The NEW ENGLAND JOURNAL of MEDICINE

Notable Articles of 2021

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

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2021

Dear Reader,

In 2020, when Covid-19 was new, our collective awareness was necessarily heightened. We needed to understand a virulent new virus quickly. How do we best care for our patients? How do we stop the spread? How do we protect ourselves? We sprinted to decisions in real time, and not necessarily with evidence-based medicine to guide us.

This year, however, was different. It was a test of endurance. In 2021, vaccines became available, but not all eligible adults in the U.S. were vaccinated. Vaccines were also not equally available globally, as the majority of them were distributed in middle- and high-income countries. Because of this, waves of Covid-19, fueled by the delta variant, rippled across the U.S. and the world.

As 2021 ends, children 5 to 11 years old have become eligible for the vaccine in some countries, and booster shots have become available to a fortunate percentage of the global population. In December, we published an article, included in our collection of Notable Articles of 2021, that shows that in unvaccinated adults with Covid-19, molnupiravir lowers the risk of hospitalization or death, the first orally-available agent to do so. Also at year's end, the omicron variant of the virus was identified. The marathon continues.

As we look back on 2021, Covid-19 is thus inescapable. But our Notable Articles collection also reflects the fact that the pace of medical advances continues, regardless of the pandemic.

One Original Article, on a four-month rifapentine-based regimen for tuberculosis, showed that four months of treatment can be similar to standard therapy for six months. According to data published this year from the Global Fund, about 1 million fewer people were treated for TB in 2020 because of the pandemic. The prospect of an even shorter short-course treatment is therefore welcome news.

Other Original Articles were built on ingenuity. One study reported that rates of dengue fever dropped in the city of Yogyakarta, Indonesia, where Wolbachia-infected mosquito populations were released. Infection with the endosymbiont *Wolbachia pipientis* bacteria made these mosquitoes resistant to dengue; this resistance ended up protecting the people in that community.

Another pioneering trial reported on a paralyzed man with anarthria (the inability to articulate speech), who was able to communicate using a model that decoded words and sentences in real time from cortical activity generated when he attempted to speak. A video provided by the authors, and available at NEJM.org, demonstrated this remarkable achievement.

Also included in this collection are two practice-changing articles that addressed the use of race in the estimation of kidney function. Many institutions had already stopped using a Black race coefficient in calculating the eGFR because it could result in inequitable treatment. These articles proposed more equitable equations and provided evidence that equations based on cystatin C have greater predictive accuracy than those derived from serum creatinine with a race coefficient. Even with this modification, says the related editorial, estimates of GFR are, by their nature, imperfect. "Most important, however," the editorial concludes, "is that estimates do no harm but rather help us care for all patients equally."

We are pleased to highlight these clinically important Notable Articles of 2021. As we head into a new year, we remain committed to bringing you the best information to treat your patients.

Sincerely,
Eric J. Rubin, M.D., Ph.D.
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The NEW ENGLAND JOURNAL of MEDICINE

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Post-Transcriptional Genetic Silencing of *BCL11A* to Treat Sickle Cell Disease

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ABSTRACT

BACKGROUND

Sickle cell disease is characterized by hemolytic anemia, pain, and progressive organ damage. A high level of erythrocyte fetal hemoglobin (HbF) comprising α- and γ-globins may ameliorate these manifestations by mitigating sickle hemoglobin polymerization and erythrocyte sickling. *BCL11A* is a repressor of γ-globin expression and HbF production in adult erythrocytes. Its down-regulation is a promising therapeutic strategy for induction of HbF.

METHODS

We enrolled patients with sickle cell disease in a single-center, open-label pilot study. The investigational therapy involved infusion of autologous CD34+ cells transduced with the BCH-BB694 lentiviral vector, which encodes a short hairpin RNA (shRNA) targeting *BCL11A* mRNA embedded in a microRNA (shmiR), allowing erythroid lineage–specific knockdown. Patients were assessed for primary end points of engraftment and safety and for hematologic and clinical responses to treatment.

RESULTS

As of October 2020, six patients had been followed for at least 6 months after receiving BCH-BB694 gene therapy; median follow-up was 18 months (range, 7 to 29). All patients had engraftment, and adverse events were consistent with effects of the preparative chemotherapy. All the patients who could be fully evaluated achieved robust and stable HbF induction (percentage HbF/(F+S) at most recent follow-up, 20.4 to 41.3%), with HbF broadly distributed in red cells (F-cells 58.9 to 93.6% of untransfused red cells) and HbF per F-cell of 9.0 to 18.6 pg per cell. Clinical manifestations of sickle cell disease were reduced or absent during the follow-up period.

CONCLUSIONS

This study validates BCL11A inhibition as an effective target for HbF induction and provides preliminary evidence that shmiR-based gene knockdown offers a favorable risk–benefit profile in sickle cell disease. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT03282656)

From the Dana–Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School (E.B.E., L.E.L., A.B., C.B., M.F.C., B.M., K.B., S.-Y.P., W.B.L., C.D., M.M.H., D.A.W.), the Harvard Stem Cell Institute, Harvard Medical School (A.B., C.B.), the Gene Therapy Program, Dana–Farber/Boston Children's Cancer and Blood Disorders Center (A.B., M.F.C., B.M., E.M., A.F., S.-Y.P., C.D., D.A.W.), the Division of Hematology, Brigham and Women's Hospital, Harvard Medical School (M. Achebe), the Connell and O'Reilly Families Cell Manipulation Core Facility, Dana–Farber Cancer Institute (H.D., R.K., K.S., H.N., S.N., J.R.), the TransLab, Boston Children's Hospital (D.A., M. Armant), and the Department of Laboratory Medicine, Boston Children's Hospital, Harvard Medical School (J.P.M.) — all in Boston; and Bluebird Bio, Cambridge, MA (O.N.). Address reprint requests to Dr. Williams at 300 Longwood Ave., Karp 08125.3, Boston, MA 02115, or at dawilliams@childrens.harvard.edu.

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Read Full Article at NEJM.org

EDITORIAL

Induction of Fetal Hemoglobin by Gene Therapy

Mark C. Walters, M.D.

Shortly after birth, fetal hemoglobin is replaced by adult hemoglobin in red cells, a process that reflects a developmental switch in the β-globin locus that favors the expression of β-globin and the suppression of γ-globin. Therapies that may abrogate this switch have long been pursued on the basis of observations that the persistence of fetal-hemoglobin production after birth mitigates the phenotypes of sickle cell disease and β-thalassemia major, as well as the absence of signs of either disease when fetal hemoglobin levels are high in utero or at birth.[1,2] Pharmacologic inhibition of the globin developmental switch would require regular and lifelong administration, and at present no agent can safely and adequately accomplish such inhibition.

An alternative was suggested by the discovery that the transcription factor BCL11a is required for globin switching.[3] This therapeutic target presents the prospect of a one-time genetic modification of the hematopoietic stem cell to permanently reestablish γ-globin expression in lieu of a defective or inactivated β-globin gene. This principle is supported by the results from two clinical trials, reported in this issue of the *Journal*, that applied different methods to abrogate BCL11a expression specifically in erythroid lineage cells. These trials herald a new generation of broadly applicable curative treatments for hemoglobinopathies.

In the two trials, investigators evaluated different technologies, with both groups finding evidence of substantial clinical benefit. The method that was pioneered by Esrick et al.[4] knocks down BCL11a protein synthesis by lentiviral gene addition of an inhibitory short-hairpin RNA under erythroid-specific regulatory control. Frangoul et al.[5] disrupted *BCL11a* transcription by targeted clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 cleavage of an erythroid-specific intronic enhancer.[6] The two methods had similar efficacy in the small series of patients that are reported. Both methods induced high levels of fetal hemoglobin (and reduced sickle hemoglobin production) with a pancellular distribution of fetal hemoglobin, which in sickle cell disease was sufficient to mitigate hemolysis and to significantly reduce vaso-occlusive clinical events. *BCL11a* modification by CRISPR-Cas9 made it possible to discontinue red-cell transfusions in a patient with transfusion-dependent thalassemia.

These striking but very early clinical outcomes raise the question of which method of BCL11a inactivation is better, and for which patients, but at present there are few answers. Signs of sickle cell disease are inhibited by relatively low levels of fetal hemoglobin, whereas the treatment of thalassemia may be complicated by genotype-driven variation in the level of adult hemoglobin: patients with genotypes associated with a lower baseline level of adult hemoglobin will require higher levels of fetal hemoglobin to establish transfusion independence. The selection of a preferred method is more likely to hinge on toxicity risks and access to the therapy.

The risks associated with these and other novel methods of genetic manipulation are the topics of investigation worldwide. Lentiviral inte-

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gration produces thousands of insertional mutations in a population of treated cells. Although no oncogenic insertional mutation has been reported in trials of lentiviral gene transfer,[7] the long-term consequences of lentiviral integrations are unknown, and very young recipients will harbor the genomic alterations for decades. The CRISPR-Cas9 modification creates a double-stranded DNA break in the hematopoietic stem cell, and activation of DNA repair pathways may reduce proliferative or regenerative capacity or select for a population of hematopoietic stem cells with a proliferative advantage.[8] Reduced stem-cell potency could delay hematologic recovery after myeloablation, and a proliferative population could lead to clonal hematopoiesis. Although off-target CRISPR-induced DNA modifications were not observed in preclinical studies, it is very likely that current screening methods lack sufficient sensitivity to detect rare but potentially deleterious off-target genomic edits. The risk of chemotherapy-induced acute leukemia, which occurs in approximately 6% of recipients after autologous transplantation for non-Hodgkin's lymphoma[9] and has been reported recently in a patient with sickle cell disease after investigational gene therapy,[10] must also enter into clinical decision making about ex vivo gene-modification therapies that rely on myeloablation with busulfan. Finally, little is known about the function of BCL11A in erythroid cells, other than its role in suppressing fetal hemoglobin expression, although preclinical work has not provided a cause for concern.

The topic of equitable access to novel therapies with curative intent for sickle cell disease commingles clinical, translational, and implementation science. The development of disease-modifying therapies for sickle cell disease was stunted for many years by inadequate research funding, which was attributable at least in part to structural racism.[11] It is encouraging that increased funding from the National Institutes of Health and other agencies, as well as industry engagement, is accelerating the development of new therapies. However, access to and delivery of these highly technical therapies in patients with sickle cell disease will be challenging and probably limited to resource-rich nations, at least in the short term. The difficult task of fostering health policy and devoting resources to affordable, accessible delivery of such therapies must parallel the clinical advances.

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

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Once-Weekly Semaglutide in Adults with Overweight or Obesity

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ABSTRACT

BACKGROUND

Obesity is a global health challenge with few pharmacologic options. Whether adults with obesity can achieve weight loss with once-weekly semaglutide at a dose of 2.4 mg as an adjunct to lifestyle intervention has not been confirmed.

METHODS

In this double-blind trial, we enrolled 1961 adults with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or greater (≥27 in persons with ≥1 weight-related coexisting condition), who did not have diabetes, and randomly assigned them, in a 2:1 ratio, to 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) or placebo, plus lifestyle intervention. The coprimary end points were the percentage change in body weight and weight reduction of at least 5%. The primary estimand (a precise description of the treatment effect reflecting the objective of the clinical trial) assessed effects regardless of treatment discontinuation or rescue interventions.

RESULTS

The mean change in body weight from baseline to week 68 was –14.9% in the semaglutide group as compared with –2.4% with placebo, for an estimated treatment difference of –12.4 percentage points (95% confidence interval [CI], –13.4 to –11.5; P<0.001). More participants in the semaglutide group than in the placebo group achieved weight reductions of 5% or more (1047 participants [86.4%] vs. 182 [31.5%]), 10% or more (838 [69.1%] vs. 69 [12.0%]), and 15% or more (612 [50.5%] vs. 28 [4.9%]) at week 68 (P<0.001 for all three comparisons of odds). The change in body weight from baseline to week 68 was –15.3 kg in the semaglutide group as compared with –2.6 kg in the placebo group (estimated treatment difference, –12.7 kg; 95% CI, –13.7 to –11.7). Participants who received semaglutide had a greater improvement with respect to cardiometabolic risk factors and a greater increase in participant-reported physical functioning from baseline than those who received placebo. Nausea and diarrhea were the most common adverse events with semaglutide; they were typically transient and mild-to-moderate in severity and subsided with time. More participants in the semaglutide group than in the placebo group discontinued treatment owing to gastrointestinal events (59 [4.5%] vs. 5 [0.8%]).

CONCLUSIONS

In participants with overweight or obesity, 2.4 mg of semaglutide once weekly plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight. (Funded by Novo Nordisk; STEP 1 ClinicalTrials.gov number, NCT03548935).

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*A complete list of investigators in the STEP 1 trial is provided in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Once-Weekly Semaglutide in Adults with Overweight or Obesity

Wilding JPH. et al. DOI: 10.1056/NEJMoa2032183

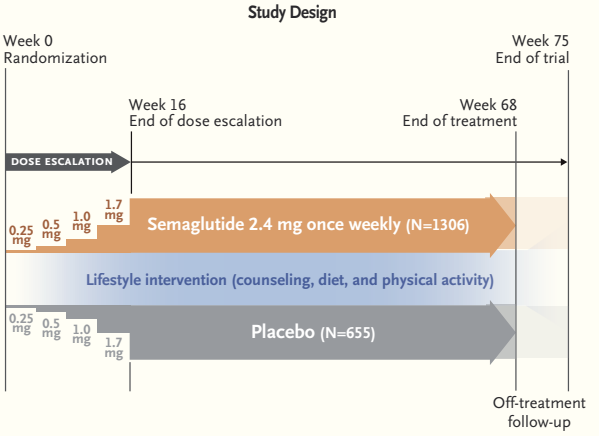
CLINICAL PROBLEM

Clinical guidelines suggest pharmacologic intervention in addition to diet and exercise to promote weight loss among adults with BMI ≥30 (or ≥27 in those with coexisting conditions). Barriers to medication use include limited efficacy, adverse effects, and cost. Subcutaneous semaglutide, a glucagon-like peptide-1 analogue FDA-approved to treat type 2 diabetes in adults, has been accompanied by weight loss in previous clinical trials.

CLINICAL TRIAL

A phase 3, double-blind, randomized, controlled trial comparing semaglutide with placebo, plus lifestyle changes, in overweight or obese adults without diabetes.

1961 participants were assigned to receive 2.4 mg of subcutaneous semaglutide (with gradual increase to the 2.4 mg dose) or placebo weekly for 68 weeks; both groups received a counseling intervention involving diet and exercise. Coprimary end points were percentage change in body weight and weight reduction ≥5%.



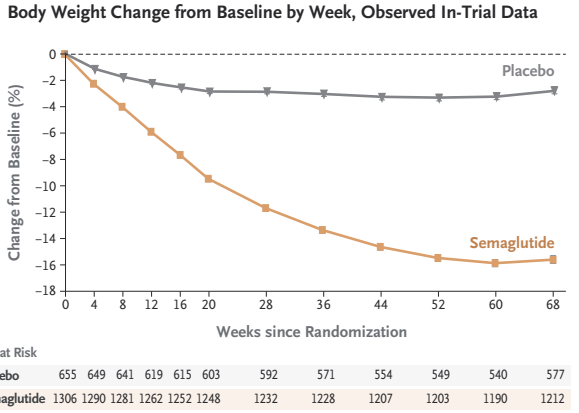
RESULTS

Efficacy:

By week 68, mean weight declined more with semaglutide than with placebo (14.9% vs. 2.4%; estimated difference, –12.4 percentage points; 95% CI, –13.4 to –11.5). In addition, more participants in the semaglutide group than in the placebo group had weight loss of ≥5% (86.4% vs. 31.5%).

Safety:

Adverse events, mainly gastrointestinal, were most often mild to moderate but led to treatment discontinuation in 7.0% of the semaglutide group and 3.1% of the placebo group. Serious adverse events, primarily gastrointestinal and hepatobiliary events, were reported more often with semaglutide.



LIMITATIONS AND REMAINING QUESTIONS

Limitations:

- 43.7% of participants had prediabetes and might have responded differentially to the effects of semaglutide on weight gain.

Further study is required to understand the following:

- Whether results would be similar in persons who differ from the study participants, who were mainly female, White, and potentially highly motivated to lose weight
- Longer-term outcomes
- The mechanism by which semaglutide affects weight-related measures of health (e.g., body composition and glycated hemoglobin) in patients without diabetes

CONCLUSIONS

Adults without diabetes who were overweight or obese had clinically relevant weight loss with weekly injections of semaglutide (2.4 mg) added to lifestyle changes.

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EDITORIAL

STEP 1 for Effective Weight Control — Another First Step?

Julie R. Ingelfinger, M.D., and Clifford J. Rosen, M.D.

Given the worldwide increase in obesity, with attendant coexisting conditions and increased risk of death, there is a pressing need to address weight loss and maintenance strategies.[1-3] Behavioral methods of weight control fail more often than not, and bariatric surgery is invasive and, often, eventually followed by regain of weight.[1-3] Medications approved for weight loss by the Food and Drug Administration, the European Medicines Agency, and other regulatory bodies have had a troubling history, with withdrawal of several approved drugs owing to serious adverse events; among these are various amphetamines (addiction), fenfluramine (cardiac toxicity), and, most recently, lorcaserin (cancer risk).[4,5] Currently available agents in the United States include the lipase inhibitor orlistat (which decreases intestinal fat absorption), phentermine–topiramate, and naltrexone–bupropion. However, none have been shown to prevent or treat type 2 diabetes mellitus, which is often associated with or develops in conjunction with obesity. During clinical trials for the two most recently approved agents for treating type 2 diabetes — the glucagon-like peptide-1 (GLP-1) agonists and sodium–glucose cotransporter-2 (SGLT-2) inhibitors (Table 1) — weight loss was noted to be substantial.[5-9] However, a major limiting factor with regard to treating obesity with the GLP-1 agonists was their daily subcutaneous administration. Oral preparations of the GLP-1 agonists have recently been approved, and that has propelled initiation of trials for both classes of drugs in persons with obesity.[6]

Wilding and colleagues now report in the *Journal* the initial results of the Semaglutide Treatment Effect in People with Obesity (STEP) 1 trial, in which 1961 patients with a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher (or ≥27 with at least one coexisting condition) were randomly assigned, in a 2:1 ratio, to receive a once-weekly subcutaneous preparation of the GLP-1 agonist semaglutide (2.4 mg) or placebo for 68 weeks.[10] Both groups received lifestyle intervention. The percent change in body weight and a reduction in weight of at least 5% from baseline were coprimary end points. The mean change in body weight was 14.9% with the active drug and –2.4% with placebo, a difference of –12.4 percentage points; 86.4% of participants in the active drug group lost 5% of more of body weight (as compared with 31.5% patients in the placebo group), and 69.1% of patients in the semaglutide group had weight loss of 10% or more (as compared with 12.0% in the placebo group). Thus, the results are encouraging, with significantly more patients in the semaglutide group having clinically important weight loss. Secondary end points (not examined in all patients) indicated that there were decreases in cardiometabolic risk factors, as well as improvements in physical function and quality of life (as assessed with the 36-item Short Form Health Survey and Impact of Weight on Quality of Life–Lite Clinical Trials Version questionnaire).

On the face of it, the STEP 1 trial (like its name) is a good beginning. However, as noted by the authors, there are concerns, including adverse events (mostly gastrointestinal — nausea, sometimes vomiting, and diarrhea), related principally to the class of agent. In addition,

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Table 1. Glucagon-Like Peptide-1 (GLP-1) Agonists and Sodium–Glucose Cotransporter-2 (SGLT-2) Inhibitors.

GLP-1 Agonists
Daily injection
Exenatide (twice daily)
Liraglutide
Lixisenatide
Weekly injection
Dulaglutide
Exenatide (extended release)
Semaglutide
Daily oral
Semaglutide
SGLT-2 Inhibitors
Daily oral
Canagliflozin
Dapagliflozin
Empagliflozin
Ertugliflozin

cholelithiasis occurred more often in the semaglutide group. It is important to note that oral semaglutide has been associated with pancreatitis and, in rodents, with thyroid C-cell tumors, which include medullary thyroid carcinoma. Semaglutide is contraindicated in persons with multiple endocrine neoplasia type 2.

Despite the positive results of this trial, the present study has some important limitations. First, the demographics in this trial are not reflective of the general U.S. population. Most of the participants were White, with only 6% Black or African American and 12% Latinx, whereas nearly 40% of the U.S. population is non-White. Similarly, males were underrepresented (26%). In addition, more than 40% of the cohort had prediabetes. These factors, taken together, raise additional questions about the efficacy of subcutaneous semaglutide in persons with obesity and normal glucose tolerance. Second, the present trial, although 68 weeks in length, still does not address long-term efficacy, since obesity is a chronic problem requiring constant attention. Third, in the real world, it seems unlikely that once-weekly subcutaneous administration would be a palatable or cost-effective solution in the long run. On the other hand, daily oral semaglutide might be far more appealing to many people. Finally, the present trial compared semaglutide with placebo. Moving forward, head-to-head trials comparing oral GLP-1 agonists with SGLT-2 antagonists or other weight-loss medications will be necessary. Similarly, given the effectiveness of bariatric surgery in regard to both weight loss and glucose tolerance, studies comparing these two distinct forms of therapy (surgery and pharmacologic therapy) will be required. In sum, we have a long way to go to control the obesity epidemic, but STEP 1 serves its name well.

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

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ORIGINAL ARTICLE

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

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ABSTRACT

BACKGROUND

Rifapentine-based regimens have potent antimycobacterial activity that may allow for a shorter course in patients with drug-susceptible pulmonary tuberculosis.

METHODS

In an open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary tuberculosis from 13 countries, we compared two 4-month rifapentine-based regimens with a standard 6-month regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (control) using a noninferiority margin of 6.6 percentage points. In one 4-month regimen, rifampin was replaced with rifapentine; in the other, rifampin was replaced with rifapentine and ethambutol with moxifloxacin. The primary efficacy outcome was survival free of tuberculosis at 12 months.

RESULTS

Among 2516 participants who had undergone randomization, 2343 had a culture positive for *Mycobacterium tuberculosis* that was not resistant to isoniazid, rifampin, or fluoroquinolones (microbiologically eligible population; 768 in the control group, 791 in the rifapentine–moxifloxacin group, and 784 in the rifapentine group), of whom 194 were coinfected with human immunodeficiency virus and 1703 had cavitation on chest radiography. A total of 2234 participants could be assessed for the primary outcome (assessable population; 726 in the control group, 756 in the rifapentine–moxifloxacin group, and 752 in the rifapentine group). Rifapentine with moxifloxacin was noninferior to the control in the microbiologically eligible population (15.5% vs. 14.6% had an unfavorable outcome; difference, 1.0 percentage point; 95% confidence interval [CI], –2.6 to 4.5) and in the assessable population (11.6% vs. 9.6%; difference, 2.0 percentage points; 95% CI, –1.1 to 5.1). Noninferiority was shown in the secondary and sensitivity analyses. Rifapentine without moxifloxacin was not shown to be noninferior to the control in either population (17.7% vs. 14.6% with an unfavorable outcome in the microbiologically eligible population; difference, 3.0 percentage points [95% CI, –0.6 to 6.6]; and 14.2% vs. 9.6% in the assessable population; difference, 4.4 percentage points [95% CI, 1.2 to 7.7]). Adverse events of grade 3 or higher occurred during the on-treatment period in 19.3% of participants in the control group, 18.8% in the rifapentine–moxifloxacin group, and 14.3% in the rifapentine group.

CONCLUSIONS

The efficacy of a 4-month rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-month regimen in the treatment of tuberculosis. (Funded by the Centers for Disease Control and Prevention and others; Study 31/A5349 ClinicalTrials.gov number, NCT02410772.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Nahid at the UCSF Center for Tuberculosis, University of California, San Francisco, 1001 Potrero Ave. 5K1, San Francisco, CA 94110, or at pnahid@ucsf.edu.

Drs. Dorman, Nahid, and Kurbatova contributed equally to this article.

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RESEARCH SUMMARY

Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis

Dorman SE et al. DOI: 10.1056/NEJMoa2033400

CLINICAL PROBLEM

The standard treatment of drug-susceptible pulmonary tuberculosis is a 6-month course of a daily rifamycin-based antimicrobial regimen. A more potent regimen with improved rifamycin exposure might shorten treatment duration, potentially improving adherence and reducing adverse effects and costs.

CLINICAL TRIAL

Design: A randomized, open-label, noninferiority trial of two 4-month rifapentine-containing regimens, as compared with a standard 6-month rifampin-containing regimen, for the treatment of drug-susceptible tuberculosis.

Intervention: 2516 participants 12 years of age or older with newly diagnosed tuberculosis were randomly assigned to a 6-month control regimen, a 4-month regimen in which rifampin was replaced with rifapentine (rifapentine group), or a 4-month regimen in which rifampin was replaced with rifapentine and ethambutol with moxifloxacin (rifapentine–moxifloxacin group). The primary efficacy outcome was survival free of tuberculosis at 12 months after randomization, and safety was assessed through day 14 after the last dose of a trial drug.

RESULTS

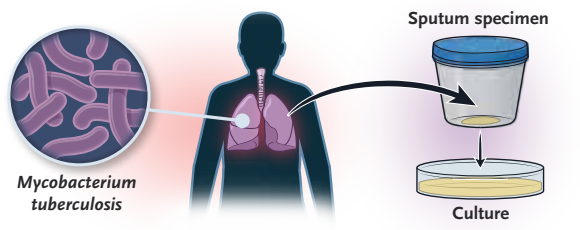
Efficacy: The rifapentine–moxifloxacin regimen, but not the rifapentine regimen, was shown to be noninferior to the control regimen.

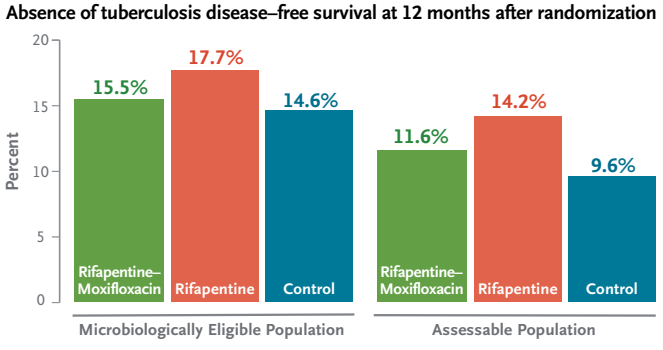
Safety: The percentages of patients who had adverse events of grade 3 or higher or who discontinued the assigned regimen prematurely did not differ significantly between the rifapentine–moxifloxacin group and the control group but were lower in the rifapentine group than in the control group.

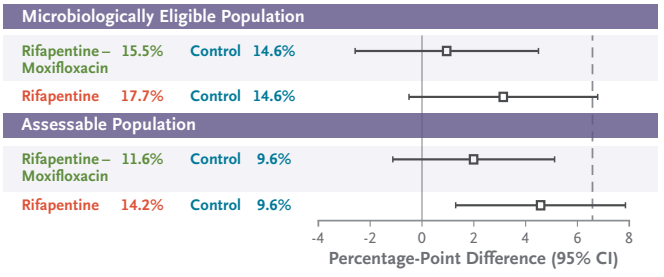
LIMITATIONS AND REMAINING QUESTIONS

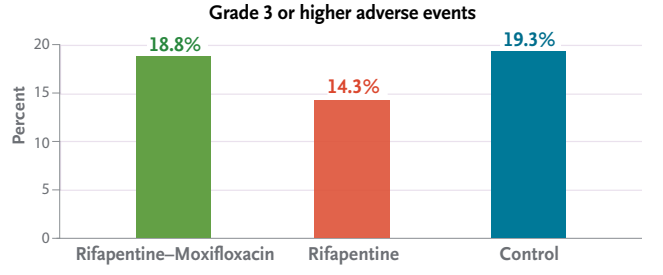
Further study is required to understand the following:

- How the trial regimens perform in HIV-coinfected patients
- Whether the shorter treatment duration offsets the likely higher cost of the rifapentine–moxifloxacin regimen









CONCLUSIONS

A 4-month regimen containing rifapentine and moxifloxacin was noninferior in efficacy and similar in safety and premature discontinuation to a standard 6-month antimicrobial regimen for the treatment of tuberculosis.

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EDITORIAL

Shortening the Short Course of Tuberculosis Treatment

Eric J. Rubin, M.D., Ph.D., and Valerie Mizrahi, Ph.D.

One of the great satisfactions of managing infectious diseases is the remarkable and rapid efficacy of antibiotics. The first uses of penicillin in the treatment of pneumococcal pneumonia produced near miraculous results, and most bacterial infections can be cured with a few days of therapy. However, tuberculosis has been an outlier. A series of landmark studies performed over several decades showed that combination therapy could result in high rates of cure among patients with tuberculosis, but the best "short course" regimen — and the one that remains in use to this day — still requires 6 months of therapy with multiple drugs.[1]

Many efforts have been made to shorten this period. There is good evidence that this may be possible, because most patients who receive standard therapy are cured well before 6 months. The longer duration is driven by a minority of patients for whom extended therapy is warranted. A "stratified medicine" approach proposed recently would entail identifying those in need of longer treatment.[2] The alternative approach is to replace the standard regimen with one that provides a durable cure for all patients in less time. However, three large studies that evaluated various fluoroquinolone-containing regimens all showed that the tested 4-month regimens were not noninferior to the 6-month course of treatment.[3-5] It was almost as though 6 months represented some strict limit — that is, until now.

In this issue of the *Journal*, the elegant study by Dorman et al.[6] tested a prediction derived from preclinical studies in animals that higher doses of rifamycins could increase the rate of clearance of infecting bacteria in tuberculosis. Thus, they designed a three-group, open-label trial of rifapentine, an alternative rifamycin that has a longer half-life than rifampin, the standard drug. Participants were randomly assigned to the standard 6-month regimen (8 weeks of once-daily rifampin, isoniazid, pyrazinamide, and ethambutol, followed by 18 weeks of once-daily rifampin and isoniazid [the control group]) or one of two experimental 4-month regimens (8 weeks of once-daily rifapentine, isoniazid, pyrazinamide, and ethambutol, followed by 9 weeks of once-daily rifapentine and isoniazid [the rifapentine group], or the same regimen but with the fluoroquinolone moxifloxacin substituted for ethambutol, followed by 9 weeks of once-daily rifapentine, isoniazid, and moxifloxacin [the rifapentine–moxifloxacin group]). The primary efficacy outcome was survival free of tuberculosis at 12 months, and the responses to treatment were ranked according to three sets of criteria (favorable, unfavorable, and not assessable); survival free of tuberculosis at 18 months was a secondary outcome. The investigators also collected information on the safety of all the regimens. The trial was designed to test the noninferiority of the two 4-month regimens to the standard 6-month regimen with respect to the primary outcome; noninferiority was shown if the upper bound of the 95% confidence interval of the between-group difference was 6.6 percentage points or less. The investigators used a hierarchical analysis that allowed them to test the noninferiority of the rifapentine regimen if the rifapentine–moxifloxacin regimen was shown to be noninferior.

A total of 2343 participants were enrolled in the trial at 34 sites from around the world. In general, the incidences of adverse events were fairly similar in the three treatment groups. The rifapentine–moxifloxacin group met the criteria for noninferiority. In one of two primary analysis populations, an unfavorable outcome occurred in 15.5% of the participants in the rifapentine–moxifloxacin group and in 14.6% in the control group (adjusted difference, 1.0 percentage points; 95% confidence interval [CI], –2.6 to 4.5), and in the other primary analysis population, unfavorable outcomes occurred in 11.6% and 9.6%, respectively (adjusted difference, 2.0 percentage points; 95% CI, –1.1 to 5.1). However, although close, noninferiority was not shown for the rifapentine regimen. Thus, a trial has shown that 4 months of treatment can be similar to standard therapy for 6 months.

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What does this mean for the future of tuberculosis therapy? There are both immediate and longer-term implications. Both rifapentine and moxifloxacin are widely available and could probably be packaged appropriately for use by national tuberculosis programs. Shortening a regimen by 2 months would make treatment somewhat less cumbersome and probably make it more cost-effective. However, the infrastructure required to ensure adherence would be largely unchanged. The need to take rifapentine after meals to maximize absorption could introduce new issues with adherence. Moreover, one of the advantages of the currently used tuberculosis drugs is that they are not widely used in other infections. In addition to necessitating rapid drug-susceptibility testing for moxifloxacin, widespread use of this antibiotic for the treatment of tuberculosis could promote resistance to fluoroquinolones in other bacteria.

This trial does, however, establish an important principle: there is no magic with 6 months of therapy. We do not know what the biologic limits of therapy are, but it might be possible to get to shorter regimens. The inability of an early biomarker, time to sputum culture conversion, to predict outcomes is disappointing. However, although the development of the standard 6-month regimen resulted from trials in humans, the rifapentine–moxifloxacin therapy was first shown to be effective in shortening therapy in animals, a finding that suggests that the development of new therapies is on an accelerated path. Indeed, additional new regimens have proved to be far better in mice than the one tested in this trial.[7] Thus, this trial not only proves that we can have a shorter short-course treatment but also suggests that an even shorter short-course treatment might one day be feasible.

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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Efficacy of Wolbachia-Infected Mosquito Deployments for the Control of Dengue

A. Utarini, C. Indriani, R.A. Ahmad, W. Tantowijoyo, E. Arguni, M.R. Ansari, E. Supriyati, D.S. Wardana, Y. Meitika, I. Ernesia, I. Nurhayati, E. Prabowo, B. Andari, B.R. Green, L. Hodgson, Z. Cutcher, E. Rancès, P.A. Ryan, S.L. O'Neill, S.M. Dufault, S.K. Tanamas, N.P. Jewell, K.L. Anders, and C.P. Simmons, for the AWED Study Group*

ABSTRACT

BACKGROUND

Aedes aegypti mosquitoes infected with the *w*Mel strain of *Wolbachia pipientis* are less susceptible than wild-type *A. aegypti* to dengue virus infection.

METHODS

We conducted a cluster-randomized trial involving releases of *w*Mel-infected *A. aegypti* mosquitoes for the control of dengue in Yogyakarta, Indonesia. We randomly assigned 12 geographic clusters to receive deployments of *w*Mel-infected *A. aegypti* (intervention clusters) and 12 clusters to receive no deployments (control clusters). All clusters practiced local mosquito-control measures as usual. A test-negative design was used to assess the efficacy of the intervention. Patients with acute undifferentiated fever who presented to local primary care clinics and were 3 to 45 years of age were recruited. Laboratory testing was used to identify participants who had virologically confirmed dengue (VCD) and those who were test-negative controls. The primary end point was symptomatic VCD of any severity caused by any dengue virus serotype.

RESULTS

After successful introgression of *w*Mel into the intervention clusters, 8144 participants were enrolled; 3721 lived in intervention clusters, and 4423 lived in control clusters. In the intention-to-treat analysis, VCD occurred in 67 of 2905 participants (2.3%) in the intervention clusters and in 318 of 3401 (9.4%) in the control clusters (aggregate odds ratio for VCD, 0.23; 95% confidence interval [CI], 0.15 to 0.35; P=0.004). The protective efficacy of the intervention was 77.1% (95% CI, 65.3 to 84.9) and was similar against the four dengue virus serotypes. The incidence of hospitalization for VCD was lower among participants who lived in intervention clusters (13 of 2905 participants [0.4%]) than among those who lived in control clusters (102 of 3401 [3.0%]) (protective efficacy, 86.2%; 95% CI, 66.2 to 94.3).

CONCLUSIONS

Introgression of *w*Mel into *A. aegypti* populations was effective in reducing the incidence of symptomatic dengue and resulted in fewer hospitalizations for dengue among the participants. (Funded by the Tahija Foundation and others; AWED ClinicalTrials.gov number, NCT03055585; Indonesia Registry number, INA-A7OB6TW.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Simmons at Monash University, 12 Innovation Walk, Clayton, VIC 3800, Australia, or at cameron.simmons@worldmosquito.org.

*A list of investigators in the AWED Study Group is available in the Supplementary Appendix, available at NEJM.org.

Drs. Utarini and Indriani and Drs. Anders and Simmons contributed equally to this article.

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EDITORIAL

Dengue — Perils and Prevention

Davidson H. Hamer, M.D.

Dengue virus (DENV) is responsible for an estimated 100 million symptomatic cases of infection and 10,000 deaths annually. The incidence of dengue has been doubling every decade since 1990.[1] Dengue has a major negative effect on stretched health care systems in low- and middle-income countries and also places a financial burden on households.[2,3] Rising global temperatures due to climate change, widespread distribution of the mosquito vector *Aedes aegypti*, increasing urbanization, population growth, environmental conditions that are conducive to mosquito breeding, and limited or nonexistent surveillance have all contributed to making dengue a worldwide threat.[2]

International travelers who contract dengue are at risk for death,[4] but they also facilitate the spread of dengue from areas in which it is endemic to areas in which it is not. Of note, the southern United States is an ideal setting for the introduction and spread of DENV, given the widespread presence of *A. aegypti* mosquitoes, the appropriate environmental conditions for transmission, and the large volume of travelers arriving from Latin America and the Caribbean, where dengue is endemic. In this context, Sharp and colleagues report a fatal case of severe dengue in a woman in Miami. Serologic testing confirmed infection with DENV serotype 2, and phylogenetic analysis suggested that the viral strain was closely related to that identified in travelers who had recently returned to Florida from Cuba.[5] This case shows the potential hazards of dengue — introduction by travelers from dengue-endemic regions into areas in which dengue is not endemic, local transmission, and severe disease leading to death.

Given the rising global burden of dengue and its associated perils, there is a need for improved prevention measures. Potential control measures include biologic and chemical larvicidal strategies, residual insecticide spraying, mosquito traps, toxic sugar baits, spatial repellents, insecticide-treated materials to reduce household-level transmission, reduction of mosquito-breeding sites, and vaccines.[2,6] In addition, three major strategies for the control of *A. aegypti* vector populations have been developed and evaluated: the sterile insect technique, release of insects with dominant lethality, and introgression with wolbachia.[6]

Although *A. aegypti* are not naturally infected with wolbachia, stable introgression with this obligate intracellular bacteria confers resistance to infection with DENV and other arboviruses.[7] This vector-control strategy has now been applied, with the use of *A. aegypti* infected with the *w*Mel strain of *Wolbachia pipientis*, in a cluster-randomized, controlled trial conducted in the city of Yogyakarta, Indonesia.[8] After obtaining community consent, the investigators placed mosquito release containers in residential properties in the clusters assigned to the wolbachia intervention. From March through December 2017, *w*Mel-infected mosquitoes were released in 9 to 14 rounds in the intervention clusters. Febrile patients who presented to local health care centers in the trial area were approached for participation if they were 3 to 45 years of age and did not have localizing symptoms suggestive of a specific

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nonarboviral infection. Participants were then classified as having virologically confirmed dengue if results of serologic testing were positive for DENV by reverse-transcriptase–polymerase-chain-reaction assay or positive for dengue nonstructural protein 1 antigen.

All 12 intervention clusters had durable establishment of *w*Mel in local *A. aegypti* populations. In an intention-to-treat analysis, the incidence of virologically confirmed dengue (the primary end point) was 77% lower among participants who lived in intervention clusters than among those who lived in control clusters (2.3% vs. 9.4%; odds ratio for virologically confirmed dengue, 0.23; 95% confidence interval, 0.15 to 0.35). In 11 of 12 intervention clusters, the proportion of participants with virologically confirmed dengue in each cluster was lower than that in the control clusters. In addition, the intervention had similar protective efficacy against all four DENV serotypes. Although the efficacy with respect to severe dengue was not directly assessed, the intervention resulted in an 86% protective efficacy against hospitalization; 0.4% of participants in intervention clusters and 3% in control clusters were hospitalized. In a per-protocol analysis, a threshold effect was identified wherein the *w*Mel frequency in the cluster of residence had to be 80% or higher to show a protective effect.

These impressive results show the efficacy of wolbachia introgression into *A. aegypti* populations as a method for the prevention of dengue in an urban setting in which dengue is endemic. This trial has several major strengths, including community engagement, use of constrained randomization, adequate power (despite disruption of the trial because of the Covid-19 pandemic), and use of virologically confirmed infection for the primary end point. In addition, measures were taken to address potential confounders, including strategies to address the possible spillover of *w*Mel mosquitoes from intervention clusters into control clusters and the use of hospitalization as a proxy for severe dengue.

Although there is clearly a need for future research to assess the durability of the *w*Mel-infected mosquito populations after introduction and replication of these findings in different contexts — potentially including areas in the southern United States, where the risk of dengue introduction is high — the use of wolbachia-infected mosquitoes has exciting potential to address the harms associated with dengue. Predictions from mathematical models have suggested that the reduced infectiousness of *w*Mel-infected *A. aegypti* could be sufficient to reduce the basic reproductive number to less than 1 and may potentially result in local elimination of disease.[9] This strategy could also be applied in the future for the prevention of other common alphavirus and flavivirus infections, including infection from chikungunya, yellow fever, and Zika viruses.[6,10]

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

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ORIGINAL ARTICLE

Neuroprosthesis for Decoding Speech in a Paralyzed Person with Anarthria

David A. Moses, Ph.D., Sean L. Metzger, M.S., Jessie R. Liu, B.S., Gopala K. Anumanchipalli, Ph.D., Joseph G. Makin, Ph.D., Pengfei F. Sun, Ph.D., Josh Chartier, Ph.D., Maximilian E. Dougherty, B.A., Patricia M. Liu, M.A., Gary M. Abrams, M.D., Adelyn Tu-Chan, D.O., Karunesh Ganguly, M.D., Ph.D., and Edward F. Chang, M.D.

ABSTRACT

BACKGROUND

Technology to restore the ability to communicate in paralyzed persons who cannot speak has the potential to improve autonomy and quality of life. An approach that decodes words and sentences directly from the cerebral cortical activity of such patients may represent an advancement over existing methods for assisted communication.

METHODS

We implanted a subdural, high-density, multielectrode array over the area of the sensorimotor cortex that controls speech in a person with anarthria (the loss of the ability to articulate speech) and spastic quadriparesis caused by a brain-stem stroke. Over the course of 48 sessions, we recorded 22 hours of cortical activity while the participant attempted to say individual words from a vocabulary set of 50 words. We used deep-learning algorithms to create computational models for the detection and classification of words from patterns in the recorded cortical activity. We applied these computational models, as well as a natural-language model that yielded next-word probabilities given the preceding words in a sequence, to decode full sentences as the participant attempted to say them.

RESULTS

We decoded sentences from the participant's cortical activity in real time at a median rate of 15.2 words per minute, with a median word error rate of 25.6%. In post hoc analyses, we detected 98% of the attempts by the participant to produce individual words, and we classified words with 47.1% accuracy using cortical signals that were stable throughout the 81-week study period.

CONCLUSIONS

In a person with anarthria and spastic quadriparesis caused by a brain-stem stroke, words and sentences were decoded directly from cortical activity during attempted speech with the use of deep-learning models and a natural-language model. (Funded by Facebook and others; ClinicalTrials.gov number, NCT03698149.)

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Dr. Moses, Mr. Metzger, and Ms. Liu contributed equally to this article.

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RESEARCH SUMMARY

Neuroprosthesis for Decoding Speech in a Paralyzed Person with Anarthria

Moses DA et al. DOI: 10.1056/NEJMoa2027540

CLINICAL PROBLEM

Paralyzed persons with anarthria (the inability to articulate speech) are often unable to operate assistive communication devices. Technology that can decode words and sentences directly from cerebral cortical activity may offer a method of assisted communication for such patients.

CLINICAL STUDY

Design: An early, single-center study (part of the BCI Restoration of Arm and Voice [BRAVO] study) was conducted with the use of an electrocorticography-based neural interface to test the feasibility of using electrocorticography signals to control complex devices for motor and speech control in adults affected by neurologic disorders of movement.

Intervention: 16 years after a brain-stem stroke resulting in quadriparesis and anarthria, a 36-year-old man underwent implantation of a subdural electrode array over the left temporal lobe. A neural network and natural-language model was then trained to decode words and sentences as the patient attempted to articulate speech.

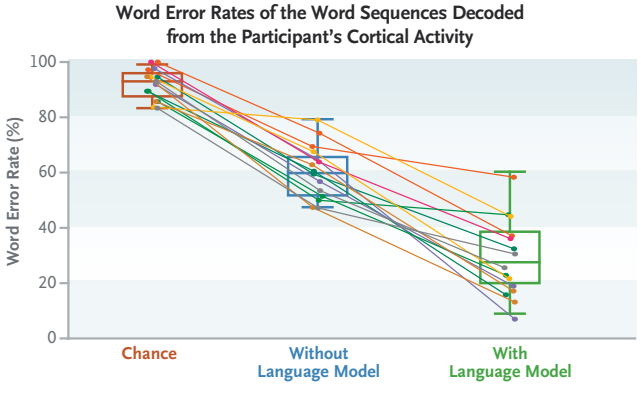
RESULTS

After 50 training sessions over 81 weeks, sentences were decoded with a median accuracy of approximately 75%, with an error rate that was better than what is generally considered to be sufficient for everyday communication. The median number of words decoded per minute was 15.2.

LIMITATIONS AND REMAINING QUESTIONS

- Additional study is needed to determine whether this approach would be successful in other paralyzed persons with anarthria and how this technology could be adopted for real-world use.

Target Sentence Example	Decoded without Language Model	Decoded with Language Model
Hello how are you	Hungry how am you	Hello how are you
I like my nurse	I right my nurse	I like my nurse
They are going outside	They are going outside	They are going outside
My family is very comfortable	Glasses family is faith comfortable	My family is very comfortable
Bring my glasses please	Please my glasses please	Bring my glasses please
What do you do	What do I you	What do I do
How do you like my music	How do you like bad bring	How do you like my music



CONCLUSIONS

In a severely paralyzed person with anarthria, a computational model was able to decode words and sentences in real time from cortical activity acquired through a neural implant during attempted speech. This study also showed that the cerebral cortex can generate electrical representations of speech and language even after 16 years of paralytic anarthria.

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EDITORIAL

Freedom of Speech

Leigh R. Hochberg, M.D., Ph.D., and Sydney S. Cash, M.D., Ph.D.

Of the many functions delegated to the human nervous system, perhaps none is more essentially human than the ability to express one's thoughts. For persons with severe speech and motor impairments, restoration of the ability to communicate even simple needs is an important goal. Cognitively intact persons who are tetraplegic and anarthric know what they want to communicate — their brains prepare messages for delivery, but those messages are trapped.

The goal in the design of brain–computer interfaces is to restore communication and mobility by harnessing voluntarily modulated brain signals to control useful external[1-3] or implanted[4] devices. Signals from the scalp (electroencephalography)[5] or brain surface (electrocorticography)[6,7] have been used to enable communication at approximately three characters per minute by persons with amyotrophic lateral sclerosis. Through the use of electrode arrays to record information-rich action potential patterns emanating from ensembles of cortical neurons, intracortical brain–computer interfaces have allowed persons with tetraplegia to type on a keyboard interface or tablet computer by thinking about the point-and-click movements of their own hand.[8] The intended handwriting of a person with cervical spinal cord injury was decoded at up to 90 characters (or approximately 18 words) per minute; such means of communication enables the use of a theoretically limitless vocabulary.[9]

Speech by an able-bodied person, at a rate of approximately 150 words per minute in the English language, is a far faster means to communicate than typing or handwriting. For persons with anarthria, it would be an extraordinary accomplishment to decode intended speech from brain signals alone. It was only recently that researchers have begun to tease apart the neurophysiologic mechanisms of how the brain turns intended speech into commands that shape articulatory structures to form an acoustic output of words and sentences. In part because of advances in machine learning that can find complex relationships within data sets, electrocorticographic activity decoded from the ventral sensorimotor cortex, superior temporal gyrus, and inferior frontal gyrus of able-bodied speakers has been decoded into computer-generated speech.[10]

In this issue of the *Journal*, Moses and colleagues[11] report a decoding system that enabled a person with anarthria caused by a brain-stem stroke to use neural activity recorded from 128 electrodes placed on the cortical surface of speech-related areas of the dominant hemisphere to create sentences derived from 50 high-value English words. The final output — a feat of neuroengineering — allowed sentences of up to 8 words to be created from neural data at a median rate of 12.5 correctly decoded words per minute; the median rate with the inclusion of all decoded words, whether correct or incorrect, was 15.2 words per minute. More than 1200 useful, grammatically correct sentences can be constructed from those words. Much of the decoded text results from the application of language modeling that adjusts the likelihood of each classified word on the basis of word probabilities and the presence of other words in a sentence. The use of these protocols improved the accuracy of the decoded sentence — the median word error rate was 26%, and 53% of the tested sentences were decoded without error. The neural-signal detection and computational analysis to decode each word took approximately 4 seconds.

One of the challenges in decoding brain activity is the first step: extracting enough useful information from a sparse data set of electrical signals. Even with the initial decoding algorithm that incorporated hours of data that were collected during the training of the classification model on individual words, the neural activity itself was classified into the correct word only about half the time. This implies that the signals that were recorded by the electrodes, each of which was 2 mm in diameter and spaced 4 mm apart from each other across the cortical surface, did not carry enough information to identify the right word consistently. An option for improving this first stage is to use more and smaller surface electrodes (microelectrocorticography) that detect the summed activity of smaller groups of neurons that could contain more

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distinct information about the intended words. Intracortical electrodes that are capable of detecting firing patterns of ensembles of single neurons[12] might also provide for faster and more accurate decoding of phonemes or larger vocabularies. Future studies will determine how these approaches can best be leveraged to improve the speed and accuracy of word and sentence decoding.

With this pioneering demonstration of how a person with anarthria caused by a brain-stem stroke can generate text just by attempting to speak, efforts to restore neurologic function for persons with amyotrophic lateral sclerosis, cerebral palsy, stroke, or other disorders move closer toward clinical benefit. Ultimately, success will be marked by how readily our patients can share their thoughts with all of us.

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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CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

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ABSTRACT

BACKGROUND

Transthyretin amyloidosis, also called ATTR amyloidosis, is a life-threatening disease characterized by progressive accumulation of misfolded transthyretin (TTR) protein in tissues, predominantly the nerves and heart. NTLA-2001 is an in vivo gene-editing therapeutic agent that is designed to treat ATTR amyloidosis by reducing the concentration of TTR in serum. It is based on the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system and comprises a lipid nanoparticle encapsulating messenger RNA for Cas9 protein and a single guide RNA targeting *TTR*.

METHODS

After conducting preclinical in vitro and in vivo studies, we evaluated the safety and pharmacodynamic effects of single escalating doses of NTLA-2001 in six patients with hereditary ATTR amyloidosis with polyneuropathy, three in each of the two initial dose groups (0.1 mg per kilogram and 0.3 mg per kilogram), within an ongoing phase 1 clinical study.

RESULTS

Preclinical studies showed durable knockout of *TTR* after a single dose. Serial assessments of safety during the first 28 days after infusion in patients revealed few adverse events, and those that did occur were mild in grade. Dose-dependent pharmacodynamic effects were observed. At day 28, the mean reduction from baseline in serum TTR protein concentration was 52% (range, 47 to 56) in the group that received a dose of 0.1 mg per kilogram and was 87% (range, 80 to 96) in the group that received a dose of 0.3 mg per kilogram.

CONCLUSIONS

In a small group of patients with hereditary ATTR amyloidosis with polyneuropathy, administration of NTLA-2001 was associated with only mild adverse events and led to decreases in serum TTR protein concentrations through targeted knockout of *TTR*. (Funded by Intellia Therapeutics and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT04601051.)

From the National Amyloidosis Centre, Division of Medicine, University College London, Royal Free Hospital (J.D.G., M.F.) and Richmond Pharmacology, St. George's University of London (J.T.) — both in London; New Zealand Clinical Research (E.G.), University of Auckland (E.G.), and the Department of Neurology, Auckland City Hospital (J.K.) — all in Auckland, New Zealand; Intellia Therapeutics, Cambridge, MA (M.L.M., J.S., D.O., K.R.W., K.W., J.P., Y.X., A.A., A.P.B., J.E.C., M.D.M., A.S., J.L., L.S.-L., D.L.); and Regeneron Pharmaceuticals, Tarrytown, NY (O.H., A.M., C.A.K., B.Z., R.S., D.E.G.). Address reprint requests to Prof. Gillmore at the Centre for Amyloidosis and Acute Phase Proteins, Division of Medicine, University College London, Royal Free Hospital, Rowland Hill St., London NW3 2PF, United Kingdom, or at j.gillmore@ucl.ac.uk.

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RESEARCH SUMMARY

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Gillmore JD et al. DOI: 10.1056/NEJMoa2107454

CLINICAL PROBLEM

In transthyretin amyloidosis, misfolded transthyretin (TTR) protein accumulates, primarily in the nerves and heart, and is ultimately fatal. Current therapies reduce amyloid formation through repeated infusions that can have serious adverse effects or require infusion premedications. These treatments slow but do not stop disease progression.

CLINICAL TRIAL

Study Design: An open-label, phase 1 clinical study evaluated the safety and pharmacodynamic effects of NTLA-2001, a CRISPR-Cas9–based in vivo gene-editing therapy targeting *TTR* in human hepatocytes, in adults with hereditary transthyretin amyloidosis and polyneuropathy with or without cardiomyopathy.

Intervention: 6 patients received a single intravenous infusion of NTLA-2001 at a dose of either 0.1 or 0.3 mg per kilogram of body weight.

RESULTS

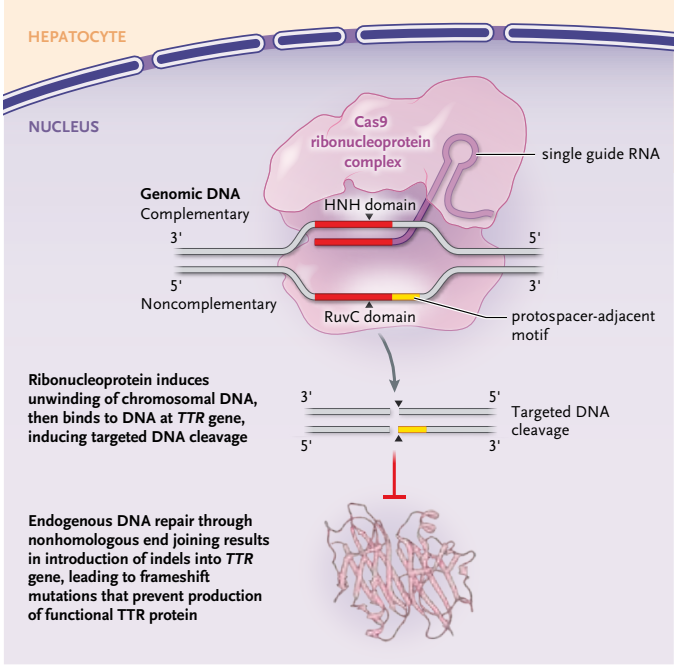
Efficacy: At 28 days after infusion, TTR levels were reduced from baseline with both doses; the reduction was greater with the larger dose.

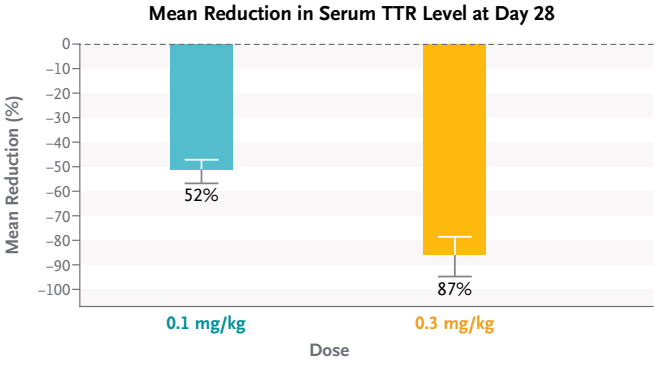
Safety: Adverse effects occurred in 3 patients and were mild.

LIMITATIONS AND REMAINING QUESTIONS

Further study is required to understand the following:

- The duration of TTR reduction after a single infusion of NTLA-2001 at the doses used in this study and at higher doses
- Clinical outcomes in these 6 patients and in larger trials
- Whether other adverse effects, including off-target gene editing, occur in the longer term





CONCLUSIONS

This trial involving a small number of patients with hereditary transthyretin amyloidosis provides proof-of-concept evidence that CRISPR-Cas9–based gene editing with NTLA-2001 greatly reduces TTR levels after a single infusion, with only mild adverse events.

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EDITORIAL

Gene Editing — A Cure for Transthyretin Amyloidosis?

Mathew S. Maurer, M.D.

Imagine that you had several family members with transthyretin amyloidosis. In their sixth decade of life, numbness developed, initially in their hands and feet, that progressed proximally over a period of years. This numbness came with associated muscle weakness, and then symptoms of autonomic dysfunction developed, including profound dizziness with changes in posture and alternating constipation and diarrhea that hindered their ability to engage socially. With disease progression, a syndrome of heart failure with worsening fatigue, shortness of breath, and edema developed. They initially needed an assistive device to walk, and ultimately they could not ambulate at all, losing their autonomy and independence. After 15 years, they eventually died from this devastating disorder. Decades later, you begin to have similar symptoms, knowing that you have inherited the same variant transthyretin and are potentially at risk for a similar fate. Now imagine that this could be prevented with a single treatment.

Transthyretin amyloidosis, also called ATTR amyloidosis, is an underdiagnosed multisystemic disease that is caused when the transthyretin protein produced by liver hepatocytes misfolds and aggregates in the nerves and heart. Formerly known as "prealbumin" because it migrates anodally to albumin on electrophoresis, transthyretin is a tetramer made up of monomers that each contain 127 amino acids and have a marked beta-pleated secondary structure. There are more than 100 variants that cause hereditary ATTR amyloidosis, which is inherited in an autosomal dominant fashion and has age-dependent, incomplete penetrance. The misfolded monomers deposit predominantly in two postmitotic organs — the myocardium and the nerves — resulting in disease characterized by polyneuropathy, cardiomyopathy, or (most commonly) a combination of the two. In addition, a large percentage of the rapidly expanding population of older adults have wild-type ATTR cardiomyopathy, which is not associated with a mutation in *TTR*, the gene encoding transthyretin.

Despite the previously dismal prognosis associated with the condition, several therapies have emerged from the elucidation of the biologic mechanisms that lead to ATTR amyloidosis. Effective therapeutic approaches include the use of transthyretin stabilizers, such as diflunisal and tafamidis, that prevent dissociation of the transthyretin tetramer into monomers, as well as oligonucleotide-based or small interfering RNA–based "silencers" that knock down transthyretin messenger RNA and prevent hepatic production of the protein.[1-4]

Traditionally, ATTR amyloidosis has been categorized for clinical and regulatory purposes on the basis of its dominant clinical presentation, although a mixed phenotype is most common. Initial therapeutic trials have focused on patients with hereditary ATTR amyloidosis with polyneuropathy, as is the case in the current report, even though many patients with systemic amyloidosis have wild-type ATTR cardiomyopathy, which is attributable to altered proteostasis with aging. Seminal studies have shown the safety and efficacy of patisiran,[2] inotersen,[3] and tafamidis.[4] Tafamidis is currently the only Food and Drug Administration–approved therapy for hereditary or wild-type ATTR cardiomyopathy. Given that the biologic mechanisms are shared among the disease types irrespective of the phenotypic presentation, emerging pharmacotherapies are anticipated to be effective across the spectrum of disease. In addition, another stabilizer[5] and subcutaneous silencers[6,7] are being evaluated in phase 3 clinical trials. Collectively, such therapies offer great hope for patients with ATTR amyloidosis, especially when applied early in the course of the disease.

In various forms of amyloidosis (amyloid A [AA], amyloid light-chain [AL], and ATTR amyloidosis), the magnitude of the decrease in levels of the precursor protein with therapy is associated with clinical outcomes.[2,8,9] Indeed, elimination of the precursor proteins that form amyloid is the current goal of therapies for patients with AL or AA amyloidosis. Similarly, the degree of knockdown is associated with

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clinical outcomes in patients with ATTR amyloidosis.[2]

Capitalizing on the development of the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system, a multidisciplinary translation-science team leveraged lipid nanoparticles to deliver this gene-editing therapy to hepatocytes and reduce the production of transthyretin, as described in this issue of the *Journal*.[10] The current approach is novel and has the potential to address all forms of ATTR amyloidosis — both wild-type and hereditary disease, manifesting as either neuropathy or cardiomyopathy. Since only a single infusion is required to permanently silence transthyretin production, adherence to treatment will not be an issue. The preclinical and in vitro data show the precision of this approach, which is essential to reduce off-target effects that could lead to harmful consequences such as genotoxicity or oncogenic transformation. Preliminary data from six brave, committed participants who had transthyretin variants with early phenotypes have shown an initial favorable safety profile along with evidence of efficacy, as indicated by the decline in serum transthyretin levels after 28 days. Although it is an amazing achievement, the results should be interpreted with caution, given the small number of select patients, the very short follow-up, and the absence of data on morbidity, mortality, or function.

Clinical research is evolving rapidly in ATTR amyloidosis, and future investigations leveraging the remarkable science described in this report will require capitalizing on already strong collaborations in the amyloidosis community among patients, caregivers, support groups, basic and clinical researchers, amyloid experts, medical subspecialists, and regulatory agencies in the design of later-phase investigations. Both for patients with ATTR amyloidosis and for their offspring who may have a variant transthyretin and a risk of systemic amyloidosis, the current work represents a potentially groundbreaking advance in medical therapeutics with profound implications for the management of other hereditary and nonhereditary diseases.

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

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ORIGINAL ARTICLE

Atogepant for the Preventive Treatment of Migraine

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ABSTRACT

BACKGROUND

Atogepant is an oral, small-molecule, calcitonin gene–related peptide receptor antagonist that is being investigated for the preventive treatment of migraine.

METHODS

In a phase 3, double-blind trial, we randomly assigned adults with 4 to 14 migraine days per month in a 1:1:1:1 ratio to receive a once-daily dose of oral atogepant (10 mg, 30 mg, or 60 mg) or placebo for 12 weeks. The primary end point was the change from baseline in the mean number of migraine days per month across the 12 weeks. Secondary end points included headache days per month, a reduction from baseline of at least 50% in the 3-month average of migraine days per month, quality of life, and scores on the Activity Impairment in Migraine–Diary (AIM-D).

RESULTS

A total of 2270 participants were screened, 910 were enrolled, and 873 were included in the efficacy analysis; 214 were assigned to the 10-mg atogepant group, 223 to the 30-mg atogepant group, 222 to the 60-mg atogepant group, and 214 to the placebo group. The mean number of migraine days per month at baseline ranged from 7.5 to 7.9 in the four groups. The changes from baseline across 12 weeks were –3.7 days with 10-mg atogepant, –3.9 days with 30-mg atogepant, –4.2 days with 60-mg atogepant, and –2.5 days with placebo. The mean differences from placebo in the change from baseline were –1.2 days with 10-mg atogepant (95% confidence interval [CI], –1.8 to –0.6), –1.4 days with 30-mg atogepant (95% CI, –1.9 to –0.8), and –1.7 days with 60-mg atogepant (95% CI, –2.3 to –1.2) ($P<0.001$ for all comparisons with placebo). Results for the secondary end points favored atogepant over placebo with the exceptions of the AIM-D Performance of Daily Activities score and the AIM-D Physical Impairment score for the 10-mg dose. The most common adverse events were constipation (6.9 to 7.7% across atogepant doses) and nausea (4.4 to 6.1% across atogepant doses). Serious adverse events included one case each of asthma and optic neuritis in the 10-mg atogepant group.

CONCLUSIONS

Oral atogepant once daily was effective in reducing the number of migraine days and headache days over a period of 12 weeks. Adverse events included constipation and nausea. Longer and larger trials are needed to determine the effect and safety of atogepant for migraine prevention. (Funded by Allergan; ADVANCE ClinicalTrials.gov number, NCT03777059.)

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*The members of the ADVANCE Study Group are listed in the Supplementary Appendix, available at NEJM.org.

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Effect of Salt Substitution on Cardiovascular Events and Death

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ABSTRACT

BACKGROUND

Salt substitutes with reduced sodium levels and increased potassium levels have been shown to lower blood pressure, but their effects on cardiovascular and safety outcomes are uncertain.

METHODS

We conducted an open-label, cluster-randomized trial involving persons from 600 villages in rural China. The participants had a history of stroke or were 60 years of age or older and had high blood pressure. The villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used a salt substitute (75% sodium chloride and 25% potassium chloride by mass), or to the control group, in which the participants continued to use regular salt (100% sodium chloride). The primary outcome was stroke, the secondary outcomes were major adverse cardiovascular events and death from any cause, and the safety outcome was clinical hyperkalemia.

RESULTS

A total of 20,995 persons were enrolled in the trial. The mean age of the participants was 65.4 years, and 49.5% were female, 72.6% had a history of stroke, and 88.4% a history of hypertension. The mean duration of follow-up was 4.74 years. The rate of stroke was lower with the salt substitute than with regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval [CI], 0.77 to 0.96; P=0.006), as were the rates of major cardiovascular events (49.09 events vs. 56.29 events per 1000 person-years; rate ratio, 0.87; 95% CI, 0.80 to 0.94; P<0.001) and death (39.28 events vs. 44.61 events per 1000 person-years; rate ratio, 0.88; 95% CI, 0.82 to 0.95; P<0.001). The rate of serious adverse events attributed to hyperkalemia was not significantly higher with the salt substitute than with regular salt (3.35 events vs. 3.30 events per 1000 person-years; rate ratio, 1.04; 95% CI, 0.80 to 1.37; P=0.76).

CONCLUSIONS

Among persons who had a history of stroke or were 60 years of age or older and had high blood pressure, the rates of stroke, major cardiovascular events, and death from any cause were lower with the salt substitute than with regular salt. (Funded by the National Health and Medical Research Council of Australia; SSaSS ClinicalTrials.gov number, NCT02092090.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Wu at Peking University Clinical Research Center, Peking University, 38 Xueyuan Rd., Haidian District, Beijing, China, or at wuyf@bjmu.edu.cn, or to Dr. Tian at the George Institute for Global Health at Peking University Health Science Center, Rm. 052A, Unit 1, Tayuan Diplomatic Office Bldg., No. 14 Liangmahe Nan Lu, Chaoyang District, Beijing, China, or at mtian@georgeinstitute.org.cn.

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Drs. Neal and Wu contributed equally to this article.

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RESEARCH SUMMARY

Effect of Salt Substitution on Cardiovascular Events and Death

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CLINICAL PROBLEM

Salt substitutes that replace part of the sodium in regular salt with potassium chloride have been shown to decrease blood pressure, but their effects on cardiovascular and safety outcomes are unclear.

CLINICAL TRIAL

Design: An unblinded, cluster-randomized trial examined cardiovascular and safety outcomes with a salt substitute as compared with regular salt in high-risk adults.

Intervention: 600 villages in rural China were assigned to use a salt substitute (75% sodium chloride, 25% potassium chloride) for all household cooking and food preservation or to continue using regular salt (100% sodium chloride). A total of 20,995 adults with a history of stroke or age ≥60 years with poorly controlled blood pressure were included. The primary outcome was stroke.

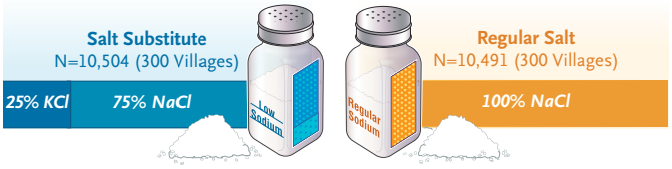
RESULTS

Efficacy: During a mean follow-up of 4.74 years, the incidence of stroke was significantly lower in the salt-substitute group than in the regular salt group. Secondary outcomes, including major cardiovascular events and death from any cause, also favored the salt substitute.

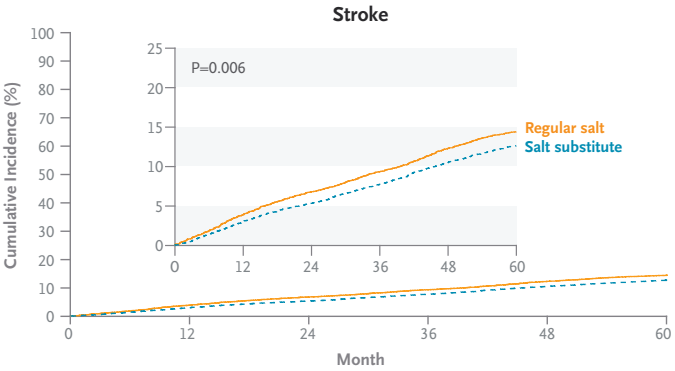
Safety: The incidence of clinical hyperkalemia did not differ between the groups.

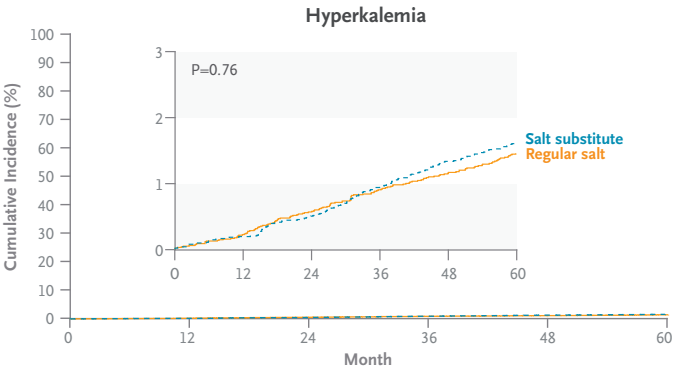
LIMITATIONS AND REMAINING QUESTIONS

- Participants were aware of the trial-group assignments.
- Whether the findings can be generalized to other settings or populations is unknown.
- Serum electrolytes were not measured serially, so some instances of hyperkalemia were likely to have been missed.



Outcomes	Salt Substitute	Regular Salt	Rate Ratio (95% CI)	P Value
	no. of events per 1000 person-yr			
Stroke	29.14	33.65	0.86 (0.77–0.96)	P=0.006
Major Adverse CV Events	49.09	56.29	0.87 (0.80–0.94)	P<0.001
Death from Any Cause	39.28	44.61	0.88 (0.82–0.95)	P<0.001
Hyperkalemia	3.35	3.30	1.04 (0.80–1.37)	P=0.76





CONCLUSIONS

In this study among patients with a mean age of 65.4 years and a history of stroke or high blood pressure, use of a salt substitute lowered the risks for stroke, major cardiovascular events, and death from any cause.

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EDITORIAL

Can Salt Substitution Save At-Risk Persons from Stroke?

Julie R. Ingelfinger, M.D.

For decades, opinions about the degree to which sodium intake affects the blood pressure level and the risk of adverse effects such as stroke have been varied, even partisan.[1] Much relevant data have shown an association between high dietary sodium intake — and also low dietary potassium intake — and increased blood pressure levels, as well as higher risks of cardiovascular disease, stroke, and death.[2] In addition, multiple studies have reported that reducing dietary sodium intake while increasing potassium intake lowers blood pressure levels and decreases morbidity. Although many debate the extent of these effects,[3] there is no doubt that salt intake in most parts of the world generally exceeds that needed for homeostasis.

Sodium intake in the form of sodium chloride does not affect everyone similarly.[3,4] Most normotensive persons have a minimal change in mean arterial pressure when they ingest a high-salt diet, whereas many persons with elevated blood pressure have a measurable increase in the blood pressure, by approximately 4 mm Hg according to one study.[5] Furthermore, persons with hypertension who are categorized as "salt sensitive" may respond to high salt intake with an increase in the blood pressure of 10 mm Hg or more.[5] How such blood-pressure responses relate to the renal handling of salt and water and the responsiveness of the renin–angiotensin–aldosterone system is key. Recent data indicate that the availability of sodium in the body varies, because much is stored in bone and in the interstitium.[6] However, identifying salt-sensitive persons is beyond clinical care in "real life" for large populations, and effecting major dietary change is difficult.

An appealing way to change both sodium and potassium intake concomitantly may be through the use of so-called salt substitutes, which are available as single products in which potassium chloride is substituted for a proportion of pure sodium chloride.[7,8] Although a smaller, individually randomized trial of several months' duration in India showed that a salt substitute could be effective,[8] very-large-scale randomized trials that examine the effect of salt substitutes in at-risk persons at home in their communities have been elusive. The Salt Substitute and Stroke Study (SSaSS), the results of which are now reported in the *Journal*,[9] may have provided some answers. The SSaSS, a trial involving 20,995 persons from 600 villages in rural China, aimed "to define the overall balance of benefits and risks of salt substitute as compared with regular salt on stroke, cardiovascular events, death, and clinical hyperkalemia." The trial compared the effect of regular salt (100% sodium chloride) with a salt substitute (75% sodium chloride and 25% potassium chloride by mass) in a high-risk population with respect to hard outcomes of stroke, cardiovascular disease, and death. Vital status was purportedly determined for all the participants.

The participants in the SSaSS were at high risk — 72.6% had a history of stroke, the mean age was 65.4 years, and 88.4% reported having received a diagnosis of hypertension. In a cluster-randomization design, the villages were randomly assigned in a 1:1 ratio to the intervention group, in which the participants used the salt substitute, or to the control group, in which the participants continued to use regular salt. The primary trial outcome was stroke, and the secondary outcomes were major adverse cardiovascular events and death from any cause. Predictably, given the population studied, the safety outcome was clinical hyperkalemia.

Use of the salt substitute led to a lower rate of stroke than the use of regular salt (29.14 events vs. 33.65 events per 1000 person-years; rate ratio, 0.86; 95% confidence interval, 0.77 to 0.96; P=0.006). The rate of major adverse cardiovascular events were also lower with the salt substitute, as was death from any cause. Hyperkalemia was not more common in the intervention group than in the control group, although serial potassium levels were not available.

How was the performance of this trial even feasible? In rural villages in China, where the SSaSS was carried out, processed food is not generally used; dietary sodium chloride is added during food preparation within each household. In contrast, in much of the world, commercial food preservation adds much sodium chloride to

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the diet, and the use of salt substitutes would not fully account for the majority of salt intake.

The results of the SSaSS appear impressive. If the strategy is feasible over time, the salt-substitute approach might have a major public health consequence in China, and possibly, elsewhere. Yet there remain a number of things we do not know. For example, serial monitoring of potassium levels was not performed in the trial, and it is possible that hyperkalemic episodes were not detected. Furthermore, persons with a history of medical conditions that may be associated with hyperkalemia (e.g., chronic kidney disease) were not studied. Because the salt substitute was distributed to families, it would have been instructive to have data on the household members without risk factors, but no such data were obtained. Finally, only one version of a salt substitute was used — 75% sodium chloride and 25% potassium chloride; no salt substitutes with higher or lower potassium chloride concentrations were evaluated. Overall, the SSaSS provides some intriguing hints, but wider effectiveness is hard to predict, given limited generalizability.

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

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Maintenance or Discontinuation of Antidepressants in Primary Care

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ABSTRACT

BACKGROUND

Patients with depression who are treated in primary care practices may receive antidepressants for prolonged periods. Data are limited on the effects of maintaining or discontinuing antidepressant therapy in this setting.

METHODS

We conducted a randomized, double-blind trial involving adults who were being treated in 150 general practices in the United Kingdom. All the patients had a history of at least two depressive episodes or had been taking antidepressants for 2 years or longer and felt well enough to consider stopping antidepressants. Patients who had received citalopram, fluoxetine, sertraline, or mirtazapine were randomly assigned in a 1:1 ratio to maintain their current antidepressant therapy (maintenance group) or to taper and discontinue such therapy with the use of matching placebo (discontinuation group). The primary outcome was the first relapse of depression during the 52-week trial period, as evaluated in a time-to-event analysis. Secondary outcomes were depressive and anxiety symptoms, physical and withdrawal symptoms, quality of life, time to stopping an antidepressant or placebo, and global mood ratings.

RESULTS

A total of 1466 patients underwent screening. Of these patients, 478 were enrolled in the trial (238 in the maintenance group and 240 in the discontinuation group). The average age of the patients was 54 years; 73% were women. Adherence to the trial assignment was 70% in the maintenance group and 52% in the discontinuation group. By 52 weeks, relapse occurred in 92 of 238 patients (39%) in the maintenance group and in 135 of 240 (56%) in the discontinuation group (hazard ratio, 2.06; 95% confidence interval, 1.56 to 2.70; P<0.001). Secondary outcomes were generally in the same direction as the primary outcome. Patients in the discontinuation group had more symptoms of depression, anxiety, and withdrawal than those in the maintenance group.

CONCLUSIONS

Among patients in primary care practices who felt well enough to discontinue antidepressant therapy, those who were assigned to stop their medication had a higher risk of relapse of depression by 52 weeks than those who were assigned to maintain their current therapy. (Funded by the National Institute for Health Research; ANTLER ISRCTN number, ISRCTN15969819.)

From the Division of Psychiatry, Faculty of Brain Sciences (Gemma Lewis, L.D., M.K., P.L., F.B., M.B., Glyn Lewis), the Research Department of Primary Care and Population Health and Priment Clinical Trials Unit (L.M., R.H., I.N., C.S.C.), and the Institute of Clinical Trials and Methodology (N.F.), University College London, London, the Department of Health Sciences and Hull York Medical School, University of York, York (S.G., S.B., J.P.), Primary Care Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, Southampton (T.K., M.M., A.H.), and Population Health Sciences (D.K.) and the Centre for Academic Mental Health (N.W., A.B.), Bristol Medical School, University of Bristol, Bristol — all in the United Kingdom; and the Department of Family Medicine, McMaster University, Hamilton, ON, Canada (D.M.). Address reprint requests to Dr. Lewis at the Division of Psychiatry, University College London, 149 Tottenham Court Rd., 6th Floor, Maple House London, London W1T 7NF, United Kingdom, or at gemma.lewis@ucl.ac.uk.

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RESEARCH SUMMARY

Maintenance or Discontinuation of Antidepressants in Primary Care

Lewis G et al. DOI: 10.1056/NEJMoa2106356

CLINICAL PROBLEM

The number of antidepressant prescriptions in primary care has risen in developed nations in recent decades, primarily because of longer treatment durations. High rates of relapse of depression after treatment discontinuation have been reported, but those studies have had numerous limitations.

CLINICAL TRIAL

Design: A randomized, double-blind, placebo-controlled, parallel-group trial involving patients in 150 general practices in the United Kingdom compared the effects of maintaining or discontinuing antidepressants among enrollees who had been taking antidepressants for at least 9 months and felt well enough to consider stopping their medication.

Intervention: 478 adults who had been receiving conventional doses of commonly prescribed antidepressants in the United Kingdom (citalopram, sertraline, fluoxetine, and mirtazapine) were randomly assigned either to maintain their current regimen or to take lower doses and eventually discontinue the antidepressant, with the use of matching placebo. The primary outcome was relapse of depression.

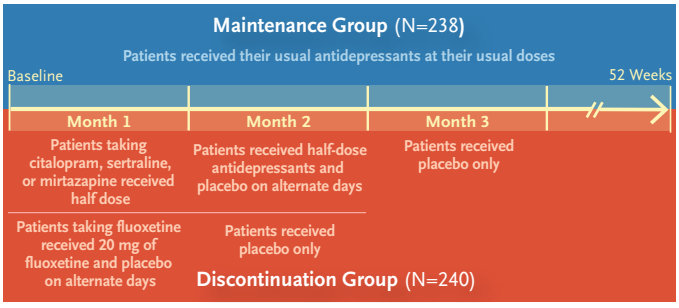
RESULTS

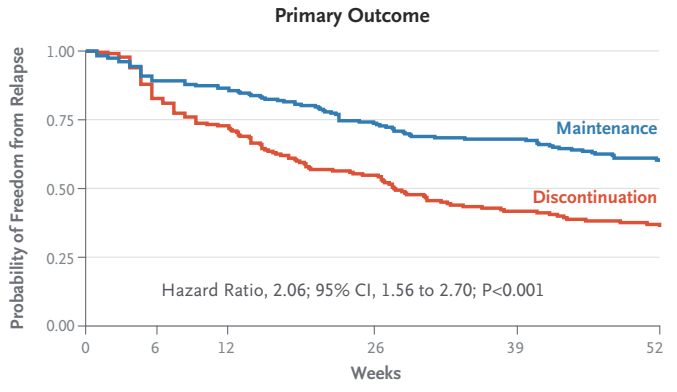
Efficacy: During the 52 weeks of the trial, the frequency of relapse of depression was significantly higher in the discontinuation group than in the maintenance group.

Safety: Patients in the discontinuation group had more symptoms of depression, anxiety, and withdrawal.

LIMITATIONS AND REMAINING QUESTIONS

- Patients taking escitalopram and those receiving doses other than usual maintenance doses of antidepressants were excluded from the trial.
- The trial lacked racial and ethnic diversity, and the findings may not be applicable to patients outside the United Kingdom.





Secondary Outcomes

	Maintenance (N=238)	Discontinuation (N=240)	Effect Size or Difference (95% CI)
Patient Health Questionnaire-9*	4.2	5.0	0.7 (0.0 to 1.4)
Generalized Anxiety Disorder-7*	3.4	4.1	0.8 (0.1 to 1.4)
Modified Toronto Side Effect Scale	4.0	3.9	0.2 (–0.3 to 0.7)
New or Worsening Symptoms	1.4	1.9	0.5 (0.1 to 0.9)
12-Item Short-Form Health Survey†			
Physical Component	48	49	0.2 (–1.3 to 1.6)
Mental Component	46	44	–2.6 (–4.4 to –0.8)

*Higher scores indicate more severe symptoms.
†Higher scores indicate better quality of life.

CONCLUSIONS

Patients in U.K. primary care practices who discontinued their antidepressant had a higher frequency of depression relapse than those who continued their existing regimen through 52 weeks.

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EDITORIAL

The Pursuit and Maintenance of Happiness

Jeffrey L. Jackson, M.D., M.P.H.

Happiness was articulated as a fundamental right by the founding fathers of the United States. Few illnesses interfere with the pursuit of happiness more than depression, and approximately 6% of the world's population is depressed at any given time. Depression is commonly encountered in primary care, with up to one third of patients having depressive symptoms and 10% meeting criteria for major depression.[1] Depressed patients typically report physical rather than emotional symptoms and as a result are often referred to specialty clinics, in which the frequency of undiagnosed depression among new patients may be even higher than that in primary care.[2] Despite recommendations by the U.S. Preventive Services Task Force for universal depression screening,[3] only 4% of primary care patients are screened.[4] Consequently, it has been estimated that in primary care practices, depression remains undiagnosed in up to 50% of the patients who have the condition.[5]

The ideal goal of treatment for depression is remission, rather than improvement, in part because maintaining remission for at least 6 months is associated with a reduced chance of relapse.[6] Nevertheless, the frequency of relapse is high.[7] Therefore, a common question asked by providers and patients is how long to continue antidepressant treatment. In this issue of the *Journal*, Lewis and colleagues report the results of a randomized trial conducted in the United Kingdom involving adults from 150 general practices who felt well enough regarding their depression to discontinue treatment.[8] The primary outcome was the first relapse of depression during a 52-week period. Not surprisingly, withdrawal symptoms were more common among those who tapered and discontinued their treatment than among those who continued to receive their typical regimen, and such symptoms were worse in the discontinuation group than in the maintenance group at 12, 26, and 39 weeks after discontinuation but may not have differed between groups at 52 weeks. The investigators' essential finding was that relapse occurred in 56% of the patients who discontinued treatment as compared with 39% of those who continued to receive antidepressants. In addition, as judged from the Kaplan–Meier curves, relapse occurred sooner in the discontinuation group than in the maintenance group.

These findings overall represent important but disappointing news, but just as disappointing were the relapse rates in both trial groups. However, there are limitations to the application of the trial results to practice. Patients with three or more previous depressive episodes were more than twice as likely to have a relapse than those with fewer episodes. This result is consistent with the findings of other studies,[9] and it is unclear whether the trial results are generalizable to primary care patients with a first episode of depression. A second caveat is that the results pertain to patients who had been treated with antidepressants for at least 2 years and were in remission at the time the trial began, and it is unclear how long they had been in remission.

How do these results affect practice? They confirm what most primary care physicians already knew or intuited. The frequency of relapse after the discontinuation of treatment is high, particularly among patients with several previous depressive episodes. I encourage patients with a single bout of depression, especially episodes that are triggered by a life event, such as loss of a loved one, to consider weaning antidepressant treatment after at least 6 months of remission.

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For those with three or more previous bouts of depression, my practice has been to recommend that they anticipate medical treatment for life or, if they wish to stop taking medication, explore nonpharmacologic approaches, such as cognitive behavior therapy.[10] Even among the patients who continue pharmacologic treatment, relapse is common, so depressed patients need close follow-up. It is useful to educate patients to monitor their depressive symptoms and alert their provider if they sense they are having a relapse. The results of this and many other trials highlight the fact that current treatment options for depressed patients are not ideal.

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

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From the Zablocki VA Medical Center and the Medical College of Wisconsin, Milwaukee.

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ORIGINAL ARTICLE

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

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ABSTRACT

BACKGROUND

The appropriate target for systolic blood pressure to reduce cardiovascular risk in older patients with hypertension remains unclear.

METHODS

In this multicenter, randomized, controlled trial, we assigned Chinese patients 60 to 80 years of age with hypertension to a systolic blood-pressure target of 110 to less than 130 mm Hg (intensive treatment) or a target of 130 to less than 150 mm Hg (standard treatment). The primary outcome was a composite of stroke, acute coronary syndrome (acute myocardial infarction and hospitalization for unstable angina), acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

RESULTS

Of the 9624 patients screened for eligibility, 8511 were enrolled in the trial; 4243 were randomly assigned to the intensive-treatment group and 4268 to the standard-treatment group. At 1 year of follow-up, the mean systolic blood pressure was 127.5 mm Hg in the intensive-treatment group and 135.3 mm Hg in the standard-treatment group. During a median follow-up period of 3.34 years, primary-outcome events occurred in 147 patients (3.5%) in the intensive-treatment group, as compared with 196 patients (4.6%) in the standard-treatment group (hazard ratio, 0.74; 95% confidence interval [CI], 0.60 to 0.92; P=0.007). The results for most of the individual components of the primary outcome also favored intensive treatment: the hazard ratio for stroke was 0.67 (95% CI, 0.47 to 0.97), acute coronary syndrome 0.67 (95% CI, 0.47 to 0.94), acute decompensated heart failure 0.27 (95% CI, 0.08 to 0.98), coronary revascularization 0.69 (95% CI, 0.40 to 1.18), atrial fibrillation 0.96 (95% CI, 0.55 to 1.68), and death from cardiovascular causes 0.72 (95% CI, 0.39 to 1.32). The results for safety and renal outcomes did not differ significantly between the two groups, except for the incidence of hypotension, which was higher in the intensive-treatment group.

CONCLUSIONS

In older patients with hypertension, intensive treatment with a systolic blood-pressure target of 110 to less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment with a target of 130 to less than 150 mm Hg. (Funded by the Chinese Academy of Medical Sciences and others; STEP ClinicalTrials.gov number, NCT03015311.)

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*A complete list of members of the STEP Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. W. Zhang, S. Zhang, Deng, Wu, Ren, Sun, Yang, Jiang, Xu, T.-D. Wang, and Y. Chen contributed equally to this article.

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RESEARCH SUMMARY

Trial of Intensive Blood-Pressure Control in Older Patients with Hypertension

Zhang W et al. DOI: 10.1056/NEJMoa2111437

CLINICAL PROBLEM

Clinical guidelines vary in their systolic blood-pressure targets for older adults, with some recommending intensive treatment aimed at a systolic blood pressure of less than 130 mm Hg. Although randomized trials show impressive cardiovascular benefits with intensive blood-pressure control in older adults, observational studies suggest that caution is warranted.

CLINICAL TRIAL

Design: A prospective, multicenter, randomized, controlled trial examined whether intensive blood-pressure control offers a greater cardiovascular benefit than standard blood-pressure control in older patients with hypertension.

Intervention: 8511 Chinese patients 60 to 80 years of age who had a systolic blood pressure of 140 to 190 mm Hg or were taking antihypertensive medication were randomly assigned to intensive treatment (systolic blood-pressure target, 110 to <130 mm Hg) or standard treatment (target, 130 to <150 mm Hg). The primary outcome was a composite of stroke, acute coronary syndrome, acute decompensated heart failure, coronary revascularization, atrial fibrillation, or death from cardiovascular causes.

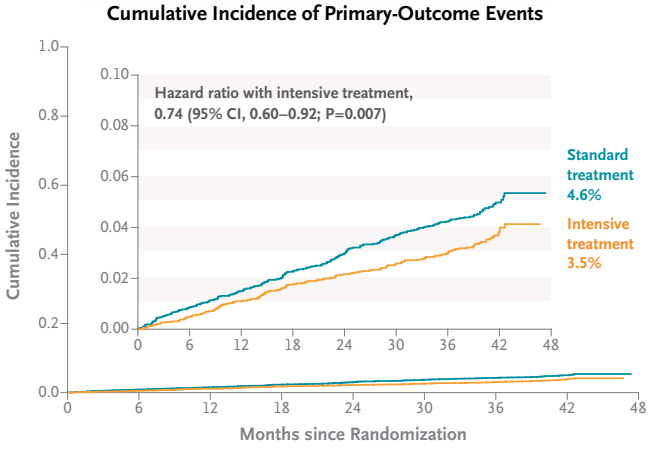
RESULTS

Efficacy: During a median follow-up of 3.34 years, primary-outcome events occurred significantly less often in the intensive-treatment group than in the standard-treatment group.

Safety: The results for most safety outcomes did not differ significantly between the two groups. Hypotension, however, occurred more often with intensive treatment.

LIMITATIONS AND REMAINING QUESTIONS

- Only Han Chinese persons were included in the trial, which limits the generalizability of the findings.
- Adults with a history of stroke were excluded.
- Additional research is needed to understand the effects of intensive blood-pressure control on quality of life, cost effectiveness, and long-term clinical outcomes.



Safety Outcomes	Intensive Treatment (N=4243)	Standard Treatment (N=4268)	Relative Risk (95% CI)	P Value
	no. of patients (%)			
Adverse events				
Hypotension	146 (3.4)	113 (2.6)	1.31 (1.02–1.68)	0.03
Dizziness	45 (1.1)	49 (1.1)	0.92 (0.61–1.39)	0.70
Serious adverse events				
Syncope	6 (0.1)	2 (<0.1)	3.02 (0.61–14.97)	0.18
Fracture	15 (0.4)	19 (0.4)	0.79 (0.40–1.56)	0.50

CONCLUSIONS

Intensive antihypertensive treatment targeting a systolic blood pressure of less than 130 mm Hg resulted in a lower incidence of cardiovascular events than standard treatment in older patients with hypertension in China.

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EDITORIAL

Moving the Goalposts for Blood Pressure — Time to Act

Mark R. Nelson, M.B., B.S., M.F.M., Ph.D.

We often lament the lack of confirmatory studies that can either reassure us all that the previous evidence for a trialed intervention is robust or indicate that the evidence is questionable. Zhang and colleagues have conducted such a study — the STEP trial[1] — which in essence investigates the veracity of the findings of the previous trial SPRINT,[2] but in an older cohort and in China, a country with a considerable burden of high blood pressure and stroke.

The investigators have demonstrated impressive organizational skills in completing recruitment for such a large multicenter trial within a calendar year. As in SPRINT, and unlike in previous studies aiming to define the systolic blood-pressure target in older patients, real and clinically significant differences in blood pressure between the intensive-treatment group (systolic blood-pressure target, 110 to <130 mm Hg) and the standard-treatment group (target, 130 to <150 mm Hg) were attained and maintained. Only a modest number of medications were needed to reach these targets (mean number administered per patient, 1.9 in the intensive-treatment group and 1.5 in the standard-treatment group), which is crucial for real-world implementation of the findings. Like SPRINT, the STEP trial was stopped early because there was a clear cardiovascular benefit in the intensive-treatment group. Unlike SPRINT, the STEP trial did not show a significant benefit in the intensive-treatment group with respect to death from any cause or death from cardiovascular causes.

As with any study, some aspects of the STEP trial muddy the waters for interpretation of the results. For example, the trial used an app (smartphone-based application) and used multiple methods of blood-pressure measurement, including an observed method of office blood-pressure measurement rather than the preferred unobserved (automated) method. One might question why the trial excluded all patients with a history of stroke, instead of restricting exclusion to those who had had a stroke within a specified period. Patients with a history of stroke are an important group in China and would be likely to benefit from better blood-pressure control once their condition has stabilized. One might also question why there was no quality-of-life measure, given the possibility of symptoms associated with low blood pressure and the high pill count for an essentially asymptomatic condition. When treating older patients, a physician's practice is likely to be influenced by quality as well as quantity of life. However, the concept pursued from SPRINT — that systolic blood-pressure targets below currently accepted levels provide real clinical benefits with relative safety — was confirmed.

So, where do we go from here? We could continue to edge down thresholds and targets for treatment to identify an ideal blood-pressure attainment, provided that we have the dollars to support sufficiently powered trials involving very large populations of patients with high risk of cardiovascular disease, but this would be a clinical *reductio ad absurdum*. Perhaps instead of waiting for more evidence, we should see this as the time to act. Although both the STEP trial and SPRINT were ostensibly trials of systolic blood-pressure targets for hypertension treatment, they were also in effect quasi trials of the treatment of elevated blood pressure in patients with high cardiovascular risk. This can be said because both study populations consisted of patients with high risk, as determined by age, clinical condition, or the Framingham Risk Score. It is this absolute risk, and not blood pressure alone, that drives therapeutic clinical benefit. Indeed, international guidelines generally base recommendations for the treatment of elevated blood pressure on absolute risk of cardiovascular disease. And yet, absolute risk still does not take precedence in decision making or is only one aspect of a hybrid model, such as in the United States, where hypertension is treated in high-risk patients at a systolic blood-pressure threshold that is 10 mm Hg lower than the threshold for other patients.[3]

Thus, we continue to manage blood pressure as an isolated risk factor rather than as an integrated part of a patient's risk profile because we adhere to the rusted-on clinical concept of hypertension. According to this concept, there is an arbitrary number above which disease is present

and below which it is absent. The STEP trial and SPRINT tell us that now is an opportune time to return elevated blood pressure to its status as a continuous-variable risk factor, instead of treating it as a dichotomous disease. After all, the origin of the word "disease" is "the absence of ease . . . discomfort" and is therefore inappropriate for an asymptomatic condition.[4] Such "disease" is evident only when major organ damage ensues. Preventive strategies must maximize avoidance of these events. Perhaps "hypertension" should henceforth be used only in its adjectival form to describe target organ damage (e.g., hypertensive nephropathy) and not as a noun to indicate a disease model. Moreover, the term can be confusing to our patients, which is another argument for its abandonment.[5]

History tells us that the association of adverse health effects with elevated blood pressure was an actuarial observational discovery made by insurance companies and was initially railed against by the medical profession, although it was later enthusiastically appropriated once effective therapies became available. The approach of focusing on the absolute risk of adverse cardiovascular events, rather than on blood pressure alone, has been promoted for decades from the Antipodes.[6] Perhaps the STEP trial is another impetus for broader adoption of this approach.

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

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New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

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ABSTRACT

BACKGROUND

Current equations for estimated glomerular filtration rate (eGFR) that use serum creatinine or cystatin C incorporate age, sex, and race to estimate measured GFR. However, race in eGFR equations is a social and not a biologic construct.

METHODS

We developed new eGFR equations without race using data from two development data sets: 10 studies (8254 participants, 31.5% Black) for serum creatinine and 13 studies (5352 participants, 39.7% Black) for both serum creatinine and cystatin C. In a validation data set of 12 studies (4050 participants, 14.3% Black), we compared the accuracy of new eGFR equations to measured GFR. We projected the prevalence of chronic kidney disease (CKD) and GFR stages in a sample of U.S. adults, using current and new equations.

RESULTS

In the validation data set, the current creatinine equation that uses age, sex, and race overestimated measured GFR in Blacks (median, 3.7 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 1.8 to 5.4) and to a lesser degree in non-Blacks (median, 0.5 ml per minute per 1.73 m^2; 95% CI, 0.0 to 0.9). When the adjustment for Black race was omitted from the current eGFR equation, measured GFR in Blacks was underestimated (median, 7.1 ml per minute per 1.73 m^2; 95% CI, 5.9 to 8.8). A new equation using age and sex and omitting race underestimated measured GFR in Blacks (median, 3.6 ml per minute per 1.73 m^2; 95% CI, 1.8 to 5.5) and overestimated measured GFR in non-Blacks (median, 3.9 ml per minute per 1.73 m^2; 95% CI, 3.4 to 4.4). For all equations, 85% or more of the eGFRs for Blacks and non-Blacks were within 30% of measured GFR. New creatinine–cystatin C equations without race were more accurate than new creatinine equations, with smaller differences between race groups. As compared with the current creatinine equation, the new creatinine equations, but not the new creatinine–cystatin C equations, increased population estimates of CKD prevalence among Blacks and yielded similar or lower prevalence among non-Blacks.

CONCLUSIONS

New eGFR equations that incorporate creatinine and cystatin C but omit race are more accurate and led to smaller differences between Black participants and non-Black participants than new equations without race with either creatinine or cystatin C alone. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Inker can be contacted at linker@tuftsmedicalcenter.org or at the Division of Nephrology, Tufts Medical Center, 800 Washington St., Box 391, Boston, MA 02111.

*The members of the Chronic Kidney Disease Epidemiology Collaboration are listed in the Supplementary Appendix, available at NEJM.org.

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ORIGINAL ARTICLE

Race, Genetic Ancestry, and Estimating Kidney Function in CKD

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ABSTRACT

BACKGROUND

The inclusion of race in equations to estimate the glomerular filtration rate (GFR) has become controversial. Alternative equations that can be used to achieve similar accuracy without the use of race are needed.

METHODS

In a large national study involving adults with chronic kidney disease, we conducted cross-sectional analyses of baseline data from 1248 participants for whom data, including the following, had been collected: race as reported by the participant, genetic ancestry markers, and the serum creatinine, serum cystatin C, and 24-hour urinary creatinine levels.

RESULTS

Using current formulations of GFR estimating equations, we found that in participants who identified as Black, a model that omitted race resulted in more underestimation of the GFR (median difference between measured and estimated GFR, 3.99 ml per minute per 1.73 m^2 of body-surface area; 95% confidence interval [CI], 2.17 to 5.62) and lower accuracy (percent of estimated GFR within 10% of measured GFR [P_{10}], 31%; 95% CI, 24 to 39) than models that included race (median difference, 1.11 ml per minute per 1.73 m^2; 95% CI, −0.29 to 2.54; P_{10}, 42%; 95% CI, 34 to 50). The incorporation of genetic ancestry data instead of race resulted in similar estimates of the GFR (median difference, 1.33 ml per minute per 1.73 m^2; 95% CI, −0.12 to 2.33; P_{10}, 42%; 95% CI, 34 to 50). The inclusion of non-GFR determinants of the serum creatinine level (e.g., body-composition metrics and urinary excretion of creatinine) that differed according to race reported by the participants and genetic ancestry did not eliminate the misclassification introduced by removing race (or ancestry) from serum creatinine–based GFR estimating equations. In contrast, the incorporation of race or ancestry was not necessary to achieve similarly statistically unbiased (median difference, 0.33 ml per minute per 1.73 m^2; 95% CI, −1.43 to 1.92) and accurate (P_{10}, 41%; 95% CI, 34 to 49) estimates in Black participants when GFR was estimated with the use of cystatin C.

CONCLUSIONS

The use of the serum creatinine level to estimate the GFR without race (or genetic ancestry) introduced systematic misclassification that could not be eliminated even when numerous non-GFR determinants of the serum creatinine level were accounted for. The estimation of GFR with the use of cystatin C generated similar results while eliminating the negative consequences of the current race-based approaches. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Go can be contacted at alan.s.go@kp.org or at the Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, CA 94612.

*A full list of the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Hsu, Yang, Feldman, and Go contributed equally to this article.

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RESEARCH SUMMARY

Race, Genetic Ancestry, and Estimating Kidney Function in CKD

Hsu C et al. DOI: 10.1056/NEJMoa2103753

CLINICAL PROBLEM

The use of race in equations to estimate the glomerular filtration rate (GFR) from the serum creatinine level has come under scrutiny. Alternative strategies to accurately estimate GFR without the use of race are needed.

STUDY

Design: Data from a multicenter, prospective, observational U.S. study involving adults with chronic kidney disease were used to examine the interplay among race, genetically derived ancestry, serum creatinine, and serum cystatin C in order to develop alternative methods of estimating GFR.

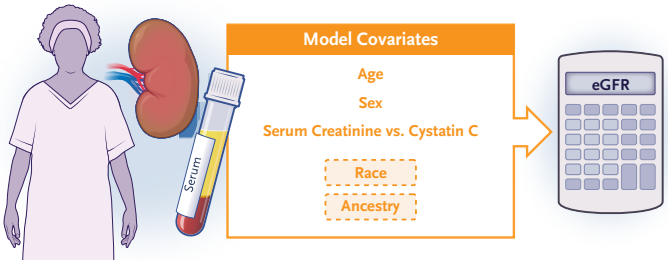
Analysis: 1248 participants for whom race (reported by the participant), ancestry genotyping, and laboratory data were available were included. Researchers assessed three strategies for estimating GFR without including race. Direct GFR measurement through urinary ^{125}I-iothalamate clearance (iGFR) was used as the reference.

RESULTS

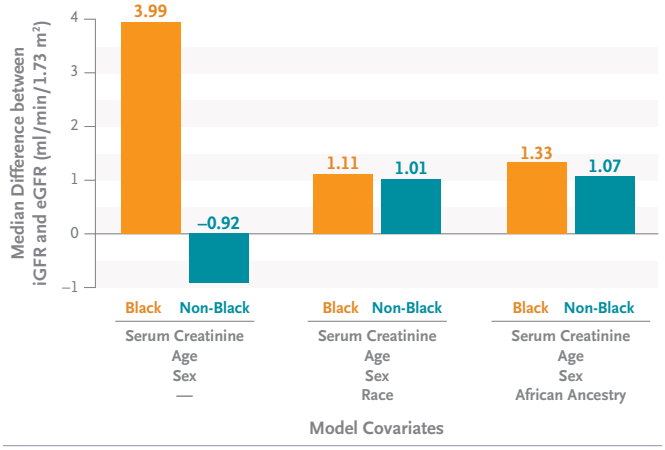
The use of the serum creatinine level, age, and sex alone underestimated the measured GFR in Black participants but not in non-Black participants. Incorporation of non-GFR determinants of the serum creatinine level that differed according to race (e.g., body-mass index [BMI]) did not resolve the GFR underestimation in Black participants. However, the use of serum cystatin C rather than serum creatinine in equations that omitted race and genetic ancestry resulted in similarly accurate GFR estimates in Black and non-Black participants; these estimates were not improved by adding race or genetic ancestry.

LIMITATIONS AND REMAINING QUESTIONS

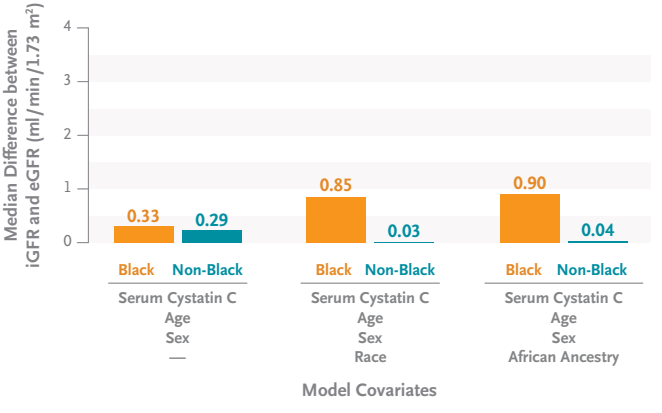
- The study included only research volunteers.
- After participants were stratified according to race, sample sizes were too small for evaluation of subgroups (e.g., according to BMI).
- The results cannot be generalized to populations outside the United States.



Model Performance and Race Coefficients from GFR Estimating Equations Based on Serum Creatinine



Model Performance and Race Coefficients from GFR Estimating Equations Based on Serum Cystatin C



CONCLUSIONS

Cystatin C–based equations rather than creatinine-based equations allowed for sufficiently accurate GFR estimates in Black and non-Black participants without the need to incorporate race.

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EDITORIAL

Time to Eliminate Health Care Disparities in the Estimation of Kidney Function

Winfred W. Williams, M.D., Joseph W. Hogan, Sc.D., and Julie R. Ingelfinger, M.D.

In the wake of the racial reckoning since the spring of 2020 in the United States, efforts have emerged to identify hidden structural determinants of systemic racism in medicine. Such efforts have led to examination of traditional medical algorithms that incorporate race modifiers and may have led to disparities in health outcomes according to racial and ethnic group. Prominent among these efforts has been reconsideration of race-based adjustments in equations that are used to calculate the estimated glomerular filtration rate (eGFR) in the assessment of kidney function. Approximately 90% of U.S. medical laboratories report the eGFR along with the serum creatinine concentration, and the use of a Black race coefficient in calculation of the eGFR has engendered numerous debates. Consequently, many institutions have already stopped using the race adjustment.

Some have argued that the way in which estimating equations for GFR were developed — they were initially derived from data on White persons[1] — doomed them to be inequitable from their inception. When GFR was directly measured from endogenous clearance of creatinine or from exogenous substances such as iothalamate, there was a difference in GFR between Black and non-Black persons. That observation led to incorporation of a race coefficient in estimating equations that would inflate GFR estimates for Black patients in order to generate unbiased GFR estimates in Black and non-Black populations.[2,3] However, concern has emerged that the inclusion of race as a coefficient in eGFR equations inequitably inflates GFR estimates in Blacks and lacks a biologic basis.[4]

One year ago, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) formed a joint task force to develop a best-practice recommendation regarding the use of race in eGFR prediction equations. The final version of that recommendation is now being published.[5] Now in the *Journal*, two investigator groups report on studies that address the use of race in the estimation of kidney function.[6,7]

Inker et al.[6] formulated and cross-validated new GFR equations that eliminate the race coefficient, and they compared them with currently used equations — the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is based on the serum creatinine concentration (eGFRcr),[3] and the 2012 CKD-EPI equation, which is based on both the serum creatinine concentration and the serum cystatin C concentration (eGFRcr-cys).[8] Hsu et al.[7] had a different, but similar, approach. They used a sample from the Chronic Renal Insufficiency Cohort study database to fit regression models of measured GFR with age, sex, and either serum creatinine or cystatin C as predictors of GFR. They then compared the accuracy and predictive bias (the difference between eGFR and measured GFR) of models that added either Black race or the percentage of African ancestry as a predictor.

Inker et al. found that the currently used 2009 CKD-EPI eGFRcr equation that includes age, sex, and race[3] overestimated measured GFR in Black participants by a median of 3.7 ml per minute per 1.73 m^2 of body-surface area (95% confidence interval, 1.8 to 5.4) and had negligible bias in non-Black participants. Agreement between measured GFR and eGFR within chronic

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kidney disease (CKD) categories in that model was 63.2% in Black participants and 68.5% in non-Black participants. The 2012 CKD-EPI eGFRcr-cys equations[8] had less bias and higher percent agreement than the corresponding eGFRcr equations.

It is crucial to understand how the newly proposed equations "eliminate" the race coefficient. The use of the current CKD-EPI equations without application of the inflation factor for Black race (15.9% for the eGFRcr equation and 8.0% for the eGFRcr-cys equation) does not affect the accuracy of eGFR estimates for non-Black persons, but it underestimates the GFR and reduces accuracy for Black persons. Another approach is to refit the eGFR equation without using race as a predictor, which leads to new values for the other coefficients. Analyses presented in both articles suggest that refitted creatinine-based prediction equations underestimate GFR for Black persons by 3 to 4 ml per minute per 1.73 m^2 and overestimate GFR for non-Black persons by 1 to 4 ml per minute per 1.73 m^2. Relative to currently used CKD-EPI equations, the change in overall accuracy with refitted equations is minor, but race disparities in classification of the CKD stage may not be fully resolved (Table S14 in the Supplementary Appendix of the article by Inker et al., available with the full text of the article at NEJM.org).

Both articles showed that equations based on cystatin C yielded lower predictive bias and greater agreement with measured GFR across race groups than GFR estimation based on creatinine alone. Moreover, they showed that bias and agreement were not affected by the inclusion of race as a predictor.

It is essential to quantify the ability of new equations to improve GFR estimation and reduce racial disparities in the diagnosis of kidney disease. Both articles relied on measures of accuracy such as predictive bias (also called statistical bias or differential bias), the percentage of estimates less than 10% or less than 30% different from measured GFR (P_{10} and P_{30}, respectively), and the correct classification (i.e., the percent agreement between measured GFR and eGFR categories within CKD stages). Although useful, these omnibus measures are difficult to interpret in a clinical context (e.g., the average bias of 3 ml per minute per 1.73 m^2 is more meaningful at a low GFR than at a high GFR[8]). Context-specific measures such as the percentage of patients with CKD who would be misclassified are needed in order to understand the effect at the patient level.

The development of accurate predictions of GFR that do not rely on adjustment for Black race and avoidance of potential race-based disparity in the accuracy of CKD diagnoses have proved to be problematic in clinical practice. Inker et al. found that, relative to the currently used 2009 CKD-EPI eGFRcr equation, the same equation refitted without race had a similar percent agreement between eGFR and measured GFR within CKD stages but retained modest statistical bias. However, Hsu et al. found that in models of eGFR that were based on serum creatinine, exclusion of race-based predictors (i.e., Black race as reported by the participants or percentage of African ancestry) yielded increased predictive bias and diminished accuracy; furthermore, the effect of excluding race as a predictor could not be mitigated by replacing race with non-GFR determinants of the serum creatinine concentration. In contrast, race had no effect on the predictive accuracy of eGFR in equations that were based on cystatin C. Both articles point to the promise of cystatin C for uniformly more accurate GFR prediction without the need to include race-based adjustments.

The much-anticipated NKF-ASN task force report[5] concludes that CKD-EPI equations that are refitted without race should be used in practice. The articles by Inker et al. and Hsu et al. provide evidence that equations based on cystatin C have greater predictive accuracy than those derived from serum creatinine. If the capacity to measure cystatin C routinely were widespread, cystatin C equations would become practical; thus, we suggest that the use of cystatin C measurements should be encouraged and funded.

Meaningful ways to alleviate health care inequities are overdue. That Black persons with CKD often lose kidney function more rapidly and have lower kidney transplantation rates than patients from other racial and ethnic groups indicates an urgent problem. The use of the most accurate estimates of GFR may permit earlier identification and care of persons at risk.[9,10] Irrespective of the equations adopted, estimates of GFR are, by their very nature, imperfect. Some promising options will take time to implement, since measurement of cystatin C is currently neither routine nor uniform. Both existing and

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newly derived equations have strengths and weaknesses, and change inevitably induces unanticipated consequences. Most important, however, is that estimates do no harm but rather help us care for all patients equally.

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

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ORIGINAL ARTICLE

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

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ABSTRACT

BACKGROUND

Patients with von Hippel–Lindau (VHL) disease have a high incidence of renal cell carcinoma owing to *VHL* gene inactivation and constitutive activation of the transcription factor hypoxia-inducible factor 2α (HIF-2α).

METHODS

In this phase 2, open-label, single-group trial, we investigated the efficacy and safety of the HIF-2α inhibitor belzutifan (MK-6482, previously called PT2977), administered orally at a dose of 120 mg daily, in patients with renal cell carcinoma associated with VHL disease. The primary end point was objective response (complete or partial response) as measured according to the Response Evaluation Criteria in Solid Tumors, version 1.1, by an independent central radiology review committee. We also assessed responses to belzutifan in patients with non–renal cell carcinoma neoplasms and the safety of belzutifan.

RESULTS

After a median follow-up of 21.8 months (range, 20.2 to 30.1), the percentage of patients with renal cell carcinoma who had an objective response was 49% (95% confidence interval, 36 to 62). Responses were also observed in patients with pancreatic lesions (47 of 61 patients [77%]) and central nervous system hemangioblastomas (15 of 50 patients [30%]). Among the 16 eyes that could be evaluated in 12 patients with retinal hemangioblastomas at baseline, all (100%) were graded as showing improvement. The most common adverse events were anemia (in 90% of the patients) and fatigue (in 66%). Seven patients discontinued treatment: four patients voluntarily discontinued, one discontinued owing to a treatment-related adverse event (grade 1 dizziness), one discontinued because of disease progression as assessed by the investigator, and one patient died (of acute toxic effects of fentanyl).

CONCLUSIONS

Belzutifan was associated with predominantly grade 1 and 2 adverse events and showed activity in patients with renal cell carcinomas and non–renal cell carcinoma neoplasms associated with VHL disease. (Funded by Merck Sharp and Dohme and others; MK-6482-004 ClinicalTrials.gov number, NCT03401788.)

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*The MK-6482-004 investigators are listed in the Supplementary Appendix, available at NEJM.org.

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RESEARCH SUMMARY

Belzutifan for Renal Cell Carcinoma in von Hippel–Lindau Disease

Jonasch E et al. DOI: 10.1056/NEJMoa2103425

CLINICAL PROBLEM

Renal cell carcinoma is common in von Hippel–Lindau (VHL) disease, and patients often undergo several surgeries in their lifetime for resection of renal tumors and other VHL-disease–associated neoplasms. The tumors stem from *VHL* gene inactivation and subsequent constitutive activation of hypoxia-inducible factor (HIF)–mediated transcriptional pathways. Belzutifan is an oral HIF-2α inhibitor.

CLINICAL TRIAL

Design: A phase 2, multinational, open-label, single-group trial examined the safety and efficacy of belzutifan in patients with VHL-disease–associated renal cell carcinoma.

Intervention: 61 adults with VHL disease and at least one measurable renal cell carcinoma tumor (and no tumors large enough [>3 cm] to necessitate immediate surgery) received belzutifan at a dose of 120 mg once daily until they had unacceptable drug-related side effects or disease progression. The primary outcome was the objective response of renal cell carcinoma to treatment, as assessed with RECIST, version 1.1.

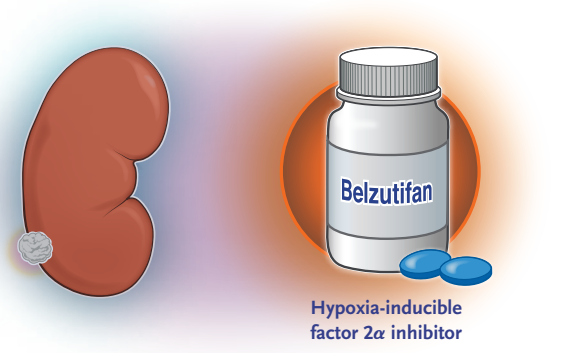
RESULTS

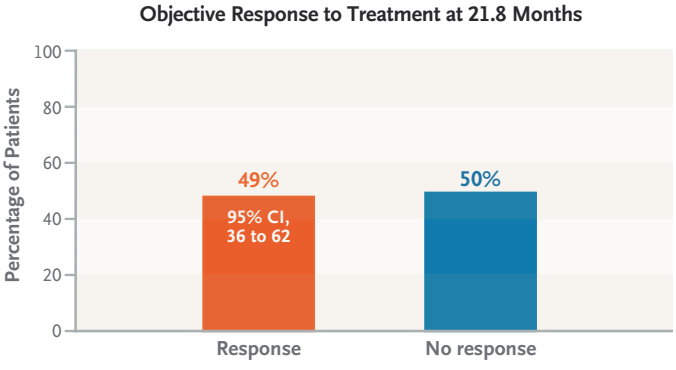
Efficacy: During a median follow-up of 21.8 months, nearly half the patients had an objective response to treatment; all responses were partial. Two patients had disease progression.

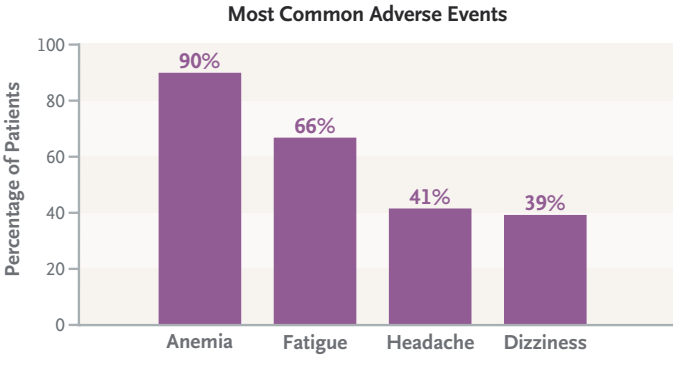
Safety: All patients had at least one treatment-related adverse event. Anemia, fatigue, headache, and dizziness were the most common and were usually grade 1 or 2. Seven patients discontinued treatment.

LIMITATIONS AND REMAINING QUESTIONS

- The study sample was modest in size and lacked a comparison group.
- How belzutifan might best be used in patients with VHL-disease–associated tumors — for example, as an alternative or as a complement to surgery — requires further study.







CONCLUSIONS

The HIF-2α inhibitor belzutifan showed efficacy against renal tumors in patients with VHL disease, with mostly low-grade adverse events.

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EDITORIAL

Changing the Course of an Orphan Disease

Manuela Schmidinger, M.D.

Patients with von Hippel–Lindau (VHL) disease, a rare autosomal dominant inherited disease,[1] have a shorter life expectancy than the general population.[2,3] A prospective analysis involving 128 patients in Italy showed that mortality among persons in the VHL population who were between 25 and 64 years of age was significantly higher than that in the general population (P=0.0001).[3] The development of clear-cell renal cell carcinoma is usually a late event in the course of VHL disease (at a mean of 34 to 61.8 years of age).[3,4] However, extrarenal manifestations of the disease typically occur earlier and are associated with substantial morbidity and mortality.

In this issue of the *Journal*, Jonasch et al.[5] report the results of a trial involving a new medical treatment for renal cell carcinoma associated with VHL disease. Belzutifan targets hypoxia-inducible factor 2α (HIF-2α), a transcription factor that drives the progression of clear-cell renal cell carcinoma.[6] Patients with VHL and evidence of clear-cell renal cell carcinoma were included in this phase 2, single-group trial. Objective response (complete or partial response; the primary end point) was observed in 49% (95% confidence interval [CI], 36 to 62) of the patients, and disease control in 98% (95% CI, 91 to 100). At 24 months, the percentage of patients with progression-free survival was 96%. Although similar response rates have been reported in patients with VHL-associated renal cell carcinoma with the use of antiangiogenic agents such as pazopanib,[7] the data in this trial stand out for the major differences shown (i.e., less serious adverse events and greater treatment adherence). Treatment-related adverse events were mostly grades 1 and 2 and consisted of anemia, fatigue, headache, and dizziness. The percentage of patients in this trial who continued to receive treatment at the time of data cutoff was substantially higher than that in the trial of pazopanib (89% vs. 32%), as was the percentage of patients who did not require a dose reduction (85% vs. 52%).[7] Treatment adherence appears particularly important in the context of a chronic disease, in which young patients may need lifelong, regular medical intervention.

The magnitude of this achievement is better understood in the context of the results of the secondary end points in the trial. Belzutifan is approved by the Food and Drug Administration not only for treatment of patients with VHL-associated renal cell carcinoma but also for patients with VHL-associated hemangioblastomas of the central nervous system (CNS) and pancreatic neuroendocrine tumors that do not necessitate immediate surgery. Indeed, the therapeutic inhibition of HIF-2α may represent a major advance in the overall management of VHL disease, which represents an enormous burden even before the occurrence of clear-cell renal cell carcinoma. Extrarenal manifestations occur early, with a mean age at onset of 26 years[3,8]; retinal hemangiomas have been reported to occur first, followed by cerebellar and brain-stem hemangioblastomas.[3] When these tumors and cysts reach a critical volume, they cause severe neurologic symptoms, blindness, or death if not treated appropriately. The current standard of care is limited to local interventions, including surgery, radiofrequency or microwave ablation, or stereotactic radiotherapy.[9] As a consequence, these patients may undergo multiple surgical procedures over many years, which, together with the disease itself, may ultimately lead to several disabilities, related mostly to the CNS, as well as visual and acoustic impairments and, finally, impaired renal, pancreatic, and adrenergic function.[3] CNS hemangioblastomas and clear-cell renal cell carcinoma remain the most common causes of death (51% and 36%, respectively).[2]

Jonasch et al. report ongoing objective responses (including complete responses) and disease stabilization in patients with non–renal cell carcinoma neoplasms such as pancreatic lesions (77% objective response and 21% disease stabilization) and hemangioblastomas (30% and 62%, respectively), as well as improvement in 100% of eyes with retinoblastomas that could be evalu-

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ated. This clinical benefit had an immediate effect on the course of the disease: the number of procedures patients underwent decreased from 327 local interventions before treatment to 3 after treatment started. Considering both the efficacy of the treatment in all VHL-associated tumors and the acceptable adverse-event profile of this HIF-2α inhibitor, early and possibly even intermittent use of belzutifan may spare patients with VHL disease multiple surgeries, decrease their risk of loss of organ function (such as renal failure and blindness), and reduce their risk of death from metastatic renal cell carcinoma or CNS hemangioblastomas.

Finally, blocking HIF-2α at the most proximal point in the pathway may represent another major step in oncology beyond the treatment of VHL-associated tumors, since HIF-2α, the target of belzutifan, controls multiple genes involved in cancer progression.[10] Moreover, the immune response to cancer is strongly regulated by hypoxia,[11] which in turn drives HIF accumulation. Thus, belzutifan is under investigation for use in the treatment of sporadic clear-cell renal cell carcinoma and other solid tumors, either as a single agent or in combination with tyrosine kinase inhibitors and immune checkpoint inhibitors (ClinicalTrials.gov number, NCT04976634).

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

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ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*

ABSTRACT

BACKGROUND

New treatments are needed to reduce the risk of progression of coronavirus disease 2019 (Covid-19). Molnupiravir is an oral, small-molecule antiviral prodrug that is active against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

METHODS

We conducted a phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of treatment with molnupiravir started within 5 days after the onset of signs or symptoms in nonhospitalized, unvaccinated adults with mild-to-moderate, laboratory-confirmed Covid-19 and at least one risk factor for severe Covid-19 illness. Participants in the trial were randomly assigned to receive 800 mg of molnupiravir or placebo twice daily for 5 days. The primary efficacy end point was the incidence hospitalization or death at day 29; the incidence of adverse events was the primary safety end point. A planned interim analysis was performed when 50% of 1550 participants (target enrollment) had been followed through day 29.

RESULTS

A total of 1433 participants underwent randomization; 716 were assigned to receive molnupiravir and 717 to receive placebo. With the exception of an imbalance in sex, baseline characteristics were similar in the two groups. The superiority of molnupiravir was demonstrated at the interim analysis; the risk of hospitalization for any cause or death through day 29 was lower with molnupiravir (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval, −11.3 to −2.4; P=0.001). In the analysis of all participants who had undergone randomization, the percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1). Results of subgroup analyses were largely consistent with these overall results; in some subgroups, such as patients with evidence of previous SARS-CoV-2 infection, those with low baseline viral load, and those with diabetes, the point estimate for the difference favored placebo. One death was reported in the molnupiravir group and 9 were reported in the placebo group through day 29. Adverse events were reported in 216 of 710 participants (30.4%) in the molnupiravir group and 231 of 701 (33.0%) in the placebo group.

CONCLUSIONS

Early treatment with molnupiravir reduced the risk of hospitalization or death in at-risk, unvaccinated adults with Covid-19. (Funded by Merck Sharp and Dohme; MOVe-OUT ClinicalTrials.gov number, NCT04575597.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. De Anda can be contacted at Merck, 309 Sumneytown Pike, North Wales, PA 19454.

*The members of the MOVe-OUT study group are listed in the Supplementary Appendix, available at NEJM.org.

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EDITORIAL

Molnupiravir — A Step toward Orally Bioavailable Therapies for Covid-19

Richard Whitley, M.D.

The Covid-19 pandemic has resulted in substantial global morbidity and mortality as well as disruption of the economies of virtually every country.[1] Some of this tragedy could have been averted with the development of deliverable, orally bioavailable, direct-acting antiviral therapeutics. Molnupiravir, the orally bioavailable prodrug of N4-hydroxycytidine (NHC), begins to address this need. Synthesized at the Emory Institute for Drug Development (EIDD), molnupiravir is active against influenza as well as multiple other RNA viruses, including SARS-CoV-2.[2] As the coronavirus pandemic emerged, EIDD developed molnupiravir for the treatment of pathogenic coronavirus infections rather than influenza. This decision was based on an extensive body of work performed in cell culture and in animal models of SARS, MERS, and ultimately, SARS-CoV-2.[3-5] NHC is phosphorylated intracellularly to its triphosphate derivative, which is incorporated into viral RNA, leading to fatal errors in replication. An added benefit is a high genetic barrier to resistance.

Jayk Bernal and colleagues now report in the *Journal* the results of a phase 2–3 placebo-controlled trial of molnupiravir that may begin to address this global problem. The drug was administered orally (800 mg [four tablets] twice daily for 5 days) and compared with a matching placebo.[6] Patients with mild-to-moderate disease and at least one risk factor for progression to severe illness (including age >60 years, obesity, diabetes, or cardiovascular disease) were eligible for enrollment. The primary end point was a composite of hospitalization or death at 29 days. At the planned interim analysis, 775 patients who were infected with SARS-CoV-2 and had symptoms of no more than 5 days' duration were enrolled; 387 patients received molnupiravir and 388 received placebo. The prespecified interim analysis was performed at approximately 50% of the planned enrollment. In the molnupiravir group, the risk of hospitalization or death was 7.3% (28 of 385 patients), as compared with 14.1% (53 of 377) in the placebo group ($P=0.001$); no deaths had occurred in the molnupiravir group at the time of this interim analysis. However, the final analysis of these peer-reviewed data shows a more modest effect. In the final data, 1433 infected volunteers were randomly assigned to molnupiravir (716 patients) or placebo (717 patients). A primary end-point event occurred in 48 of 709 molnupiravir recipients (6.8%) and 68 of 699 placebo recipients (9.7%), an absolute difference of approximately 3 percentage points. One death occurred in the treatment group, and nine among placebo recipients. Numerous potential reasons for the lessening of the drug effect include preexisting SARS-CoV-2 nucleocapsid antibodies and lower viral load at enrollment.

In the patients with available sequence data, molnupiravir was found to be active against the three predominant circulating variants (delta, gamma, and mu) and showed a modest antiviral effect. Adverse events were similar in the two groups.

This clinical trial potentially provides a tool in the management of Covid-19, pending evaluation by the Food and Drug Administration (FDA), the European Medicines Agency, and other licensing bodies. Several points warrant emphasis. First, molnupiravir therapy was initiated within 72 hours after symptom onset in nearly 50% of patients;

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however, we must strive for therapy to begin within 72 hours in all patients, as shown in studies of influenza.[7] Since SARS-CoV-2 infection must be confirmed, a point-of-care companion diagnostic test would be of value. Molnupiravir is less beneficial when administered late in the disease course — namely, after patients have had symptoms for more than 3 to 5 days or after they are hospitalized, as shown in reports of two phase 2 trials of molnupiravir.[8,9] Second, the safety database is small and will require careful monitoring for the emergence of side effects. Third, potential mutagenic toxicity has been a concern, since the drug is mutagenic in Chinese hamster ovary cells.[10] However, there is a body of data that address concerns related to the potential mutagenicity and genotoxicity of molnupiravir.[11] Given the totality of data, regulatory authorities in the United Kingdom have stated that the risk of mutagenicity or genotoxicity in the clinical use of molnupiravir is low, and it was licensed for use in the United Kingdom on November 4, 2021.[12] The U.K. summary report on molnupiravir recommends licensure for SARS-CoV-2–infected persons 18 years of age or older who have one risk factor for progression to severe illness — a population similar to that described in the article by Jayk Bernal et al. The report notes a low risk of genotoxicity, a concern for some physicians.[10] Molnupiravir was not recommended for women who are pregnant or breast-feeding or for those who might become pregnant during treatment. The FDA will review these data, most likely before the end of the year, in considering an Emergency Use Authorization. Fourth, the sponsor has indicated in the lay press that drug patents will be made available to the World Health Organization patent pool and to manufacturers of generic drugs so that molnupiravir can be produced for developing countries, ideally at low cost.

Vaccines must be the primary mode of protection against SARS-CoV-2; however, orally bioavailable medications will become an essential tool for physicians in the management of this horrible disease. Of note, although the data have not been peer-reviewed, Pfizer has announced the efficacy of its orally bioavailable protease inhibitor, Paxlovid, and Gilead has reported a benefit of ambulatory therapy with remdesivir. Data for both medications demand peer review. The availability of medications with different mechanisms of action offers the opportunity for creating combination therapies that are potentially synergistic and less likely to lead to resistance.

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

From the University of Alabama at Birmingham, Birmingham.

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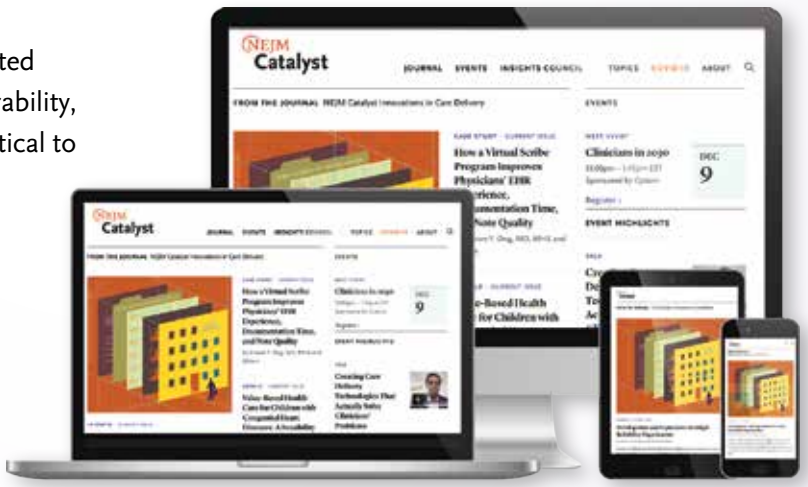

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