatto, M.A. Bohren, S. Miller, F. Althabe, M. Gülmezoglu, J.M. Smith, K. Hemming, and A. Coomarasamy

### ABSTRACT

#### BACKGROUND

Delays in the detection or treatment of postpartum hemorrhage can result in complications or death. A blood-collection drape can help provide objective, accurate, and early diagnosis of postpartum hemorrhage, and delayed or inconsistent use of effective interventions may be able to be addressed by a treatment bundle.

#### METHODS

We conducted an international, cluster-randomized trial to assess a multicomponent clinical intervention for postpartum hemorrhage in patients having vaginal delivery. The intervention included a calibrated blood-collection drape for early detection of postpartum hemorrhage and a bundle of first-response treatments (uterine massage, oxytocic drugs, tranexamic acid, intravenous fluids, examination, and escalation), supported by an implementation strategy (intervention group). Hospitals in the control group provided usual care. The primary outcome was a composite of severe postpartum hemorrhage (blood loss,  $\geq 1000$  ml), laparotomy for bleeding, or maternal death from bleeding. Key secondary implementation outcomes were the detection of postpartum hemorrhage and adherence to the treatment bundle.

#### RESULTS

A total of 80 secondary-level hospitals across Kenya, Nigeria, South Africa, and Tanzania, in which 210,132 patients underwent vaginal delivery, were randomly assigned to the intervention group or the usual-care group. Among hospitals and patients with data, a primary-outcome event occurred in 1.6% of the patients in the intervention group, as compared with 4.3% of those in the usual-care group (risk ratio, 0.40; 95% confidence interval [CI], 0.32 to 0.50;  $P < 0.001$ ). Postpartum hemorrhage was detected in 93.1% of the patients in the intervention group and in 51.1% of those in the usual-care group (rate ratio, 1.58; 95% CI, 1.41 to 1.76), and the treatment bundle was used in 91.2% and 19.4%, respectively (rate ratio, 4.94; 95% CI, 3.88 to 6.28).

#### CONCLUSIONS

Early detection of postpartum hemorrhage and use of bundled treatment led to a lower risk of the primary outcome, a composite of severe postpartum hemorrhage, laparotomy for bleeding, or death from bleeding, than usual care among patients having vaginal delivery. (Funded by the Bill and Melinda Gates Foundation; E-MOTIVE ClinicalTrials.gov number, NCT04341662.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Devall can be contacted at a.j.devall@bham.ac.uk or at the Institute of Metabolism and Systems Research, WHO Collaborating Centre on Global Women's Health, College of Medical and Dental Sciences, University of Birmingham, 4th Fl. E., Heritage Bldg., Mindelsohn Way, Edgbaston, Birmingham B15 2TH, United Kingdom.

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## RESEARCH SUMMARY

# Randomized Trial of Early Detection and Treatment of Postpartum Hemorrhage

Gallos I et al. DOI: 10.1056/NEJMoa2303966

**CLINICAL PROBLEM**

Postpartum hemorrhage remains the leading cause of maternal complications and death worldwide, despite evidence-informed recommendations for prevention and treatment. Challenges include delayed or no detection of postpartum hemorrhage, inconsistent use of interventions, and poor uptake of recommendations at the point of care.

**CLINICAL TRIAL**

**Design:** An international, cluster-randomized trial assessed a multicomponent clinical intervention, as compared with usual care, for the detection and treatment of postpartum hemorrhage in patients having vaginal delivery.

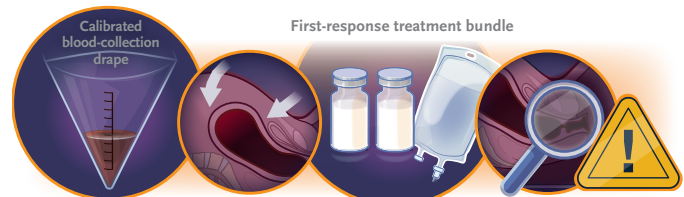
**Intervention:** 80 hospitals in Africa were randomly assigned either to receive the trial intervention for 7 months, with a 2-month transition period for training and implementation, or to continue providing usual care. The intervention included a calibrated blood-collection drape for the early detection of postpartum hemorrhage and a bundle of first-response treatments (uterine massage, oxytocic drugs, tranexamic acid, intravenous fluids, examination, and escalation of treatment when needed). The primary outcome was a composite of severe postpartum hemorrhage (blood loss,  $\geq 1000$  ml), laparotomy for bleeding, or maternal death from bleeding.

**RESULTS**

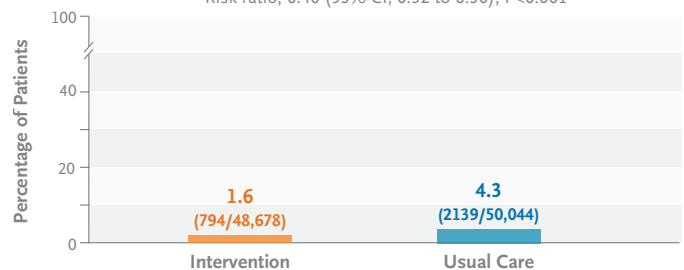
Primary-outcome events occurred significantly less often in the intervention group than in the usual-care group. Key secondary implementation outcomes, including detection of postpartum hemorrhage and adherence to the treatment bundle, also favored the intervention group.

**LIMITATIONS AND REMAINING QUESTIONS**

- The trial was conducted in low- and middle-income countries; further implementation research is needed in high-income settings.
- The uncalibrated drapes that were used in the control hospitals to gather trial-outcome data were transparent; therefore, providers would have been able to see the blood collecting in the drape, which may have influenced their actions and attenuated the observed effect of the intervention.

**Multicomponent Clinical Intervention**

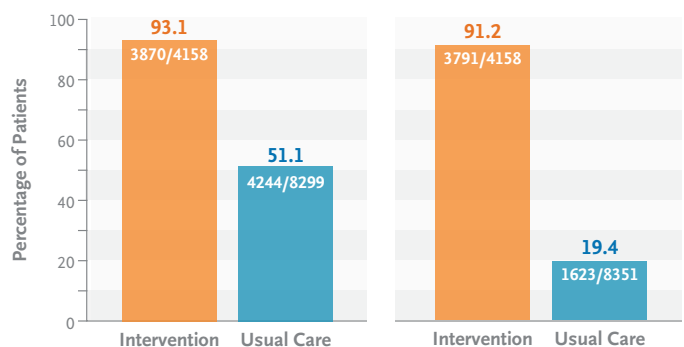
Supported by training, local champions, and audits

**Composite of Severe Postpartum Hemorrhage, Laparotomy for Bleeding, or Maternal Death from Bleeding**Risk ratio, 0.40 (95% CI, 0.32 to 0.50);  $P < 0.001$ **Detection of Postpartum Hemorrhage**

Rate ratio, 1.58 (95% CI, 1.41 to 1.76)

**Adherence to Treatment Bundle**

Rate ratio, 4.94 (95% CI, 3.88 to 6.28)

**CONCLUSIONS**

Among patients having vaginal delivery in Africa, use of a multicomponent clinical intervention led to a lower risk of severe postpartum hemorrhage, laparotomy for bleeding, or maternal death from bleeding than usual care.

## EDITORIAL



## Early Detection and Bundled Treatment for Postpartum Hemorrhage

Adeline A. Boatin, M.D., M.P.H., and Joseph Ngonzi, M.D., M.Med., Ph.D.

Postpartum hemorrhage is the leading cause of maternal death in developing regions, accounting for 20% of maternal deaths, most of which are preventable.<sup>1</sup> This opportunity for prevention is evident by the decrease over time in the contribution of postpartum hemorrhage to maternal death in developed regions, where it accounts for 8% of maternal deaths.<sup>1</sup>

Bleeding after childbirth is normal and part of the physiologic transition that occurs in the postdelivery period. However, the transition to abnormal bleeding can be swift. Postpartum hemorrhage, which is traditionally defined as blood loss of more than 500 ml, can develop within minutes and can escalate rapidly, with severe sequelae, including disseminated intravascular coagulation, multiorgan dysfunction, and death.<sup>2</sup>

Active management of the third stage of labor (including the administration of oxytocin, uterine massage, and, with signs of placental separation, umbilical-cord traction) has been a cornerstone in the prevention of postpartum hemorrhage for several decades.<sup>2,3</sup> Although uterine massage and umbilical-cord traction are no longer considered to be essential in the most recent World Health Organization (WHO) recommendations<sup>2</sup> for the prevention and treatment of postpartum hemorrhage, guidelines continue to recommend oxytocin, a heat-sensitive uterotonic agent, as the most effective tool for prevention and treatment.<sup>2,3</sup> In 2019, carbetocin, a heat-stable oxytocin analogue, and tranexamic acid, an antifibrinolytic agent, were both added to the core list of medicines for reproductive health in the 21st edition of the *WHO Model List of Essential Medicines*.<sup>4</sup> Carbetocin was shown to be noninferior to oxytocin for the

prevention of blood loss of at least 500 ml or the use of additional uterotonic agents in women undergoing vaginal delivery.<sup>5</sup> Recommendations call for the use of carbetocin if oxytocin is not available, if a cold chain to maintain the stability of oxytocin is hard to achieve, or if the cost of carbetocin in that area is similar to that of other uterotonic agents.<sup>6</sup> In another large trial, tranexamic acid reduced the risk of death due to bleeding among women with postpartum hemorrhage and is recommended as an addition (within 3 hours after birth) to standard treatments for postpartum hemorrhage.<sup>7,8</sup> However, despite this growing list of tools with documented benefit, a lack of consistent implementation in resource-poor settings translates to many preventable deaths from postpartum hemorrhage.<sup>9</sup>

In this issue of *the Journal*, Gallos et al.<sup>10</sup> report findings from the E-MOTIVE trial, an international, cluster-randomized trial of early detection and treatment of postpartum hemorrhage after vaginal delivery. The trial targeted two challenges: a delay in the recognition and diagnosis of postpartum hemorrhage and a delayed and inconsistent use of interventions for management of postpartum hemorrhage. The intervention included early detection, with the use of a calibrated drape, combined with a treatment bundle that was applied in parallel, rather than sequentially, and that included uterine massage, oxytocin, tranexamic acid, intravenous fluids, and examination and escalation as needed. The intervention was supported by several implementation strategies: training (simulation-based and peer-assisted), provision of a trolley or carry case containing all medicines and devices, local cham-



pions (midwives and doctors), and monthly auditing and feedback to provide data on rates of detection, bundle use, and rates of outcome measures. The primary outcome was a composite of severe postpartum hemorrhage (blood loss,  $\geq 1000$  ml), postpartum laparotomy for bleeding, or maternal death from bleeding.

Across four countries (Kenya, Nigeria, South Africa, and Tanzania), 80 hospitals were randomly assigned to the intervention or usual standard care; data from 78 hospitals were available, and outcomes in 206,455 patients were analyzed. A primary-outcome event occurred in 1.6% of the patients in the intervention group and in 4.3% of those in the usual-care group (risk ratio, 0.40; 95% confidence interval, 0.32 to 0.50;  $P < 0.001$ ), a result that was driven mostly by a lower risk of severe postpartum hemorrhage in the intervention group. Results for the key secondary implementation outcomes correspondingly favored the intervention group; postpartum hemorrhage was detected in 93.1% of the patients in the intervention group and in 51.1% of those in the usual-care group, and adherence to the treatment bundle was documented in 91.2% and 19.4%, respectively.

The E-MOTIVE trial sought to target postpartum hemorrhage by improving detection and implementing bundled, rather than sequential, treatment. The scalability of the trial intervention is supported by the use of components that can be administered by a midwife and are accessible in facilities with fewer resources and by the local procurement of oxytocin and tranexamic acid. However, important questions remain regarding the ability to scale up this intervention, given the current variability in implementation of many of its components despite availability and recommendations for their use.<sup>2,3,9</sup> This trial was supported by a robust implementation strategy, which included training, champions, auditing, and feedback. More work will be needed to understand the contribution of these components to the success of this approach and the cost and infrastructure needed to sustain them and to identify and disseminate an effective framework for broad implementation.

In summary, the E-MOTIVE trial showed that the early detection and a bundled treatment for postpartum hemorrhage with the use of readily available and recommended medicines and intervention strategies substantially reduced the risk of severe outcomes from postpartum hemorrhage. The next challenge will be to achieve widespread adoption and implementation at scale in resource-limited environments.

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

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# The NEW ENGLAND JOURNAL of MEDICINE

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## Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

A. Anand, S.J. Mathew, G. Sanacora, J.W. Murrough, F.S. Goes, M. Altinay, A.S. Aloysi, A.A. Asghar-Ali, B.S. Barnett, L.C. Chang, K.A. Collins, S. Costi, S. Iqbal, M.K. Jha, K. Krishnan, D.A. Malone, S. Nikayin, S.E. Nissen, R.B. Ostroff, I.M. Reti, S.T. Wilkinson, K. Wolski, and B. Hu

### ABSTRACT

#### BACKGROUND

Electroconvulsive therapy (ECT) and subanesthetic intravenous ketamine are both currently used for treatment-resistant major depression, but the comparative effectiveness of the two treatments remains uncertain.

#### METHODS

We conducted an open-label, randomized, noninferiority trial involving patients referred to ECT clinics for treatment-resistant major depression. Patients with treatment-resistant major depression without psychosis were recruited and assigned in a 1:1 ratio to receive ketamine or ECT. During an initial 3-week treatment phase, patients received either ECT three times per week or ketamine (0.5 mg per kilogram of body weight over 40 minutes) twice per week. The primary outcome was a response to treatment (i.e., a decrease of  $\geq 50\%$  from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report; scores range from 0 to 27, with higher scores indicating greater depression). The noninferiority margin was  $-10$  percentage points. Secondary outcomes included scores on memory tests and patient-reported quality of life. After the initial treatment phase, the patients who had a response were followed over a 6-month period.

#### RESULTS

A total of 403 patients underwent randomization at five clinical sites; 200 patients were assigned to the ketamine group and 203 to the ECT group. After 38 patients had withdrawn before initiation of the assigned treatment, ketamine was administered to 195 patients and ECT to 170 patients. A total of 55.4% of the patients in the ketamine group and 41.2% of those in the ECT group had a response (difference, 14.2 percentage points; 95% confidence interval, 3.9 to 24.2;  $P < 0.001$  for the noninferiority of ketamine to ECT). ECT appeared to be associated with a decrease in memory recall after 3 weeks of treatment (mean [ $\pm$ SE] decrease in the T-score for delayed recall on the Hopkins Verbal Learning Test–Revised,  $-0.9 \pm 1.1$  in the ketamine group vs.  $-9.7 \pm 1.2$  in the ECT group; scores range from  $-300$  to  $200$ , with higher scores indicating better function) with gradual recovery during follow-up. Improvement in patient-reported quality-of-life was similar in the two trial groups. ECT was associated with musculoskeletal adverse effects, whereas ketamine was associated with dissociation.

#### CONCLUSIONS

Ketamine was noninferior to ECT as therapy for treatment-resistant major depression without psychosis. (Funded by the Patient-Centered Outcomes Research Institute; ELEKT-D ClinicalTrials.gov number, NCT03113968.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Anand can be contacted at [aanand7@bwh.harvard.edu](mailto:aanand7@bwh.harvard.edu) or at the Mass General Brigham, Department of Psychiatry, Building for Transformative Medicine, 60 Fenwood Rd., Boston, MA 02115.

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RESEARCH SUMMARY

# Ketamine versus ECT for Nonpsychotic Treatment-Resistant Major Depression

Anand A et al. DOI: 10.1056/NEJMoa2302399

**CLINICAL PROBLEM**

In more than a third of patients with major depression, treatment with antidepressant drugs fails to control symptoms. Electroconvulsive therapy (ECT) and subanesthetic intravenous ketamine are both used for treatment-resistant major depression, but the comparative effectiveness of the two treatments remains uncertain.

**CLINICAL TRIAL**

**Design:** A prospective, multicenter, open-label, randomized, noninferiority trial compared subanesthetic intravenous ketamine with ECT in adults 21 to 75 years of age with treatment-resistant major depression without psychosis who reported an unsatisfactory response to  $\geq 2$  adequate trials of antidepressant treatment in their lifetime.

**Intervention:** 403 patients were assigned to receive 3 weeks of treatment with either ketamine (0.5 mg per kilogram of body weight over a 40-minute period twice per week) or ECT (three times per week). The primary outcome was a response to treatment, defined as a decrease from baseline of  $\geq 50\%$  in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16; range, 0 to 27; higher scores indicate greater depression). Secondary outcomes included quality of life, assessed on a 16-item scale (range, 16 to 112; higher scores indicate better quality of life).

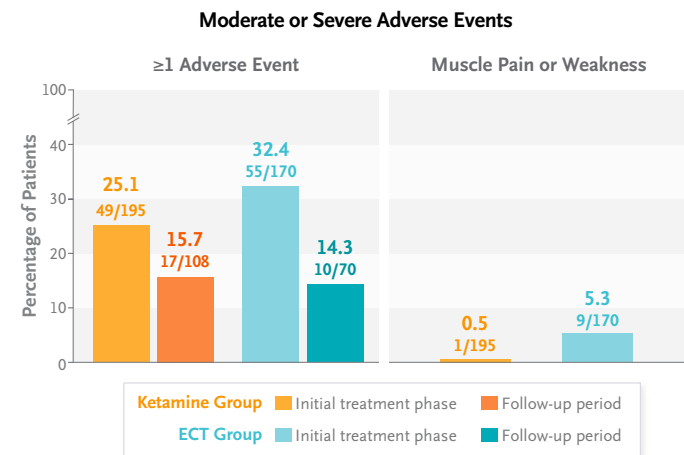
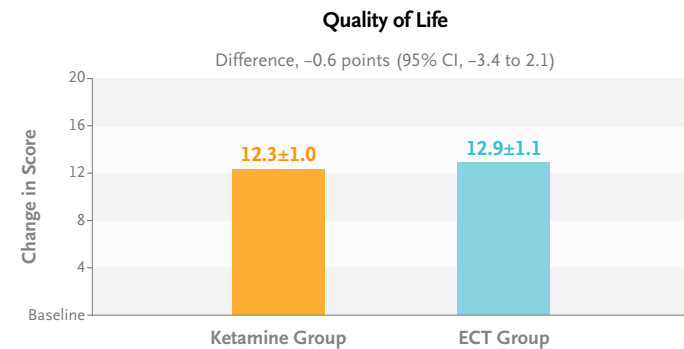
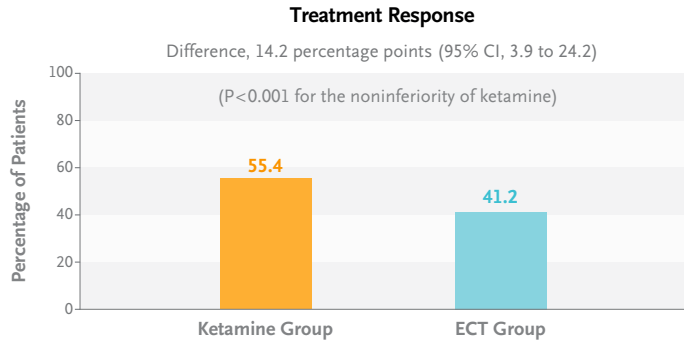
**RESULTS**

**Efficacy:** During the initial 3-week treatment phase, which was completed by 365 patients, ketamine was shown to be noninferior to ECT with respect to treatment response.

**Safety:** The incidence of moderate or severe adverse events, including musculoskeletal adverse events, was higher in the ECT group than in the ketamine group. New suicidal ideation was reported in 6 patients during the initial treatment phase (4 in the ketamine group and 2 in the ECT group) and in 5 patients during the follow-up period (4 and 1, respectively); 1 patient in the ketamine group had a suicide attempt.

**LIMITATIONS AND REMAINING QUESTIONS**

- More patients withdrew from the ECT group than from the ketamine group before treatment.
- ECT was initially administered as right unilateral treatment and was changed to bilateral treatment only if the response was inadequate.
- Whether more sessions of ECT would have led to additional patients having a response is not known.



**CONCLUSIONS**

Among adults with treatment-resistant major depression without psychosis, subanesthetic intravenous ketamine was noninferior to ECT.

## EDITORIAL



## Ketamine and ECT in Depression — Risks and Rewards

Robert Freedman, M.D.

Investigators from five referral clinics for electroconvulsive therapy (ECT) report in the *Journal* the results of an open-label, randomized, non-inferiority trial of ECT or ketamine infusion in patients with moderately severe depression.<sup>1</sup> After randomization, 365 patients (170 in the ECT group and 195 in the ketamine group) were included in the primary analysis. At the conclusion of the 3-week, randomized, active-treatment phase, 41% of the patients in the ECT group and 55% of those in the ketamine group reported a 50% or greater reduction in symptoms, findings that are consistent with moderate-to-excellent responses to treatment.<sup>2</sup> Patients who had a response were followed for an additional 6 months. By the end of the 6-month follow-up period, relapse had occurred in 56% of the patients in the ECT group and in 34% of those in the ketamine group. The incidence of expected adverse effects of memory loss from ECT and dissociative symptoms from ketamine had decreased by the 6-month mark, and patient-reported quality of life was similar in the two treatment groups. The investigators concluded that ketamine was noninferior to ECT in the treatment of moderately severe depression in this trial.

When thinking about this trial, one should note that these patients represent a severely affected, chronically ill group of men and women with depression in midlife. All had had multiple episodes of depression with onset in adolescence or early adulthood. Most had family histories of depression, and many had made suicide attempts. Most patients had coexisting severe anxiety or post-traumatic stress disorder, and some had

coexisting alcohol use disorder. All the patients had been treated with a wide range of psychotropic medicines. Some had received previous treatment with either ECT or ketamine. Patients with psychotic symptoms were excluded because ketamine can induce psychotic symptoms. Menopause, cerebrovascular illness, loss of parental and occupational roles, and other concomitant issues of midlife may have contributed to their depression.

Proponents of ECT will note that, as pointed out by the authors of the trial, unilateral delivery of electricity to the nondominant hemisphere, in an effort to minimize memory loss, resulted in inadequate induced-seizure duration in many patients. These patients were switched to bilateral treatment (electrode placement on both sides of the head), but the duration of seizures during the first 3 weeks of the trial may not have been sufficient and may have led to the slightly lower response in the ECT group. It is noteworthy that all the patients who were considered for trial entry were initially referred for ECT because they and their clinicians thought that ECT was their best option.

The positive response to ketamine is not without precedent.<sup>2</sup> Ketamine has mixed pharmacologic properties as an anesthetic, an opiate, and a sympathomimetic. The agent thus combines properties that many persons — not only those with severe depression — find rewarding. Accordingly, ketamine is also widely used recreationally.<sup>3</sup> The question raised by this trial and others is how clinicians and regulatory agencies should regard its use and abuse.<sup>4</sup> For someone

who is chronically ill with depression, 3 weeks of lightened mood is undoubtedly a gift. Many patients have reported ketamine therapy to be life-changing,<sup>5</sup> and many clinicians are enthusiastic about bringing this gift to patients who otherwise seem unreachable. However, the results of this current trial suggest that the 3-week treatment was not life-changing. Ketamine treatment was effective, but by 6 months, a brief period in a lifetime of depression, the quality of life was no better with the agent than with ECT.

Patients who have received oxycodone or other opiates from physicians for pain have reported initial highly positive responses similar to those reported by patients who received ketamine in the current trial, but prescription use was associated with a subsequent epidemic of addiction to both oxycodone and heroin.<sup>6,7</sup> The follow-up period of the current trial was not long, nor did it assess future drug-seeking behavior among those who did or did not have a response to ketamine. The experience with oxycodone is that a highly pleasurable release from pain, including the pain of depression, can indelibly change behavior. Prescription drug-monitoring programs include ketamine as a Schedule III narcotic medication, but there are no barriers to stop a patient who has received ketamine in a referral clinic for severe depression from going to another provider who uses less stringent criteria to provide treatment.<sup>8</sup> We need to remember that only a minority of physicians were responsible for the oxycodone epidemic.

Patients in an ECT-referral clinic may seem to be an unlikely nidus for a wave of drug addiction, but even in this trial, treatment with ketamine was continued during the 6-month follow-up period in 41% of the participants who had been assigned to receive ketamine in the initial

3-week treatment phase. A longer duration of treatment increases the likelihood of both drug dependence and cognitive adverse effects, including dissociation, paranoia, and other psychotic symptoms.<sup>9</sup> ECT clinics have informed consent documents that list the various cognitive and other adverse effects of that treatment. A similar informed consent document for ketamine should caution patients and clinicians that temporary relief may come with longer-term costs.

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

From the Departments of Psychiatry and Pharmacology, University of Colorado Denver School of Medicine, Aurora.

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# The NEW ENGLAND JOURNAL of MEDICINE

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## Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group\*

### ABSTRACT

#### BACKGROUND

Whether vaccination during pregnancy could reduce the burden of respiratory syncytial virus (RSV)-associated lower respiratory tract illness in newborns and infants is uncertain.

#### METHODS

In this phase 3, double-blind trial conducted in 18 countries, we randomly assigned, in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive a single intramuscular injection of 120  $\mu$ g of a bivalent RSV prefusion F protein-based (RSVpreF) vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. A lower boundary of the confidence interval for vaccine efficacy (99.5% confidence interval [CI] at 90 days; 97.58% CI at later intervals) greater than 20% was considered to meet the success criterion for vaccine efficacy with respect to the primary end points.

#### RESULTS

At this prespecified interim analysis, the success criterion for vaccine efficacy was met with respect to one primary end point. Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants, respectively, were evaluated. Medically attended severe lower respiratory tract illness occurred within 90 days after birth in 6 infants of women in the vaccine group and 33 infants of women in the placebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); these results did not meet the statistical success criterion. No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the vaccine group (13.8% of women and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).

#### CONCLUSIONS

RSVpreF vaccine administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified. (Funded by Pfizer; MATISSE ClinicalTrials.gov number, NCT04424316.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Munjal can be contacted at [iona.munjal@pfizer.com](mailto:iona.munjal@pfizer.com) or at Vaccine Research and Development, Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965.

\*The members of the MATISSE Study Group are listed in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

Drs. Kampmann, Madhi, and Munjal contributed equally to this article.

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RESEARCH SUMMARY

# Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

Kampmann B et al. DOI: 10.1056/NEJMoa2216480

**CLINICAL PROBLEM**

In infants, respiratory syncytial virus (RSV) is a common cause of acute lower respiratory tract illness and a leading cause of death, particularly in low- and middle-income countries. A phase 2b trial showed that maternal vaccination with a bivalent RSV prefusion F protein-based (RSVpreF) vaccine has promise in protecting infants against RSV-associated illness.

**CLINICAL TRIAL**

**Design:** An international, phase 3, randomized, placebo-controlled trial examined the efficacy and safety of vaccinating women with an uncomplicated singleton pregnancy at 24 through 36 weeks' gestation to prevent RSV-associated illness in infants.

**Intervention:** 7392 women were randomly assigned to receive one 120- $\mu$ g dose of RSVpreF vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth.

**RESULTS**

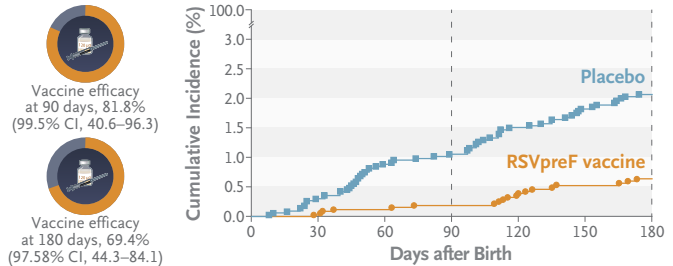
**Efficacy:** At this prespecified interim analysis, the RSVpreF vaccine was effective against medically attended severe RSV-associated lower respiratory tract illness within 90 days after birth, and protection was maintained through 180 days. The statistical success criterion for vaccine efficacy was not met for medically attended RSV-associated lower respiratory tract illness (the second primary end point).

**Safety:** No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the two groups.

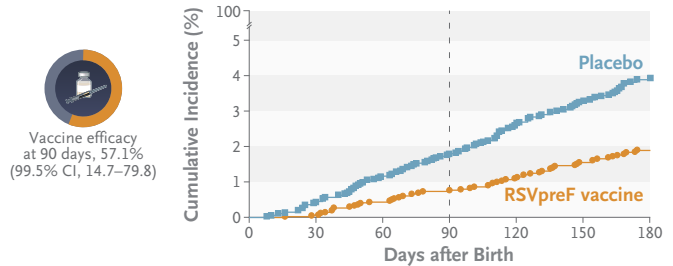
**LIMITATIONS AND REMAINING QUESTIONS**

- Women with high-risk pregnancies were excluded from the trial, which limits generalizability of the results, since the offspring in such cases could be at higher risk for severe illness.
- Given the small sample size, safety data were limited.
- Limited data were available from low-income countries, where the vaccine could have the greatest effect.

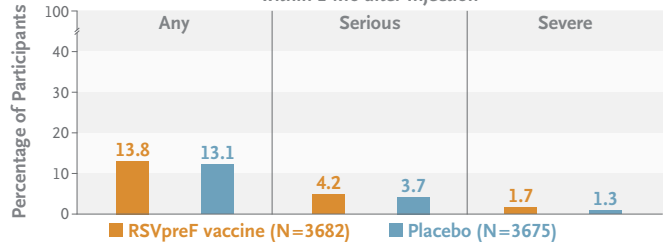
**Severe RSV-Associated Lower Respiratory Tract Illness**



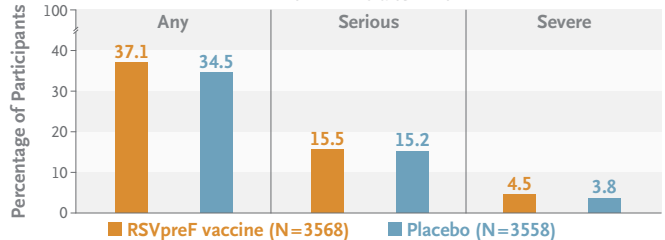
**RSV-Associated Lower Respiratory Tract Illness**



**≥1 Adverse Event in Maternal Participants within 1 Mo after Injection**



**≥1 Adverse Event in Infant Participants within 1 Mo after Birth**



**CONCLUSIONS**

When administered to women late in pregnancy, RSVpreF vaccine was effective against medically attended severe RSV-associated lower respiratory tract illness in infants.



## EDITORIAL



## RSV Illness in the Young and the Old — The Beginning of the End?

Ruth A. Karron, M.D.

Respiratory syncytial virus (RSV) infection was reported 66 years ago among young children with lower respiratory tract illness who were hospitalized in Baltimore.<sup>1</sup> RSV infection has since emerged as the most frequent cause of hospitalization among infants in the United States and as the leading cause of pneumonia in young children worldwide. Among children younger than 5 years of age, RSV is associated with approximately 33 million cases of lower respiratory tract illness, 3.6 million hospital admissions, and more than 100,000 deaths each year.<sup>2</sup> Infants younger than 6 months of age are at greatest risk for RSV-associated illness and death, and more than 95% of RSV-associated deaths occur in low- and middle-income countries.<sup>2</sup> RSV infection also causes severe lower respiratory tract illness in older adults, particularly in those who are frail or have underlying cardiopulmonary disease. Approximately 60,000 to 160,000 RSV-associated hospitalizations and 6000 to 10,000 RSV-associated deaths occur each year in older adults in the United States.

A substantial research-and-development pipeline of prophylactic products against RSV (<https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/>) includes vaccines and long-acting “vaccine-like” monoclonal antibodies that build on the success of palivizumab for prevention of severe RSV illness in the highest-risk infants. The overarching strategy has been to provide passive immunity to the youngest infants, either through maternal immunization or through direct administration of long-acting monoclonal antibodies, and to provide active immunity to

older infants, children, and older adults through vaccination. These efforts have been made with care to avoid the tragic enhanced RSV illness that occurred in the 1960s in children who had not previously been infected with RSV and who received a formalin-inactivated RSV vaccine.<sup>3</sup> The development of many of these products that either directly provide or induce potent RSV neutralizing antibodies was made possible through elucidation of the structure of the RSV fusion (F) glycoprotein in its highly immunogenic prefusion and less immunogenic postfusion conformations.<sup>4</sup>

Walsh et al.<sup>5</sup> and Kampmann et al.<sup>6</sup> now report in the *Journal* the results of phase 3 trials of a vaccine containing RSV F in the prefusion conformation. RSVpreF, a bivalent vaccine containing RSV F from subtype A and B viruses, was evaluated in older adults in the RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease (RENOIR) trial and in infants of women who received it in the Maternal Immunization Study for Safety and Efficacy (MATISSE) trial. The RENOIR trial enrolled 35,971 adults 60 years of age or older in seven countries, and the MATISSE trial enrolled 7392 pregnant women in 18 countries. Both trials were conducted during the coronavirus disease 2019 (Covid-19) pandemic. The trial sponsor, investigators, and participants persevered not only in the face of pandemic-associated logistic hurdles but also through RSV seasons that were tremendously altered, such that accrual of RSV cases was substantially impeded. Data from pre-specified interim analyses were reported for

each trial, with additional reports anticipated at the end of the trial (after two RSV seasons in the RENOIR trial and when infant participants reach 12 or 24 months of age in the MATISSE trial).

The interim analysis of the RENOIR trial was conducted after 44 cases of RSV lower respiratory tract illness had accrued, before all the participants completed the first RSV season. Both primary end points were met, with 66.7% vaccine efficacy against RSV-associated lower respiratory tract illness with two or more signs or symptoms and 85.7% vaccine efficacy against RSV-associated lower respiratory tract illness with three or more signs or symptoms. Perhaps owing to the predominance of adults at the younger end of the age spectrum in the RENOIR trial (62.5% of the participants were 60 to 69 years of age), an insufficient number of cases of severe RSV-associated lower respiratory tract illness (hospitalization and illness warranting the use of oxygenation or mechanical ventilation) had accrued for evaluation. RSVpreF vaccine generally had acceptable safety and side-effect profiles, but one case of the Guillain-Barré syndrome and one case of the Miller-Fisher syndrome were reported at 7 and 8 days after vaccination, respectively.

The interim analysis of the MATISSE trial was conducted when 79% of the infants had completed 180 days of follow-up; 80 evaluable cases of medically attended RSV-associated lower respiratory tract illness had occurred within 90 days after birth and 174 cases had occurred within 180 days after birth. Although results with respect to a primary efficacy end point of medically attended RSV-associated lower respiratory tract illness within 90 days after birth did not meet the prespecified statistical success criterion, vaccine efficacy was 51.3% against this outcome within 180 days after birth. It is notable that the efficacy against severe RSV-associated lower respiratory tract illness was 81.8% within 90 days after birth (the coprimary end point) and 69.4% within 180 days after birth. RSVpreF vaccine did not prevent medically attended lower respiratory tract illness of any cause, perhaps because only 22% of the cases of medically attended lower respiratory tract illness were associated with RSV infection, an atypically low proportion that was probably related to the pandemic.

Along with the results of recent trials of other RSV prefusion F vaccines in older adults<sup>7,8</sup> and of nirsevimab (a monoclonal antibody to the RSV fusion protein) in infants,<sup>9</sup> the results of the RENOIR and MATISSE trials move us closer to prevention of RSV illness in the old and young. However, critical scientific questions about the RSVpreF vaccine and cross-cutting programmatic questions remain. In older populations, the greatest benefit of RSVpreF vaccine will be prevention of RSV-associated hospitalization and death, but the interim analysis of the RENOIR trial was not powered to address these outcomes. Data regarding protection through a second RSV season and concomitant administration of other vaccines, especially those for influenza and Covid-19, are also needed, as are postmarketing evaluations to assess whether the incidence of serious neurologic outcomes (observed in two recipients of the vaccine) is above the background incidence of these conditions.

In high-income countries, complex policy decisions about whether to offer maternal immunization with RSV preF vaccine or a long-acting RSV monoclonal antibody in infants will be required. In the United States, substantial efforts would be needed to increase the percentage of pregnant women who receive the RSVpreF vaccine above the 57 to 61% reported for influenza and tetanus-diphtheria-acellular pertussis vaccines.<sup>10</sup> If both the RSVpreF vaccine for pregnant women and RSV monoclonal antibodies for infants are available, enhanced communication between obstetrical and pediatric care providers will be necessary to ensure appropriate use of each product. Doubly protecting healthy term infants with the use of RSVpreF vaccine antenatally and an RSV monoclonal antibody postnatally while leaving many of the infants in the world unimmunized would waste valuable products and exacerbate worldwide inequities in child health.

For young infants in low- and middle-income countries, who are at the greatest risk for severe RSV-associated illness and death, additional information about the use of RSVpreF vaccine in low-resource settings, including the effect of the vaccine on lower respiratory tract illness of any cause, will help to ensure funding and guide decision making. Finally, protection of older infants and children is needed, and this can be

most safely accomplished by the development of other vaccines that induce humoral and cellular immune responses in populations that have not been previously infected with RSV.<sup>3</sup>

These two articles and previous articles<sup>7-9</sup> describe landmark accomplishments in the fight against RSV illness. This progress is remarkable, but substantial additional work to guide decision making and implementation is essential. We are only at the beginning of the end.

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

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## Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

O. Egbuna, B. Zimmerman, G. Manos, A. Fortier, M.C. Chirieac, L.A. Dakin, D.J. Friedman, K. Bramham, K. Campbell, B. Knebelmann, L. Barisoni, R.J. Falk, D.S. Gipson, M.S. Lipkowitz, A. Ojo, M.E. Bunnage, M.R. Pollak, D. Altshuler, and G.M. Chertow, for the VX19-147-101 Study Group\*

### ABSTRACT

#### BACKGROUND

Persons with toxic gain-of-function variants in the gene encoding apolipoprotein L1 (*APOL1*) are at greater risk for the development of rapidly progressive, proteinuric nephropathy. Despite the known genetic cause, therapies targeting proteinuric kidney disease in persons with two *APOL1* variants (G1 or G2) are lacking.

#### METHODS

We used tetracycline-inducible *APOL1* human embryonic kidney (HEK293) cells to assess the ability of a small-molecule compound, inaxaplin, to inhibit *APOL1* channel function. An *APOL1* G2-homologous transgenic mouse model of proteinuric kidney disease was used to assess inaxaplin treatment for proteinuria. We then conducted a single-group, open-label, phase 2a clinical study in which inaxaplin was administered to participants who had two *APOL1* variants, biopsy-proven focal segmental glomerulosclerosis, and proteinuria (urinary protein-to-creatinine ratio of  $\geq 0.7$  to  $< 10$  [with protein and creatinine both measured in grams] and an estimated glomerular filtration rate of  $\geq 27$  ml per minute per  $1.73 \text{ m}^2$  of body-surface area). Participants received inaxaplin daily for 13 weeks (15 mg for 2 weeks and 45 mg for 11 weeks) along with standard care. The primary outcome was the percent change from the baseline urinary protein-to-creatinine ratio at week 13 in participants who had at least 80% adherence to inaxaplin therapy. Safety was also assessed.

#### RESULTS

In preclinical studies, inaxaplin selectively inhibited *APOL1* channel function in vitro and reduced proteinuria in the mouse model. Sixteen participants were enrolled in the phase 2a study. Among the 13 participants who were treated with inaxaplin and met the adherence threshold, the mean change from the baseline urinary protein-to-creatinine ratio at week 13 was  $-47.6\%$  (95% confidence interval,  $-60.0$  to  $-31.3$ ). In an analysis that included all the participants regardless of adherence to inaxaplin therapy, reductions similar to those in the primary analysis were observed in all but 1 participant. Adverse events were mild or moderate in severity; none led to study discontinuation.

#### CONCLUSIONS

Targeted inhibition of *APOL1* channel function with inaxaplin reduced proteinuria in participants with two *APOL1* variants and focal segmental glomerulosclerosis. (Funded by Vertex Pharmaceuticals; VX19-147-101 ClinicalTrials.gov number, NCT04340362.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Egbuna can be contacted at [ogo\\_egbuna@vrtx.com](mailto:ogo_egbuna@vrtx.com) or at Vertex Pharmaceuticals, 50 Northern Ave., Boston, MA 02210.

\*A list of the investigators in the VX19-147-101 Study Group is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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RESEARCH SUMMARY

# Inaxaplin for Proteinuric Kidney Disease in Persons with Two APOL1 Variants

Egbuna O et al. DOI: 10.1056/NEJMoa2202396

**CLINICAL PROBLEM**

Persons with toxic gain-of-function APOL1 variants are at increased risk for proteinuric chronic kidney disease (CKD), including focal segmental glomerulosclerosis (FSGS), a severe and rapidly progressing form of CKD. Treatments for proteinuric CKD associated with APOL1 variants are lacking.

**CLINICAL STUDY**

**Design:** A phase 2a, international, single-group, open-label study assessed the efficacy and safety of inaxaplin — a selective, oral, small-molecule inhibitor of APOL1 channel function — in participants with two high-risk APOL1 variants and biopsy-proven FSGS.

**Intervention:** 16 adults with two APOL1 variants, FSGS, and nephrotic- or subnephrotic-range proteinuria received inaxaplin for 13 weeks (15 mg once daily for 2 weeks, then 45 mg once daily thereafter). The primary efficacy outcome was the percent change from the baseline urinary protein-to-creatinine ratio at week 13.

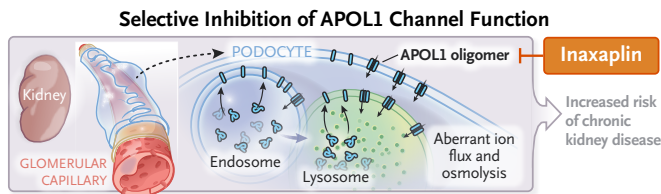
**RESULTS**

**Efficacy:** 13 evaluable participants had a mean reduction in the urinary protein-to-creatinine ratio of nearly 50%. A decrease was seen within 2 weeks and continued through week 13.

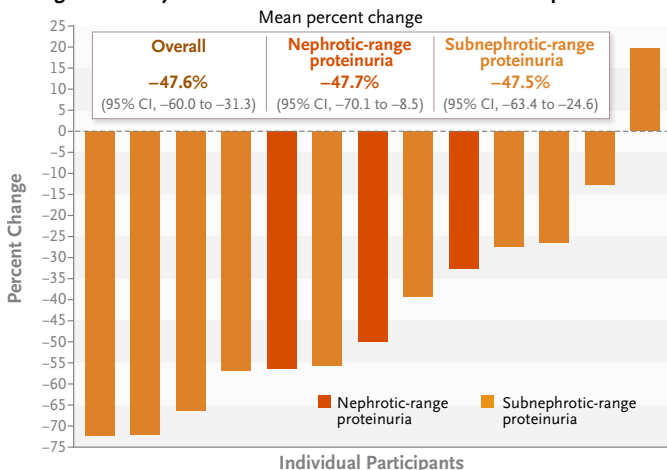
**Safety:** Nearly all inaxaplin recipients had adverse events, all of which were mild or moderate. No adverse events led to treatment discontinuation.

**LIMITATIONS AND REMAINING QUESTIONS**

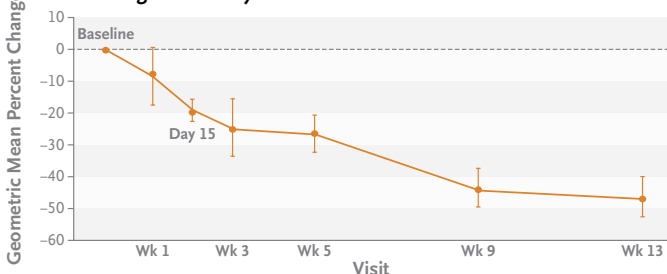
- The study was small and of short duration and did not include a placebo group.
- One participant with subnephrotic-range proteinuria did not have a decrease in proteinuria with inaxaplin therapy; the mechanism underlying this lack of response is unknown.
- Whether longer treatment with inaxaplin could prevent or slow progression to end-stage kidney disease is uncertain; its potential adverse effects are also unknown.



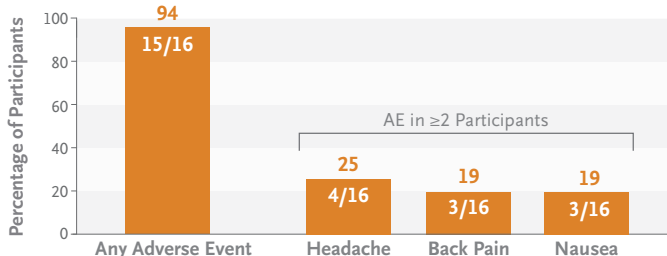
Change in Urinary Protein-to-Creatinine Ratio in Each Participant at Wk 13



Change in Urinary Protein-to-Creatinine Ratio over Time



Adverse Events



**CONCLUSIONS**

In persons with focal segmental glomerulosclerosis and two high-risk APOL1 variants, the APOL1 function inhibitor inaxaplin was associated with reductions in proteinuria over a 13-week treatment period.

## EDITORIAL

## SCIENCE BEHIND THE STUDY

## Inhibiting APOL1 to Treat Kidney Disease

Winfred W. Williams, M.D., and Julie R. Ingelfinger, M.D.

In this issue of the *Journal*, Egbuna and colleagues<sup>1</sup> report the results of a short-term phase 2a study of a small-molecule drug called inaxaplin in patients with focal segmental glomerulosclerosis (FSGS) who have two risk alleles of the gene encoding apolipoprotein L1 (APOL1). The investigators found that inaxaplin significantly reduced proteinuria. An accompanying editorial by Powe<sup>2</sup> comments on the findings of the study and why this therapeutic agent may be a key, new tool in the management of the disproportionate burden of chronic kidney disease in persons of African ancestry.

**WHAT IS FSGS?**

FSGS describes a histologic pattern of glomerular injury. The glomeruli (roughly a million in each kidney) are vascular structures through which blood is continuously filtered. The filter consists of three major components: a barrier of endothelial cells that line the glomerular capillaries, a trilaminar basement membrane, and a layer of podocytes — specialized epithelial cells characterized by many projections (so-called foot processes), which look like octopus tentacles on electron micrographs. These processes wrap around and interdigitate on the outer surface of the glomerular capillaries, forming unique cell junctions, known as slit diaphragms, that delineate the interdigitations (Fig. 1). Under normal circumstances, the physical and chemical properties of these gaps, in addition to the integrity of the three major components of the filtering mechanism, prevent molecules larger than 5 nm from passing into the proximal tubule of the nephron. Small molecules, such as water, glucose, and electrolytes, pass through and form glomerular ultrafiltrate in the early proximal tubule, which is further processed by each portion of the nephron to produce the final urine.

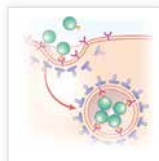
## Key Concepts

**Small-molecule drug**

A chemical compound with a low molecular weight (typically 0.1 to 0.6 kD). Small-molecule drugs are smaller than biologic drugs, such as monoclonal antibodies (typically 150 kD) and oligonucleotides (typically 4 to 10 kD). Because of their small size, they can penetrate the cell membrane and bind intracellular targets. They are generally more stable than biologic drugs and can be administered orally.

**Trypanosoma brucei**

A protozoan parasite transmitted by the blood-feeding flies of the genus *Glossina* (the tsetse fly), a vector that is widespread in sub-Saharan Africa. This parasite causes African trypanosomiasis (sleeping sickness), which is characterized by severe swelling of the lymph nodes, poor sleep, and neurologic, cognitive, and psychiatric symptoms. In the absence of treatment, trypanosomiasis is fatal.

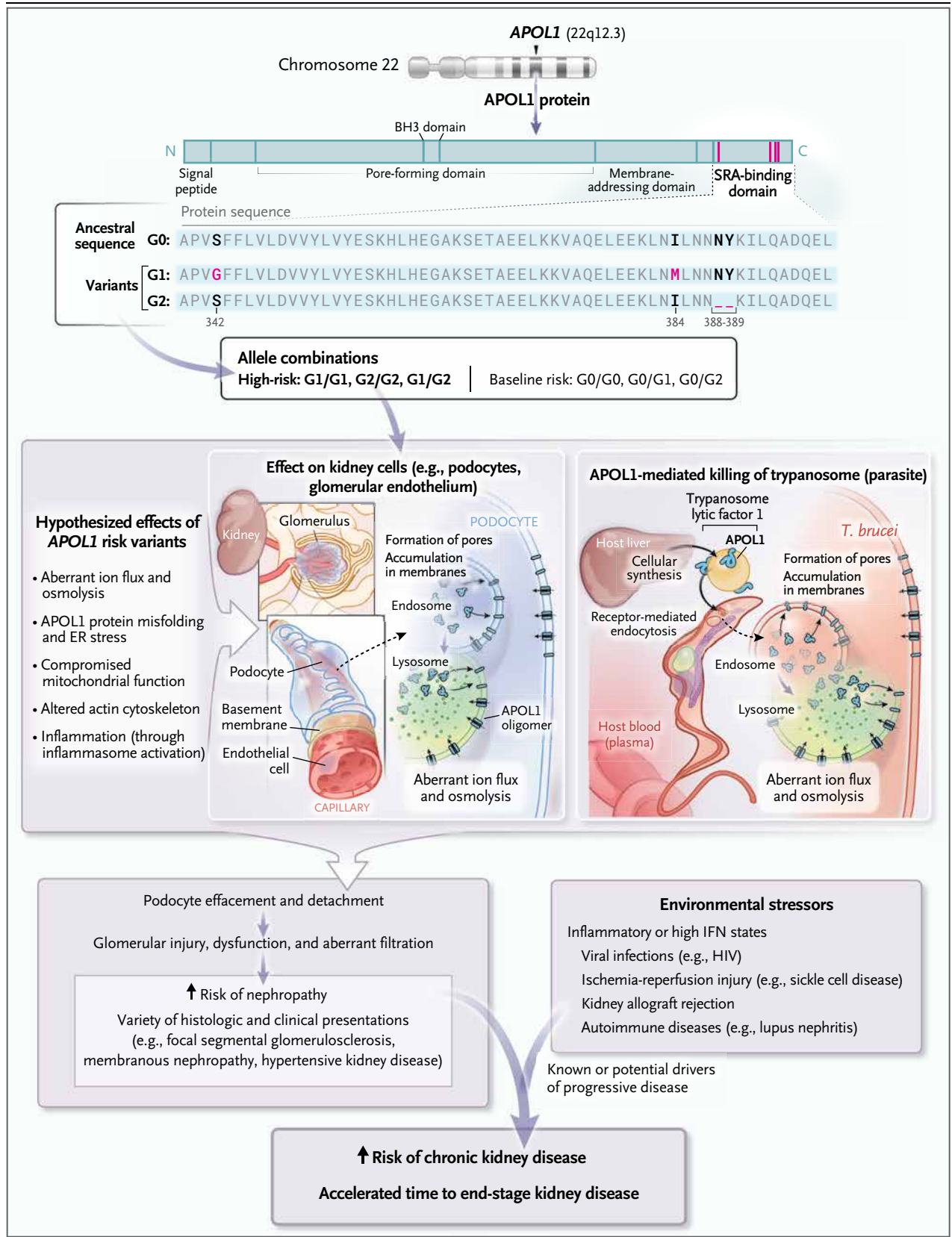
**Endocytosis**

A process by which cells actively internalize extracellular substances by invagination of the cellular membrane and subsequent formation of vesicles. Types of endocytosis are phagocytosis (e.g., microorganisms), pinocytosis (e.g., fluid), and receptor-mediated endocytosis (e.g., binding of extracellular molecules to specific receptors).

 An expanded illustrated glossary is available at [NEJM.org](https://www.nejm.org)

In FSGS, podocyte injury leads to effacement of the foot processes from the surface of the capillaries and impaired glomerular filtration in which larger molecules, such as proteins, pass into the urine. When proteinuria exceeds approximately 3 g per day (nephrotic-range proteinuria), nephrotic syndrome — which is marked by hypoproteinemia and edema, changes in immune function (loss of immunoglobulins), hypercoagulability (loss of





**Figure 1 (facing page). Effect of the APOL1 G1 Variant on Trypanosome and Podocytes.**

Variant apolipoprotein L1 (APOL1) is the trypanolytic toxin in the trypanosome lytic factors 1 and 2 (TLF1 and TLF2, both of which are molecular complexes). After the uptake of the TLF1 complex into the trypanosome by means of endocytosis, the acidic milieu of the endosome results in the release of APOL1 from the complex, a change in its conformation to a porelike structure, and insertion into the endosomal membrane. Fusion of the endosome with the lysosome and plasma membranes results in the transfer of APOL1 to these membranes, where it mediates changes in ionic flux across them. In the case of disease-causing trypanosomes, variant APOL1 is believed to cause trypanolysis by facilitating, through its pore, augmented flux of chloride into the lysosome, with ensuing osmotic swelling and lysosome rupture. This proposed mechanism of trypanolysis is thought to be directly analogous to APOL1-mediated damage to podocytes, which confers a risk of proteinuric forms of kidney disease. Other mechanisms of APOL1-mediated injury to and death of the podocyte (and glomerular endothelial cell) have been proposed. ER denotes endoplasmic reticulum, HIV human immunodeficiency virus, IFN interferon, SRA serum resistance–associated, and *T. brucei* *Trypanosoma brucei*.

normal anticoagulant proteins), and toxicity to nephron tubules — may ensue. Thus, many of the clinical signs and symptoms of FSGS are related to aberrant glomerular filtration and resultant proteinuria.

Egbuna et al. measured proteinuria by calculating the ratio of protein to creatinine in the urine, the so-called urinary protein-to-creatinine ratio. The primary outcome of the study was the percent decrease in the urinary protein-to-creatinine ratio at 13 weeks.

**WHO IS AFFECTED BY FSGS?**

FSGS and other types of kidney disease affect African Americans and persons of recent African descent to a much greater extent than persons of European ancestry.<sup>3</sup> Indeed, many Black persons with end-stage kidney disease have close relatives who receive dialysis or have so-called silent kidney disease, which is characterized by decreased kidney function and proteinuria. Historically, the predominant theories underlying the excess burden of kidney disease among Black patients focused on social determinants of health and lack of access to timely, preventive measures to detect associated maladies such as diabetes and hypertension.

However, in 2008, two groups of investigators reported that a specific locus on chromosome 22 was associated with kidney disease in Black persons.<sup>4,5</sup> Two years later, two groups independently reported the actual gene (*APOL1*) and the two variants (G1 and G2) in this gene that drive the association between the chromosome 22 locus and kidney disease.<sup>6,7</sup> That said, social determinants of health and genetic variants are not mutually exclusive in their effect on risk. For example, *APOL1*-associated disease is often detected late (partly because of social-determinant barriers), after kidney injury has occurred and beyond the time at which preventive drug therapy to preserve kidney function is likely to be maximally effective.

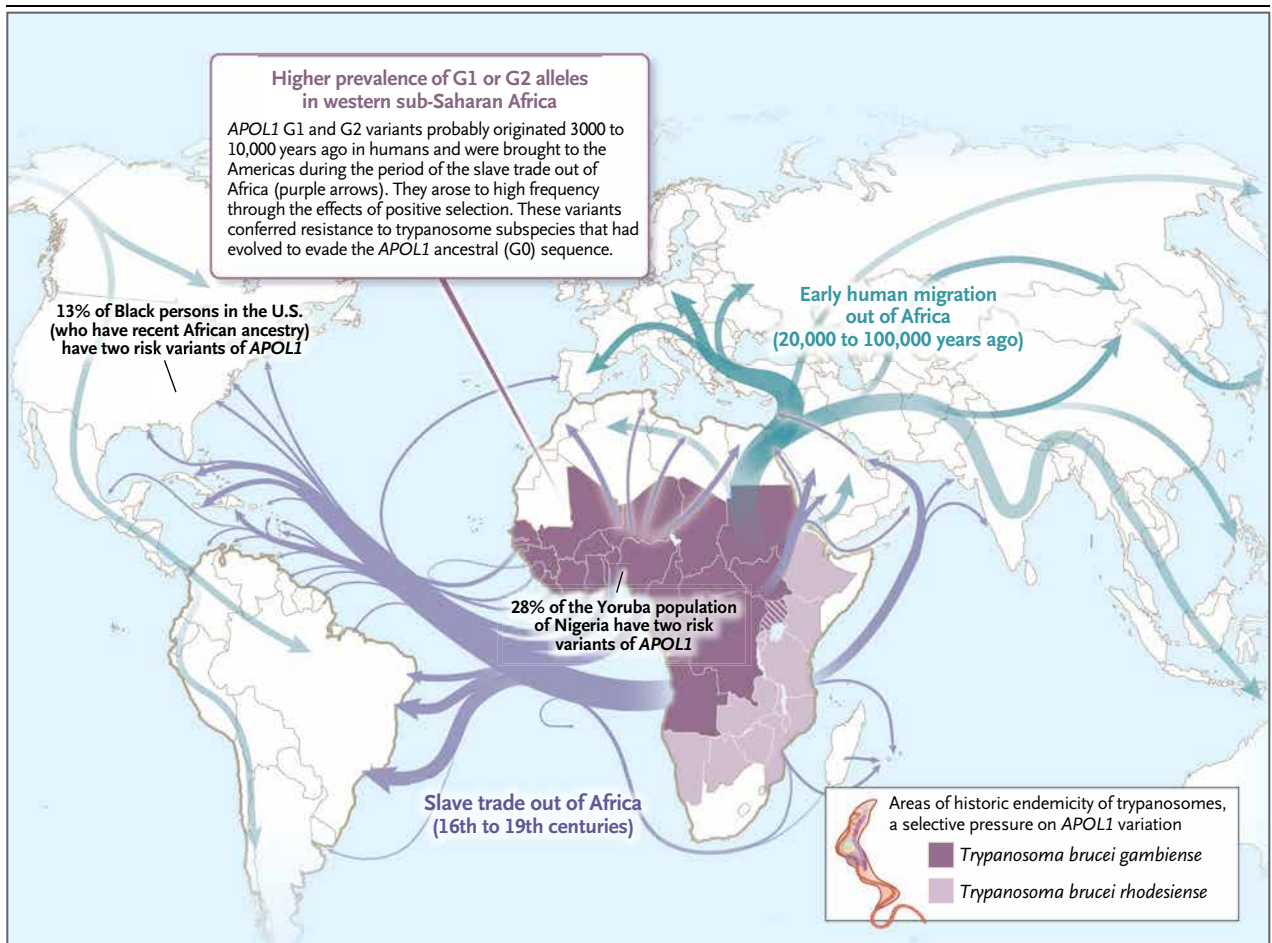
**WHAT DOES APOL1 DO?**

Present in only humans and a few primate species, *APOL1* is expressed in the kidney, liver, lung, pancreas, and placenta. Other than conferring protection against infection by *Trypanosoma brucei* (see Key Concepts), this protein has no known function and is not critical to the maintenance or survival of human cells.

*APOL1* is secreted by cells into the blood, where it forms a complex either with high-density lipoprotein, to form trypanosome lytic factor 1 (TLF1), or with IgM, to form trypanosome lytic factor 2 (TLF2). TLF1 and TLF2 undergo uptake into the trypanosome by means of endocytosis. The acidic environment of endosomes and lysosomes catalyzes a change in the conformation of TLF1 to a porelike structure, which then inserts into the plasma and lysosomal membranes. This porelike structure has been considered to be selective for anions, particularly chloride ions, by some investigators and selective for cation channels by others. Transmembrane chloride flux, osmotic swelling, and possibly rupture of the lysosome are thought to lead to death of the trypanosome (Fig. 1),<sup>8</sup> but the precise means by which TLF1 and TLF2 kill the trypanosome are incompletely elucidated.

**WHAT EXPLAINS THE PREVALENCE OF THE G1 AND G2 VARIANTS?**

The high prevalence of the G1 and G2 variants of *APOL1* among West Africans and among Black persons in the United States (approximately 13% of whom carry two risk alleles) can be explained



**Figure 2. Global Migration and Prevalence of APOL1 G1 and G2 Variants.**

The high prevalence of the G1 and G2 variants of *APOL1* among West Africans and among Black persons in the United States can be explained by the adaptive evolution of humans living in regions where trypanosomiasis is endemic.<sup>9,10</sup> The *APOL1* G1 and G2 variants inactivate the serum resistance–associated factors of *Trypanosoma brucei rhodesiense* and *T. brucei gambiense*, thus ensuring the lytic activity of APOL1 against the parasites. These variants almost certainly conferred a fitness advantage. They arose in West Africa after the first human migrations from Africa to other continents and were thus carried by West Africans, 400 years ago, during the forced emigration that was part of the European slave trade, which is why these variants occur in African persons (predominately West Africans) and in persons of recent African descent.

by the adaptive evolution of humans living in regions where trypanosomiasis is endemic. The subspecies *T. brucei rhodesiense* and *T. brucei gambiense* evolved to evade the trypanolytic activity of nonvariant (G0) APOL1 by forming mutations that resulted in the synthesis of serum resistance–associated factors; these bind to and inactivate APOL1 G0. Human evolution responded in kind: the resultant *APOL1* G1 and G2 variants inactivate the serum resistance–associated factors of *T. brucei rhodesiense* and *T. brucei gambiense* and have thereby restored lytic activity

against the parasites. These variants almost certainly confer a fitness advantage: a greater likelihood of surviving until and beyond reproductive years in regions where *T. brucei rhodesiense* and *T. brucei gambiense* are prevalent. The prevalence of the G1 and G2 variants among persons in sub-Saharan Africa has therefore increased by means of natural selection; these variants are analogous to the sickle hemoglobin variant, which confers protection against malaria. This adaptation took place after the first human migrations from Africa to other

continents, which is why these variants occur only in African persons (mainly in West Africa) and in persons of recent African descent (Fig. 2).

#### HOW DOES VARIANT APOL1 DAMAGE KIDNEY CELLS?

The mechanisms are not well established, but the podocyte appears to be particularly vulnerable to the damaging effects of the G1 and G2 variants. Some researchers posit that the mechanism is similar to that by which trypanosomes are killed — by disrupting the integrity of membranes, especially that of the lysosome and plasma membrane. Moreover, pores (membrane channels) that are formed by APOL1 G1 and G2 in the plasma membrane are permeable to cations; this permeability potentially contributes to or even causes cytotoxic effects.<sup>11</sup> A study of a mouse model showed that variant APOL1 impairs autophagosome maturation and acidification of the endosome of the podocyte, leading to an increase in inflammatory mediators of cell death, actual cell (podocyte) death, FSGS, and proteinuria.<sup>12</sup> In a different study, FSGS developed in two transgenic mouse models, one with two copies of human APOL1 G1 and the other with two copies of APOL1 G2 (but not mice with two copies of APOL1 G0), after exposure to the cytokine interferon- $\gamma$ .<sup>13</sup> These results support the hypothesis that several kidney diseases with heavy proteinuria that are characterized by changes in podocyte morphologic characteristics and function are mediated by inflammation and that proinflammatory cytokines contribute to risk.

#### HOW DOES INAXAPLIN WORK?

Inaxaplin is a four-ringed small molecule that putatively inhibits APOL1 protein-mediated in-

duction of pore formation in podocytes, thereby abrogating aberrant channel-mediated ion flux; however, clarification is needed. A phase 3 trial is under way.

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

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## EDITORIAL



## A Step Forward for Precision Equity in Kidney Disease

Neil R. Powe, M.D.

Chronic kidney disease (CKD) is a public health problem worldwide. In the United States, for the past four decades, CKD in its most severe form, end-stage kidney failure leading to dialysis or transplantation, limits lifespan and quality of life and has disproportionately affected persons of African descent at four times the rate among White persons.<sup>1,2</sup> Effective strategies to disrupt the multifactorial drivers of this health disparity, including environment, lifestyle, access to and quality of care, health and health care policies, and biologic factors, have been elusive.<sup>3</sup> Although many experts in health-disparities research hold strong beliefs that one factor trumps others in impeding health equity, no single factor dominates.<sup>4</sup>

In 2010, the important discovery of a link between variants in the apolipoprotein L1 (*APOL1*) gene on chromosome 22 and end-stage kidney failure suggested that there might now be a precise, encompassing, disease-modifying target.<sup>5</sup> The *APOL1* risk variants G1 and G2, which commonly occur in descendants from sub-Saharan Africa, with a frequency of approximately 13% among African Americans, probably arose from natural selection, owing to the protection they provide against the endemic parasites *Trypanosoma brucei rhodesiense* and *T. brucei gambiense* that cause African trypanosomiasis (sleeping sickness). The first link was shown in persons with hypertension-attributed kidney disease and focal segmental glomerulosclerosis (FSGS), a syndrome that is increasing in incidence. FSGS is more common among Black persons than among non-Black persons, is diagnosed on the basis of pathological testing, and involves a

glomerulopathy that most often progresses to end-stage kidney failure.<sup>6</sup> This condition has multifaceted causes, clinical and laboratory manifestations, pathologic features, and treatment responses.<sup>7,8</sup>

In this issue of the *Journal*, Egbuna et al.<sup>9</sup> report a sequence of investigations: in vitro experiments, in vivo studies in animals, and a small clinical study involving 16 Black participants with FSGS who were homozygous for G1 or G2 or heterozygous for G1 and G2. These investigations explored the efficacy and safety of inaxaplin, a small molecule that inhibits *APOL1* function and therefore represents a potential treatment for *APOL1*-associated nephropathy.<sup>9</sup> Orally administered inaxaplin inhibited *APOL1* ion channel function in human embryonic kidney (HEK293) cells, and it also reduced proteinuria in both transgenic *APOL1* G2-homozygous mice and in the clinical study. No severe adverse reactions in humans were reported.

How excited should we be? This research appears to be a major scientific breakthrough with enormous implications, especially for persons of African ancestry. Demonstration of proof-of-concept may, with further reinforcing studies, transform the lives of persons with FSGS and two *APOL1* risk variant alleles. Although one might question the strength of the findings implicating a causal mechanism of inhibition of *APOL1* ion channel function to reduce proteinuria that applies to G1 variants as well as to G2 variants, until now interventions focusing on a mechanistic pathway that might alter the course of *APOL1* nephropathy have been lacking.

Cautious enthusiasm is prudent here. Comparative effectiveness is essential to establish. This open-label study had no comparator group and had numerous participant-exclusion criteria, including hypertensive kidney disease. A blinded, placebo-controlled trial of usual care plus inaxaplin as compared with usual care plus placebo in a broader patient population would provide assurance that the presence and magnitude of positive outcomes with inaxaplin therapy are observed independent of access to health care, natural history, or other factors. The study examined an objective but intermediate end point — proteinuria, a biomarker of glomerular injury. The Food and Drug Administration has, under some circumstances, accepted proteinuria as a marker for the purposes of full or accelerated medication approval.<sup>10</sup> Firm agreement of a relation between treatment effects on change in proteinuria and treatment effects on progressive kidney disease outcomes within the relevant disease context is needed.<sup>10,11</sup> Therefore, the enrollment and random assignment of a larger number of participants who would be followed for a longer duration, with the assessment of traditional clinically meaningful end points (e.g., change in the estimated glomerular filtration rate, end-stage kidney failure, and death), will probably be necessary in order to judge effectiveness as well as long-term safety.

Even if future research surmounts present limitations, the power of precision medicine may still take time. Measurement of APOL1 is currently not routine in clinical practice, which will be a necessary step in the implementation and widespread adoption of inaxaplin treatment. To date, testing for APOL1 risk variants has had limited prognostic value, including in the evaluation of prospective kidney donors, largely because strategies to modify risk are nonexistent. However, the promise of studies such as this one might catalyze the willingness of laboratories to gear up for, and the propensity of clinicians to order, APOL1 testing.

The results of these investigations by Egbuna et al. constitute a step forward in making the promise of precision medicine a reality by

means of industry–academia collaboration and the targeting of the large excess risk of end-stage kidney failure among Black persons in the United States for which the two prevalent APOL1 risk variants (occurring in one in eight Black adults) contribute to health inequity. Precision equity is the use of innovative approaches for disease prevention and treatment that takes into consideration differences among persons' genes, environments, and lifestyles to address health disparities and achieve health equity. Small bites at the multifactorial causes of racial disparities, taken together with other interventions, can be epic disrupters of the inexorable progression of kidney disease and lead to long, healthy, and productive lives.

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

From the University of California, San Francisco, and the Priscilla Chan and Mark Zuckerberg San Francisco General Hospital, San Francisco.

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## Treatment Strategy for Rifampin-Susceptible Tuberculosis

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### ABSTRACT

#### BACKGROUND

Tuberculosis is usually treated with a 6-month rifampin-based regimen. Whether a strategy involving shorter initial treatment may lead to similar outcomes is unclear.

#### METHODS

In this adaptive, open-label, noninferiority trial, we randomly assigned participants with rifampin-susceptible pulmonary tuberculosis to undergo either standard treatment (rifampin and isoniazid for 24 weeks with pyrazinamide and ethambutol for the first 8 weeks) or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. The noninferiority margin was 12 percentage points.

#### RESULTS

Of the 674 participants in the intention-to-treat population, 4 (0.6%) withdrew consent or were lost to follow-up. A primary-outcome event occurred in 7 of the 181 participants (3.9%) in the standard-treatment group, as compared with 21 of the 184 participants (11.4%) in the strategy group with an initial rifampin–linezolid regimen (adjusted difference, 7.4 percentage points; 97.5% confidence interval [CI], 1.7 to 13.2; noninferiority not met) and 11 of the 189 participants (5.8%) in the strategy group with an initial bedaquiline–linezolid regimen (adjusted difference, 0.8 percentage points; 97.5% CI, –3.4 to 5.1; noninferiority met). The mean total duration of treatment was 180 days in the standard-treatment group, 106 days in the rifampin–linezolid strategy group, and 85 days in the bedaquiline–linezolid strategy group. The incidences of grade 3 or 4 adverse events and serious adverse events were similar in the three groups.

#### CONCLUSIONS

A strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment for tuberculosis with respect to clinical outcomes. The strategy was associated with a shorter total duration of treatment and with no evident safety concerns. (Funded by the Singapore National Medical Research Council and others; TRUNCATE-TB ClinicalTrials.gov number, NCT03474198.)

The authors' affiliations are listed in the Appendix. Prof. Paton can be contacted at [nick\\_paton@nus.edu.sg](mailto:nick_paton@nus.edu.sg) or at Yong Loo Lin School of Medicine, NUHS Tower Block Level 10, 1E Kent Ridge Rd., Singapore 119228.

\*A complete list of members of the TRUNCATE-TB Trial Team is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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## RESEARCH SUMMARY

# Treatment Strategy for Rifampin-Susceptible Tuberculosis

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## CLINICAL PROBLEM

The global standard treatment for drug-susceptible tuberculosis is a 24-week rifampin-based regimen, but adherence can be challenging. Clinical trials have shown a high probability of cure with shorter regimens, which suggests that a 24-week regimen may not be needed.

## CLINICAL TRIAL

**Design:** A phase 2–3, international, adaptive, randomized, open-label, noninferiority trial assessed the efficacy and safety of a strategy involving shorter initial treatment for rifampin-susceptible tuberculosis.

**Intervention:** 674 participants 18 to 65 years of age were randomly assigned to undergo either standard treatment with a 24-week rifampin-based regimen or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96.

## RESULTS

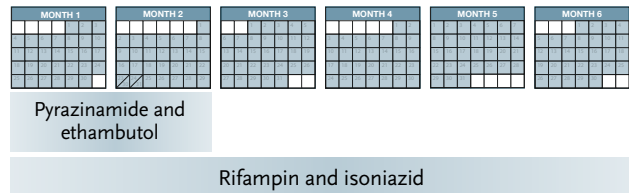
**Efficacy:** The strategy with an initial rifampin–linezolid regimen did not meet the noninferiority criterion, whereas the strategy with an initial bedaquiline–linezolid regimen was noninferior to standard treatment and was associated with a shorter total duration of treatment.

**Safety:** The incidence of grade 3 or 4 adverse events, serious adverse events, and respiratory disability did not differ significantly between the standard-treatment group and the two strategy groups.

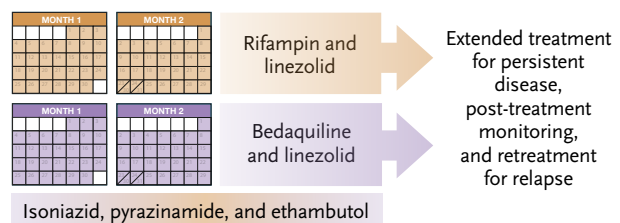
## LIMITATIONS AND REMAINING QUESTIONS

- Noninferiority of the treatment strategy was assessed with only two regimens, and the strategy could be refined with the use of alternative regimens.
- No HIV-positive persons were enrolled; further evaluation is warranted in this population.

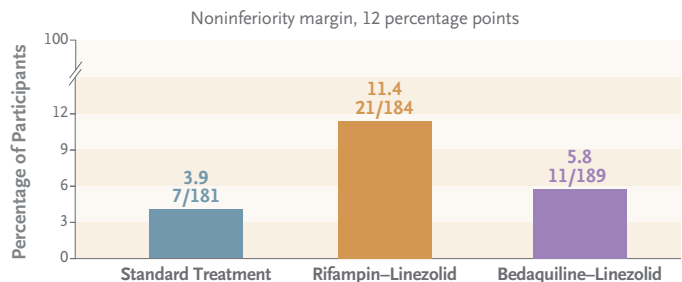
## Standard Treatment (24 Wk)



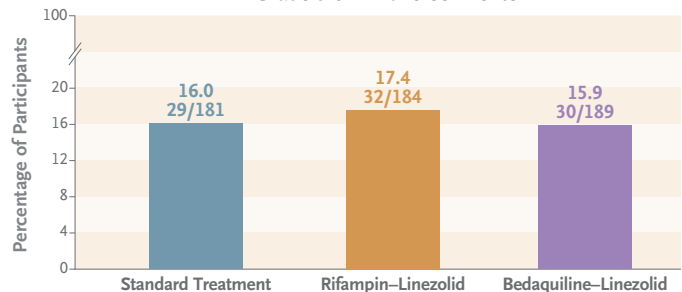
## Strategy Groups Included in the Noninferiority Analysis



## Death, Ongoing Treatment, or Active Disease



## Grade 3 or 4 Adverse Events



## CONCLUSIONS

Among participants with rifampin-susceptible pulmonary tuberculosis, a strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment with respect to clinical outcomes, with no apparent safety concerns.

## EDITORIAL



## Shortening Tuberculosis Treatment — A Strategic Retreat

Véronique Dartois, Ph.D., and Eric J. Rubin, M.D., Ph.D.

Our current treatment regimen for tuberculosis, which goes by the somewhat ironic name of “directly observed therapy, short course,” is anything but short. Patients are treated, generally on a daily basis, for 6 months, which necessitates an infrastructure to deliver and observe therapy. This logistic burden has led to a push for shorter treatments. Although many initial attempts failed, a recent study suggested that a newer regimen could lead to a similar probability of cure in 4 months.<sup>1</sup> This is certainly an advantage, and yet the newer regimen, if widely used, would still require a similarly burdensome infrastructure. Can we do even better and get to a point where the logistics would not be so limiting? The investigators of the TRUNCATE-TB (Two-Month Regimens Using Novel Combinations to Augment Treatment Effectiveness for Drug-Sensitive Tuberculosis) trial,<sup>2</sup> the results of which are now published in the *Journal*, attempted to do that. But rather than focusing on a regimen alone, they chose a treatment strategy.

The trial design is a bit complex and initially had five groups. Participants had to have a nucleic acid amplification test that was positive for tuberculosis with no genotypic evidence of rifampin resistance. The investigators excluded some higher-risk patients initially but then changed the entry criteria to include this population. Participants who were randomly assigned to the control group received standard tuberculosis treatment for 24 weeks (8 weeks of isoniazid, rifampin, ethambutol, and pyrazinamide, followed by 16 weeks of isoniazid and rifampin); this group served as a comparator for a planned noninferiority analysis. Participants in the four other groups received an intensified regimen

that contained five drugs. The plan was to drop two of these groups on the basis of early stopping rules. In fact, none of these groups met those standards, so enrollment was stopped in two groups on the basis of logistic criteria (pill burden and regulatory concerns) in order to preserve statistical power. The two remaining groups received either high-dose rifampin plus linezolid or bedaquiline plus linezolid, each in combination with isoniazid, pyrazinamide, and ethambutol.

For the groups that received an intensified regimen, the strategy consisted of treatment for 8 weeks and then reassessment for persistent disease (symptoms and a positive sputum smear). If the reassessment was negative, treatment was stopped; if positive, participants continued treatment for another 4 weeks. Those who remained positive could be switched to standard treatment to complete 24 weeks. Those who had a relapse in any group were retreated with a standard regimen with adjustments made according to antibiotic susceptibility testing. Participants were followed closely for evidence of relapse through week 96. The primary outcome was a composite of death, ongoing treatment, or active disease at week 96. For the treatment strategy to be declared noninferior, the upper limit of the confidence interval for the difference between the strategy group and the standard-treatment group in the risk of the primary outcome had to be less than 12 percentage points. This is a somewhat low threshold; for example, a recent treatment-shortening trial used a noninferiority margin of 6.6 percentage points.<sup>1</sup> As it turned out, one of the strategy groups failed to meet even that loose criterion, whereas the other would have succeeded at either margin.

The trial enrolled 675 participants at 18 sites in five countries. Impressively, almost all completed the trial and follow-up period. Altogether, 7 participants (3.9%) had a primary-outcome event in the control group, as compared with 21 (11.4%) in the rifampin–linezolid group (adjusted difference, 7.4 percentage points; 97.5% confidence interval [CI],  $-1.7$  to  $13.2$ ) and with 11 (5.8%) in the bedaquiline–linezolid group (adjusted difference, 0.8 percentage points; 97.5% CI,  $-3.4$  to  $5.1$ ). With these results, only the strategy involving treatment with the bedaquiline–linezolid regimen was declared noninferior to standard treatment. In the bedaquiline–linezolid group, 162 participants (85.7%) did not receive therapy beyond 8 weeks. According to the definitions used in the trial, extension of therapy was not a “failure” but was part of the treatment strategy. Altogether, the mean total length of treatment in the bedaquiline–linezolid group (84.8 days) was less than half that in the standard-treatment group (180.2 days).

One risk that is associated with a shorter course could be the development of antibiotic resistance. There were two cases of acquired drug resistance in the bedaquiline–linezolid group and none in the standard-treatment group. Bedaquiline has a long terminal half-life that generates lingering subtherapeutic concentrations for several months after the end of therapy, which results in de facto monotherapy and a prolonged window for the potential acquisition of drug resistance in cases of relapse. Although a much larger number of patients would need to be treated to detect any significant difference, the small number of cases of drug resistance in this trial does not pose substantial concerns.

In many ways, the results of this trial are not surprising. We have long known that most patients with tuberculosis who are treated even with standard regimens do not have a relapse after 4 months of treatment; in fact, several appear to be cured after only 2 months of treatment.<sup>3</sup> And the inclusion of bedaquiline and linezolid in regimens for drug-resistant tuberculosis has allowed for shorter regimens.<sup>4-6</sup> What is striking is that each of these drugs has posed considerable concerns about toxic effects in the past. Bedaquiline still carries a black-box warning that resulted from very early trials showing increased mortality among treated patients. Linezolid can lead to dose-limiting toxic effects that

have been a substantial issue in other trials. Because of these effects, whether these drugs could be used safely for the treatment of drug-susceptible tuberculosis has been unclear. In the TRUNCATE-TB trial, the toxic effects appeared to be quite limited. In fact, this is one of many trials that suggest that the original concerns about bedaquiline might be overstated, at least for patients who undergo prescreening with electrocardiography.

Will these data change practice? Two months of treatment might not be revolutionary but could be very helpful. However, some obstacles remain. There was a very high degree of adherence to treatment in this trial, far higher than the level likely to occur outside the context of a clinical trial. Lower adherence could mean increased treatment failure at 2 months. In addition, the treatment strategy involved careful assessments of patients to identify those who would receive extended courses of therapy. Although this approach is possible within the confines of a trial, it could require considerable resources that are not now available in many tuberculosis control programs.

Perhaps the biggest accomplishment of this trial is a step forward in the adaptive clinical trial design that may help to accelerate regimen development and to rapidly test many more 2-month therapies that are selected on the basis of recent treatment-shortening trial results.<sup>4-7</sup> For shorter treatments, positive results that are similar to the results for standard treatment and are observed across various patient populations, including those with a high burden of cavitary tuberculosis, would garner the confidence needed to influence practice in lower-resource settings.

Treatment algorithms such as that used in the TRUNCATE-TB trial are fundamental to tuberculosis control. Although implementing them could be a challenge, any added burden might be offset by reduced costs, better adherence, and increased patient satisfaction. Thus, for tuberculosis, a strategy might be more than just a regimen.

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

From the Center for Discovery and Innovation, Nutley, NJ (V.D.).

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## Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

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### ABSTRACT

#### BACKGROUND

Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthase is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. In preclinical and phase 1 studies, baxdrostat had 100:1 selectivity for enzyme inhibition, and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels.

#### METHODS

In this multicenter, placebo-controlled trial, we randomly assigned patients who had treatment-resistant hypertension, with blood pressure of 130/80 mm Hg or higher, and who were receiving stable doses of at least three antihypertensive agents, including a diuretic, to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks or placebo. The primary end point was the change in systolic blood pressure from baseline to week 12 in each baxdrostat group as compared with the placebo group.

#### RESULTS

A total of 248 patients completed the trial. Dose-dependent changes in systolic blood pressure of  $-20.3$  mm Hg,  $-17.5$  mm Hg,  $-12.1$  mm Hg, and  $-9.4$  mm Hg were observed in the 2-mg, 1-mg, 0.5-mg, and placebo groups, respectively. The difference in the change in systolic blood pressure between the 2-mg group and the placebo group was  $-11.0$  mm Hg (95% confidence interval [CI],  $-16.4$  to  $-5.5$ ;  $P < 0.001$ ), and the difference in this change between the 1-mg group and the placebo group was  $-8.1$  mm Hg (95% CI,  $-13.5$  to  $-2.8$ ;  $P = 0.003$ ). No deaths occurred during the trial, no serious adverse events were attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level to 6.0 mmol per liter or greater occurred in 2 patients, but these increases did not recur after withdrawal and reinitiation of the drug.

#### CONCLUSIONS

Patients with treatment-resistant hypertension who received baxdrostat had dose-related reductions in blood pressure. (Funded by CinCor Pharma; BrigHTN Clinical-Trials.gov number, NCT04519658.)

From CinCor Pharma (M.W.F., Y.-D.H., W.M., C.P.) and Brigham and Women's Hospital, Harvard Medical School (D.L.B.) — both in Boston; CinRx Pharma (M.P., J.I., B.M.) and Medpace (N.A., A.S.) — both in Cincinnati; and the Department of Clinical Pharmacology, William Harvey Research Institute, Queen Mary University of London, London (M.J.B.). Dr. Brown can be contacted at [morris.brown@qmul.ac.uk](mailto:morris.brown@qmul.ac.uk) or at Queen Mary University of London, Charterhouse Sq., London EC1M 6BQ, United Kingdom.

\*The BrigHTN Investigators are listed in the Supplementary Appendix, available at [NEJM.org](https://www.nejm.org).

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## RESEARCH SUMMARY

## Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

Freeman MW et al. DOI: 10.1056/NEJMoa2213169

## CLINICAL PROBLEM

Aldosterone synthase, the enzyme that controls synthesis of aldosterone, is a target for treatment of hypertension, but selective inhibition of aldosterone synthase is difficult to achieve. The investigational drug baxdrostat has shown high selectivity for aldosterone synthase in pre-clinical and phase 1 studies; data on its efficacy and safety in patients with treatment-resistant hypertension are needed.

## CLINICAL TRIAL

**Design:** A multicenter, double-blind, dose-ranging, randomized, placebo-controlled trial assessed the efficacy and safety of baxdrostat in adults with treatment-resistant hypertension.

**Intervention:** 275 patients who were receiving stable doses of at least three antihypertensive medications, including a diuretic, and who had a blood pressure of at least 130/80 mm Hg while seated were randomly assigned to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) or placebo once daily for 12 weeks. The primary efficacy end point was the least-squares mean (LSM) change in mean seated systolic blood pressure from baseline to the end of week 12.

## RESULTS

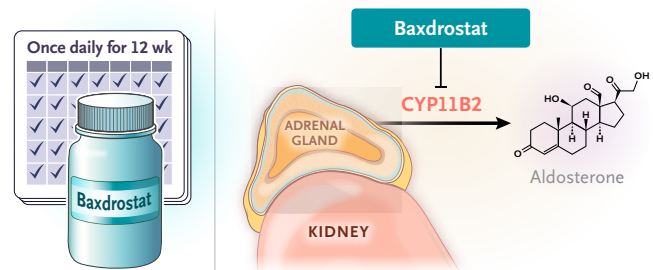
**Efficacy:** Patients in the 1-mg baxdrostat group and those in the 2-mg baxdrostat group had significantly greater decreases in systolic blood pressure than those in the placebo group.

**Safety:** Most adverse events were mild and deemed by the investigators to be unrelated to baxdrostat. Two patients had baxdrostat-associated increases in potassium levels to 6.0 mmol per liter or greater; these increases did not recur after withdrawal and reinitiation of the drug.

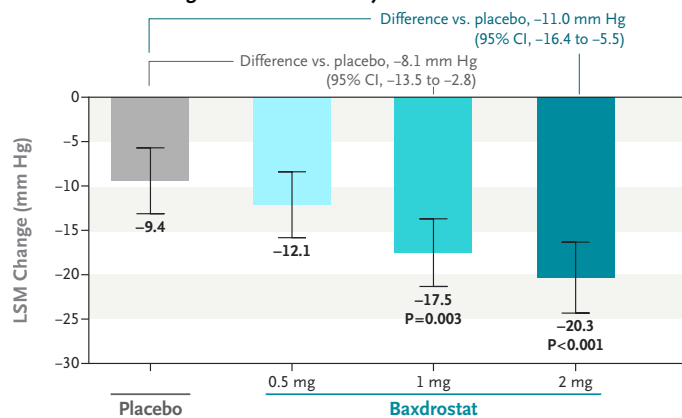
## LIMITATIONS AND REMAINING QUESTIONS

- The trial did not assess the benefits and risks of aldosterone synthase inhibition beyond 12 weeks or in comparison with other antihypertensive medications.
- The selection of patients with an estimated glomerular filtration rate above 45 ml per minute per 1.73 m<sup>2</sup> of body-surface area reduced the likelihood of hyperkalemia.

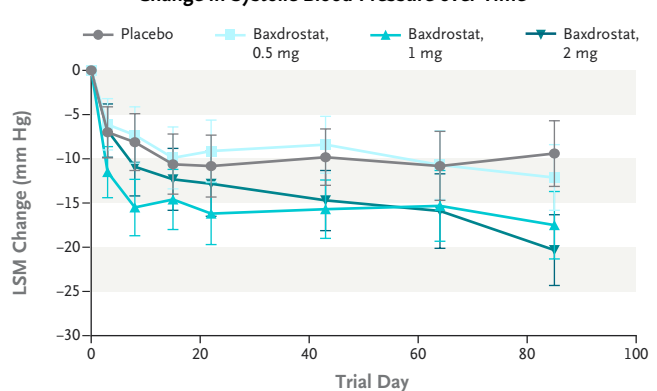
## Selective Inhibition of Aldosterone Synthase (CYP11B2)



## Change from Baseline in Systolic Blood Pressure



## Change in Systolic Blood Pressure over Time



## CONCLUSIONS

In adults with treatment-resistant hypertension, aldosterone synthase inhibition with baxdrostat at a dose of 1 mg or 2 mg daily led to significantly greater reductions in systolic blood pressure over 12 weeks than placebo.

## EDITORIAL



## Decreasing the Effects of Aldosterone in Resistant Hypertension — A Success Story

Michel Azizi, M.D., Ph.D.

Despite the availability of several medications to treat hypertension, approximately 20% of patients with this condition have apparent resistant hypertension, which is defined as in-office systolic and diastolic blood pressure that is not decreased to less than 130/80 mmHg despite lifestyle measures and treatment with the maximum tolerated doses of three or more drugs, including a diuretic, a renin–angiotensin system blocker, and a calcium-channel blocker.<sup>1</sup> Resistant hypertension is associated with an increased risk of premature cardiovascular events.<sup>1</sup> The initial workup should rule out pseudo-resistant hypertension with the use of out-of-office blood-pressure measurements, nonadherence to anti-hypertensive medications, and secondary hypertension.<sup>1</sup>

Resistant hypertension is commonly a salt-retaining state, mainly because of inappropriate and excessive aldosterone secretion,<sup>1</sup> so the treatment of this condition should combine decreased sodium intake, increased use of diuretic therapy, and the addition of a mineralocorticoid receptor antagonist such as spironolactone (at a dose of 25 to 50 mg per day).<sup>1</sup> However, the use of spironolactone is limited<sup>2,3</sup> because it increases the risk of hyperkalemia among patients with a decreased estimated glomerular filtration rate (GFR), and it has antiandrogenic and progestogenic side effects, given its nonselective mineralocorticoid receptor effects.<sup>4</sup> Although eplerenone is a more selective mineralocorticoid receptor antagonist than spironolactone, it is less potent.<sup>4</sup> Furthermore, mineralocorticoid receptor antag-

onists induce a renin-dependent counterregulatory increase in aldosterone levels,<sup>4</sup> and this increase may stimulate nongenomic mineralocorticoid receptor–independent effects.<sup>5</sup>

Inhibition of aldosterone synthesis is another option to reduce the deleterious effects of aldosterone excess.<sup>6</sup> Aldosterone production is controlled by the regulated transcription of *CYP11B2*, which encodes aldosterone synthase in the adrenal zona glomerulosa.<sup>6</sup> Aldosterone synthase successively catalyzes the three final enzymatic steps leading to aldosterone production (11 $\beta$ -hydroxylation of 11-deoxycorticosterone to corticosterone, followed by 18-hydroxylation of corticosterone [18-OH-B] and 18-oxidation of 18-OH-B). The final step in cortisol synthesis in the adrenal zona fasciculata involves 11 $\beta$ -hydroxylase, which is encoded by *CYP11B1*. The substantial homology between *CYP11B2* and *CYP11B1* and their encoded proteins (>93% identical) has made the several-decade search for selective aldosterone synthase inhibitors difficult. Low doses of LCI-699 (osilodrostat), the first aldosterone synthase inhibitor in clinical development, suppressed aldosterone secretion and decreased blood pressure in patients with hypertension but also inhibited *CYP11B1* and thus cortisol synthesis, outcomes that precluded its clinical use for treating hypertension.<sup>6</sup>

In this issue of the *Journal*, Freeman et al.<sup>7</sup> report the results of a 12-week, phase 2, placebo-controlled, dose-ranging trial involving 275 patients with resistant hypertension. A commentary on resistant hypertension by Leopold and

**Table 1. Similarities and Differences between Aldosterone Synthase Inhibition with Baxdrostat and Mineralocorticoid Receptor Antagonism.**

Variable	Aldosterone Synthase Inhibition with Baxdrostat	Mineralocorticoid Receptor Antagonism
<b>Enzyme activities</b>		
Aldosterone synthase activity (CYP11B2)	Decreased	Increased
11 $\beta$ -hydroxylase activity (CYP11B1)	Unchanged	Unchanged
<b>Hormone levels</b>		
Aldosterone pathway		
Plasma aldosterone level	Decreased	Increased
Plasma 11-deoxycorticosterone level	Increased	Increased
Cortisol pathway		
Plasma cortisol level	Unchanged	Unchanged
Plasma 11-deoxycortisol level	Unchanged	Unchanged
Plasma corticotropin level	Unchanged	Unchanged
<b>Receptor status</b>		
Mineralocorticoid receptor	Unblocked and not stimulated	Blocked
Mineralocorticoid receptor–independent nongenomic pathway	Not stimulated	Stimulated
<b>Pharmacodynamic effects</b>		
Serum potassium level*	Increased	Increased
Blood pressure	Decreased	Decreased
Plasma renin activity	Increased	Increased

\* Greater increases in serum potassium levels may be observed in persons with a low estimated glomerular filtration rate or with intake of drugs that increase the serum potassium level (e.g. nonsteroidal antiinflammatory drugs, potassium supplements, potassium-sparing diuretics, and renin–angiotensin system blockers).

Ingelfinger<sup>8</sup> also appears in this issue. In the trial conducted by Freeman et al., the patients received once-daily baxdrostat, a new CYP11B2 inhibitor with in vitro selectivity that is more than 100 times as high as that for CYP11B1 and that has a plasma half-life of approximately 30 hours.<sup>9</sup> In the modified intention-to-treat population involving 274 patients, the 1-mg and 2-mg doses of baxdrostat, added to unchanged background therapy, induced large additional decreases in in-office systolic blood pressure (difference between the 1-mg group and the placebo group,  $-8.1$  mm Hg, and difference between the 2-mg group and the placebo group,  $-11.0$  mm Hg), but the difference between the 0.5-mg group and placebo was not significant. An unusually large placebo effect in the change in systolic blood pressure ( $-9.4$  mm Hg) was ob-

served; this effect would probably have been limited if 24-hour ambulatory blood-pressure measurements had been used to exclude patients with “white-coat” resistant hypertension (i.e., elevated blood pressure in the office but normal pressure in ambulatory settings).

The baseline serum aldosterone levels in the patients were in the low range of normal levels — findings that were consistent with the classic persistent aldosterone breakthrough seen in patients with resistant hypertension who currently receive a renin–angiotensin system blocker.<sup>1</sup> Baxdrostat decreased these baseline levels by 40 to 60%. Baxdrostat did not decrease baseline serum cortisol levels — findings that confirmed its CYP11B2 selectivity<sup>9</sup> — although plasma corticotropin and 11-deoxycortisol levels were not reported.

After aldosterone suppression, serum potassium levels increased in a dose-dependent manner with baxdrostat, similar to results with mineralocorticoid receptor antagonists.<sup>10</sup> Although only six cases of reversible hyperkalemia (potassium level,  $\geq 5.5$  mmol per liter) occurred, the risk of hyperkalemia with baxdrostat is probably underestimated, since patients with an estimated GFR of less than 45 ml per minute per 1.73 m<sup>2</sup> of body-surface area were excluded from this trial. Baxdrostat increased plasma renin activity in a dose-dependent manner, probably through an additional negative sodium balance in patients who were already receiving a diuretic; this may have contributed to the antihypertensive effect of baxdrostat.<sup>6</sup> It also probably contributed to the dose-related decreases from baseline in the estimated GFR (10.7 ml per minute per 1.73 m<sup>2</sup> in patients who received the 2-mg dose of baxdrostat). Monitoring of serum potassium and creatinine levels will be necessary if baxdrostat becomes commercially available, as it is necessary for mineralocorticoid receptor antagonists. Clearly, the combination of baxdrostat and a mineralocorticoid receptor antagonist should be avoided, because that combination would greatly increase the risk of severe hypoaldosteronism.<sup>11</sup>

These trial results open new perspectives for treating patients with resistant hypertension, as well as for treating those with primary aldosteronism, which includes massive aldosterone excess.<sup>6</sup> However, larger and longer trials that include 24-hour ambulatory blood-pressure monitoring as well as complete steroid profiling are warranted, including an active control group treated with a mineralocorticoid receptor antagonist. Although both aldosterone synthase inhibitors and mineralocorticoid receptor antagonists lower blood pressure, they do so through different molecular and hormonal mechanisms targeting the aldosterone pathway (Table 1).

Thus, investigation of both the similarities and differences of these treatments in terms of efficacy and safety are critical to define more precisely the lowest and highest effective and safe dose of baxdrostat. Although no major safety issues were seen in this short trial, as-yet-unknown adverse effects cannot be ruled out.<sup>9</sup>

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

From Université Paris Cité; Assistance Publique–Hôpitaux de Paris, Department of Hypertension and Département Médico–Universitaire Cardiologie Rein Transplantation Neurovasculaire, Hôpital Européen Georges Pompidou; and INSERM Centre d'Investigation Clinique 1418 — all in Paris.

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## EDITORIAL

## SCIENCE BEHIND THE STUDY

Elizabeth G. Phimister, Ph.D., *Editor*

## Aldosterone and Treatment-Resistant Hypertension

Jane A. Leopold, M.D., and Julie R. Ingelfinger, M.D.

**Aldosterone has long been a pharmacologic target for the treatment of hypertension. Thus, an article by Freeman et al.<sup>1</sup> and an accompanying editorial by Azizi<sup>2</sup> in this issue of the Journal are of keen interest. Freeman et al. describe a trial of a new drug called called baxdrostat that inhibits aldosterone synthase in patients with treatment-resistant hypertension.**

**WHAT IS HYPERTENSION, AND WHY SHOULD WE CARE?**

The definition of ideal or “normal” blood pressure, which is presently based on population-level data, is a blood pressure of 120/80 mm Hg

or lower in adults.<sup>3,4</sup> Hypertension is defined as blood pressure of 130/80 mm Hg or higher; this definition is based on evidence from epidemiologic studies and clinical trials that examined the relationship between higher blood pressures and major adverse cardiovascular events.<sup>3,4</sup> According to the Centers for Disease Control and Prevention, 116 million adults in the United States, or 47% of adults in the population, have hypertension. The prevalence of hypertension is higher among men than among women, among non-Hispanic Black adults than among non-Hispanic White or Asian adults, and among persons in the southeastern United States than among those in the rest of the country.<sup>3,4</sup>

We should care about hypertension because it contributes to disparities in health care, and disparities in economic resources, environmental conditions, and access to health care surely contribute to the prevalence of hypertension. Hypertension is associated with increased risks of stroke, coronary artery disease, and other cardiovascular diseases; heart failure; atrial fibrillation; chronic kidney disease; and death.<sup>3,4</sup> The death rate attributable to hypertension has increased by 34.2% over the past decade; in 2020, hypertension was a primary or contributing cause of more than 670,000 deaths, or 20% of all deaths in the United States.<sup>3,4</sup> Furthermore, although hypertension is a modifiable risk factor, only 24% of adults with hypertension have adequately controlled blood pressure, which is defined as a blood pressure of less than 130/80 mm Hg in persons who have received lifestyle interventions and medications. These numbers point to a substantial unmet need — the effective management of hypertension.

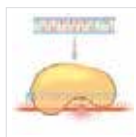
**HOW IS TREATMENT-RESISTANT HYPERTENSION DEFINED?**

For several reasons, blood pressure in a patient with hypertension may not be lowered to ideal target levels, despite the use of antihypertensive medications. These reasons include nonadherence

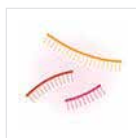
## Key Concepts

**Small-molecule drug**

A chemical compound with a low molecular weight (typically 0.1 to 0.6 kD). Small-molecule drugs are smaller than biologic drugs, such as monoclonal antibodies (typically 150 kD) and oligonucleotides (typically 4 to 10 kD). Because of their small size, they can penetrate the cell membrane and bind intracellular targets. They are generally more stable than biologic drugs and can be administered orally.

**Small (or short) interfering RNA (siRNA)**

A short, double-stranded regulatory RNA molecule of 21 to 23 nucleotides that interferes with the expression of a specific gene by binding to a complementary sequence in the messenger RNA of that gene and targeting it for enzymatic degradation. Chemically modified siRNAs are the basis of some approved drugs and drugs in development.

**Antisense oligonucleotide**

A short single strand (typically 12 to 30 nucleotides) of chemically modified RNA that targets messenger RNA (mRNA) to prevent translation into protein. Antisense oligonucleotides can bind directly to mRNA, leading to mRNA degradation; they can inhibit generation of mature mRNA by blocking splicing of precursor forms of mRNA; or they can block ribosome recruitment to inhibit protein translation. Antisense oligonucleotides can also be designed to target other RNAs, such as microRNAs and long noncoding RNAs. They are the basis of some approved drugs and drugs in development.

 An expanded illustrated glossary is available at [NEJM.org](https://www.nejm.org)



to prescribed medications, “white-coat hypertension” (hypertension that is present only during clinic visits but not at other times), mismeasured blood pressure, or concomitant use of medications or substances that can elevate blood pressure. Treatment-resistant hypertension is defined as hypertension in a patient who is taking three or more medications, including a diuretic, to lower blood pressure,<sup>5</sup> and for whom misdiagnosis (owing to nonadherence, mismeasurement, and so on) has been ruled out.

#### ABSENT A MISDIAGNOSIS, WHAT CAUSES TREATMENT-RESISTANT HYPERTENSION?

Treatment-resistant hypertension may be attributable to volume overload, untreated obstructive sleep apnea, and renovascular disease. It may also occur in patients with hormonal dysregulation associated with hyperparathyroidism, thyroid disease, or rare conditions such as pheochromocytoma, paraganglioma, or reninoma. Treatment-resistant hypertension also occurs in patients with undiagnosed primary aldosteronism (Conn’s syndrome) or hypercortisolism (Cushing’s syndrome). Some patients with treatment-resistant hypertension have been found to have increased aldosterone production, even though they do not have primary aldosteronism (Fig. 1).

#### IS SODIUM RETENTION A MAJOR FEATURE OF TREATMENT-RESISTANT HYPERTENSION?

Yes. Many patients with treatment-resistant hypertension have salt-sensitive hypertension, a condition in which increased sodium intake results in increased blood pressure through sodium and water retention. This process occurs because of activation of the sympathetic nervous system that impairs the suppression of the renin-angiotensin-aldosterone system; consequently, levels of aldosterone increase (Fig. 1). Aldosterone increases sodium reabsorption and thus passive water reabsorption across the distal tubule of the nephron, thereby contributing to hypertension. Although a decrease in salt intake may reduce blood pressure, it is usually insufficient to achieve normotension.

#### CAN MEDICATION TARGET OR TREAT IT?

Fortunately, yes. The Prevention and Treatment of Hypertension with Algorithm-based Therapy-2

(PATHWAY-2) trial showed that spironolactone is effective. These findings provide support for the concept that high dietary sodium intake and elevated levels of aldosterone mediate treatment-resistant hypertension.

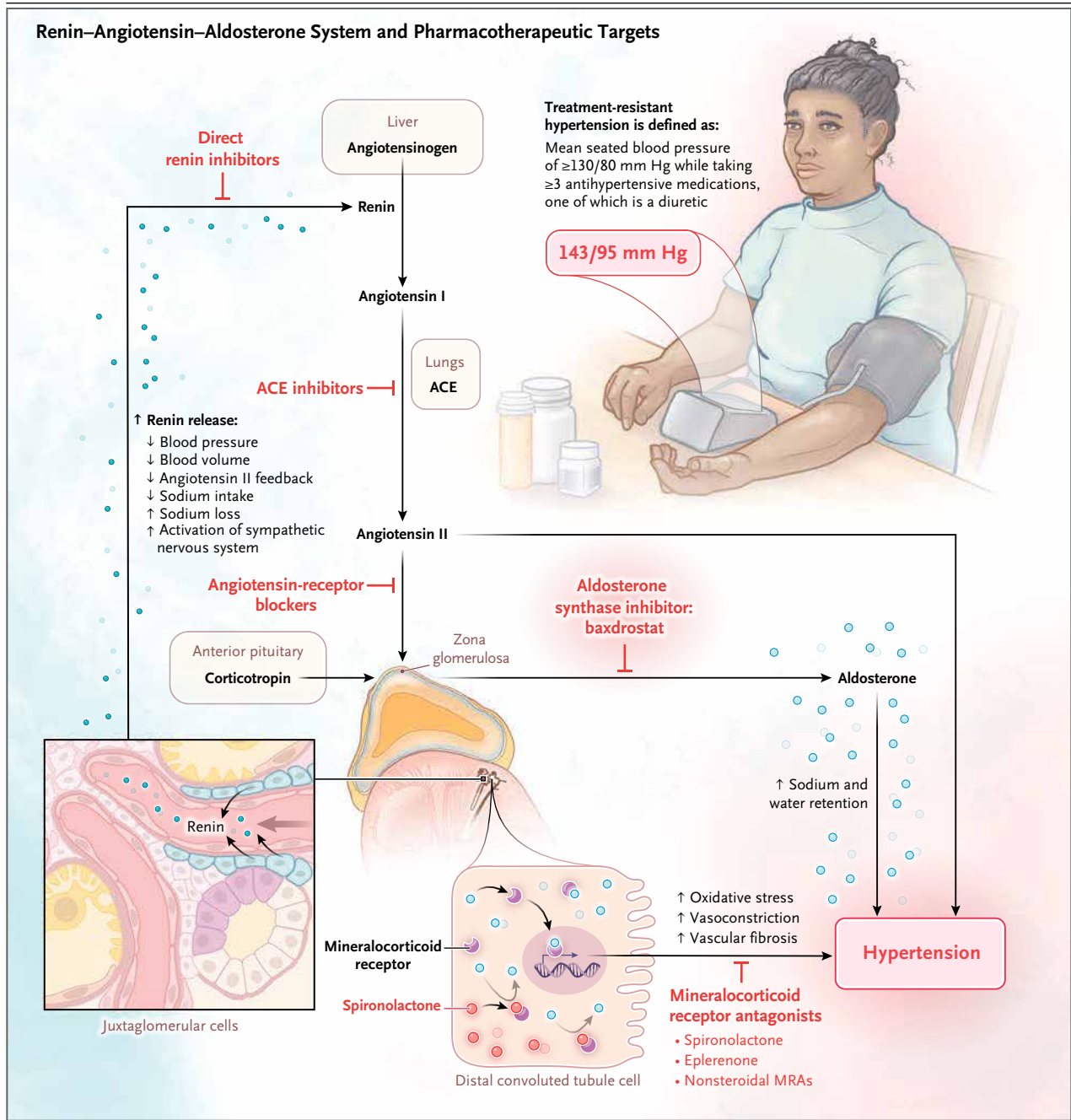
#### HOW DOES SPIRONOLACTONE WORK?

Spironolactone competes with aldosterone to bind to the mineralocorticoid receptor (also known as the aldosterone receptor), which is expressed in the distal convoluted tubule cells of the kidney. The binding of spironolactone to the receptor inhibits aldosterone-dependent sodium-potassium exchange, leading to excretion of sodium and water and retention of potassium. Spironolactone is considered to be a weak diuretic and is usually administered with another drug that targets the proximal tubules in order to increase diuresis. In some patients, the use of spironolactone may cause hyperkalemia. Spironolactone is nonselective — it binds androgen and progesterone receptors, leading to off-target effects such as gynecomastia.

#### Figure 1 (next page). Treatment-Resistant Hypertension and Aldosterone Synthesis.

Treatment-resistant hypertension is defined as a blood pressure that is higher than the goal of less than 130/80 mm Hg in patients who are receiving at least three medications, including a diuretic. The synthesis of aldosterone, a pharmacologic target for the treatment of hypertension, is regulated by the proteins renin and angiotensin. In response to stimuli, the juxtaglomerular cells of the kidney secrete renin, which cleaves angiotensinogen into two fragments, one of which is angiotensin I. Angiotensin I is converted to angiotensin II, primarily in the lungs, by angiotensin-converting enzyme (ACE). Angiotensin II, a potent vasoconstrictor, stimulates cells in the zona glomerulosa of the adrenal gland to synthesize and secrete aldosterone. Corticotropin released by the pituitary gland also stimulates adrenal aldosterone production, albeit to a lesser degree than angiotensin II. Drug classes that are commonly used to treat hypertension and their sites of action in the renin-angiotensin-aldosterone system are shown. Baxdrostat blocks aldosterone synthase (also known as CYP11B2), thereby inhibiting the synthesis of aldosterone. Other drugs used to block the actions of aldosterone (e.g., spironolactone, eplerenone, and nonsteroidal mineralocorticoid receptor antagonists [MRAs]) inhibit the activation of the mineralocorticoid receptor by aldosterone.

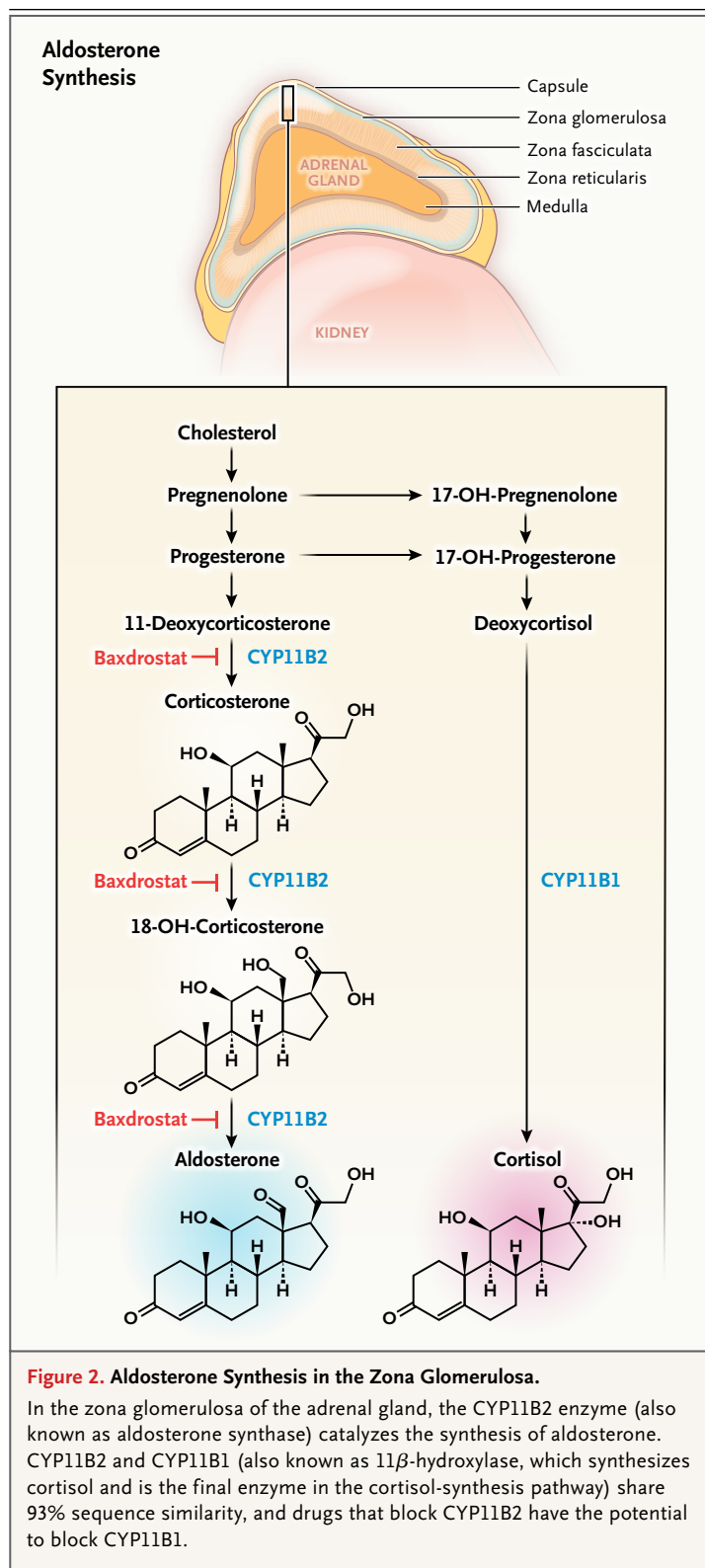




**HOW DOES BAXDROSTAT AFFECT ALDOSTERONE LEVELS?**

Baxdrostat, a small-molecule drug (see **Key Concepts**) decreases levels of aldosterone by inhibiting its synthesis. It does so by inhibiting the CYP11B2 enzyme (also known as aldosterone synthase) that catalyzes the final steps of aldo-

sterone synthesis from cholesterol (Fig. 2). Moreover, it is highly selective for CYP11B2. This selectivity is good because the CYP11B2 enzyme has 93% sequence similarity with CYP11B1 (also known as  $11\beta$ -hydroxylase), the final enzyme in the cortisol-synthesis pathway. This high degree of similarity led to cross-reactivity and suppres-



sion of cortisol synthesis by earlier aldosterone synthase inhibitors, which rendered these compounds inappropriate as antihypertensive agents. Freeman et al. found that in addition to lowering plasma aldosterone levels and blood pressure, baxdrostat had no substantive effect on plasma cortisol levels.

#### WHAT'S NEXT?

Among the new therapeutic agents that target the renin–angiotensin–aldosterone system in patients with treatment-resistant hypertension are nonsteroidal mineralocorticoid receptor antagonists and antisense oligonucleotide or small interfering RNA therapies. Nonsteroidal mineralocorticoid receptor antagonists such as finerenone and esaxerenone have a longer plasma half-life than spironolactone and are specific for the mineralocorticoid receptor, with no evident hormonal side effects.<sup>6</sup> Antisense oligonucleotides and RNA-interference oligonucleotides that are designed to target the synthesis of angiotensinogen in the liver are under investigation in patients with treatment-resistant hypertension.<sup>6</sup>

Inhibition of aldosterone synthesis with baxdrostat may expand the possible choices of therapeutic agents for treatment-resistant hypertension. The benefits of inhibiting aldosterone synthesis may also extend beyond treatment-resistant hypertension, because elevated levels of aldosterone have been implicated in the pathobiology of pulmonary hypertension, obesity, and insulin resistance and metabolic syndrome.

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

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## ORIGINAL ARTICLE

# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group\*

## ABSTRACT

**BACKGROUND**

The effects of empagliflozin in patients with chronic kidney disease who are at risk for disease progression are not well understood. The EMPA-KIDNEY trial was designed to assess the effects of treatment with empagliflozin in a broad range of such patients.

**METHODS**

We enrolled patients with chronic kidney disease who had an estimated glomerular filtration rate (eGFR) of at least 20 but less than 45 ml per minute per 1.73 m<sup>2</sup> of body-surface area, or who had an eGFR of at least 45 but less than 90 ml per minute per 1.73 m<sup>2</sup> with a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of at least 200. Patients were randomly assigned to receive empagliflozin (10 mg once daily) or matching placebo. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m<sup>2</sup>, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from cardiovascular causes.

**RESULTS**

A total of 6609 patients underwent randomization. During a median of 2.0 years of follow-up, progression of kidney disease or death from cardiovascular causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). Results were consistent among patients with or without diabetes and across subgroups defined according to eGFR ranges. The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

**CONCLUSIONS**

Among a wide range of patients with chronic kidney disease who were at risk for disease progression, empagliflozin therapy led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo. (Funded by Boehringer Ingelheim and others; EMPA-KIDNEY ClinicalTrials.gov number, NCT03594110; EudraCT number, 2017-002971-24.)

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\*A complete list of members of the EMPA-KIDNEY Collaborative Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Herrington and Staplin and Drs. Landray, Baigent, and Haynes contributed equally to this article.

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## RESEARCH SUMMARY

# Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group DOI: 10.1056/NEJMoa2204233

## CLINICAL PROBLEM

Sodium–glucose cotransporter 2 inhibitors appear to slow the progression of kidney disease in patients with diabetes and albuminuria. However, most patients with chronic kidney disease do not have diabetes and have low levels of albuminuria, and the effects of empagliflozin therapy in these patients are unclear.

## CLINICAL TRIAL

**Design:** This international, randomized, parallel-group, double-blind, placebo-controlled trial assessed the efficacy of empagliflozin in patients with chronic kidney disease, with or without diabetes and with a range of albuminuria levels.

**Intervention:** 6609 patients with an estimated glomerular filtration rate (eGFR) of 20 to <45 ml per minute per 1.73 m<sup>2</sup> of body-surface area, or with an eGFR of 45 to <90 ml per minute per 1.73 m<sup>2</sup> and a urinary albumin-to-creatinine ratio of ≥200 (with albumin measured in milligrams and creatinine measured in grams), were assigned to receive 10 mg of empagliflozin or placebo daily. In this study, 54% of patients had chronic kidney disease without diabetes and 34% had an eGFR of <30 ml per minute per 1.73 m<sup>2</sup>. The primary outcome was the first occurrence of progression of kidney disease or death from cardiovascular causes.

## RESULTS

**Efficacy:** During a median follow-up of 2 years, progression of kidney disease or death from cardiovascular causes occurred in a significantly smaller percentage of patients in the empagliflozin group than in the placebo group.

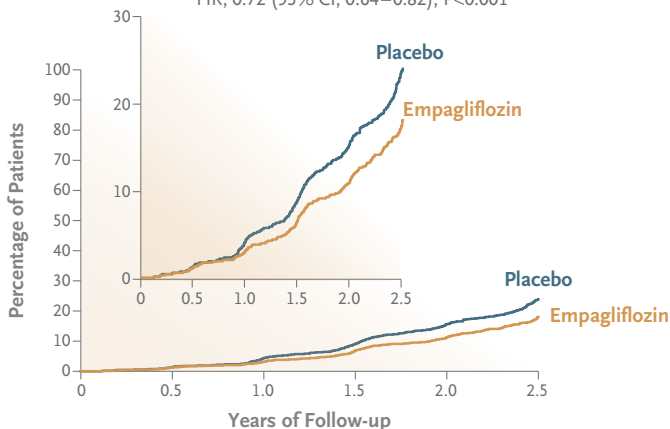
**Safety:** Ketoacidosis occurred in numerically more patients in the empagliflozin group than in the placebo group, as did lower-limb amputations. The incidence of serious adverse events overall and according to major organ class was similar in the two groups.

## LIMITATIONS AND REMAINING QUESTIONS

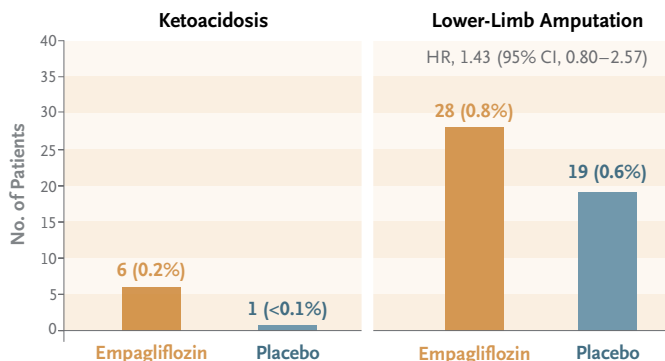
- Fewer cardiovascular events occurred than expected, potentially affecting secondary and tertiary outcome assessments.
- Further study of patients with a urinary albumin-to-creatinine ratio of less than 300 may be useful.

## Progression of Kidney Disease or Death from Cardiovascular Causes

HR, 0.72 (95% CI, 0.64–0.82); P<0.001



## Safety Outcomes



## CONCLUSIONS

Among a wide range of patients with chronic kidney disease who were at risk for progression, empagliflozin therapy was associated with a lower risk of disease progression or death from cardiovascular causes than placebo.

## EDITORIAL

## Chronic Kidney Disease — Another Step Forward

Phyllis August, M.D., M.P.H.

Chronic kidney disease (CKD) will be the fifth highest cause of years of life lost worldwide by 2040.<sup>1</sup> CKD is defined as a sustained estimated glomerular filtration rate (eGFR) of less than 60 ml per minute per 1.73 m<sup>2</sup> of body-surface area or a urinary albumin excretion of 30 mg or more per day, or both, for more than 3 months. The Kidney Disease: Improving Global Outcomes 2012 guidelines classified CKD and the risk of progression on the basis of both eGFR and the degree of albuminuria (the lower the eGFR and the higher the albuminuria, the worse the prognosis).<sup>2</sup> Albuminuria is both a risk marker and a therapeutic target. For more than three decades, drugs that block the renin-angiotensin system (RAS) have been the most widely used strategy to slow CKD progression. These drugs both lower systemic blood pressure and intraglomerular pressure and decrease albuminuria, and they may prevent glomerulosclerosis. The degree of albuminuria reduction by RAS blockers appears to track with the ability of these agents to preserve kidney function.<sup>3</sup> When patients with a reduced GFR but normoalbuminuria (most patients with CKD) receive RAS blockers, they do not have the same level of renoprotection as those with clinically significant albuminuria.<sup>4</sup> The reduced benefit from RAS blockade in patients with CKD who have normoalbuminuria underscores the need for additional approaches to renoprotection.

Enter sodium-glucose cotransporter 2 (SGLT2) inhibitors. The SGLT2 protein in the proximal tubule of the kidney mediates both glucose and sodium reabsorption; inhibition of SGLT2 results in glucosuria, osmotic diuresis, and modest natriuresis. A plausible mechanism for renoprotection is that increased sodium delivery to the macula densa cells of the juxtaglomerular apparatus, through tubuloglomerular feedback, causes afferent arteriolar vasoconstriction, decreases hyperfiltration and intraglomerular pressure, and thus preserves glomeruli. Originally developed to treat hyperglycemia in patients with type 2 diabetes, SGLT2 inhibitors were shown to

improve cardiovascular and kidney outcomes in patients with diabetes with or without CKD.<sup>5,6</sup> Subsequent studies of SGLT2 inhibitors that were restricted to patients with CKD with albuminuria showed reduced CKD progression.<sup>7,8</sup>

The EMPA-KIDNEY trial (Study of Heart and Kidney Protection with Empagliflozin), the results of which are published in this issue of the *Journal*,<sup>9</sup> is a step forward. A total of 6609 patients with or without diabetes, with an eGFR of at least 20 but less than 45 ml per minute per 1.73 m<sup>2</sup>, regardless of albuminuria level, or with an eGFR of at least 45 but less than 90 ml per minute per 1.73 m<sup>2</sup> with a urinary albumin-to-creatinine ratio of at least 200 (with albumin measured in milligrams and creatinine measured in grams), were randomly assigned to receive empagliflozin (10 mg once daily) or placebo. Most patients were receiving RAS inhibitors at baseline. The patients had lower baseline eGFR levels and a lower mean urinary albumin-to-creatinine ratio (48% of patients had a urinary albumin-to-creatinine ratio of  $\leq 300$ ) than those in previous studies. The primary outcome of the trial was progression of kidney disease (defined as end-stage kidney disease [ESKD], a sustained decrease in the eGFR to  $<10$  ml per minute per 1.73 m<sup>2</sup>, a sustained decrease from baseline in the eGFR of  $>40\%$ , or death from renal causes) or death from cardiovascular causes. Empagliflozin treatment resulted in a lower risk of progression of kidney disease or death from cardiovascular causes than placebo (hazard ratio, 0.72; 95% confidence interval, 0.64 to 0.82). The trial was stopped early for efficacy after a median follow-up of 2 years. Blood pressure, body weight, and the urinary albumin-to-creatinine ratio were lower in the empagliflozin group than in the placebo group. There were no between-group differences in the incidence of serious adverse events.

Because this trial enrolled patients with CKD with or without diabetes and patients who had lower eGFR levels and normoalbuminuria, the results provide support for prescribing SGLT2



inhibitors to prevent CKD progression in a broader range of patients than previously studied. Two questions remain. In most trials, and for most participants in this trial, SGLT2 inhibitors were added to RAS inhibitors, since RAS inhibitors are standard care. The results of subgroup analyses in the EMPA-KIDNEY trial suggest that among the 981 patients who were not receiving RAS blockade, the effect of empagliflozin treatment was not as evident. Therefore, whether SGLT2 inhibitors are equally effective without RAS blockade is unclear. The second issue is whether SGLT2 inhibitors are effective in patients with normoalbuminuria. In this trial, empagliflozin treatment reduced the risk of progression of kidney disease or death from cardiovascular causes among patients with or without diabetes, although to a lesser degree among those without diabetes. The incidence of progression of kidney disease or death from cardiovascular causes among the patients in the empagliflozin group who had normal or moderate albuminuria (a urinary albumin-to-creatinine ratio of 30 to 300) was similar to that among the patients in the placebo group, perhaps because of a lower risk of progression of CKD and fewer kidney outcomes in these patients. The benefit observed among the patients with lower eGFRs was impressive, but whether it was observed primarily in those with albuminuria also requires clarification.

The EMPA-KIDNEY trial adds to the evidence that SGLT2 inhibitors reduce the risk of progression of CKD or death from cardiovascular disease when added to RAS blockade. Furthermore, the safety profile of SGLT2 inhibitors is reassuring after almost a decade of clinical use. Analysis of the effects of SGLT2 inhibitors on CKD

progression on the basis of both eGFR and albuminuria may provide more nuanced guidance for treatment. Longer follow-up to show reductions in the risk of ESKD and death would engender additional confidence. Finally, improved understanding of the mechanisms of renoprotection will further enable clinicians to prescribe the right drug at the right time to the right patient.

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

From the Division of Nephrology and Hypertension, Departments of Medicine and Transplantation Medicine, Weill Cornell Medicine, and the Theresa Lang Center for Research and Education, New York–Presbyterian Hospital, New York.

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## ORIGINAL ARTICLE

# Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated KRAS G12C

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## ABSTRACT

**BACKGROUND**

From the Department of Medicine, Memorial Sloan Kettering Cancer Center, New York (R.Y.); Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill (J.W.); Sarah Cannon Research Institute, Tennessee Oncology, Nashville (M.S.P.); Virginia Cancer Specialists, NEXT Oncology—Virginia, Fairfax (A.I.S.); US Oncology Research, the Woodlands (A.I.S.), and Mary Crowley Cancer Research, Dallas (M.B.) — both in Texas; the University of California Irvine School of Medicine, Chao Family Comprehensive Cancer Center, Orange (S.-H.I.O.), and Mirati Therapeutics, San Diego (J.G.C., K.V., T.K., H.D.-T.) — all in California; the Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University School of Medicine, Atlanta (T.A.L.); Medical Oncology, Mayo Clinic, Phoenix, Arizona (T.S.B.-S.); Belfer Center for Applied Cancer Science and the Department of Medical Oncology, Dana-Farber Cancer Institute (C.P.P., G.A.H.), and the Department of Medicine, Division of Hematology—Oncology, Massachusetts General Hospital (S.J.K.) — both in Boston. Dr. Klemptner can be contacted at [sklemptner@partners.org](mailto:sklemptner@partners.org) or at the Department of Medicine, Division of Hematology—Oncology, Massachusetts General Hospital, Boston, MA 02114. Dr. Yaeger can be contacted at [yaegerr@mskcc.org](mailto:yaegerr@mskcc.org) or at the Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065.

A complete list of the KRYSTAL-1 trial investigators is provided in the Supplementary Appendix, available at [NEJM.org](http://NEJM.org).

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Adagrasib, an oral small-molecule inhibitor of mutant KRAS G12C protein, has shown clinical activity in pretreated patients with several tumor types, including colorectal cancer. Preclinical studies suggest that combining a KRAS G12C inhibitor with an epidermal growth factor receptor antibody could be an effective clinical strategy.

**METHODS**

In this phase 1–2, open-label, nonrandomized clinical trial, we assigned heavily pretreated patients with metastatic colorectal cancer with mutant KRAS G12C to receive adagrasib monotherapy (600 mg orally twice daily) or adagrasib (at the same dose) in combination with intravenous cetuximab once a week (with an initial loading dose of 400 mg per square meter of body-surface area, followed by a dose of 250 mg per square meter) or every 2 weeks (with a dose of 500 mg per square meter). The primary end points were objective response (complete or partial response) and safety.

**RESULTS**

As of June 16, 2022, a total of 44 patients had received adagrasib, and 32 had received combination therapy with adagrasib and cetuximab, with a median follow-up of 20.1 months and 17.5 months, respectively. In the monotherapy group (43 evaluable patients), a response was reported in 19% of the patients (95% confidence interval [CI], 8 to 33). The median response duration was 4.3 months (95% CI, 2.3 to 8.3), and the median progression-free survival was 5.6 months (95% CI, 4.1 to 8.3). In the combination-therapy group (28 evaluable patients), the response was 46% (95% CI, 28 to 66). The median response duration was 7.6 months (95% CI, 5.7 to not estimable), and the median progression-free survival was 6.9 months (95% CI, 5.4 to 8.1). The percentage of grade 3 or 4 treatment-related adverse events was 34% in the monotherapy group and 16% in the combination-therapy group. No grade 5 adverse events were observed.

**CONCLUSIONS**

Adagrasib had antitumor activity in heavily pretreated patients with metastatic colorectal cancer with mutant KRAS G12C, both as oral monotherapy and in combination with cetuximab. The median response duration was more than 6 months in the combination-therapy group. Reversible adverse events were common in the two groups. (Funded by Mirati Therapeutics; KRYSTAL-1 ClinicalTrials.gov number, NCT03785249.)

## RESEARCH SUMMARY

# Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

Yaeger R et al. DOI: 10.1056/NEJMoa2212419

## CLINICAL PROBLEM

*KRAS* G12C mutations occur in 3 to 4% of patients with metastatic colorectal cancer. Adagrasib — an oral, small-molecule inhibitor of mutant *KRAS* G12C protein — has shown promising clinical activity in patients with *KRAS* G12C-mutated tumors, including colorectal cancer. Whether combining adagrasib with an epidermal growth factor receptor (EGFR) antibody could be an effective treatment strategy is unknown.

## CLINICAL TRIAL

**Design:** A phase 1–2, open-label, nonrandomized clinical trial assessed the safety and efficacy of adagrasib, either as monotherapy or combined with the EGFR inhibitor cetuximab, in heavily pretreated patients with metastatic colorectal cancer with a *KRAS* G12C mutation.

**Intervention:** 44 patients with measurable disease according to RECIST, version 1.1, received oral adagrasib alone twice daily, and 32 patients with measurable or evaluable disease according to the same criteria received adagrasib twice daily plus intravenous cetuximab either once weekly or once every 2 weeks. The primary outcome in the monotherapy group was objective response (complete or partial response). The primary outcome in the combination-therapy group was safety.

## RESULTS

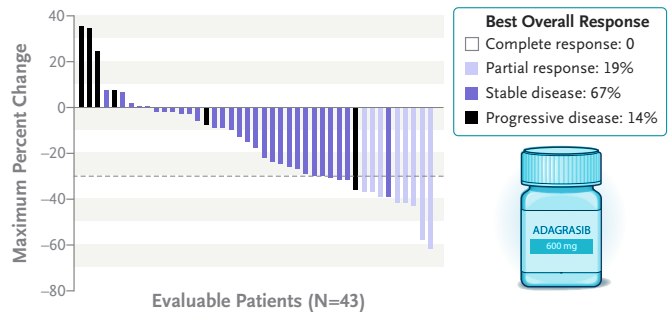
**Efficacy:** Among evaluable patients, 19% (95% CI, 8 to 33) in the monotherapy group had an objective response, with a median response duration of 4.3 months. In the combination-therapy group, 46% (95% CI, 28 to 66) had a response, with a median response duration of 7.6 months.

**Safety:** Treatment-related adverse events were common and generally reversible. Grade 3 or 4 treatment-related adverse events occurred in 34% of the patients in the monotherapy group and 16% of the patients in the combination-therapy group.

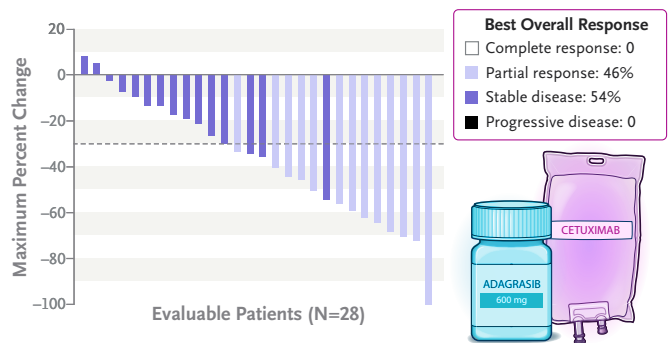
## LIMITATIONS AND REMAINING QUESTIONS

- The nonrandomized trial design precluded comparisons between treatment groups.
- The activity and safety of adagrasib plus cetuximab as compared with standard chemotherapy are unknown and are currently under investigation.

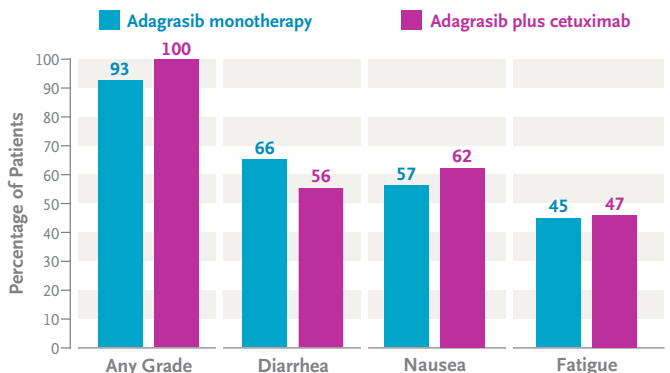
### Best Tumor Change from Baseline — Adagrasib Monotherapy



### Best Tumor Change from Baseline — Adagrasib plus Cetuximab



### Treatment-Related Adverse Events



## CONCLUSIONS

Among previously treated patients with metastatic colorectal cancer with a *KRAS* G12C mutation, adagrasib — used alone or in combination with cetuximab — showed promising antitumor activity and resulted in no new safety concerns.

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## Lecanemab in Early Alzheimer's Disease

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### ABSTRACT

#### BACKGROUND

The accumulation of soluble and insoluble aggregated amyloid-beta ( $A\beta$ ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to  $A\beta$  soluble protofibrils, is being tested in persons with early Alzheimer's disease.

#### METHODS

We conducted an 18-month, multicenter, double-blind, phase 3 trial involving persons 50 to 90 years of age with early Alzheimer's disease (mild cognitive impairment or mild dementia due to Alzheimer's disease) with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were randomly assigned in a 1:1 ratio to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary end point was the change from baseline at 18 months in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB; range, 0 to 18, with higher scores indicating greater impairment). Key secondary end points were the change in amyloid burden on PET, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog14; range, 0 to 90; higher scores indicate greater impairment), the Alzheimer's Disease Composite Score (ADCOMS; range, 0 to 1.97; higher scores indicate greater impairment), and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-MCI-ADL; range, 0 to 53; lower scores indicate greater impairment).

#### RESULTS

A total of 1795 participants were enrolled, with 898 assigned to receive lecanemab and 897 to receive placebo. The mean CDR-SB score at baseline was approximately 3.2 in both groups. The adjusted least-squares mean change from baseline at 18 months was 1.21 with lecanemab and 1.66 with placebo (difference,  $-0.45$ ; 95% confidence interval [CI],  $-0.67$  to  $-0.23$ ;  $P < 0.001$ ). In a substudy involving 698 participants, there were greater reductions in brain amyloid burden with lecanemab than with placebo (difference,  $-59.1$  centiloids; 95% CI,  $-62.6$  to  $-55.6$ ). Other mean differences between the two groups in the change from baseline favoring lecanemab were as follows: for the ADAS-cog14 score,  $-1.44$  (95% CI,  $-2.27$  to  $-0.61$ ;  $P < 0.001$ ); for the ADCOMS,  $-0.050$  (95% CI,  $-0.074$  to  $-0.027$ ;  $P < 0.001$ ); and for the ADCS-MCI-ADL score,  $2.0$  (95% CI,  $1.2$  to  $2.8$ ;  $P < 0.001$ ). Lecanemab resulted in infusion-related reactions in 26.4% of the participants and amyloid-related imaging abnormalities with edema or effusions in 12.6%.

#### CONCLUSIONS

Lecanemab reduced markers of amyloid in early Alzheimer's disease and resulted in moderately less decline on measures of cognition and function than placebo at 18 months but was associated with adverse events. Longer trials are warranted to determine the efficacy and safety of lecanemab in early Alzheimer's disease. (Funded by Eisai and Biogen; Clarity AD ClinicalTrials.gov number, NCT03887455.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. van Dyck can be contacted at [christopher.vandyck@yale.edu](mailto:christopher.vandyck@yale.edu) or at the Alzheimer's Disease Research Unit, Division of Aging and Geriatric Psychiatry, Yale School of Medicine, 1 Church St., 8th Fl., New Haven, CT 06510.

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## RESEARCH SUMMARY

## Lecanemab in Early Alzheimer's Disease

van Dyck CH et al. DOI: 10.1056/NEJMoa2212948

## CLINICAL PROBLEM

Some evidence suggests that amyloid removal slows the progression of Alzheimer's disease. Lecanemab, an anti-amyloid monoclonal antibody with high affinity for soluble amyloid protofibrils, is being tested in early Alzheimer's disease.

## CLINICAL TRIAL

**Design:** A phase 3, multicenter, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of lecanemab in patients 50 to 90 years of age with early Alzheimer's disease.

**Intervention:** 1795 participants in North America, Europe, and Asia were assigned to receive intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks) or placebo. The primary efficacy end point was the change in the score on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) from baseline, with higher scores indicating greater impairment.

## RESULTS

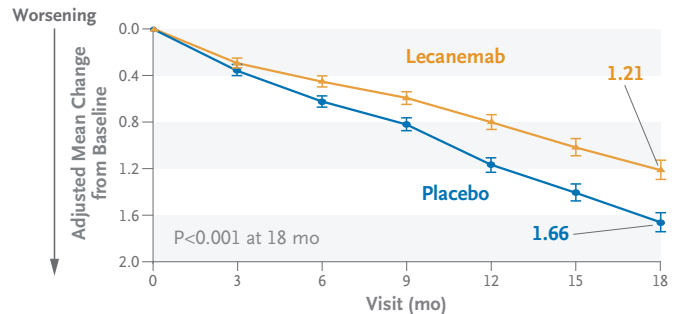
**Efficacy:** At 18 months, mean CDR-SB scores had worsened in both groups. The mean change in CDR-SB score was smaller (indicating less cognitive and functional decline) in the lecanemab group.

**Safety:** Overall incidences of adverse events were similar in the two groups. The most common adverse events in the lecanemab group included infusion-related reactions and amyloid-related imaging abnormalities with edema or effusions.

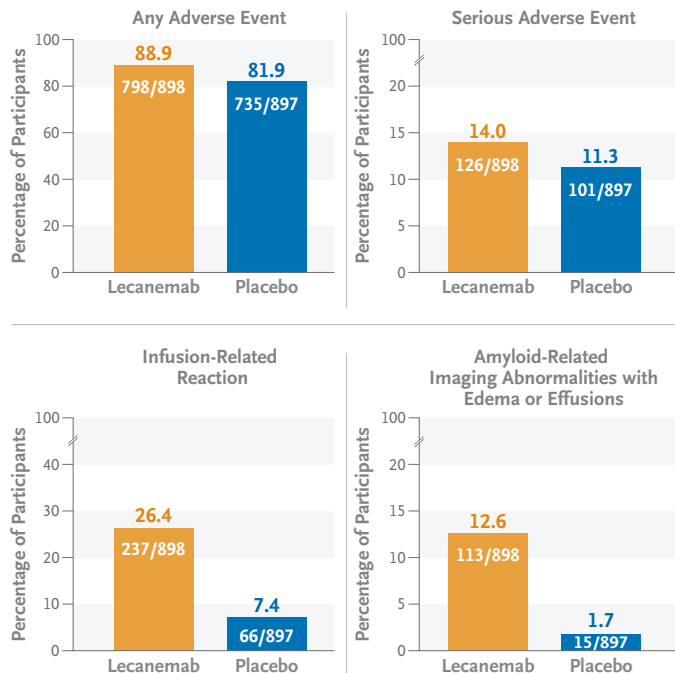
## LIMITATIONS AND REMAINING QUESTIONS

- Longer-term follow-up is needed; an open-label extension study is ongoing.
- The trial was conducted during the Covid-19 pandemic and, as a result, faced challenges including missing data, missed doses, delayed assessments, and intercurrent illnesses.
- Occurrences of amyloid-related imaging abnormalities may have led to unblinding of participants and investigators.

## Change in CDR-SB Score (Range 0–18)

Difference in least-squares mean change,  $-0.45$  (95% CI,  $-0.67$  to  $-0.23$ )

## Safety Outcomes



## CONCLUSIONS

In patients with early Alzheimer's disease, lecanemab was associated with moderately less decline on measures of cognition and function than placebo over a period of 18 months.



## EDITORIAL



## Moving the Needle on Alzheimer's Disease with an Anti-Oligomer Antibody

Sam Gandy, M.D., Ph.D., and Michelle E. Ehrlich, M.D.

In the current issue of the *Journal*, van Dyck and colleagues<sup>1</sup> report the encouraging results of an 18-month, phase 3 trial of lecanemab that involved participants with early Alzheimer's disease. The primary end point was the change from baseline in the score on the Clinical Dementia Rating–Sum of Boxes. Key secondary end points were the change from baseline in amyloid burden as assessed by means of positron emission tomography, the score on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale, the Alzheimer's Disease Composite Score, and the score on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale for Mild Cognitive Impairment. For each of these five end points, lecanemab was statistically better than placebo, although the effect sizes were modest. Lecanemab is one of several anti-amyloid antibodies to undergo evaluation in clinical trials but the first to show significant between-group differences in its prespecified end points. These findings raise the question of what might make lecanemab different.

In 2001, a total of 11 members of a family in northern Sweden who had early-onset familial Alzheimer's disease were reported to harbor a specific mutation in the gene encoding amyloid precursor protein (*APP*). The mutation, *APP*<sup>E693G</sup>, was dubbed the “Arctic” mutation.<sup>2</sup> The mutation is within amyloid-beta ( $A\beta$ ); in the same study, human kidney cells transfected with *APP*<sup>E693G</sup> secreted unexpectedly low levels of “Arctic  $A\beta$ ” peptides. Biophysical investigation of Arctic  $A\beta$  provided a clue to how low levels of a mutant  $A\beta$  could cause Alzheimer's disease.  $A\beta$  peptides

can exist in at least two conformations: unstructured aggregates known as soluble oligomers or protofibrils, or plaques composed of insoluble fibrils. The location of the Arctic mutation within the  $A\beta$  sequence prevented amyloid fibril formation,<sup>3</sup> leading  $A\beta$  peptides to form soluble  $A\beta$  oligomers and protofibrils rather than insoluble fibrils. Although soluble  $A\beta$  oligomers and protofibrils are known to be formed by wild-type  $A\beta$  as well, the Arctic mutation provided the first evidence that any *APP* mutations might act by producing oligomers and protofibrils as the preponderant conformation. The first pathogenic *APP* mutation, *APP*<sup>E693Q</sup> (Dutch type) was reported in 1990,<sup>4</sup> and the identical amino acid is altered in both the Arctic and Dutch  $A\beta$ , leading both to form soluble oligomers.<sup>5</sup> In 2004, wild-type, Dutch, and Arctic  $A\beta$  peptides were injected into rodent brains and observed to impair long-term potentiation,<sup>6</sup> a popular laboratory model for memory formation. Until that point, overproduction of “long”  $A\beta$ <sub>42</sub> had been considered to underlie early-onset familial Alzheimer's disease. Soon thereafter, researchers targeted Arctic  $A\beta$  oligomers with a mouse anti- $A\beta$  monoclonal antibody approach; lecanemab is a genetically humanized monoclonal antibody against oligomers and protofibrils that was tested in the current clinical trial.

Many  $A\beta$  research studies are performed with the use of chemically synthesized peptides,<sup>6</sup> and those synthetic peptides may or may not mimic the structure of  $A\beta$  that is biologically generated in the brain. To approach this question, we generated a mouse model in which the oligomer-

forming APP<sup>E693Q</sup> accumulated in all brain neurons.<sup>7</sup> These mice had changes in learning behavior that are associated with presynaptic dysfunction,<sup>7,8</sup> but A $\beta$  fibrils did not develop. The same appeared to be true of human carriers of APP<sup>E693G</sup>, according to Schöll et al.<sup>9</sup> Thus, data from studies in both animals and humans support the clinical relevance of A $\beta$  oligomers, even though they cannot yet be detected in living patients with the use of imaging or body-fluid analysis. Despite the efficient purging of A $\beta$  fibrils by lecanemab, residual A $\beta$  oligomers may explain, at least in part, why lecanemab does not produce a larger clinical effect.

One or two APOE  $\epsilon$ 4 alleles are present in approximately half of patients with Alzheimer's disease, and in the lecanemab trial, a side effect of brain swelling or bleeding was apparently related to the dose of APOE  $\epsilon$ 4. After the randomized phase of the trial was completed, two patients receiving open-label lecanemab died due to cerebral hemorrhage, but the APOE status of one of those patients has not yet been disclosed. In a case report involving the other patient, who had cerebral hemorrhages while receiving tissue plasminogen activator (t-PA) for acute stroke, homozygosity for APOE  $\epsilon$ 4 was noted.<sup>10</sup> Although both situations were complex, it seems reasonable to conclude that if lecanemab is approved, informed consent might include a warning against concurrent use of t-PA and possibly other drugs that modulate cerebral intravascular hemostasis.

A downstream step in the progression of Alzheimer's disease is accumulation of abnormally phosphorylated tau, and both amyloid and tau are currently being studied as imaging and body-fluid biomarkers that might predict the presence of pathologic processes in Alzheimer's disease before the onset of clinical symptoms.<sup>11</sup> This observation raises the possibility that effective secondary-prevention strategies might spare these cognitively intact, biomarker-positive persons from the development of clinical dementia. Lecanemab or other oligomer-reducing interventions might be included in such a strategy. It is also likely that non-A $\beta$  targets will be required to maximize benefits of treatment. Among these, glia and the immune-inflammatory system have attracted much recent attention,<sup>12</sup> but we cannot yet say which molecules should be targeted,

whether they should be activated or inhibited, or when during the disease we should target them.<sup>13,14</sup> Thus, there remains much work ahead, but that should not distract from the achievement of the current trial in moving the needle on Alzheimer's disease, however modestly.

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

From the Departments of Neurology (S.G., M.E.E.), Psychiatry (S.G.), Pediatrics (M.E.E.), and Genetics and Genomic Sciences (M.E.E.), and the Alzheimer's Disease Research Center (S.G.), Icahn School of Medicine at Mount Sinai, New York, and James J. Peters Department of Veterans Affairs Medical Center, Bronx (S.G.) — both in New York.

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IN DEPTH

# Combating Misinformation as a Core Function of Public Health

Janine Knudsen, MD, Maddie Perlman-Gabel, MSPH,  
Isabella Guerra Uccelli, Jessica Jeavons, JD, MA,  
Dave A. Chokshi, MD, MSc

Vol. 4 No. 2 | February 2023

DOI: [10.1056/CAT.22.0198](https://doi.org/10.1056/CAT.22.0198)



The New York City Department of Health and Mental Hygiene determined that the spread of misinformation about Covid-19 was having a harmful health impact, particularly on communities of color with low vaccination rates. It established a dedicated Misinformation Response Unit to monitor messages containing dangerous misinformation presented on multiple media platforms, including social media, non-English media, and international sites, and proliferating in community forums. The Misinformation Response Unit and the Health Department collaborated with more than 100 community partners to tailor culturally appropriate, scientifically accurate messages to different populations. The Health Department and its partners were able to rapidly identify messages containing inaccurate information about Covid-19 vaccines, treatment, and other issues and to support the delivery of accurate information to various populations. Although the harms of misinformation and benefits of addressing the problem require additional evaluation, internal and external interviews suggested that the Misinformation Response Unit helped the Health Department counter misinformation and disseminate accurate scientific information to the community, thus improving health and vaccine equity during the Covid-19 pandemic.

## The Challenge of Misinformation

Misinformation has run rampant during the Covid-19 public health emergency, challenging the communication and trust-building efforts of public health and medical professionals. Nearly

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## ORIGINAL ARTICLE

# Intraoperative Fluorescence Guidance for Breast Cancer Lumpectomy Surgery

Barbara L. Smith, M.D., Ph.D.,<sup>1</sup> Kelly K. Hunt, M.D.,<sup>2</sup> David Carr, M.D.,<sup>3</sup> Peter W. Blumencranz, M.D.,<sup>4</sup> E. Shelley Hwang, M.D., M.P.H.,<sup>5</sup> Michele A. Gadd, M.D.,<sup>1</sup> Kimberly Stone, M.D.,<sup>6</sup> Donna L. Dyess, M.D.,<sup>7</sup> Daleela Dodge, M.D.,<sup>8</sup> Stephanie Valente, D.O.,<sup>9</sup> Nayana Dekhne, M.D.,<sup>10</sup> Patricia Clark, M.D.,<sup>11</sup> Marie Catherine Lee, M.D.,<sup>12</sup> Laila Samiian, M.D.,<sup>13</sup> Beth-Anne Lesnikoski, M.D.,<sup>13</sup> Lynne Clark, M.D.,<sup>14</sup> Kate Porta Smith, M.P.H., C.C.R.P.,<sup>15</sup> Manna Chang, Ph.D.,<sup>15</sup> Daniel K. Harris, Ph.D.,<sup>15</sup> Brian Schlossberg, Ph.D.,<sup>15</sup> Jorge Ferrer, Ph.D.,<sup>15</sup> Irene L. Wapnir, M.D.,<sup>6</sup> for the INSITE Study Team\*

## Abstract

**BACKGROUND** Although lumpectomy and mastectomy provide equivalent survival for patients with breast cancer, local recurrence after lumpectomy increases breast cancer mortality. Positive lumpectomy margins, which imply incomplete tumor removal, are the strongest predictor of local recurrence and are identified days after surgery, necessitating a second surgery.

**METHODS** In this prospective trial, we assessed margin status with or without pegulicanine fluorescence-guided surgery (pFGS) for stages 0 to 3 breast cancers. To prevent surgeons from performing smaller than standard lumpectomies in anticipation of pFGS assistance, patients were randomly assigned 10:1 to pFGS or control groups, thus randomization was not designed to provide a control group for evaluating device performance. In patients undergoing pFGS, additional pFGS-guided cavity margins were excised at sites of pegulicanine signal. We evaluated three coprimary end points: the percentage of patients for whom pFGS-guided margins contained cancer, sensitivity, and specificity.

**RESULTS** Overall, 406 patients received 1.0 mg/kg intravenous pegulicanine followed by lumpectomy. Among 392 patients randomly assigned, 316 had invasive cancers, and 76 had in situ cancers. In 27 of 357 patients undergoing pFGS, pFGS-guided margins removed tumor left behind after standard lumpectomy, 22 from cavity orientations deemed negative on standard margin evaluation. Second surgeries were avoided by pFGS in 9 of 62 patients with positive margins. On per-margin analysis, pFGS specificity was 85.2%, and sensitivity was 49.3%. Pegulicanine administration was stopped for adverse events in six patients. Two patients had grade 3 serious adverse events related to pegulicanine.

**CONCLUSIONS** The use of pFGS in breast cancer surgery met prespecified thresholds for removal of residual tumor and specificity but did not meet the prespecified threshold

\*A complete list of investigators in the INSITE Study Team is provided in the Supplementary Appendix, available at [evidence.nejm.org](https://evidence.nejm.org).

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## EDITORIAL

# Something to Dye For: Toward Better Breast Lumpectomy Margins

Lauren C. Turza, M.D.,<sup>1</sup> and Craig D. Shriver, M.D., F.A.C.S., COL, USA (Ret)<sup>2</sup>

**T**he development of fluorescence imaging in oncology led to the possibility of using intraoperative devices to improve the precision of surgical techniques.<sup>1</sup> In this issue of *NEJM Evidence*, Smith et al.<sup>2</sup> report results from a prospective multicenter trial evaluating the ability of intravenous pegulicanine with an optical head device and software to intraoperatively identify lumpectomy margins with residual breast cancer and excise them immediately. Identifying these margins intraoperatively avoids the need for a second surgery, which is required when margins are positive on the final pathology. The promising results in this report are good news for the field as it moves forward to further refinement and wide acceptance of the technique.

In this trial involving patients undergoing surgery for breast cancer, the investigators assessed margin status both with and without pegulicanine fluorescence-guided surgery (pFGS).<sup>2</sup> Patients were randomly assigned in a 10-to-1 ratio to pFGS or control groups, with allocation only revealed once the surgeon completed the standard lumpectomy. Randomization, therefore, was not intended to provide a control group for evaluating device performance but rather to ensure that surgeons completed the lumpectomy as they typically would have. For patients undergoing pFGS, surgeons excised additional pFGS-guided cavity margins at sites of pegulicanine signal.

Nine (14.5%) of 62 patients with positive final pathologic lumpectomy margins avoided a second surgery as the device identified these margins intraoperatively.<sup>2</sup> This is a step in the right direction, and additional refinements in the technique will hopefully result in an even better rate of avoiding re-excision lumpectomy. Although the feasibility studies of this technique showed that margin detection sensitivities of this technology were 76.3 to 100%,<sup>3,4</sup> the sensitivity in the current study was only 49%.<sup>2</sup> The substantially lower sensitivity in this trial compared with the prior studies is an area for possible improvement. Also, although this trial understandably limited the taking of additional margins to no more than two, excising all positive pFGS margins — in the context of the reported specificity of 85% — may help more patients avoid a second surgery, which is the primary benefit of this technique.

This multicenter trial also shows the potential to successfully export this technique to surgeons across multiple sites.<sup>2</sup> This dissemination is critical to achieving the equitable distribution of precision surgical approaches that benefit patients. This is reminiscent of the multicenter trial in 1998 that showed these same proof-of-concept and expansion ideas for

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the use of sentinel node biopsy for early-stage breast cancer.<sup>5</sup> In addition, when comparing this technique versus other technical approaches that have a similar goal of decreasing the second surgery rate, results of this trial show promising improvements over others. Multicenter trials looking at other approaches to avoid a second surgery after lumpectomy reported a decrease in the rate of re-excision using novel techniques and devices, including the cavity shave margin (CSM) trial (decrease in re-excision from 21 to 10%), and the MarginProbe Trial (decrease in re-excision from 26 to 20%).<sup>6,7</sup>

The impact of this technology on cosmesis is also critical. Smith et al.<sup>2</sup> indirectly assessed cosmesis based on the volume change between standard lumpectomy and lumpectomy with pFGS margins. In this trial, the standard lumpectomy removed an average tissue volume of 74.9 cm<sup>3</sup>, with the pFGS margin removing an additional average of 21.8±20.1 cm<sup>3</sup>. By comparison, in the CSM trial, the volume removed during a standard lumpectomy was 74.2 cm<sup>3</sup> versus 115.1 cm<sup>3</sup> when shave margins were taken.<sup>6</sup> This report did not include questionnaires regarding cosmesis. However, given that the volumes removed during the CSM trial were on average slightly higher than the volumes removed in the current trial,<sup>2</sup> and no difference in perception of cosmesis in the CSM trial was noted between the intervention and control groups,<sup>6</sup> it is likely that this pFGS technique had a limited impact on cosmesis.

One current limitation regarding the pFGS technique is the timing and location of blue dye injection to assist in sentinel node biopsy, which cannot be done before the use of pegulicianine. According to the authors,<sup>2</sup> this issue is currently being studied. Surgeons also need to be careful not to extend the use of this technique to patients outside of the inclusion criteria for this trial until further research is conducted with broader patient populations. Further studies are needed to determine the true clinical utility of this technique on in-breast recurrence rates. In addition, although this technique might be considered as a potential tool for the de-escalation of radiation therapy in highly selected patients undergoing breast-conserving therapy, this is a separate question that would need to be studied in a stand-alone, prospective randomized trial. This technology may also be useful when adjuvant radiation can be omitted and for women undergoing a concurrent level II oncoplasty (the removal of up to 50% of the breast tissue

during partial mastectomy in ptotic moderate- to large-sized breasts) in which a positive margin may lead to the recommendation of a mastectomy.

## Disclosures

Author disclosures are available at [evidence.nejm.org](https://evidence.nejm.org).

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## EDITORIAL

# Why We Support and Encourage the Use of Large Language Models in *NEJM AI* Submissions

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## Abstract

Large language models (LLMs) promise to revolutionize many aspects of the creation and dissemination of scientific knowledge; however, their use in scientific writing remains controversial, because of concerns about authorship, originality, factual inaccuracies, and “hallucinations” or confabulations. As a result, several publication venues have explicitly prohibited their use. At *NEJM AI*, we have elected instead to allow the use of LLMs for submissions, as long as authors take complete responsibility for the content and properly acknowledge the use of LLMs. However, this policy does not allow an LLM to be listed as a coauthor. We believe that the use of LLM tools can help scientists enhance the quality of their scientific work and democratize both the creation and consumption of scientific knowledge, thereby helping us maximally enable the scientific workforce to produce robust, novel scientific findings and disseminate them broadly.

Large language models (LLMs) have recently emerged as a powerful tool across many areas of biomedicine. They are able to rapidly summarize large amounts of text, generate high-quality text from a short description, create code that can help support data analysis, produce images on the basis of a verbal description, and much more. On the surface, it appears plausible that an LLM can generate an entire scientific paper, which can then be submitted, as is, for publication. This possibility complicates proper attribution of a text’s authorship, and it raises the specter of a potential flood of low-quality scientific work that was not originated or overseen by a human but nonetheless was submitted for peer-reviewed publication. As a consequence, some publication venues have elected to prohibit the use of LLMs in submissions. Most notably, at the time of writing, *Science* has stated a policy whereby “[t]ext generated from AI, machine learning, or similar

\*A complete list of the editors and editorial board of *NEJM AI* is available at [ai.nejm.org](https://ai.nejm.org).

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algorithmic tools cannot be used in papers published in *Science* journals, nor can the accompanying figures, images, or graphics be the products of such tools, without explicit permission from the editors. In addition, an AI program cannot be an author of a *Science* journal paper.”

Historically, there have been multiple occasions where people have resisted the use of “overly powerful” tools in various contexts. For years, calculators were banned in schools (and in some cases, still are) because of a perceived imperative to have students do their own calculations. In the early days of information technology, even word processors were banned in some organizations because they might reduce typing skills. There are clearly some contexts — such as education, where students are learning and being evaluated on foundational skills — where access to LLMs might be counterproductive. However, our primary goal at *NEJM AI* is to increase the quality of scientific publications, which includes several aspects such as novelty, rigor, and accessibility to others. If powerful tools, such as LLMs, help us achieve those goals, we should welcome their use.

Moreover, we are, as of yet, far from a world in which an LLM can generate an original and correct piece of scientific research — human involvement is still paramount. To use an LLM effectively, one needs to suggest the core premise of the work, identify the most relevant resources, often generate new data that did not exist, explore different analysis approaches, distill conclusions, and engage in multiple iterations before new and interesting scientific output is created.

At *NEJM AI*, we have therefore elected to allow the use of LLMs. Our two key conditions are first, that the use of LLMs is appropriately acknowledged by the authors. This standard is the same as for any tool or resource that is used in a substantive way by authors in their scientific work, including experimental reagents, animal models, data sets, software systems, or third-party copyediting services. Second, we require that the authors be completely accountable for the correctness and originality of the submitted work. Likewise, the same quality standards for clarity, exposition, and strength of the scientific arguments will be applied to all papers submitted to *NEJM AI*, regardless of how the text was generated. Using an LLM does not absolve one of the responsibility to write well and to avoid plagiarism. Above all, the insights in any paper we consider must be original, novel, and clearly articulated.

It is important to note, however, that this policy does not allow an LLM to be listed as a coauthor on any submission. This is because LLMs cannot be held accountable for the content of their work. To properly disclose the use of an LLM, authors should include a statement describing how the LLM was used in the acknowledgments section of the submission. For more details on the proper ways to disclose the use of an LLM, please see our guidance to authors.

We believe that the potential benefits of LLMs in scientific writing are considerable. LLMs can help scientists contextualize their work, democratize knowledge, enhance data analysis, and produce better scientific output. They can also help non-English native speakers and those with language disabilities express their ideas more effectively. As such, the use of LLMs could help reduce the language barrier for scientists around the world and improve the quality of the scientific literature. This is increasingly important as science becomes more globalized and insights are produced by a diverse range of individuals from different cultural, linguistic, and educational backgrounds.

Moreover, it is important to recognize that a ban on the use of LLMs is likely not enforceable. Although some tools for recognizing LLM-generated text have been developed, they are, as of yet, too inaccurate to be reliable. Several efforts to detect the use of an LLM in the classroom have resulted in instances of students being falsely accused of using an LLM when it was prohibited. As such, a prohibition on the use of LLMs would disadvantage those authors who are law-abiding by preventing them from benefiting from all the advantages outlined above.

The existence of LLMs (whether approved or not) does pose risks. As is the case for many technologies — ranging from nuclear power and computers to stem cell research and genetic engineering to cryptography — LLMs may enable and accelerate behaviors both good and bad. We live in a time of rapid progress for AI tools, and as such, editorial policies must be sufficiently agile. We will continue to reevaluate the proper use of AI tools in all parts of the scientific process to update this policy, as the landscape will almost surely change dramatically over the coming years. At *NEJM AI*, we believe that our fundamental goal in scientific discovery and publication should be to maximally enable humankind to produce robust, novel scientific findings and disseminate them broadly. The better the tools that we provide to scientists, the greater their ability to do so.

## Disclosures

Author disclosures are available at [ai.nejm.org](https://ai.nejm.org).

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