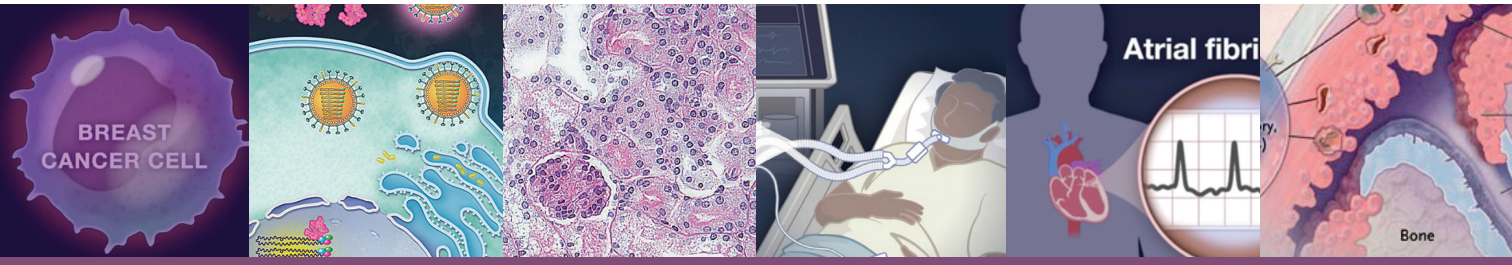
The NEW ENGLAND JOURNAL of MEDICINE




# Notable Articles of 2020

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

NEJM GROUP

The NEW ENGLAND JOURNAL of MEDICINE

December 2020

Dear Reader,

History has shown that the world would always be wise to prepare for a pandemic. The past decade provided some early lessons with emerging infectious diseases: West Africa and Ebola, the Arabian Peninsula and MERS. Nonetheless, in 2020, SARS-CoV-2 has challenged the health care community in ways that were difficult to predict.

Reports started to emerge in December 2019 that a new virus had been seen in China. During the early months of 2020 and the pandemic, we knew little about Covid-19 transmission or severity. As the number of cases rose, many treatments were used off-label and outside the boundaries of clinical trials. We had little choice but to make decisions based on observational data. Because of this, it was hard to know whether the treatments were working. During this chaotic time, physicians, nurses, and other health care workers took care of patients at real risk to themselves.

Months passed. The uniform desperation felt at the beginning of the pandemic lessened. We saw that rapidly initiated, high-quality randomized clinical trials were possible in epidemic conditions, even in the trying circumstances that prevailed in Wuhan, China, in January and February. As we became more familiar with the Covid-19 virus, more effective protocols emerged to treat patients, thanks to an explosion of randomized, controlled trials that gave us better information. As the year progressed, we saw the development of many vaccine candidates at impressive speed.

Still, with a handful of exceptions, the number of Covid-19 cases continues to rise in most of the world.

As 2020 comes to a close and we look back at the most notable articles published in the *New England Journal of Medicine* (NEJM), four Covid-19 trials are striking. The first, published online at the end of January, reported on transmission dynamics in Wuhan and demonstrated, even at the very earliest time points, human-to-human transmission. Another, the RECOVERY trial, reported on dexamethasone in hospitalized patients with Covid-19. From RECOVERY, we learned that there is a clear benefit to treatment with dexamethasone and that it can decrease the death rate among this very ill population. The final two Covid articles, published in December, report on mRNA vaccines that appear to give us a pathway out of what has been a global disaster.

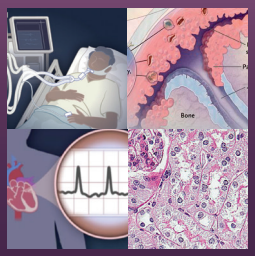
Other NEJM articles also emerged as practice changing. This collection includes studies of breast cancer, prostate cancer, heart failure, and atrial fibrillation. All fourteen studies in this collection are relevant to the practice of medicine.

While we now, at year's end, better understand Covid-19, the disease continues to be a tragedy. We, like many others, expect a difficult winter managing this disease. But we hold to the certainty that eventually this pandemic will end.

Until then, we will continue to bring you the best information to treat your patients.

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

800.843.6356 | F: 781.891.1995 | NEJMGROUP@MMS.ORG
860 WINTER STREET, WALTHAM, MA 02451-1413
NEJMGROUP.ORG

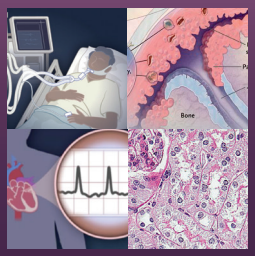


# Notable Articles of 2020
# Table of Contents



*(continued on next page)*

The *New England Journal of Medicine* is a publication of NEJM Group, a division of the Massachusetts Medical Society.



# Notable Articles of 2020
# Table of Contents

*(continued from previous page)*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

# Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

## ABSTRACT

### BACKGROUND

Patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly selective inhibitor of the HER2 tyrosine kinase.

### METHODS

We randomly assigned patients with HER2-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine, who had or did not have brain metastases, to receive either tucatinib or placebo, in combination with trastuzumab and capecitabine. The primary end point was progression-free survival among the first 480 patients who underwent randomization. Secondary end points, assessed in the total population (612 patients), included overall survival, progression-free survival among patients with brain metastases, confirmed objective response rate, and safety.

### RESULTS

Progression-free survival at 1 year was 33.1% in the tucatinib-combination group and 12.3% in the placebo-combination group (hazard ratio for disease progression or death, 0.54; 95% confidence interval [CI], 0.42 to 0.71; P<0.001), and the median duration of progression-free survival was 7.8 months and 5.6 months, respectively. Overall survival at 2 years was 44.9% in the tucatinib-combination group and 26.6% in the placebo-combination group (hazard ratio for death, 0.66; 95% CI, 0.50 to 0.88; P=0.005), and the median overall survival was 21.9 months and 17.4 months, respectively. Among the patients with brain metastases, progression-free survival at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group (hazard ratio, 0.48; 95% CI, 0.34 to 0.69; P<0.001), and the median progression-free survival was 7.6 months and 5.4 months, respectively. Common adverse events in the tucatinib group included diarrhea, palmar–plantar erythrodysesthesia syndrome, nausea, fatigue, and vomiting. Diarrhea and elevated aminotransferase levels of grade 3 or higher were more common in the tucatinib-combination group than in the placebo-combination group.

### CONCLUSIONS

In heavily pretreated patients with HER2-positive metastatic breast cancer, including those with brain metastases, adding tucatinib to trastuzumab and capecitabine resulted in better progression-free survival and overall survival outcomes than adding placebo; the risks of diarrhea and elevated aminotransferase levels were higher with tucatinib. (Funded by Seattle Genetics; HER2CLIMB ClinicalTrials.gov number, NCT02614794.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Winer at the Dana–Farber Cancer Institute, 450 Brookline Ave., Boston, MA 02215, or at eric_winer@dfci.harvard.edu; or to Dr. Murthy at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1354, Houston, TX 77030, or at rmurthy1@mdanderson.org.

This article was published on December 11, 2019, and updated on December 27, 2019, at NEJM.org.

N Engl J Med 2020;382:597-609.
DOI: 10.1056/NEJMoa1914609


Read Full Article at NEJM.org

# Major Strides in HER2 Blockade for Metastatic Breast Cancer

Priyanka Sharma, M.D.

Breast cancer that is characterized by amplification or overexpression of human epidermal growth factor receptor 2 (HER2) accounts for 15 to 20% of all forms of the disease. The advent of HER2-targeted drugs, such as trastuzumab, pertuzumab, lapatinib, and the antibody-drug conjugate trastuzumab emtansine, has revolutionized the treatment of both early-stage and metastatic HER2-positive breast cancer.[1-4] The increasing availability of HER2-targeted agents has led to improved outcomes for patients with HER2-positive metastatic breast cancer, as reported in a study in which overall survival rose from a median of 38.7 months to 51.1 months from 2008 through 2012.[5]

The standard first-line systemic treatment for HER2-positive metastatic breast cancer consists of trastuzumab plus pertuzumab combined with a taxane, and trastuzumab emtansine is the recommended second-line therapy. However, there is no single accepted standard for third-line therapy and beyond, and currently available options provide only modest efficacy. In addition, as survival of patients with HER2-positive metastatic breast cancer is improving with the clinical adoption of effective systemic therapies, the central nervous system (CNS) is increasingly becoming a sanctuary site, with brain metastasis occurring in almost 50% of patients.[6] Although HER2-targeted systemic therapies have led to great strides in the treatment of extracranial disease, currently available agents have shown very limited activity against CNS disease.

In this issue of the *Journal*, investigators present the results of two clinical trials that evaluated new anti-HER2 agents as third-line or later therapy for HER2-positive metastatic breast cancer.[7,8] In the first article, Murthy et al. report the results of the HER2CLIMB trial, in which 612 patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine were randomly assigned to receive trastuzumab and capecitabine with or without tucatinib. Tucatinib is an oral HER2 tyrosine kinase inhibitor that is highly selective for the kinase domain and, unlike other HER2 tyrosine kinase inhibitors, has minimal inhibition of epidermal growth factor receptor, which may lead to a more favorable safety profile. According to the trial design, HER2CLIMB enrolled a large proportion of patients with brain metastases (47%, which included 28% who had treated brain metastases and 19% who had progressive or untreated brain metastases).

The median duration of progression-free survival was 7.8 months in the tucatinib-combination group and 5.6 months in the placebo-combination group, corresponding to 46% lower risk of disease progression or death in the tucatinib-combination group (hazard ratio, 0.54; $P<0.001$). The median duration of overall survival was 21.9 months in the tucatinib-combination group and 17.4 months in the placebo-combination group, corresponding to 34% lower risk of death in the tucatinib-combination group (hazard ratio, 0.66; $P=0.005$). In an important finding, the benefit of tucatinib was maintained in patients with brain metastases, with a median duration of progression-free survival of 7.6 months in the tucatinib-combination group and 5.4 months in the placebo-combination group (hazard ratio for disease progression or death, 0.48; $P<0.001$). Whether the observed CNS efficacy is a result of intracranial response in progressive or untreated disease, a delay in or prevention of new brain lesions in patients with treated disease, or both remains to be seen. Unlike the experience with previous tyrosine kinase inhibitor combinations, in which unacceptable side effects have been a concern, only 5.7% of the patients discontinued tucatinib because of adverse events. The remarkable results of the HER2CLIMB trial are bound to be practice changing for patients with HER2-positive metastatic breast cancer who have undergone previous therapy with trastuzumab, pertuzumab, and trastuzumab emtansine, and additional details regarding CNS activity will further refine the placement of tucatinib in treatment algorithms.

In the second article, Modi et al. report the results of DESTINY-Breast01, an open-label, single-group, phase 2 study of trastuzumab deruxtecan



Back to Table of Contents

(DS-8201). Trastuzumab deruxtecan is an antibody drug conjugate with a potent topoisomerase I inhibitor as the payload. It has a higher drug-to-antibody ratio than trastuzumab emtansine (8 to 1 vs. 3 to 1) and a highly permeable payload that potentially allows bystander cytotoxic effects on neighboring tumor cells. The patients who were enrolled in the DESTINY-Breast01 study had undergone a median of six lines of prior therapy for advanced HER2-positive breast cancer. Trastuzumab deruxtecan monotherapy led to an impressive objective response rate of 60.9% and a median duration of progression-free survival of 16.4 months in a heavily pretreated population in which 100% of the patients had received a previous antibody-drug conjugate (trastuzumab emtansine). The trial included 13% of patients with treated brain metastases who had a median duration of progression-free survival similar to that of the entire trial population (18.1 months). Enthusiasm for this tremendous antitumor activity was dampened somewhat by the substantial risk (13.6%) of interstitial lung disease, which led to death in 2.2% of the patients. The exact mechanism leading to pulmonary toxicity is not clear. It is hoped that close monitoring, thorough assessment of potential risk factors, and the early initiation of appropriate diagnostic and treatment measures in future trials will provide further guidance on ways to reduce the incidence and severity of this toxic effect.

Another recent study of a new anti-HER2 therapy in a heavily pretreated population is the SOPHIA trial, in which the substitution of trastuzumab with margetuximab (a novel Fc-engineered HER2 antibody with increased affinity for the Fc gamma receptor CD16A) in a chemotherapy backbone led to a modest improvement in progression-free survival at the time of the September 2019 data cutoff (5.7 months vs. 4.4 months; hazard ratio, 0.71; P<0.001), with exploratory analyses suggesting that the Fc receptor CD16A genotype may influence the efficacy of margetuximab.[9]

In summary, the HER2CLIMB and DESTINY-Breast01 trials represent major advances in the treatment of HER2-positive metastatic breast cancer and mark the beginning of the next frontier of highly effective HER2-targeted agents. On December 20, 2019, the Food and Drug Administration (FDA) approved the use of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive breast cancer who have undergone at least two anti-HER2 regimens.[10] The submission to the FDA of a biologics license application for tucatinib is expected this year. In the near future, as the oncology community and patients are able to take advantage of these novel drugs, the selection of the most effective agent or combination in the clinic will be based on the status of CNS disease, the toxicity profile, prior treatment, the preference and coexisting illnesses of the patients (including risk factors for interstitial lung disease and the choice of single vs. multiple drugs), and perhaps genotype. Furthermore, important consideration will also have to be given to cost and access. There are several countries in the world where trastuzumab emtansine is not yet available, and efforts are needed to improve access to newer, presumably more expensive HER2-targeted drugs. In ongoing trials (ClinicalTrials.gov numbers, NCT03523585, NCT03529110, and NCT03975647), investigators are evaluating the initiation of tucatinib and trastuzumab deruxtecan in earlier lines of therapy, when these agents may have an even greater effect on the lives and disease course of patients with HER2-positive breast cancer.

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

From the University of Kansas Medical Center, Department of Internal Medicine, Kansas City.

1. Baselga J, Cortés J, Kim S-B, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109-19.
2. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006;355:2733-43.
3. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
4. Swain SM, Baselga J, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med 2015;372:724-34.
5. Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. Eur J Cancer 2018;96:17-24.
6. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. Clin Cancer Res 2011;17:4834-43.
7. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 2020;382:597-609.
8. Modi S, Saura C, Yamashita T, et al. Trastuzumab deruxte-



Back to Table of Contents

can in previously treated HER2-positive breast cancer. N Engl J Med 2020;382:610-21.

**9.** Rugo H, Im S, Cardoso F, et al. Phase 3 SOPHIA study of margetuximab + chemotherapy vs trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies: second interim overall survival analysis. Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, December 10–14, 2019. abstract.

**10.** FDA approves fam-trastuzumab deruxtecan-nxki for unresectable or metastatic HER2-positive breast cancer. Silver Spring, MD: Food and Drug Administration, 2019 (https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-unresectable-or-metastatic-her2-positive-breast-cancer).

DOI: 10.1056/NEJMe1916310

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 5, 2020 VOL. 382 NO. 10

# Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Niekerk, M.D., Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-TB Trial Team*

## ABSTRACT

### BACKGROUND

Patients with highly drug-resistant forms of tuberculosis have limited treatment options and historically have had poor outcomes.

### METHODS

In an open-label, single-group study in which follow-up is ongoing at three South African sites, we investigated treatment with three oral drugs — bedaquiline, pretomanid, and linezolid — that have bactericidal activity against tuberculosis and to which there is little preexisting resistance. We evaluated the safety and efficacy of the drug combination for 26 weeks in patients with extensively drug-resistant tuberculosis and patients with multidrug-resistant tuberculosis that was not responsive to treatment or for which a second-line regimen had been discontinued because of side effects. The primary end point was the incidence of an unfavorable outcome, defined as treatment failure (bacteriologic or clinical) or relapse during follow-up, which continued until 6 months after the end of treatment. Patients were classified as having a favorable outcome at 6 months if they had resolution of clinical disease, a negative culture status, and had not already been classified as having had an unfavorable outcome. Other efficacy end points and safety were also evaluated.

### RESULTS

A total of 109 patients were enrolled in the study and were included in the evaluation of efficacy and safety end points. At 6 months after the end of treatment in the intention-to-treat analysis, 11 patients (10%) had an unfavorable outcome and 98 patients (90%; 95% confidence interval, 83 to 95) had a favorable outcome. The 11 unfavorable outcomes were 7 deaths (6 during treatment and 1 from an unknown cause during follow-up), 1 withdrawal of consent during treatment, 2 relapses during follow-up, and 1 loss to follow-up. The expected linezolid toxic effects of peripheral neuropathy (occurring in 81% of patients) and myelosuppression (48%), although common, were manageable, often leading to dose reductions or interruptions in treatment with linezolid.

### CONCLUSIONS

The combination of bedaquiline, pretomanid, and linezolid led to a favorable outcome at 6 months after the end of therapy in a high percentage of patients with highly drug-resistant forms of tuberculosis; some associated toxic effects were observed. (Funded by the TB Alliance and others; ClinicalTrials.gov number, NCT02333799.)

From the Clinical HIV Research Unit, Faculty of Health Sciences, University of Witwatersrand, Johannesburg (F.C., N.N., P.H.), Sizwe Tropical Disease Hospital, Sandringham (F.C., P.H.), Task Applied Science and Stellenbosch University, Cape Town (A.H.D.), King DiniZulu Hospital Complex, Durban (N.N.), and the TB Alliance, Pretoria (C.V.N., M.O.) — all in South Africa; the TB Alliance, New York (D.E., C.M.M., E.E., J.M., J.T., M.L., M.S.); and the MRC Clinical Trials Unit at UCL (A.M.C., G.H.W.) and the UCL Centre for Clinical Microbiology (T.D.M., A.B., R.H.), University College London, London. Address reprint requests to Dr. Crook at the MRC Clinical Trials Unit at UCL, 90 High Holborn, London, WC1V 6LJ, United Kingdom, or at angela.crook@ucl.ac.uk.

*Additional team members are listed in the Supplementary Appendix, available at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Final Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available under a CC BY license at PMC6955640.

N Engl J Med 2020;382:893-902.
DOI: 10.1056/NEJMoa1901814


Read Full Article at NEJM.org

EDITORIALS

# Triumph and Tragedy of 21st Century Tuberculosis Drug Development

Guy Thwaites, F.R.C.P., and Payam Nahid, M.D., M.P.H.

Since the discovery of the first antituberculosis drugs 75 years ago, the pursuit of a short, effective, and affordable regimen that has acceptable side effects and is capable of curing most patients most of the time has been a major public health priority. Such a "pan-tuberculosis" regimen is seen by many as essential in reducing the global tuberculosis burden.[1]

The successful development of two new antituberculosis drugs — bedaquiline and pretomanid — represents an important step forward in the pursuit of pan-tuberculosis regimens fit for the 21st century. Conradie and colleagues now report in the *Journal* that when this all-oral regimen was combined with a third drug — linezolid, repurposed from its licensed indication for gram-positive bacterial infections — and given for 26 to 39 weeks to patients with extensively drug-resistant or complicated multidrug-resistant tuberculosis, it produced a favorable outcome in 98 of 109 patients (90%) at 6 months after the end of treatment.[2] Cure rates for extensively drug-resistant tuberculosis were less than 50% before the advent of new drugs.[3] Therefore, this is a triumph, and the authors are to be congratulated for their vision and courage in tackling the most difficult-to-treat forms of tuberculosis.

The tragedy being confronted, however, is the overlapping realities of the persisting need for new regimens and the spectacular inadequacy of support for their development and the tools needed for their effective use in the field. Our current tuberculosis regimen was the product of a remarkable series of global, iterative, randomized, controlled trials conducted between 1947 and 1980.[4] The resulting "short-course chemotherapy" was an oral regimen, containing rifampin, isoniazid, and pyrazinamide, that cured the large majority of people with tuberculosis if it was taken for 6 months. This regimen, despite known toxicities, has produced extraordinary gains, curing approximately 58 million people since the year 2000.[5] However, 30 years of its global use has revealed the serious limitations of depending on a single, one-size-fits-all regimen to treat a challenging infectious disease.[6] Predictable toxicities and the development of resistance are directly relevant to ongoing efforts to develop other regimens,[7] including the new regimen studied by Conradie et al.

During the early global adoption of rifampin-based short-course chemotherapy, the possibility that resistance would become a barrier to ending the epidemic was considered unlikely. As a result, the development of accessible and affordable laboratory tools for the detection of drug resistance was not prioritized. Thus, when resistance did inevitably emerge, the tools to detect and manage it were too inefficient, too costly, and too far from the clinic to halt the spread of rifampin resistance. The acquisition of resistance is also a risk for the bedaquiline–pretomanid–linezolid regimen. Conradie reports one patient who had a relapse caused by bacteria with reduced susceptibility to bedaquiline. When this evidence is considered together with other reports of primary resistance to bedaquiline,[8] along with the described toxicities of linezolid, the need for monitoring of the QT interval, and the residual uncertainty about hepatotoxicity of pretomanid,[9] it suggests a risk of going back to where we started: a situation in which a pan-tuberculosis regimen with known toxicities that are likely to result in pauses in or discontinuation of treatment is sent to the field without adequate tools for monitoring resistance.

The other major tragedy is that every year tuberculosis still affects approximately 10 mil-



Back to Table of Contents

lion people and kills 1.5 million.[5] In light of these figures, we should not be dependent on one small, single-group, single-country study for evidence of the efficacy of the newest tuberculosis regimen. The study was rigorously conducted and laudably designed to report on definitive outcomes of durable cure and relapse; however, such approaches for the development of tuberculosis regimens do not correspond with the magnitude of the problem. Tuberculosis does not present insurmountable hurdles for the conduct of clinical trials. Even the creation of multidrug regimens with new agents from different developers is feasible, as evidenced by the recent history of treatment for human immunodeficiency virus infection and hepatitis C, both of which have new regimens developed and defined through multiple large trials. In contrast and tragically, the majority of evidence available to the World Health Organization in 2020 as it formulates treatment guidelines for drug-resistant tuberculosis comes from noncomparative or observational studies.[10,11] Such studies should serve as the adjunct to an evidence base of robust randomized, controlled clinical trials, rather than as its leading edge.

A rejuvenated program of innovative phase 2 and phase 3 clinical trials of new drugs and regimens, in conjunction with continued investment in tools for detecting and monitoring resistance, is required worldwide. It will take substantially greater investment and coordinated forms of collaboration among sponsors, industry, academic partners, and policy decision makers to develop and implement new evidence-based regimens that are fitting for a disease that has killed hundreds of millions of people. Until that happens, if the current inadequate investment path is held, history is bound to repeat itself — and for all the jubilation that comes with developing a new effective regimen, there will be more tragedy yet to come.

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

From the Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam (G.T.); the Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom (G.T.); and the UCSF Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine, University of California, San Francisco (P.N.).

1. Wallis RS, Cohen T, Menzies NA, Churchyard G. Pan-tuberculosis regimens: an argument for. Lancet Respir Med 2018;6:239-40.
2. Conradie F, Diacon AH, Ngubane N, et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med 2020;382:893-902.
3. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis 2010;51:6-14.
4. Mitchison D, Davies G. The chemotherapy of tuberculosis: past, present and future. Int J Tuberc Lung Dis 2012;16:724-32.
5. Global tuberculosis report 2019. Geneva: World Health Organization, 2019 (https://www.who.int/tb/global-report-2019).
6. Imperial MZ, Nahid P, Phillips PPJ, et al. A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis. Nat Med 2018;24:1708-15.
7. Dheda K, Gumbo T, Lange C, Horsburgh CR Jr, Furin J. Pan-tuberculosis regimens: an argument against. Lancet Respir Med 2018;6:240-2.
8. Xu J, Wang B, Hu M, et al. Primary clofazimine and bedaquiline resistance among isolates from patients with multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2017;61:61.
9. Keam SJ. Pretomanid: first approval. Drugs 2019;79:1797-803.
10. WHO consolidated guidelines on drug-resistant tuberculosis treatment. Geneva: World Health Organization, 2019 (https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/).
11. Rapid Communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization, 2019 (https://www.who.int/tb/publications/2019/rapid_communications_MDR/en/).

DOI: 10.1056/NEJMe2000860




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 12, 2020 VOL. 382 NO. 11

# Conservative Oxygen Therapy during Mechanical Ventilation in the ICU

The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*

## ABSTRACT

### BACKGROUND

Patients who are undergoing mechanical ventilation in the intensive care unit (ICU) often receive a high fraction of inspired oxygen ($F_{IO_2}$) and have a high arterial oxygen tension. The conservative use of oxygen may reduce oxygen exposure, diminish lung and systemic oxidative injury, and thereby increase the number of ventilator-free days (days alive and free from mechanical ventilation).

### METHODS

We randomly assigned 1000 adult patients who were anticipated to require mechanical ventilation beyond the day after recruitment in the ICU to receive conservative or usual oxygen therapy. In the two groups, the default lower limit for oxygen saturation as measured by pulse oximetry ($S_{PO_2}$) was 90%. In the conservative-oxygen group, the upper limit of the $S_{PO_2}$ alarm was set to sound when the level reached 97%, and the $F_{IO_2}$ was decreased to 0.21 if the $S_{PO_2}$ was above the acceptable lower limit. In the usual-oxygen group, there were no specific measures limiting the $F_{IO_2}$ or the $S_{PO_2}$. The primary outcome was the number of ventilator-free days from randomization until day 28.

### RESULTS

The number of ventilator-free days did not differ significantly between the conservative-oxygen group and the usual-oxygen group, with a median duration of 21.3 days (interquartile range, 0 to 26.3) and 22.1 days (interquartile range, 0 to 26.2), respectively, for an absolute difference of −0.3 days (95% confidence interval [CI], −2.1 to 1.6; P=0.80). The conservative-oxygen group spent more time in the ICU with an $F_{IO_2}$ of 0.21 than the usual-oxygen group, with a median duration of 29 hours (interquartile range, 5 to 78) and 1 hour (interquartile range, 0 to 17), respectively (absolute difference, 28 hours; 95% CI, 22 to 34); the conservative-oxygen group spent less time with an $S_{PO_2}$ exceeding 96%, with a duration of 27 hours (interquartile range, 11 to 63.5) and 49 hours (interquartile range, 22 to 112), respectively (absolute difference, 22 hours; 95% CI, 14 to 30). At 180 days, mortality was 35.7% in the conservative-oxygen group and 34.5% in the usual-oxygen group, for an unadjusted odds ratio of 1.05 (95% CI, 0.81 to 1.37).

### CONCLUSIONS

In adults undergoing mechanical ventilation in the ICU, the use of conservative oxygen therapy, as compared with usual oxygen therapy, did not significantly affect the number of ventilator-free days. (Funded by the New Zealand Health Research Council; ICU-ROX Australian and New Zealand Clinical Trials Registry number, ACTRN12615000957594.)

The members of the writing committee (Diane Mackle, M.N., Rinaldo Bellomo, M.D., Michael Bailey, Ph.D., Richard Beasley, M.D., D. Sc., Adam Deane, M.D., Ph.D., Glenn Eastwood, R.N., Ph.D., Simon Finfer, M.D., Ross Freebairn, M.D., Victoria King, R.N., Natalie Linke, R.N., Edward Litton, M.D., Ph.D., Colin McArthur, M.D., Shay McGuinness, M.D., Rakshit Panwar, M.D., and Paul Young, M.D., Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Dr. Young at the Intensive Care Unit, Wellington Regional Hospital, Private Bag 7902, Wellington South, New Zealand, or at paul.young@ccdhb.org.nz.

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

This article was published on October 14, 2019, at NEJM.org.

N Engl J Med 2020;382:989-98.
DOI: 10.1056/NEJMoa1903297


Read Full Article at NEJM.org

EDITORIAL

# Oxygen Therapy for the Critically Ill

Derek C. Angus, M.D., M.P.H.

The administration of supplemental oxygen is one of the world's most used therapies and is a cornerstone of care in the intensive care unit (ICU). The primary rationale is to avoid hypoxemia in patients with, or at risk for, impaired pulmonary gas exchange. Oxygen is generally considered to be widely available (which may not be true in less developed countries), inexpensive, and very safe. Consequently, it is typically administered liberally with an upward titration of the fraction of inspired oxygen ($F_{IO_2}$) to achieve a high level of arterial oxygen saturation (e.g., >96%), with less attention on avoidance of excess use. However, the use of supplemental oxygen is not without risk. An elevated level of the partial pressure of arterial oxygen ($P_{aO_2}$), or hyperoxemia, increases the production of toxic reactive oxygen species, which can cause injury, especially in the lungs, retinae, and central nervous system. High $F_{IO_2}$ values in patients with alveolar–capillary units that are poorly ventilated can also lead to absorption atelectasis. Liberal oxygen use is associated with increased mortality in observational studies, but residual confounding complicates an interpretation of these studies.[1]

In 2016, Girardis et al.[2] reported the findings of a single-center randomized trial of the use of a conservative oxygen strategy and a liberal oxygen strategy; the trial had been stopped prematurely after the enrollment of 434 patients. In this trial, patients who were assigned to receive conservative therapy had lower mortality than those who received usual care (11.6% vs. 20.2%; P=0.01). Subsequent retrospective studies also supported a benefit with conservative oxygen use.[3,4] Together, this evidence led to updated clinical practice guidelines that emphasized a more conservative approach and spurred the launch of numerous randomized trials.[5,6]

The results of two of these trials are reported in this issue of the *Journal*. In an article that was originally published online in the *Journal* on October 14, 2019, Mackle and colleagues[7] report the results of ICU-ROX (Intensive Care Unit Randomized Trial Comparing Two Approaches to Oxygen Therapy). In this trial, which was conducted in Australia and New Zealand, 1000 adults in the ICU who were receiving mechanical ventilation underwent randomization to conservative-oxygen therapy or usual care. There were large differences in the administration of oxygen in the two groups. For example, patients in the conservative-oxygen group spent more time with an $F_{IO_2}$ level of 0.21 (equivalent to breathing room air) than those in the usual-oxygen group (median duration, 29 hours vs. 1 hour; absolute difference, 28 hours; 95% confidence interval [CI], 22 to 34). However, there was no significant difference in the primary outcome of the number of ventilator-free days (21.3 vs. 22.1 days; difference, −0.3 days; 95% CI, −2.1 to 1.6; P=0.80) or in mortality. The authors reported no safety concerns with the conservative strategy and, in exploratory analyses, found a potential benefit in patients with acute hypoxic encephalopathy. This effect could plausibly be due to mitigation of cerebral ischemia–reperfusion injury.

In another article in the current issue of the *Journal*, Barrot et al. report the results of the LOCO$_2$ (Liberal Oxygenation versus Conservative Oxygenation in Acute Respiratory Distress Syndrome) trial.[8] In this French multicenter trial, the original design called for the randomization of 850 patients with acute respiratory distress syndrome (ARDS) to a conservative or liberal oxygen strategy. However, the trial was stopped prematurely owing to concerns about the safety of the conservative strategy and futility. Among



Back to Table of Contents

the 205 enrolled patients, the primary outcome of mortality at 28 days was 34.3% in the conservative-oxygen group and 26.5% in the liberal-oxygen group (difference, 7.9 percentage points; 95% CI, −4.8 to 20.6); mortality at 90 days was 44.4% and 30.4%, respectively (difference, 14.0 percentage points; 95% CI, 0.7 to 27.2). There were also five episodes of mesenteric ischemia, all in the conservative-oxygen group.

Thus, despite preliminary evidence supporting conservative oxygen use, ICU-ROX did not show a benefit, and the $LOCO_2$ trial suggested potential harm. What might explain this discrepancy? Of course, the different findings may be due to chance: the confidence intervals are broad in both trials, especially in the $LOCO_2$ trial, and neither trial rejected the null hypothesis of no between-group difference. Alternatively, some important design features may be responsible.

Before addressing specific features of the two trials, it is useful to consider two issues common to any trial of alternative strategies for oxygen supplementation. First, oxygen titration relies on imperfect approximations. Ideally, $F_{IO_2}$ values would be adjusted continuously (or at least very rapidly) to ensure that the $Pa_{O_2}$ remains within a target range (e.g., 60 to 100 mm Hg) all, or nearly all, the time. However, it is not possible to monitor the $Pa_{O_2}$ continuously. Instead, clinicians monitor arterial saturation by measuring the pulse oximetry ($Sp_{O_2}$), which calibrates well with the $Pa_{O_2}$ but is prone to error in critical situations, such as when patients undergo hypoperfusion (and are most at risk for hypoxemia). The difficulties with monitoring arterial oxygenation include fidelity (the ability to keep the $Pa_{O_2}$ within the ideal range) and the ability to measure fidelity (since intermittent arterial sampling may miss important deviations from the target range). Second, critically ill patients often have heterogeneous organ injury with heterogeneous regional perfusion abnormalities. A particular systemic oxygenation target could help some tissue beds and harm others, with variable net effects on the patients' outcomes that may be hard to predict. Thus, even if study interventions and patient populations were similar, small differences in the implementation and monitoring of the titration protocol or case mix could yield different results.

Although the two trials in question are broadly similar, they had three key differences. First, ICU-ROX enrolled a broad cohort of patients undergoing mechanical ventilation, whereas the $LOCO_2$ trial enrolled only patients with ARDS. As such, the patients in the $LOCO_2$ trial had worse gas-exchange impairment requiring higher $F_{IO_2}$ levels and longer periods of support with mechanical ventilation. Thus, patients in the $LOCO_2$ trial may have been more prone to hypoxemia, especially in the conservative-oxygen group. Furthermore, because the $LOCO_2$ trial focused on ARDS, it is likely that fewer patients with the conditions that appeared to benefit from a conservative strategy were enrolled than in other trials, including those with acute hypoxic encephalopathy, as noted in post hoc analyses of ICU-ROX. Second, in the $LOCO_2$ trial, the investigators targeted an $Sp_{O_2}$ level of at least 96% in the control group, whereas the control group in ICU-ROX was usual care, in which clinicians may have used lower targets. Third, in ICU-ROX, the conservative strategy called for an oxygen saturation of 90 to 96%, whereas in the $LOCO_2$ trial, the target was 88 to 92% (and a correspondingly lower $Pa_{O_2}$ target range). With a target oxygen level as low as 88%, patients in the conservative-oxygen group in the $LOCO_2$ trial were potentially more prone to hypoxemia. And because the target ranges for the two groups were closer in ICU-ROX, the opportunity to detect any difference was potentially reduced.

So what is next? Determining how to use oxygen supplementation in patients undergoing mechanical ventilation remains an important question, but it requires more nuance than first anticipated. Future trials will have to address how a particular target is both set and achieved in each group and how the consequences of a particular target affect particular patients and particular organ injuries. In the meantime, avoiding excess oxygen (i.e., not administering supplemental oxygen when the $Sp_{O_2}$ is 96% or greater and not starting supplemental oxygen when the $Sp_{O_2}$ is 92% or 93%) seems sensible, as per recent guidelines.[5] However, given the results of the $LOCO_2$ trial, the lower range of the $Sp_{O_2}$ target in any conservative strategy, especially in patients requiring a high level of $F_{IO_2}$, should perhaps be 90%, as was used in ICU-ROX, rather than 88%.



Back to Table of Contents

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

From the University of Pittsburgh School of Medicine, Pittsburgh.

**1.** Helmerhorst HJF, Roos-Blom M-J, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness: a systematic review, meta-analysis, and meta-regression of cohort studies. Crit Care Med 2015;43:1508-19.
**2.** Girardis M, Busani S, Damiani E, et al. Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the Oxygen-ICU randomized clinical trial. JAMA 2016;316:1583-9.
**3.** Chu DK, Kim LH-Y, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. Lancet 2018;391:1693-705.
**4.** Helmerhorst HJF, Schultz MJ, van der Voort PHJ, et al. Effectiveness and clinical outcomes of a two-step implementation of conservative oxygenation targets in critically ill patients: a before and after trial. Crit Care Med 2016;44:554-63.
**5.** Siemieniuk RAC, Chu DK, Kim LH-Y, et al. Oxygen therapy for acutely ill medical patients: a clinical practice guideline. BMJ 2018;363:k4169.
**6.** Perner A, De Jong A, Shankar-Hari M. Trials on oxygen supplementation in sepsis: better late than never. Intensive Care Med 2020;46:116-8.
**7.** The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Conservative oxygen therapy during mechanical ventilation in the ICU. N Engl J Med 2020;382:989-98.
**8.** Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. N Engl J Med 2020;382:999-1008.

DOI: 10.1056/NEJMe2000800




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 26, 2020 VOL. 382 NO. 13

# Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia

Qun Li, M.Med., Xuhua Guan, Ph.D., Peng Wu, Ph.D., Xiaoye Wang, M.P.H., Lei Zhou, M.Med., Yeqing Tong, Ph.D., Ruiqi Ren, M.Med., Kathy S.M. Leung, Ph.D., Eric H.Y. Lau, Ph.D., Jessica Y. Wong, Ph.D., Xuesen Xing, Ph.D., Nijuan Xiang, M.Med., Yang Wu, M.Sc., Chao Li, M.P.H., Qi Chen, M.Sc., Dan Li, M.P.H., Tian Liu, B.Med., Jing Zhao, M.Sc., Man Liu, M.Sc., Wenxiao Tu, M.Med., Chuding Chen, M.Sc., Lianmei Jin, M.Med., Rui Yang, M.Med., Qi Wang, M.P.H., Suhua Zhou, M.Med., Rui Wang, M.D., Hui Liu, M.Med., Yinbo Luo, M.Sc., Yuan Liu, M.Med., Ge Shao, B.Med., Huan Li, M.P.H., Zhongfa Tao, M.P.H., Yang Yang, M.Med., Zhiqiang Deng, M.Med., Boxi Liu, M.P.H., Zhitao Ma, M.Med., Yanping Zhang, M.Med., Guoqing Shi, M.P.H., Tommy T.Y. Lam, Ph.D., Joseph T. Wu, Ph.D., George F. Gao, D.Phil., Benjamin J. Cowling, Ph.D., Bo Yang, M.Sc., Gabriel M. Leung, M.D., and Zijian Feng, M.Med.

## ABSTRACT

### BACKGROUND

The initial cases of novel coronavirus (2019-nCoV)–infected pneumonia (NCIP) occurred in Wuhan, Hubei Province, China, in December 2019 and January 2020. We analyzed data on the first 425 confirmed cases in Wuhan to determine the epidemiologic characteristics of NCIP.

### METHODS

We collected information on demographic characteristics, exposure history, and illness timelines of laboratory-confirmed cases of NCIP that had been reported by January 22, 2020. We described characteristics of the cases and estimated the key epidemiologic time-delay distributions. In the early period of exponential growth, we estimated the epidemic doubling time and the basic reproductive number.

### RESULTS

Among the first 425 patients with confirmed NCIP, the median age was 59 years and 56% were male. The majority of cases (55%) with onset before January 1, 2020, were linked to the Huanan Seafood Wholesale Market, as compared with 8.6% of the subsequent cases. The mean incubation period was 5.2 days (95% confidence interval [CI], 4.1 to 7.0), with the 95th percentile of the distribution at 12.5 days. In its early stages, the epidemic doubled in size every 7.4 days. With a mean serial interval of 7.5 days (95% CI, 5.3 to 19), the basic reproductive number was estimated to be 2.2 (95% CI, 1.4 to 3.9).

### CONCLUSIONS

On the basis of this information, there is evidence that human-to-human transmission has occurred among close contacts since the middle of December 2019. Considerable efforts to reduce transmission will be required to control outbreaks if similar dynamics apply elsewhere. Measures to prevent or reduce transmission should be implemented in populations at risk. (Funded by the Ministry of Science and Technology of China and others.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Feng at the Chinese Center for Disease Control and Prevention, No. 155 Changbai Rd., Changping District, Beijing, China, or at fengzj@chinacdc.cn; to Dr. G.M. Leung or Dr. Cowling at the School of Public Health, Li Ka Shing Faculty of Medicine, University of Hong Kong, 21 Sassoon Rd., Pokfulam, Hong Kong, China, or at gmleung@hku.hk or bcowling@hku.hk, respectively; or to Dr. B. Yang at the Hubei Center for Disease Control and Prevention, No. 35 Zhuodaoquan North Rd., Hongshan District, Wuhan, Hubei, China, or at 49205957@qq.com.

Drs. Q. Li, X. Guan, P. Wu, and X. Wang and Drs. B. Cowling, B. Yang, M. Leung, and Z. Feng contributed equally to this article.

This article was published on January 29, 2020, and last updated on January 31, 2020, at NEJM.org.

N Engl J Med 2020;382:1199-207.
DOI: 10.1056/NEJMoa2001316


Read Full Article at NEJM.org

EDITORIAL

# Covid-19 — Navigating the Uncharted

Anthony S. Fauci, M.D., H. Clifford Lane, M.D., and Robert R. Redfield, M.D.

The latest threat to global health is the ongoing outbreak of the respiratory disease that was recently given the name Coronavirus Disease 2019 (Covid-19). Covid-19 was recognized in December 2019.[1] It was rapidly shown to be caused by a novel coronavirus that is structurally related to the virus that causes severe acute respiratory syndrome (SARS). As in two preceding instances of emergence of coronavirus disease in the past 18 years[2] — SARS (2002 and 2003) and Middle East respiratory syndrome (MERS) (2012 to the present) — the Covid-19 outbreak has posed critical challenges for the public health, research, and medical communities.

In their *Journal* article, Li and colleagues[3] provide a detailed clinical and epidemiologic description of the first 425 cases reported in the epicenter of the outbreak: the city of Wuhan in Hubei province, China. Although this information is critical in informing the appropriate response to this outbreak, as the authors point out, the study faces the limitation associated with reporting in real time the evolution of an emerging pathogen in its earliest stages. Nonetheless, a degree of clarity is emerging from this report. The median age of the patients was 59 years, with higher morbidity and mortality among the elderly and among those with coexisting conditions (similar to the situation with influenza); 56% of the patients were male. Of note, there were no cases in children younger than 15 years of age. Either children are less likely to become infected, which would have important epidemiologic implications, or their symptoms were so mild that their infection escaped detection, which has implications for the size of the denominator of total community infections.

On the basis of a case definition requiring a diagnosis of pneumonia, the currently reported case fatality rate is approximately 2%.[4] In another article in the *Journal*, Guan et al.[5] report mortality of 1.4% among 1099 patients with laboratory-confirmed Covid-19; these patients had a wide spectrum of disease severity. If one assumes that the number of asymptomatic or minimally symptomatic cases is several times as high as the number of reported cases, the case fatality rate may be considerably less than 1%. This suggests that the overall clinical consequences of Covid-19 may ultimately be more akin to those of a severe seasonal influenza (which has a case fatality rate of approximately 0.1%) or a pandemic influenza (similar to those in 1957 and 1968) rather than a disease similar to SARS or MERS, which have had case fatality rates of 9 to 10% and 36%, respectively.[2]

The efficiency of transmission for any respiratory virus has important implications for containment and mitigation strategies. The current study indicates an estimated basic reproduction number ($R_0$) of 2.2, which means that, on average, each infected person spreads the infection to an additional two persons. As the authors note, until this number falls below 1.0, it is likely that the outbreak will continue to spread. Recent reports of high titers of virus in the oropharynx early in the course of disease arouse concern about increased infectivity during the period of minimal symptoms.[6,7]

China, the United States, and several other countries have instituted temporary restrictions on travel with an eye toward slowing the spread of this new disease within China and throughout the rest of the world. The United States has seen a dramatic reduction in the number of travelers from China, especially from Hubei province. At least on a temporary basis, such restrictions may have helped slow the spread of the virus: whereas 78,191 laboratory-confirmed cases had been identified in China as of February 26, 2020, a total of 2918 cases had been confirmed in 37 other countries or territories.[4] As of February 26,



Back to Table of Contents

2020, there had been 14 cases detected in the United States involving travel to China or close contacts with travelers, 3 cases among U.S. citizens repatriated from China, and 42 cases among U.S. passengers repatriated from a cruise ship where the infection had spread.[8] However, given the efficiency of transmission as indicated in the current report, we should be prepared for Covid-19 to gain a foothold throughout the world, including in the United States. Community spread in the United States could require a shift from containment to mitigation strategies such as social distancing in order to reduce transmission. Such strategies could include isolating ill persons (including voluntary isolation at home), school closures, and telecommuting where possible.[9]

A robust research effort is currently under way to develop a vaccine against Covid-19.[10] We anticipate that the first candidates will enter phase 1 trials by early spring. Therapy currently consists of supportive care while a variety of investigational approaches are being explored.[11] Among these are the antiviral medication lopinavir–ritonavir, interferon-1$\beta$, the RNA polymerase inhibitor remdesivir, chloroquine, and a variety of traditional Chinese medicine products.[11] Once available, intravenous hyperimmune globulin from recovered persons and monoclonal antibodies may be attractive candidates to study in early intervention. Critical to moving the field forward, even in the context of an outbreak, is ensuring that investigational products are evaluated in scientifically and ethically sound studies.[12]

Every outbreak provides an opportunity to gain important information, some of which is associated with a limited window of opportunity. For example, Li et al. report a mean interval of 9.1 to 12.5 days between the onset of illness and hospitalization. This finding of a delay in the progression to serious disease may be telling us something important about the pathogenesis of this new virus and may provide a unique window of opportunity for intervention. Achieving a better understanding of the pathogenesis of this disease will be invaluable in navigating our responses in this uncharted arena. Furthermore, genomic studies could delineate host factors that predispose persons to acquisition of infection and disease progression.

The Covid-19 outbreak is a stark reminder of the ongoing challenge of emerging and reemerging infectious pathogens and the need for constant surveillance, prompt diagnosis, and robust research to understand the basic biology of new organisms and our susceptibilities to them, as well as to develop effective countermeasures.

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

From the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD (A.S.F., H.C.L.); and the Centers for Disease Control and Prevention, Atlanta (R.R.R.).

This editorial was published on February 28, 2020, at NEJM.org.

1. Pneumonia of unknown cause — China: disease outbreak news. Geneva: World Health Organization, January 5, 2020 (https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/).
2. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14:523-34.
3. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020;382:1199-207.
4. Coronavirus disease 2019 (COVID-19): situation report — 36. Geneva: World Health Organization, February 25, 2020 (https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200225-sitrep-36-covid-19.pdf?sfvrsn=2791b4e0_2).
5. Guan W, Ni Z, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. DOI: 10.1056/NEJMoa2002032.
6. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med 2020;382:929-36.
7. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med 2020;382:1177-9.
8. Coronavirus disease 2019 (COVID-19) in the U.S. Atlanta: Centers for Disease Control and Prevention, February 26, 2020 (https://www.cdc.gov/coronavirus/2019-ncov/cases-in-us.html).
9. Fong MW, Gao H, Wong JY, et al. Nonpharmaceutical measures for pandemic influenza in nonhealthcare settings — social distancing measures. Emerging Infect Dis 2020;26(5) (Epub ahead of print).
10. DRAFT landscape of COVID-19 candidate vaccines — 18 February 2020. Geneva: World Health Organization (https://www.who.int/blueprint/priority-diseases/key-action/list-of-candidate-vaccines-developed-against-ncov.pdf).
11. WHO R&D blueprint: informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection. Geneva: World Health Organization, January 24, 2020 (https://apps.who.int/iris/bitstream/handle/10665/330680/WHO-HEO-RDBlueprint%28nCoV%29-2020.1-eng.pdf).
12. Lane HC, Marston HD, Fauci AS. Conducting clinical trials in outbreak settings: points to consider. Clin Trials 2016;13:92-5.

DOI: 10.1056/NEJMe2002387

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 9, 2020 VOL. 382 NO. 15

# Initial Invasive or Conservative Strategy for Stable Coronary Disease

D.J. Maron, J.S. Hochman, H.R. Reynolds, S. Bangalore, S.M. O'Brien, W.E. Boden, B.R. Chaitman, R. Senior, J. López-Sendón, K.P. Alexander, R.D. Lopes, L.J. Shaw, J.S. Berger, J.D. Newman, M.S. Sidhu, S.G. Goodman, W. Ruzyllo, G. Gosselin, A.P. Maggioni, H.D. White, B. Bhargava, J.K. Min, G.B.J. Mancini, D.S. Berman, M.H. Picard, R.Y. Kwong, Z.A. Ali, D.B. Mark, J.A. Spertus, M.N. Krishnan, A. Elghamaz, N. Moorthy, W.A. Hueb, M. Demkow, K. Mavromatis, O. Bockeria, J. Peteiro, T.D. Miller, H. Szwed, R. Doerr, M. Keltai, J.B. Selvanayagam, P.G. Steg, C. Held, S. Kohsaka, S. Mavromichalis, R. Kirby, N.O. Jeffries, F.E. Harrell, Jr., F.W. Rockhold, S. Broderick, T.B. Ferguson, Jr., D.O. Williams, R.A. Harrington, G.W. Stone, and Y. Rosenberg, for the ISCHEMIA Research Group*

## ABSTRACT

### BACKGROUND

Among patients with stable coronary disease and moderate or severe ischemia, whether clinical outcomes are better in those who receive an invasive intervention plus medical therapy than in those who receive medical therapy alone is uncertain.

### METHODS

We randomly assigned 5179 patients with moderate or severe ischemia to an initial invasive strategy (angiography and revascularization when feasible) and medical therapy or to an initial conservative strategy of medical therapy alone and angiography if medical therapy failed. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest. A key secondary outcome was death from cardiovascular causes or myocardial infarction.

### RESULTS

Over a median of 3.2 years, 318 primary outcome events occurred in the invasive-strategy group and 352 occurred in the conservative-strategy group. At 6 months, the cumulative event rate was 5.3% in the invasive-strategy group and 3.4% in the conservative-strategy group (difference, 1.9 percentage points; 95% confidence interval [CI], 0.8 to 3.0); at 5 years, the cumulative event rate was 16.4% and 18.2%, respectively (difference, −1.8 percentage points; 95% CI, −4.7 to 1.0). Results were similar with respect to the key secondary outcome. The incidence of the primary outcome was sensitive to the definition of myocardial infarction; a secondary analysis yielded more procedural myocardial infarctions of uncertain clinical importance. There were 145 deaths in the invasive-strategy group and 144 deaths in the conservative-strategy group (hazard ratio, 1.05; 95% CI, 0.83 to 1.32).

### CONCLUSIONS

Among patients with stable coronary disease and moderate or severe ischemia, we did not find evidence that an initial invasive strategy, as compared with an initial conservative strategy, reduced the risk of ischemic cardiovascular events or death from any cause over a median of 3.2 years. The trial findings were sensitive to the definition of myocardial infarction that was used. (Funded by the National Heart, Lung, and Blood Institute and others; ISCHEMIA ClinicalTrials.gov number, NCT01471522.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Maron at the Department of Medicine, Stanford University School of Medicine, 1265 Welch Rd., Medical School Office Bldg. x314, Stanford, CA 94305, or at david.maron@stanford.edu; or to Dr. Hochman at the New York University Grossman School of Medicine–New York University Langone Health, 530 First Ave., Skirball 9R, New York, NY 10016, or at judith.hochman@nyumc.org.

*A full list of ISCHEMIA Research Group members is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Maron and Hochman contributed equally to this article.

This article was published on March 30, 2020, at NEJM.org.

N Engl J Med 2020;382:1395-407.
DOI: 10.1056/NEJMoa1915922



Read Full Article at NEJM.org

EDITORIALS

# Managing Stable Ischemic Heart Disease

Elliott M. Antman, M.D., and Eugene Braunwald, M.D.

The preferred contemporary approach to the management of stable ischemic heart disease, also referred to as chronic coronary syndrome,[1] is not well defined. Two strategies are commonly used.[2] The conservative strategy uses guideline-based medical therapy, including antianginal drugs as well as disease-modifying agents, such as hypolipidemic, antithrombotic, and renin–angiotensin blocking therapies. The invasive strategy adds coronary angiography, followed by either percutaneous coronary intervention or coronary-artery bypass grafting, to guideline-based medical therapy. Important advances have occurred in both strategies, leading to equipoise as to which approach is preferable for patients with stable ischemic heart disease.[3,4]

The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA), the results of which are now reported in the *Journal*, tested whether an initial invasive strategy would result in better outcomes than a conservative strategy among patients with stable ischemic heart disease and moderate or severe myocardial ischemia. In the main trial, 5179 patients underwent randomization at 320 centers in 37 countries.[5] Another 777 patients who had advanced chronic kidney disease in addition to the other conditions were included in a separate trial (ISCHEMIA-CKD).[6] Both trials used a patient-centric approach by incorporating sophisticated analyses of angina-related quality of life.[7,8]

These trials have a number of important positive features. More patients underwent randomization in each trial than in previous trials addressing this issue. The patients had, on average, excellent control of low-density–lipoprotein cholesterol and systolic blood pressure, as well as glycated hemoglobin in those with diabetes.[5,9] The presence of moderate or severe ischemia was determined with stress imaging in the majority of patients. In ISCHEMIA, the majority of patients also underwent coronary computed tomographic angiography at screening to confirm the presence of coronary obstruction and to rule out left main coronary artery disease; the results of the imaging studies were confirmed on blinded review at core laboratories. Unlike in previous trials, randomization to the conservative and invasive strategies in these trials was carried out before coronary angiography was performed, thereby reducing the likelihood of bias.

In ISCHEMIA, 96% of the patients in the invasive-strategy group underwent coronary angiography, whereas only 26% of the patients in the conservative-strategy group did so, for an ischemic event or inadequate control of symptoms. The corresponding percentages in ISCHEMIA-CKD were 85% and 32%. Of note, in ISCHEMIA-CKD, half the patients in the invasive-strategy group did not undergo revascularization, most often because they did not have obstructive coronary disease, despite having a positive stress test. In the two trials, the power was reduced because enrollments and aggregated event rates were lower than anticipated, leading to changes in the planned sample sizes and, in ISCHEMIA, to a change in the primary end point.[10]

There was no significant difference between the two strategies in the rate of death from cardiovascular causes, myocardial infarction, or hospitalization for unstable angina, heart failure, or resuscitated cardiac arrest (the primary end point in ISCHEMIA) or in the rate of death from any cause or myocardial infarction (the primary end point in ISCHEMIA-CKD).[5,6] In ISCHEMIA, rates of death from any cause were quite low, at approximately 6.4% at 4 years in both groups. In ISCHEMIA-CKD, death rates were higher, at approximately 27% at 3 years, again without a difference between the two groups. The most straightforward conclusion is that, insofar as "hard" end points are concerned, the two strategies seem to have been equally efficacious in the two trials. In ISCHEMIA, the patients in the invasive-strategy group reported substantially fewer anginal symptoms than the patients in the conservative-strategy group,[7] although the magnitude of this



Back to Table of Contents

benefit depended on angina frequency at baseline (and 35% had no angina at baseline). In ISCHEMIA-CKD, there was no benefit with regard to angina-related health status with the invasive strategy.[8]

Possible reasons for the lack of difference in "hard" outcomes in ISCHEMIA are the relatively low risk for clinical events among the trial patients and the potential effect of practice patterns that may have excluded more-symptomatic patients from the trial in countries with a low threshold for revascularization. Of note, in ISCHEMIA, the Kaplan–Meier curves showed a trend for a greater number of myocardial infarctions (predominantly procedural) in the invasive-strategy group than in the conservative-strategy group during the first 6 months of the trial, but as the trial proceeded, the curves crossed, and more myocardial infarctions (predominantly spontaneous) occurred in the conservative-strategy group. At 4 years, the cumulative incidence of death from cardiovascular causes or myocardial infarction (based on the primary definition) was higher in the conservative-strategy group than in the invasive-strategy group (13.9% vs. 11.7%). It is possible that ISCHEMIA ended before a substantial difference in favor of the invasive strategy emerged. Since it is unlikely that ISCHEMIA will be repeated, it is especially important to extend follow-up with the patients before contact with them is lost; additional events may enhance our understanding of the effect of the trajectory of the event curves and ascertain the durability of the benefit of an invasive strategy with regard to control of angina. It would also be helpful to develop a risk score for the trial patients in order to determine the outcomes at various levels of risk.[11]

As pointed out by the authors of ISCHEMIA, when myocardial infarction was analyzed according to a secondary definition (see the Supplementary Appendix, available with the full text of the article at NEJM.org), the number and pattern of myocardial infarctions differed, leading to results that favored the conservative strategy throughout follow-up. Both the primary and the secondary definitions of myocardial infarction were complex. Analyses of the prespecified but not yet reported end points of "complicated" and "large" myocardial infarctions would be of interest and potentially informative to the clinical community.

Although there is some uncertainty regarding the interpretation of the ISCHEMIA results — given that the difference in outcomes between the two strategies is driven by results for myocardial infarction, and those results depend on the definition used in the analysis — the invasive strategy does not appear to be associated with clinically meaningful differences in outcomes during 4 years of follow-up. This finding underscores the benefits of disease-modifying contemporary pharmacotherapy for coronary artery disease. Thus, provided there is strict adherence to guideline-based medical therapy, patients with stable ischemic heart disease who fit the profile of those in ISCHEMIA and do not have unacceptable levels of angina can be treated with an initial conservative strategy. However, an invasive strategy, which more effectively relieves symptoms of angina (especially in patients with frequent episodes[7]), is a reasonable approach at any point in time for symptom relief.

Among patients with stable ischemic heart disease who have advanced chronic kidney disease, the risk of clinical events is more than three times as high as the risk among those without chronic kidney disease, but an initial invasive strategy does not appear to reduce event rates or relieve angina symptoms for these patients.[6,8] Therefore, patients with stable ischemic heart disease and chronic kidney disease can usually be treated with a conservative strategy.[12]

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

From the Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School — both in Boston.

This editorial was published on March 30, 2020, at NEJM.org.

1. Knuuti J, Wijns W, Saraste A, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
2. Braunwald E. Coronary-artery surgery at the crossroads. N Engl J Med 1977;297:661-3.
3. Stone GW, Hochman JS, Williams DO, et al. Medical therapy with versus without revascularization in stable patients with moderate and severe ischemia: the case for community equipoise. J Am Coll Cardiol 2016;67:81-99.
4. Chacko L, Howard JP, Rajkumar C, et al. Effects of percutaneous coronary intervention on death and myocardial infarction stratified by stable and unstable coronary artery disease: a meta-analysis of randomized controlled trials. Circ Cardiovasc Qual Outcomes 2020;13(2):e006363.
5. Maron DJ, Hochman JS, Reynolds HR, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med 2020;382:1395-407.
6. Bangalore S, Maron DJ, O'Brien SM, et al. Management of coronary disease in patients with advanced kidney disease. N Engl J Med. DOI: 10.1056/NEJMoa1915925.
7. Spertus JA, Jones PG, Maron DJ, et al. Health-status outcomes with invasive or conservative care in coronary disease. N Engl J Med 2020;382:1408-19.
8. Spertus JA, Jones PG, Maron DJ, et al. Health status after invasive or conservative care in coronary and advanced kidney



Back to Table of Contents

disease. N Engl J Med. DOI: 10.1056/NEJMoa1916374.
**9.** Hochman JS, Reynolds HR, Bangalore S, et al. Baseline characteristics and risk profiles of participants in the ISCHEMIA randomized clinical trial. JAMA Cardiol 2019;4:273-86.
**10.** ISCHEMIA Trial Research Group. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. Am Heart J 2018;201:124-35.
**11.** Antman EM, Loscalzo J. Precision medicine in cardiology. Nat Rev Cardiol 2016;13:591-602.
**12.** Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013;382:339-52.

DOI: 10.1056/NEJMe2000239




Back to Table of Contents

ORIGINAL ARTICLE

# Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol

Kausik K. Ray, M.D., M.Phil., R. Scott Wright, M.D., David Kallend, M.D., Wolfgang Koenig, M.D., Lawrence A. Leiter, M.D., Frederick J. Raal, Ph.D., Jenna A. Bisch, B.A., Tara Richardson, B.A., Mark Jaros, Ph.D., Peter L.J. Wijngaard, Ph.D., and John J.P. Kastelein, M.D., Ph.D., for the ORION-10 and ORION-11 Investigators*

APRIL 16, 2020
VOL. 382 NO. 16

## ABSTRACT

### BACKGROUND

Inclisiran inhibits hepatic synthesis of proprotein convertase subtilisin–kexin type 9. Previous studies suggest that inclisiran might provide sustained reductions in low-density lipoprotein (LDL) cholesterol levels with infrequent dosing.

### METHODS

We enrolled patients with atherosclerotic cardiovascular disease (ORION-10 trial) and patients with atherosclerotic cardiovascular disease or an atherosclerotic cardiovascular disease risk equivalent (ORION-11 trial) who had elevated LDL cholesterol levels despite receiving statin therapy at the maximum tolerated dose. Patients were randomly assigned in a 1:1 ratio to receive either inclisiran (284 mg) or placebo, administered by subcutaneous injection on day 1, day 90, and every 6 months thereafter over a period of 540 days. The coprimary end points in each trial were the placebo-corrected percentage change in LDL cholesterol level from baseline to day 510 and the time-adjusted percentage change in LDL cholesterol level from baseline after day 90 and up to day 540.

### RESULTS

A total of 1561 and 1617 patients underwent randomization in the ORION-10 and ORION-11 trials, respectively. Mean (±SD) LDL cholesterol levels at baseline were 104.7±38.3 mg per deciliter (2.71±0.99 mmol per liter) and 105.5±39.1 mg per deciliter (2.73±1.01 mmol per liter), respectively. At day 510, inclisiran reduced LDL cholesterol levels by 52.3% (95% confidence interval [CI], 48.8 to 55.7) in the ORION-10 trial and by 49.9% (95% CI, 46.6 to 53.1) in the ORION-11 trial, with corresponding time-adjusted reductions of 53.8% (95% CI, 51.3 to 56.2) and 49.2% (95% CI, 46.8 to 51.6) ($P<0.001$ for all comparisons vs. placebo). Adverse events were generally similar in the inclisiran and placebo groups in each trial, although injection-site adverse events were more frequent with inclisiran than with placebo (2.6% vs. 0.9% in the ORION-10 trial and 4.7% vs. 0.5% in the ORION-11 trial); such reactions were generally mild, and none were severe or persistent.

### CONCLUSIONS

Reductions in LDL cholesterol levels of approximately 50% were obtained with inclisiran, administered subcutaneously every 6 months. More injection-site adverse events occurred with inclisiran than with placebo. (Funded by the Medicines Company; ORION-10 and ORION-11 ClinicalTrials.gov numbers, NCT03399370 and NCT03400800.)

From the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, London (K.K.R.); the Department of Cardiology, Mayo Clinic, Rochester, MN (R.S.W.); the Medicines Company, Zurich, Switzerland (D.K.); Deutsches Herzzentrum München, Technische Universität München, and Deutsches Zentrum für Herz-Kreislauf-Forschung (German Center for Cardiovascular Research), partner site Munich Heart Alliance, Munich, and the Institute of Epidemiology and Medical Biometry, University of Ulm, Ulm — all in Germany (W.K.); Li Ka Shing Knowledge Institute, St. Michael's Hospital, University of Toronto, Toronto (L.A.L.); the Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.); the Medicines Company, Parsippany, NJ (J.A.B., T.R., P.L.J.W.); Summit Analytical, Denver (M.J.), and the Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam (J.J.P.K.). Address reprint requests to Dr. Ray at the Imperial Centre for Cardiovascular Disease Prevention, Department of Primary Care and Public Health, Imperial College London, Reynolds Bldg., St. Dunstans Rd., London W6 8RP, United Kingdom, or at k.ray@imperial.ac.uk.

*A list of the ORION-10 and ORION-11 investigators is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Ray and Wright contributed equally to this article.

This article was published on March 18, 2020, at NEJM.org.

N Engl J Med 2020;382:1507-19.
DOI: 10.1056/NEJMoa1912387






Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2020 VOL. 382 NO. 23

# Oral Relugolix for Androgen-Deprivation Therapy in Advanced Prostate Cancer

Neal D. Shore, M.D., Fred Saad, M.D., Michael S. Cookson, M.D., M.M.H.C., Daniel J. George, M.D., Daniel R. Saltzstein, M.D., Ronald Tutrone, M.D., Hideyuki Akaza, M.D., Alberto Bossi, M.D., David F. van Veenhuyzen, M.B., Ch.B., M.Pharm.Med., Bryan Selby, M.S., Xiaolin Fan, Ph.D., Vicky Kang, M.D., Jackie Walling, M.B., Ch.B., Ph.D., and Bertrand Tombal, M.D., Ph.D., for the HERO Study Investigators*

## ABSTRACT

### BACKGROUND

Injectable luteinizing hormone–releasing hormone agonists (e.g., leuprolide) are the standard agents for achieving androgen deprivation for prostate cancer despite the initial testosterone surge and delay in therapeutic effect. The efficacy and safety of relugolix, an oral gonadotropin-releasing hormone antagonist, as compared with those of leuprolide are not known.

### METHODS

In this phase 3 trial, we randomly assigned patients with advanced prostate cancer, in a 2:1 ratio, to receive relugolix (120 mg orally once daily) or leuprolide (injections every 3 months) for 48 weeks. The primary end point was sustained testosterone suppression to castrate levels (<50 ng per deciliter) through 48 weeks. Secondary end points included noninferiority with respect to the primary end point, castrate levels of testosterone on day 4, and profound castrate levels (<20 ng per deciliter) on day 15. Testosterone recovery was evaluated in a subgroup of patients.

### RESULTS

A total of 622 patients received relugolix and 308 received leuprolide. Of men who received relugolix, 96.7% (95% confidence interval [CI], 94.9 to 97.9) maintained castration through 48 weeks, as compared with 88.8% (95% CI, 84.6 to 91.8) of men receiving leuprolide. The difference of 7.9 percentage points (95% CI, 4.1 to 11.8) showed noninferiority and superiority of relugolix ($P<0.001$ for superiority). All other key secondary end points showed superiority of relugolix over leuprolide ($P<0.001$). The percentage of patients with castrate levels of testosterone on day 4 was 56.0% with relugolix and 0% with leuprolide. In the subgroup of 184 patients followed for testosterone recovery, the mean testosterone levels 90 days after treatment discontinuation were 288.4 ng per deciliter in the relugolix group and 58.6 ng per deciliter in the leuprolide group. Among all the patients, the incidence of major adverse cardiovascular events was 2.9% in the relugolix group and 6.2% in the leuprolide group (hazard ratio, 0.46; 95% CI, 0.24 to 0.88).

### CONCLUSIONS

In this trial involving men with advanced prostate cancer, relugolix achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide, with a 54% lower risk of major adverse cardiovascular events. (Funded by Myovant Sciences; HERO ClinicalTrials.gov number, NCT03085095.)

From the Carolina Urologic Research Center, Myrtle Beach, SC (N.D.S.); the University of Montreal Hospital Center, Montreal (F.S.); the Department of Urology, University of Oklahoma Health Sciences Center, Oklahoma City (M.S.C.); the Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC (D.J.G.); Urology San Antonio, San Antonio, TX (D.R.S.); Chesapeake Urology, Towson, MD (R.T.); the Department of Strategic Investigation on Comprehensive Cancer Network, Interfaculty Initiative in Information Studies–Graduate School of Interdisciplinary Information Studies, University of Tokyo, Tokyo (H.A.); the Department of Radiation Oncology, Gustave Roussy Cancer Institute, Villejuif, France (A.B.); Myovant Sciences, Brisbane, CA (D.F.V., B.S., X.F., V.K., J.W.); and Service d'Urologie, Cliniques Universitaires Saint Luc, Brussels (B.T.). Address reprint requests to Dr. Shore at the Carolina Urologic Research Center, 823 82nd Pkwy., Suite B, Myrtle Beach, SC 29572, or at nshore@gsuro.com.

*A full list of the HERO Study Investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on May 29, 2020, at NEJM.org.

N Engl J Med 2020;382:2187-96.
DOI: 10.1056/NEJMoa2004325

EDITORIALS

# Cardiovascular Disease and Androgen Axis–Targeted Drugs for Prostate Cancer

Celestia S. Higano, M.D.

Cardiovascular disease is the leading cause of death in men in the United States and in the developed world. Men with prostate cancer have a higher incidence of cardiovascular disease than those without, and among men with prostate cancer, cardiovascular disease is the principal non–cancer-related cause of death.[1,2] The relationship of androgen-deprivation therapy (ADT) to fatal cardiovascular events is uncertain because of conflicting evidence; nonetheless, the general consensus is that men with preexisting cardiovascular disease are at increased risk for cardiovascular toxic effects when treated with ADT.[3]

The phase 3 HERO trial now reported in the *Journal* shows that relugolix, an oral gonadotropin-releasing hormone (GnRH) antagonist, produced sustained testosterone suppression to less than 50 ng per deciliter (1.7 nmol per liter) through week 48, the primary end point.[4] Once-daily relugolix was compared in a 2:1 trial design with the GnRH agonist leuprolide, which was delivered by subcutaneous or intramuscular injection every 3 months. Testosterone suppression with relugolix was both noninferior and superior to that with leuprolide, a milestone required for ultimate regulatory approval by health authorities. Relugolix was also superior to leuprolide with respect to several secondary end points: suppression of testosterone at days 4 and 15, suppression of testosterone to less than 20 ng per deciliter (0.7 nmol per liter) at day 15, and suppression of follicle-stimulating hormone at week 24.

Degarelix is currently the only GnRH antagonist that is commercially available to treat prostate cancer, and it is administered as a monthly subcutaneous injection. If degarelix is not administered properly, profound and painful injection-site reactions can occur, but we have found in our own clinic that proper training of those who administer the drug can almost completely eliminate this problem.[5]

The observation that a GnRH antagonist may have a lesser effect on cardiovascular disease than a GnRH agonist was first raised in a pooled analysis of six phase 3 trials comparing degarelix with a GnRH agonist in 2328 men.[6] In this post hoc analysis, the subgroup of men with preexisting cardiovascular disease (30%) had twice the incidence of cardiac events after 1 year when treated with a GnRH agonist than when treated with a GnRH antagonist. However, no significant difference between treatments was observed among men without a history of cardiovascular disease. In a more recently reported randomized phase 2 trial involving 80 men, 20% of those treated with a depot GnRH agonist every 3 months had a major cardiovascular or cerebrovascular event, as compared with 3% of those treated with a GnRH antagonist ($P=0.01$).[7]

In the HERO trial, which enrolled 934 men, the incidence of major adverse cardiovascular events after 48 weeks of treatment was 2.9% (exact 95% confidence interval [CI], 1.7 to 4.5) with relugolix and 6.2% (exact 95% CI, 3.8 to 9.5) with leuprolide, which represents a 54% lower risk with the GnRH antagonist than with the GnRH agonist. In the subgroup of men with a history of cardiovascular events, the incidence was 3.6% in the relugolix group and 17.8% in the leuprolide group, indicating that the risk differed by a factor of 4.8.[4]

None of the trials comparing a GnRH antagonist with a GnRH agonist evaluated cardiovascular events as a primary end point, although such events were a prespecified secondary end point in the phase 2 trial. The PRONOUNCE trial is a phase 3 global trial that was designed to prospectively study the incidence of major adverse



Back to Table of Contents

cardiovascular events as a primary end point among men with preexisting cardiovascular disease.[8] A total of 544 patients have undergone randomization, but after a feasibility analysis, recruitment has been halted and may not resume. Nonetheless, this appears to be the largest trial ever conducted with ADT and a cardiovascular primary end point.

Also now presented in the *Journal* is the third interim analysis of overall survival among men with nonmetastatic, castration-resistant prostate cancer treated with enzalutamide, a second-generation antiandrogen, or placebo in the PROSPER trial.[9] The initial publication of this phase 3 trial showed a 71% lower risk of metastases or death among men who received enzalutamide than among those who received placebo.[10] The latest report of the PROSPER trial now shows an overall survival advantage for enzalutamide, with a median overall survival of 67.0 months (95% CI, 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (hazard ratio for death, 0.73; 95% CI, 0.61 to 0.89; P=0.001).

Patients who were enrolled in the PROSPER trial had nonmetastatic, castration-resistant prostate cancer that was considered to be "high risk" by virtue of a prostate-specific antigen (PSA) doubling time of 10 months or less, although they had no evidence of metastatic disease or cancer-related symptoms. Two additional phase 3 trials comparing ADT plus a second-generation antiandrogen (apalutamide[11] or darolutamide[12]) with ADT plus placebo in this same population have shown similar results with respect to both prolonged metastasis-free survival and overall survival in the active-treatment groups. All three agents now have regulatory approval in the United States for use in nonmetastatic, castration-resistant prostate cancer, regardless of PSA doubling time.

Although metastasis-free and overall survival were improved in the enzalutamide group of the PROSPER trial, an increased risk of adverse events was observed, including falls, fatigue, hypertension, and death from cardiovascular causes. In men with risk factors for cardiovascular disease (such as hypertension, obesity, diabetes, and hyperlipidemia) who do not have a PSA doubling time of 10 months or less, the risk–benefit ratio of treating with enzalutamide should be considered in these asymptomatic men who may have a more indolent course of disease than those with a PSA doubling time of 10 months or less.

Enzalutamide was originally approved in 2012 for the treatment of men with metastatic, castration-resistant prostate cancer who had previously been treated with docetaxel. Since then, our clinical experience and understanding of the toxic effects have increased. Apalutamide and darolutamide were approved in the United States in 2018 and 2019, respectively, so there has been less time to observe the real-world toxic effects of these agents and data from trials comparing second-generation antiandrogens are lacking. Given the findings of the PROSPER trial and the many years of postmarketing data that also point to increased cardiovascular risk,[13] the importance of coexisting conditions and the necessity for close monitoring should be factored into the choice of agent, if any, for men with nonmetastatic, castration-resistant prostate cancer.

Androgen-deprivation monotherapy with a GnRH agonist and the addition of the newer, second-generation androgen-signaling blockers to ADT were found in these trials to be associated with an increase in cardiovascular events in men with preexisting cardiovascular disease. When considered together, these trials raise the question of whether the use of a GnRH antagonist, either oral or subcutaneous, might result in improved cardiovascular outcomes, especially for those at highest risk. To that end, it might be time to consider treating men who have preexisting cardiovascular risk factors with a GnRH antagonist rather than an agonist. Even though no level 1 outcome data exist for the superiority of a GnRH antagonist over a GnRH agonist with respect to cardiovascular events or death from cardiovascular causes, the testosterone-suppression data for GnRH antagonists, oral or subcutaneous, are level 1. Therefore, it is likely that the anticancer effects of a GnRH antagonist will not be inferior to those of a GnRH agonist and may be beneficial in terms of cardiovascular events that may be life-limiting. Close monitoring will be required because exposure to oral relugolix for longer than 48 weeks has not been studied and many oral agents are associated with adherence problems, especially if they cause adverse effects.

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



Back to Table of Contents

From the University of Washington, Seattle.

This editorial was published on May 29, 2020, at NEJM.org.

**1.** Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J 2019;40:3889-97.
**2.** Leong DP, Fradet V, Shayegan B, et al. Cardiovascular risk in men with prostate cancer: insights from the RADICAL PC study. J Urol 2020;203:1109-16.
**3.** Bhatia N, Santos M, Jones LW, et al. Cardiovascular effects of androgen deprivation therapy for the treatment of prostate cancer: ABCDE steps to reduce cardiovascular disease in patients with prostate cancer. Circulation 2016;133:537-41.
**4.** Shore ND, Saad F, Cookson MS, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187-96.
**5.** Barkin J, Burton S, Lambert C. Optimizing subcutaneous injection of the gonadotropin-releasing hormone receptor antagonist degarelix. Can J Urol 2016;23:8179-83.
**6.** Albertsen PC, Klotz L, Tombal B, Grady J, Olesen TK, Nilsson J. Cardiovascular morbidity associated with gonadotropin releasing hormone agonists and an antagonist. Eur Urol 2014;65:565-73.
**7.** Margel D, Peer A, Ber Y, et al. Cardiovascular morbidity in a randomized trial comparing GnRH agonist and GnRH antagonist among patients with advanced prostate cancer and preexisting cardiovascular disease. J Urol 2019;202:1199-208.
**8.** Melloni C, Slovin SF, Blemings A, et al. Cardiovascular safety of degarelix versus leuprolide for advanced prostate cancer: the PRONOUNCE trial study design. JACC: CardioOncology 2020;2:70-81.
**9.** Sternberg CN, Fizazi K, Saad F, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197-206.
**10.** Hussain M, Fizazi K, Saad F, et al. Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2018;378:2465-74.
**11.** Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med 2018;378:1408-18.
**12.** Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2019;380:1235-46.
**13.** Iacovelli R, Ciccarese C, Bria E, et al. The cardiovascular toxicity of abiraterone and enzalutamide in prostate cancer. Clin Genitourin Cancer 2018;16(3):e645-e653.

DOI: 10.1056/NEJMe2016433




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 11, 2020 VOL. 382 NO. 24

# Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria

M. Balwani, E. Sardh, P. Ventura, P.A. Peiró, D.C. Rees, U. Stölzel, D.M. Bissell, H.L. Bonkovsky, J. Windyga, K.E. Anderson, C. Parker, S.M. Silver, S.B. Keel, J.-D. Wang, P.E. Stein, P. Harper, D. Vassiliou, B. Wang, J. Phillips, A. Ivanova, J.G. Langendonk, R. Kauppinen, E. Minder, Y. Horie, C. Penz, J. Chen, S. Liu, J.J. Ko, M.T. Sweetser, P. Garg, A. Vaishnaw, J.B. Kim, A.R. Simon, and L. Gouya, for the ENVISION Investigators*

## ABSTRACT

### BACKGROUND

Up-regulation of hepatic delta-aminolevulinic acid synthase 1 (ALAS1), with resultant accumulation of delta-aminolevulinic acid (ALA) and porphobilinogen, is central to the pathogenesis of acute attacks and chronic symptoms in acute hepatic porphyria. Givosiran, an RNA interference therapy, inhibits ALAS1 expression.

### METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned symptomatic patients with acute hepatic porphyria to receive either subcutaneous givosiran (2.5 mg per kilogram of body weight) or placebo monthly for 6 months. The primary end point was the annualized rate of composite porphyria attacks among patients with acute intermittent porphyria, the most common subtype of acute hepatic porphyria. (Composite porphyria attacks resulted in hospitalization, an urgent health care visit, or intravenous administration of hemin at home.) Key secondary end points were levels of ALA and porphobilinogen and the annualized attack rate among patients with acute hepatic porphyria, along with hemin use and daily worst pain scores in patients with acute intermittent porphyria.

### RESULTS

A total of 94 patients underwent randomization (48 in the givosiran group and 46 in the placebo group). Among the 89 patients with acute intermittent porphyria, the mean annualized attack rate was 3.2 in the givosiran group and 12.5 in the placebo group, representing a 74% lower rate in the givosiran group ($P<0.001$); the results were similar among the 94 patients with acute hepatic porphyria. Among the patients with acute intermittent porphyria, givosiran led to lower levels of urinary ALA and porphobilinogen, fewer days of hemin use, and better daily scores for pain than placebo. Key adverse events that were observed more frequently in the givosiran group were elevations in serum aminotransferase levels, changes in serum creatinine levels and the estimated glomerular filtration rate, and injection-site reactions.

### CONCLUSIONS

Among patients with acute intermittent porphyria, those who received givosiran had a significantly lower rate of porphyria attacks and better results for multiple other disease manifestations than those who received placebo. The increased efficacy was accompanied by a higher frequency of hepatic and renal adverse events. (Funded by Alnylam Pharmaceuticals; ENVISION ClinicalTrials.gov number, NCT03338816.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Balwani at the Icahn School of Medicine, Genetics and Genomic Sciences, 1 Gustave L. Levy Pl., Box 1497, New York, NY 10029, or at manisha.balwani@mssm.edu.

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

Drs. Balwani and Sardh contributed equally to this article.

N Engl J Med 2020;382:2289-301.
DOI: 10.1056/NEJMoa1913147



Read Full Article at NEJM.org

EDITORIAL

# Givosiran — Running RNA Interference to Fight Porphyria Attacks

Gloria Gonzalez-Aseguinolaza, Ph.D.

The porphyrias are a group of rare and ultra-rare devastating disorders of heme biosynthesis. The majority of these disorders are inherited, and patients present with disabling symptoms that have a profound effect on their quality of life. The subtypes of acute hepatic porphyria — including acute intermittent porphyria (the most common subtype), hereditary coproporphyria, variegate porphyria, and delta-aminolevulinic acid (ALA) dehydratase–deficiency porphyria — are characterized by the occurrence of severe neurovisceral attacks.

The genetic deficit that causes acute hepatic porphyria reduces heme availability under conditions of increased heme demands, which leads to activation of the heme-synthesis pathway and up-regulation of the first and rate-limiting enzyme of the pathway, ALA synthase 1 (ALAS1), which in turn leads to an increase in the production and accumulation of the neurotoxic metabolites aminolevulinic acid and porphobilinogen. The elevation of these metabolites is accompanied by diffuse and severe abdominal pain, vomiting, tachycardia, and hypertension. Occasionally quadriparesis or even death occurs owing to bulbar and respiratory paralysis. Furthermore, patients who have recurrent attacks are at risk for long-term complications, such as hepatocellular carcinoma, chronic renal failure, chronic neuropathy, and hypertension.[1]

In 1966, Granick reported a key discovery[2]: hemin (also called hematin) repressed the induction of ALAS1 in chick embryo liver cells in vitro. This finding led to the clinical use of hemin to terminate or ameliorate severe attacks in patients with acute intermittent porphyria.[3] In such patients, hemin is given periodically to prevent attacks or control chronic symptoms. However, long-term therapy with hemin can cause thrombotic complications and may produce iron overload. Moreover, cases of transient renal insufficiency have been reported. Thus, there is an urgent need for new effective therapies for patients with severe forms of acute intermittent porphyria.

Recently, Sardh et al.[4] described the results of a phase 1 trial of givosiran, an RNA interference therapeutic designed to block the synthesis of the ALAS1 enzyme, in patients with acute intermittent porphyria. The monthly subcutaneous administration of givosiran prevented the accumulation of toxic molecules such as aminolevulinic acid and porphobilinogen and resulted in a lower attack rate and lower number of hemin doses than placebo.

In this issue of the *Journal*, Balwani et al.[5] describe the results of the phase 3 ENVISION trial of givosiran involving 94 patients with acute hepatic porphyria, including 89 who had acute intermittent porphyria. Patients were randomly assigned to receive either givosiran at a dose of 2.5 mg per kilogram of body weight or placebo, administered by subcutaneous injection once a month for 6 months. Treatment with givosiran led to a 74% lower annualized rate of composite porphyria attacks (the primary end point) than placebo. The patients in the givosiran group also met several secondary end points, including lower levels of urinary ALA and porphobilinogen and lower use of hemin and analgesic drugs. Both the Food and Drug Administration and the European Medicines Agency have recently approved givosiran for adults with acute hepatic porphyria, and the European Medicines Agency has approved the drug for adolescents 12 years of age or older.



Back to Table of Contents

Despite the striking findings of the ENVISION trial, some limitations remain. The follow-up duration of 6 months is relatively short for a chronic disease. More important, the higher frequency of adverse events and severe adverse events in the givosiran group than in the placebo group is worrisome. In addition to having a higher frequency of injection-site adverse events, patients who received givosiran were more likely to have nausea, chronic kidney disease, a decreased estimated glomerular filtration rate, rash, liver damage, and fatigue than were those who received placebo. Serious adverse events included worsening of chronic kidney disease and abnormal liver-function results; the latter led to the discontinuation of givosiran by one patient.

Local injection-site reactions have also been reported in patients who are being treated for other inherited disorders with similar RNA interference drugs, such as inclisiran,[6] fitusiran,[7] and patisiran,[8] which suggests that such reactions may be associated with this class of drug. However, administration of the other cited drugs was not associated with hepatic or renal toxic effects, which indicates that the serious adverse events seen in patients receiving givosiran are associated with its mechanism of action. Might the toxic effects of givosiran be caused by excessive inhibition of ALAS1 activity and concomitant reductions in heme storage and the capacity of the liver to detoxify?

The interpretation of the safety data is complicated by the fact that chronic kidney disease and liver damage are common coexisting illnesses and long-term complications of acute hepatic porphyria,[1] and these disorders may have been exacerbated by givosiran treatment. Other remaining questions include whether it will it be possible to predict which patients with this disorder will have serious adverse events and whether givosiran treatment should be restricted to patients with no previous history of chronic kidney disease or elevated liver-enzyme levels.

Given the limited treatment options for patients with acute hepatic porphyria and the excellent therapeutic efficacy data observed in the ENVISION trial, subcutaneous monthly administration of givosiran represents a very attractive option to replace intravenous hemin administration to reduce ALAS1 activity. That said, the collection and analysis of long-term data, together with a better understanding of givosiran-related toxic effects, are essential.

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

From the Gene Therapy and Regulation of Gene Expression Program, Center for Applied Medical Research, University of Navarra, Pamplona, Spain.

1. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. N Engl J Med 2017;377:862-72.
2. Granick S. The induction in vitro of the synthesis of delta-aminolevulinic acid synthetase in chemical porphyria: a response to certain drugs, sex hormones, and foreign chemicals. J Biol Chem 1966;241:1359-75.
3. Watson CJ. Hematin and porphyria. N Engl J Med 1975;293:605-7.
4. Sardh E, Harper P, Balwani M, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med 2019;380:549-58.
5. Balwani M, Sardh E, Ventura P, et al. Phase 3 trial of RNAi therapeutic givosiran for acute intermittent porphyria. N Engl J Med 2020;382:2289-301.
6. Ray KK, Landmesser U, Leiter LA, et al. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N Engl J Med 2017;376:1430-40.
7. Pasi KJ, Rangarajan S, Georgiev P, et al. Targeting of antithrombin in hemophilia A or B with RNAi therapy. N Engl J Med 2017;377:819-28.
8. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. N Engl J Med 2018;379:11-21.

DOI: 10.1056/NEJMe2010986

ORIGINAL ARTICLE

# Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*


## ABSTRACT

### BACKGROUND

Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death.

### METHODS

In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the preliminary results of this comparison.

### RESULTS

A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.91 to 1.55).

### CONCLUSIONS

In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. (Funded by the Medical Research Council and National Institute for Health Research and others; RECOVERY ClinicalTrials.gov number, NCT04381936; ISRCTN number, 50189673.)


The members of the writing committee (Peter Horby, F.R.C.P., Wei Shen Lim, F.R.C.P., Jonathan R. Emberson, Ph.D., Marion Mafham, M.D., Jennifer L. Bell, M.Sc., Louise Linsell, D.Phil., Natalie Staplin, Ph.D., Christopher Brightling, F.Med. Sci., Andrew Ustianowski, Ph.D., Einas Elmahi, M.Phil., Benjamin Prudon, F.R.C.P., Christopher Green, D.Phil., Timothy Felton, Ph.D., David Chadwick, Ph.D., Kanchan Rege, F.R.C.Path., Christopher Fegan, M.D., Lucy C. Chappell, Ph.D., Saul N. Faust, F.R.C.P.C.H., Thomas Jaki, Ph.D., Katie Jeffery, Ph.D., Alan Montgomery, Ph.D., Kathryn Rowan, Ph.D., Edmund Juszczak, M.Sc., J. Kenneth Baillie, M.D., Ph.D., Richard Haynes, D.M., and Martin J. Landray, Ph.D.) assume responsibility for the overall content and integrity of this article.

The affiliations of the members of the writing committee are listed in the Appendix. Address reprint requests to Drs. Horby and Landray at RECOVERY Central Coordinating Office, Richard Doll Bldg., Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, United Kingdom, or at recoverytrial@ndph.ox.ac.uk.

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

Drs. Horby, Lim, and Emberson and Drs. Haynes and Landray contributed equally to this article.

This article was published on July 17, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2021436

EDITORIAL

# Research in the Context of a Pandemic

H. Clifford Lane, M.D., and Anthony S. Fauci, M.D.

The current literature on the treatment of coronavirus disease 2019 (Covid-19) is filled with anecdotal reports of therapeutic successes in clinical trials with small numbers of patients and observational cohort studies claiming efficacy with little regard to the effect of unrecognized confounders. For the field to move forward and for patients' outcomes to improve, there will need to be fewer small or inconclusive studies and more studies such as the dexamethasone trial now reported by the RECOVERY Collaborative Group[1] in the *Journal*.

In the RECOVERY trial, the benefit of the glucocorticoid dexamethasone for patients with Covid-19 who were receiving mechanical ventilation at the time of randomization was clearly shown. A 28-day mortality of 29.3% was reported for patients in the dexamethasone group as compared with 41.4% in the usual care group. In contrast, no benefit for dexamethasone was seen in patients not requiring oxygen at the time of randomization, with 28-day mortality of 17.8% and 14.0% for the dexamethasone group and the usual care group, respectively. For the heterogeneous group of patients receiving oxygen without invasive mechanical ventilation, mortality was 23.3% in the dexamethasone group and 26.2% in the usual care group. These findings, while limited to patients with Covid-19, provides clarity to an area of therapeutic controversy and probably will result in many lives saved. The use of dexamethasone already has been endorsed by several treatment-guideline panels, including that convened by the U.S. National Institutes of Health.[2]

The RECOVERY trial and the recently published randomized, controlled trial of remdesivir[3] provide clear guidance on therapeutic strategies for Covid-19 along with insights into the pathogenesis of the disease. Remdesivir, a directly acting antiviral drug, has its most favorable effect in hospitalized patients with Covid-19 who have modest pulmonary disease. This effect probably correlates to a time in the infection when viral replication is driving the pathogenic process. In contrast, the antiinflammatory and immunosuppressive dexamethasone has its greatest therapeutic effect in patients who have more advanced disease, a time during which pathogenic effects may be driven by the immune and inflammatory responses.

The RECOVERY trial takes an approach to clinical research popularized in the field of cardiovascular disease by enrolling large numbers of patients into a simple trial as opposed to smaller numbers of patients into a more complex, rigid, and granular study.[4] Both approaches have strengths and weaknesses. Large simple trials are especially useful for addressing questions such as whether a repurposed drug or standard procedure is of value, whereas the latter approach is more suited to the study of novel agents whose mechanisms of therapeutic effect may be unclear. In addition, the RECOVERY trial is using a platform or master-protocol approach in which agents can be added or subtracted from the randomization as data emerge from the trial or as new agents become available. In addition to the current report of efficacy of dexamethasone, RECOVERY investigators have reported a lack of efficacy for hydroxychloroquine and for lopinavir–ritonavir and continue to study the role of dexamethasone in children, as well as the roles of azithromycin, tocilizumab, and convalescent plasma.[1] The key to the success of the RECOVERY trial has been its pace of enrollment. The ability to rapidly enroll thousands of patients into the trial no doubt was facilitated by the National Health Service in the United Kingdom and the fact that the trial was available to essentially the entire patient population of the country. As noted



Back to Table of Contents

by the authors, 15% of all the patients who were hospitalized with Covid-19 in the United Kingdom were enrolled in the trial.

It was once widely held that the setting of an outbreak is not an appropriate venue for conducting rigorous clinical research because when people are dying, any and all possible therapies should be "given a chance," rather than studied in rigorous ways. Such was the case during the 2014–2016 Ebola outbreak in West Africa, when many small studies were launched and few, if any, provided conclusive results. A thorough review of that situation by the U.S. National Academies of Sciences, Engineering, and Medicine concluded that "randomized, controlled trials are the most reliable way to identify the relative benefits and risks of investigational products, and . . . every effort should be made to implement them during epidemics."[5] These findings were endorsed by the global research community and led to an adequately powered randomized, controlled trial during the 2018–2020 Ebola outbreak in the Democratic Republic of the Congo that clearly identified two effective therapies.[6]

Despite the decreases in death and complications that are likely to result from appropriate treatment of patients with remdesivir and dexamethasone, far too many people with Covid-19 will die. It is our responsibility in the global medical research community to rapidly design, implement, and complete studies of the most promising therapeutic agents and vaccines against this disease. These agents include monoclonal antibodies, more selective immunosuppressive agents, and vaccines built on platforms ranging from nucleic acids to proteins to recombinant viruses. Such efforts will benefit from national and global coordination and public–private partnerships, including Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) in the United States,[7] the ACCORD (Accelerating Covid-19 Research and Development) platform in the United Kingdom,[8] and the SOLIDARITY effort by the World Health Organization.[9] Scientifically robust and ethically sound clinical research remains the quickest and most efficient pathway to effective treatment and prevention strategies for patients with Covid-19.

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

From the Division of Clinical Research, National Institute of Allergy and Infectious Diseases (NIAID) (H.C.L.), and the Office of the Director, NIAID (A.S.F.), National Institutes of Health, Bethesda, MD.

This editorial was published on July 17, 2020, at NEJM.org.

1. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.
2. Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda, MD: National Institutes of Health (https://www.covid19treatmentguidelines.nih.gov).
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2007764.
4. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. J Clin Epidemiol 1995;48:23-40.
5. National Academies of Sciences, Engineering, and Medicine. Integrating clinical research into epidemic response: the Ebola experience. Washington, DC: National Academies Press, 2017.
6. Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293-303.
7. Collins FS, Stoffels P. Accelerating COVID-19 therapeutic interventions and vaccines (ACTIV): an unprecedented partnership for unprecedented times. JAMA 2020;323:2455-7.
8. COVID-19 treatments could be fast-tracked through new national clinical trial initiative. Press release of the U.K. Department of Health and Social Care, April 29, 2020 (https://www.gov.uk/government/news/covid-19-treatments-could-be-fast-tracked-through-new-national-clinical-trial-initiative).
9. "Solidarity" clinical trial for COVID-19 treatments. Geneva: World Health Organization, 2020 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments).

DOI: 10.1056/NEJMe2024638




Back to Table of Contents

EDITORIAL

# The RECOVERY Platform

Sharon-Lise T. Normand, Ph.D.

In a platform trial, patients with a single disease are randomly assigned to a group of different therapies on the basis of a decision algorithm to determine whether any therapy has benefit.[1] The principle underpinning such trials allows for the execution of efficient, less expensive designs by enrolling populations quickly and collecting minimal data to answer more than one question. These are sensible principles and, when successful, result in trials that provide clear answers to several questions in a timely and efficient way.

In using this approach, investigators designed the RECOVERY trial involving hospitalized patients with coronavirus disease 2019 (Covid-19) in the United Kingdom to assess the efficacy of different treatments using a single end point: mortality within 28 days after randomization; preliminary results are now reported in the *Journal*.[2] A total of 11,303 patients were randomly assigned to one of four treatment groups (dexamethasone, hydroxychloroquine, lopinavir–ritonavir, or azithromycin) or to usual care. Patients could undergo further randomization to receive either no additional treatment or convalescent plasma, and those with progressive Covid-19 could be randomly assigned to receive no additional treatment or tocilizumab.

What lessons do we take from the outcomes of the 6425 patients who were assigned to receive dexamethasone or usual care in the RECOVERY trial? First, broad populations of patients with Covid-19, along with multiple hospitals and trial coordinators, can be rapidly deployed in a trial. No doubt the swift enrollment in the RECOVERY trial was due to the nature of the pandemic, but the rapidity of trial design, logistics, coordination, and execution are the work of the investigators. Second, minimal data collection with the use of a single online follow-up form as well as routine health care data and national registry data can provide meaningful outcomes. A well-established public health care system probably played a large role in the data availability. Third, dexamethasone showed promise for reducing short-term mortality relative to usual care. Fourth, the benefits of dexamethasone may be restricted to the sickest of Covid-19 patients, those who had been placed on mechanical ventilation at the time of randomization.

Are the findings from the RECOVERY trial clinically directive? In the total sample, the age-adjusted rate ratio of mortality for dexamethasone relative to usual care was 0.83 (95% confidence interval [CI], 0.75 to 0.93; P<0.001), with an absolute mortality benefit for dexamethasone of 2.8 percentage points. However, the adjusted rate ratio of mortality benefit among patients who were receiving mechanical ventilation was 0.64 (95% CI, 0.51 to 0.81), an absolute mortality reduction of 12.1 percentage points. Although there were no standardized criteria regarding who received mechanical ventilation, this finding is probably robust and may be helpful in guiding clinical care.

The platform design for RECOVERY has some limitations. Decisions that were made on removing or adding therapies are difficult in the best of circumstances and even more so in the context of the Covid-19 pandemic. Prespecification of rules for making these decisions is fundamental in platform trials, but this was not the case in RECOVERY. The possibility of chance should not be discounted, since the more analyses that are undertaken, the more likely an apparent benefit is due to chance. A data monitoring committee viewed unblinded results from five interim analyses overall and in several important subgroups. The platform used the same control group as a comparator for each of the four remaining drugs and convalescent plasma that



Back to Table of Contents

were randomly assigned. If by chance patients in the control group had particularly poor outcomes, several treatments may have appeared to be better than they would if each treatment had independent controls. The investigators elected not to randomize patients within hospitals owing to a concern about blinding. Randomization with the use of permuted blocks within hospitals would have offered protection to maintain the blind. Hospital practice tendencies, such as the choice of patients for mechanical ventilation, may have influenced the effect of dexamethasone and the other randomized therapies.

Fidelity to the scientific method is a major safeguard and a key determinant of the validity of the results of an investigation. In the era of Covid-19, the need for answers has generated enormous pressures across the research enterprise, from designing and conducting studies to reporting and vetting the results. Kudos to the RECOVERY investigators and trial participants for the rapid enrollment in the trial during a pandemic that has transformed lives worldwide. The results represent an important step in the fight against one aspect of the disease and undoubtedly will have an effect on practice. However, the methodologic caveats raised here are important to other investigators who are developing and revising treatment protocols in hospitals and to the broader research community struggling to produce reliable results in an efficient way, even in the face of a pandemic.

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

From the Department of Health Care Policy, Harvard Medical School, and the Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston.

This editorial was published on July 21, 2020, at NEJM.org.

1. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med 2017;377:62-70.
2. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. N Engl J Med. DOI: 10.1056/NEJMoa2021436.

DOI: 10.1056/NEJMe2025674




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

# Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

A. Drilon, G.R. Oxnard, D.S.W. Tan, H.H.F. Loong, M. Johnson, J. Gainor, C.E. McCoach, O. Gautschi, B. Besse, B.C. Cho, N. Peled, J. Weiss, Y.-J. Kim, Y. Ohe, M. Nishio, K. Park, J. Patel, T. Seto, T. Sakamoto, E. Rosen, M.H. Shah, F. Barlesi, P.A. Cassier, L. Bazhenova, F. De Braud, E. Garralda, V. Velcheti, M. Satouchi, K. Ohashi, N.A. Pennell, K.L. Reckamp, G.K. Dy, J. Wolf, B. Solomon, G. Falchook, K. Ebata, M. Nguyen, B. Nair, E.Y. Zhu, L. Yang, X. Huang, E. Olek, S.M. Rothenberg, K. Goto, and V. Subbiah

## ABSTRACT

### BACKGROUND

*RET* fusions are oncogenic drivers in 1 to 2% of non–small-cell lung cancers (NSCLCs). In patients with *RET* fusion–positive NSCLC, the efficacy and safety of selective RET inhibition are unknown.

### METHODS

We enrolled patients with advanced *RET* fusion–positive NSCLC who had previously received platinum-based chemotherapy and those who were previously untreated separately in a phase 1–2 trial of selpercatinib. The primary end point was an objective response (a complete or partial response) as determined by an independent review committee. Secondary end points included the duration of response, progression-free survival, and safety.

### RESULTS

In the first 105 consecutively enrolled patients with *RET* fusion–positive NSCLC who had previously received at least platinum-based chemotherapy, the percentage with an objective response was 64% (95% confidence interval [CI], 54 to 73). The median duration of response was 17.5 months (95% CI, 12.0 to could not be evaluated), and 63% of the responses were ongoing at a median follow-up of 12.1 months. Among 39 previously untreated patients, the percentage with an objective response was 85% (95% CI, 70 to 94), and 90% of the responses were ongoing at 6 months. Among 11 patients with measurable central nervous system metastasis at enrollment, the percentage with an objective intracranial response was 91% (95% CI, 59 to 100). The most common adverse events of grade 3 or higher were hypertension (in 14% of the patients), an increased alanine aminotransferase level (in 12%), an increased aspartate aminotransferase level (in 10%), hyponatremia (in 6%), and lymphopenia (in 6%). A total of 12 of 531 patients (2%) discontinued selpercatinib because of a drug-related adverse event.

### CONCLUSIONS

Selpercatinib had durable efficacy, including intracranial activity, with mainly low-grade toxic effects in patients with *RET* fusion–positive NSCLC who had previously received platinum-based chemotherapy and those who were previously untreated. (Funded by Loxo Oncology and others; LIBRETTO-001 ClinicalTrials.gov number, NCT03157128.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Drilon at Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065, or at drilona@mskcc.org; or to Dr. Subbiah at the University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Unit 455, Houston, TX 77030, or at vsubbiah@mdanderson.org.

Drs. Drilon, Oxnard, and Tan contributed equally to this article.

N Engl J Med 2020;383:813-24.
DOI: 10.1056/NEJMoa2005653


Read Full Article at NEJM.org

EDITORIALS

# Selpercatinib Aimed at *RET*-Altered Cancers

Razelle Kurzrock, M.D.

A remarkable increase has occurred in the number of highly targeted drugs that have efficacy in patients with advanced cancers that harbor specific genomic alterations. Prime examples are the NTRK inhibitors that target *NTRK* fusions, which are found in only approximately 0.3% of cancers.[1,2] As many as 75% of the patients with tumors that bear NTRK fusions and who have received these agents have had a response. These results have led to the Food and Drug Administration (FDA) approval of the use of the NTRK inhibitors larotrectinib and entrectinib in adult and pediatric patients with *NTRK* fusion–positive solid tumors, regardless of the tissue of origin. Similarly, pembrolizumab, an immune checkpoint blockade antibody that targets programmed cell death protein 1, has been approved by the FDA for the treatment of all solid tumors with one of two specific molecular markers — microsatellite instability that derives from a defect in mismatch-repair genes and a high tumor mutational burden. Both of these markers have been associated with durable responses to pembrolizumab in a large subgroup of patients with advanced cancers.[3,4] In this issue of the *Journal*, Wirth et al.[5] and Drilon et al.[6] report that the potent RET inhibitor selpercatinib (LOXO-292) is now poised to alter the landscape of another genomic subgroup — *RET*-altered cancers.

The *RET* proto-oncogene encodes a transmembrane receptor tyrosine kinase that is composed of an intracellular kinase, a large extracellular domain, and a transmembrane domain.[1-4] RET functions as the receptor for the glial-cell line–derived neurotropic factor family of growth factors. Subsequent to ligand binding, autophosphorylation on intracellular tyrosine residues of RET generates docking sites for downstream signaling adaptors, activating multiple key cancer effectors.

*RET* aberrations can result in gain-of-function (ligand-independent) kinase activation through mutations, fusions or rearrangements, or amplifications. Overall, among diverse cancers, *RET* aberrations have been identified in approximately 2% of cases, with mutations being the most common alteration. Mutations constitute approximately 37% of *RET* alterations, followed by fusions (approximately 31%) and amplifications (approximately 25%).[7] *RET* missense mutations, which have been described in various types of cancers and in hereditary conditions, can occur in extracellular cysteine residues, triggering aberrant receptor dimerization or, in the intracellular kinase domain, promoting ligand-independent kinase activation.[7,8]

Activating *RET* germline mutations are associated with familial medullary thyroid cancer alone or as part of multiple endocrine neoplasia type 2. More than 50% of sporadic medullary thyroid cancers also harbor activating *RET* mutations. Alternatively, RET activation can occur through gene rearrangements that create an activated fusion protein. *RET* fusions are observed in 10 to 20% of papillary thyroid cancers as well as in small subgroups of non–small-cell lung cancers (NSCLCs) and colorectal, breast, and other cancers.[7,8] RET is thus an attractive therapeutic target.

Previously approved multikinase inhibitors such as vandetanib and cabozantinib, which have ancillary RET inhibitor activity, also have activity against RET-driven cancers. However, the use of these drugs is limited by their off-target side effects. In contrast, next-generation, highly potent, and selective RET inhibitors such as selpercatinib offer the potential for improved efficacy and a more satisfactory side-effect profile. The early-phase clinical trial of selpercatinib described in this issue of the *Journal* included a



Back to Table of Contents

cohort of patients with thyroid cancer and a cohort of patients with NSCLC. In both the part of the trial involving patients with *RET*-altered thyroid cancer (reported by Wirth et al.) and the part of the trial involving patients with *RET*-altered NSCLCs (reported by Drilon et al.), selpercatinib produced durable responses in a majority of patients, and only approximately 3% of the patients discontinued selpercatinib because of drug-related adverse events.

Wirth and colleagues report that among 55 patients with *RET*-mutated medullary thyroid cancer that was previously treated with other RET inhibitors such as vandetanib, cabozantinib, or both, 69% had a response to selpercatinib, and 82% had progression-free survival at 1 year. Among 88 patients with *RET*-mutated medullary thyroid cancer who had not previously received vandetanib or cabozantinib, 73% had a response to selpercatinib, and 92% had progression-free survival at 1 year. Finally, 15 of 19 patients (79%) with previously treated *RET* fusion–positive thyroid cancer had a response.

*RET* fusions are oncogenic drivers in 1 to 2% of NSCLCs.[7,8] Drilon and colleagues report that among 105 patients with *RET* fusion–positive NSCLC who had previously received at least platinum-based chemotherapy, 64% had a response, and the median duration of response was 17.5 months. Furthermore, among 39 previously untreated patients, 85% had a response, and 90% of the responses were ongoing at 6 months. Finally, 10 of 11 patients (91%) with central nervous system metastasis had an intracranial response.

Taken together, these results show that selpercatinib had marked and durable antitumor activity in most patients with *RET*-altered thyroid cancer or NSCLC. *RET* abnormalities now join other genomic alterations such as *NTRK* fusions, tumor mutational burden, and deficient mismatch-repair genes across cancers and *ALK*, *BRAF*, *EGFR*, *MET*, and *ROS1* alterations in NSCLC that warrant molecular screening strategies. Next steps may include introducing these agents earlier in the course of the disease, addressing genomic co-alterations with customized combination-therapy strategies, and using additional techniques such as transcriptome analysis in order to fully understand the molecular landscape of cancer.[9,10]

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

From the Center for Personalized Cancer Therapy and the Division of Hematology and Oncology, Moores Cancer Center, University of California, San Diego, San Diego.

1. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in *TRK* fusion–positive cancers in adults and children. N Engl J Med 2018;378:731-9.
2. Okamura R, Boichard A, Kato S, Sicklick JK, Bazhenova L, Kurzrock L. Analysis of *NTRK* alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. JCO Precis Oncol 2018;2018:10.1200/PO.18.00183.
3. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509-20.
4. Goodman AM, Kato S, Bazhenova L, et al. Tumor mutational burden as an independent predictor of response to immunotherapy in diverse cancers. Mol Cancer Ther 2017;16:2598-608.
5. Wirth LJ, Sherman E, Robinson B, et al. Efficacy of selpercatinib in *RET*-altered thyroid cancers. N Engl J Med 2020;383:825-35.
6. Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in *RET* fusion–positive non–small-cell lung cancer. N Engl J Med 2020;383:813-24.
7. Kato S, Subbiah V, Marchlik E, Elkin SK, Carter JL, Kurzrock R. *RET* aberrations in diverse cancers: next-generation sequencing of 4,871 patients. Clin Cancer Res 2017;23:1988-97.
8. Subbiah V, Cote GJ. Advances in targeting RET-dependent cancers. Cancer Discov 2020;10:498-505.
9. Sicklick JK, Kato S, Okamura R, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744-50.
10. Rodon J, Soria J-C, Berger R, et al. Genomic and transcriptomic profiling expands precision cancer medicine: the WINTHER trial. Nat Med 2019;25:751-8.

DOI: 10.1056/NEJMe2024831




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 1, 2020 VOL. 383 NO. 14

# Early Rhythm-Control Therapy in Patients with Atrial Fibrillation

P. Kirchhof, A.J. Camm, A. Goette, A. Brandes, L. Eckardt, A. Elvan, T. Fetsch, I.C. van Gelder, D. Haase, L.M. Haegeli, F. Hamann, H. Heidbüchel, G. Hindricks, J. Kautzner, K.-H. Kuck, L. Mont, G.A. Ng, J. Rekosz, N. Schoen, U. Schotten, A. Suling, J. Taggeselle, S. Themistoclakis, E. Vettorazzi, P. Vardas, K. Wegscheider, S. Willems, H.J.G.M. Crijns, and G. Breithardt, for the EAST-AFNET 4 Trial Investigators*

## ABSTRACT

### BACKGROUND

Despite improvements in the management of atrial fibrillation, patients with this condition remain at increased risk for cardiovascular complications. It is unclear whether early rhythm-control therapy can reduce this risk.

### METHODS

In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, we randomly assigned patients who had early atrial fibrillation (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either early rhythm control or usual care. Early rhythm control included treatment with antiarrhythmic drugs or atrial fibrillation ablation after randomization. Usual care limited rhythm control to the management of atrial fibrillation–related symptoms. The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary outcome was the number of nights spent in the hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated.

### RESULTS

In 135 centers, 2789 patients with early atrial fibrillation (median time since diagnosis, 36 days) underwent randomization. The trial was stopped for efficacy at the third interim analysis after a median of 5.1 years of follow-up per patient. A first-primary-outcome event occurred in 249 of the patients assigned to early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to usual care (5.0 per 100 person-years) (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94; P=0.005). The mean (±SD) number of nights spent in the hospital did not differ significantly between the groups (5.8±21.9 and 5.1±15.5 days per year, respectively; P=0.23). The percentage of patients with a primary safety outcome event did not differ significantly between the groups; serious adverse events related to rhythm-control therapy occurred in 4.9% of the patients assigned to early rhythm control and 1.4% of the patients assigned to usual care. Symptoms and left ventricular function at 2 years did not differ significantly between the groups.

### CONCLUSIONS

Early rhythm-control therapy was associated with a lower risk of adverse cardiovascular outcomes than usual care among patients with early atrial fibrillation and cardiovascular conditions. (Funded by the German Ministry of Education and Research and others; EAST-AFNET 4 ISRCTN number, ISRCTN04708680; ClinicalTrials.gov number, NCT01288352; EudraCT number, 2010-021258-20.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kirchhof at the Department of Cardiology, University Heart and Vascular Center, Universitätsklinikum Hamburg–Eppendorf Hamburg, Martinistraße 52, Gebäude Ost 70, 20246 Hamburg, Germany, or at p.kirchhof@uke.de.

*A complete list of the EAST-AFNET 4 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 29, 2020, and updated on October 13, 2020, at NEJM.org.

N Engl J Med 2020;383:1305-16.
DOI: 10.1056/NEJMoa2019422


Read Full Article at NEJM.org

EDITORIALS

# Revisiting Rate versus Rhythm Control in Atrial Fibrillation — Timing Matters

T. Jared Bunch, M.D., and Benjamin A. Steinberg, M.D., M.H.S

Treatment approaches for atrial fibrillation are characterized broadly into two categories: "rhythm control," attempting to maintain sinus rhythm, and "rate control," to slow ventricular rate. In the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM), in which rhythm control was compared with rate control in 4060 patients with atrial fibrillation, there were no significant differences between rhythm control and rate control at 5 years with respect to mortality (23.8% and 21.3%, respectively; P=0.08) or the percentage of patients with ischemic stroke (7.1% and 5.5%, P=0.79).[1] A meta-analysis of five randomized trials of rhythm control as compared with rate control likewise showed no significant differences with respect to all-cause mortality and stroke, although the results appeared to favor rate control.[2] Therefore, rate-control strategies are used preferentially, and rhythm-control strategies are recommended primarily to improve atrial fibrillation–related symptoms.[3]

In AFFIRM, rhythm-based treatment in two thirds of the patients consisted of amiodarone or sotalol, and, at 5 years of follow-up, the prevalence of sinus rhythm was 63% (35% in the rate-control group), with 38% having crossed over to rate control, primarily because of side effects or poor efficacy of the drugs.[1] However, in a post hoc analysis, the presence of sinus rhythm was significantly associated with a lower risk of death (hazard ratio, 0.53; 99% confidence interval [CI], 0.39 to 0.72).[4] In hindsight, this trial did not clearly answer the question of whether maintaining sinus rhythm is beneficial, owing to the limited efficacy and risks associated with the antiarrhythmic drugs that were used, including proarrhythmic effects.[5]

Advances in atrial fibrillation rhythm control have led to greater safety and effectiveness and, with augmented experience, improvements in patient selection. Dronedarone, a newer antiarrhythmic drug (not available in previous trials), was found to be associated with lower risks of stroke and of the composite outcome of stroke, acute coronary syndrome, or death from cardiovascular causes than placebo.[6] Catheter ablation has become broadly available and, when successful, minimizes exposure to antiarrhythmic drugs and favorably affects clinical outcomes.[7] In the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial,[8] ablation was associated with a lower risk of recurrent atrial fibrillation (hazard ratio, 0.52; 95% CI, 0.45 to 0.60) and of the composite of mortality or hospitalization for cardiovascular causes (hazard ratio, 0.83; 95% CI, 0.74 to 0.93) than antiarrhythmic drugs. Because atrial fibrillation represents a progressive disease driven by systemic vascular disease and worsening atrial cardiomyopathy, studies have shown improved efficacy of rhythm therapy when it is started earlier.[9] However, it has not been clear whether earlier rhythm control improves clinical outcomes.

Enter the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial (EAST-AFNET 4), an international, randomized, open, blinded-outcome-assessment trial comparing early rhythm control with usual care among patients with atrial fibrillation and additional cardiovascular risk factors, the results of which are now published in the *Journal*.[10] A defining aspect of the trial is that these patients had atrial fibrillation that had recently been diagnosed (<1 year earlier), with one third of the patients having their first episode of atrial fibrillation. Patients who were randomly assigned to early rhythm control had a lower risk of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome (hazard ratio, 0.79; 96% CI, 0.66 to 0.94; P=0.005), as well as a lower risk of the individual components of death from cardiovascular causes (hazard ratio, 0.72; 95% CI, 0.52 to 0.98) and stroke (hazard ratio, 0.65; 95% CI, 0.44 to 0.97). The number of nights spent in the hospital did not differ significantly between the treatment groups. Rhythm-



Back to Table of Contents

control–related adverse events were infrequent, occurring in 4.9% of patients in the group assigned to early rhythm control, with drug-related bradycardia the most common event.

The rhythm-control approach at 2 years in the group assigned to early rhythm control was broad and somewhat evenly distributed among catheter ablation (19%), class 1c antiarrhythmic drugs, dronedarone, amiodarone, and "other" drugs. Long-term adherence to rhythm control remained a challenge, as in previous trials, with 65% still receiving active rhythm control at 24 months. Sinus rhythm was present at 24 months in 82% of the patients assigned to early rhythm control and 60% of the patients assigned to usual care; only 15% of those assigned to usual care ultimately received rhythm control.

The strongest predictor of survival in AFFIRM was not the presence of sinus rhythm but the use of warfarin, which was continued in 70% of patients; ischemic strokes in either treatment group largely occurred in patients in whom anticoagulation was withheld.[4] In EAST-AFNET 4, the use of anticoagulation was common and continued over time (approximately 90% of patients in both groups at 2 years), and the incidence of stroke was correspondingly low (0.6% of patients assigned to early rhythm control and 0.9% of patients assigned to usual care).

A limitation of EAST-AFNET 4, with its low event rates, was that 9.0% and 6.6% of follow-up years in the early-rhythm-control group and usual-care group, respectively, were lost because patients withdrew from the trial or were lost to follow-up (characteristics of the patients not presented). The burden of atrial fibrillation was not reported, and its role as a contributor to outcomes remains unknown. The reported percentages of patients with sinus rhythm were probably overestimated, since they were assessed by electrocardiography rather than continuous monitoring.

The results of this trial support the use of rhythm control to reduce atrial fibrillation–related adverse clinical outcomes when applied early in the treatment of patients with atrial fibrillation. The use of other cardiovascular therapies (including anticoagulants, renin–angiotensin–aldosterone system inhibitors, beta-blockers, and statins) in the trial probably contributed to the low rates of stroke, heart failure, acute coronary syndrome, and death and highlight the need to treat atrial fibrillation with comprehensive management.[11]

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

From the Department of Medicine, School of Medicine, University of Utah, Salt Lake City.

This editorial was published on August 29, 2020, at NEJM.org.

1. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
2. de Denus S, Sanoski CA, Carlsson J, Opolski G, Spinler SA. Rate vs rhythm control in patients with atrial fibrillation: a meta-analysis. Arch Intern Med 2005;165:258-62.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014;130(23):e199-e267.
4. Corley SD, Epstein AE, DiMarco JP, et al. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 2004;109:1509-13.
5. Dan G-A, Martinez-Rubio A, Agewall S, et al. Antiarrhythmic drugs — clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP). Europace 2018;20:731-732an.
6. Connolly SJ, Crijns HJGM, Torp-Pedersen C, et al. Analysis of stroke in ATHENA: a placebo-controlled, double-blind, parallel-arm trial to assess the efficacy of dronedarone 400 mg BID for the prevention of cardiovascular hospitalization or death from any cause in patients with atrial fibrillation/atrial flutter. Circulation 2009;120:1174-80.
7. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. J Cardiovasc Electrophysiol 2011;22:839-45.
8. Packer DL, Mark DB, Robb RA, et al. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. JAMA 2019;321:1261-74.
9. Bunch TJ, May HT, Bair TL, et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. Heart Rhythm 2013;10:1257-62.
10. Kirchhof P, Camm AJ, Goette A, et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med 2020;383:1305-16.
11. Piccini JP, Allred J, Bunch TJ, et al. Rationale, considerations, and goals for atrial fibrillation centers of excellence: a Heart Rhythm Society perspective. Heart Rhythm 2020 May 5 (Epub ahead of print).

DOI: 10.1056/NEJMe2027180




Back to Table of Contents

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 8, 2020 VOL. 383 NO. 15

# Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

## ABSTRACT

### BACKGROUND

Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure in patients regardless of the presence or absence of diabetes. More evidence is needed regarding the effects of these drugs in patients across the broad spectrum of heart failure, including those with a markedly reduced ejection fraction.

### METHODS

In this double-blind trial, we randomly assigned 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

### RESULTS

During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001). The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.70; 95% CI, 0.58 to 0.85; P<0.001). The annual rate of decline in the estimated glomerular filtration rate was slower in the empagliflozin group than in the placebo group (–0.55 vs. –2.28 ml per minute per 1.73 $m^2$ of body-surface area per year, P<0.001), and empagliflozin-treated patients had a lower risk of serious renal outcomes. Uncomplicated genital tract infection was reported more frequently with empagliflozin.

### CONCLUSIONS

Among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes. (Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Reduced ClinicalTrials.gov number, NCT03057977.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Packer at Baylor Heart and Vascular Institute, 621 N. Hall St., Dallas, TX 75226, or at milton.packer@baylorhealth.edu.

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

This article was published on August 28, 2020, at NEJM.org.

N Engl J Med 2020;383:1413-24.
DOI: 10.1056/NEJMoa2022190


Read Full Article at NEJM.org

# More Evidence for SGLT2 Inhibitors in Heart Failure

John A. Jarcho, M.D.

In 2015, the *Journal* published the results of EMPA-REG OUTCOME, a cardiovascular outcomes trial of the sodium–glucose contransporter 2 (SGLT2) inhibitor empagliflozin in patients with type 2 diabetes at high cardiovascular risk.[1] Among the patients who received empagliflozin, the investigators found a significant reduction in major adverse cardiovascular events (cardiovascular death, myocardial infarction, or stroke), as well as in death from cardiovascular causes, death from any cause, progression of renal disease, and hospitalization for heart failure.

Subsequent cardiovascular outcomes trials of other SGLT2 inhibitors have varied in the extent to which they have confirmed the various benefits seen in EMPA-REG OUTCOME.[2,3] However, the benefit with respect to hospitalization for heart failure has been consistent across all the drugs in the class.[4] This observation led to the question of whether the benefit of SGLT2 inhibitors in heart failure might be independent of the presence of diabetes.

This question was answered in the affirmative in 2019 with the publication of the DAPA-HF trial.[5] In DAPA-HF, 4744 patients with heart failure and a reduced ejection fraction were randomly assigned to receive either dapagliflozin or placebo in addition to standard heart-failure therapy. Of the enrolled patients, 41.8% had diabetes mellitus. At a median of 18 months, the primary outcome of cardiovascular death or worsening heart failure was significantly lower in the dapagliflozin group than in the placebo group (16.3% vs. 21.2%; hazard ratio, 0.74; 95% confidence interval [CI], 0.65 to 0.85; P<0.001). A subgroup analysis indicated that the benefit seen was independent of the presence or absence of diabetes. DAPA-HF thus provided a rationale for a novel therapy for heart failure. On May 5 of this year, the Food and Drug Administration (FDA) approved dapagliflozin specifically for the treatment of patients with heart failure and a reduced ejection fraction.

Now reported in the *Journal* are the results of the EMPEROR-Reduced trial, which examines the potential benefit of another SGLT2 inhibitor, empagliflozin, in 3730 patients with heart failure and a reduced ejection fraction.[6] As in DAPA-HF, a substantial proportion of the patients (50.2%) did not have diabetes. The patients in this trial had on average more severe heart failure than those in the DAPA-HF trial, with a mean ejection fraction of 27% versus 31% and a median level of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) of 1907 versus 1437; in addition, more than 70% of the patients enrolled in EMPEROR-Reduced had an ejection fraction of 30% or less. The median duration of follow-up was 16 months. As in DAPA-HF, the incidence of the primary outcome of cardiovascular death or hospitalization for heart failure was significantly lower with empagliflozin than with placebo (19.4% vs. 24.7%; hazard ratio, 0.75; 95% CI, 0.65 to 0.86; P<0.001). Again, the benefit was seen regardless of diabetes status.

In both DAPA-HF and EMPEROR-Reduced, the two components of the primary outcome were analyzed individually but were not formally tested for significance. In DAPA-HF, the hazard ratio for cardiovascular death considered alone was 0.82 (95% CI, 0.69 to 0.98), a result that is nominally significant if the inflation of the alpha error owing to multiple testing is disregarded. In contrast, in EMPEROR-Reduced, the hazard ratio for cardiovascular death alone was 0.92 (95% CI, 0.75 to 1.12), a result that is not nominally significant.

Is this apparent difference in the effect on cardiovascular death real? There are some reasons to consider this possibility. Two different drugs were used, and, as noted earlier, the individual SGLT2 inhibitors do not seem to have entirely consistent cardiovascular effects. On the other hand, as the authors point out in their Discussion section, the effects of dapagliflozin and empagliflozin on cardiovascular death in patients with diabetes without heart failure trend in the opposite direction, with empagliflozin showing a significant benefit on cardiovascular death that was not seen with dapagliflozin. Another possible consideration is that, as noted, the patients in EMPEROR-Reduced had on aver-



Back to Table of Contents

age more severe heart failure than those in DAPA-HF; perhaps these drugs are less effective in more advanced heart failure. A subgroup analysis of cardiovascular death according to ejection fraction, baseline NT-proBNP level, or NYHA class might help in examining this question. It is also possible, of course, that the apparent difference in effect on cardiovascular death is a chance finding; the confidence intervals for the two point estimates certainly overlap. A definitive answer to this question would likely require a head-to-head randomized trial.

When new heart-failure therapies are investigated, it is important to consider whether they provide benefit in addition to established therapies. This question applies in particular to sacubitril–valsartan, which has been adopted rather gradually in clinical practice despite receiving FDA approval in 2015 and a class I guidelines recommendation in 2016.[7] In DAPA-HF, only 10.7% of the patients were receiving sacubitril–valsartan, as compared with 19.5% of those in EMPEROR-Reduced. In both trials, subgroup analyses did not suggest that the benefit of empagliflozin varied according to the use of sacubitril–valsartan.

The results of the EMPEROR-Reduced trial confirm that the findings in DAPA-HF were no fluke and substantially strengthen the rationale for the use of SGLT2 inhibitors in patients with heart failure and a reduced ejection fraction. Guidelines committees will now need to contend with the evidence. The Canadian Cardiovascular Society and the Canadian Heart Failure Society have already done so: they have recommended the use of SGLT2 inhibitors in patients with mild or moderate heart failure who have an ejection fraction of 40% or less to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality.[8] The EMPEROR-Reduced data will provide further impetus for other groups to address this question.

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

This editorial was published on August 28, 2020, at NEJM.org.

1. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.
4. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.
5. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.
6. Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020:383;1413-24.
7. Yancy CW, Jessup M, Bozkurt B, et al. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation 2016;134(13):e282-e293.
8. O'Meara E, McDonald M, Chan M, et al. CCS/CHFS heart failure guidelines: clinical trial update on functional mitral regurgitation, SGLT2 inhibitors, ARNI in HFpEF, and tafamidis in amyloidosis. Can J Cardiol 2020;36:159-69.

DOI: 10.1056/NEJMe2027915

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

# Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

## ABSTRACT

### BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

### METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 $\mu$g per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

### RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

### CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

This article was published on December 10, 2020, and updated on December 16, 2020, at NEJM.org.

N Engl J Med 2020;383:2603-15.
DOI: 10.1056/NEJMoa2034577


Read Full Article at NEJM.org

EDITORIALS

# SARS-CoV-2 Vaccination — An Ounce (Actually, Much Less) of Prevention

Eric J. Rubin, M.D., Ph.D., and Dan L. Longo, M.D.

The Covid-19 epidemic continues to rage, especially in countries that have been unable or unwilling to institute strong public health measures. A return to normality has increasingly come to rely on the success of vaccines to prevent disease and, we hope, limit further spread of infection. However, this hope has been tempered by several unknowns. No existing vaccines have been shown to be effective against infection with any betacoronavirus, the family that includes SARS-CoV-2, which causes Covid-19. SARS, caused by another betacoronavirus, ended on its own before serious efforts at vaccine development were undertaken, and the rather small number of MERS cases has not yet justified the large-scale effort and investment required to determine whether preclinical vaccine candidates are efficacious. In addition, strategies to increase the speed of vaccine development have themselves had only limited testing. A relatively small number of people have received adenovirus-vectored vaccines, and no vaccines based on mRNA technologies have yet been approved. Would these new products be effective and safe?

Today we have part of the answer, and it is strongly encouraging. The vaccine BNT162b2 is a modified RNA that encodes a version of the SARS-CoV-2 spike protein containing mutations that lock the protein into a conformation that can induce neutralizing antibody responses. Early clinical trials showed that it could induce both humoral and cellular immunity, although we did not know until now whether these responses would protect against symptomatic infection. Today we know.

We are publishing today in the *Journal* the results of a phase 3, double-blind, randomized, controlled trial of a new RNA vaccine.[1] In this trial, 21,720 participants received BNT162b2 and 21,728 received placebo. Both groups received two injections spaced 21 days apart. Persons with obesity or other coexisting conditions were well represented, and more than 40% of participants were older than 55 years of age. Participants notified trial sites if they had symptoms that were consistent with Covid-19, and they were tested to diagnose infection. They recorded in daily diaries any adverse events they were experiencing. The primary outcomes were safety and the incidence of symptomatic Covid-19 with onset occurring at least a week after the second dose of vaccine or placebo, although all symptomatic infections are reported. The findings in this report include the first 170 cases of Covid-19 detected in the primary population and cover a median of 2 months of safety data. The investigators plan to continue to follow the participants, although once the vaccine becomes freely available, maintaining randomization may be a challenge.

The results were impressive. In the primary analysis, only 8 cases of Covid-19 were seen in the vaccine group, as compared with 162 in the placebo group, for an overall efficacy of 95% (with a 95% credible interval of 90.3 to 97.6%). Although the trial does not have the statistical power to assess subgroups, efficacy appeared to be similar in low-risk and high-risk persons, including some from communities that have been disproportionately affected by disease, and in participants older than 55 years of age and those younger than 55. Adverse events were largely consistent with vaccine reactogenicity, with mostly transient and mild local reactions



Back to Table of Contents

such as injection-site pain and erythema; systemic reactions such as fever, fatigue, and adenopathy were uncommon. This pattern appears to be similar to that of other viral vaccines and, at least with this number of participants and this follow-up period, does not arouse specific concern.

There are nonetheless minor issues. The number of severe cases of Covid-19 (one in the vaccine group and nine in the placebo group) is too small to draw any conclusions about whether the rare cases that occur in vaccinated persons are actually more severe. For practical reasons, the investigators relied on trial participants to report symptoms and present for testing. Since reactogenicity was more common in vaccine recipients, it is possible that they were less inclined to believe that minor symptoms were due to Covid-19 and therefore less likely to refer themselves for testing. And some important data, such as the rate of asymptomatic disease (as measured by seroconversion to a viral nucleoprotein that is not a component of the vaccine), have not yet been reported.

Nevertheless, the trial results are impressive enough to hold up in any conceivable analysis. This is a triumph. Most vaccines have taken decades to develop, but this one is likely to move from conception to large-scale implementation within a year. The sequence of the virus that led to the development of the specific viral RNA sequence required to design the vaccine didn't become known until it had been determined and widely disseminated by the Chinese Center for Disease Control and Prevention in January 2020. There is a lot of credit to go around: to the scientists who shared data and who developed the underlying methods and implemented them to create a vaccine, to the clinical trialists who performed high-quality work in the setting of a health emergency, to the thousands of participants who volunteered to take part in the trial, and to the governments that helped create performance standards and a market for the vaccine. And all this stands as a template for the many other Covid-19 vaccines currently in development, some of which have already completed their phase 3 trials.

Important questions of course remain. Only about 20,000 people have received this vaccine. Will unexpected safety issues arise when the number grows to millions and possibly billions of people? Will side effects emerge with longer follow-up? Implementing a vaccine that requires two doses is challenging. What happens to the inevitable large number of recipients who miss their second dose? How long will the vaccine remain effective? Does the vaccine prevent asymptomatic disease and limit transmission? And what about the groups of people who were not represented in this trial, such as children, pregnant women, and immunocompromised patients of various sorts?

The logistic challenges of manufacturing and delivering a vaccine remain daunting. This vaccine, in particular, requires storage at –70°C, a factor that may limit its deployment in some areas. Nevertheless, the remarkable level of safety and efficacy the vaccine has demonstrated thus far make this a problem that we should welcome solving. What appears to be a dramatic success for vaccination holds the promise of saving uncounted lives and giving us a pathway out of what has been a global disaster.

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

This editorial was published on December 10, 2020, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.

DOI: 10.1056/NEJMe2034717

ORIGINAL ARTICLE

# Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, and T. Zaks, for the COVE Study Group*

## ABSTRACT

### BACKGROUND

Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications. The mRNA-1273 vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19.

### METHODS

This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 $\mu$g) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.

### RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

### CONCLUSIONS

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. El Sahly at the Departments of Molecular Virology and Microbiology and Medicine, 1 Baylor Plaza, BCM-MS280, Houston, TX 77030, or at hana.elsahly@bcm.edu; or to Dr. Baden at the Division of Infectious Diseases, Brigham and Women's Hospital, 15 Francis St., PBB-A4, Boston, MA 02115, or at lbaden@bwh.harvard.edu.

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

Drs. Baden and El Sahly contributed equally to this article.

This article was published on December 30, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2035389







Back to Table of Contents

EDITORIAL

# A New Vaccine to Battle Covid-19

Barton F. Haynes, M.D.

The United States and many parts of the world have now lost control of the Covid-19 pandemic owing to the respiratory spread of SARS-CoV-2 and to inconsistent adherence to effective public health measures, including wearing masks and maintaining social distancing. Persons infected with SARS-CoV-2 are frequently asymptomatic, yet they have high respiratory viral loads, and they are major purveyors of viral spread. These factors have led to the current explosion of Covid-19 hospitalizations and deaths, with Covid-19 now a major cause of death in the United States. Our only hope is safe and effective vaccines that can be widely deployed to provide herd immunity that can control viral spread.

Since January 2020, when the first sequencing of SARS-CoV-2 became public, the scientific community has worked toward rapid development of mRNA, protein, viral vector, and other types of Covid-19 vaccines. Two vaccine efficacy trials have been completed, and the two vaccines have recently received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA). The first vaccine given such authorization, an mRNA in lipid nanoparticles (LNPs), BNT162b2 from Pfizer and BioNTech, showed 95% vaccine efficacy.[1] Today, the *Journal* is publishing the trial results establishing the efficacy of a second mRNA-LNP vaccine, mRNA-1273 from Moderna.[2] In the mRNA-1273 Coronavirus Efficacy (COVE) trial, 30,420 volunteers were randomly assigned to receive either vaccine or placebo (15,210 in each group). Symptomatic Covid-19 was confirmed in 185 participants in the placebo group and 11 in the mRNA-1273 group, for a vaccine efficacy of 94.1% (95% confidence interval, 89.3 to 96.8). For participants 18 to less than 65 years of age, the efficacy was 95.6%, and for those 65 years or older the efficacy was 86.4%. Both the Moderna vaccine and the Pfizer–BioNTech vaccine begin to protect recipients approximately 10 days after the first dose, with maximum protection after the second dose.

The safety profile of the mRNA-1273 vaccine for the median 2-month follow-up showed no safety concerns; the frequency of unsolicited adverse events and severe adverse events during 28 days after injection was similar in the vaccine and placebo groups. Solicited adverse events at the injection site occurred more frequently with the vaccine than with placebo, occurring in 88.6% of vaccinees after the second dose. The safety and immunogenicity of the mRNA-1273 vaccine in older adults has been previously reported.[3]

One of the concerns regarding Covid-19 vaccines that has emerged from studies of the earlier SARS and Middle East respiratory syndrome (MERS) outbreaks is the possibility that a Covid-19 vaccine could enhance disease, a phenomenon called vaccine-associated enhanced disease (VAED).[4,5] In the COVE trial, severe Covid-19 developed in 30 participants, all in the placebo group; thus, the mRNA-1273 vaccine provided 100% protection against severe Covid-19 disease, with no evidence of VAED.[2] In the earlier SARS and MERS preclinical studies, VAED occurred with low neutralizing antibodies.[4,5] Thus, it will be important for the FDA and the Centers for Disease Control and Prevention to continue to monitor clinical trials for safety after issuing an EUA, including assessment of VAED risk.

Several major issues remain regarding the



Back to Table of Contents

ability of Covid-19 vaccines to mitigate the SARS-CoV-2 pandemic. First, what are the nature and the duration of the protective immune response to SARS-CoV-2? Evidence in vaccinated monkeys suggests that SARS-CoV-2 neutralizing antibodies are the primary mode of protection, and CD8 T-cell responses can augment protection.[6] How long neutralizing antibodies will last is not known, although follow-up studies in the phase 1 mRNA-1273 trial demonstrated persistence of neutralizing antibodies 3 months after the second dose of vaccine.[7] Second, since reactogenicity was more common in vaccine recipients, it is possible that they were less inclined to believe that minor symptoms were due to Covid-19 and therefore less likely to refer themselves for testing in the trial.[8] Third, analysis of virus escape from protective immune responses and long-term follow-up for rare safety events are needed.[4,5] Finally, the trial was not powered to determine whether mRNA-1273 could protect against asymptomatic SARS-CoV-2 infection, a question that is critical to controlling the pandemic. Studies designed to answer this question are ongoing or planned.

That the mRNA-1273 Covid-19 and the BNT162b2 Covid-19 vaccines protect with near-identical 94 to 95% vaccine efficacies — and that both vaccines were developed and tested in less than a year — are extraordinary scientific and medical triumphs. This happened because the scientific community was prepared from years of technology development for other vaccines, such as those against HIV, influenza, respiratory syncytial virus, and Zika, and because clinical trials consortia were established that rapidly carried out Covid-19 efficacy trials.[4,9] If mRNA-LNP vaccines significantly contribute to control of the pandemic, mRNA technology has the potential to radically change vaccine design for future viral outbreaks.

Although the Covid-19 pandemic is currently raging, the prospects for control of this and future pandemics are bright. The recent FDA issuance of EUAs for these extraordinarily protective vaccines provide us with much-needed hope at a time when so many are suffering. The next challenge is to get these and the next Covid-19 vaccines to the people most at risk as quickly as possible.

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

From the Departments of Medicine and Immunology, Duke Human Vaccine Institute, Duke University School of Medicine, Durham, NC.

This editorial was published on December 30, 2020, at NEJM.org.

1. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383:2603-15.
2. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. DOI: 10.1056/NEJMoa2035389.
3. Anderson EJ, Rouphael NG, Widge AT, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383:2427-38.
4. Graham BS. Rapid COVID-19 vaccine development. Science 2020;368:945-6.
5. Haynes BF, Corey L, Fernandes P, et al. Prospects for a safe COVID-19 vaccine. Sci Transl Med 2020;12(568):eabe0948.
6. McMahan K, Yu J, Mercado NB, et al. Correlates of protection against SARS-CoV-2 in rhesus macaques. Nature 2020 December 4 (Epub ahead of print).
7. Widge AT, Rouphael NG, Jackson LA, et al. Durability of responses after SARS-CoV-2 mRNA-1273 vaccination. N Engl J Med. DOI: 10.1056/NEJMc2032195.
8. Rubin EJ, Longo DL. SARS-CoV-2 vaccination — an ounce (actually, much less) of prevention. N Engl J Med 2020;383:2677-8.
9. Sempowski GD, Saunders KO, Acharya P, Wiehe KJ, Haynes BF. Pandemic preparedness: developing vaccines and therapeutic antibodies for COVID-19. Cell 2020;181:1458-63.

DOI: 10.1056/NEJMe2035557




Back to Table of Contents

NEJM Catalyst | Innovations in Care Delivery

# A journal for transforming health care delivery

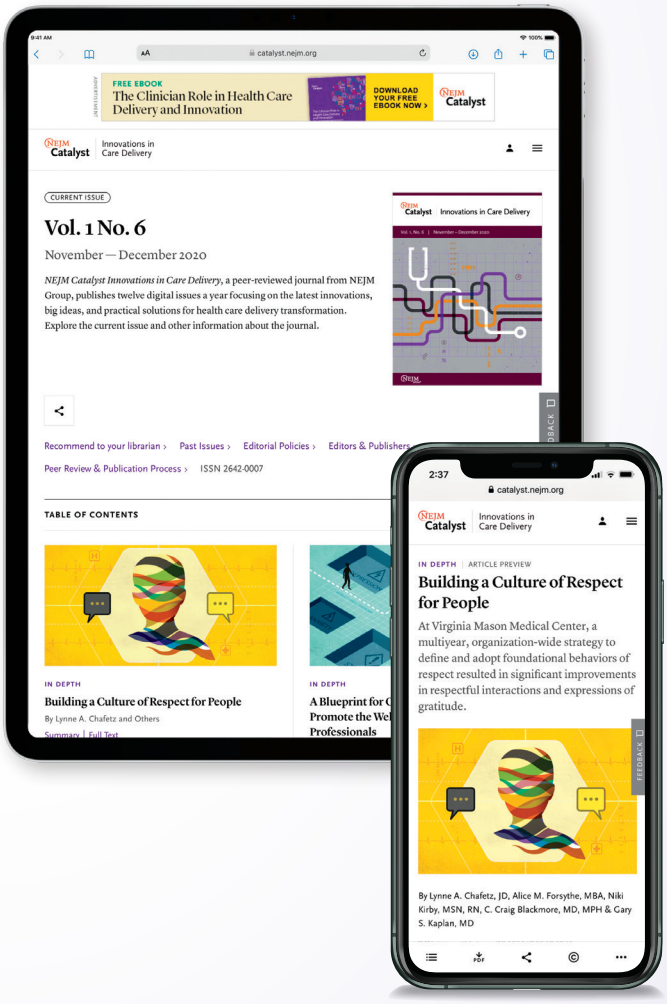
## Practical innovations for health care leaders

NEJM Catalyst accelerates the transformation of health care delivery with its peer-reviewed digital journal, *NEJM Catalyst Innovations in Care Delivery*. Each monthly issue explores the best ideas and strategies with the most potential for change.

A subscription to *NEJM Catalyst Innovations in Care Delivery* includes:

- Rigorous in-depth articles
- Data-driven case studies
- Current and archived web events
- Insights Council research reports
- Podcast interviews with health care innovators

Join thousands of global health care leaders and clinicians who turn to NEJM Catalyst for important innovations and practical solutions.




**LEARN MORE AT CATALYST.NEJM.ORG**

NEJM GROUP